An evidence-based approach to the urgent referral of suspected oral cancer in England

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Abstract

Background

Reports that UK outcomes for several cancers, including oral, were inferior to comparable European countries prompted the UK Government's 'NHS Cancer Plan'; a central aim was reduction of late presentation. One key policy was the English 'two-week rule' (TWR) system for suspected cancer, specifying a maximum of 14 days between referral and specialist consultation. For oral cancer, little research has been undertaken on several key areas including its influence on stage on presentation and how the system might be improved.

Aim

To conduct evidence-based evaluation of the policy for urgent referral of suspected oral cancer in England and conduct 4 studies in areas where important evidence is absent or sparse.

Methods

(1) A time-series study examining stage on diagnosis of oral cancer before and after the TWR (2) A qualitative study comparing the views of specialists in England and the Netherlands on their head and neck cancer referral systems (3) A systematic review comparing oral cancer referrals from doctors and dentists (4) A Delphi study of expert opinion on the priority of the methods of encouraging early oral cancer diagnosis.

Findings

English/UK outcomes for oral cancer are probably genuinely worse than the European best. The causes are multiple and complex, although late diagnosis is an important cause.

A time-series study of 1483 patients between 1992-2012 suggests the TWR system has not influenced the trend in late oral cancer presentation. Socio-economic differences in late presentation are reducing but persist and oral cancer presentation is increasing.

A qualitative study highlighted similarities between the English TWR system and the more flexible Dutch system but also differences. The Dutch system featured more direct professional communication, greater flexibility and more rapid referral of head and neck cancer.

A systematic review confirmed both GPs and dentists refer oral cancer. Overall, dentists may refer earlier stage disease and refer some cancers following routine inspections, in the absence of symptoms.

In a Delphi study experts consider rapid referral systems high priority for oral cancer but a range of measures were also considered useful.

Conclusions

The current TWR urgent referral system alone may be limited in reducing late oral cancer presentations. Earlier referral may be improved by more flexible referral systems with better communication and by improving access to regular dental inspections, particularly for those at high risk.

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Statement of contributions

I am the sole author of this thesis, which is an original and independent work.

The following contributed to the thesis:

My supervisors Professor Clare Bankhead and Dr. Annette Plüddemann gave guidance on strategy, study design and protocols, analysis, interpretation of results and presentation.

Professor Simon Rogers (University of Edge Hill) discussed aspects of socio-economic deprivation and access to cancer staging data at Aintree Hospital, Liverpool, in relation to Chapter 3.

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Contents

Section	Content	Page
	Abstract	i
	Acknowledgements	ii
	Statement of contributions and word count	iii
	Contents	iv
	Tables and Figures	xii
	Abbreviations	xiv
	Publications	xvi
1	**CHAPTER 1: Introduction**	1
1.1	**This thesis - why?**	1
1.2	**Oral Cancer**	3
1.2.1	Incidence	3
1.2.2	Staging of oral cancer	3
1.2.3	Mortality and survival	4
1.2.4	Causes	5
1.2.5	Treatment	6
1.2.6	Socio-economic influences and UK regional variations	7
1.3	**The urgent referral of suspected cancer in England**	8
1.3.1	General points – screening and early diagnosis	8
1.3.2	The ‘two-week rule’ (TWR)	9
1.3.3	History and development of the TWR	10
1.3.4	TWR introduction	11
1.3.5	Further development of English urgent cancer referral	11
1.4	**What is known about the effectiveness of the UK fast-track system for suspected cancer?**	12
1.4.1	Early reaction to the English TWR system	12
1.4.2	Access targets	13
1.4.3	Target-driven policy – ‘hitting the target and missing the point’	13
1.4.4	Studies on diagnostic effectiveness	14

1.4.5 Influence on clinical outcomes 15

1.4.6 Improving TWR urgent referral – beyond clinical judgement? 18

1.4.7 Effectiveness of the English TWR system for oral cancer 18

Chapter 1 references 19

2 CHAPTER 2: Literature Review and Theoretical Framework 27

2.1 Urgent cancer referral - historical aspects 27

2.2 Evidence influencing policy change – the EUROCARE studies 27

2.2.1 EUROCARE and English cancer outcomes – worse than the European best? 28

2.2.2 The EUROCARE studies - strengths, weaknesses and criticisms 31

2.2.3 Are the 'relatively poor' UK cancer outcomes genuine? 33

2.2.4 The UK in relation to the rest of the world (CONCORD-3 studies) 35

2.3 Explaining international differences – why might England fall behind the best in Europe? 36

2.3.1 Treatment 37

2.3.1.1 *Surgery* 37

2.3.1.2 *Radiotherapy* 38

2.3.1.3 *Chemotherapy* 39

2.3.2 Patient factors 39

2.3.2.1 *Co-morbidities* 40

2.3.2.2 *Age* 40

2.3.2.3 *Behaviours* 41

2.3.2.4 *Socio-economic factors* 41

2.4 Diagnostic Delay 42

2.4.1 Models of delay 45

2.4.2 What is known about delay at various stages of cancer 'diagnostic pathways'? 49

2.4.3 Types of cancer, age, sex and social differences 49

2.4.4. System influences 51

2.5 How does delay relate to cancer outcomes? 52

2.6 Oral cancer: outcomes, delays and fast-track referral 56

2.6.1 The EUROCARE studies – oral cancer 56

2.6.2 Delay and oral cancer 58

2.6.3 Causes of delay - patient factors 59

2.6.4 Professional delay 61

2.6.5 Relationship between delay and outcome 62

2.6.6 Urgent referral of oral cancer in England – the TWR 65

2.6.7 Screening for oral cancer 65

2.7 Summary 66

2.8 Question development 68

2.9 Aim and objectives 69

2.10 Thesis structure and studies in relation to the objectives 69

Chapter 2 references 70

3 CHAPTER 3: The impact of the 'two-week rule' on stage at diagnosis of oral cancer and the relationship to socio-economic inequalities 82

3.1 Abstract 82

3.2 Background 83

3.3 Aim and objectives 84

3.4 Methods 85

3.4.1 Choice of study design 85

3.4.2 Patient and public involvement 86

3.4.3 Ethics 86

3.4.4 Data source 86

3.4.4.1 *Databases of cancer staging - historical* 86

3.4.4.2 *National data* 87

3.4.4.3 *Database for Head and Neck Oncology (DAHNO) and head and neck audit (HANA) data* 87

3.4.4.4 *Aintree Hospitals (Merseyside) head and neck cancer database* 88

3.4.5 Staging data for this study 89

3.4.6 Socio-economic deprivation data 89

3.4.7 Analyses 90

3.5 Results 92

3.5.1 Presenting oral cancers: numbers and stage at diagnosis 92

3.5.2 Deprivation 'groups' and percentage of late cancer 95

3.5.3 *'Joinpoint'* regression analysis 96

3.5.4 Associations with late presentation 98

3.6 Discussion 99

3.6.1 Increasing numbers of oral cancers 99

3.6.2 Stage on presentation before and after the TWR-NICE guidance referral system 100

3.6.3 Intra-oral sites 101

3.6.4 Relationship to socio-economic deprivation 101

3.6.5 Socio-economic deprivation in the study population 101

3.7 Strengths and limitations of this study 102

3.8 Conclusions and implications 104

3.8 Related publication 105

Chapter 3 references 105

4 CHAPTER 4: Head and neck cancer referral in England and the Netherlands: an international qualitative study of secondary care surgical specialists' views 109

4.1 Abstract 109

4.2 Introduction 110

4.2.1 Cancer Referral in the English and Dutch Health Systems 111

4.3 Aim and objectives 112

4.4 Methods 112

4.4.1 Research methodology 112

4.4.2 Ethical approval 114

4.4.3 Patient involvement 114

4.4.4 Study populations and sample strategy 114

4.4.5 Recruitment procedure 115

4.4.6 Interviewing and data collection 115

4.5 Analysis 118

4.5.1 Transcription, familiarisation and thematic analysis 118

4.5.2 Memo writing 118

4.6 Rigour 119

4.7 Results 119

4.7.1 Participants 119

4.7.2 Themes 120

4.8 Discussion 126

4.8.1 Summary and main findings 126

4.8.2 Comparison with existing literature 128

4.8.3 Reflexivity 129

4.8.4 Strengths and limitations 130

4.9 Conclusions 130

4.9.1 Implications for practice and research 131

4.10 Sources of support 131

4.11 Related publication 131

Chapter 4 references 132

5 CHAPTER 5: A comparison of primary care doctors and dentists in the referral of oral cancer: a systematic literature review 135

5.1 Abstract 135

5.2 Introduction 136

5.3 Aim and objectives 137

5.4 Methods 137

5.4.1 About systematic reviews and choice of study design 137

5.4.2 Types of studies 138

5.4.3 Search methods 139

5.4.4 Selection of studies 139

5.4.5 Data extraction 139

5.4.6 Study quality and bias 140

5.4.7 Missing data 142

5.4.8 Synthesis and analysis of data 142

5.4.9 Subgroups 143

5.4.10 Heterogeneity 143

5.4.11 Publication bias 144

5.5 Results 144

5.5.1 Search outcome 144
5.5.2 Description of included studies 145
5.5.3 Description of excluded studies 145
5.5.4 On-going studies 145
5.5.5 Study quality and risk of bias 145
5.5.6 Referral source, diagnostic stage and delay 155
5.5.6.1 Percentages of cases referred by primary care medical and dental practitioners 155
5.5.6.2 Meta-analysis: relative risk of dental or medical referral 156
5.5.6.3 Stage of oral cancer on referral 157
5.5.6.4 Delay on presentation 159
5.5.6.5 Other reported findings 160
5.6 Discussion 161
5.6.1 GP and dentist referrals 161
5.6.2 Stage on presentation 162
5.6.3 Differences in delay between medical and dental referrals 164
5.6.4 Implications for practice and research 165
5.6.5 Strengths and weaknesses 167
5.7 Related publication 167
Chapter 5 references 167
6 CHAPTER 6: Prioritisation of approaches to the early diagnosis of oral cancer: a Delphi study of UK experts 173
6.1 Abstract 173
6.2 Background 174
6.3 Delphi studies 174
6.3.1 About Delphi studies 174
6.3.2 Delphi process 176
6.3.3 Advantages and disadvantages 176
6.3.4 When are Delphi studies used? 176
6.3.5 Choice of the Delphi method for this study 177
6.4 Aim and objectives 177
6.5 Methods 177

6.5.1 Ethical approval 177

6.5.2 Generation of item list 178

6.5.3 Participant identification 179

6.5.4 Consent 180

6.5.5 Data collection 180

6.5.6 Delphi procedure 180

6.6 Results 181

6.6.1 Response rates and demographics of experts 181

6.6.2 Round 1 questionnaire 182

6.6.3 Round 2 questionnaire 184

6.6.4 Comments 187

6.7 Subgroups 189

6.8 Discussion 189

6.8.1 General points 189

6.8.2 Relationship to findings in other studies in this thesis 190

6.8.3 Comparison with existing literature 191

6.8.4 Strengths and weaknesses 192

6.8.5 Implications for policy, practice and research 193

6.9 Conclusions 193

Chapter 6 references 194

7 CHAPTER 7: Summary, discussion and conclusions 197

7.1 Overview of the thesis findings 197

7.1.1 Literature review and questions 197

7.1.2 Summary of findings from the studies 198

7.2 Discussion 199

7.2.1 Does the TWR ‘work’ for oral cancer? 199

7.2.2 International differences in referral systems 200

7.2.3 Other approaches to encourage early diagnosis of oral cancer? 201

7.2.4 Priority of the various methods of encouraging early oral cancer diagnosis 202

7.2.5 Earlier diagnosis or ‘prevention first’? 203

7.3	**Strengths and weaknesses of the thesis**	203
7.4	**Implications for policy**	204
7.5	**Implications for research**	212
7.6	**Overall conclusions**	213
7.7	**Final thoughts – some reflections**	214
	Chapter 7 references	216
	APPENDICES	219
	Guide to appendices	219
1	**Ethics approval letters**	220
2	**Two-week rule oral cancer guidelines**	225
3	**Qualitative study semi-structured questionnaire**	226
4	**Systematic review data collection form**	227
5a	**Screenshots – examples of online Delphi study**	228
5b	**Round 1 Delphi questionnaire**	230
5c	**Delphi panel members**	231
6	**Study protocols**	232
7	**Literature update system**	268

Tables and Figures

Tables

Table number	Title	Page
1.1	Staging of Oral Cancer (AJCC v8 2016-18)	4
1.2	English cancer access targets (April 2020)	12
2.1	The EUROCARE studies on cancer survival	28
2.2	Case mix survival from all adult cancers: 1 year and 5-year survival	29
2.3	Cancer survival examples EUROCARE 3 (2003) and 5 (2014)	30
2.4	Possible explanations for international survival differences	36
2.5	Examples of survival percentages of common cancers by stage	42
2.6	1-year and 5-year conditional survival: lung, head and neck, colon cancers	43
3.1	Numbers of presenting oral cancers by year and stage 1992-2012	92
3.2	Percentages of Merseyside population 55-59 years, 60-64 years, 65-69 years and 70-74 years	94
3.3	Percentages of cancer presenting 'late' and social deprivation groups	95
3.4	Associations with late (stage 3 &4) presentation – clinical and demographic factors	98
4.1	Categories of qualitative questions in policy research, according to Ritchie and Spencer	116
4.2	Profile of participants	120
5.1	Evaluation of bias – Hammer checklist	141
5.2	Evaluation of study quality – the 'MINORS' scale	142
5.3	Included studies (ordered by date of publication)	147
5.4	Excluded Studies	151
5.5	Study quality	153
5.6	Assessment of bias (Single author evaluation)	154
5.7	Numbers in each study and percentages referred by GPs and dentists	155
5.8	Stage of oral cancer on referral – studies comparing GPs and dentists	158
5.9	Delay – studies comparing GPs and dentists	160
6.1	Items for Delphi questionnaire	179
6.2	Response rates and demographics	182
6.3	Percentage of respondents awarding Likert scores of effectiveness	183
6.4	Percentage of respondents scoring 6 or 7 on Likert scale (round 1)	183
6.5	Percentage of respondents scoring 5, 6 or 7 on Likert scale (round 2)	185
6.6	Agreement/disagreement with round 1 priority and suggested category if disagreement	186
6.7	Comments	188
6.8	Subgroups	189
7.1	Summary of key recommendations for policy	211
7.2	Implications for research	212

Figures

Figure number	Title	Page
1.1	Age-standardised rates for oral and oropharyngeal cancer	7
1.2	GP referrals for suspected cancer in England 2009/10 to 2017/18	15
2.1	Intervals in cancer pathway, according to Walter (2012)	46
2.2	Illustration of time intervals in cancer diagnosis, up to start of treatment	48
2.3	1-year and 5-year survival for oral cancer, EUROCARE -3, -4 and -5	53
2.4	Conditional (on surviving 1 year) 5-year oral cancer survival	57
3.1a	Graph showing numbers of oral cancers presenting at each of stages 1 to 4, by year 1992-2012	93
3.1b	Bar chart showing percentage of oral cancers presenting at each of stages 1 to 4, by year 1992-2012	93
3.2	Merseyside population 1992-2012	94
3.3	Joinpoint regression analysis of percentage of 'late' (stage 3 & 4) presentations, 1992-2012	96
3.4a	Joinpoint analysis of late presentations (stage 3 a& 4) in the 711 patients living in 'more deprived' areas	97
3.4b	Joinpoint analysis of late presentations (stage 3 a& 4) in the 711 patients living in 'less deprived' areas	97
5.1	Prisma flow diagram of search outcome	144
5.2	Forest plot for relative risk of medical/dental referral (all studies)	156
5.3	Forest plot for relative risk of medical/dental referral (UK studies)	159
5.4	Forest plot relative risk of medical/dental referral of early (stage 1 and 2) oral cancer	155
6.1	Percentage including method as one of 'two most effective methods' of encouraging early diagnosis	184
7.1	Thesis and links to evidence-based policy	206

Abbreviations

Abbreviation	Meaning
AJCC	American Joint Committee on Cancer
APC	Annual percentage change
BAHNO	British Association of Head and Neck Oncologists
BAOMS	British Association of Oral and Maxillofacial Surgeons
CI	Confidence interval
CMO	Chief Medical Officer
CNS	Central nervous system
COE	Conventional oral examination
CRUK	Cancer Research UK
DOH	Department of Health (UK)
EBM	Evidence-based medicine
EBP	Evidence-based policy
EMA	European Medicines Agency
ENT	Ear, nose and throat (otolaryngology)
GDP	Gross Domestic Production
GP	General Practitioner
HCP	Healthcare professional
HPV	Human papilloma virus
ICBP	International Cancer Benchmarking Partnership
IMD	Index of multiple deprivation
ITS	Interrupted time series
MDT	Multi-disciplinary team
MINORS	Methodological index for non-randomised studies
MSc	Master of Science
NCRAS	National Cancer Registration Analysis Service
NHL	Non-Hodgkin lymphoma
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence

NPV	Negative predictive value
OMFS	Oral and maxillofacial surgery
OPMD	Oral potentially malignant disorder
PPI	Public and patient involvement
PPV	Positive predictive value
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QUORUM	Quality of reporting of meta-analysis
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma/cancer
TNM	Tumour – Node – Metastasis classification of cancer
TWR/TWW	Two-week rule/two-week wait
UAT	Upper aero-digestive tract
VU	Vrije Universiteit (Amsterdam)
WHO	World Health Organisation

Publications

Published chapters from this thesis

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Related work published when studying for DPhil

Rogers SN, Staunton A, Girach R, Langton S and Lowe D (2019) *Audit of the two-week pathway for patients with suspected cancer of the head and neck and the influence of socioeconomic status* British Journal of Oral and Maxillofacial Surgery 57 419-424

Williamson S, Beaver K and Langton S (2020) *Exploring health care professionals views on alternative approaches to cancer follow-up and barriers and facilitators to implementation of a recovery package* European Journal of Oncology Nursing 46 1-7

Other work on urgent suspected cancer referral

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

CHAPTER 1: Introduction

ABOUT ORAL CANCER AND THE ENGLISH URGENT SUSPECTED CANCER REFERRAL SYSTEM – 'THE TWO-WEEK RULE' (TWR)

1.1 This thesis - why?

I 'discovered' evidence-based healthcare relatively late in my career, when I matriculated for the Oxford MSc in Evidence-Based Healthcare in 2012. At that time, I had been a consultant surgeon, specialising in oral and facial cancer, for 17 years. I had been a regional training program director, national tutor for maxillofacial surgery, a senior examiner at the Royal College of Surgeons, clinical director of cancer services, a board member of my UK specialty journal and a member of one of the NICE (National Institute for Health and Care Excellence) cancer committees. However, up to this time I had received very limited formal training in research or research methods.

The Oxford MSc gave me considerable insight into the process of evidence-based practice ('ask question, find research, appraise, apply and evaluate outcomes') and many new skills, particularly in relation to previously-unfamiliar research methods, such as qualitative studies and systematic reviews. I began to think about the challenges I faced in many aspects of my own professional work and how a structured, evidence-based approach might help find answers. I had, of course, enough experience in complicated surgical and health management issues to realise at an early stage that a simple application of the 5-step evidence-based process alone did not easily solve the complex surgical problems that I managed in oral cancer and the complexity is perhaps greater in managerial, policy and committee work with the associated political, financial and inter-personal issues. Nevertheless, I had no doubt of the enormous value of the use of evidence-based approach in healthcare.

I found two aspects of evidence-based practice particularly interesting: firstly, the potential of good evidence to challenge the consensus view or 'received wisdom' and secondly the ability to identify outcomes that would seem to be counter-intuitive.

Given my professional background, I developed an increasing interest in the use of evidence to inform and evaluate health policy – specifically in relation to oral cancer, my main clinical interest. This led to my MSc dissertation, a systematic review of the diagnostic effectiveness of the UK government policy in relation to oral cancer referral, examining the sensitivity and positive predictive value of the 'two-week rule' (TWR) system for this type of cancer. The 'two-week rule system' is the English implementation of UK fast-track suspected cancer referral policy. Introduced in 2000, it requires that there is a maximum period of 14 days between primary care referral and specialist consultation. The system is facilitated by lists of key ('red flag') signs and symptoms (NICE 2015) to assist primary care practitioners.

However, in the light of my MSc dissertation it became clear that several important questions regarding the urgent referral system for suspected oral cancer (and, indeed, other types) remained unanswered by adequate evidence. The system was introduced as part of the UK Government's Cancer Plan (2000) following reports of poor UK cancer outcomes compared to the best in Europe, yet the validity of the studies that prompted the sea-change in cancer policy seemed uncertain. Furthermore, even if it is accepted that UK cancer outcomes are 'genuinely' poor, it remained unclear exactly why this is the case. The TWR has been in place for almost 20 years but there is relatively little evidence on how the system might be improved. There also remained perhaps the most important question – whether the system has resulted in earlier-stage cancer being diagnosed. It made no sense to me that a policy – which clearly consumed an enormous amount of resources – could be in place for many years, yet nobody knew clearly whether it was achieving its main aim, improving cancer outcomes.

My on-going interest in these questions, which form the core of this thesis, a wish to expand on my earlier work and an overall desire to improve the early diagnosis of oral cancer are the principal 'drivers' of this work.

1.2 Oral Cancer

1.2.1 Incidence

Oral cancer is the sixteenth most common cancer in the world (Miranda-Filho et al 2020). In the UK for the year 2018-19 8302 cases were diagnosed and the number of presenting UK oral cancers is increasing rapidly, by 49% in the last decade and by 135% in the last 20 years (Oral Health Foundation 2020).

Oral cancer is a subtype of head and neck cancer, which includes cancers of nasopharynx, oropharynx, hypopharynx and larynx and paranasal sinuses, the majority being squamous cell carcinomas. Salivary gland malignancies and lymphomas are much less common whilst connective tissue malignancies (sarcomas) are rare. Most head and neck cancers are biologically similar, exist in close anatomical proximity and have common aetiological factors, principally smoking, excessive alcohol consumption and human papilloma virus (HPV) infection (Cancer Research UK 2013). These facts, in addition to the need for broadly similar services and expertise for treatment, means they are generally considered as a group (Haward 2004).

1.2.2 Staging of oral cancer

In this thesis, the American Joint Committee on Cancer (AJCC) staging system for oral cancer is used. 8 editions of the staging have been published from the first in 1977 (AJCC 1977) to the 8th edition in 2016 – updated June 2018 (AJCC 2018). The system is based on 'TNM' staging: tumour (T) node (N) and distant metastasis (M). Table 1.1 represents the 8th version (2016) including the June 2018 update. The staging system progressively evolves with increasing knowledge of factors that influence tumour prognosis. For example, in the 8th edition, depth of invasion of oral cancer was for the first time included in the staging (AJCC 2016).

TNM classification is known to achieve a reasonably precise evaluation of the extent of disease but for practical purposes (a cancer with four 'Ts', three 'Ns' and two 'Ms' generates 24 TNM categories) the various TNM categories are grouped together into 'stages.' The AJCC aim to ensure that these groups are 'more-or-less homogeneous' in relation to survival (AJCC 1992).

Over the years, the stage groupings have essentially remained the same, although the concept of *clinical* staging, based on clinical and imaging findings before treatment, and *pathological* staging, based on histological assessment of surgical specimens, was introduced for the 7th edition (AJCC 2009). Pathological staging is more accurate, although not always possible if, for example, radiotherapy is utilised as a sole treatment modality and no surgical specimens are available.

Table 1.1 - Staging of Oral Cancer (*American Joint Committee on Cancer [AJCC] *v8 2016-18)

Tumour stage (T)	**Definition**
Tx	Primary tumour cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumour < 2cm with depth of invasion (DOI) < 5mm
T2	Tumour < 2cm with DOI < 5mm Or tumour < 2 cm and <4cm with DOI <10mm
T3	< 2 cm and <4cm with DOI >10mm or >4cm with DOI <10mm
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease
T4b	Very advanced local disease
Node stage	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node< 3 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node > 3 cm but ⍰ 6 cm in greatest dimension ENE -ve
N2b	Metastasis in multiple ipsilateral lymph nodes, > 6 cm in greatest dimension and ENE-ve
N2c	Metastasis in bilateral or contralateral lymph nodes, > 6 cm in greatest dimension and ENE -ve
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE -ve **OR** metastasis in any lymph node(s) with clinically overt ENE +ve
N3b	Metastasis in any lymph node(s) with clinically overt ENE +ve
Metastases	
M0	No distant spread
M1	The cancer has spread to distant sites outside the head and neck region
Stage groups	
Stage 1	T1 N0 M0
Stage 2	T2 N0 M0
Stage 3	T3 N0 M0 **OR** T1 to T3 N1 M0
Stage 4a	T4a, N0 /N1, M0 **OR** T1 to T4a, N2, M0
Stage 4b	T4b, any N, M0 **OR** Any T, N3, M0
Stage 4c	Any T, Any N, M1

ENE = extra-nodal extension

1.2.3 Mortality and survival

The survival of oral cancer is poor. 5-year survival rates are in the order of 50%, having remained much the same for the past 50 years, despite advances in both surgery and radiotherapy (Crossman et al 2016;

Stefanuto et al 2014). In 2019, there were 2722 deaths in the UK from oral cancer (Oral Health Foundation 2020). Disease stage at presentation has a major influence on survival (Mehanna et al 2010; Mao et al 2004) and poor survival rates are thought to be closely related to advanced stage at presentation. Furthermore, spread to the lymph nodes considerably worsens prognosis – spread to the nodes approximately halves survival for a given stage of primary cancer (Gómez et al 2010). Three-year survival for stage 1 and 2 (early) disease is over 90% whilst for stage 3 and 4 (late) disease 3 year survival is less than 50% (Cancer Research UK 2018). Unfortunately, approximately 50% of oral cancers present at advanced stage 3 or 4 (Stefanuto et al 2014).

1.2.4 Causes

Historically, oral cancer has been associated in at least 75% - 85% of cases with a combination of cigarette smoking, heavy alcohol consumption and patients over 40 (Hashibe et al 2007; Blot et al 1988). The risk for smokers is 10 times or more the risk for non-smokers. High alcohol consumption and smoking operate synergistically; heavy drinkers and smokers have a risk of developing oral cancer over 15 times that of individuals who neither drink nor smoke (Blot al 1988). While tobacco use, in all its forms, remains the foremost risk factor for individuals over 50 and in the anterior oral cavity, there is some evidence these cancers are decreasing (Bossetti et al 2020). However, cancers of the oro-pharynx associated with human papilloma virus (HPV) are becoming increasingly prevalent and it is believed that up to 90% of cancers at this site are HPV-related (Young et al 2015). It seems that HPV-related oral cancers represent a unique disease process in the oro-pharynx (Oral Cancer Foundation 2019). Many such patients neither smoke nor drink excessively and often present relatively young, at 30-50 years of age (Sudhof et al 2011). There is evidence that HPV related head and neck cancers may have better survival rates than other types (Fakhry al 2008). In more anterior oral sites, an HPV association is much less common (Hübbers and Akgül 2015). In September 2019, the UK NHS began to offer HPV vaccine, previously available only to girls in relation to cervical cancer prevention, to children of both sexes in school year 8 (children of 12 to 13 years). The impact of such a vaccination programme on oral cancer in the UK will clearly take time to be directly evaluated in longitudinal data but it has been suggested that vaccination may well have a *'substantial effect'* (De Felice et al 2019).

Considerable work has focused on how public awareness of oral cancer and its causes might be enhanced.

The West of Scotland Cancer Awareness Programme (WoSCAP) on oral cancer was initiated in 2003 (BBC 2003; Rogers 2007). This 'mass media' programme – the first in the UK at the time - involved five regional health boards providing for a population of 2.5 million. Based on social cognitive theory, the campaign included targeted television and radio advertisements, posters and mail-drops (BBC 2003; Rogers 2007). The effects of this programme appeared to be mixed, as although over two thirds of patients attending rapid-access clinics were aware of the campaign, the oral cancer incidence in these individuals was 5%, compared to a positive predictive value of almost 9% identified in a systematic rule of UK head and neck referrals (Langton et al 2016). Furthermore, 30% of referrals were considered 'inappropriate' by the examining clinicians (Rodgers et al 2007).

Overall, how effective are 'awareness' campaigns for oral cancer? Macpherson (2018) notes – in relation to national campaigns - that whilst such initiatives increase patient knowledge and health service attendance in the short-term, evidence of long-term benefits is 'very limited'. Furthermore, it is noted that many individuals who respond in such campaigns are of low risk for oral cancer. Similarly, local community-based campaigns tend to result in short-term benefits with very limited changes in long-term behaviours (Croucher et al 2011). Macpherson (2018) concludes that in order to influence appropriate behaviour change, *'a longer-term multifaceted approach, acknowledging the social determinants of health',* together with further research on what makes campaigns effective, are needed.

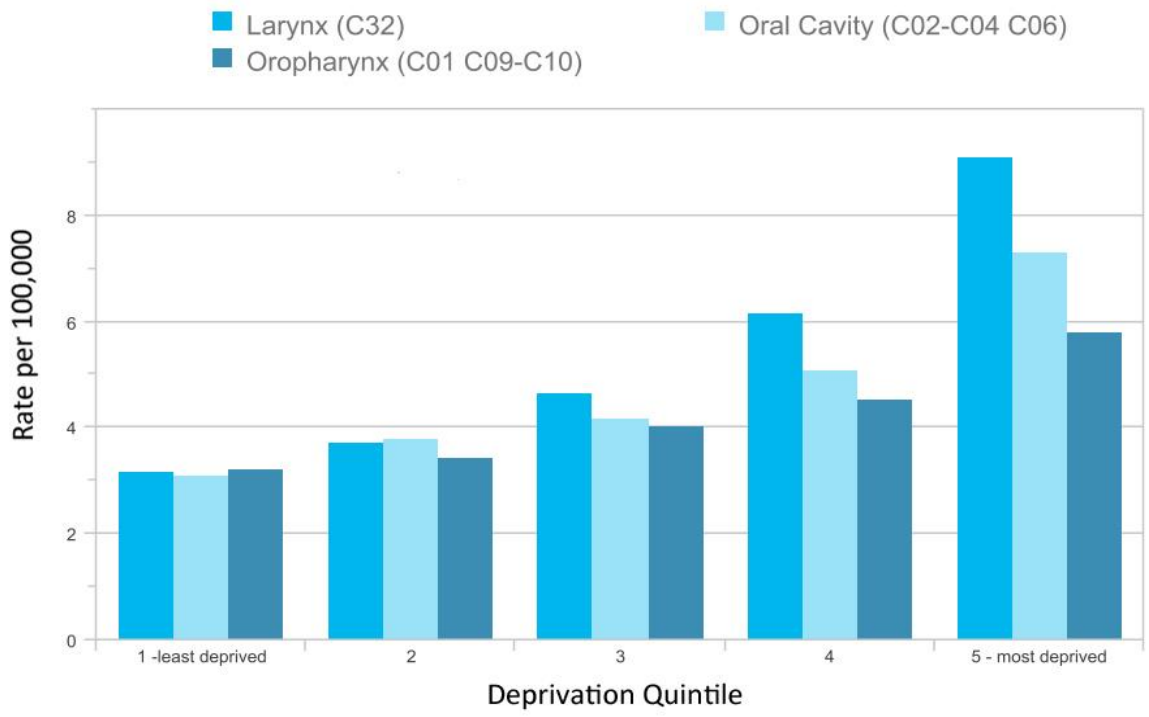
1.2.5 Treatment

The most common treatments for oral cancer are surgery and radiotherapy. For small tumours, single modality treatment is often effective and has a high cure rate, with relatively low morbidity. Advanced tumours require much more extensive treatment, often employing a combination of extensive surgery, complex reconstruction and radiotherapy or radio-chemotherapy. The side effects of such treatment and the detrimental influence on quality of life are often very severe (Mehanna et al 2010).

1.2.6 Socio-economic influences and UK regional variations

Oral cancer is known to be more likely to occur in individuals from lower socio-economic backgrounds who also experience poorer outcomes than those from more affluent backgrounds (Conway et al 2010; Rylands et al 2016; Cancer Research UK 2020[a]) [Figure 1.1]

Figure 1.1 - Age-standardised rates for oral and oropharyngeal cancer (larynx also included) males 2006 - 2010 by deprivation quintile



Source: Cancer Research UK (2020)

Persisting socio-economic inequalities in cancer, including incidence and outcome, are well documented in a very extensive range of published literature (Fidler and Bray 2018). The influence is evident globally, with higher incidence and mortality for most cancers in the socio-economically deprived; breast and prostate are notable exceptions, which have higher incidence in the more advantaged, possibly due to screening access (Wilson et al 2020). It is established that the association between deprivation and many cancer types is complex although for several, the increased burden in the deprived population is largely attributable to modifiable causes including tobacco, excess alcohol

consumption, obesity and physical inactivity (Wilson et al 2020). In the UK, inequalities in health, including cancer, are a Government priority (Public Health England 2018).

For oral cancer, the link to deprivation is evident in both higher income and lower middle-income countries. The association with mortality is not linear, being stronger with increasing levels of deprivation. The association is complex due to the various risk factors involved; oral cancer has strong links to smoking and alcohol which are associated with socio-economic deprivation (Ravaghi et al 2020). However, in multi-variate analysis of risk factors influencing oral cancer mortality, deprivation alone has been shown to be a significant predictor after adjustment for alcohol, smoking and ethnicity (Ravaghi et al 2020). The exact causes remain elusive, although several possible explanations have been suggested including poor nutrition and access to health services, including dental care (Warnakulasuriya 2009).

There is considerable English regional variation in incidence with rates in the North East and North West higher than England overall and the South East, South West and East of England lower (Public Health England 2020). In a study of 30,651 English oral cancers, the highest incidences were recorded in the North West and North East with rates of approximately 8 cases per 100,000 per year in 2011. In contrast, the rate in London for the same year was less than 6 per 100,000 (McCarthy et al 2015).

1.3 The urgent referral of suspected cancer in England

1.3.1 General points – screening and early diagnosis

A cancer ‘strategy’ has several facets, including prevention, screening and early diagnosis of which prevention is probably the most important (NHS England 2016; World Health Organisation (WHO) 2019). However, it is clearly difficult to prevent every case of cancer and therefore screening and early diagnosis, which aim to diagnose cancer at the earliest stage, are vital components in improving cancer outcomes. Although early diagnosis is the focus of this thesis, it is important to distinguish ‘screening’ from ‘early diagnosis’.

The World Health Organisation (2019) defines screening as *'the presumptive identification of unrecognised disease in a healthy, asymptomatic population'.* Screening is a complex public health strategy, which, according to the WHO, requires: (1) mechanisms for invitation and recall (2) participation of 70% of the population (3) adequate infrastructure and finance (4) a robust monitoring and evaluation framework. Currently, the NHS screens for 3 cancers: breast, cervix and colorectal.

In contrast, 'early diagnosis' aims to detect the signs and symptoms of cancer as early as possible. The WHO (2019) defines a number of 'steps' or processes that together comprise an early diagnosis system. These include: (1) cancer awareness and access to care (2) clinical evaluation and staging (3) access to treatment. The 2000 NHS Cancer Plan (Department of Health 2000) introduced a range of measures, including prevention, screening and improved treatment and focused strongly on cutting access times for cancer diagnosis and treatment, specifying waiting time for diagnosis and treatment.

1.3.2 The 'two-week rule'

The English urgent cancer referral system is currently based on the 'two-week rule' (TWR). This rule states that suspected cancer referrals from primary care are required to be seen by an appropriate specialist within 14 days. Primary care practitioners (both GPs and dentists for oral cancer) are provided with lists of signs and symptoms to assist in referral, which are periodically reviewed and updated (NICE 2015; NICE 2017).

Guideline-driven urgent referral of suspected cancer is a policy introduced by the UK government as part of the 'Cancer Plan' in 2000. However, the exact implementation in each UK nation differs slightly – for example the English 'two-week rule' (TWR) does not exist as such in Scotland, where the system is known as the 'urgent suspicion of cancer' (Scottish Government 2019) and in Northern Ireland the TWR applies to breast cancer but not to other types (Cancer Research UK 2020[b]).

The situation is further confused in some of the published literature, where papers frequently refer to 'the UK two-week rule' - which, strictly speaking, applies in England (Pacifico et al 2007; Robinson et

al 2003). Additionally, studies on comparative national outcomes may refer to the British nations separately or collectively (Gatta et al 2015).

In this thesis, I have aimed to be as accurate as possible when referring to 'the UK' and 'England' (or another UK nation) in relation to results, descriptions or published work.

1.3.3 History and development of the TWR

The system has its origins in the Department of Health document: '*A Policy Framework for Commissioning Cancer Services: Report by the Expert Group on Cancer to the Chief Medical Officers of England and Wales*' (Department of Health 1995), generally known as the *'Calman-Hine Report'.*

In the years preceding this report, deficiencies in UK cancer care were increasingly being reported. Public and political perceptions focused on what the media described as a 'cancer lottery' (Haward 2006), in which the outcome of treatment depended on being referred to an appropriate cancer specialist rather than a non-specialist and descriptive reports demonstrated considerable variations in cancer services for which there was no clear justification (Sainsbury et al 1995; Richards et al 1996). In 1995, the first 'EUROCARE' studies based on European cancer registry information were published, comparing cancer outcomes between different countries (Berrino et al 1995). UK outcomes for some cancers were shown to be worse than those in many European countries.

Haward (2006) noted: *'these issues on their own might not have led to a coherent response without serendipity'*. However, both Calman and Hine had backgrounds in cancer and were *'well placed to make judgements about cancer care'*. Bypassing the standing subcommittee on cancer, a 12-member expert advisory group was formed to develop and implement the Cancer Plan.

The central theme of the Calman-Hine report was the considerable variation in UK cancer services and that patients should have equal and rapid access to the best treatment to deliver the best cure rates. Although the report did not cover prevention, other important principles included early identification of cancer and national screening programmes. It was noted: *'…policy-development process included a serious attempt to assess evidence on topics identified …although not evidence-based in the modern sense of the use of explicit methods to search for and assess studies, it marked a genuine attempt to*

introduce and assess key evidence' (Haward 2006). Cornford and Oswald (2004) believe that whilst Calman and Hine did not mention the TWR specifically, the influence of the report on the development of the TWR system is clear.

1.3.4 TWR introduction

The New NHS Modern, Dependable (Department of Health 1997) announced the TWR. The policy was put into effect for breast cancer in April 1999 and for all other cancers by December 2000. Referral guidelines were developed for each cancer type and specified in '*Referral Guidelines for Suspected Cancer'* (Department of Health, 2000[a]). This document also described the need to achieve a balance when developing referral criteria – ensuring cancers are not being missed yet not overwhelming secondary services with referrals. Cornford and Oswald (2004) note that *The New NHS Modern, Dependable* focuses on 'quality' of care including 'prompt access', 'equality' and 'fairness' but does not address survival, a key theme of the Calman-Hine report.

1.3.5 Further development of the English urgent cancer referral

In September 2000 two further 'fast-track' measures were announced – introduced in 2005 - (table 1.2) specifying, firstly, a maximum 31 days from diagnosis to treatment and, secondly, a maximum 62 days GP referral to treatment (Department of Health 2000b). Subsequently, he *Review of Cancer Waiting Times Standards* was published in 2011, addressing four questions: (1) Should cancer waiting times be retained? (2) Should specific waiting time standards be changed? (3) Should specific cancer types be excluded from the standards? (4) How can the system be improved? Whilst, interestingly, the report stated: '*it is impossible to quantify whether the targets had led to improvement in cancer survival*' it concluded that the *'almost unanimous view of clinicians and managers'* was that targets (including, of course, the TWR) were beneficial for patients. It was therefore decided to retain the TWR system. Further guidelines for cancer referral, published in 2005 (NICE 2005) were updated in June 2015 (NICE 2015). The initial guidelines included symptoms with varying positive predictive values (PPV); in the updated 2015 version a 'threshold' symptom PPV of 3% was used in guideline development (NICE

2017). More recently, a 28-day referral-to-diagnosis target was introduced (NHS England 2020) (table 1.2).

Table 1.2 – English cancer access targets (April 2020)

TARGET	WHERE IT APPLIES	MEETING THE TARGET
14 day *'two week rule'*	GP suspects cancer, refers to specialist	Cancer specialist must see the patient within 14 days of GP referral
31 day	Specialists makes decision to treat to the start of treatment	First treatment must start within 31 days of the specialist's decision to treat
62 day	From date of GP referral to the start of treatment	First treatment must start within 62 days of date referral from GP
28 day *'faster diagnosis target'* *(introduced April 2020)*	From GP referral to cancer confirmed/refuted	Diagnosis of cancer or cancer ruled out within 28 days of GP referral to specialist care

Source: Araghi et al 2020

1.4 What is known about the effectiveness of the English fast-track system for suspected cancer?

1.4.1 Early reaction to the English TWR system

The system of fast-track referral and diagnosis of cancer has been in place since 2000 and it would be reasonable to assume that any benefits should now be evident. However, objective evidence of clear benefit, particularly regarding improvements in survival – or, as a proxy, stage on presentation - has been relatively slow to emerge.

In the years immediately following the publication of the Cancer Plan, there was considerable adverse criticism of the then-new system of fast-track cancer referral and diagnosis. In June 2001, a commentary was published in the British Medical Journal on the TWR system: *'Is the two-week rule for cancer referrals working? Not too well'* (Jones et al 2001). Criticisms included the 'poorly-defined' predictive values of the 'red flag' symptoms, the risk to routine referrals as hospitals strived to achieve cancer

targets and that referrals could meet referral guidelines but be considered 'inappropriate' by secondary care. In 2007 Jiwa and Saunders published a leading article in the British Medical Journal: '*Fast track referral for cancer has not improved patient outcomes in the UK'.* The article was critical of 'tick box' referrals from general practitioners, suggesting that many other aspects needed to be considered such as patients' help-seeking behaviour and doctor-patient communication.

1.4.2 Access targets

The TWR 'target' was rapidly achieved, with over 90% compliance by 2003. In January 2017 94% of such referrals were seen within 14 days (NHS England 2017).

Spurgeon et al (2000) comment that suspected cancer cases were in fact gaining access to specialist opinion more rapidly than routine cases prior to the introduction of the TWR but referral standards varied widely between GPs. Unfortunately, there were no data in their survey on how effectively GPs selected patients pre-TWR to use as a 'baseline' for comparison with the post-TWR period. However, it is known that there is still considerable variation in the use of the TWR referral system by primary care practitioners – the National Cancer Registration Analysis Service (NCRAS) report up to a three-fold variation in referral rates between English Primary Care Trusts (PCTs) that are not explained by demographics (National Cancer Intelligence Network 2010). Therefore, it could be reasonably argued that despite the introduction of the protocol/guidance driven TWR system, a wide variation in the rate of primary care to specialist referral of cancer persists. Early studies on the timeliness of cancer treatment commented that the TWR in isolation was ineffective in reducing waiting times for treatment, as patients simply waited longer following diagnosis (Robinson et al 2003). However, this was largely addressed by the previously-described 31-day and 62-day UK Government 'time to treatment' targets

1.4.3 Target-driven policy – 'hitting the target and missing the point'?

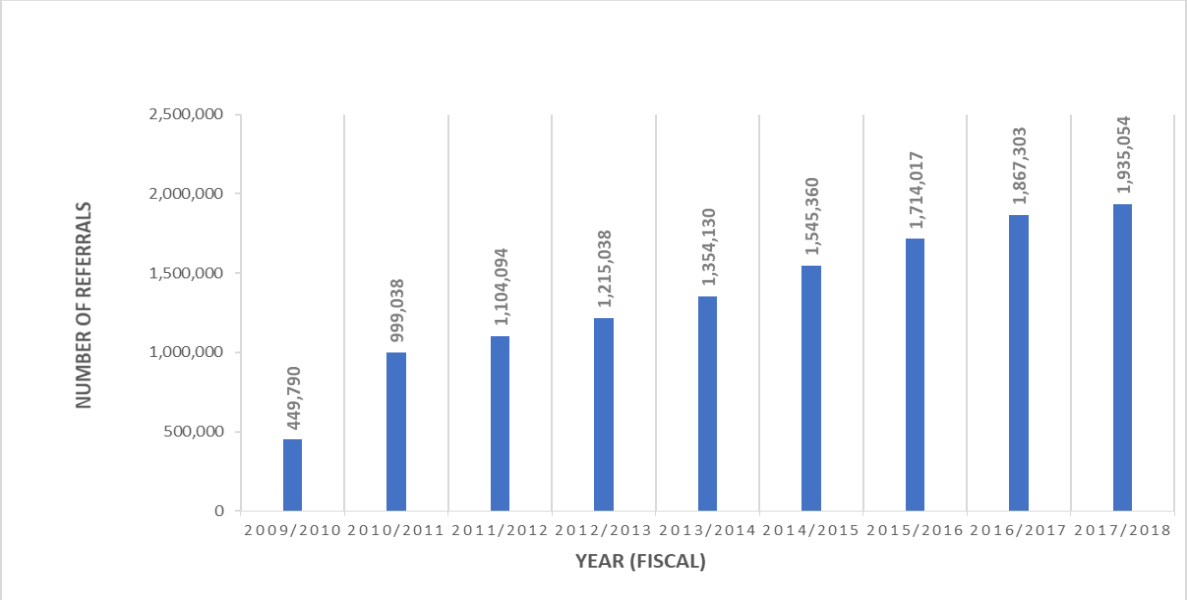
Since the UK Labour government of the late 1990s, successive governments have set performance targets in many areas of the NHS (Berry et al 2015). As previously noted, NHS early diagnosis and treatment of cancer policies are 'driven' by a series of targets. Many health outcomes, including cancer, are complex to evaluate and, faced with this, successive governments have been inclined to set simple

targets, such as access times, in the hope of improving outcomes (Berry et al 2015). However, the use of performance targets in the NHS has been the subject of considerable debate. On one hand there is clear evidence that targets in healthcare impact on behaviours such as improving waiting times, provide a simple measure of performance in a complex system and align performance to government policies and priorities (Gubb and Bevan 2009). However, on the other hand, there have been instances where the target is met but patients do not actually benefit ('hitting the target but missing the point'), a tendency to meet targets at the expense of other 'untargeted' areas and reports of data manipulation to 'achieve' targets (Bevan and Hood 2006).

1.4.4 Studies on diagnostic effectiveness

Many studies have examined the diagnostic accuracy of the TWR by measuring positive predictive value ('conversion rate') and sensitivity ('detection rate'), including several systematic reviews (Lewis et al 2005; Thorne et al 2006; Thorne et al 2009; Kumar et al 2012; Langton et al 2016). For many cancers, the positive predictive value of the TWR is in the order of 10% (Potter et al 2007; Debnath et al 2002). The sensitivity of TWR referrals has been shown to be in the order of 40% for many cancers including breast (Cant and Yu, 2005), colorectal (Flashman et al 2000), gynaecological (Morrison et al 2003; Abdelraheim 2017) and head and neck (Langton et al 2016). Therefore, for these types it seems that approximately 90% of TWR referrals do not have cancer and approximately 60% of cancers present via other routes. The low positive predictive value and sensitivity of the TWR have been the subject of considerable debate over many years (Jones, Rubin and Hungin, 2001; Jiwa and Saunders 2007). Since the introduction of the TWR, several studies have noted falling conversion rate, together with increasing numbers of referrals (Langton et al 2016; Potter et al 2007; Thorne et al 2009). For example, in Langton's systematic review, which included 17 studies on head and neck cancer TWR referrals from 2000 to 2014, 'early' studies up to 2008 had a pooled conversion rate of 10.6%, whilst for 'late' studies from 2009 onwards it was 6.6%. The number of NHS GP referrals for cancer has increased markedly over the years and inevitably leads to questions about cost and capacity (figure 1.3).

Figure 1.3 - GP referrals for suspected cancer in England 2009/10 to 2017/18



Source: NHS England combined performance summary (2018)

1.4.5 Influence on clinical outcomes

Although the TWR may have several benefits, such as increasing patient satisfaction by ensuring a rapid diagnosis of suspicious symptoms (Ndukwe et al 2010), if the aim of reducing mortality is to be achieved a link between the TWR and survival or, as a proxy, stage on diagnosis needs to exist. Indeed, Harrison and Foot (2012) state*: 'for the two-week rule to be effective……the stage at which patients were identified should have fallen since its introduction'.*

In 2011 - the TWR had been in place for 12 years - the UK Department of Health 'Review of Cancer Waiting Times Standards' (Department of Health, 2011) stated: *'….it is impossible to quantify whether the targets have led to improvements in cancer survival….'.* However, a few studies have examined the TWR-NICE guidance fast-track system in relation to survival.

Bevis et al (2006) studied 193 colorectal cancer patients and compared the presentation stage of patients referred via the TWR with those referred 'routinely', finding no difference in disease stage at presentation between the two groups. Walsh and his colleagues (2006) studied two groups of colorectal cancer patients, presenting before and after the introduction of the TWR. In the TWR group there was a 5-day reduction from referral to specialist consultation but no difference in 2-year survival between

the two groups. Schneider et al (2013), again studying a cohort of colorectal cancer patients, identified no difference in survival between patients referred on the fast track pathway and those referred on a non-fast track pathway. Sharp et al (2010) studying oesophago-gastric patients, found that the TWR resulted in more rapid treatment but did not improve outcome. More recent work on upper and lower gastro-intestinal (GI) cancers (Fallon et al 2019) compared TWR referrals with non-TWR referrals, studying: (1) diagnostic stage (2) delivery of curative treatment (3) survival. For all 3 outcomes in upper and lower GI cancers, no statistically significant benefit was demonstrated in relation to TWR referrals. Similarly, Aslam et al (2017) found that the TWR was not associated with improved survival for patients with colorectal cancer.

Pencavel et al (2010) reported a series of sarcoma patients and found that between 2004 and 2008 TWR referrals rose 25-fold but accounted for less than 1% of diagnosed sarcomas thus concluding: *'Current guidelines have had no impact on the early diagnosis and treatment of soft tissue sarcoma……'.* A retrospective audit by Wong (2017) compared 147 head and neck cancers referred via the TWR with 89 non-TWR cases. The study included 2 oral cancer patients. Kaplan-Meir survival analysis showed no difference between TWR and non-TWR cases.

Nevertheless, some work has shown the TWR system to be beneficial. Pacifico et al (2007) studied a series of patients attending a melanoma clinic and demonstrated improved survival compared to a group of patients treated before the inception of a 'TWR clinic'. The authors reported that this was the first published supportive evidence for the TWR in relation to skin cancer. Work by Møller et al (2015) studied 215,284 cancer patients in relation to the propensity of their general practice to use the urgent referral system (evaluated on standardised referral ratio and sensitivity of referrals). The hazard ratio for death (any cause) for practices with the lowest use of the urgent referral pathway was 1.07 (95% CI 1.05-1.08) whilst that for practices with the highest use of the pathway was 0.96 (95% CI 0.94-0.99). A more recent study by Round et al (2020), including 1.4 million cancer patients diagnosed 2011-2014 found that higher general practice referral rates were associated with a lower hazard of death for colorectal (hazard ratio [HR] 0.95, 95% CI 0.93 to 0.97) , lung (HR 0.95, 95% CI 0.94 to 0.97) breast (HR 0.96, 95% CI 0.93 to 0.99) and prostate (HR 0.88, 95% CI 0.85 to 0.91). An international study

undertaken by Rose et al (2015), used a series of clinical 'vignettes' and evaluated the proportion of primary care practitioners in 6 countries (Australia, Canada, UK, Denmark, Norway and Sweden) opting to refer or investigate in relation to each vignette. The study demonstrated a statistically significant correlation ($p<0.05$) between primary care practitioners' readiness to refer/investigate symptoms and cancer survival rates in 4 out of 5 vignettes.

However, it has been noted that evidence on early diagnosis for one type of cancer is not always readily transferred to another type. Neal (2009) comments on the difficulties of comparing cancers that behave very differently and Lyratzopoulos, Wardle and Rubin (2014) argue that *'considering different cancers separately is critical for gaining insight into the challenges of diagnosis.*' Furthermore, the relationship between diagnostic delay and survival remains poorly understood and is almost certainly complex.

Have cancer intervals (see figure 2.2 for definitions) changed following the introduction of urgent referral systems such as the TWR? Neal et al (2014) analysed 37,588 cancers from the UK General Practice Research Database. Delay was evaluated for two periods: 2001-2002 and 2007-2008, before and after the 2005 updated cancer guidelines. The study showed an overall mean diagnostic interval reduction between the two periods of 5.4% (95%CI 2.4-8.5). There were significant reductions for kidney (20.4 days 95% CI 0.5 to 41.5 p= 0.05), head and neck (21.2 days, 95% CI 0.2–41.6 p=0.04), bladder (16.4 days, 95% CI 6.6–26.5 p=0.001), colorectal (9.0 days, 95% CI 3.2–14.8 p=0.002), oesophageal (13.1 days, 95% CI 3.0–24.1 P =0.006) and pancreatic (12.6 days, 95% CI 0.2–24.6 p=0.04). There was little difference between those who presented specifically with NICE guidance-defined symptoms and those who did not. The authors' conclusion was that *'NICE guidelines may have contributed to the reduction in diagnostic intervals.'* However in a scoping review undertaken in Australia (Malalasekera et al 2018), 24 studies (out of 128 included) examined the effect of fast-track referral systems for lung cancer. The study found that there was no evidence of a significant difference, either for GP to specialist interval (p=0.33) or overall treatment interval (p=0.88) when comparing patients referred with a fast-track system to those referred not using such a system.

1.4.6 Improving TWR urgent referral – beyond clinical judgement?

The TWR system provides a set of guidelines for cancer diagnosis that are combined with the clinical judgement of primary care practitioners to decide on the need for secondary care evaluation. The system has been essentially the same since its introduction in 1999-2000, albeit with some relatively minor modifications to the guidelines. However, several methods of improving referrals have been suggested. These include the use of risk calculation tools such as RAT - risk assessment tool (Hamilton 2013) and 'clinician advice' such as being conscious of 'themes' often associated with delay, such as persistent infection and non-resolving pain, together with 'safety-netting' (Morgan and Wilkes 2017). A prediction scoring system has been developed for head and neck cancers, with a sensitivity of 31% and specificity of 92% (Lau et al 2018).

1.4.7 Effectiveness of the English TWR system for oral cancer

In common with other cancers, there is considerable evidence on the diagnostic effectiveness of the TWR urgent referral system. Studies examining oral cancer specifically (rather than head and neck cancer in its entirety) have identified TWR positive predictive values (PPV) of 6.0% (Shah 2004), 6.3%, (East 2005), 7.9% (Singh 2006), 11.1% (Miller 2012), 6.1% (Miller 2012) and 2.8% (Roy 2018) and a sensitivity of 33% (Shah 2004). In the paper by Roy (2018) it was noted that 26% of patients were discharged following their first appointment with no further investigations and 16% had no detectable clinical abnormality on examination. A systematic review of TWR referrals in head and neck cancer, including oral cancer (Langton et al 2016), calculated a pooled PPV of 8.8% and pooled sensitivity of 40.8%, indicating approximately 60% of head and neck referrals do not present via a TWR referral. Furthermore, it was identified that the PPV of TWR referrals had fallen from 2000 to 2014 but referrals had steadily risen. Concern over the effect that this has on resources and clinical efficiency has been expressed by several authors (Roy 2018).

However, despite the abundance of evidence on the 'process' of the fast-track referral system for oral cancer probably the most important question, whether the fast track system results in increased oral cancer survival – or, as a reasonable proxy, earlier stage at diagnosis – remains unclear and the evidence

to date is, unfortunately, weak. This was noted in a commentary (in relation to all cancer types) by Bankhead (2017): *'What is currently lacking is research that directly addresses whether the introduction of the 2-week wait process has led to improved survival'*. There is some limited outcome information. Data from the National Cancer Registration and Analysis Service (NCRAS) on oral cancer indicate that between 2006 and 2013 there was little difference in 1-year survival between TWR referrals and other 'routine' referrals (77% vs 78%) but emergency presentations had a survival rate much worse (44%). During the same period, 34% of cases presented via the TWR system whilst 6% presented as emergencies. The proportion presenting via the TWR also steadily increased from 24% in 2006 to 33% in 2012 (NCRAS, 2016). However, robust data on survival outcomes, comparing the periods before and after the 2000 cancer plan and introduction of the TWR-NICE guidance referral systems remain, to date, elusive.

Chapter 1 references

Abdelraheim AR, Khairy M, Mohammed M et al (2017) *Two week waits: What are we waiting for*? European Journal of Obstetrics and Gynecology and Reproductive Biology 215 112-117

American Joint Committee on Cancer [AJCC] (1977) *Manual for Staging of Cancer* available at: https://cancerstaging.org (accessed August 2020)

American Joint Committee on Cancer [AJCC] (1992) *Cancer Staging Manual 4th edition* available at: https://cancerstaging.org (accessed August 2020)

American Joint Committee on Cancer [AJCC] (2009) *Cancer Staging Manual 7th edition* available at: https://cancerstaging.org (accessed August 2020)

American Joint Committee on Cancer [AJCC] (2016) *AJCC cancer staging manual 8th edition* available at: https://cancerstaging.org (accessed August 2020)

Araghi AS, Harris Y and Kyzas P (2020) *An audit to analyse the two-week wait pathway at an oral cancer specialist district general hospital* British Dental Journal 228 693-699

Aslam MI, Chaudhri S, Singh B (2017) *The 'two-week wait' referral pathway is not associated with improved survival for patients with colorectal cancer* International Journal of Surgery 43 181-185

Bankhead C (2017) *The 2-week wait and other initiatives to improve cancer diagnosis: Has it altered survival? The answer is unclear – the evidence is too weak* European Journal of Cancer Care 26:e12712 https//doi.org/10.1111.ecc.12712

BBC News (2003) *Mouth cancer campaign launched* available at: http://news.bbc.co.uk/1/hi/scotland/3214245.stm

Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T and Esteve J (1995) *Survival of Cancer Patients in Europe: The EUROCARE Study* IARC Scientific Publication No. 132, IARC: Lyon

Berry N, Gardner T and Anderson I (2015) *On targets: How targets can be most effective in the English NHS* available at: https://www.health.org.uk/sites/default/files/OnTargets.pdf (accessed August 2020)

Bevan G and Hood C (2006) *What's measured is what matters: targets and gaming in the English public healthcare system* Public Administration 84 517-538

Bevis PM, Donaldson OW, Card M, Durdey P, Thomas MG, Sylvester PA and Longman RJ (2007) *The association between referral source and stage of disease in colorectal cancer* Colorectal Disease 10 58-62

Blot, WJ, McLaughlin JK, Winn DM et al (1988) *Smoking and drinking in relation to oral and pharyngeal cancer.* Cancer Res 48(11) 3282-3287

Bossetti C, Carioli G, Santucci C et al (2020) *Global trends in oral and pharyngeal cancer incidence and mortality* International Journal of Cancer 147 1040-1049

Cancer Research UK (2013) *Oral cancer* available at: http://www.cancerresearchuk.org/ (accessed August 2020)

Cancer Research UK (2017) *Oral cancer incidence statistics* available at: ww.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oral-cancer/incidence (accessed August 2020)

Cancer Research UK (2018) *Mouth and Oropharyngeal Survival* available at: https://www.cancerresearchuk.org/about-cancer/mouth-cancer/survival

Cancer Research UK (2020[a]) *Head and Neck Cancer Subtypes (C01, C09-C10, C02-C04, C32*) available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers (accessed August 2020)

Cancer Research UK (2020[b]) *Your urgent cancer referral explained* available at: https://www.cancerresearchuk.org/cancer-symptoms/what-is-an-urgent-referral (accessed August 2020)

Cant PJ and Yu DSL (2000) *Impact of the '2 week wait' directive for suspected cancer on service provision in a symptomatic breast clinic* British Journal of Surgery 87 1082-1086

Conway D, McKinney P, McMahon A, Ahrens W, Schmeisser N et al (2010) *Socioeconomic factors associated with risk of upper aerodigestive tract cancer in Europe* European Journal of Cancer 46 588-598

Cornford CS and Oswald N (2004) *The 2-week rule for patients with suspected breast cancer: what can be learnt by analysing policy documents?* Health Policy 68 263-266

Crossman T *et al* (2016) *Role of general practice in the diagnosis of oral cancer* British Journal of Oral and Maxillofacial Surgery 54 208–212

Croucher R, Islam SS and Nunn H (2011) *Campaign awareness and oral cancer knowledge in UK resident adult Bangladeshi: a cross-sectional study* British Journal of Cancer 105 925-930

Debnath D, Dielehner N and Gunning KA (2002) *Guidelines, compliance and effectiveness: a 12 months' audit in an acute district general healthcare trust on the two-week rule for suspected colorectal cancer* Postgraduate Medical Journal 78 748-751

De Felice F, Polimeni A and Tombolini (2019) *Human papillomavirus (HPV) vaccine and HPV-related head and neck cancer: What's next?* Oral Oncology 93 125-126

Department of Health (1995) *A policy framework for commissioning cancer services: a report by the Expert Group on Cancer to the Chief Medical Officers of England and Wales* available at: https://webarchive.nationalarchives.gov.uk/ (accessed August 2020)

Department of Health (1997) *The New NHS. Modern. Dependable*: London available at*:* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/266003/newnhs.pdf (accessed August 2020)

Department of Health, (2000[a]) *Referral guidelines for suspected cancers* Department of Health: London available at ice.org.uk/guidance/cg27/documents/referral-for-suspected-cancer-clinical-guideline-second-consultation-full-version2 (accessed August 2020)

Department of Health (2000[b]) *The NHS Cancer Plan. A plan for investment a plan for reform* Department of Health: London available at: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyandGuidance/DH_4009609 (accessed August 2020)

Department of Health (2011) *Review of Cancer Waiting Times Standards* available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213787/dh_123395.pdf (accessed August 2020)

East SC, Stocker JL and Avery BS (2005) *Is the two-week rule of any benefit to patients with oral cancer?* British Journal of Oral and Maxillofacial Surgery 43 511-512

Fakhry C, Westra WH, Li S, Cmelak A et al (2008) *Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial* Journal of the National Cancer Institute 100 261-269

Fallon M, Adil MD, Ahmed K et al (2019) *Impact of 'two-week wait' referral pathway of the diagnosis, treatment and survival in upper and lower gastrointestinal cancers* Postgraduate Medical Journal 95 470-475

Fidler MM and Bray F (2018) *Global Cancer Inequalities* Frontiers in Oncology 8 293

Flashman K, O'Leary DP, Senapati A and Thompson MR (2004) *The Department of Health's 'two- week standard' for bowel cancer: is it working?* Gut 53 387-391

Gatta G, Botta L Sánchez MJ (2015) *Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study* European Journal of Cancer 51 2130-2143

Gómez I, Warnakulasuriya S, Varela-Centelles PI, López-Jornet P, Suárez-Cunqueiro M, Diz-Dios P and Seoane J (2010) *Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay?* Oral Diseases 16 333-342

Gubb J and Bevan G (2009) *Have targets done more harm than good in the English NHS?* British Medical Journal 338 442-443

Hamilton W, Green T Martins T et al (2013) *Evaluation of risk assessment tools for suspected cancer in general practice: a cohort study* British Journal of General Practice 63 30-36

Harrison AJ and Foot, CS (2012) *Targets and prioritisation: the case of cancer in the English NHS* Quality in Primary Care 20 125-129

Hashibe M, Brennan P, Benhamou S et al (2007) *Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium* Journal of the National Cancer Institute 99 777-78

Haward RA (2004) *Improving outcomes in head and neck cancers – the manual* available at https://www.nice.org.uk/guidance/csg6/resources/improving-outcomes-in-head-and-neck-cancers-update-pdf-773377597 (accessed August 2020)

Haward RA (2006) *The Calman-Hine report: a personal retrospective on the UK's first comprehensive policy on cancer services* Lancet Oncology 7 336-346

Hübbers CU and Akgül B (2015) *HPV and cancer of the oral cavity* Virulence 6 244-248

Jiwa M and Saunders C (2007) *Fast track referral for cancer has not improved patient outcomes in the UK* British Medical Journal 335 267-268

Jones R, Rubin G and Hungin P (2001) *Is the two-week rule for cancer referrals working? Not too well* British Medical Journal 322 1555-1556

Kumar, R, Drinnan M, Mehanna H and Paleri V (2012) *Efficacy of the two-week wait referral system for head and neck cancer: a systematic review* Annals of the Royal College of Surgeons (Suppl) 94 102-106

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Lau K, Wikinson J and Moorthy R (2018) *A Web-Based Prediction Score for Head and Neck Cancer Referrals* Clinical Otolaryngology 43 1043-1049

Lewis R, Collins R, Flynn A, Dean ME, Myers L, Wilson P, Eastwood A (2005) *A systematic review of cancer waiting time audits* Quality and Safety in Healthcare 14 62-66

Lyratzopoulos G, Wardle J and Rubin G (2014) *Rethinking diagnostic delay in cancer: how difficult is the diagnosis?* British Medical Journal 2014;349:g7400

Macpherson LMD (2018) *Raising awareness of oral cancer from a public and health professional perspective* British Dental Journal 225 809-814

Malasekera A, Blinman PL, Dhillon HM et al (2018) *Times to Diagnosis and Treatment of Lung Cancer in New South Wales, Australia: A Multicenter, Medicare Data Linkage Study* Journal of Oncology Practice 14 E621-E530

Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316

McCarthy CE, Field JK, Rajlawat BP et al (2015) *Trends and regional variation in the incidence of head and neck cancers in England: 2002 to 2011* International Journal of Oncology 47 204-210

Mehanna H, West CML, Nutting C and Paleri V (2010) *Head and neck cancer – part 2: treatment and prognostic factors* British Medical Journal 341 721-725

Miller CC and Hierons RJ (2012) *Two audits of the diagnosis of oral cancer and the two-week rule following referrals from primary care practitioners in Newcastle* Primary Dental Care 19(2) 63-68

Miranda-Filho A and Bray F (2020) *Global patterns and trends in cancers of the lip, tongue and mouth* Oral Oncology https://doi.org/10.1016/j.oraloncology.2019.104551

Møller H, Gildea C, Meechan D, Rubin G, Round T, and Vedsted P (2015) *Use of the English urgent referral pathway for suspected cancer and mortality in patients with cancer: cohort study* British Medical Journal 351 h5102

Morgan I and Wilkes S (2017) *Improving early diagnosis of cancer in UK general practice* British Journal of General Practice 67 276-277

Morrison J, Gillespie S and Mackenzie IZ (2003) *'Two week wait' standards for suspected gynaecological malignancy. On target, but missing the point* Journal of British Menopause Society 9 170-172

Mouth Cancer Foundation *Oral Cancer Action Month* available at: https://www.mouthcancerfoundation.org/events/mouth-cancer-action-month (accessed November 2020)

National Cancer Intelligence Network (2010) *Urgent GP referral rates for suspected cancer* available at http://www.ncin.org.uk/publications/data_briefings/gp_referral_rates (accessed August 2020)

National Cancer Registration and Analysis Service (NCRAS) (2016) *Oral Cavity Cancer: Survival Trends in England* available at: http://www.ncin.org.uk/publications/data_briefings/oralcancer (accessed August 2020)

Ndukwe N, Borowski DW, Lee A, Orr A, Dexter-Smith S and Agarwal KA (2010) *The two-week rule for suspected colorectal cancer: Patient experience and psychological impact* International Journal of Healthcare and Quality Assurance 25 (1) 75-85

Neal RD (2009) *Do diagnostic delays in cancer matter?* British Journal of Cancer 109 S9-S12

Neal RD, Din NU Hamilton W et al (2014) *Comparison of cancer diagnostic intervals before and after implementation of NICE guidelines: analysis of data from the UK General Practice Research Database* British Journal of Cancer 110 584-592

NHS (2007) *Cancer reform strategy* available at: https://www.nhs.uk/NHSEngland/NSF/Documents/Cancer%20Reform%20Strategy.pdf (accessed August 2020)

NHS England (2016) *Better prevention and public health* available at: https://www.england.nhs.uk/cancer/prevention/ (accessed August 2020)

NHS England (2017) *Provider-based cancer waiting times for January 2017* available at: https://www.england.nhs.uk/statistics (accessed August 2020)

NHS England (2018) *Combined Performance Summary* available at: https://www.england.nhs.uk/statistics/statistical-work-areas/combined-performance-summary/ (accessed August 2020)

NHS England (2020) *Diagnosing cancer earlier and faster* available at: https://www.england.nhs.uk/cancer/early-diagnosis/ (accessed August 2020)

NICE (2005) *Referral guidelines for suspected cancer* available at: https://www.nice.org.uk/guidance/cg27 (accessed August 2020)

NICE (2015) *Suspected cancer: recognition and referral* available at: https://www.nice.org.uk/guidance/ng12/chapter/1-recommendations (accessed August 2020)

NICE (2017) *Suspected cancer: recognition and referral (2017 update)* available at: https://www.nice.org.uk/guidance/ng12 (accessed August 2020)

Oral Health Foundation (2020) *The State of Mouth Cancer UK Report 2018/2019* available at: https://www.dentalhealth.org/stateofmouthcancer (accessed August 2020)

Oral Cancer Foundation (2019) *Oral Cancer Facts* available at: https://oralcancerfoundation.org/facts/ (accessed August 2020)

Oxford Cancer Intelligence Unit (2010) *Profile of Head and Neck Cancers in England: Incidence, Mortality and Survival* available at: http://www.ncin.org.uk/view?rid=69 (accessed August 2020)

Pacifico MD, Pearl RA and Grover R (2007) *The UK Government two-week rule and its evidence on melanoma prognosis: and evidence-based study* Annals of the Royal College of Surgeons of England 89 609-615

Pencavel TD, Strauss DC, Thomas GP et al (2010) *Does the two-week rule pathway improve the diagnosis of soft tissue sarcoma? A retrospective review of referral patterns and outcomes over five years in a regional sarcoma centre* Annals of the Royal College of Surgeons 92 417-421

Potter S, Govindarjulu S, Shere M, Braddon F and Greenwood R (2007) *Referral patterns, cancer diagnoses and waiting times after the introduction of the two-week wait rule for breast cancer: a prospective cohort study* British Medical Journal 335 288 – 290

Public Health England (2018) *Inequalities in health* available at: https://www.gov.uk/government/publications/health-profile-for-england-2018/chapter-5-inequalities-in-health

Public Health England (2020) *Oral cancer in England* available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/891699/Oral_cancer_report_170420.pdf (accessed August 2020)

Ravaghi V, Durkan C, Jones K et al (2020) *Area level deprivation and oral cancer in England* 2012-2-16 Cancer Epidemiology 69 101840

Richards MA, Wolfe CDA, Tilling K et al (1996) *Variations in the management and survival of women under 50 years with breast cancer in the South East Thames region. British Journal of Cancer* British Journal of Cancer 73 751-757

Robinson D, Bell CMJ, Moller H, and Basnett I (2003) *Effect of the UK government's two-week target on waiting times in women with breast cancer in southeast England* British Journal of Cancer 89 492-496

Rodgers J, Macpherson LMD, Smith GLF et al (2007) *Characteristics of patients attending rapid access clinics during the West of Scotland Cancer Awareness Programme oral cancer campaign* British Dental Journal. 202(11):E28

Rose PW, Rubin G, Perera-Salazar R et al (2015) *Explaining variation in cancer survival between 11 jurisdictions in the International Cancer Benchmarking Partnership: a primary care vignette study* British Medical Journal Open 5: e007212

Round T, Gildea C, Ashworth M et al (2020) *Association between use of urgent suspected cancer referral and mortality and stage at diagnosis: a 5-year national cohort study* British Journal of General Practice 70 e389-e398

Roy S and Anjum K (2018) *The two-week wait – a qualitative analysis of suspected head and neck cancer referrals* British Dental Journal 225 159-163

Rylands J Lowe D and Rogers S (2018) *Outcomes by area of residence deprivation in a cohort of oral cancer patients: Survival, health-related quality of life, and place of death* Oral Oncology 52 30-36

Sainsbury R, Rider L, Smith A and Macadam A (1995) *Does it matter where you live? Treatment variation for breast cancer in Yorkshire* British Journal of Cancer 71 1275-1278

Schneider C, Bevis PM, Durdey P, Thomas MG, Sylvester PA and Longman RJ (2013) *The association between referral source and outcome in patients with colorectal cancer* The Surgeon 11 141-146

Scottish Government (2019) *Scottish referral guidelines for suspected cancer* available at: https://www.gov.scot/publications/scottish-referral-guidelines-suspected-cancer-january-2019/ (accessed August 2020)

Shah HV, Williams RW and Irvine GH (2005) *Fast-track referrals for oral lesions: A prospective study* British Journal of Oral and Maxillofacial Surgery 44 207-208

Sharp D, Williams RN, Ubhi SS, Sutton CD, Bowrey DJ (2010) *The 'two-week wait' referral pathway allows prompt treatment but does not improve outcome for patients with oesophago-gastric cancer* European Journal of Surgical Oncology 36 977-981

Singh P and Warnakulasuriya S (2006) *The two-week wait cancer initiative on oral cancer; the predictive value of urgent referrals to an oral medicine unit* British Dental Journal 11 717-720

Spurgeon P, Barwell F, and Kerr D (2000) *Waiting times for cancer patients in England after general practitioners' referrals: retrospective national survey* British Medical Journal 320 838-839

Srivastavan A and Thomson SB (2009) *Framework analysis: a qualitative methodology for applied policy research* Journal of Administration and Governance 4(2) 72-79

Stefanuto P, Doucet JC and Robertson C (2014) *Delays in treatment of oral cancer: a review of the current literature* Oral and Maxillofacial Surgery 117 424-429

Sudhof HH, Schwarze HP, Winder D et al (2011) *Evidence for a causal relation for HPV in head and neck cancers* European Archives of Otolaryngology 268 1541-1547

Thorne K, Hutchings HA and Elwyn G (2006) *The effects of the two-week rule on NHS colorectal diagnostic services: a systematic literature review* BMC Health Services Research 6 43

Thorne K, Hutchings HA and Elwyn G (2009) *The two-week rule for NHS gastrointestinal cancer referrals: a systematic review of effectiveness* The Open Colorectal Cancer Journal 2 27-33

Walsh SR, Gilson NL, Brown K and Novell JR (2006) *Trends on colorectal cancer survival following the 2-week rule* Colorectal Disease 9 207-209

Warnakulasuriya S (2009) *Significant oral cancer risk associated with low socioeconomic status* Evidence-Based Dentistry 10 4-5

Wilson LF, Green Ac, Jordan SJ et al (2020) *The proportion of cancers attributable to social deprivation: a population based analysis of Australian health* data Cancer Epidemiology 67 101742

Wong W, Fischer S and Cruickshank HE (2017) *Clinical outcome of head and neck cancer patients: a comparison between ENT patients referred via the 2 weeks wait pathway and alternative routes in the UK health system* European Archives of Otorhinolaryngology 274 415-420

World Health Organisation (2019) *Cancer Prevention* available at: https://www.who.int/cancer/prevention/en/ (accessed August 2020)

Young D, Xiao CC, Murphy B (2015) *Increase in head and neck cancer in younger patients due to human papillomavirus (HPV)* Oral Oncology 51 727-730

CHAPTER 2: Literature review and theoretical framework

EVIDENCE THAT ENGLISH CANCER OUTCOMES WERE WORSE THAN THE BEST IN EUROPE AND POSSIBLE CAUSES. THE INFLUENCE OF DELAYED DIAGNOSIS FOR CANCER IN GENERAL AND FOR ORAL CANCER.

2.1 Urgent cancer referral - historical aspects

The importance of rapid referral of suspected cancer has long been recognised (Elwood and Moorhead 1980; Macarthur et al 1983; Jones et al 1985) and this has included oral cancer (Shafer 1975). However, in the UK there was no specific urgent referral of cancer policy until the introduction of the English 'two-week rule' (TWR) system - and its equivalent in other UK countries – in 2000. What evidence has influenced the development of the policy?

2.2 Evidence influencing policy change – the EUROCARE studies

Comparative cancer survival statistics, using data from registries, have been in existence for at least 60 years (Cutler, 1964). However, the EUROCARE project – comparing European countries' outcomes - has been one of the largest projects of this type (Berrino 2003). The initial EUROCARE report was published in 1995 (Berrino et al 1995) and since then four further versions have been published (Berrino et al 1999; Sant et al 2003; Sant et al 2009; De Angelis at al 2014) [table 2.1].

The first EUROCARE studies had a considerable impact on UK cancer policy, reporting that survival for most adult cancers in the UK was generally lower than in comparable European countries. It was estimated that had English survival rates matched the best in Europe between 1985 and 1994, 13,000 premature deaths would have been avoided (Richards 2009) and therefore the NHS Cancer Plan (2000) focused strongly on survival, with an aim to reduce cancer death rates by 20% by 2010. One important part of the Cancer Plan was a drive to reduce delayed diagnosis and the TWR urgent referral system was one of the cornerstones of policy to achieve this aim.

Because of the extent of influence of the EUROCARE studies on UK cancer policy, they are discussed in some detail.

Table 2.1 – The EUROCARE studies on cancer survival

EUROCARE version	Year of Publication	Number of countries	Years studied	Main reference
EUROCARE 1	1995	12	1978-1984	Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T and Esteve J (1995) *Survival of Cancer Patients in Europe: The EUROCARE Study* IARC Scientific Publication No. 132, IARC: Lyon
EUROCARE 2	1999	17	1985-1989	Berrino F, Capocaccia R, Esteve J et al (1999) *Survival of cancer patients in Europe: the EUROCARE-2 study* IARC scientific publications no 151. International Agency for Research on Cancer, Lyon
EUROCARE 3	2003	22	1990-1994	Sant M, Aareleid F, Berrino F, Bielska Lasota M, Carli PM et al (2003) *EUROCARE-3 survival of cancer patients diagnosed 1990-1994 – results and commentary* Annals of Oncology 14 61-118
EUROCARE 4	2009	23	1995-1999	Sant M, Allemani C, Santaquilani M, Arnold Knijn, Marchesi F and Capocaccia R (2009) *EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary* European Journal of Cancer 45 931-991
EUROCARE 5	2014	29	1999-2007	De Angelis R, Sant M, Coleman MP, Franchisi S, Baili P et al (2014) *Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5 – a population-based study* The Lancet Oncology 15 23-34
EUROCARE 6	In preparation		Up to 2013	Protocol available at: http://www.eurocare.it/LinkClick.aspx?fileticket=g3W0LonFUL8%3D&tabid=93

Note: Many separate studies are generated under the broad 'umbrella' of each EUROCARE version – see www.eurocare.it

2.2.1 EUROCARE and UK cancer outcomes – worse than the European best?

In the UK, public reaction to the publication of the EUROCARE studies has been marked, including much coverage in the media. Example headlines include:

'Cancer survival in Britain the worst in Europe' (Daily Telegraph, 05.12.13)

'Cancer care shame as UK survival is one of EU's worst' (Daily Express 05.12.13)

'UK cancer survival rates lag behind Europe for nine of the ten most common forms' (The Independent 05.12.13)

What evidence has supported these claims? Consider 1-year and 5-year survival in EUROCARE-5 (De Angelis 2014) for cancer 'overall' (table 2.2). The UK ranks considerably below the European average in both categories and below nations with similar socio-economic structure.

Table 2.2 Case mix survival from all adult cancers: 1 year and 5-year survival rankings for cancers 1999-2007 (derived from EUROCARE-5, 2014)

1-YEAR RELATIVE SURVIVAL			5-YEAR RELATIVE SURVIVAL		
Rank	**Country**	**% 1-year relative survival**	**Rank**	**Country**	**% 5-year relative survival**
1	Sweden	81.1	1	Iceland	57.6
2	Belgium	78.9	2	Austria	56.7
3	Switzerland	78.3	3=	Sweden	56.4
4	Iceland	78.3	3=	Germany	56.4
5	France	77.8	5=	Italy	56.3
6	Finland	76.9	5=	Belgium	56.3
7	Germany	76.7	7	Switzerland	55.7
8	Norway	76.2	7=	Finland	55.7
9	Austria	75.9	9	Portugal	54.8
10	Italy	74.9	10	France	54.5
11	Portugal	74.0	11	Norway	54.1
12	Netherlands	73.0	12	Spain	52.9
13	Spain	71.5	13	Netherlands	52.6
14	Ireland	70.3	14	Ireland	51.8
15	Malta	70.0	15	Malta	51.3
16	Denmark	69.8	16	Czech Republic	50.0
17	Czech Republic	68.3	17	Croatia	49.8
18	**UK**	**67.9**	**18**	**UK**	**48.9**
19	Slovenia	67.7	18=	Denmark	48.9
20	Estonia	65.9	20	Slovenia	47.8
21	Slovakia	65.4	21	Estonia	46.9
22	Lithuania	63.8	22	Lithuania	46.7
23	Croatia	62.1	23	Slovakia	45.5
24	Poland	61.7	24	Poland	44.5
25	Latvia	60.9	25	Latvia	43.3
26	Bulgaria	58.2	26	Bulgaria	39.2
	EUROPEAN MEAN	72.5		EUROPEAN MEAN	52.5

Data from Baili et al (2015)

For weights (associated with the frequency of the cancer in the country in question) used in case-mix standardisation see Baili et al (2015)

The picture is similar if several types of cancer are evaluated individually. As an example, consider English outcomes, compared to Germany, Sweden and the European mean for colon, breast and ovary in EUROCARE-3 (2003) and EUROCARE-5 (2014) which study patients from years 1990-1994 and 1999-2007 respectively (table 2.3).

Table 2.3 Cancer survival examples EUROCARE 3 (2003) and 5 (2014)

2.3a – Colon cancer survival (male) EUROCARE-3 (2003)

COUNTRY	1-year age standardised relative survival (95% CI)	5-year age standardised relative survival (95% CI)
England	64.7% (64.1-65.4)	45.7% (44.8-46.5)
Germany	70.9 (67.8-74.2)	50.5 (46.1-55.3)
Sweden	73.6 (72.4-74.8)	52.2 (50.6-53.9)
European mean	68.8 (68.0-69.7)	49.2 (48.1-50.4)

2.3b – Breast cancer survival (female) EUROCARE-3 (2003)

COUNTRY	1-year age standardised relative survival (95% CI)	5-year age standardised relative survival (95% CI)
England	91.0% (90.8-91.2)	73.6% (73.3-74.0)
Germany	93.4% (92.4-94.5)	75.4% (73.4-77.5)
Sweden	96.5% (96.2-96.8)	82.6% (82.0-83.3)
European mean	93.5% (93.3-93.7)	76.1% (75.6-76.6)

2.3c – Ovary cancer survival EUROCARE-3 (2003)

COUNTRY	1-year age standardised relative survival (95% CI)	5-year age standardised relative survival (95% CI)
England	59.1% (58.4-59.9)	31.5% (30.8-32.3)
Germany	66.7% (62.8-70.9)	40.8% (36.1-46.0)
Sweden	74.6% (73.3-76.0)	41.3% (39.7-42.9)
European mean	65.7% (64.8-66.6)	36.7% (35.6-37.7)

2.3d - Colon cancer survival (male) EUROCARE-5 (2014)

COUNTRY	1-year age standardised relative survival (95% CI)	5-year age standardised relative survival (95% CI)
England	72.2 (72.0-72.5)	51.3% (51.0-51.7)
Germany	81.5% (81.2-81.9)	62.2% (61.7-62.8)
Sweden	82.5% (81.9-83)	61.1% (60.3-62.0)
European mean	77.6% (77.4-77.7)	57.0% (56.8-57.3)

2.3e - Breast cancer survival (female) EUROCARE-5 (2014)

COUNTRY	1-year age standardised relative survival (95% CI)	5-year age standardised relative survival (95% CI)
England	93.5% (93.4-93.6)	79.3 (79.0-75.0)
Germany	95.3% (95.1-95.5)	83.6% (83.2-84.0)
Sweden	97.3% (97.0-97.5)	86.0% (85.4-86.5)
European mean	94.8% (94.7-94.9)	81.8% (81.6-82.0)

2.3f – Ovary cancer survival EUROCARE-5 (2014)

COUNTRY	1-year age standardised relative survival (95% CI)	5-year age standardised relative survival (95% CI)
England	62.6% (62.2-63.1)	30.6% (30.0-31.1)
Germany	73.7% (72.9-74.4)	40.3% (39.3-41.3)
Sweden	81.1% (80.1-82.1)	44.1% (42.6-45.6)
European mean	70.3% (69.9-70.7)	37.6% (37.2-38.0)

Clearly, these tables are not exhaustive (to include every cancer in all EUROCARE studies would not be practical within the limits of a thesis) but they do serve as examples to reflect a typical pattern, with English survival rates behind not only countries with similar socio-economic structures but also somewhat poorer than the European average. Over the years, there has been a survival improvement Europe-wide but English rates remain poorer than the best in Europe.

Therefore, it would seem - certainly on initial assessment of the EUROCARE studies - that UK cancer outcomes have, for many years, been inferior to the best in Europe, although The international differences are rather less when 5-year '*conditional'* (on surviving 1 year) survival rates are considered. This is discussed in section 2.5. However, overall, the studies need to be viewed in the light of their methodology, strengths and weaknesses.

2.2.2 The EUROCARE studies - strengths, weaknesses and criticisms

Whilst the EUROCARE studies have been a major 'driver' of cancer policy, including development of UK urgent referral pathways, it is important to recognise their strengths and limitations when interpreting cancer outcomes in different European countries.

Following the publication of the 3rd version of EUROCARE (Sant et al 2003), one of the senior authors of the studies (Berrino 2003) outlined their strengths and weaknesses. The EUROCARE studies are a considerable achievement; the largest co-operative registry-based cancer study of its kind, including in excess of 20 million cancers from over 20 countries. However, comparative cancer outcome statistics are prone to many sources of inaccuracy, including lead-time bias, length-time bias, stage migration and overdiagnosis (Oke and Fanshawe 2020). Therefore, comparisons of cancer patient survival are amongst the most controversial of epidemiological studies.

Survival differences themselves are difficult to interpret as 'survival' may depend on later death or earlier diagnosis, the latter not being of any real benefit to the patient (lead-time bias). Furthermore, increased survival may be due to earlier diagnosis or better treatment and to clarify this issue accurate, standardised data on stage at diagnosis are needed.

In addition to the challenges of survival data interpretation, Berrino (2003) acknowledged the importance of understanding the methodology of the studies, including statistical methodology,

completeness of case identification, completeness of follow-up and disease definition. The principal statistical method is calculation of relative survival – the ratio of observed survival to that expected in a 'standard' population of the same age, sex and environment.

How the findings are interpreted is also an important consideration. Summarising EUROCARE-4, Møller et al (2009) describe the problems that exist in analysing and interpreting the studies. EUROCARE cancer outcomes are often analysed by cancer type separately, each having the same 'weight' regardless of both fatality and incidence. Alternatively, aggregate survival for all types of cancer could be used to compare countries (as in table 2.2) but, obviously, would be influenced heavily by the most common cancer types, thus missing the detail derived from less common cancers.

Completeness of case identification does, of course, depend on accurate incidence data and inconsistencies exist – for example, cancer registries that do not employ death certificates in cancer registration activity may overestimate survival. A case in point is Spain, which was shown to have high cancer survival in EUROCARE-3. However, Møller (2009) points out that inadequate recording of events in some registries was evident and following 'apparent correction' Spain's cancer survival statistics in EUROCARE-4 were no longer amongst the leading nations.

Completeness of follow-up is another source of error acknowledged by Berrino (2003). A survey of lung patients from several registers that had apparently survived 5 years found that 1.4% were, in fact, dead (Sant 1995), although the error was considered 'not likely to heavily bias' international comparisons. A further source of inaccuracy in such comparisons is tumour classification and, notably, this occurs in relation to head and neck cancers. This type of cancer should, ideally, be classified according to the International Classification of Diseases (ICD) 4th digit subsite (e.g. oral, larynx, sub-glottis) but very few cancer registries recognised this in the early EUROCARE studies (Berrino et al 1998). Additionally, Berrino notes that the delays that occur prior to publication of data (table 2.1) may mean that data may not be as relevant to 'the present time'.

Another important consideration is that some registers obtain data from a small proportion of the country. Several countries where cancer outcomes are consistently good either have a small population (such as Malta or Iceland) or have limited coverage of registration. For example, in EUROCARE- 4 (Sant et al 2009), 100% national coverage was provided for UK, Sweden and Denmark but France

(17%), Germany (1%) and Spain (12-16%) provided data from only a small part of the country. Wilkinson (2009), commenting on the validity of EUROCARE-4, noted that on initial assessment it would seem the UK has worse cancer outcomes than France or Germany, yet differences in registry coverage make comparisons difficult. Interestingly, it was also noted that 40% of the *entire* EUROCARE-4 cohort consisted of UK patients.

Overall, much of the criticism of the EUROCARE studies has focused on three deficiencies: delay in reporting, population coverage and the failure of the studies to explain why differences exist. Munro (2014[a]), commenting on EUROCARE-5, praises the considerable achievement of studying 22 million patients from 29 countries yet notes the difficulties that arise from comparing countries with complete coverage with those with only partial registration – clearly, such comparisons may mislead. Munro also criticises the 'league table mentality', suggesting this approach is not helpful in developing insight into cancer outcomes. He suggested that cancer registries needed to record more detail regarding socio-economic information, staging and treatment, concluding: *'until more is known about the individual attributes of patients the interpretation of EUROCARE studies will be far from straightforward'.*

2.2.3 Are the 'relatively poor' UK cancer outcomes genuine?

Bearing in mind the criticisms of the validity of the EUROCARE studies, the important question arises whether the 'relatively poor' UK cancer survival rates, compared to Europe, are genuine and this has caused much debate (Foot and Harrison, 2011). Considerable work has taken place to resolve this issue. In a study of EUROCARE-4 outcomes from a UK perspective (Møller 2009) an analysis was made of 42 cancer types from 23 countries, identifying cancer survival rates, by type, that were in the upper and lower quintiles (i.e. top 20% and bottom 20%). While Eastern European outcomes (e.g. Slovenia, Poland, Czech Republic) were consistently poorer than those from the UK the authors suggested that a 'rational comparison' would select countries with similar prosperity, healthcare systems and, importantly, data quality, to the UK. Norway, Sweden and Finland were considered by the authors to be similar in these ways. However, for overall cancer survival both 1-year and 5-year UK survival rates were poorer than in all these countries. For example, analysis of English 5-year conditional (on 1-year survival) outcomes for 42 cancer types revealed that whilst only 4 types were in the bottom quintile

only 5 were in the top quintile. The study concluded: '*Where, then, does this leave the assessment of cancer survival in the United Kingdom? Too low, unfortunately'*

Following this work, the International Cancer Benchmarking Partnership (ICBP) (Butler et al 2013), formed to study international variation in cancer survival, undertook a study analysing cancer registry survival data in Australia, Canada, Denmark, Norway, Sweden and UK, all of which have 100% cancer registration, similar socio-economic structure and comprehensive health services (Coleman et al 2011). The study included over 2 million patients. Focusing on colorectal, lung, breast and ovarian cancers, the authors found a steady improvement between 1995 and 2007 for all four cancers but identified highest survival in Australia, Canada and Sweden with UK nations showing, persistently, the lowest survival. Beral and Peto (2010) suggested that the relatively lower UK breast cancer survival in this study was likely to be an 'artefact' due to registration errors. However, Woods et al (2011) argue convincingly against this theory demonstrating that even 'implausibly extreme levels' of the hypothesised errors could not explain the international differences.

A recent study by the ICBP evaluated the influence of different registration practices on international survival variation in the light of different registration practices (Eden et al 2019). 8 jurisdictions were included: 2 in Canada, 2 in Australia, together with England, Northern Ireland Sweden and Norway (Eden et al 2019). Survival in each of the jurisdictions was adjusted to account for differences in registries. Variations in registration practice accounted for up to 7.3 percentage point difference between adjusted and unadjusted one-year survival rates, depending on cancer site and jurisdiction. The study concluded that 'consistent registration practices' were needed internationally.

However, further work by the ICBP has addressed additional questions in relation to the influence of variation in registration practices on international cancer outcome differences. An international study (ICBP SURVMARK-2) focused on variations in the recording of date of incidence in England, Norway and Northern Ireland and the comparability of survival estimates in the light of such differences (Myklebust et al 2020). Cancers of oesophagus, stomach, colon, rectum, liver, pancreas lung and ovary were included. Three methods of recording date of incidence were identified: firstly, prioritising the

date of pathological confirmation secondly, prioritising the date of hospital admission and thirdly prioritising the earliest available version of the pathology date. The study concluded that in countries with high-quality cancer registries differing definitions of date of incidence only marginally affected estimates of net survival.

A large ICBP (ICBP SURVMARK-2) population-based study comparing cancer survival in seven high-income countries included 3.9 million patients from UK, Australia, Canada, New Zealand, Denmark, Norway and Ireland (Arnold et al 2019). Cancers examined were oesophagus, stomach, colon, rectum, pancreas, lung and ovary. The study showed that between 1995 and 2014 survival improved in each country across almost all cancer types. However, cancers survival was consistently higher in Australia, Canada and Norway than the UK. 5-year survival examples from the most recent 5 year period of the study (2010-2014) include: stomach - Australia 32.8% (95%CI 31.3-31.5), UK 20.8% (95% CI 20.8.21.4); colon – Australia 70.8% (95% CI 70.5-71.5), UK 58.9% (95%CI 58.6-59.3) and lung – Australia 21.4% (95% CI 20.8-22.0), UK 14.7% (95% CI 14.5-15.0).

A study by Walters et al (2015) assessed whether England was closing the international gap in cancer survival, comparing English rates with Australia, Canada, Denmark, Norway and Sweden. The cancers studied were stomach, colon, rectum, lung, breast and ovary for the periods 1995-1999, 2000-2004, 2005-2009 and overall 1995-2009. Survival has increased in England since the mid-1990s; nevertheless by 2009 English survival rates remained worse than those in Australia, Canada, Norway and Sweden.

2.2.4 The UK in relation to the rest of the world (CONCORD-3 studies)

The CONCORD-3 studies (Allemani et al 2018) included 37.5 million cancer patients diagnosed between 2000 and 2014. 71 countries provided data and 18 different cancer types were included: oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast (women), cervix, ovary, prostate, and melanoma of the skin in adults, and brain tumours, leukaemias, and lymphomas in both adults and children. 47 out of 322 included registries (rather than countries) provided 100% ‘coverage’. Oral and other types of head and neck cancer were not included. Highest survival rates, in general, were found in USA, Canada and the Nordic European nations. Differences in survival between these countries and

the countries with the worst outcomes (e.g. South Africa, Nigeria, Ecuador) are very large. The studies do confirm that for several cancers the UK outcomes – whilst being much better than most South American and African nations - are poorer than many countries with comparable socio-economic structure. For example, comparing European breast cancer survival in CONCORD-3, the UK, with outcomes comparable to those in Estonia and Slovenia ranks considerably behind Sweden, Germany, France and Italy.

Therefore, there is considerable evidence that the survival differences are likely to be genuine and, despite improvement since 1995, Hamilton (2015) considers that: '*we* [England] *remain stubbornly behind other European countries*.' Foot and Harrison (2011) summarise the position: *'there is robust evidence that England has worse survival than other comparable countries.'*

2.3 Explaining international differences – why might UK fall behind the best in Europe*?*

There are many possible explanations for international differences in cancer outcomes. These include stage at diagnosis, treatment, patient factors and the 'biology' of the cancer itself and have been outlined by Foot and Harrison (2011) (table 2.4).

Table 2.4 – Possible explanations for international survival differences

Stage	Treatment	Patient factors
Stage at diagnosis	Surgery	Co-morbidity
Patient delay	Radiotherapy	Age
Professional delay	Chemotherapy	Health related behaviour
System delay	Co-ordination of treatment	Socio-economic factors

Table adapted from Foot and Harrison How to improve cancer survival (2011)

Many studies have examined the causes of different mortality rates in different countries, regions and parts of the same country and multiple factors are usually involved in explaining the differences (Mokdad et al 2017). Foot and Harrison (2011) observe that factors often inter-relate with each other;

for example, surgical treatment may not be possible in the presence of significant co-morbidities. The causes of international differences are therefore likely to be multiple, complex, interactive and difficult to define (Rose et al 2015).

Delay is, therefore, only one of a complex 'web' of factors likely to cause international survival variations. Urgent referral systems for cancer – such as the English TWR system, the focus of this thesis - aim to improve cancer outcomes by reducing delay. However, this section gives an overview of the various possible causes of relatively poor UK/English cancer outcomes, before discussing delay in detail.

2.3.1 Treatment

2.3.1.1 Surgery

The main methods for treating cancer include surgery, radiotherapy and chemotherapy. Foot and Harrison (2011) identify a fourth factor, the overall co-ordination of treatment, such as the UK 'multidisciplinary cancer team' or 'MDT' (Fleissig et al 2006).

International comparisons of treatment outcomes are not by any means new (Morrison et al 1976) and several studies have focused on the differences in cancer outcomes in relation to surgery. A recent study, including 139,457 patients, examined survival for colorectal cancer in relation to surgical treatment, comparing outcomes in Denmark, England, Norway and Sweden (Majano et al 2019). The study found that the proportion of patients treated with resection surgery was consistently lower in England than the other countries and that '*survival paralleled the relative provision of resection surgery'.* Interestingly, the study also demonstrated that older patients in England (two groups, >75 years and >85 years) were less likely to receive surgery than in the other countries. This study suggests that surgical management influences – at least in part - international differences in cancer outcomes. However, a study comparing European and US survival after surgery for colorectal cancer suggested that whilst there were wide variations in surgical practice with higher resection rates in the US (92% vs 85%) and higher 3-year survival in the US (69% vs 57%), most of the differences were attributable to stage on diagnosis (Ciccolallo et al 2005). A study by Erridge et al (2009) compared survival for lung cancer in Scotland

with British Columbia, Canada (BC) in relation to surgical treatment. The hazard for death in Scotland compared to BC was 1.5, whilst treatment aimed at cure was 14% in Scotland, 26% in BC, multivariate analysis indicated that survival differences could only be partially explained by treatment differences.

There is evidence that surgical treatment in centralised, specialist centres results in improved survival of cancer patients (Rahman et al 2018; Afshar et al 2017; Kilsdonk et al 2018). Foot and Harrison (2011) suggest that this may be due to improved training, higher caseload, improved support services and better equipment. Overall, it seems that variations in treatment do influence survival but to exactly what extent remains unclear.

2.3.1.2 Radiotherapy

The standards of radiotherapy in the UK – and the scope for improvement – were the subject of a paper produced by Cancer Research UK (Cullen et al 2014). The paper recognised that the UK radiotherapy service was short of being a *'world-class service'* (presumably meaning that the service was inferior to the best in the world) and explored the barriers to service improvement. These included: (1) inadequate capital investment (2) staff shortages (3) ineffective leadership (4) fragmentation of services (5) inequitable resources. The paper was based largely on expert opinion (*'a total of 35 experts who were deemed to be credible, experienced and qualified'*) and whilst it identified problems and proposed detailed solutions, there was scarce evidence of quantifiable differences between UK and other countries' outcomes.

So, what evidence exists that variation in radiotherapy provision contribute to differences in mortality? The position is not fully known but several studies do shed some light on the situation. A paper by Datta et al (2014) studied radiotherapy infrastructure in Europe and estimated a deficiency of 659 radiation oncologists in the UK, with a projected need for 763 more by 2020; in contrast, Norway had a slight excess of 2 oncologists with a projected need for 73 *less* by 2020. The UK had 5.11 radiotherapy units per million, comparable with the Slovak republic (4.97) Latvia (5.26) and Lithuania (5.54) but considerably less than many other countries with similar socio-economic structure such as Netherlands (7.58), Germany (6.41) and Sweden (7.99).

Harrison and Foot (2011) conclude: *'there is scope to improve outcomes by increasing access to radiotherapy'.*

2.3.1.3 Chemotherapy

The influence of drugs on international differences in cancer outcomes is, again, not clear. A report by Richards (2010), examining drug usage in 14 countries, noted that the UK's usage of cancer hormones and drugs launched 6-10 years previously ranked in the 'intermediate' range (rank 5-9) but for cancer drugs launched in the previous 5 years the UK ranked 'low' (10-14). In a study by Hartmann and Droschel (2017) it was shown that in France and Germany approximately 80% of health technology assessments (HTA) for cancer drugs were positive but 'approximately every third assessment' was negative in the UK. Two controversial papers from the Swedish Karolinska Institute (Wilking and Jonsson 2005; Jonsson and Wilking 2007), sponsored by an unrestricted grant from the drug manufacturer Roche, studied access to cancer drugs in 19 European countries. The authors identified 'international inequity' in access to new cancer drugs and reported a link between access to new drugs and survival, although the research was criticised for its methodology, particularly the use of survival data from the early 1990s with drug data from 2002 onwards (Willyard 2007).

However, access to a broader range of drugs is not necessarily linked to improved outcomes. A study by Davis (2017) assessed the benefit of 48 cancer drugs for 68 indications approved by the European Medicines Agency (EMA) between 2009 and 2013. Of the 68 indications only 51% showed improvement in survival or quality of life and 49% remained 'uncertain'. Of 23 indications showing a survival benefit, the benefit was judged to be 'clinically meaningful', on the Medical Oncology Magnitude of Clinical Benefit Scale (European Society for Medical Oncology 2020), in only 48%.

2.3.2 Patient Factors

Previous work has identified four groups of patient factors: (1) co-morbidity and fitness (2) age (3) health related behaviours (4) general social/economic factors (Harrison and Foot, 2011). These factors do not always operate independently.

2.3.2.1 Co-morbidities

Many studies have examined the impact of co-morbidities on cancer outcomes (Sarfati et al 2016). Co-morbidities may affect development, stage on diagnosis, treatment and overall outcomes (Sarfati et al 2016). There are many reasons for this. Cancer and other diseases may share common risk factors, such as smoking, excessive alcohol and obesity (Extermann 2007). Certain chronic conditions may predispose to cancer – for example, pulmonary tuberculosis increases the risk of lung cancer (Wu et al, 2011) and diabetes is associated with several cancers, such as colorectal, pancreatic and breast, not solely because of common risk factors such as obesity but also because of disordered cellular proliferation associated with altered insulin levels (Giovannucci et al 2010). Co-morbidities may also impact on timely diagnosis, either by increasing opportunities for early diagnosis or, conversely, acting as a 'distraction', resulting in later diagnosis (Terret et al 2009; Fleming et al 2005). Overall, the influence on international differences is not fully understood. However, a study by Imperatori et al (2006), comparing Varese in Italy with Teesside, UK, in the surgical treatment of lung cancer, identified that surgical resection was the strongest multivariate predictor of survival. However, the resection rate in Teesside was less than a third that in Varese (7% and 24% respectively, $p<0.001$) and the 3-year survival in Teesside half that in Varese (7% & 14%, $p<0.001$); co-morbidities resulted in a significantly lower resection rate ($p<0.001$).

2.3.2.2 Age

Although age is associated with greater co-morbidity, age relates to cancer survival as an independent factor (Chen et al 2016). Worse stage on diagnosis (Sakakibara 2018), mortality (Ganly et al 2015) and morbidity (Eguchi 2017) are associated with increasing age. EUROCARE-5 data (Minicozzi et al 2017) indicate relatively advanced stage and poor stage-specific survival for the elderly across Europe and the authors concluded: *'this finding suggests that elderly patients do not have equitable access to treatment, perhaps for structural reasons or because clinicians are reluctant to apply standard treatments because of co-morbidities'.*

Age-related differences may partly explain some differences in outcomes between the UK and Europe. An analysis of population-base cancer registry data comparing Australia, Canada, Denmark, Norway, Sweden and the UK (Coleman et al 2011) showed that in the UK older people experienced outcomes comparatively worse than old people in the other countries. Exactly why this should be the case is not clear but late presentation, greater co-morbidity and age bias have been suggested (Foot and Harrison 2011).

2.3.2.3 Behaviours

There are many well-known associations between cancer incidence and behaviours/habits such as smoking (Gandini et al 2008), alcohol (Praud et al 2015), diet (Grosso et al 2017) and exercise (Moore et al 2016). Several lifestyle factors, including diet and exercise, are also associated with improved prognosis. A systematic review including 12,108 breast cancer patients examining the relationship between physical exercise survival demonstrated an inverse relationship between exercise and mortality (Ibrahim et al 2010). Similar findings have been reported for other cancers, such as colorectal and prostate and consistent recurrence differences of up to 35% are reported between the most and least active cancer survivors (Taaffe 2018).

It is possible that different social habits may influence international differences in cancer outcomes. For example, the habit of consuming hot Calvados in Normandy, France is associated with a high local incidence of oesophageal cancer unexplained by total alcohol consumption and considered to be due to a high level of acetaldehyde and possibly high temperature of the beverage (Linderborg et al 2008).

2.3.2.4 Socio-economic factors

The influence of socio-economic inequalities on cancer incidence, mortality and morbidity is well known and is supported by a considerable body of published literature (Woods et al 2006; Fidler and Bray 2018; Holm et al 2013). Socio-economic factors impact on most cancers (Coleman et al 2001). Many reasons exist for social inequality in relation to cancer, including lifestyle, co-morbidity, stage at diagnosis, screening access and treatment differences (Fredericksen et al 2009; Parikh et al 2003; Woods et al 2006). Interestingly, there is some evidence to suggest that when access to treatment is

equal, such as in a trial, social differences in outcome 'disappear' (Nur et al 2008; Abdel-Rahman et al 2014). Social differences in cancer outcome are present even in European countries with the best outcomes such as Switzerland and Sweden (Burton-Jeangros et al 2017; Berglund 2010). However, there is some evidence that the difference between socio-economic groups for some cancers, such as breast, is greater in the UK than in other countries such as Australia (Woods et al 2006). Therefore, it is possible socio-economic differences may partly explain outcome differences. In the UK, there are considerable variations in cancer outcomes for different regions; areas with the best outcomes often comparing well with Europe whilst regions with poor outcomes compare badly (Munro 2014[b]).

2.4 Diagnostic delay

An urgent suspected cancer referral system – the main subject of this thesis – aims to reduced diagnostic delay. The following sections, therefore, consider delay in some detail.

The relationship between increasing stage at diagnosis and worse prognosis is, of course, well-established, although it varies amongst different cancer types (table 2.5):

Table 2.5 – Examples of survival percentages of common cancers by stage

Cancer type	Stage 1	Stage 2	Stage 3	Stage 4
Breast (5-year, women)	98.8%	90.1%	72.2%	27.9%
Prostate (5-year)	100%	100%	96.5%	47.7%
Lung (1-year)	85.1%	71.3%	46.1%	16.7%
Melanoma (1 year)	100%	98.4%	93.6%	47.6%

Source: Office for National Statistics (2019) 'Cancer survival in England: national estimates for patients followed up to 2017'

There is considerable evidence that differences in stage on diagnosis and delay in diagnosis account for some of the differences between cancer outcomes in the UK and the best in Europe. Some evidence

derives from epidemiological studies. Consider the following examples (table 2.6), extracted from EUROCARE-5 (de Angelis et al, 2014):

Table 2.6: 1-year and 5-year conditional (on surviving 1 year) survival: lung, head and neck, colon cancers

SITE	COUNTRY	1-year survival (95% CI) %	Percentage difference from England	5-year survival, conditional on surviving 1 year (95% CI) %	Percentage difference from England
Lung	England	30.3 (30.1-30.5)	0.0	29.0 (28.5-29.6)	0.0
	Sweden	41.8 (41.1-42.5)	11.5	35.2 (33.8-36.5)	6.2
	Netherlands	40.0 (39.6-40.4)	9.7	33.4 (32.7-24.1)	4.4
	Italy	42.3 (41.9-42.7)	12.0	33.8 (33.1-34.5)	3.8
Head and Neck	England	70.3 (69.7-70.9)	0.0	65.6 (64.6-66.6)	0.0
	Sweden	74.1 (72.8-75.4)	3.8	65.6 (63.4-57.8)	0.0
	Netherlands	74.7 (73.7-75.7)	4.4	65.7 (64.1-67.5)	0.1
	Italy	73.7 (72.8-74.5)	3.4	59.9 (58.6-61.3)	-5.7
Colon	England	72.2 (72.0-72.5)	0.0	71.1 (70.6-71.5)	0.0
	Sweden	82.5 (81.9-83.0)	10.3	74.1 (73.2-75.1)	3.0
	Netherlands	78.0 (77.6-78.4)	5.8	74.5 (73.9-75.2)	3.4
	Italy	81.3 (81.0-81.6)	9.1	74.8 (74.3-75.3)	3.7

Source: EUROCARE-5

The countries selected for comparison are all developed nations with comprehensive healthcare systems. In 2016 England's NHS spent 9.8% of GDP on healthcare and is funded from general taxation, Sweden spent 10.9% of GDP and is similarly public-funded and free at 'the point of contact', in the Netherlands 10.5% of GDP funded the health service, derived from compulsory medical insurance whilst Italy spent 8.8% of GDP on a system mostly public funded through taxation (Commonwealth Fund 2020).

The example table includes three types of cancer but reflects a picture common in the EUROCARE studies - the survival differences between UK and other European nations tend to be greatest in the first year following diagnosis and *conditional* 5-year survival (i.e. conditional on surviving one year) in the UK is much closer to other European countries. The implication, of course, is that cancers are presenting at a later stage in the UK.

The overall situation is more complex than would seem at first sight. Thomson and Forman (2009) studied the 1-year, 5-year and conditional 5-year survival rates for 26 cancers, using data from EUROCARE-4, comparing England with the European average (the authors acknowledged that the use of this average is less than ideal). For several cancers, including breast, oesophagus, liver, pancreas, cervix and brain, there was a statistically significant difference for 1-year survival and 5-year survival but not for 5-year conditional survival, again implying late presentation as an explanation for poor English survival rates. A second group showed lower than European 1-year survival which was absent in 5-year and 5-year conditional survival rates, including bone, 'soft tissue', uterus, non-Hodgkin lymphoma and bladder; this group was considered likely to benefit most from earlier diagnosis. For a third group of cancers, including lung, colon, prostate, kidney, thyroid, ovary and stomach lower survival rates at 1 year were also evident in the 5-year and 5-year conditional groups, implying that improved stage at diagnosis would not entirely eradicate outcome variation at 5 years. A further implication here is that there is unlikely to be a 'one size fits all' solution for all cancers and different types almost certainly require to be considered separately.

The EUROCARE studies, up to and including version 5, do not include data on stage at diagnosis and clearly an understanding of the link between stage and outcome is important. Obtaining accurate, comprehensive cancer stage on diagnosis data has provided a challenge for many years (McPhail 2015; Samson et al 2009) and one problem when attempting to make international comparisons is the comparability of data from different cancer registries (Walters et al 2012). Nevertheless, several international comparative studies have examined cancer stage on diagnosis in relation to outcome. A study by Walters et al (2013) examined lung cancer survival in relation to stage on diagnosis, comparing Australia, Canada, Denmark, Norway, Sweden and UK. 1-year survival ranged from 30% in the UK to 46% in Sweden. Canada and Sweden had the highest proportion of earliest (stage 1) disease, 20.0% and 19.6% respectively, whilst the UK (14.8%) and Denmark (11.0%) had lower proportions. Both the UK and Denmark had a lower survival, considered to be partly because of the worse stage distribution. However, there were also wide disparities in stage-specific survival, probably due to treatment differences. The authors concluded that international variations were partly explained by stage at

diagnosis but treatment differences were also contributing. Interestingly, between 2% and 43% of staging data were missing in this study.

A study on stage at diagnosis in England by McPhail et al (2015), using data from the National Cancer Registration Service, examined stage data from 2012 in relation to breast, prostate, lung, ovary and colorectal cancers. The authors commented: *'for the first time, stage completeness is high enough for robust analysis'.* For all cancers, survival decreased with increasing stage but for breast, prostate and colorectal a major reduction in survival was evident for stage 4 cancers, whilst for lung and ovary there were substantial reductions in survival for each increasing stage. Missing stage data ranged from 10.2% (lung) to 18.4% (prostate).

In summary, it is likely that delay and differences in cancer stage are an important cause of international variations. However, the links between delay and stage on diagnosis are not straightforward and there are many possible reasons for delay.

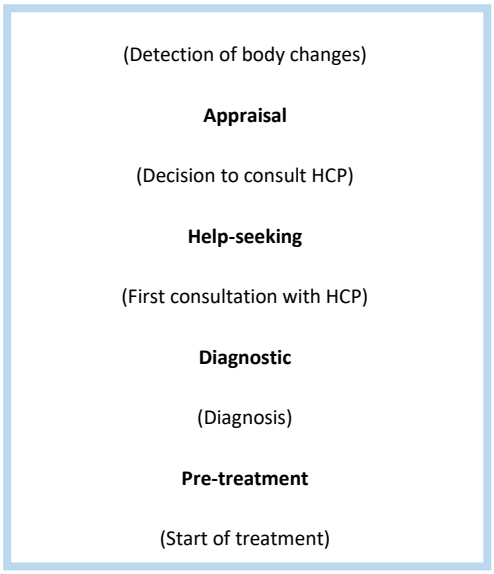
2.4.1 Models of delay

Delay in the diagnosis and treatment of cancer can occur at all points in the 'cancer diagnosis pathway', from symptom recognition to the start of treatment. Several theoretical models of 'delay' have been described. A three-stage model (not originally in relation to cancer) was proposed by Safer et al (1979): *Appraisal delay* (the time taken for a patient to determine that a symptom is a sign of illness), *Illness delay* (the time taken from the onset of illness to decide to consult a health professional – 'HCP'), *Utilisation delay* (the time from decision to seek care to consulting a HCP). This early model does not, of course, address the 'system' aspect of delay (referral, hospital processes and so on) and therefore has limited value in the context of cancer treatment pathways.

A more complex model was proposed by Andersen et al (1995): *Appraisal delay* (the time taken for a patient to determine that a symptom is a sign of illness) *Illness delay* (the time taken from the onset of illness to decide to consult a HCP) *Behavioural delay* (time taken to act on the illness delay decision) *Scheduling delay* (delay in first receiving medical attention from decision to seek it) and *Treatment delay* (delay in starting treatment from consulting a HCP).

The Andersen model was reviewed and updated, in relation to cancer, by Walter et al (2012). The model proposed by Walter defined 5 events and 4 intervals in the cancer pathway (figure 2.1):

Figure 2.1 – Intervals in cancer pathway, according to Walter (2012)



Adapted from Walter et al (2012)

Walter also defines the factors contributing to delay:

- Patient factors (demographic, co-morbidities, psychological, cultural, previous experience)
- Healthcare providers and system factors (including access, healthcare policy)
- Disease factors (including site, growth rate)

The authors conclude by stating that authors of studies on cancer diagnosis and delay should explicitly apply a theoretical model to inform measurement and description, resulting in greater consistency in such studies.

Over the years many studies on delay have used different time points and definitions which may complicate comparisons (*figure 2.2*). The 'Aarhus statement' defines the main time points of the diagnostic pathway. This work – which includes a 20-item checklist for early cancer diagnosis researchers - aims to enhance the design and reporting of early cancer diagnosis studies by ensuring

consistency of definitions such as time points and methods (Weller et al 2012). The framework and checklist have been used in several recent studies (Seoane et al 2016; Coxon 2018).

However, historically, studies have, in general, examined three aspects of the diagnostic pathway:

- Patient delay (the interval from symptom recognition to consulting a doctor)
- Practitioner or 'primary care' delay (the interval from consultation to specialist referral)
- Hospital or 'secondary' delay (interval from referral to diagnosis or start of treatment)

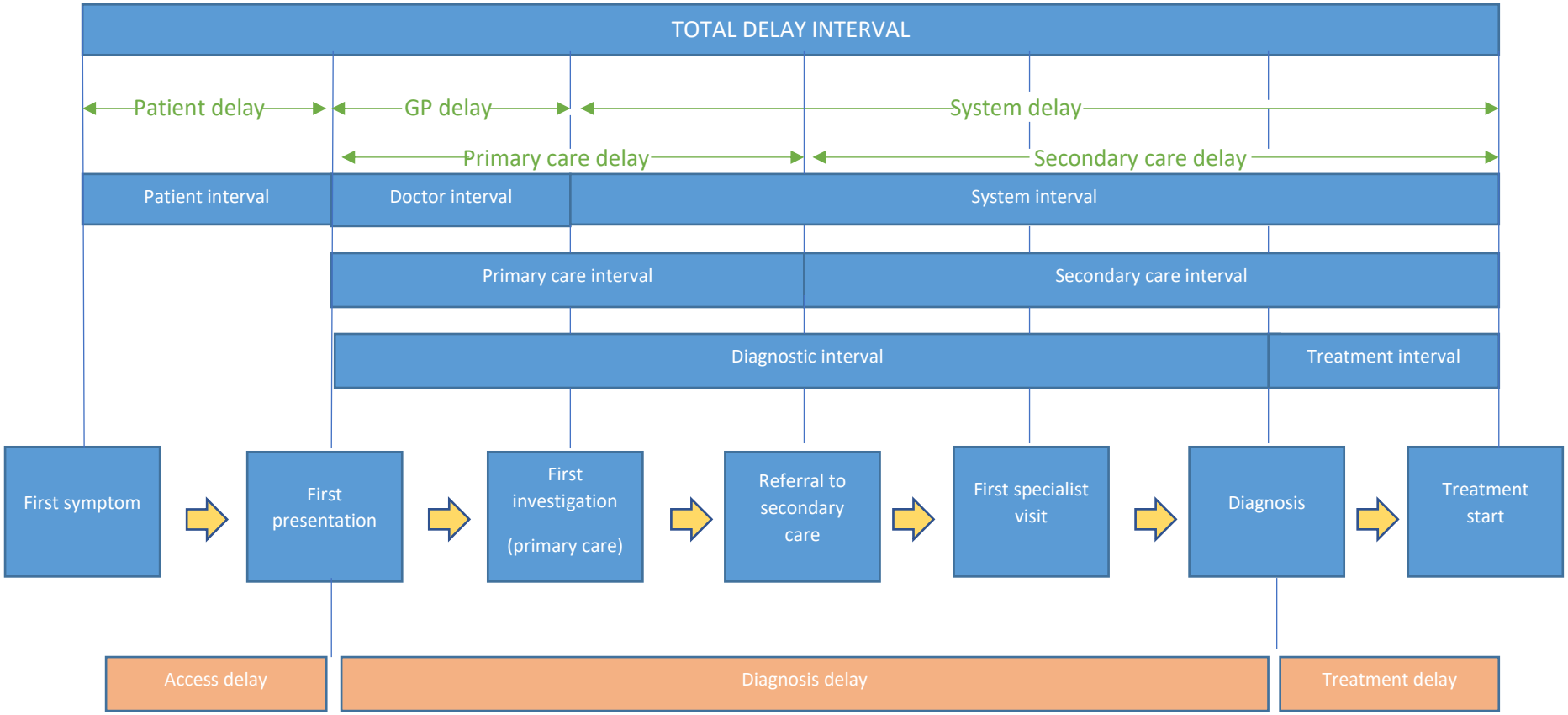
Hansen et al (2011) point out that different types of delay present different challenges that require different solutions. For example, system delay requires a shortening of clinical pathways whilst long patient delay implies a need for better patient education and symptom awareness. It should be borne in mind that there are two important potential complications with such studies. Firstly, as Walter (2012) points out, different definitions of events and time intervals (and there are several) may make comparisons challenging. Secondly, studies that include data regarding patient intervals, such as onset of symptoms, are likely to suffer from recall bias.

Figure 2.2 – Illustration of time intervals in cancer diagnosis, up to start of treatment

Blue: Time intervals defined in 'The Aarhus statement' on early cancer studies (2012)

Orange: World Health Organisation (WHO) (2017) definitions of delay in cancer diagnosis

Green: delay 'framework' defined by Olesen (2009)



Adapted and 'fused' from: Weller et al (2012), Olesen et al (2009) and WHO (2017)

2.4.2 What is known about delay at various stages of cancer 'diagnostic pathways'?

Many studies have evaluated delay in cancer diagnosis and management, examining overall delay and the contribution of different types of delay in relation to various cancers. An audit of over 17,000 cancer patients (Swann et al 2018) examined reasons for delay in diagnosis. In 22% of cases, delay had occurred. Of these, patient factors were responsible in 26%, clinician factors in 28% and 'system' factors in 34%. However, within these rather broad categories there are many different influences on the overall delay in cancer treatment. What factors might influence delay? This is clearly a complex question as different factors may impact on different parts of the treatment pathway and indeed similar overall delays may or may not be influenced equally by different stages of the diagnostic process. Studies have examined several possible influencing factors, including type of cancer, gender, age and socio-economic status.

2.4.3 Types of cancer, age, sex and social differences

There is good evidence to show that delay, at all timepoints in the referral pathway, varies according to the type of cancer, although exactly how remains uncertain. A study of diagnostic delay in over 65,000 UK patients, in relation to 6 cancers - breast, colorectal, lung, ovary, prostate and non-Hodgkin's lymphoma (NHL) - reported a broad range of 'total diagnostic delay' (Allgar and Neal, 2005). Shortest mean delay was for breast (55.2 days) followed by lung (88.5 days), ovary (90.3 days), NHL (102.8), colorectal (125.7) and prostate (148.5). Median pre-hospital delay ranged from 30 days for breast cancer and 59 days for colorectal cancer, whilst GP referral median delay was 11 days for breast and 21 days for prostate. Whilst the authors' overall conclusion was that *'reducing diagnostic delays may improve UK survival'*, it was notable that at all diagnostic points breast cancer showed the least delay whilst other cancers, such as prostate, showed longer delays. Interestingly, patients who saw a GP prior to diagnosis had longer delay than those that did not.

A Danish study (Hansen et al 2011), with a similar 'GP gatekeeper' system to the UK, evaluated delay in 2,212 cancers. The study was based on data collected via GP questionnaires, from which information on time-points such as referral to hospital and start of treatment was obtained. Median patient delay

ranged from 14 days (breast) to 70 days (melanoma) whilst overall median delay ranged from 65 days for breast to 130 days for prostate and 134 days for bladder – providing further evidence that different cancers are subject to different delays. In this study, median delay relating to primary care was very low, ranging from 0 days - for 7 out of 11 cancers studied - to a maximum of 7 days (self-reported by the GPs). However, prolonged delays in relation to secondary care system and diagnostic delay were noted with overall median delays of 46 days and 29 days respectively. In secondary care, there were wide variations in delay – for example, median breast 'system delay' was 37 days but 75 days for prostate. The authors concluded that, overall, shortening of clinical pathways was needed, together with research into patient awareness of cancer.

Forbes et al (2014), using a patient questionnaire, studied risk factors for 'patient' delay in cancer presentation in 2371 patients with 15 cancer types and provided some further insight into the differences that exist between cancer types and possible links to socio-economic deprivation. Overall, 21% of patients delayed over 3 months. Whilst neither age nor sex were associated with delay, the study demonstrated an association with social deprivation and late presentation (relative risk for most deprived compared to least 1.51, 95%CI 1.18-1.88 $p < 0.01$). Breast cancer patients were least likely to delay (8%) whilst prostate (44%) and colorectal (37%) most likely.

A study of 18,618 cancers, including 15 different types (Din et al 2014) identified a more complex situation, finding age and gender inequalities for some but not all cancer types. For example, mean diagnostic interval was greater for older patients with leukaemia and bladder, kidney and lung cancers, yet shorter with increasing age for gastric and pancreatic cancers. Diagnostic intervals for females (in gender non-specific cancer types) were longer for bladder, colorectal, gastric, head and neck, lung and lymphoma. Longer diagnostic intervals were found for cancers presenting with 'non-NICE symptoms' (i.e. symptoms not included in the guidance for English GPs).

Further influencing factors have been identified by Foot and Harrison (2011). These include presentation complexity and multiple presentations. Lyratzopoulos et al (2014) note that multiple presentations, prior to diagnosis, occur in between 30% and 50% of pancreas, ovary and stomach cancers but in less than 10% of breast cancer cases. The authors consider this reflects the 'symptom

signature', where some cancers, such as breast, present with specific symptoms (for example breast lump) whilst others, such as pancreas, often present with vague, non-specific symptoms. Practitioner factors influencing speed of diagnosis, enumerated by Macleod et al (2009), include practitioner knowledge, for example in relation to haematological malignancy (Abel et al 2008) and oral cancer (Greenwood et al 2001), examination skills, such as skin lesion examination (van Rijsingen et al 2014) and review of patients with 'possible cancer' symptoms or *'safety netting'* (Nicholson et al 2016[a]).

2.4.4 System influences

Factors related to system and policy may also influence cancer delay. Foot et al (2010) identified two important aspects: firstly, referral guidelines and secondly, primary care to secondary care communication and co-ordination.

Referral guidelines may be important in two ways: firstly, the guidelines themselves and secondly how they are used by practitioners. A study by Nicholson et al (2016[b]) examined international variation in adherence to cancer guidelines, comparing primary care practitioners in Australia, Canada, Denmark, Norway, Sweden and the UK. Three cancers were studied, lung, colorectal and ovary and, using a series of clinical 'vignettes'; the responses of the practitioners were compared to the relevant guideline(s). Guidelines varied considerably between the different countries – for example, only the UK and Denmark had guidelines for ovarian cancer. Furthermore, the 'format' of guidelines differed between countries, the UK 'prescriptive' symptom-based NICE guidelines contrasting with the more algorithm-based Canadian guidelines and the Swedish and Norwegian guidelines which were more open to clinical judgement. UK guideline adherence was lower for the lung cancer vignette than in other countries (47% vs 58%) but similar (45% vs 46%) or higher (67% vs 38%) for the two colorectal vignettes. The authors concluded that poor guideline adherence did not explain survival differences. However, several interesting findings in relation to practitioners' cancer referral habits were identified. Non-UK practitioners were more likely than UK ones to act definitively outside the relevant guidelines, while one in five UK practitioners admitted 'reporting a symptom profile that fitted the referral criteria'. However, as the authors comment, the GPs may or may not be 'bending the rules' for the 'right' patients. A comparative international study on European health system factors that influenced primary care

practitioners' (PCP) referrals for suspected cancer was undertaken by the Örenäs Research Group (Harris et al 2018). 20 countries were included and there was considerable variation. However, five factors were most influential in PCPs' decisions: ability to refer; direct patient access to specialist care; perception of being under pressure; expectations of PCP role and the belief that quality comes before cost. Of all 20 countries' responses, evaluated on a Likert scale, English GPs – who, of course, have the TWR system - gave the highest-ranked mean response for 'having access to a fast-track specialist appointment system' but awarded low Likert scores for 'ability to contact a specialist for advice' and 'I am able to refer to a specialist I know personally', particularly when compared to 'similar' countries such as France and Germany.

Secondary cancer care – and the flow of the patient through the diagnostic process - in England is co-ordinated through the multidisciplinary team (MDT), introduced following the Calman-Hine report (Department of Health 1995). Several studies have demonstrated multiple benefits for this approach, including improved overall survival (Munro et al 2015; Kesson et al 2012). However, how might such an approach reduce diagnostic or treatment delay? An early study in the UK by Flessig et al (2006) suggested that MDT working enhanced primary care–specialist communication. Denton and Conron (2016) defined important aspects of the MDT in facilitating early diagnosis in relation to lung cancer, emphasising the correct processing of initial referrals and timely patient decisions. A systematic review by Prades et al (2015) included 51 studies on cancer MDTs. 29 studies demonstrated improved outcomes including more accurate diagnosis, improved survival and better staging; of the 29 studies 6 identified improved early and appropriate referral patterns.

2.5 How does delay relate to cancer outcomes?

In 1906 the British surgeon Charles P. Childe wrote: *"Cancer itself is not incurable. It becomes incurable from the simple fact that its unfortunate victims harbour and nurse their cancers till it is too late"* (Childe 1906). Clearly, the concept that timely diagnosis and treatment of cancer results in better outcomes is not new, although it appears that Childe, at the beginning of the last century, focused entirely on patient delay and rather less on practitioner and system delay!

Neal (2009) summarises the issue succinctly*: 'The important question is how much of this preventable delay leads to poorer outcomes. If people could be diagnosed earlier, what difference would this make to survival and other clinical outcomes?'*

Potentially, longer diagnostic intervals may have several adverse effects including more advanced stage, greater morbidity from disease and treatment and psychological problems (Neal 2015). On the other hand, problems resulting from early diagnosis include lead time bias - earlier diagnosis, but outcome remains the same (Hutchison & Shapiro 1968) and over-diagnosis, typically of very slow-growing tumours for which treatment gives no benefit over not actively treating - and may have many disadvantages (Welch and Black 2010). It would seem intuitive that delays in diagnosis result in more advanced stages of cancer which translate into poorer outcomes. However, the situation is less clear than one might assume and has led to considerable controversy. Whilst some studies indicate that outcomes worsen in relation to delay, others report the opposite effect, the so-called 'waiting time paradox' (Neal 2015).

What evidence has examined the influence of diagnostic delay on cancer outcomes? A study on breast cancer by Richards et al (1999) assessed 2964 breast cancer patients presenting between 1975 and 1990. Survival was measured from the first symptom noticed by the patient and from the date of diagnosis. 32% of patients who had symptoms for more than 12 weeks had advanced or metastatic disease, compared to 10% of patients with symptoms for less than 12 weeks (p=0.001). 10 years after the onset of symptoms, survival was 52% for <12 weeks delay and 47% for >12 weeks delay although the authors noted that Kaplan-Meier curves began to diverge markedly from about 4 years onwards. This study provided some of the early UK evidence for the benefits of reducing diagnostic delay. Similarly, a large study of 94,544 breast cancer patients in the USA (Belcher et al 2016) showed lower 'time to surgery' was significantly associated with survival. However, other studies on 'treatment interval' in breast cancer demonstrate an association neither with survival (Eastman et al 2013; Mujar et al 2013) nor stage (Wright et al 2010).

A Danish study on the GP presentation-diagnosis interval for colorectal cancer (CRC) (Tørring et al 2011) found that risk of 3-year mortality increased with intervals of over 5 weeks for patients presenting

with 'red flag' cancer symptoms; interestingly, the association was 'reversed' but not statistically significant for patients presenting with 'vague' symptoms. The authors concluded: *'this study provides evidence for the hypothesis that the length of the diagnostic interval affects mortality in CRC patients.'* Nevertheless, no association was found in several CRC studies (Pruitt et al 2013; Roland et al 2013). The paper by Roland specifically questioned whether 'time to delivery of treatment' was a reliable measure of quality of care. The study concluded: *'We must deliver quality health care in an efficient and timely manner; however, the metric of interval to treatment may not measure reliably the quality of care received'.* However, it has been suggested (Tørring et al 2011) that some studies showing such 'counterintuitive outcomes' may be influenced by confounders, such as age and co-morbidities, if these are not considered in the study design.

The association of time-to-diagnosis and outcome was the subject of a systematic review by Neal et al (2015), which included 177 articles reporting 209 studies. 28 different types of cancer were included and several types of diagnostic interval. The authors also focused on studies that attempted to address the 'waiting time paradox' by excluding, in subgroup analysis, patients who were diagnosed very quickly or had a very poor outcome, such as death from an extremely aggressive cancer within a few weeks of diagnosis. Studies were presented by cancer site in three groups: 'positive indication' 'no indication' and 'negative indication', depending on the type of association between delay and outcome in each study. The results of the review were very mixed, although negative associations were relatively infrequent (22 out of 209 studies). 91 studies demonstrated a positive association and the remainder no association. Unsurprisingly, the degree of heterogeneity precluded meta-analysis. The authors noted an association between shorter diagnostic intervals and improved outcomes for breast, colorectal, head and neck, testicular and melanoma and concluded: *'…we believe it is reasonable to assume that efforts to expedite the diagnosis of symptomatic cancer are likely to have benefits for patients……although these benefits vary between cancers.'*

A similar conclusion was reached in a study by Tørring et al (2019) investigating the relationship between stage on diagnosis and selected components of the primary care (presentation to referral) and secondary care (referral to diagnosis) intervals (see figure 2.2). Breast, lung, colorectal and ovarian

cancers were included. The pattern differed for the primary and secondary care intervals. A 'U' shaped statistically significant relationship between delay and outcome was identified in secondary care, with initially decreasing and then increasing odds of advanced cancer; a 'flat' relationship was seen in relation to primary care delay. The authors concluded: *'some cancers may progress even within the relatively short time frame of regulated diagnostic intervals'* and that the 'waiting time paradox' reflected bias from secondary care 'prioritisation' – in other words, very ill patients are prioritised but have worse outcomes.

There is, therefore, increasing evidence that delay at various points in the 'diagnosis pathway' may influence outcomes in several types of cancer. However, it is also arguable that which part of the treatment pathway is considered and type of cancer are also important. Whilst evidence for the link between delay and, say, colo-rectal cancer outcomes seems reasonably convincing, for other cancers this may be less so. For example, a study on prostate cancer (Morini et al 2018) – which does have a very variable clinical progress and often 'indolent' course (Gulati et al 2012) – found that the time between diagnosis and surgical treatment did not affect outcomes.

The complex methodological issues of studies on this subject need to be considered. Neal (2009) notes that different cancers need to be considered separately and what may apply to one type of cancer does not necessarily apply to another one. Furthermore, as previously described, there are many different definitions and classifications of delay and different ways of measuring such delays. For example, in measuring 'patient delay' recall bias, noted earlier, is one obvious confounder but, additionally, the evaluation of such delay may be influenced by the way the question is asked and qualitative studies on patient experiences have demonstrated cancer symptoms may have been apparent to the patient longer than was initially believed (Bankhead et al 2005). Whilst medical records are not prone to recall bias, they do depend on the accuracy of symptom recording and which symptoms the health professional considers 'notable'. Outcome measures also need to be considered and whilst survival is the most important outcome, other outcomes such as stage at diagnosis, which correlates well with survival, treatment options and quality of life are also reported (Schorr et al 2017). A further aspect is the health-system context which may complicate comparisons between outcomes in different countries.

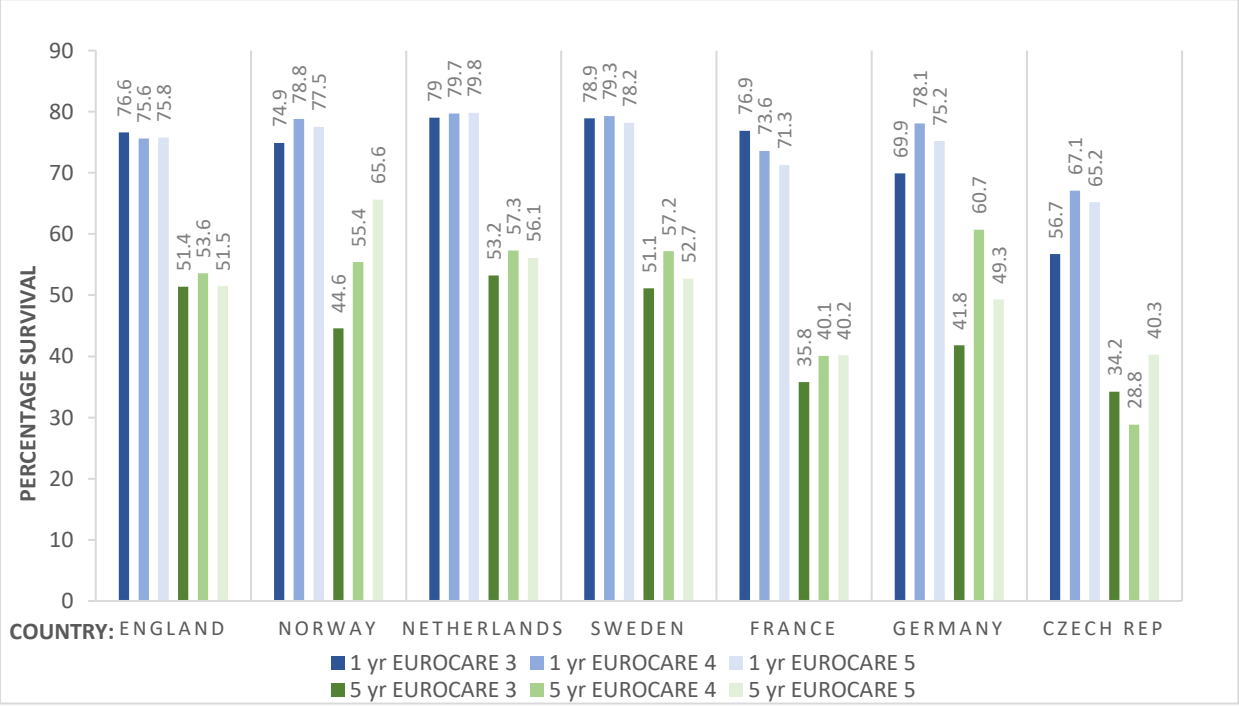
2.6 Oral cancer: outcomes, delays and fast-track referral

It has already been noted that when evaluating delays, fast track referral and other aspects of early cancer diagnosis, different types of cancer need to be considered separately. Therefore, the following sections examine what is known about the early diagnosis of oral cancer, the cancer on which this thesis focuses.

2.6.1 *The EUROCARE studies – oral cancer*

One of the main 'drivers' of UK cancer policy has been the comparative outcomes for cancer across Europe in the 'EUROCARE' studies. How do English outcomes for oral cancer compare with those from other European countries? Figure 2.3 includes 1-year and 5-year survival data for England, compared with 3 small European countries with comprehensive healthcare systems (Norway, Sweden and Netherlands), 2 large European countries (France and Germany) and 1 Eastern European country (Czech Republic).

Figure 2.3 - 1-year and 5-year standardised survival for oral cancer, EUROCARE -3, -4 and -5

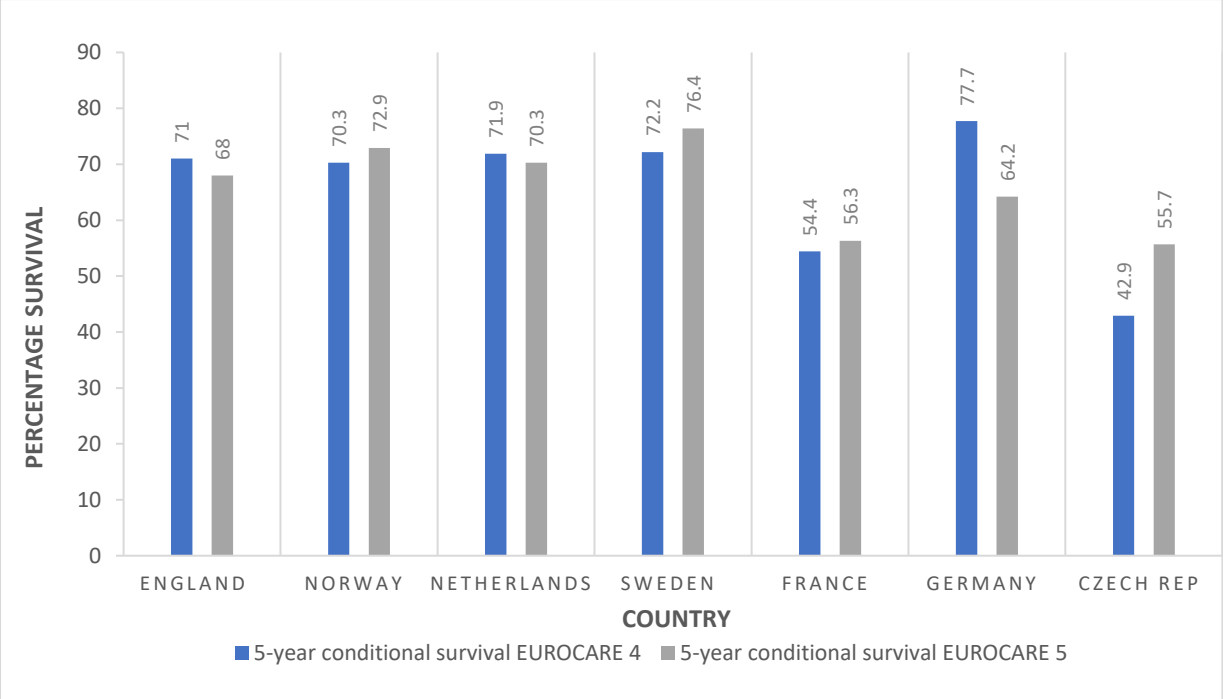


Data from: Sant M et al (2003), Sant M et al (2009) and de Angelis R et al (2014)

In EUROCARE 5, 1- year survival and 5-year conditional survival from oral cancer are slightly lower in Scotland and Wales than England but not significantly so. Survival for oral cancer in Northern Ireland is slightly higher than in England.

Data from 1990 to 2007 are included, across 3 studies (EUROCARE 3, 4 and 5) covering the periods specified in table 2.1. In England, 1-year oral cancer survival has changed very little over the 17-year period, remaining in the order of 76%, persistently behind Norway, Netherlands and Sweden, slightly better than France and considerably better than the Czech Republic, which has poorer socio-economic structure than the other countries here (De Angelis et al, 2014). 5-year survival in England has, again, changed little over the period covered by the 3 EUROCARE studies, remaining in the order of 52%. For the most recent reported study period, Norway (65.6%), Netherlands (56.1%) and Sweden (52.7%) have higher survival rates, France (40.2%) and Czech Republic (40.3%) considerably lower. However, if 5-year *conditional* survival rates (on surviving 1 year) are considered (Figure 2.4), English survival rates are closer to the higher survival rates of Norway, Netherlands and Sweden and higher than France and Germany in EUROCARE 5, suggesting that late diagnosis has an important influence.

Figure 2.4 – Conditional (on surviving 1 year) 5-year oral cancer survival – EUROCARE 4 and 5[1]



Data from: Sant M et al (2009) and de Angelis R et al (2014)

Abdel-Rahman et al (2009) calculated 'excess cancer deaths' in the UK, relative to the best and average European outcomes for several common cancers, using data from EUROCARE 2, 3 and 4. For oral

[1] Conditional oral cancer survival rates not available in EUROCARE 3

cancer, for the periods 1990-94 and 1995-99 (EUROCARE 3 and 4) it was calculated that the UK suffered *less* 'excess deaths' than the European average. However, compared to the European best, 119 and 257 'excess deaths' from oral cancer were reported for each period respectively. (For perspective, it is notable that when the UK was compared, in the same study, to the European best, for breast the 'excess deaths' were 11,739 and 9,831; for prostate 11,739 and 7,958). As discussed previously, comparative results do have to be considered in the light of study validity. The EUROCARE studies report data from several years in the past; for example, the EUROCARE 5 study on head and neck cancer (Gatta et al 2015), included data up to 2007. Furthermore, 100% population 'coverage' (as in the UK) does not occur in all countries. In EUROCARE 4, 5,814 English oral cancers were included; 5,386 were included for *all* Southern Europe (comprising Croatia, Spain, Italy, Malta, Slovenia and Portugal). Another example, in EUROCARE 4, French oral cancer numbers were derived from only 11% of the population. Munro (2014) has suggested – referring to the principles of cancer outcome statistics in general: *'…any comparisons excluding the banlieues défavorisées of Paris but including impoverished areas of Glasgow are likely to mislead'.* This is particularly likely to be so for oral cancer, with strong associations between deprivation and both incidence and outcome (Auluck 2016).

Overall, the gap between English 1-year survival and the best European survival rates is less for oral cancer than for breast and colon (table 2.3). Nevertheless, it would seem, for oral cancer, late diagnosis is likely to be contributing to the differences in survival rates between England and European nations.

2.6.2 Delay and oral cancer

Oral cancer survival relates closely to stage on diagnosis. In 2013, in England, 1-year survival for 'early' (stage 1 and 2) oral cancer was 92% for men, 94% for women; the respective figures for 'late' (stage 3 and 4) disease were 68% and 64%. 3-year survival for early presentations was 81% for men and 82% for women; for late presentations, survival was 47% and 45% respectively (National Cancer Intelligence Network 2013). Unfortunately, between 40% and 50% of oral cancers present at late stage (Rogers et al 2009; Rogers et al 2011) which has obvious implications for survival. Furthermore, treatment for late stage disease requires more radical treatment with associated severe morbidity and poor quality of life (Doss et al 2017).

2.6.3 Causes of delay – patient factors

Why does presentation delay occur for oral cancer? Studies on this cancer – in common with other types - have suffered from a lack of precise definitions of the various delay periods, making comparisons between studies difficult (Gigliotti et al 2019). Few studies have used the formal definitions of delay periods defined by Olesen (2009), the 'Aarhus Statement' of Weller (2012) or the World Health Organisation (2017). However, many studies indicate that patient delay (or 'appraisal period') – the time between noticing a symptom and seeking professional help – is responsible for most of the overall delay. A study in the UK (Hollows 2000) found a mean patient delay period of 22.5 weeks with 29% of patients delaying more than 3 months. A further UK study by McGurk et al (2005), including two cohorts of 319 and 160 oral cancers, found that patients accounted for delay in 81% and 78% of cases respectively, with a mean delay of 3 months. A study in Canada found a mean and median patient delay of 21.7 weeks and 4.5 weeks (Yu et al 2008) and a study in the USA found a mean patient delay of 4.8 months (range 0.5 to 36 months). A study in Germany of 646 oral cancers found that 63.5% had patient delays of 3 to 4 months (Friedrich 2010). Studies in Asia (Kerdpon et al 2001) and South America (Morelatto et al 2007) report similar outcomes, confirming high external validity of the findings in relation to patient delay for oral cancer.

The reasons for patient delay in oral cancer are imperfectly understood but several studies have shed light on the situation. For many cancers, non-recognition of the seriousness of symptoms is the main reason for patient delay (Macleod at al 2009) and this would also seem to be case for oral cancer. Rogers et al (2011) undertook a survey-based study of 115 oral cancer patients, focusing on the symptoms experienced before diagnosis. Approximately half the patients interpreted their symptoms as 'something minor' that would resolve spontaneously. Nearly all the patients stated they would have obtained professional advice had they been more aware of oral cancer. Similarly, a study by Crossman et al (2016) examined barriers to visiting a professional with oral symptoms and by far the most commonly stated reason (74%) was failure to realise that symptoms were serious. In a qualitative study of oral cancer patients' responses to symptoms prior to diagnosis, undertaken in in Scotland (Grant et al 2010), re-interpretation of symptoms was a common finding and many participants commented that

'something so small and painless couldn't be serious'. 'Not bothering the doctor or dentist' and self-treatment with products purchased from a pharmacy were also identified in this study as barriers to early access to diagnosis and treatment.

Studies on the influence of socio-economic factors in relation to patients' presentation delay have provided a mixed picture. A study by Rogers et al (2007) found that socio-economic deprivation was associated with the incidence of oral cancer but not with delay. A study by Peacock et al (2008) suggested that greater delay in the USA (privately and insurance funded) compared to Canada (publicly funded) may be influenced by the health system.

Public knowledge of oral cancer is relatively poor and this has changed little over many years. A qualitative study in the north east of England of an at-risk group of patients (male smokers and drinkers aged 45-60) identified a lack of awareness of the disease and a perception that health information on the disease was either confusing or untrustworthy. The authors considered this was linked to a fatalistic view of serious disease (Lowry and Craven 1999). In a survey of oral cancer awareness of 535 people in Liverpool, only 1% mentioned oral cancer when asked to name cancers that they had heard of (Rogers et al 2011). Lack of oral cancer knowledge is evident in both developed and third-world countries (Horowitz et al 2002; Monteiro et al 2012; Reddy et al 2012).

Evidence on the influence of public awareness campaigns on delay in oral cancer presentation have demonstrated very variable benefits. Stefanuto et al (2014) point out: *'One might think that this* [campaigns] *would lead to greater public knowledge and ultimately less patient delay'* and some research does demonstrate benefits in relation to increased public knowledge. In a telephone survey of dentists and 'consumers' following an American Dental Association oral cancer campaign (Stahl et al 2004) a majority of dentists agreed that public awareness of oral cancer was improved by the campaign and the study concluded – possibly optimistically – *'health promotion interventions aimed at consumers and dentists invariably will result in the detection of oral cancers at early and curable stages'.* In a study on the effect of an information leaflet, delivered at a GP practice in Italy, participants in intervention and control groups completed an oral cancer knowledge questionnaire before the

intervention group read the leaflet. One year later both groups repeated the questionnaire. Questionnaire 'scores' showed a significant difference ($p<0.001$) at 1 year for the intervention group and the authors concluded that the study confirmed the effectiveness of an oral cancer information leaflet (Petti et al 2006). On the other hand, a study in Florida on public oral cancer awareness before and after a billboard information campaign demonstrated limited and non-significant improvements in oral cancer awareness (Papas et al 2004). In the UK, difficulty in accessing primary care services was not identified as a frequently encountered factor for oral cancer patients by Crossman et al (2016). However, one problem identified in a paper by West (2006) was that knowledge of signs of mouth cancer is lower in individuals who, because of habits and behaviours, are most at risk. Furthermore, there is evidence to suggest that the link between alcohol and oral cancer has not been recognised by those at risk (Warnakulasuriya et al 1999). Varella-Centelles et al (2017) take the argument forward and suggest – convincingly – that strategies focused specifically on patients most at risk are needed to reduced diagnostic delay for oral cancer. However, the overall situation regarding 'patient awareness' has been summarised by Stefanuto (2014): *'Patients cannot be relied upon to present for examination. Some oral cancers and precancerous lesions may be asymptomatic and even though most are symptomatic patients may misrepresent their symptoms'.*

2.6.4 Professional delay

Studies on professional delay and oral cancer have, again, produced mixed results. Stefanuto (2014) notes that the literature contains many definitions of 'professional delay' making comparisons complicated. An early UK study by Scully et al (1986) found a median delay between primary care consultation and specialist referral of 31 days. A rather shorter mean referral delay of 8.4 days was identified in a UK study by Hollows (2000). A 2007 study in Liverpool identified a mean primary care practitioner delay of 22 days, although 78% of the 325 patients included were referred the same day as presentation (Rogers et al 2007). Rogers' study was, of course, undertaken after the introduction of the UK 2000 Cancer Plan with its associated treatment targets and primary care guidelines. Allison et al (1998) studied oral cancer delays in Canada and in their cohort of 188 cases 71% of patients had 'professional delay' (defined as the period of time between the initial consultation with a HCP and the

first consultation with the treating specialist) of up to 1 month; 14.5% had 1 to 3 months delay and 14.5% over 3 months delay.

Why might professional delay in oral cancer referral occur? Causes may include lack of practitioner knowledge (Carter et al 2007), lack of examination skills (Meskin 1994) and 'mis-diagnosis' through treating patients symptomatically or relating symptoms to a problem other than cancer (Grafton-Clarke al 2019). It might be assumed that because of the ease of access to the mouth, examination would be relatively simple. However, a study in Scotland of 357 GPs and 331 dentists, on the role of primary care professionals in oral cancer prevention and detection, (Macpherson et al 2003) reported that 85% of GPs and 63% of dentists felt 'less than confident' in oral cancer detection, with 70% of GPs identifying lack of training as an important barrier. This study concluded that education to improve primary care practitioners' diagnostic skills for oral cancer was needed.

Although the focus of this thesis is the period up to presentation at specialist care, professional delay can, of course, also occur in secondary care. A study by Patel and Brennan (2012) identified a median delay of 37 days from date of biopsy to date of surgery for oral cancer. In England, following the 2000 Cancer Plan, the target for treatment is 31 days from formal diagnosis and 62 days from primary care referral; these targets should be achieved, in each treating hospital, for 85% of patients. Unfortunately, the target has been consistently failed since 2013; a recent study (Araghi et al 2020) found that only 77.7% of oral cancer patients were being treated within 62 days.

2.6.5 Relationship between delay and outcome

For oral cancer, in common with several other cancers, it would seem entirely logical that longer delay results in more advanced stage and, consequently, poorer outcomes. However, studies examining the relationship between delay and outcome for oral cancer give a mixed picture. A systematic review by Goy et al (2009) examined the evidence for an association between diagnostic delay and stage at diagnosis for head and neck cancer. The review included 27 studies on head and neck cancers of all types, with 15 focusing specifically on oral cancer; within this group there was considerable variation

– some studied oral cavity in isolation whilst others included lip and oropharyngeal cancers. In the review, four oral cancer studies evaluated the association between total delay and stage on diagnosis (Mashberg et al 1989; Gorsky et al 1995; Pitphat et al 2002; Scott et al 2005); none demonstrated a significant association. Eight of ten studies examining patient delay in oral cancer found no association with stage on diagnosis (Amir et al 1999; Guggenheimer et al 1989; Dimitroulis et al 1992; Jovanovic et al 1992; Kowalski et al 1994; Wildt et al 1995; Kerdpon et al 2001; Onizawa et al 2003). In the previously mentioned systematic review by Neal (2015), for included oral cancer studies, a positive association between patient interval and stage was noted in 2 studies (Kumar 2001; Brouha 2005). However, there was no association between diagnostic interval and survival in 2 studies (Teppo et al 2008; Seoane et al 2010), symptom onset to diagnosis (Wildt 1995) or symptom onset to treatment (McGurk 2005). However, a further systematic review on head and neck cancer including 5 on oral cancer (Seoane et al 2012) identified delay of 'any type' was associated with increased mortality (RR 1.34, 95% CI 1.12-1.61).

A study by Allison et al (1998), calculated odds ratios for 'late' (stage 3 and 4) disease in relation to 'professional' delay. Compared to cases delayed for less than 1 month, odds ratios were 1.56 for 1-3 months delay and 3.16 for over 3 months delay. Similar results were reported by Kowalski (1994). Allison suggested that a proportion of patients may have had 'early' (stage 1 and 2) disease on first presentation but professional delay resulted in progress to 'late' (stage 3 and 4) disease. A systematic review by Chen et al (2008) on all head and neck cancer types demonstrated significant increased risk of local recurrence with increasing delay to radiotherapy and a marginal decrease in survival. Similarly, a study by Murphy et al (2016) showed rapidly increasing risk of mortality with head and neck radiotherapy delay of over 60 days (although the risk fell slightly over the first 30 days). These studies suggest that professional delay may influence oral cancer outcomes. However, why does research show an inconsistent relationship between delay and oral cancer outcome? One possible reason is methodological flaws – or at least inconsistency. The importance of adjustment for confounders in studies evaluating the impact of delay on oral cancer outcome is emphasised by Seoane (2012). Gigliotti et al (2019) note the different definitions of end points and the risk of misclassifications. Studies on

patient delay are, of course, retrospective in nature and may be subject to recall bias. Gigliotti notes several other methodological problems including defining 'symptom onset' which is subjective and influenced by cultural and social factors. Heterogeneity of included cancer types may also influence outcomes; as noted above, in studies 'oral' cancers may or may not include, for example, 'oropharyngeal' or 'lip'. Furthermore, even within the oral cavity, specific areas may be associated with a greater risk of advanced disease (Seoane-Romero et al 2012).

Two clinical-pathological theories are often proposed to explain the absence of a clear relationship between patient delay and oral cancer stage on presentation. The 'traditional' (and arguably simplistic) explanation, which assumes oral cancers have similar thresholds for symptom development, is that small cancers present with delay, as they grow slowly whilst large, rapidly growing tumours present without delay. For example, a very slow-growing cancer may remain small and despite diagnostic delay remains small at the time of presentation. On the other hand, a rapidly growing cancer presents with little delay but nevertheless reaches a large size or gives rise to more obvious symptoms (such as neck nodes) at the time of presentation (Gigliotti et al 2019). An alternative theory, suggested by McGurk et al (2005), is the so-called 'silent tumour hypothesis' which proposes that some oral cancers may reach a large size before symptoms develop that cause the patient to seek medical advice. In explaining this theory, McGurk states: *'The error is to assume that symptoms are related to the size of the tumour'.*

A study investigating the association between hospital interval (as part of a multivariate model) and survival for oral cancer (Lopez-Cedrun et al 2019) demonstrated a significantly higher mortality for 'short' (<18 days) and 'long' (26-55 days) intervals but not for 'medium' intervals (19-25 days. In common with other work (Tørring et al 2019), the authors considered the 'V shaped' association was subject to a 'severity bias' in the speed of treatment. Van Harten (2014) studied 2493 head and neck cancer patients and found that a time to treatment of less than 30 days was – paradoxically - associated with *lower* disease-specific survival (hazard ratio 0.838). Again, one explanation was that patients with more advanced cancers were treated more rapidly. A study on the relationship between diagnostic delay and survival of 221 head and neck cancer by Teppo and Alho (2008) included 62 tongue cancers. For tongue, the relationship between diagnostic delay and survival at 2 and 5 years was not significant

(p=0.72 and 0.61 respectively). However, a study of treatment waiting times, undertaken in the Netherlands including 13,140 head and neck patients, (van Harten et al 2015) found that for every 7 days of increased waiting there was a statistically significant increased risk of death (HR 1.07 95%CI 1.06-1.07) although, interestingly, no significant difference between those treated before 30 days (the Dutch head and neck target for treatment delay).

2.6.6 Urgent referral of oral cancer in England – the TWR

The influence of the TWR on oral cancer has been discussed in section 1.4.7. It achieves a positive predictive value of 8%-9% and a sensitivity in the order of 40% (Langton et al 2014). Both primary care doctors and dentists use the system but very little is known about its influence on oral cancer mortality or stage on diagnosis.

2.6.7 Screening for oral cancer

A brief outline of screening is included to give a more complete picture of factors that might influence the early diagnosis of oral cancer by shortening the interval to specialist consultation and diagnosis. To date, no country has implemented a screening program for oral cancer. Why should this be the case, as oral cancer is clearly a serious health problem with, as discussed previously, an overall mortality in the order of 50%, unchanged in decades? A paper from the Global Oral Cancer Forum (Speight et al 2017) provides a comprehensive and detailed analysis of the problem. The authors point out that the mouth is easy to examine, abnormalities are easily seen and oral cancer is preceded, in most cases, by a so-called 'oral potentially malignant disorder' (OPMD), usually a white patch (leukoplakia) or a red patch (erythroplakia) (Warnakulasuriya et al 2007). The existence of these pre-malignant lesions, in an easily accessible site suggests that screening might well be feasible.

Conventional oral examination (COE) has been evaluated for diagnostic effectiveness in several studies, identifying sensitivity in the order of 75%-99% and specificity in the order of 98%-99% (Chang et al 2011; Jullien et al 1995) It should be noted, however, that the 'gold standard' in these diagnostic studies is identification of an oral pre-malignant disorder (OPMD), not actual oral cancer. Only 5% of OPMDs progress to malignancy (Napier and Speight 2008). Nevertheless, studies, including systematic reviews

(Walsh et al 2013; Wanrnakulasuriya et al (2015) demonstrate sensitivities and specificities of the same order as those found in breast and cervical screening programs (Speight et al 2017). Several adjunctive techniques have been described for enhancing COE including toluidine blue, 'Visilite', 'Microlux' and OralCDx, the subject of a systematic review by Patton et al (2008). The authors concluded: '*Overall, there is insufficient evidence to support or refute the use of visually based examination adjuncts.'*

To date, only one randomised controlled trial (RCT), in India, has studied the effect of an oral cancer screening program (Sankaranarayanan et al 2013). Four rounds of screening of the intervention group of over 96,000 people took place over a 15-year period; the control group of just over 95,000 received no screening. In the intervention group 91% were screened at least once. Overall, data from the studies indicated that there was no significant difference in mortality between intervention and control groups. However, there was a significant difference for males in a high-risk subgroup (male smokers). The authors concluded that opportunistic screening of high-risk individuals is probably effective (Subramanian 2009), a conclusion that has been reached by other authors (Wanrnakulasuriya et al 2015; Epstein et al 2015). However, it has also been observed that those most at risk are least likely to attend for such screening (Netuveli et al 2006). In the UK, cancer screening programs currently exist for breast, cervix and bowel. There is no program for oral cancer (Cancer Research UK 2019). Unfortunately, no controlled trials on improved mortality in response to oral cancer screening - studies would need to be very large indeed - and the lack of controlled studies is cited by the UK National Screening Committee as a reason for not supporting a screening program. Similar conclusions have been reached in the USA (Wanrnakulasuriya et al 2015; Moyer 2014).

2.7 Summary

The belief that UK cancer outcomes were relatively poor was strongly driven by the 'EUROCARE' studies (section 2.2), although it is recognised that methodologically they are less than perfect and interpretation is not straightforward (section 2.2.2). They include retrospective data, variable standards of cancer reporting amongst included countries, variable 'coverage' of the populations amongst nations and give few indications why international differences exist. Nevertheless, for many cancers – and

probably oral cancer – subsequent work indicates differences between England/UK and the best European outcomes are probably 'genuine' (sections 2.2.3; 2.2.4).

It is likely that the causes of such international differences are complex, involving many factors. However, one important pattern is that whilst UK 1-year survival for several cancers, including oral cancer, is consistently below the best European rates, 5-year conditional survival compares well with other countries. This suggests delayed presentation may be an important factor (sections 2.4; 2.6.1).

In response to reports of poor cancer outcomes, the UK government's 2000 Cancer Plan was developed and included measures to improve timely diagnosis and treatment, with a focus on reducing delay at all stages of the cancer 'pathway'. This included the English 'two-week rule' (TWR) urgent suspected cancer referral system to improve the delay in the primary to secondary care interval (section 1.3.2).

However, the relationship between delay and outcome is complex and, furthermore, for many cancers, including oral, most of the delay occurs during the 'patient interval'; nevertheless, there is increasing evidence that delay between presentation and diagnosis may influence outcomes (figure 2.2; sections 2.6.3; 2.6.5) and therefore efforts to reduce diagnostic delay are probably justified. However, the TWR and other such 'target driven' systems - although aiming to reduce diagnostic delay - have been subject to considerable criticism (sections 1.4.1; 1.4.3). For many cancers, including oral, the positive predictive value of the system is less than 10% and the sensitivity approximately 40%. Although some work has demonstrated little or no outcome benefit in relation to the system in England, several studies have shown a positive correlation between greater primary care use of the TWR system and cancer outcome. However, there is little work directly demonstrating improved survival or improved stage on diagnosis for oral cancer in relation to the English TWR referral system (section 1.4.5;1.4.7).

2.8 Question development

Harrison and Foot (2012) state*: 'for the two-week rule to be effective……the stage at which patients were identified should have fallen since its introduction'* (section 1.4.4). As I have described, for oral

cancer (and, indeed, many other types), there is very little evidence to show that this key aspect has been enhanced by the TWR system (section 1.4.7). Therefore, the first question addressed in this thesis is: has the TWR system resulted in an earlier stage on diagnosis compared to the period before its introduction?

The TWR has been in place – at the time of writing - for 20 years, yet relatively little is known about firstly, how this referral system compares with other referral systems (section 2.4.4) and secondly, how the system might be improved (section 1.4.6). One country with better outcomes for oral and head and neck cancer[2] is the Netherlands (section 2.6.1). With this in mind, the second question addressed is: might aspects of the Dutch referral system for suspected head and neck cancer possibly account for some of the differences in outcome between the two countries?

There is no formal screening system for oral cancer in England or, at the time of writing, anywhere else in the world (section 2.6.7). However, oral cancer is referred to specialist care by both primary care doctors and dentists. Individuals who attend a dentist regularly receive an inspection of the mouth including examination of the oral mucosa and therefore, effectively, a 'screen' for oral cancer. From this, the third question in this thesis arises. Do differences exist between oral cancer cases referred by primary care doctors and dentists including delay and stage on presentation? Furthermore, is there evidence that the 'informal screening' results in the diagnosis of some oral cancers at a pre-symptomatic stage, prior to developing 'red flag' signs and symptoms that might trigger an urgent referral?

This thesis focuses on the fast-track referral of oral cancer as a method of enhancing early diagnosis. However, there are many methods that might be used to achieve the same end, including population screening, public and professional education and focusing on high-risk individuals as well as 'broader' interventions such as addressing socio-economic inequalities (sections 1.2.6; 2.6.3; 2.6.4; 2.6.7). In a resource-limited environment, it seems logical to prioritise the various approaches. In particular, how

[2]Oral cancer is one type of 'head and neck cancer' all types having similar causes and close anatomical proximity (consider 'base of tongue' and 'oropharynx', for example) They are generally regarded as a group, require similar treatments and are usually referred to the same specialists. Hence this study looks at 'head and neck cancer referrals' which, of course, includes oral cancer.

important do experts consider an urgent referral system such as the TWR and the methods identified in this thesis, compared to other methods of encouraging early cancer diagnosis?

2.9 Aim and objectives

The overall aim of the thesis is to examine, in an evidence-based manner, the system for urgent referral of suspected oral cancer to specialist care, the 'two-week rule' (TWR), including evidence that led to its development and to undertake 4 studies that aim to shed light on important questions identified in the literature in relation to the urgent referral system for oral cancer in England.

The specific objectives are:

1. To evaluate the influence of the TWR system on stage on diagnosis of oral cancer in England.
2. To compare the English and Dutch systems for head and neck/oral cancer, focusing on the views of secondary care specialists in each country.
3. To compare oral cancer referrals from primary care doctors and dentists.
4. To prioritise the various methods of encouraging early oral cancer diagnosis, focusing on the priority of 'fast-track' systems (such as the TWR) compared to other methods.

2.10 Thesis structure and studies in relation to the objectives

Chapters 1 & 2

Introduction and literature review.

Chapter 3

Aim: To evaluate the influence of the TWR system on stage on diagnosis of oral cancer in England

Study: *'The impact of the 'two-week rule' on stage-on-diagnosis of oral cancer and the relationship to socio-economic inequalities'.* A retrospective 'time series' cohort study examining the stage on presentation of oral cancer from 1992 to 2012 (before and after the implementation of the TWR referral system) in a population of Merseyside patients.

Chapter 4

Aim: To compare the English and Dutch systems for head and neck/oral cancer, focusing on the views of secondary care specialists in each country

Study: *'Head and neck cancer referral in England and The Netherlands: an international qualitative study of secondary care surgical specialists' views'* A qualitative study exploring and comparing the views of two groups of head and neck cancer surgeons in England and The Netherlands on their respective head and neck cancer referral systems.

Chapter 5

Aim: To compare oral cancer referrals from primary care doctors and dentists

Study: *'A comparison of primary care doctors and dentists in the referral of oral cancer: a systematic literature review'* This study is a systematic review evaluating the differences between GPs' and dentists' referrals for oral cancer focusing on 3 outcomes: percentage of all cases referred by each profession, delay and stage on diagnosis.

Chapter 6

Aim: To prioritise the various methods of encouraging early oral cancer diagnosis, focusing on the priority of 'fast-track' systems - such as the TWR - compared to other methods

Study: '*Prioritisation of approaches to the early diagnosis of oral cancer: a Delphi study of UK experts'* This chapter is a Delphi study of UK experts in oral cancer with the aim of identifying how the various approaches to early oral cancer diagnosis might be prioritised.

Chapter 7

Discussion and conclusions

Chapter 2 references

Abdel-Rahman M, Stockton D, Rachet B (2009) *What if cancer survival in Britain was the same as in Europe: how many deaths are avoidable?* British Journal of Cancer 101 S115-S124

Abdel-Rahman ME, Butler J, Sydes MR et al (2014) *No socioeconomic inequalities in ovarian cancer survival within two randomised clinical trials* British Journal of Cancer 111 589-597

Abel GA, Friese CR, Magazu LS et al (2008) *Delays in referral and diagnosis for chronic haematological malignancies: a literature review* Leukaemia and Lymphoma 49 1352-1359

Afshar M, Goodfellow H, Jackson-Spence F et al (2017) *Centralisation of radical cystectomies for bladder cancer in England, a decade on from the 'Improving Outcomes Guidance': the case for super centralisation* British Journal of Urology International 121 217-224

Allemani C, Matsuda T, Di Carlo, V et al (2018) *Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries* The Lancet 391 1023-1075

Allgar VL and Neal RD (2005) *Delays in the diagnosis of six cancers: analysis of data from the National Survey of NHS Patients: Cancer* British Journal of Cancer 92 1959-1970

Allison P, Franco E, Black M et al (1998) *The role of professional diagnostic delays in the prognosis of upper aerodigestive tract carcinoma* Oral Oncology 34 147-153

Amir Z, Kwan SYL, Landes D et al (1999) *Diagnostic delays in head and neck cancers* European Journal of Cancer Care 8 198– 203

Andersen BL, Cacioppo JT, and Roberts DC (1995) *Delay in seeking a cancer diagnosis: delay stages and psychophysiological comparison processes* British Journal of Social Psychology 34 33–52

Araghi A, Harris Y and Kyzas P (2020) *An audit to analyse the two-week wait pathway at an oral cancer specialist district general hospital* British Dental Journal 228 693-699

Arnold M, Rutherford MJ, Bardot MJ, Ferlay J et al (2019) *Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study* Lancet Oncology 20 1493-1505

Auluck A, Walker BB, Hislop G et al (2016) *Socio-economic deprivation: a significant determinant affecting stage of oral cancer diagnosis and survival* BMC Cancer 16 569

Backemar L, Lagergren P, Johar A et al (2015) *Impact of co-morbidity on mortality after oesophageal cancer surgery* British Journal of Surgery 102 1097-1105

Baili P, Di Salvo P, Marcos-Gragers R et al (2015) *Age and case mix-standardised survival for all cancer patients in Europe 1999–2007: Results of EUROCARE-5, a population-based study* European Journal of Cancer 51 2120-2129

Bankhead CR, Kehoe ST and Austoker J (2005) *Symptoms associated with diagnosis of ovarian cancer: a systematic review* British Journal of Obstetrics and Gynaecoogy 112 857-865

Belcher RJ, Ruth K, Sigurdson ER et al (2016) *Time to surgery and breast cancer in the United States* JAMA Oncology 3 330-339

Beral V and Peto R (2010) *UK cancer survival statistics are misleading and make survival look worse than it is* British Medical Journal 2010;341:c4112

Berglund A, Holmberg L, Tishelman C (2010) *Social inequalities in non-small cell lung cancer management and survival: a population-based study in central Sweden* Thorax 65 327-333

Berrino F (2003) *The EUROCARE study: strengths, limitations and perspectives of population-based, comparative survival studies* Annals of Oncology 14 Sup 5 v9-v13

Berrino F and Gatta G (1998) *Variation in survival in patients with head and neck cancer by the site of origin of the tumours* European Journal of Cancer 34 2154-2161

Berrino F, Capocaccia R, Esteve J et al (1999) *Survival of cancer patients in Europe: the EUROCARE-2 study* IARC scientific publications no 151. International Agency for Research on Cancer, Lyon

Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T and Esteve J (1995) *Survival of Cancer Patients in Europe: The EUROCARE Study* IARC Scientific Publication No. 132, IARC: Lyon

Brouha X, Tromp D, Hordijk G et al (2005) *Oral and pharyngeal cancer patients: analysis of patient delay at different tumor stages* Head and Neck 27 939-945

Burton-Jeangros C, Cullati S, Manor O et al (2017) *Cervical cancer screening in Switzerland: cross-sectional trends (1992–2012) in social inequalities* European Journal of Public Health 27 167-173

Butler J, Foot C, Bomb M Hiom S Coleman M et al (2013) *The International Cancer Benchmarking Partnership: An international collaboration to inform cancer policy in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom* Health Policy 112 148-155

Cancer research UK (2019) *Understanding cancer screening* available at: https://www.cancerresearchuk.org/about-cancer/screening/understanding-cancer-screening (accessed August 2020)

Carter LM and Ogden GR (2007*) Oral cancer awareness of general medical and general dental practitioners* British Dental Journal DOI: 10.1038/bdj.2007.630

Chang IH, Jiang RS, Wong RK et al (2011) *Visual screening of oral cavity cancer in a male population: experience from a medical center* Journal of the Chinese Medical Association 74 561-566

Chen Z, King W, Pearcey R et al (2008) *The relationship between waiting time for radiotherapy and clinical outcomes: A systematic review of the literature* Radiotherapy and Oncology 87 3-16

Chen H, Zhou M, Tian W et al (2016) *Effect of age on breast cancer patient prognoses: a population-based study using the SEER 18 database* PLOS ONE 11 e165409

Childe CP (1906) *Control of a scourge or how cancer is curable* Methuen. London

Ciccolallo L, Capocaccia R, Coleman MP et al (2005) *Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery* Gut 54 268-273

Coleman MP, Babb P, Sloggett A (2001) *Socioeconomic inequalities in cancer survival in England and Wales* Cancer 91 (S1) 208-216

Coleman MP, Forman D, Bryant H, Butler J Rachet B et al (2011) *Cancer survival in Australian Canada, Denmark, Norway, Sweden and the UK 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population -based cancer registry data* Lancet 377 127-138

Commonwealth Fund (2020) *International Profiles of Health Care Systems* available at: https://www.commonwealthfund.org/international-health-policy-center/countries (accessed August 2020)

Coxon D, Campbell C Walter FM (2018) *The Aarhus statement on cancer diagnostic research: turning recommendations into new survey instruments* BMC Health Services Research 18 667

Crossman T *et al* (2016) *Role of general practice in the diagnosis of oral cancer* British Journal of Oral and Maxillofacial Surgery 54 208–212

Cullen J, Drabble D, Castellanos C and Brissett L (2014) *Recommendations for achieving a world-class radiotherapy service in the UK* available at: https://www.tavinstitute.org/wp-content/uploads/2014/05/Tavistock_Projects_Recommendations-for-achieving-a-world-class-radiotherapy-service-in-the-UK-.pdf (accessed August 2020)

Cutler SJ (Editor) (1964) *International symposium on the end results of cancer therapy* NCI monograph 15 Bethesda MD National Cancer Institute

Datta NR, Samiei M, Bodis S (2014) *Radiotherapy infrastructure and human resources in Europe – Present status and its implications for 2020* European Journal of Cancer 50 2735-2743

Davis C, Naci H, Gurpinar et al (2017) *Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13* British Medical Journal doi: 10.1136/bmj.j4530

De Angelis R, Sant M, Coleman MP, Franchisi S, Baili P et al (2014) *Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5 – a population-based study* The Lancet Oncology 15 23-34

Denton E and Conron M (2016) *Improving outcomes in lung cancer: the value of the multidisciplinary health care team* Journal of Multidisciplinary Healthcare 9 137-144

Department of Health (1995) *A policy framework for commissioning cancer services: a report by the Expert Group on Cancer to the Chief Medical Officers of England and Wales* available at: https://webarchive.nationalarchives.gov.uk/ (accessed August 2020)

Dimitroulis G, Reade P, Wiesenfield D (1992) *Referral patterns of patients with oral squamous cell carcinoma, Australia* European Journal of Cancer Part B: Oral Oncology 28 (1) 23-27

Din NU, Okoumunne OC, Rubin G et al (2015) *Age and gender variations in cancer diagnostic intervals in 15 cancers: analysis of data from the UK clinical practice datalink* PLoS ONE 10(5): e0127717

Doss JG, Ghani WMN, Razak IA et al (2017) *Changes in health-related quality of life of oral cancer patients treated with curative intent: experience of a developing country* International Journal of Oral and Maxillofacial Surgery 46 687-698

Eastman A, Tammaro Y, Moldrem A et al (2013) *Outcome of delays in time to treatment in triple negative breast cancer* Annals of Surgical Oncology 20 1880-1885

Eden M, Harrison S, Griffin M et al. *Impact of variation in cancer registration practice on observed international cancer survival differences between International Cancer Benchmarking Partnership (ICBP) jurisdictions* Cancer Epidemiology 58 184-192

Eguchi T, Baines S, Lee M et al (2017) *Impact of increasing age on cause-specific mortality and morbidity in patients with stage 1 non-small cell lung cancer: a competing risks analysis* Journal of Clinical Oncology 35 281-290

Elwood JM and Gallagher RP (1985) *Factors influencing early diagnosis of cancer of the oral cavity* Canadian Medical Association Journal 133 651-656

Elwood JM and Moorhead WP (1980) *Delay in diagnosis and long-term survival in breast cancer* British Medical Journal 280 1291-1294

Epstein JB and Huber MA (2015) *The benefit and risk of screening for oral potentially malignant epithelial lesions and squamous cell carcinoma* Oral Surgery Oral Medicine Oral Pathology Oral Radiology 120 537-540

Erridge SC, Murray B, Williams L et al (2009) *Improved survival from lung cancer in British Columbia compared to Scotland—Are different treatment rates the whole story?* Lung Cancer 64 358-366

European Society for Medical Oncology (2020) *ESMO magnitude of clinical benefit scale (ESMO-MCBS)* available at: https://www.esmo.org/guidelines/esmo-mcbs (accessed August 2020)

Extermann M (2007) *Interaction between comorbidity and cancer* Cancer Control 14 13-22

Fidler MM and Bray F (2018) *Global cancer inequalities* Frontiers in Oncology 8 293

Fleissig A, Jenkins V, Catt S and Fallowfield (2006) *Multidisciplinary teams in cancer care: are they effective in the UK?* Lancet Oncology 7 935-943

Fleming ST, Pursley HG, Newman B et al (2005) *Co-morbidity as a predictor of stage of illness foo patients with breast cancer* Medical Care 43 132-40

Foot C and Harrison T (2011) *How to improve cancer survival Explaining England's relatively poor rates* The King's Fund available at: https://www.kingsfund.org.uk/sites/default/files/How-to-improve-cancer-survival-Explaining-England-poor-rates-Kings-Fund-June-2011.pdf (accessed August 2020)

Foot C, Naylor C and Imison C (2010) *The quality of diagnosis and referral in general practice* available at: https://www.kingsfund.org.uk/sites/default/files/Diagnosis%20and%20referral.pdf (accessed August 2020)

Forbes LJL, Warburton F, Richards MA et al (2014) *Risk factors for delay in symptomatic presentation: a survey of cancer patients* British Journal of Cancer 111 582-588

Fredericksen BL, Osler M, Harling H et al (2009) *Do patient characteristics, disease, or treatment explain social inequality in survival from colorectal cancer?* Social Science and Medicine 69 1107-1115

Friedrich RE (2010) *Delay in diagnosis and referral patterns of 646 patients with oral and maxillofacial cancer: A report from a single institution in Hamburg, Germany* Anticancer Research 30 1833-1836

Gandini S, Botteri E, Iodice et al (2008) *Tobacco smoking and cancer: A meta-analysis* International Journal of Cancer 122 155-164

Ganly I, Nixon IJ Wang LY et al (2015) *Survival from differentiated thyroid cancer: what has age got to do with It?* Thyroid 25 1106-1116

Gatta G, Botta L Sánchez MJ (2015) *Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study* European Journal of Cancer 51 2130-2143

Gigliotti J, Madathi S and Makhoul N (2019) *Delays in oral cavity cancer* International Journal of Oral and Maxillofacial Surgery 48 1131-1137

Giovannucci E, Harlan DM, Archer MC et al (2010) *Diabetes and cancer: a consensus report* Diabetes Care 33 1674-1685

Gorsky M and Dayan D (1995) *Referral delay in diagnosis of oro/oropharyngeal cancer in Israel* European Journal of Cancer B Oral Oncol 31B 166– 168

Goy J, Hall SF, Feldman-Stewart D et al (2009) *Diagnostic delay and disease stage in head and neck cancer: A systematic review* Laryngoscope 119 889-898

Grafton-Clarke C, Chen K and Wilcock J (2018) *Diagnosis and referral delays in primary care for oral squamous cell cancer: a systematic review* British Journal of General Practice 69 e112-e126

Grant E, Silver K, Bauld L et al (2010) *The experiences of young oral cancer patients in Scotland: Symptom recognition and delays in seeking professional help* British Dental Journal 208 465-471

Greenwood M and Lowry RJ (2001) *Primary care clinicians' knowledge of oral cancer: a study of dentists and doctors in the North East of England* British Dental Journal 191 510-512

Grosso G, Bella F, Godos J et al (2017) *Possible role of diet in cancer: systematic review and multiple meta-analyses of dietary patterns, lifestyle factors, and cancer risk* Nutrition Reviews 75 405-419

Guggenheimer J, Verbin RS, Johnson JT et al (1989) *Factors underlying the delay of oral and oropharyngeal carcinomas* Cancer 64 932– 935

Gulati R, Wever EM, Tsodikov A et al (2012) *What if I don't treat my PSA-detected prostate cancer? Answers from three natural history models* Cancer Epidemiology, Biomarkers and Prevention 20 740-750

Hamilton W (2015) *NICE guideline for suspected cancer reduces referral threshold* Guidelines in Practice available at https://www.guidelinesinpractice.co.uk/cancer/nice-guideline-for-suspected-cancer-reduces-referral-threshold/352661.article (accessed August 2020)

Hansen RP, Vedted P, Sokolowski I et al (2011) *Time intervals from first symptom to treatment of cancer: a cohort study of 2,212 newly diagnosed cancer patients* BMC Health Services Research 11 284 291

Harris M, Vedsted P, Esteva M et al (2018) *Identifying important health system factors that influence primary care practitioners' referrals for cancer suspicion: a European cross-sectional survey* BMJ Open 2018;8:e022904. doi:10.1136/ bmjopen-2018-022904

Harrison JD, Choy ET, Spillane E et al (2008) *Australian breast cancer specialists' involvement in multidisciplinary treatment planning meetings* Breast 17 335-340

Hartmann M and Dröschel (2017) *Delays in access to new cancer medicines and unjustifiable price rises for old ones disadvantage patients unnecessarily* Available at: https://www.mpeurope.org/2017/01/28/delays-in-access-to-new-cancer-medicines-and-unjustifiable-price-rises-for-old-ones-disadvantage-patients-unnecessarily/ (accessed August 2020)

Hollows P, McAndrew PG and Perini MG (2000) *Delays in the referral and treatment of oral squamous cell carcinoma* British Dental Journal 188 262-265

Holm LV, Hansen DG, Larsen PV et al (2013) *Social inequality in cancer rehabilitation: A population-based cohort study* Acta Oncologica 52 410-422

Horowitz AM, Canto MT and Child WL (2002) *Maryland adults' perspectives on oral cancer prevention and early detection* Journal of the American Dental Association 133 1058-1063

Hutchison GB and Shapiro S (1968) *Lead Time Gained by Diagnostic Screening for Breast Cancer* Journal of the National Cancer Institute 41 665-681

Ibrahim EM & Al-Homaidh A (2011) *Physical activity and survival after breast cancer diagnosis: meta-analysis of published studies* Medical Oncology 28 753-765

Imperatori A, Harrison RN, Leitch DN et al (2006) *Lung cancer in Teesside (UK) and Varese (Italy): a comparison of management and survival Thorax* 61 232-239

Jones WG and Appleyard I (1985) *Delay in diagnosing testicular tumours* British Medical Journal (Clinical Research Edition) 290 1550

Jönsson B and Wiking N (2007) *A global comparison regarding patient access to cancer drugs* Annals of Oncology 18 Supp 3 p1-75

Jovanovic A, Kostense PJ, Schulten EAJM, Snow GB, Van Der Waal I (1992) *Delay in Diagnosis of Oral Squamous Cell Carcinoma; A Report from The Netherlands* European Journal of Cancer. Part B: Oral Oncology 28(1) 37-38

Jullien JA, Downer MC, Zakrzewska JM et al (1995) *Evaluation of a screening test for the early detection of oral cancer and precancer* Community Dental Health23 84-88

Kerdpon D and Sprilung H (2001) *Factors related to advanced stage oral squamous cell cancer in Southern Thailand* Oral Oncology 37 216-221

Kesson EM, Allardice GM, George WD et al (2012) *Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women* British Medical Journal doi: 344:e2718

Klisdonk MJ, Siesling S, van Dijk BAC et al (2018) *What drives centralisation in cancer care?* PLOS ONE 13 pp:e195673

Kowalski L Franco E Torloni H Fava A de Andrade Sobrinho J et al (1994) *Lateness of diagnosis of oral and oropharyngeal carcinoma: factors related to the tumour, the patient and health professionals* European Journal of Cancer Part B, Oral Oncology 30B (3) 167-173

Kumar S, Heller RF, Pandey U et al (2001) *Delay in presentation of oral cancer: a multifactor analytical study* National Medical Journal of India 14 13-17

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Linderborg K, Joly JP, Visapää JP (2008) *Potential mechanism for Calvados-related oesophageal cancer* Food and Chemical Toxicology 46 476-479

Lopez-Cedrun JL, Otero-Rico A, Vázquez-Mahia I et al (2019) *Association between hospital interval and survival in patients with oral cancer: a waiting time paradox* PLoS ONE 14(10) e224067

Lowry RJ and Craven MA (1999) *Smokers' and drinkers' awareness of oral cancer: a qualitative study using focus groups* British Dental Journal 187 668-670

Lyratzopoulos G, Wardle J and Rubin G (2014) *Rethinking diagnostic delay in cancer: how difficult is the diagnosis?* British Medical Journal doi: 349:g7400

Macarthur C and Smith A (1983) *Delay in the diagnosis of colorectal* cancer British Journal of General Practice 33 159-161

Macpherson LMD, McCann MF, Gibson J et al (2003) *The role of primary healthcare professionals in oral cancer prevention and detection* British Dental Journal 195 277-281

Macleod U, Mitchell ED, Burgess C et al (2009) *Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers* British Journal of Cancer 101 S92-S101

Majano SB, Di Girolamo C, Rachet B et al (2019) *Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study* Lancet Oncology 20 74-87

Mashberg A, Merletti F. Boffetta P et al (1989) *Appearance, site of occurrence, and physical and clinical characteristics of oral carcinoma in Torino Italy* Cancer 63 2522– 2527

McGurk M, Chan C, Jones J et al (2005) *Delay in diagnosis and its effect on outcome in head and neck cancer* British Journal of Oral and Maxillofacial Surgery 43 281-284

McPhail, Johnson S Greenberg D et al (2015) *Stage at diagnosis and early mortality in England* British Journal of Cancer 112 S108-S115

Meskin LH (1994) *Oral cancer the forgotten disease* Journal of the American Dental Association DOI:https://doi.org/10.14219/jada.archive.1994.0125

Minicozzi P, Innos K, Sánchez MJ et al (2017) *Quality analysis of population-based information on cancer stage at diagnosis across Europe, with presentation of stage-specific cancer survival estimates: A EUROCARE-5 study* European Journal of Cancer 84 335-353

Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C et al (2017) *Trends and patterns of disparities in cancer mortality among US counties, 1980-2014* Journal of the American Medical Association 317 388-406

Møller H, Liknlater KM and Robinson D (2009) *A visual summary of the EUROCARE-4 results: a UK perspective* British Journal of Cancer 101 S110-S114

Monteiro LS, Salazar F, Pacheco J (2012) *Oral Cancer Awareness and Knowledge in the City of Valongo, Portugal* https://doi.org/10.1155/2012/376838

Moore SC, Lee I, Weiderpass E et al (2016) *Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults* Journal of American Medical Association Internal Medicine 176 916-825

Morelatto RA, Herrera MC, Fernandez EN et al (2007) *Diagnostic delay of oral squamous cell carcinoma in two diagnosis centers in Cordoba, Argentina* Journal of Oral Pathology and Medicine 36 405-408

Morini M, Muller RL, de Castro Junior PCB et al (2018) *Time between diagnosis and surgical treatment on pathological and clinical outcomes in prostate cancer: does it matter?* World Journal of Urology 36 1225-1231

Morrison AS, Lowe RC, Macmahon B et al (1976). *Some international differences in treatment and survival in breast cancer* International journal of cancer 18. 269-73

Moyer VA (2014) *Screening for oral cancer: US preventative services task force recommendation statement* Annals of Internal Medicine 160 55–60.

Mujar M, Dahlui M and Yip CH (2013) *Delays in time to primary treatment after a diagnosis of breast cancer: does it impact survival?* Preventive Medicine 56 222-224

Munro A, Brown M, Niblock P et al (2015) *Do Multidisciplinary Team (MDT) processes influence survival in patients with colorectal cancer? A population-based experience* BMC Cancer 15:686

Munro AJ (2014[a]) *Interpretation of EUROCARE-5* Lancet Oncology 15 2-3

Munro AJ (2014[b]) *Comparative cancer survival in European countries* British Medical Bulletin 110 5-22

Napier SS and Speight PM (2008) *Natural history of potentially malignant oral lesions and conditions: an overview of the literature* Journal of Oral Pathology and Medicine 37 1-10

National Cancer Intelligence Network (2013) *Oral Cavity Cancer: recent survival trends* available at: http://www.ncin.org.uk/publications/data_briefings/oral_cavity_cancer_recent_survival_trends (accessed August 2020)

Murphy CT, Galloway TJ, Handorf EA et al (2016) *Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States* Journal of Clinical Oncology 24 169-178

Myklebust TA, Andersson T, Bardot A et al (2020) *Can different definitions of date of cancer incidence explain observed international variation in cancer survival? An ICBP SURVMARK-2 study* Cancer Epidemiology 67:101759

Neal RD (2009) *Do diagnostic delays in cancer matter?* British Journal of Cancer 109 S9-S12

Neal RD, Tharmanathan P, France B et al (2015) *Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review* British Journal of Cancer 112 S92-S107

Netuveli G, Sheiham A and Watt RG (2006) *Does the "inverse screening law" apply to oral cancer screening and regular dental check-ups?* Journal of Medical Screening 13 47-50

NHS (2009) *Cancer survival rates* available at: https://www.nhs.uk/news/genetics-and-stem-cells/cancer-survival-rates/ (accessed August 2020)

NHS (2013) *UK cancer survival rates below European average* available at: https://www.nhs.uk/news/cancer/uk-cancer-survival-rates-below-european-average/ (Accessed August 2020)

Nicholson BD, Mant D and Bankhead C (2016[a]) *Can safety-netting improve cancer detection in patients with vague symptoms?* British Medical Journal British Medical Journal doi: 355:i5515

Nicholson BD, Mant D, Neal RD et al (2016[b]) *International variation in adherence to referral guidelines for suspected cancer: a secondary analysis of survey data* British Journal of General Practice 66 e1061113

Nur U, Rachet B and Parmar MKB (2008) *No socioeconomic inequalities in colorectal cancer survival within a randomised clinical trial* British Journal of Cancer 99 1923-1928

Office for National Statistics (2019) *Cancer survival in England: national estimates for patients followed up to 2017* available at: ons.gov.uk/releases/cancersurvivalinenglandadultstageatdiagnosisandchildhoodpatientsfollowedupto2017 (accessed August 2020)

Oke J and Fanshawe T (2020) *Cancer statistics A survival guide* https://doi.org/10.1111/j.1740-9713.2020.01355.x

Olesen F, Hansen RP and Vedsted P (2009) *Delay in diagnosis: the experience in Denmark* British Journal of Cancer 101 (supp. 2) S5-S8

Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T et al (2003) *Factors associated with diagnostic delay of oral squamous cell carcinoma* Oral Oncology 39 781-788

Papas RK, Logan HL and Tomar SL (2004) *Effectiveness of a community-based oral cancer awareness campaign (United States)* Cancer Causes and Control 15 121-1311

Parikh S, Brennan P and Boffetta P (2003) *Meta-analysis of social inequality and the risk of cervical cancer* International Journal of Cancer 105 687-691

Patel UA and Brennan TE (2012) *Disparities in head and neck cancer: assessing delay in treatment initiation* Laryngoscope 122 1756-1760

Patton LL, Epstein JB and Kerr AR (2008) *Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature* Journal of the American Dental Association 139 896-905

Peacock ZS, Pogrel AM, and Schmidt BL (2008) *Exploring the Reasons for Delay in Treatment of Oral Cancer* Journal of the American Dental Association 139 1346-1352

Petti S and Scully C (2006) *Oral cancer knowledge and awareness: Primary and secondary effects of an information leaflet* Oral Oncology 43 408-415

Pitiphat W, Diehl SR, Laskaris, G et al (2002) *Factors associated with delay in the diagnosis of oral cancer* Journal of Dental Research 81 192– 197

Prades J, Remue E, van Hoof E et al (2015) *Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes* Health Policy 119 464-474

Praud D, Rota M, Rehm J et al (2015) *Cancer incidence and mortality attributable to alcohol consumption* International Journal of Cancer 138 1380-1387

Pruitt SL, Harzke AJ, Davidson NO et al (2013) *Do diagnostic and treatment delays for colorectal cancer increase risk of death?* Cancer Causes Control 24 961-977

Rahman RA, Moriarty M, McVey G et al (2018) *Outcome following centralisation of pancreatic cancer care in Ireland* Annals of Oncology 29 Sup 8 253

Reddy BS, Doshi D, Reddy MP et al (2012) *Oral cancer awareness and knowledge among dental patients in South India* Journal of Cranio-Maxillofacial Surgery 40 521-524

Richards MA (1999) *The influence on survival of delay in the presentation and treatment of symptomatic breast cancer* British Journal of Cancer 79 858-864

Richards MA (2009) *The size of the prize for earlier diagnosis of cancer in England* British Journal of Cancer 101 S125-S129

Richards MA (2010) *Extent and causes of international variation in drug usage* available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/216249/dh_117977.pdf (accessed August 2020)

Rogers S, Pabla R, McSorley A, Lowe D, Brown J et al (2007) *An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma* Oral Oncology 43 648-655

Rogers SN, Brown JS, Woolgar JA (2009) *Survival following primary surgery for oral cancer* Oral Oncology 34 147-153

Rogers SN, Hunter R and Lowe D (2011) *Awareness of oral cancer in the Mersey region* British Journal of Oral and Maxillofacial Surgery 49 176-181

Roland CL, Schwarz RE, Tong L et al (2013) *Is timing to delivery of treatment a reliable measure of quality of care for patients with colorectal adenocarcinoma?* Surgery 154 421-428

Rose PW, Rubin G, Perera-Salazar R et al (2015) *Explaining variation in cancer survival between 11 jurisdictions in the International Cancer Benchmarking Partnership: a primary care vignette study* British Medical Journal Open 5: e007212

Safer MA, Thraps Q, Jackson TC et al (1979) *Determinants of three stages of delay in seeking care at a medical clinic* Medical Care 17 11-29

Sakakibara A, Matsui K, Katayama T et al (2019) *Age-related survival disparity in stage IB and IIB cervical cancer patients* Journal of Obstetrics and Gynaecology Research 45 686-694

Samson P, O'Grady G and Keating J (2009) *An international comparison study of stage of colorectal cancer at diagnosis: How does New Zealand compare*? New Zealand Medical Journal 122 74-83

Sankaranarayanan R, Ramadas K, Thara S et al (2013) Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India Oral Oncology 49 314-321

Sant M & Gatta G (1995) *Survival of Cancer Patients in Europe: The EUROCARE Study* IARC Scientific Publication No. 132, IARC: Lyon

Sant M, Aareleid F, Berrino F, Bielska Lasota M, Carli PM et al (2003) *EUROCARE-3 survival of cancer patients diagnosed 1990-1994 – results and commentary* Annals of Oncology 14 61-118

Sant M, Allemani C, Santaquilani M, Arnold Knijn, Marchesi F and Capocaccia R (2009) *EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary* European Journal of Cancer 45 931-991

Sarfati D, Koczwara B and Jackson C (2016) *The impact of comorbidity on cancer and its treatment* CA: A Cancer Journal for Clinicians 66 337-350

Schorr M, Carlson LE, Lau HY et al (2017) *Distress levels in patients with oropharyngeal vs. non-oropharyngeal squamous cell carcinomas of the head and neck over 1 year after diagnosis: a retrospective cohort study* Supportive Care in Cancer 25 3225-3223

Scott, SE Grunfeld, EA and McGurk M (2005) *The idiosyncratic relationship between diagnostic delay and stage of oral cell carcinoma* Oral Oncology 41 396– 403

Scully C, Malmos D, Levers BG, Porter SR and Prime SS (1986) *Sources and patterns of referrals of oral cancer: role of general practitioners* British Medical Journal 293 599-601

Seoane J, Alvarez-Novoa P, Gomez I et al (2016) *Early oral cancer diagnosis: The Aarhus statement perspective. A systematic review and meta-analysis* Head and Neck 38 E2182-E2189

Seoane J, Pira-Fernandez A, Gomez I et al 2010 *Proliferative activity and diagnostic delay in oral cancer* Head and Neck 32 1377-1384

Seoane J, Takkouche B, Varella-Centelles P et al (2012) *Impact of delay on survival to head and neck cancers: a systematic review and meta-analysis* Clinical Otolaryngology 37 99-106

Seoane-Romero JM, Vazquez-Mahia I, Varella-Centelles P et al (2012) *Factors related to late stage diagnosis of oral squamous cell carcinoma* Medicina Oral Patologia Oral y Cirugia Bucal 17 e35-e40

Shafer WG (1975) *Initial mismanagement and delay in oral cancer* Journal of the American Dental Association 90 1262-1264

Speight PM, Epstein J, Kujan O et al (2017) *Screening for oral cancer - a perspective from the Global Oral Cancer Forum* Oral and Maxillofacial Pathology 123 680-687

Stahl B, Meskin LH and Brown LJ (2004) *The American Dental Association's oral cancer campaign: the impact on consumers and dentists* Journal of the American Dental Association 135 1261-1267

Stefanuto P, Doucet JC and Robertson C (2014) *Delays in treatment of oral cancer: a review of the current literature* Oral and Maxillofacial Surgery 117 424-429

Swann R, McPhail S, Witt J et al (2018) *Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit* British Journal of General Practice 68 (666): e63-e72.

Taaffe D (2018) *Exercise and survival after a cancer diagnosis; the evidence so far* Journal of Science and Medicine in Sport 21S S73

Teppo H and Alho OP (2008) *Relative importance of diagnostic delays in different head and neck cancers* Clinical Otolaryngology 33 325-330

Terret C, Castel-Kremer E, Albrand G et al (2009) *Effects of comorbidity on screening and early diagnosis of cancer in the elderly* Lancet Oncology 10 80-87

Thomson CS and Forman D (2009) *Cancer survival in England and the influence of early diagnosis: what can we learn from recent EUROCARE results?* British Journal of Cancer 101 S102-S109

Tørring ML, Frydenberg M Hansen RP et al (2011) *Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care* British Journal of Cancer 104 934-940

Tørring ML, Falborg AZ, Jensen H et al (2019) *Advanced-stage cancer and time to diagnosis: An International Cancer Benchmarking Parnership (ICBP) cross-sectional study* European Journal of Cancer Care 2019;28:e13100.

van Harten MC, de Ridder M, Hamming-Vrieze O et al (2014) *The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center* Oral Oncology 50 282-290

van Harten MC, Hoebers FJ, Kross KW et al (2015) *Determinants of treatment waiting times in the Netherlands and their relation to survival* Oral Oncology 52 272-278

van Rijsingen MJC, van Bon B, van der Wilt GJ et al (2014) *The current and future role of general practitioners in skin cancer care: an assessment of 268 general practitioners* British journal of Dermatology 170 1366-1368

Varela-Centelles P, López-Cedrún JL, Fernández-Sanromán J et al (2017) *Key points and time intervals for early diagnosis in symptomatic oral cancer: a systematic review* International Journal of Oral and Maxillofacial Surgery 46 1-10

Walsh S, Bruce C, Bennington S, Ravi S (2002) *The fourteen-day rule and colorectal cancer* Annals of the Royal College of Surgeons of England 84 386-388

Walter F, Webster A, Scott S et al (2012) *The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis* Journal of Health Services Research 17 110-118

Walters S, Benitez-Majano S, Muller P, Coleman MP et al (2015) *Is England closing the international gap in cancer survival?* British Journal of Cancer 113 848-860

Walters S, Maringe C, Butler J et al (2012) *Comparability of stage data in cancer registries in six countries: Lessons from the International Cancer Benchmarking Partnership* International Journal of Cancer 132 676-685

Walters S, Maringe C, Coleman MP et al (2013) *Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007* Thorax 68 551-564

Warnakulasuriya KAAS, Harris CK, Scarrott DM et al (1999) *An alarming lack of public awareness towards oral cancer* British Dental Journal 187 319-322

Warnakulasuriya S, Johnson NW, van der Waal I (2007) *Nomenclature and classification of potentially malignant disorders of the oral mucosa* Journal of Oral pathology and Medicine 36 575-580

Warnakulasuriya S, Fennell N, Diz P et al (2015) An *appraisal of oral cancer and pre-cancer screening programmes in Europe: a systematic review* Journal of Oral Pathology and Medicine 44 559-570

Welch NG and Black WC (2010) *Overdiagnosis in cancer* Journal of the National Cancer Institute 102 605-613

Weller D, Vedsted P, Rubin G et al (2012) *The Aarhus statement: improving design and reporting of studies on early cancer diagnosis* British Journal of Cancer 106 1262-1267

West R, Alkhatib MN, McNeill A et al (2006) *Awareness of mouth cancer in Great Britain* British Dental Journal 200 167-16

Wildt J, Bundgaard T, Bentzen SM (1995) *Delay in the diagnosis of oral squamous cell carcinoma* Clinical Otolaryngology 20 21-15

Wilking N and Jönsson B (2005) *A pan-European comparison regarding patient accesss to cancer drugs* Stockholm: Karolinska Instituet and Stockholm School of Economics

Wilkinson E (2009) *Questions remain over validity of EUROCARE* data Lancet 374 964-965

Willyard C (2007) *Karolinska Institute under fire for controversial report* Nature Medicine 13 1124

Woods LM, Coleman MP, Lawrence G, Rashbass J et al (2011) *Evidence against the proposition that 'UK cancer statistics are misleading': simulation study with Cancer Registry data* British Medical Journal doi: 342:d3399

Woods LM, Rachet B, and Coleman LP (2006) *Origins of socio-economic inequalities in cancer survival: a review Annals* of Oncology 17 5-19

World Health Organisation (2017) *Guide to early cancer diagnosis* available at: https://www.who.int/cancer/publications/cancer_early_diagnosis/en/ (accessed August 2020)

Wright GP, Wong JH, Morgan JW et al (2010) *Time from diagnosis to surgical treatment of breast cancer: factors influencing delays in initiating treatment* American Surgeon 76 1119-1122

Yu T, Wood RE and Tenenbaum HC (2008) *Delays in diagnosis of head and neck cancers* Journal of Canadian Dental Association 74 61

CHAPTER 3: The impact of the 'two-week rule' on stage-at-diagnosis of oral cancer and the relationship to socio-economic inequalities

3.1 Abstract

Background

The 'two-week rule' (TWR) fast-track cancer referral system for head and neck cancers was introduced by the UK government in 2000 to facilitate earlier diagnosis. However, little work has compared stage on diagnosis of cancer before and after the implementation of the system.

Objectives

(1) Describe the presentation of oral cancer in Merseyside from 1992-2012.
(2) To evaluate whether stage on presentation has improved after the introduction of the TWR using data from a clinical database in Merseyside 1992-2012.
(3) To assess the relationship between stage on presentation and social deprivation 1992-2012.
(4) To assess the change in presentation for different sites within the oral cavity.

Method and setting

Patients were identified using the Aintree (Liverpool) head and neck oncology database, containing all diagnoses of oral squamous cell carcinoma (SCC) between 1992 – 2012. Cancers were clinically staged using the American Joint Committee on Cancer (AJCC) stage groupings and divided into 'early' (stage 1 and 2) and 'late' (stage 3 and 4). Index of Multiple Deprivation (IMD) 2004 data were derived from patient postcodes. 'Joinpoint' regression analysis software was used to identify statistically significant change in trend in presentation of 'late' oral cancers overall and in relation to socio-economic deprivation. Further regression analysis was undertaken to identify the association of other factors with late-stage presentation.

Results

1483 consecutive oral cancer patients were studied. Median (IQR) age was 63 (55-73) years and 61% were male. 36% of cancers were located on anterior 2/3rds tongue, 30% floor of mouth, and 34% elsewhere.

'Late' tumour presentation was 52% (95% CI 46.8 to 56.4%) for 1992-2000, and 44% (95% CI 41.4 to 47.5%) for 2001-2012 (P=0.01). Joinpoint regression analysis of 'late' presentation indicated a steady fall 1992-2012, at an annual percentage decrease of 1.27% (95% CI -2.3 to -0.2). No statistically significant change in trend was identified either overall or within deprivation groups following the TWR.

For patients in 'more deprived' neighbourhoods, 'late' tumour presentation was: 56% and 47%; in 'less deprived' areas: 48% and 42%, before and after the introduction of the TWR, respectively.

Year of diagnosis, tumour site and IMD2004 were significantly associated with 'late' presentation, and location of tumour was also associated with time period and IMD2004.

Main conclusions

Stage on presentation improved between 1992-2012 but Joinpoint analysis showed no significant change in trend following the introduction of the TWR. The rate of improvement was highest for most deprived; nevertheless, socio-economic inequalities still exist and this should be a focus of further initiatives and research.

3.2 Background

This chapter presents a study that aims, primarily, to answer one of the most fundamental questions in relation to the English two-week rule (TWR) and associated guidance system for oral cancer: has the system resulted in an earlier stage on diagnosis?

Much of the background to this study, including the influence of stage on outcome, the development of the urgent suspected cancer system and its known effectiveness have been discussed in some detail in previous chapters. To avoid unnecessary repetition, these aspects are described in this section in outline only.

Evidence from the EUROCARE studies (Gatta et al 2015), over a period of 20 years, has shown UK outcomes for some cancers, including oral cancer, have been worse than the best in Europe and further work confirms that the relatively poor outcomes are probably 'genuine' (Hamilton 2012).

For oral cancer, late presentation is likely to be an important cause of such outcomes in England; for head and neck cancer, including oral cancer, UK 5-year conditional (on surviving 1 year) survival rates compare well with the best in Europe, yet 1-year survival rates are still worse than in several European countries.

As discussed in detail in earlier chapters, the government response to early reports of poor cancer outcomes was the 2000 Cancer Plan, which included measures to encourage early cancer diagnosis. One 'cornerstone' of policy was the 'two-week rule' (TWR) fast-track referral system which specifies a maximum of 14 days from GP referral to specialist evaluation for suspected cancer.

However, Harrison and Foot (2012) observe: *'for the two-week rule to be effective……the stage at which patients were identified should have fallen since its introduction'*. Much published research has focused on the process of cancer referral via the TWR (Langton et al 2016) but there is relatively little evidence, for all cancer types, on whether the introduction of the TWR and NICE associated guidance has resulted in cancer cases presenting at an earlier stage.

Data on oral cancer from the National Cancer Registration and Analysis Service (NCRAS) indicate that between 2006 and 2013 there was little difference in 1-year survival between TWR referrals and other 'routine' referrals (77% vs 78%), but emergency presentation survival was considerably worse (44%). During the same period, 34% of cases presented via the TWR system whilst 6% presented as emergencies. The proportion of oral cancers presenting via the TWR also steadily increased from 24% in 2006 to 33% in 2012 (National Cancer Intelligence Network 2013). However, for oral cancer there is a paucity of evidence on whether the TWR has been effective in improving outcomes or resulting in earlier diagnosis of disease (Langton 2016).

3.3 Aim and Objectives

The overall aim of this study is to assess the impact of the UK fast-track referral system on stage on the diagnosis of oral cancer. The study also examines changes in relation to socio-economic deprivation, bearing in mind that a key UK government health focus is the relationship of social inequalities and cancer (Cancer Research UK 2006; Department of Health 2011). Socio-economic differences in survival from head and neck cancers are among the largest of any malignancies (Robertson and Greenlaw 2010). Oral cancer has a well-established link to social deprivation and is known to have both increased incidence and poorer outcome for the more socially deprived (Thorne et al 1998). In view of the differences in causes of oral cancer at different intra-oral sites described in section 1.4.4, analysis in relation to various oral sites was also undertaken.

The specific objectives of this study are:

(1) Describe the presentation of oral cancer, by stage, in Merseyside from 1992-2012.

(2) Evaluate the stage on presentation of oral cancers in Merseyside from 1992 to 2012, comparing the periods before and after the introduction of the TWR and NICE guidance in 2000.

(3) Study the relationship of stage on presentation to social deprivation from 1992 to 2012, comparing the periods before and after the introduction of the TWR in 2000.

(4) Examine the changes in stage on presentation in relation to different intra-oral sites.

3.4 Methods

3.4.1 Choice of study design

Several designs of study can potentially be used for evaluation of guideline strategies. These include randomised trials, 'quasi-experimental' designs, including uncontrolled and controlled before-after studies and time-series studies and, rarely, observational studies (Grimshaw et al 2000; Eccles et al 2003).

Randomised designs are considered the 'gold standard' method of evaluating healthcare interventions and allow confounders to be distributed evenly between the intervention and control groups. The arguments supporting randomised designs for the evaluation of clinical interventions are considered at least as strong when applied to guideline strategies and policies (Eccles 2003); indeed, given the complexity and number of potential confounding factors associated with organisational performance, it is not easy to adjust for such factors in non-randomised designs.

However, for this study there were obvious practical barriers to the development of a randomised trial; the 'two-week rule/NICE guidance system' is a national policy, in place for 20 years. For this reason, a non-randomised method was used. Three such 'quasi-experimental' designs are commonly used and include uncontrolled before-after studies, controlled before-after studies and time-series designs (Eccles et al 2003). Uncontrolled before-after studies measure performance before and after an intervention and are simple to conduct but are considered a relatively weak design as it is difficult to attribute change in outcome with the intervention; the results of such studies do, therefore, need to be interpreted with caution (Eccles et al 2003). Controlled before-after studies include a control group in addition to the intervention group; the groups are compared before and after the intervention and observed differences are assumed to be caused by the intervention. However, this design was not practical for this study for obvious reasons.

Therefore, the time-series design was chosen. Such a design aims to determine whether an intervention causes an effect significantly different to the 'underlying' trend. Time-series designs increase the confidence that the effect is caused by the intervention and are typically used when control groups are

impossible to identify (Grimshaw 2000). However, such designs are not perfect and may be influenced by confounders occurring at the same time as the intervention. For example, in this study the 2000 Cancer Plan could arguably have increased patient awareness and hence earlier presentation, although it is known that patient awareness of oral cancer has been poor in the past and remains poor (Macpherson 2018). One important aspect of this design is to have sufficient data points to establish the pre-intervention trend. For this study, data on stage on diagnosis for oral cancer pre-intervention were available from 1992 to 1999, providing less points than some consider ideal - Crabtree (1990) suggests 20 - although it was considered that comprehensive data on oral cancer presentation stage were very unlikely to be easily available before 1992.

3.4.2 Patient and public involvement (PPI)

As part of developing this study, a formal presentation, using lay language, was made to a patient involvement group at the Churchill Hospital, Oxford, followed by a discussion, comments and questions. The study received the support of the participants who felt that this evaluation of current health policy on cancer was useful and potentially of benefit to future patients.

3.4.3 Ethics

No formal ethical approval was required for this study, as the data were collected as part of 'routine' care. This was confirmed by the Medical Sciences Inter-Divisional Research Ethics Committee of the University of Oxford on 25th January 2017.

3.4.4 Data source

Obtaining stage-on-presentation data for oral cancer over the years presented a challenge. The following sections discuss the possible sources of staging data that were considered and the reason for the choice of the Merseyside database for this study.

3.4.4.1 Databases of cancer staging - historical

Computerised cancer databases were relatively rare until the early 1990s; the National Cancer Data Base (NCDB) in the USA was established in 1989 (Cooper et al, 2009). In the UK, even in the 1990s,

computerised cancer databases were still considered innovative and were usually developed and maintained by interested clinicians at local level (Worrell and Corrigan, 1995). Therefore, there are few sources of UK data that describe stage on presentation of any cancers prior to the inception of the TWR.

3.4.4.2 National data

In 2012, the seventh annual report of the UK *National Head and Neck Cancer Audit* was published (Health and Social Care Information, 2012). Within this extensive report, the proportion of cases where staging was recorded is noted, by Trust. Nationally, the mean proportion of cases where this staging was recorded was 81% with a range of 0% to 100% between providers. 37 Trusts provided staging data on less than 60% of cases. Interestingly, the document comments:

'Recording cancer site and accurate stage is a key medical responsibility, with best practice suggesting that this should be clearly documented and captured at the MDT[3]*. Staging remains a key influence on outcome. It is important that this improves to achieve 100 per cent of cases staged, to allow valid comparisons to be made'*

However, given the quality of these data on staging it was evident that some improvements were required before valid comparisons could be made.

3.4.4.3 Database for Head and Neck Oncology (DAHNO) and head and neck audit (HANA) data

National staging data were included in the UK DAHNO database (DAHNO 2015). The first report was produced in 2004-2005, the database existed until 2014 and the final report was produced in October 2015. An updated database – Head and Neck Audit (HANA 2017) - was established in 2015 with NHS England funding, with the aim of completing the first data collection by October 2016.

At an early stage in the planning of this thesis, an application was made to DAHNO for access to their data and initially this was formally agreed by the organisation responsible. However, despite repeated attempts at contact, and many reassurances, no data were received. However, there are considerable deficiencies in these data with, in the penultimate national report of 2015, unknown T staging in 9.7%

[3] Multidisciplinary team (hospital meeting for formal discussion of cancer cases)

and unknown N staging in 9.2% (DAHNO, 2015). Indeed, the British Association of Head and Neck Oncologists' (BAHNO) report on the HANA database (2017) notes:

'Previous DAHNO improved year-on-year but had several organizational flaws mainly related to technology and a lack of flexibility and user friendliness. Also, historically, DAHNO focused on process and management'.

Furthermore, DAHNO does not include staging data prior to the inception of the TWR in 2000, making comparisons before and after the TWR impossible.

3.4.4.4 Aintree Hospitals (Liverpool, Merseyside) head and neck cancer database

A few enthusiastic clinicians have maintained, for many years, accurate databases of head and neck cancer treated in their units (Worrell and Corrigan, 1995). One such example is the Merseyside Regional Head and Neck Cancer unit. Since 1992, patients diagnosed and treated for head and neck cancer have been entered into this database which contains comprehensive and accurate, validated information. This database was one of the first computerised databases of head and neck cancer in the UK (Rogers et al, 2009) and therefore is one of the few resources containing accurate data on presentation stage for several years prior to the inception of the UK TWR in 2000 and for the years following its introduction. The Aintree database has been in regular use since 1992 and includes data on presentation, treatment, outcome for oral cancers including surgical data and records of complications. The database is maintained with regular validation checks for completeness and accuracy of information (Brown et al 2006). The database has been utilised in several previous publications since its inception (Brown et al 1999; Brown et al 2003; Rogers et al 2009; Shaw 2009). Therefore, this was considered a well-curated database of consecutive patients that avoids selection bias.

An approach was made to Professor Simon Rogers, Consultant Maxillofacial Surgeon Liverpool and Professor, Evidence-based Practice Research Centre, Edge Hill University who kindly agreed to share data from the Merseyside database and work co-operatively on this study.The data included TNM staging using the American Joint Committee on Cancer (AJCC) standards (see table 1.1).

3.4.5 Staging data for this study

Cancers were classified into group stages 1 to 4 using staging following clinical examination and CT/MRI scanning. One disadvantage of such 'clinical staging' is that a small percentage of apparently N_0 (node negative) cases will, following neck dissection surgical treatment and laboratory examination of surgical specimens, demonstrate lymph nodes positive for cancer. However, if 'pathological' staging is used patients treated with radiotherapy alone do not provide a neck specimen for pathological examination and hence their neck pathology remains unknown. In short, both 'clinical' and 'pathological' staging have disadvantages in a study of this type. For consistency, clinical staging was employed. Cases were further classified as (a) *'early'* presentations, comprising stage 1 and 2 cases and (b) *'late'* presentations, comprising stage 3 and 4 cases. 'Early' and 'late' categories have been utilised in much previous work on oral cancer (Scott et al 2005; Jehannin-Ligier et al 2017) the rationale being the marked difference not only in survival but also in treatment requirements and treatment-related morbidity.

3.4.6 Socio-economic deprivation data

Patient postcode was used to obtain Index of Multiple Deprivation (IMD) data. The overall IMD is an area level aggregation of several specific aspects of deprivation and the official measure of relative deprivation for small areas of England. Each small area is known as a 'lower layer super output area' (LSOA) and typically includes approximately 1000 households. Following discussion between all involved in the study it was decided to use IMD 2004 (Ministry of Housing, Communities and Local Government 2019) as it incorporated data indicators relating to 2001, a year close to the centre of the period studied. The IMD 2004 consists of seven weighted domains (weight %):

1. Income deprivation (22.5%)
2. Employment deprivation (22.5%)
3. Health deprivation and disability (13.5%)
4. Education skills and training deprivation (13.5%)
5. Barriers to housing and services (9.3%)

6. Living environment deprivation (9.3%)
7. Crime (9.3%)

Each domain contains several indicators. For example, 'income deprivation' includes assessments of income support households, job-seekers allowance households, tax credit households, disabled persons' tax credit households and national asylum seekers' households. The domains are weighted according to relative importance, weights being determined by *'a consultation process and the wider academic literature'* (Office of the Deputy Prime Minister 2004) and are subsequently combined to give a ranking for deprivation. It should be borne in mind that a *higher* IMD index value represents *less* deprivation – each small area in England is ranked from 1 (most deprived) to 32,844 (least deprived).

Patient postcodes came from an amalgam of sources, mainly from datasets used for other studies including the years relevant to this study. Checks were made against patient postcode using available electronic records relevant to the time the patient first presented. Specifically, the records for patients presenting in the two years of 1997 and 2003 were checked and for 84% and 90% of patients respectively their postcode was from the time they first presented.

3.4.7 Analyses

To identify change in the stage-on-presentation trend, particularly following the introduction of the TWR, 'Joinpoint' Regression Program version 4.6.0.0 (Surveillance Research Program of the National Cancer Institute, Calverton, USA, 2018), was used to calculate the best-fitting line through the years of data.

'Joinpoint' employs an algorithm to determine whether a multiple-segmented line fits better than a straight line. Each line is connected by an aptly named 'joinpoint' which indicates a statistically significant ($p<0.05$) change in trend. The test of significance uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series.

An alternative approach to analysis of longitudinal data – considered but not used in this study – is the interrupted time series (ITS) method described by Kontopantelis et al 2015. These authors define 3 approaches to the method: 'basic', 'advanced' and 'expert'. In its most basic form, ITS regression

simply describes the pre-intervention slope, the change in level at the intervention point and the slope following the intervention. More complex models evaluate aspects such as changes in relation to population characteristics and predictions of the outcome had the intervention not taken place.

However, a decision was made to use 'Joinpoint' for the following reasons:

- A well-established method of analysing trend changes in longitudinal data (Rea et al 2017).
- Increasing popularity of the method for cancer studies, such as mortality changes over time (Dehkordi et al 2014).
- A free program with straightforward data entry and graphical results output (National Cancer Institute 2018).

'Joinpoint' analyses were made for the percentage of all late (stage 3 and 4) cancers and for least and most deprived groups (defined by a median split of the Merseyside data).

One further consideration is *exactly* when the urgent referral system came into practical effect. The system was implemented in late 2000, yet it is well known that the implementation of a health policy at local level is complex, including financial and human resource planning, infrastructure development and 'stakeholder' engagement (Wright 2017). In short, it takes time. Therefore, it is reasonable to assume that a delay occurs before the policy was 'up and running'. The time of a significant change in trend would be identified by 'Joinpoint'.

The Chi-squared test was used to test the association of patient groups with 'late' presentation. SPSS version 25 was used for data management, for descriptive statistics and for the Chi-squared tests. Binary regression (STATA binreg procedure, rr link option) was used to assess the association of clinical and demographic variables with late presentation (stage 3 or 4). It was also used to assess the association of period (1992-2000, 2001-2012) on whether patients presented 'late' after adjustment for other factors as independent predictors and similarly the association with IMD deprivation status. Risk ratios were estimated, as were 95% confidence intervals.

3.5 Results

3.5.1 Presenting oral cancers: numbers and stage at diagnosis (table 3.1, figures 3.1a and 3.1b)

There were 1485 patients with primary oral cancers included in this study, with clinical staging known for 1483. From 1992 to 2012 the number of presenting oral cancers in Merseyside steadily increased. The annual percentage change (APC), calculated in 'Joinpoint' was 5.8% (95% CI 4.5-7.1). Over the 21-year period 438 were diagnosed 1992-2000 and 1045 diagnosed 2001-2012. (Table 4.1). The percentages presenting with late (stage 3 or 4) tumours were 52% (226/438) 95%CI 46.8-56.4%, for 1992-2000, and 44% (464/1045) 95%CI 41.4-47.5%, for 2001-2012, (P=0.01). Median (IQR) age at diagnosis was 63 (55-73) years and 61% (905) were male. Tumour location was anterior 2/3rds of tongue for 36% (529), floor of mouth for 30% (438), buccal for 18% (264), lower gum for 11% (160) and elsewhere for 6% (92).

Table 3.1 – Numbers of presenting oral cancers by year and stage 1992-2012

Year	Total Oral Cancers	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)
1992	34	8 (23.5)	12 (35.3)	6 (17.7)	8 (23.5)
1993	60	6 (10.0)	22 (36.7	12 (20.0)	20 (33.3)
1994	41	4 (9.8)	10 (24.4)	11 (26.8)	16 (39.0)
1995	39	5 (12.8)	13 (33.3)	6 (15.4)	15 (38.5)
1996	56	13 (23.2)	17 (30.3)	10 (17.9)	16 (28.6)
1997	45	11 (24.4)	16 (35.6)	7 (15.6)	11 (24.4)
1998	50	10 (20.0)	16 (32.0)	12 (24.0)	12 (24.0)
1999	61	14 (22.9)	12 (19.7)	7 (11.5)	28 (45.9)
2000	52	16 (30.8)	7 (13.5)	9 (17.3)	20 (38.4)
1992-2000	**438**	**87 (19.9)**	**125 (28.5)**	**80 (18.3)**	**146 (33.3)**
2001	55	18 (32.7)	12 (21.8)	6 (10.9)	19 (34.6)
2002	46	10 (21.7)	14 (30.4)	6 (13.0)	16 (34.9)
2003	73	14 (19.2)	19 (26.0)	8 (11.0)	32 (43.8)
2004	68	14 (20.6)	20 (29.4)	5 (7.4)	29 (42.6)
2005	74	23 (31.1)	14 (18.9)	5 (6.8)	32 (43.2_
2006	83	28 (33.7)	20 (24.1)	7 (8.4)	28 (33.7)
2007	94	29 (30.8)	20 (21.3)	14 (14.9)	31 (33.0)
2008	117	40 (34.2)	31 (26.5)	7 (6.0)	39 (33.3)
2009	113	34 (30.1)	22 (19.5)	4 (3.5)	53 (46.9)
2010	98	36 (36.7)	21 (21.4)	(8.2)	33 (33.7)
2011	108	38 (35.2)	26 (24.1)	11 (10.2)	33 (30.6)
2012	116	55 (47.4)	23 (19.8)	9 (7.8)	29 (25.0
2001-2012	**1045**	**339 (32.4)**	**242 (23.2)**	**90 (8.6)**	**374 (35.8)**
TOTAL	**1483**	**426 (28.7)**	**367 (24.7)**	**170 (11.5)**	**520 (35.1)**

Figure 3.1 a and b: Presenting oral cancers

Figure 3.1a: Graph showing numbers of oral cancers presenting at each of stages 1 to 4, by year 1992-2012

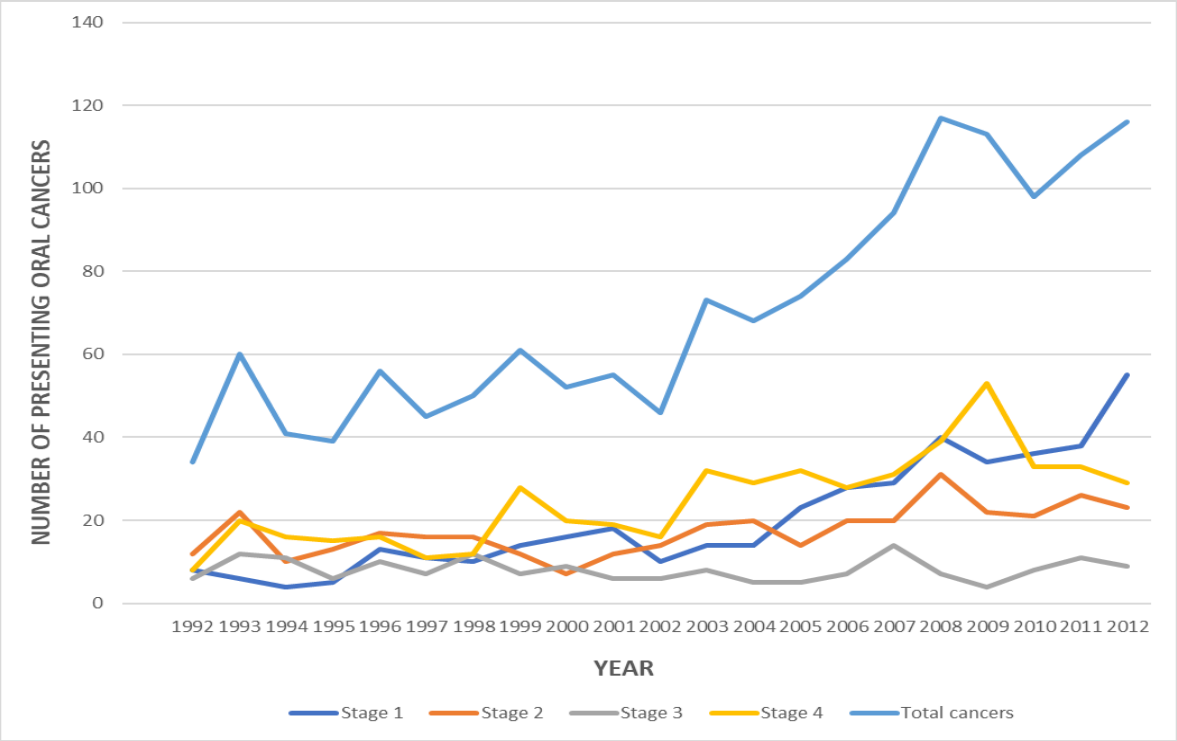
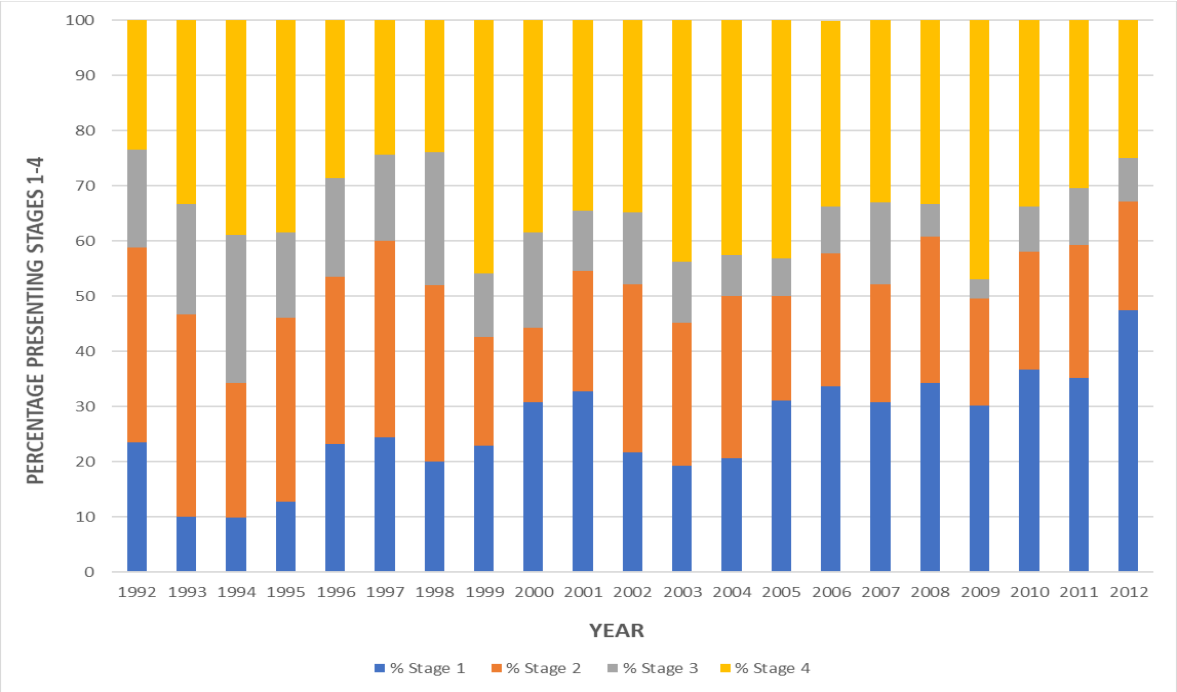
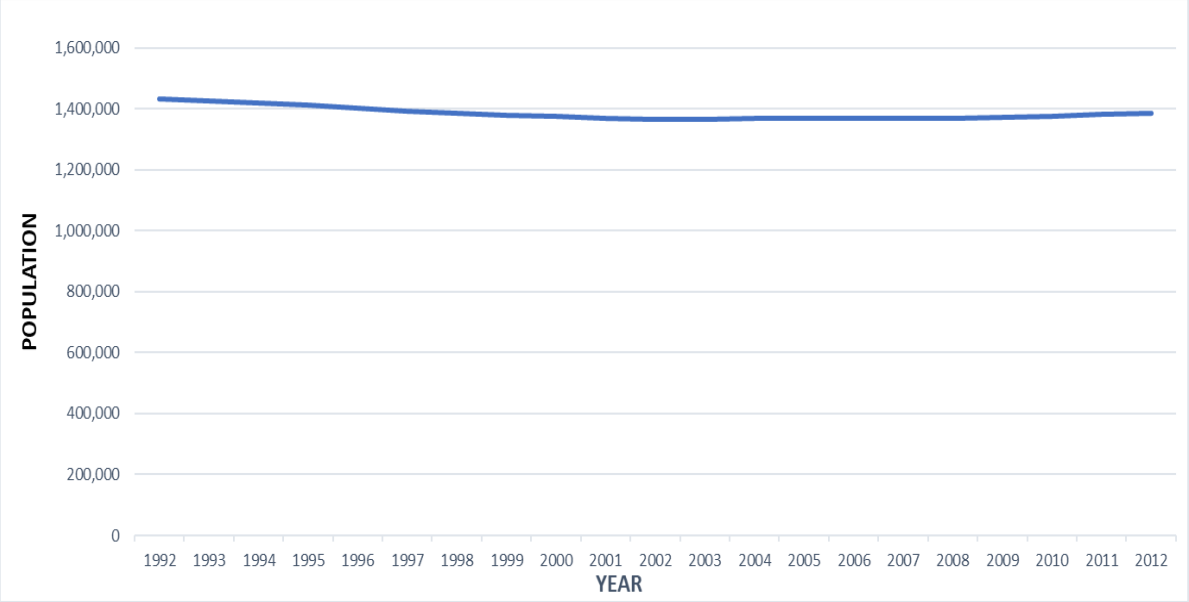


Figure 3.1b: Bar chart showing percentage of oral cancers presenting at each of stages 1 to 4, by year 1992-2012



The increase is neither attributable to increasing population nor marked increase in the age-groups associated with the highest incidence of oral cancer. The population of Merseyside fell slightly over the early and middle years of the study, from 1,433,000 to 1,366,000 before increasing again to 1,416,800 (figure 3.3, table 3.2).

Figure 3.2 – Merseyside population 1992-2012



Population statistics provided by Liverpool City Council

Table 3.2 – Percentages of Merseyside population 55-59 years, 60-64 years, 65-69 years and 70-74 years

Year	Total	% 55-59	%60-64	%65-69	%70-74
1992	1,433,000	5.34	5.39	4.89	4.17
1996	1,401.800	5.31	5.17	4.73	4.25
2000	1,374,000	5.31	5.20	4.83	4.34
2004	1,367,000	6.21	5.03	4.85	4.30
2008	1,368,000	6.10	5.81	4.62	4.31
2012	1,386,000	6.15	5.88	5.22	4.14

Consideration was given to calculating incidence rates. However, this presented several difficulties:

1. Centralisation of cancer services was not fully implemented until the late 1990s.
2. Changing referral base and patterns over the years.
3. Changes in consultant staffing
4. Changes in local authority borders.

Therefore, because of known inaccuracies in both ‘numerators’ and ‘denominators’, incidence rates were not calculated from these data.

3.5.2 Deprivation 'groups' and percentage of late cancer

For 1422 patients residing in England (Welsh and Isle of Man residents were excluded) analysis was undertaken in relation to IMD deprivation. Patients were divided into two groups by their median IMD2004 rank of 8261 - rank 1 is the residential neighbourhood in England assigned as the most deprived and rank 32482 is the least deprived neighbourhood.

For the 711 'more deprived' group the median IMD rank was 1722 (range 400 to 4072); for the 711 'less deprived' it was 18450 (range 13155 to 24042). 88% (625/711) of the 'more deprived' patients were living in the most deprived '20%' of small areas in England; all but 6 lived in the most deprived 25%. In the 'more deprived' group the percentage of cancers presenting late was 56% (95% CI 48.7 – 62.5%) for 1992 to 2000 (118/212 cases) and 47% (95% CI 42.2 – 51.2%) for 2001 to 2012 (233/499 cases), p=0.03.In the 'less deprived' group the percentage of cancers presenting late was 48% (95% CI 40.9 -54.9%) for 1992 to 2000 (99/207 cases) and 42% (95%CI 37.5-46.3%) for 2001 to 2012 (211/504 cases), p=0.16 (table 3.3).

Table 3.3 - Percentages of cancer presenting 'late' and social deprivation groups

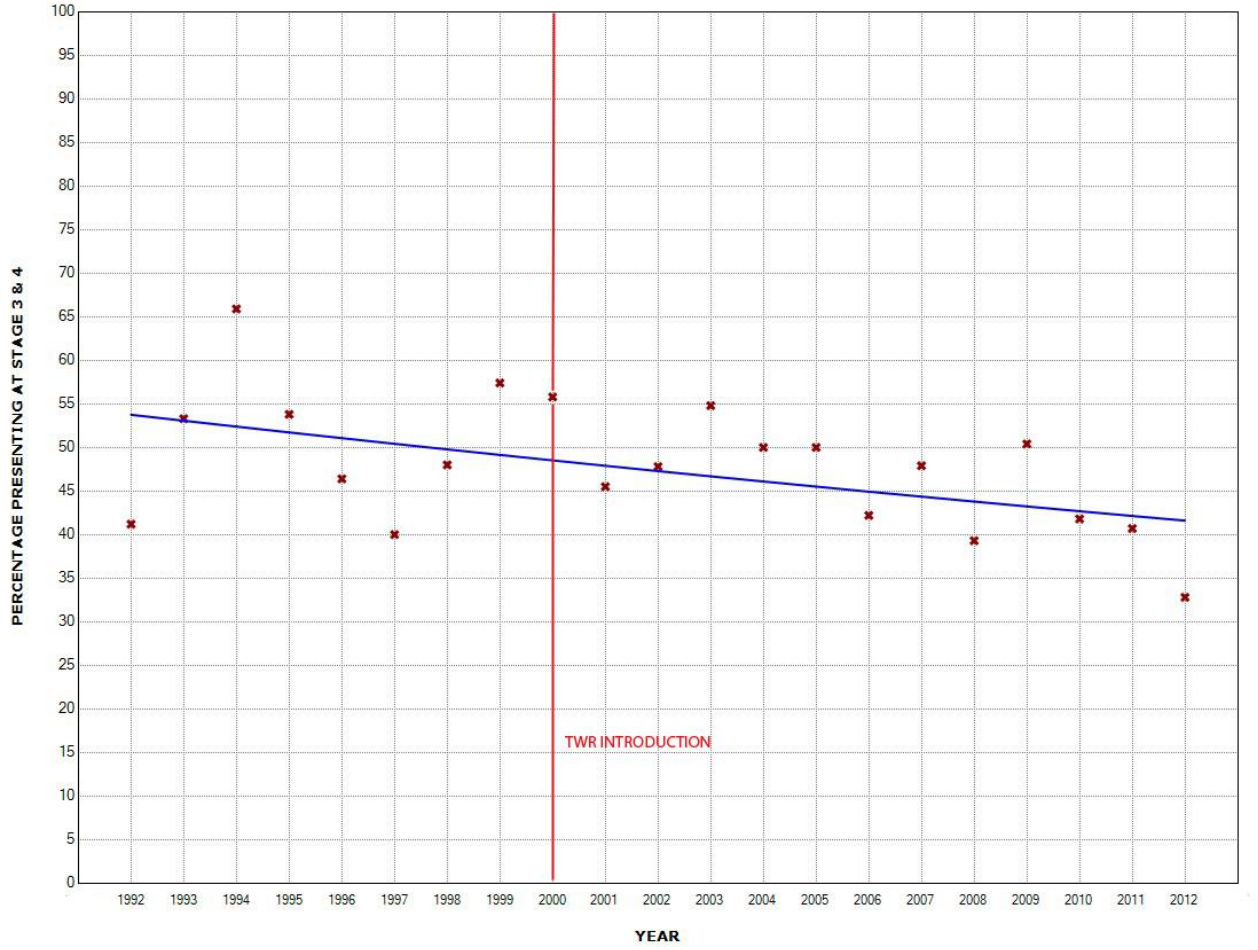
Year	Total cancers	Stage 1	Stage 2	Stage 3	Stage 4	% stage 3 or 4 (Late) cancer	%Late stages (MORE DEPRIVED areas)		%Late stages (LESS DEPRIVED areas)[4]	
							%	n	%	n
1992	34	8	12	6	8	41.2	47.4	9/19	28.6	4/14
1993	60	6	22	12	20	53.3	60.9	14/23	44.1	15/34
1994	41	4	10	11	16	65.9	73.7	14/19	61.9	13/21
1995	39	5	13	6	15	53.8	41.2	7/17	68.4	13/19
1996	56	13	17	10	16	46.4	46.9	15/32	47.8	11/23
1997	45	11	16	7	11	40.0	47.8	11/23	36.8	7/19
1998	50	10	16	12	12	48.0	72.2	13/18	34.5	10/29
1999	61	14	12	7	28	57.4	56.7	17/30	56.7	17/30
2000	52	16	7	9	20	55.8	58.1	18/31	50.0	9/18
1992-2000	438	87	125	80	146	51.6	55.7	118/212	47.8	99/207
2001	55	18	12	6	19	45.5	56.0	14/25	32.1	9/28
2002	46	10	14	6	16	47.8	47.6	10/21	52.2	12/23
2003	73	14	19	8	32	54.8	57.5	23/40	48.4	15/31
2004	68	14	20	5	29	50.0	48.3	14/29	51.4	19/37
2005	74	23	14	5	32	50.0	52.8	19/36	48.6	17/35
2006	83	28	20	7	28	42.2	45.2	19/42	40.0	16/40
2007	94	29	20	14	31	47.9	53.2	25/47	42.9	18/42
2008	117	40	31	7	39	39.3	39.3	24/61	41.2	21/51
2009	113	34	22	4	53	50.4	53.2	33/62	48.9	23/47
2010	98	36	21	8	33	41.8	48.6	18/37	36.2	21/58
2011	108	38	26	11	33	40.7	42.9	18/42	38.3	23/60
2012	116	55	23	9	29	32.8	28.1	16/57	32.7	17/52
2001-2012	1045	339	242	90	374	44.4	46.7	233/499	41.9	211/504
TOTAL	**1483**	**426**	**367**	**170**	**520**	**46.5**	**49.4**	**351/711**	**43.6**	**310/711**

[4]*Comprises the 50% of patients living in 'more deprived' neighbourhoods, as determined by the median split of IMD2004 ranking of the area lived in.

3.5.3 Joinpoint regression analysis

'Joinpoint' regression analysis of 'late' (stage 3 or 4) presentations from 1992 to 2012 indicated a steady fall in the percentage of 'late' oral cancer over the period of the study; the annual percentage change (APC) was -1.27 (95% CI -2.3 to -0.2). A 'zero joinpoint' model was selected by the software indicating that no statistically significant change in trend was identified at any point in the study (figure 4.4)

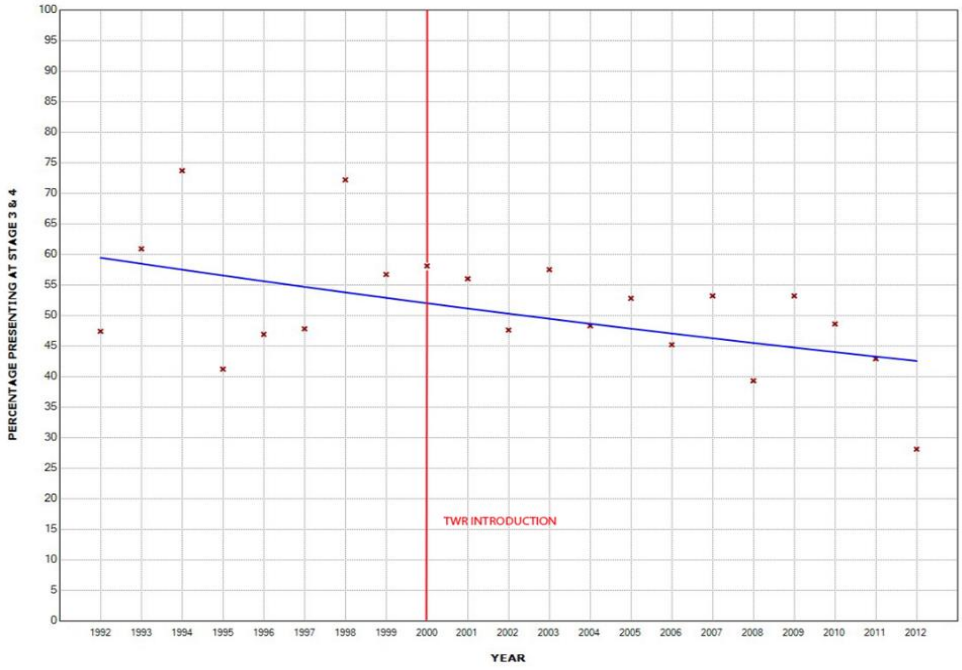
Figure 3.3 – Joinpoint regression analysis of percentage of 'late' (stage 3 & 4) presentations, 1992-2012, showing a steady reduction in late disease overt the period studies but with no significant change in trend observed following the introduction of the TWR



Model selected by *Joinpoint*: 0 joinpoints. Annual percentage change (APC) = -1.27 (95% CI -2.3 to -0.2)

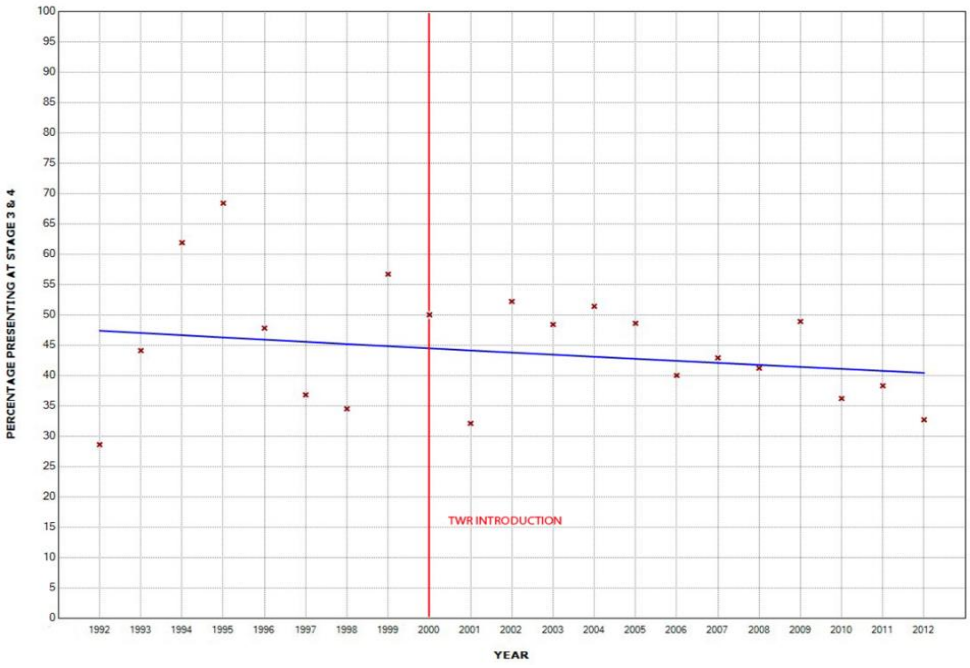
Similar analyses were carried out for the 'more' and 'less' deprived groups (median split). For neither group was a statistically significant change in trend calculated. However, a greater APC was observed in the 'more deprived' group -1.66 (95%CI -3.0 to -0.3) compared to the 'less deprived' group -0.79 (95% CI -2.5 to +0.9) (figures 4.5a and 4.5b).

Figure 3.4a - Joinpoint analysis of late presentations (stage 3 a& 4) in the 711 patients living in 'more deprived' areas showing a steady reduction in late disease overt the period studies but with no significant change in trend observed following the introduction of the TWR



Model selected by *Joinpoint*: 0 joinpoints. Annual percentage change (APC) = -1.66 (95%CI -3.0 to -0.3)

Figure 3.4b - Joinpoint analysis of late presentations (stage 3 a& 4) in the 711 patients living in 'less deprived' areas showing a steady reduction in late disease overt the period studies but with no significant change in trend observed following the introduction of the TWR



Model selected by *Joinpoint*: 0 joinpoints. Annual percentage change (APC) = -0.79 (95% CI -2.5 to +0.9)

3.5.4 Associations with late presentation (table 3.4)

In binary regression, year of diagnosis, cancer site and IMD2004 grouping were significantly associated with 'late' presentation.

Table 3.4 - Associations with late (stage 3 &4) presentation – clinical and demographic factors

Variable		'Late' stage oral cancer %	n	P value[5]	Risk ratio	95% CI for Risk ratio
	TOTAL	61	690/1483			
Year of diagnosis	1992-2000	52	226/438	0.01	1.00	Reference
	2001-2012	44	464/1045		0.86	0.77-0.96
Gender	Male	48	437/905	0.10	1.00	Reference
	Female	44	253/578		0.91	0.81-1.02
Age	<55	42	151/357	0.09	1.00	Reference
	55-64	45	201/444		1.07	0.91-1.25
	65-74	48	179/374		1.13	0.96-1.33
	75-84	52	159/307		1.22	1.04-1.44
Tumour site	Buccal	55	144/264	<0.001	1.00	Reference
	Lower gum	84	135/160		1.55	1.36-1.76
	Tongue (ant 2/3)	27	144/529		0.50	0.42-0.60
	Floor of Mouth	47	207/438		0.87	0.75-1.00
	Other	65	60/92		1.20	0.99-1.44
IMD2004 split by	More deprived	49	351/711	0.03	1.13	1.01-1.27
Median rank	Less deprived	44	310/711		1.00	Reference
IMD2004 quintiles[6]	Rank ≤1089	52	148/286	<0.001	1.47	1.21-1.78
within sample	1090-4748	46	130/283		1.30	1.07-1.60
Rank 1=most deprived	4749-12168	52	146/283		1.47	1.21-1.78
	12169-20414	48	137/286		1.36	1.12-1.66
	≥20415	35	100/284		1.00	Reference
IMD2004 quintiles[7]	Rank ≤6496	49	306/625	<0.001	1.65	1.27-2.16
(England)	6497-12993	53	136/255		1.80	1.36-2.38
Rank 1=most deprived	12994-19490	47	108/228		1.60	1.20-2.14
	19491-25985	40	69/172		1.36	0.99-1.85
	25986-32482	30	42/142		1.00	Reference

Year of diagnosis: The risk ratio for patients presenting 2001-2012 relative to those presenting 1992-2000 was 0.86 (95% CI 0.77-0.96), p=0.009; adjustment for each other variable in table 11 made little difference to the ratio (range 0.85-0.86) other than adjusting for tumour location, following which the risk ratio (95% CI) was 0.93 (0.85-1.02), p=0.13.

[5] Chi squared test
[6] Calculated on an even 20% quintile split of the IMD ranks of the patients in the sample
[7] Calculated on the distribution of IMD ranks across the whole of England

Deprivation: The risk ratio for the 50% of patients living in the 'most deprived' neighbourhoods relative to 'less deprived' neighbourhoods was 1.13 (95% CI 1.01-1.27), P=0.03. Adjustment for each other variable in table 11 made little difference to the ratio (range 1.13-1.16), other than adjusting for tumour location, following which the risk ratio was 1.05 (95% CI 0.96-1.15), p=0.30.

Oral cancer sub-site: 84% of lower gum cancers presented late compared to 27% of tumours of the anterior two-thirds of the tongue. Oral site was associated with IMD2004 grouping (P<0.001) and borderline with time-period (P=0.06). There was an increase in cancers of the anterior two-thirds tongue from 30% (132/438) 1992-2000 to 38% (397/1045) 2001-2012, with slight declines for all other locations. Patients with floor of mouth cancers were more likely to live in more deprived areas; 56% (236/425) lived in the most deprived quintile of areas within England compared to between 30-41% for other tumour locations. Furthermore, 63% (267/425) were within the 'more deprived' half of the sample compared to 35-48% for other tumour locations.

3.6 Discussion

3.6.1 *Increasing numbers of oral cancers*

The increase in oral cancers identified in this study reflects the national picture; oral cancer rates in the UK increased by 32%-33% between 2002 and 2012 (Rumgay 2015) and it would seem, therefore, that much work needs to be done on the prevention of oral cancer although the reasons for the increase are not entirely clear. Smoking and alcohol are the most important causes of oral cancer (Hashibe et al 2009). However, since the 1970s UK smoking rates have markedly declined, although alcohol consumption has steadily increased from the 1960s to the present day (National Archives 2016). More recently, oral cancers associated with human papilloma virus (HPV) subtype HPV-16 are becoming increasingly prevalent, especially in the oro-pharyngeal region (Young et al 2015). The data for this study were collected at the central head and neck unit in Merseyside and increasing numbers will be influenced to an extent by centralisation of the oral cancer service following the Calman-Hine report on

cancer services (Department of Health 1995). Nevertheless, by the mid to late 1990s almost all oral cancers in Merseyside were managed at the central unit and are, therefore, included in these data.

3.6.2 Stage on presentation before and after the TWR-NICE guidance referral system

This study found that from 1992 to 2012 the percentage of oral cancers presenting 'late' (stage 3 and 4) reduced at an APC of 1.27% per year – with, of course, a corresponding increase in the proportion presenting 'early' (stage 1 and 2). However, in this study, no trend change in the stage on presentation of oral cancer was observed in the period following the introduction of the TWR referral system. The stage on presentation of oral cancer was improving prior to the TWR and continued to improve at a similar rate following its introduction. It is therefore difficult, in the light of the results in this study, to define the exact effect that the introduction of the TWR has had on stage-on-presentation of oral cancer.

There is very limited published work to date in relation to the effect of UK cancer policy on oral cancer outcomes (Langton et al 2016). Published work, in relation to several other cancer types, has presented a mixed picture of changes in survival trends following the implementation of the TWR and associated policies in the NHS Cancer Plan. A study on colorectal cancer, comparing patients referred via the TWR and other methods found no difference in disease stage between patients referred by each pathway (Bevis et al 2007). A further study on colorectal cancer compared groups diagnosed before and after the TWR; Kaplan-Meier assessment showed no difference in 2-year survival between the groups (Walsh et al 2006). A study on 2746 sarcoma referrals reported that the TWR had 'no impact' on early diagnosis (Pencavel et al 2010). Conversely, in a study on melanoma, tumours were thinner after the introduction of the TWR and survival improved (Pacifico et al 2007). In a study of 8049 general practices in England, Moller et al (2015) reported that practices with the lowest use of fast-track referral had higher cancer mortality rates. However, in a large study of English cancer survival trends from 1996-2013, for 21 cancers but not including head and neck cancer, 26 of the cancer-sex combinations showed steady mortality improvement but with no significant acceleration after the Cancer Plan implementation (Exarchacou et al 2018), a pattern reflected in relation to stage on diagnosis in this study.

3.6.3 Intra-oral sites

Differences were observed in the change in proportion presenting late at different oral sites. The most marked trend in reduction of late-stage presentation was noted in floor of mouth when compared to anterior tongue and other oral sites, which showed little evidence of reduction over time. The observation regarding floor of mouth may be attributable to reduction in smoking, as it is believed that there is a relationship between this and advanced-stage tongue and floor of mouth cancer (Bezerra et al 2018).

3.6.4 Relationship to socio-economic deprivation

This study identified an overall steady improvement in stage-on-diagnosis of oral cancer in Merseyside from 1992 to 2012 and both the least and most socially deprived groups benefited in this respect. Interestingly, the annual percentage change was greater for the most deprived. Nevertheless, despite this improvement there was a persistent gap to 2012 between the social groups, with a greater proportion of late disease in the most deprived. It is known that oral cancer – like cancer of the lung and oesophagus - is more likely to be diagnosed in socially deprived groups, and socio-economic difference in survival from head and neck cancers are among the largest of any malignancies (Robertson and Greenlaw 2010). Published work has shown that a 'deprivation gap' exists for most cancer types and in some cancer types – for example, brain in men and lung in women – the gap would appear to be increasing (Exarchacou et al 2018). For oral cancer, it is believed that much of the difference can be related to lifestyle factors, especially higher smoking rates amongst the socio-economically deprived (National Cancer Intelligence Network 2010) although not exclusively. The nature of the causes of socio-economic differences in head and neck cancers is complex and some deprivation effects on survival from head and neck cancers might be mitigated through earlier detection and referral (Robertson and Greenlaw 2010).

3.6.5 *Socio-economic deprivation in the study population*

The population of this study, for the purposes of analysis, has been dichotomised by median IMD score into 'less' and 'more' deprived groups. These are defined within the Merseyside population studied, not in relation to the national distribution of IMD. As oral cancer has strong associations with social

deprivation, how does the study population relate to the rest of the country? The study population includes Knowsley and Liverpool, which are the second and third most deprived local authority areas in England (Ministry of Housing, Communities and Local Government, 2019). For example, 50.9% of the current Liverpool population falls within the national 10% of the most deprived (Merseyside Fire and Rescue Service, 2013). However, Aintree head and neck centre also treats patients from a large area of West Cheshire, Wirral and the West Lancashire coast which include areas that are considerably less deprived. For example, in 2015 Cheshire West included 212 LSOAs, of which only 14 were amongst the most deprived 10% of LSOAs nationally. Nevertheless, much work has indicated that the rise in oral cancer incidence occurs, mainly, in deprived areas of residence (Conway et al 2007).

3.7 Strengths and limitations of this study

To my knowledge, this is the first published study examining changes in stage on presentation of oral cancer before and after the introduction of the UK two-week rule and associated guidance for practitioners. The study also examines the change in stage on presentation in relation to socio-economic deprivation.

The study includes validated staging data for 1483 patients diagnosed with oral cancer over a 21-year period, using the Merseyside head and neck cancer database. Selection and information bias were considered to be low. An important advantage of this database is that it includes accurate staging data from the early 1990s onwards, allowing a stage on presentation comparison to be made before and after the introduction of the NHS Cancer Plan and TWR. The data period is up to 2012 but this was considered appropriate for comparing the periods before and after the introduction of the TWR. An increasing presentation of oral cancers was noted in Merseyside consistent with the national trend; however, due to shifting referral boundaries, changing consultant staff and different referral patterns over a 21-year period incidence rates are difficult to calculate with accuracy from these data.

The study is confined to a single unit, in a region where the incidence of oral cancer is the second highest in the UK (Conway et al 2008). The findings in this study may be influenced by several factors, including the socio-economic structure of the population and regional incidence of the disease. Whilst

regions with similar populations are likely to reflect the outcomes of this study, a comparison with areas of different socio-economic structure and oral cancer incidence would be of interest and value. A further consideration is the fact that in the years immediately following the introduction of the TWR, less than 50% of head and neck cancers were diagnosed via TWR referrals, although there is evidence that the percentage is increasing (Langton et al 2016). The choice of database for this study was, to an extent, pragmatic bearing in mind the availability and validity of the Merseyside data and the unavailability of accurate national data. However, the question remains whether conclusions drawn from these data reasonably reflect the national situation.

The concept of external validity has been in existence for at least 70 years. Commenting on the Framingham cardiovascular risk studies based on the population of Framingham, Massachusetts, USA in 1950, Dawber (1951) suggested that the limited geographic coverage '…*clearly limits the generality of conclusions which can be reached'*. More recently, it has been suggested that there is an increasing concern that a cohort population *'that is not representative of the nation as a whole or of the average person cannot produce valuable insights beyond its local setting'* (Uphoff et al 2017). It has been suggested that the recent increase in 'big data' (Raghupathi 2014) has encouraged this view. However, Uphoff (2017) points out that historically important research findings have been made from cohorts that are not representative of the whole population, for example the very well-known study of doctors' mortality in relation to smoking (Doll and Bradford Hill, 1954).

It can, of course be, argued that cohort studies do not always – some authors would say 'rarely' (Uphoff 2017) - represent the whole population. On the other hand, this study provides a detailed insight into a local population with a high incidence of oral cancer and high level of socio-economic deprivation.

In this study clinical staging (including MRI/CT examination when available) was used. The problem with clinical staging is that a small percentage of apparently node negative (N_0) cases will, following neck dissection, demonstrate positive nodes. However, if 'pathological' staging is used patients treated with radiotherapy alone do not provide a neck specimen for pathological examination and hence their neck pathology remains unknown. In short, both 'clinical' and 'pathological' staging have disadvantages in a study of this type. For consistency, clinical staging was used.

Regarding deprivation, several versions of IMD existed during the years of the study. IMD 2004 was used for the entire study as it represented a wide range of years included in the study. The vast majority of patient postcodes were recorded at the time of diagnosis but a minority were later. IMD focuses on areas but lacks sensitivity to individual deprivation.

The evaluation of policy effects when randomised controlled trials are not possible is not entirely straightforward. The challenges and some possible solutions were outlined in a review paper by Basu et al (2018) and include distinguishing health effects caused be confounding factors from those resulting from the policy, distinguishing time-trend effects and identifying a suitable comparator population. In this study changes in stage on diagnosis could also have been caused by several factors including increased patient awareness of symptoms and improving practitioner knowledge.

3.8 Conclusions and implications

This study found that the stage on presentation of oral cancer in Merseyside has steadily improved from 1992 to 2000. The improvement continued following the introduction of the TWR in 2001 but 'Joinpoint' analysis did not demonstrate a change in trend. Improvements in stage on diagnosis were evident in both the least and most deprived social groups with the most deprived showing more rapid improvement. However, throughout the study the most deprived presented later than the least deprived and the 'gap' persisted to the end of the study. Despite the improvement in stage on presentation of oral cancer, the number of cases diagnosed per year increased at an annual percentage change of 5.8% for the duration of the study. Amongst oral sites, the most marked reduction in the proportion of late cases was observed in floor of mouth cancers, possibly due to reduction in smoking.

In summary, the introduction of the TWR did not make a notable difference to the steady improvement over time in stage on presentation. Although the rate of improvement in stage on presentation was greatest for the more deprived groups, deprivation inequality remains with the most deprived presenting with more advanced cancer and this should be a focus of further initiatives and research. Furthermore, in the light of the increasing incidence of oral cancer, more work needs to focus on the causes and prevention of the disease.

3.9 Related publication

Langton S, Lowe D, Rogers SN, Plüddemann A and Bankhead C (2019) *The impact of the UK 'two-week rule' on stage-on-diagnosis of oral cancer and the relationship to socio-economic inequalities* Journal of Cancer Policy 20 1-8

Chapter 3 references

Basu S, Meghani A and Siddiqi A (2017) *Evaluating the health impact of large-scale public policy changes: classical and novel approaches* Annual Review of Public Health 38 351-370

Bevis PM, Donaldson OW, Card M, Durdey P, Thomas MG, Sylvester PA and Longman RJ (2007) *The association between referral source and stage of disease in colorectal cancer* Colorectal Disease 10 58-62

Bezerra NVF, Leite KLD, de Medeiros MMD et al (2018) *Advanced-stage tongue and mouth floor cancer is related to tobacco and alcohol use* Journal of Public Health 26 151-156

Brown JS, Rogers SN, McNally DN et al (1999) *A modified classification for the maxillectomy defect* Head and Neck 22 17-26

Brown JS, Devine JC, Magennis P et al (2003) *Factors that influence the outcome of salvage in free tissue transfer* British Journal of Oral and Maxillofacial Surgery 41 16-20

Brown JS, Magennis P Rogers SN et al (2006) *Trends in head and neck microvascular reconstructive surgery in Liverpool (1992–2001)* British Journal of Oral and Maxillofacial Surgery 44 364-370

Cancer Research UK (2006) *Cancer and health inequalities: an introduction to current evidence* available at: http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@nre/@pol/documents/generalcontent/crukmig_1000ast-3344.pdf (Accessed August 2020)

Conway DI, Brewster DH, McKinney PA et al (2007) *Widening socio-economic inequalities in oral cancer incidence in Scotland, 1976–2002* British Journal of Cancer 96 818-820

Conway DI, Petticrew M, Marlborough H et al (2008) *Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies* International Journal of Cancer 122 2911-2819

Cooper JS, Porter K, Mallin K, Hoffman HT et al (2009) *National cancer database report on cancer of the head and neck: 10-year update* Head and Neck 31(6) 748-758

Crabtree BF, Ray SC, Schmidt PM, O'Connor PJ (1990) *The individual over time; time series applications in health care research* Journal of Clinical Epidemiology 43 241-260

DAHNO (2015) *National Head and Neck Cancer Audit* 2014 available at: http://content.digital.nhs.uk/catalogue/PUB18081/clin-audi-supp-prog-head-neck-dahn-13-14.pdf (Accessed August 2014)

Dawber TR, Meadors GF, Moore FE (1951) *Epidemiologic approaches to heart disease: the Framingham Study* American Journal of Public Health 41 279-86.

Dehkordi ZF, Tazhibi M and Babazade S (2014) *Application of joinpoint regression in determining breast cancer incidence rate change points by age and tumor characteristics in women aged 30–69 (years) and in Isfahan city from 2001 to 2010* Journal of Education and Health Promotion 3 115

Department of Health (1995) *A policy framework for commissioning cancer services: a report by the Expert Group on Cancer to the Chief Medical Officers of England and Wales* Available at: https://webarchive.nationalarchives.gov.uk/20080817211349/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4071083 (accessed August 2020)

Department of Health (2011) *Improving outcomes: a strategy for cancer: Assessment of the impact on equalities* available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213785/dh_123394.pdf (accessed August 2020)

Doll R and Bradford Hill A (1954) *The mortality of doctors in relation to their smoking habits* British Medical Journal 1(4877) 1451–1455

Eccles M, Grimshaw J, Campbell M et al (2003) *Research designs for studies evaluating the effectiveness of change and improvement strategies* Quality and Safety in Healthcare 12 47-52

Exarchacou A, Rachet B, Belot A et al (2018) *Impact of national cancer policies on cancer survival trends and socioeconomic inequalities in England, 1996-2013: population based study* British Medical Journal doi: 360:k764

Gatta G, Botta L Sánchez MJ (2015) *Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study* European Journal of Cancer 51 2130-2143

Grimshaw J, Campbell M, Eccles M et al (2000) *Experimental and quasi-experimental designs for evaluating guideline implementation strategies* Family Practice 17 S11-S16

Hamilton, W (2012) *Emergency admissions of cancer as a marker of diagnostic delay* British Journal of Cancer 107 1205-1206

HANA (2017) *Head and Neck Audit* available at: https://savingfaces.co.uk/current-projects/national-head-and-neck-cancer-audit/ (accessed August 2020)

Harrison AJ and Foot, CS (2012) *Targets and prioritisation: the case of cancer in the English NHS Quality in Primary Care* 20 125-129

Hashibe M, Brennan P, Benhamou S et al (2007) *Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium* Journal of the National Cancer Institute 99 777-78

Health and Social Care Information (2012) *National Head and Neck Cancer Audit 2011* available at: https://webarchive.nationalarchives.gov.uk/20180321184500/http://digital.nhs.uk/catalogue/PUB06288 (Accesssed August 2020)

Jehannin-Ligier K, Dejardin O, Lapotre-Ledoux B et al (2017) *Oral cancer characteristics in France: Descriptive epidemiology for early detection* Journal of Stomatology, Oral and Maxillofacial Surgery 118 84-89

Kontopantelis E, Doran T, Springate DA et al (2015) *Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis* British Medical Journal Open 350:h2750 | doi: 10.1136/bmj.h2750

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Macpherson LMD (2018) *Raising awareness of oral cancer from a public and health professional perspective* British Dental Journal 225 809-814

Merseyside Fire and Rescue Service (2013) *Profile of Merseyside* available at: http://www.merseyfire.gov.uk/aspx/pages/equality/pdf/Profile_of_Merseyside_Demography_Equality_and_Diversity.pdf (accessed August 2020)

Ministry of Housing, Communities and Local Government (2019) *The English Indices of Deprivation 2019 (IoD2019)* available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/835115/IoD2019_Statistical_Release.pdf (Accessed August 2020)

Møller H, Gildea C, Meechan D, Rubin G, Round T, and Vedsted P (2015) *Use of the English urgent referral pathway for suspected cancer and mortality in patients with cancer: cohort study* British Medical Journal 351 h5102

National Archives (2016) *An overview of 40 years of data (General Lifestyle Survey Overview - a report on the 2011 General Lifestyle Survey)* available at: https://webarchive.nationalarchives.gov.uk/20160105214118/http://www.ons.gov.uk/ons/rel/ghs/general-lifestyle-survey/2011/rpt-40-years.html (accessed August 2020)

National Cancer Institute (2018) *Joinpoint Trend Analysis Software* available at: https://surveillance.cancer.gov/joinpoint/ (accessed August 2020)

National Cancer Intelligence Network (2010) *Urgent GP referral rates for suspected cancer* available at http://www.ncin.org.uk/publications/data_briefings/gp_referral_rates (accessed August 2020)

National Cancer Intelligence Network (2013) *Oral Cavity Cancer: recent survival trends* available at: http://www.ncin.org.uk/publications/data_briefings/oralcancer (accessed August 2020)

Office of the Deputy Prime Minister (2004) *The English Indices of Deprivation 2004* available at: https://webarchive.nationalarchives.gov.uk/20100407164233/http://www.communities.gov.uk/archived/general-content/communities/indicesofdeprivation/216309/ (accessed August 2020)

Pacifico MD, Pearl RA and Grover R (2007) *The UK Government two-week rule and its evidence on melanoma prognosis: and evidence-based study* Annals of the Royal College of Surgeons of England 89 609-615

Pencavel TD, Strauss DC, Thomas GP et al (2010) *Does the two-week rule pathway improve the diagnosis of soft tissue sarcoma? A retrospective review of referral patterns and outcomes over five years in a regional sarcoma centre* Annals of the Royal College of Surgeons 92 417-421

Raghupathi W and Raghupathi V (2014) *Big data analytics in healthcare: promise and potential* Health Information Science and Systems https://dx.doi.org/10.1186%2F2047-2501-2-3

Rea F, Pagan E, Compagnoni MM et al (2017) *Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies* Epidemiology Biostatistics and Public Health 14 e12616-1 - e12616-8

Robertson G and Greenlaw N (2010) *Explaining the effects of socio-economic deprivation on survival in a national prospective cohort study of 1909 patients with head and neck cancers* Cancer Epidemiology 34 682-688

Rogers SN, Brown JS, Woolgar JA (2009) *Survival following primary surgery for oral cancer* Oral Oncology 34 147-153

Rumgay H (2015) *Mouth cancer rates are increasing, but why?* Available at: http://scienceblog.cancerresearchuk.org/2015/11/13/mouth-cancer-rates-are-increasing-but-why/ (accessed August 2020)

Scott, SE Grunfeld, EA and McGurk M (2005) *The idiosyncratic relationship between diagnostic delay and stage of oral cell carcinoma* Oral Oncology 41 396– 403

Shaw RJ, Lowe D, Woolgar JS (2009) *Extracapsular spread in oral squamous cell carcinoma* Head and Neck 32 714-722

Thorne P, Etherington D and Birchall MA (1998) *Head and neck cancer in the South West of England: Influence of socio-economic status* Clinical Otolaryngology and Allied Sciences 23 277

Uphoff E, Snall N, McEachan R and Pickett K (2017) *The relevance of a local cohort: the case for generalisability over representativeness* International Journal of Epidemiology Blog available at: https://ije-blog.com/2017/09/07/the-relevance-of-a-local-cohort-the-case-for-generalisability-over-representativeness/ (accessed August 2020)

Walsh SR, Gilson NL, Brown K and Novell JR (2006) *Trends on colorectal cancer survival following the 2-week rule* Colorectal Disease 9 207-209

Worrall SF and Corrigan M (1995) *An audit of one surgeon's experience of oral squamous carcinoma using a computerised malignancy database* Annals of the Royal College of Surgeons of England 77 332-336

Wright A (2017) *What's so important about health policy implementation?* The Scottish Parliament available at: https://www.researchgate.net/publication/320101578_What's_so_important_about_health_policy_implementation (accessed August 2020)

Young D, Xiao CC, Murphy B (2015) *Increase in head and neck cancer in younger patients due to human papillomavirus (HPV)* Oral Oncology 51 727-730

CHAPTER 4: Head and neck cancer referral in England and the Netherlands: an international qualitative study of secondary care surgical specialists' views

4.1 Abstract

Background

One-year head and neck cancer survival in England has been reported to be worse than that in the best-performing countries in Europe, despite 5-year conditional survival rates being similar, implying a later stage of presentation in England. One country with better 1-year survival rates is the Netherlands. Many possible explanations exist but one may be the system of referral from primary care to the specialist.

Aim

To study and compare the views of secondary care specialists in England and the Netherlands on their respective systems for the referral of suspected head and neck cancer from primary to secondary care and attempt to identify aspects that might have an impact on outcomes for head and neck cancer.

Design and setting

Semi-structured qualitative interviews of head and neck cancer surgical specialists in England and the Netherlands.

Results

Twenty-four specialists, 12 in England and 12 in the Netherlands, were interviewed about their national referral system for head and neck cancer. By far the most common theme was communication between primary care and specialists. Surgeons in England identified this as the aspect most lacking in the English 'two-week rule' system, whilst Dutch specialists felt strongly that the good communication that existed in their system was one of its best points. Other themes that emerged included varying views on the educational needs of primary care practitioners, criticism of 'tick box' referrals in England and the problem of managing large numbers of referrals that do not have cancer.

Conclusions

Overall, specialists in both countries identified good aspects of their respective primary care-specialist referral systems for suspected head and neck cancer. However, specialists in England felt strongly that the two-week rule/NICE guidance system could be improved with better direct communication between primary and secondary care and this, in turn, might improve speed of referral, the quality of referrals, reduce unnecessary referrals and assist with educating GPs. It is not clear whether such improvements would improve head and neck cancer survival rates but further research and piloting of such a system should be considered in England.

4.2 Introduction

This chapter presents a qualitative study comparing the referral systems for suspected head and neck cancer in England and the Netherlands, in a series of interviews with English and Dutch surgical specialists and focuses on possible aspects of the respective referral systems that might account for outcome differences.

The evidence that led to the conclusion that some English cancer outcomes were inferior to the best in Europe has been discussed in detail in Chapter 2. Data from the EUROCARE-5 studies indicate that for head and neck cancer – including oral cancer - UK 5-year conditional (on 1-year survival) outcomes compare well with the best in Europe, yet 1-year survival is still poorer than in several other countries (Gatta et al, 2015). Many consider that the on-going relatively poor English cancer outcomes are at least partly due to diagnostic delays resulting in a more advanced stage when cancer is identified (Neal 2009).

One example of a country with better head and neck cancer outcomes than England is the Netherlands, where 1-year survival for 2000-2007 was reported in Gatta's 2015 study to be 74.7% (95% CI 73.7-75.7) compared to 1-year survival rates in England of 70.3% (95% CI 69.7-70.9). 5-year conditional survival rates for the same period were very similar – the Netherlands 65.7% (95% CI 64.1-67.5); England 65.6% (95% CI 64.6-66.6).

However, determining exactly why diagnostic delay occurs is a complicated problem for all cancers and probably has many components requiring different solutions (Hamilton, 2012; MacArtney et al 2017). Many studies have attempted to identify factors causing delay in cancer diagnosis and the differences between developed European countries with comprehensive healthcare systems (Oderkirk et al 2013). The International Cancer Benchmarking Partnership, initiated by the Department of Health in England, (Butler et al, 2013) has explored several possible causes of international variation in cancer outcome, including patient knowledge of cancer and willingness to consult a health professional (Forbes et al 2013), international variation in primary care practitioners' willingness to refer (Rose et al 2015), and socio-economic inequalities (Quaife et al, 2015).

For head and neck cancer, a considerable number of studies have focused on the causes and effects of delay, including systematic reviews (Seoane et al, 2012; Goy et al 2009) and much published work has focused on the diagnostic accuracy of the referral system (Langton et al 2016).

However, while for the more common cancers some work has focused on clinicians' views on the diagnostic pathway (Redaniel et al, 2015), there has been relatively little work studying clinicians' views on the fast-track diagnostic process for head and neck cancer (Bethell and Leftwick 2015) and nearly all such research has been conducted in single countries (Tudor Car 2016; Dahlhaus et al 2013).

The purpose of this study is, therefore, to gain an in-depth insight into the views of head and neck cancer specialists in England and the Netherlands on their early cancer referral systems, with an emphasis on their perceived strengths and limitations and how the referral process might be made more effective. The study aims to compare the suspected head and neck cancer referral system in each country through the views of the surgical specialists and to identify aspects of both systems of fast-track cancer referral that might potentially contribute to head and neck survival differences.

4.2.1 Cancer Referral in the English and Dutch Health Systems

In 2018, the English and Dutch health systems served populations of 53 million (66 million all UK) and 17 million respectively. In 2016 the Netherlands spent 10.8% of GDP on health care whilst England spent 9.8%. In England, health care is universal, free at the point of delivery and most funding is derived from general taxation. In the Netherlands an insurance-based system provides funding; all residents are required by law to purchase statutory health insurance from private insurers. In both countries, the GP provides a central gatekeeping service and refers, when required, to secondary care services which are, in both England and the Netherlands, almost entirely hospital based (Commonwealth Fund, 2020).

The English system for fast-track cancer referral, including suspected head and neck and oral cancer, is the 'two-week rule' (TWR) which requires that referrals from a GP are seen by a specialist within 14 days. GPs are provided with a list of signs and symptoms of potential cancer to assist with referral (NICE 2015). Patients present in secondary care to both specialists in head and neck cancer and to

'general' maxillofacial/ENT specialists who then normally refer to a head and neck colleague if cancer is evident.

In the Netherlands there is no government-specified fast-track cancer referral system. Hospital and specialist care (except emergency care) are accessible only upon GP referral. GPs are guided with an on-line evidence-based guideline system (NHG-Standaarden 2019) and refer to a specialist if alarm symptoms are present. Both secondary and tertiary centre specialists aim to assess new cancer patients within a week, and, if necessary, the same day after consultation by telephone. Head and neck cancer cases in a secondary ENT centre setting may be referred to a dedicated outpatient clinic in a tertiary head and neck centre the same week.

4.3 Aim and objectives

The overall aim of this study is to compare, qualitatively, the systems for the urgent referral of head and neck cancer in England and the Netherlands in a series of interviews with specialist surgeons in each country.

The objectives include:

1. Identification of barriers and facilitators in each system.
2. Identifying differences in the systems that might account for differences in outcome.
3. Obtaining views on how the systems might be improved.

4.4 Methods

4.4.1 Research methodology

A qualitative methodology was chosen for this study. Such designs are useful to explore areas where there is a limited understanding and are therefore less amenable to methods such as questionnaires, which may lack subtlety, breadth and depth (Pope et al 2006).

The in-depth approach of a qualitative study may provide a clearer picture of a 'process' (in this case cancer referral) by addressing how and why it occurs (Silverman 2000). It has been suggested that

qualitative studies of professional experiences of a policy may help to demonstrate its workability and sustainability (Edvardsson et al 2011). Another benefit of the qualitative approach – particularly when little is known about the subject in question - is that it may identify important aspects that merit further, possibly quantitative, study (Hammarberg 2016). Furthermore, the qualitative approach may reveal findings not easily identified in quantitative studies, in this case shedding new light on the differences between the two national policies for urgent suspected cancer referral, which in turn might help identify possible causes for differences in outcomes between the two countries.

The specific approach used in this study is 'qualitative descriptive'. According to Sandelowski (2000) the expected outcome of qualitative description is: *'a straightforward descriptive summary of the informational contents of data organised in a way that best fits the data'* although she emphasises that descriptions must have 'descriptive validity' and be presented in a way that observers of the event *'would regard as truthful'*. Compared to other qualitative approaches, such as interpretative, qualitative descriptive studies focus on 'low inference description'; this does not imply less rigour but, according to Colorafi (2016), is a question of *'the amount of logical reasoning required to move from a database premise to a conclusion'*. Whilst sampling strategies limit the conclusions that can be drawn from a qualitative study, one key feature of sampling for a qualitative descriptive study is the acceptability of nearly all sampling methods (Colorafi 2016). Quantitative data may also be included in such studies if they represent a 'means to an end' in the study (Sandelowski 2010). In this study data from the interviews were subject to content and thematic analysis, with an emphasis on comparison between the English and Dutch systems of urgent suspected cancer referral, in order to derive conclusions.

Overall, the qualitative descriptive approach was selected for several reasons. Colorafi et al (2016) consider that: '*qualitative description is especially amenable to health environments research because it provides factual responses to questions about how people feel about a particular space'* which is appropriate for the aim of this study. Secondly, it provides a data-rich insight into the experiences of the specialists receiving the head and neck cancer referrals. Thirdly, it identifies aspects of the referral process, inter-personal and inter-professional experiences that would not be easily revealed in other methods, such as questionnaires.

4.4.2 Ethical approval

Ethical approval for the study was obtained in England from the Medical Sciences Interdivisional Research Ethics Committee of the University of Oxford (CUREC reference R52175/RE001) and in the Netherlands from the Medical Ethical Committee of the VU University Medical Centre Amsterdam, reference 2017.116 (see Appendix 1, p211).

4.4.3 Patient involvement

Public and patient involvement (PPI) was carried out in accordance with good clinical practice. A formal presentation was delivered to a group of PPI volunteers at the Churchill Hospital, Oxford in April 2017 who were invited to comment on and discuss the study. The PPI showed considerable interest in the study and thought it would be useful to 'see how they manage cancer in other countries.'

4.4.4 Study populations and sample strategy

Secondary care surgical specialists who received referrals for head and neck cancer from primary care were chosen for this study. Such specialists have extensive experience of head and neck cancer referrals compared to primary care practitioners who may see as few as two cases in an entire career (Alho et al, 2006).

The Netherlands was chosen as the country to compare with England. The Netherlands has a superior 1-year survival rate for oral cancer, yet very similar 5-year conditional survival (on surviving for one year) to England. This suggests that later presentation – possibly influenced by the referral system -may be a factor in higher overall Dutch survival.

Purposive sampling was undertaken, according to the principles suggested by Coyne (1997) who points out the need for samples to reflect the 'real world' situation. With this in mind, the samples were purposively selected to obtain consistency across the Dutch and English participants with respect to:

- ENT and maxillo-facial head and neck specialists.
- Sex of participants.

- 'Secondary' care specialists (general ENT and maxillofacial surgeons) and 'tertiary' (head and neck only specialists).
- Age and experience of participants

Potential participants were identified through national lists of specialists and professional networks. Participants were required to be accredited surgical specialists; trainees were excluded. Sampling continued to the point when data saturation, with no new themes likely to emerge, was judged to have been achieved. This was the case after approximately 9 interviews in each country – validated by undertaking a further 3 interviews for confirmation. Therefore, 12 interviews in each country was considered reasonable.

In this study emerging theories during the interviews did not contribute to the sampling strategy, which was, however, influenced by the literature review in this thesis.

4.4.5 Recruitment procedure

Recruitment in England was undertaken by me and in the Netherlands by a Dutch colleague (and co-author of the published version of this chapter). National lists of specialists were scrutinised and professional contacts were also identified. Recruitment continued as the study progressed, following the purposive strategy defined above to obtain a sample to the point of data saturation. Potential participants were contacted in the first instance by an email outlining the nature and purpose of the study. If they expressed an interest, they were contacted again by email and provided with a detailed participant information sheet, prior to arranging a suitable time and place for interview.

4.4.6 Interviewing and data collection

Interviews in the Netherlands took place between June 2017 and October 2017; those in England were conducted from August 2017 to February 2018. I was the single interviewer in both countries. In preparation for this study, I attended the course *'Qualitative studies; from design to publication'* organised by Newcastle University. This included practical exercises in both interviewing technique and workshops on the analysis of interview transcriptions.

At interview, the participant information sheet was reviewed and formal consent signed. A semi-structured interviewing technique was used, employing a flexible interview template, based on existing literature from a wide range of sources, including scoping for this thesis and my own earlier work on urgent suspected cancer systems (Langton et al 2016). As this study (and indeed the thesis) focuses on a policy, the interview questions were also influenced by the work of Ritchie and Spencer (1994) who suggest that in qualitative research on policy four main categories of question can usefully be addressed: contextual, diagnostic, evaluative and strategic. Several questions from within these categories were considered likely to be of value in exploring and comparing referral systems and were used to inform the questions at interview. (table 4.1)

Table 4.1 Categories of qualitative questions in policy research, according to Ritchie and Spencer (1994)

Category	Objective	Example questions (in relation to this study)
Contextual	Nature of 'what exists'	*What is the nature of people's experiences?* *What elements operate within a system?*
Diagnostic	Reasons for 'what exists'	*What factors underlie perceptions?* *Why do needs arise?*
Evaluative	Appraising effectiveness	*What barriers exist?* *How are objectives achieved?*
Strategic	Identifying new theories/plans etc	*How can systems be improved?*

Modified version, adapted from Srivastava and Thomson (2009)

Three possible types of individual interview were considered: structured, unstructured and semi-structured. Structured interviews involve asking exactly the same pre-specified questions to all participants but may limit the interviewer's in-depth questioning and respondents' choice of response. Unstructured interviews have no pre-determined questions and generally the interviewer initiates the interview with a broad question and continues accordingly (Srivastava 2009 et al). It was considered that this very flexible approach offered insufficient consistency across two international sites. Therefore, a semi-structured approach – offering a balance between the two previous approaches – was used for this study. A template of questions was developed (Appendix 3, p216) but the open-ended character of the questions meant that the participants were not limited in their responses.

Interviews were conducted on a face-to-face individual basis rather than in a focus group. There were several reasons for this choice. Head and neck surgery is a relatively small specialty and from a logistical perspective it was considered likely to be difficult to assemble a group of senior clinicians at one time to conduct interviews. Guest et al (2015) note that focus group interviews usually require two data collectors and typically take twice as much time to conduct; this was likely to prove difficult with one interviewer working in two countries. The literature comparing information gained from group and individual interviews provides a mixed picture. On one hand, group dynamics may stimulate discussion whilst on the other some reports indicate that individual interviews uncover greater detail and personal insights (Guest et al 2015). On considering the various options, it was decided to undertake individual interviews.

An iterative approach to further question development was used as interviews progressed and, although the flexible template provided a 'core' and some consistency between countries, the areas explored were not restricted to the template alone.

Interviews were conducted in English. I was accompanied to the interview sites (but not the interview room itself) in the Netherlands by one of my English-speaking Dutch collaborators who was available for any language issues; in practice language proved not to be a problem as all the Dutch participants spoke English well. Interviews took place in a variety of environments, at the convenience of participants, including, in several instances, their own homes. All interviews commenced with the same broad question: '*Could you describe the typical referral process of a suspected head and neck cancer patient to your out-patient clinic***?'.** Interviews typically lasted 30 to 40 minutes and all were securely audio-recorded.

Although interviews were not restricted to pre-determined questions, several important issues were included in the interview template:

- Strengths and limitations of the referral system in the participant's country;
- View of the effectiveness of the system and how it might be improved;
- Referrals that only have a small possibility of cancer and the effect on the system;

- The quality of referrals and the quality of the information provided by primary care;
- The need for education of primary care practitioners and what form it might take.

Interviews were undertaken by a single researcher (me) and as I am an experienced head and neck surgeon, it is acknowledged that this may have influenced the interviewees and the interview process. This is discussed further in the section on 'reflexivity'.

4.5 Analysis

4.5.1 Transcription, familiarisation and thematic analysis

Recorded interviews were transcribed verbatim by a professional transcriber (identified from an Oxford University list of 'approved' transcribers) and the transcribed files were imported into *NVivo 11 Pro* qualitative analysis software (version 11.4.1.1064, QSR International, 2017). Analysis commenced following the first interview and continued during the interviews and beyond. As a first step, each transcript was read and re-read to develop familiarisation, as advised by Pope and Mays (2006). Following familiarisation, coding of the transcripts was undertaken, initially 'line by line' to identify key phrases and concepts and these were subsequently grouped and developed into themes. The analysis was facilitated with NVivo although not exclusively; for example, whilst I used the 'coding stripes' facility of the software extensively, I preferred to use hand-written memos, developed immediately after interviews. Initial coding themes were cross-checked by one of my DPhil supervisors.

Respondent validation was carried out with a limited number of respondents, who agreed that the transcriptions were accurate and representative of the interview.

4.5.2 Memo writing

Memo writing was undertaken in relation to the interviews and to assist with analysis and interpretation. These were recorded by hand immediately after the interviews, for example:

'This is the 3rd Dutch one to talk about the 'need to see patients' in the sense of ensuring that the hospital/department gets the financial income. Maybe why they don't mind seeing lots of patients without cancer??'

4.6 Rigour

Miles et al (2014) define 5 'standards' to assist in establishing the rigour of a qualitative study. These are: objectivity, dependability, credibility, transferability and application. In relation to this study rigour was ensured as follows:

Objectivity: Colorafi (2016) describes this as 'reasonable freedom from researcher bias'. To achieve this aim in this study, the methodology has been described in detail, the sequence of information gathering has been made clear (hence an audit trail is available), a section on 'reflexivity' is included and study data (such as interview transcriptions) have been retained.

Dependability: To increase consistency in this study several principles were followed. Procedures were derived from a specified research question, data were collected 'consistently' (same interviewer and semi-structured interview template) and purposive sampling was undertaken in each country.

Credibility: To ensure credibility, interpretations have been based on data from the study, coding was confirmed by a second researcher and 'respondent validation' was carried out.

Transferability: In this study the respondents' characteristics have been outlined and the limitations of 'generalisability' when sampling from only two countries has been acknowledged.

Application: In order to ensure the findings are available to potential 'stakeholders' (such as clinicians, policymakers and other researchers), this study has been published in the British Journal of Oral and Maxillofacial Surgery.

4.7 Results

4.7.1 Participants

12 participants were interviewed in each country. A summary of the participants' profiles is given in table 4.2. The participants in England included 8 clinicians who specialised in head and neck cancer surgical treatment and 4 who received head and neck cancer referrals from primary care but referred to 'tertiary' colleagues for surgery. The participants in the Netherlands included 5 'head and neck' specialists and 7 'general' specialists.

Table 4.2 – Profile of participants

Country	Interviewee identifier number	Sex	Age (years)	Specialty, maxillofacial (OMFS) or otorhinolaryngology (ENT)	Specialist's hospital department (secondary or tertiary)
Netherlands	NL-1	M	44	ENT	Secondary
Netherlands	NL-2	F	37	ENT	Secondary
Netherlands	NL-3	M	43	ENT	Secondary
Netherlands	NL-4	M	45	OMFS	Secondary
Netherlands	NL-5	M	59	ENT	Secondary
Netherlands	NL-6	M	36	ENT	Secondary
Netherlands	NL-7	M	58	ENT	Tertiary
Netherlands	NL-8	M	42	ENT	Tertiary
Netherlands	NL-9	M	39	OMFS	Tertiary
Netherlands	NL-10	F	49	ENT	Tertiary
Netherlands	NL-11	M	45	OMFS	Tertiary
Netherlands	NL-12	M	58	ENT	Secondary
MEAN NETHERLANDS	**-**	-	**46.25**	**-**	**-**
TOTAL NETERLANDS	**12**	**10M 2F**	-	**8 ENT; 4 OMFS**	**5 Secondary; 7 tertiary**
England	ENG-1	M	49	OMFS	Tertiary
England	ENG-2	M	54	ENT	Tertiary
England	ENG-3	M	53	ENT	Secondary
England	ENG-4	M	56	OMFS	Tertiary
England	ENG-5	M	53	OMFS	Secondary
England	ENG-6	M	55	OMFS	Secondary
England	ENG-7	M	58	OMFS	Tertiary
England	ENG-8	M	60	ENT	Secondary
England	ENG-9	F	43	ENT	Tertiary
England	ENG-10	M	51	OMFS	Tertiary
England	ENG-11	M	45	ENT	Secondary
England	ENG-12	M	56	ENT	Tertiary
MEAN ENGLAND	-	**-**	**52.75**	**-**	**-**
TOTAL ENGLAND	**12**	**11M 1F**	**-**	**6 ENT; 6 OMFS**	**5 Secondary; 7 tertiary**

4.7.2 Themes

From the interviews several themes emerged:

Theme 1: COMMUNICATION ***'The other thing that's largely broken down is the inter-personal contact between specialists and general practitioners'*** ***(English head and neck surgeon)***

By far the most common theme in this study amongst the English participants was the lack of direct communication between primary and secondary care practitioners during the referral process. Many

English specialists, particularly those aged over 50, felt that this had been better in the past and the two-week rule system did not facilitate inter-clinician discussion. There was a strong view that improved communication between primary and secondary care would improve the effectiveness and efficiency of head and neck cancer referral:

'It is just a shame to me that we are encouraged not to pick up the phone. The general practitioners don't pick up the phone and refer any more. I genuinely feel that that's a quicker way forward for a lot of the patients' (English surgeon ENG-1)[8]

'We have lost the direct contact with primary care practitioners, which historically was a phone call. Dr Smith phones you up and says, listen, I am worried about Mrs Jones who I think has got a cancer. You see the patient that afternoon and you can use a lot of the filtering systems through the direct patient, doctor to doctor contact.' (English surgeon ENG-6)

'It's all based on that person to person communication. You can run a healthcare system in as protocolised way as you choose. That doesn't overcome that human interaction aspect of this. I cannot speak too strongly that that is important especially in something as complex as head and neck. I think it's critical.' (English surgeon ENG-2)

'In the 17 years I've been a consultant I have seen GPs and secondary care clinicians move further and further and further apart in a general sense. We don't really interact socially. We don't really interact academically.' (English surgeon ENG-3)

Specialists in the Netherlands, on the other hand, reported very close and direct communication with their primary care colleagues and often commented on the importance of this relationship:

'I think it's very important that the GP must feel confident to call the specialist. It must be easy for them to call. They don't know. That is an important thing. Of course, we make time for those people. The first weeks are important to do it quickly.' (Dutch surgeon NL-6)

'It's necessary that you have short lines. And you only have short lines if you know the names and you know the person and you have them on the phone every now and then. I think this system works.' (Dutch surgeon NL-10)

'If they want they can always talk to us. They have got a special telephone number to call the department' (Dutch surgeon NL-11)

Theme 2: SPEED OF REFERRAL '*If I see the letter myself or have talked to the GP, I let them come the same day or the day after.' (Dutch ENT surgeon)*

English specialists commented on the lack of influence they had on both the process and speed of referral of suspected head and neck cancer:

'The typical referral process is a standard two-week referral form, which comes in a standard proforma. We actually have no interaction with the process prior to the patients arriving at the clinic.' (English surgeon ENG-4)

[8] Participant number, denoted English (ENG) or Dutch (NL)

'These patients ought to be seen very quickly, much quicker than the 14 days allocated, perhaps two or three days.' (English surgeon ENG-9)

'If you were referred to the neck lump clinic on Tuesday afternoon, you have to wait eight days for an appointment. I aim to see most patients at less than seven days and currently that is only about 50% of patients. As a rule, I think we could be quicker.' (English surgeon ENG-9)

Whilst both English and Dutch specialists agreed there was a need to see suspected cancer patients rapidly, the Dutch clinicians were often able to see patients much more quickly than in England. They also had substantial influence on the referral process:

'I always offer to see the patient the same day. Same day or the day after. As soon as possible. Patients appreciate it if they can come the same day and well, just meet the surgeon and to get started with all the diagnostics.' (Dutch surgeon NL-5)

'We call the patients and invite them for a visit on the outpatient clinics on Monday or on Wednesday so that's twice a week, so they never have to wait longer than five days.' (Dutch surgeon NL-5)

Theme 3: REFERRALS THAT DO NOT HAVE CANCER *'So you sort of see a 25-year-old, the history says they get mouth ulcers once every two months for the last two years. They have ticked oral cancer and they have got a two-week referral. In my experience it is fairly common.' (English head and neck surgeon)*

This was a common theme in the English interviews. There was a mixed view – on one hand, frustration at the perceived inefficiency of large numbers of patients referred with only a remote chance of cancer whilst on the other hand an acknowledgement that a system such as the two-week rule by design 'casts a wide net'. English clinicians expressed concern that other 'routine' cases might be disadvantaged by the large number of suspected cancer referrals with only a very small risk of the disease. They also suggested that GPs in some instances referred on the fast-track pathway when the prospect of cancer was low for fear of missing a cancer diagnosis:

'I think it is inevitably going to be part of a process where screening occurs and you are going to have to look at a lot of people with symptoms before you actually find the cancers. In some respects, from a patient's perspective and population perspective I think it's good because they are getting seen quicker. But from a resource perspective, I think it's appalling.' (English surgeon ENG-1)

'I think our colleagues in the primary care sector are quite acutely aware of that. I think they would rather send something which they probably know in the back of their mind that it probably isn't, but they are not willing to take that chance and put it in a routine referral and so they will just put it on a two-week referral and I think that probably accounts for a lot of why we are getting a lot - 80-90% of them - that are just benign disease.' (English surgeon ENG-5)

'But currently the way things stand, it penalises people in the routine pathway and encourages patients, doctors and dentists to use the two-week rule pathway for non-malignant conditions.' (English surgeon ENG-10)

Specialists in the Netherlands, particularly 'general' ENT/maxillofacial surgeons, who received the bulk of GP referrals rather than those in tertiary centres, also experienced many referrals with only a small risk of cancer but were more inclined to view this as inevitable. They also felt that direct discussion with general practitioners was helpful in deciding the urgency of the case:

'It's part of the job. It's better that we do the whole work up and get to say, lucky you, you haven't got cancer.' (Dutch surgeon NL-3)

'You have patients who are referred with either a bit of a bulk at the tongue base which might just be lingual tonsil which is a bit bulky and all the alarm bells are sounding and you try to figure out if it's cancer or not. We get the lateral neck mass which turns out to be a bronchogenic cyst and not the lymph node from the unknown primary. We get them. We all get them.' (Dutch surgeon NL-3)

'If I speak to a general practitioner, I tell him what I think of his story and then I tell him, we will see the patient within one hour the same day, a few days or a few weeks. We agree. He follows my suggestion, nearly always. It's seldom a general practitioner thinks the sense of urgency is larger than I suspect. We will tend to stay on the same side, of course.' (Dutch surgeon NL-1)

Specialists in the Netherlands were also keen to ensure that they, rather than another surgical unit, received referrals and felt it important that a good relationship with GPs was maintained:

'Yes, we have a good relationship with the GPs in our area. Also, we must have that, because when we don't have a good relationship they send the patient to other hospitals and we need patients'. (Dutch surgeon NL-5)

Theme 4: QUALITY OF REFERRALS '*I think it's utterly awful that patients can be referred with a diagnosis of a suspected malignancy with a tick in a box.*' *(English head and neck surgeon)*

Amongst the English specialists there was a wide range of views on the quality of referrals. One prominent theme was a dislike for 'tick box' referrals without any additional information and many felt that the referrals were better when some further clinical information was included. However, other participants noted that often symptoms did indeed require urgent investigation:

'Essentially what we've created is a tick box exercise, so you tick a box in terms of where you feel that they might follow the criteria with actually very little in the way of free text and actually, as you and I know, the free text actually gives you more information. Very few people actually put any free text in now at all.' (English surgeon ENG-1)

'Just ticking a box that says, you know, hoarse voice with no duration of symptoms or anything like that.' (English surgeon ENG-11)

'I think if you referred an unresolved lump in the neck that is actually a fair cop. That is exactly what secondary care should be dealing with, because unless you have got access to an ultrasound scan and aspiration services you aren't going to get a diagnosis on that.' (English surgeon ENG-2)

Dutch specialists had very few criticisms of the quality of referrals:

'I really think that the quality of the general practitioners here is fairly good.' (Dutch surgeon NL-1)

'It's only rarely that I really think, okay, this is really a late referral by somebody and so I think, in general, everything is doing okay.' (Dutch surgeon NL-4)

Theme 5: PRIMARY CARE CHALLENGES *'But again, I am aware of the pressures GPs are under, where they haven't got much time, six, seven minutes to really see a patient and then sort things out.' (English head and neck surgeon)*

Specialists in England and the Netherlands commented on the difficulties faced by primary care practitioners. English specialists commented both in terms of pressure of time and the difficulties of identifying head and neck malignancy in the primary care setting:

'The GP is overworked. They are not having adequate time to see patients. They are ticking boxes and getting them off the plate as quickly as possible.' (English surgeon ENG-5)

'What we used to have was 'urgent', 'soon' and 'routine'. We don't stratify the referrals any more. So, if a doctor or a dentist wants to have somebody seen quickly they just use that pathway.' (English surgeon ENG-4)

'The difficulty with head and neck cancer diagnosis is that the GP can't nasendoscope the patient. To a certain extent that diagnostic test is not available to them and therefore, the need for somebody to examine the larynx and pharynx becomes the issue.' (English surgeon ENG-3)

The overall view in the Netherlands was very similar, with specialists also commenting on the volume of work in general practice and the difficulties identifying head and neck cancer:

'I think the GP is a busy man or woman here in the Netherlands, they have a lot of busy practices.' (Dutch surgeon NL-9)

'The GPs, they have to know so many things, but they are not specialists.' (Dutch surgeon NL-9)

Theme 6: PRIMARY CARE EDUCATION *'A typical graduate who comes through UK medical schooling would have done, at the most five days of ENT, if they are lucky' (English ENT surgeon)*

In both England and the Netherlands there was a broad range of views regarding the need for education of general practitioners in head and neck cancer. On one hand some practitioners advocated regular primary care education, either face-to-face or internet based whilst others suggested that such education

was of limited value. Participants in England suggested that whilst primary care education was, potentially, useful the practicalities of delivering it remained challenging:

'The logical idea is that if we take a chunk of our time to educate primary care about what oral cancer looks like and what pre-malignant areas are and all that kind of stuff that will reap the benefits, because they won't refer as much unnecessary stuff that is filling up the clinics using resource that could otherwise be used more appropriately. My experience of that is that it doesn't work. All that happens is they send in more.' (English surgeon ENG-9)

'The most important thing would be to make the doctors and the dentists more aware of the clinical signs and symptoms and to be able to educate them and tell them about which would be the appropriate cases and what cancers looks like.' (English surgeon ENG-9)

'I have done myself a few sessions and teaching sessions and lectures to the primary care physicians. Unfortunately, I must admit that there was a very poor response in attending these sessions.' (English surgeon ENG-9)

'One of my roles is about making sure examination of the oral cavity is in the curriculum for every doctor. It's hard to get it in, but I have insisted it goes in.' (English surgeon ENG-12)

'I teach the GP ST3s every year for the region. I get two hours to teach them about head and neck cancer. So we do try and put the information out there. But we know that because head and neck cancer is not that common, most GPs will only look after one or two head and neck patients in their whole career.' (English surgeon ENG-11)

In the Netherlands several views emerged, broadly similar to those in England. In the Netherlands specialists generally agreed that primary care practitioners' knowledge of ENT cancer was not extensive. The views on the need and type of education were, however, very diverse ranging from marked enthusiasm for training sessions to the opinion that such training was of little value at all:

'The GPs here don't have a lot of ENT knowledge.' (Dutch surgeon NL-7)

'You know that it's just as common as leukaemia or whatever and everybody knows about that but nobody knows about head and neck cancer, which is strange.' (Dutch surgeon NL-3)

Interviewer: *'What about an education programme for GPs. Do you think that would be a useful thing in head and neck cancer identification?*
Respondent: *'No.'* (Dutch surgeon NL-8)

Theme 7: THE ENGLISH SYSTEM OF REFERRAL: PERCEIVED BENEFITS '*It works well. I think it does, anyway just from my experience over the last ten years. It's not perfect by a long shot, nothing is. Certainly, it's getting better.' (English maxillofacial surgeon)*

Many English specialists, whilst being aware of shortcomings in 'two-week rule/NICE guidance' system did believe that it had benefits:

'I think there is no question that it's a very patient-centred process. It is valued by patients that come and use it and they certainly appreciate the speed at which things are done.' (English surgeon ENG-5)

'The best points? Probably the fact that we now have designated two-week cancer referral slots in our clinic, so we are not looking to crow-bar them into an existing clinic' (English surgeon ENG-4)

'I am not against targets. I actually think targets concentrate the mind and where they work really well is actually in the hospital care setting. It's a thing that concentrates minds.' (English surgeon ENG-2)

'Pathways gave us a lever and we forget that we had a huge ridiculous waiting list in the 80s and 90s to access to care for all sorts of things. Two-week wait emphasised cancer.' (English surgeon ENG-7)

Theme 8: THE DUTCH SYSTEM OF REFERRAL – PERCEIVED BENEFITS '*I am quite happy with the way the admission to the hospital is working. I am quite happy with it. I don't see - I rarely see problems'* (Dutch maxillofacial surgeon)

The Dutch specialists were, overall, very happy with their system of referral and considered GP-specialist communication, speed of service and highly centralised secondary treatment centres to be key benefits:

'I think it's good. There is a quick referral from the GP and also quick referral from the general ENT to the head and neck.' (Dutch surgeon NL-11)

'I think one of the big advantages of the Dutch system is the fact that it's head and neck oncology is restricted to the eight academic centres and three or four maybe preferred partners as we call them that really, I think that is the biggest advantage in achieving a good outcome.' (Dutch surgeon NL-4)

'I think that is very important that there is a telephone number which you can get easily and they arrange it very fast.' (Dutch surgeon NL-9)

4.8 Discussion

4.8.1 Summary and main findings

This study highlights both similarities and marked differences in the views of English and Dutch specialists of their systems of fast-track head and neck cancer referral.

In several respects, both countries face similar problems, such as the limited head and neck cancer experience of primary care practitioners, the large number of suspected cases referred that do not have cancer and the uncertainty regarding the best approach to education.

However, there are aspects where marked differences exist. One important area identified in this study is primary care to specialist care communication. The most common theme amongst the English participants was the diminishing direct communication between the GP and specialist, often to the point of being non-existent, in the referral of head and neck cancer. There was a broadly-held view that

professional discussion would be helpful in both reducing the number of referrals with benign conditions and allow urgent cases to be seen more rapidly. Interestingly, the importance of good, direct primary care to specialist communication was also the commonest theme amongst the Dutch participants. In marked contrast to England, telephone discussions about patients were common, often using dedicated telephone numbers. Such communication was reported to facilitate both stratification of urgency and, when appropriate, very rapid referral. They frequently saw the patients the same day as referral and felt that this brought several benefits including the ability to commence investigations at the earliest opportunity and reduce the period of patient anxiety. In England, specialists noted that whilst nearly every patient referred with suspected head and neck cancer was seen within the required 14 days there was no 'stratification' of urgency and nearly all patients were seen after 12 or 13 days, thus meeting the prescribed target but with little or no input from head and neck cancer experts up to that time. Furthermore, nearly all the English participants emphatically disliked a 'tick box' referral with no further information in the correspondence

Participants from both countries mentioned that a high proportion of referrals did not have cancer. A systematic review by Langton et al (2016) reported that 8.8% of head and neck English TWR referrals were diagnosed with cancer and positive predictive values of this order are typical for many cancer types referred via the English TWR including gastro-intestinal (Thorne et al 2009), breast (Potter et al 2008), colo-rectal (Thorne et al 2006), CNS (Pengiran et al 2003) and gynaecology (Morrison et al 2003). Similarly, in the Netherlands, van Boven et al (2017) reported low positive predictive values for symptoms of potential cancer presenting to primary care including haemoptysis (2.7%) rectal bleeding (2.6%) and haematuria (2.2%). However, in this study it was notable that specialists in the Netherlands were more inclined to accept investigating 'negative' cases as 'just part of the process' in contrast to their English counterparts, several of whom commented on the impact that many negative suspected cancer cases had an adverse effect on other patients. In contrast, several Dutch specialists commented on the 'need to see patients' and the risks of them being sent to 'rival' hospitals – presumably a financial need - which may, at least in part, explain the Dutch relative enthusiasm for seeing many cases where cancer is absent.

In both countries, participants commented on the difficulties of diagnosing a relatively uncommon malignancy such as head and neck for a generalist in primary care with very limited clinical time. However, many English specialists felt the TWR system was being utilised, in some instances, to gain access to secondary care when the risk of malignancy was remote. In both countries there was a wide range of views on the need and type of education for GPs in head and neck cancer although in both countries the delivery of training was considered challenging.

Despite being critical of several aspects of the TWR/NICE guidance system in England, there were many comments on the benefits. These included the patient-centred process, the development of clinics organised around the need to see potential cancer patients in a timely manner and the importance of an established access target to promote 'focus'.

4.8.2 Comparison with existing literature

The most prevalent theme in this study was the importance of communication between primary care and specialist. The English participants felt this was inadequate – particularly following the introduction of the TWR/NICE guidance system - whilst Dutch participants often employed direct contact, usually by telephone, to facilitate rapid referral and assist with 'stratification' of urgency. The primary-secondary care interface has long been recognised to be of importance in patient management in general (Kvamme et al, 2001) and many studies have emphasised the importance of close communication in effective cancer care (Tudor Car et al 2016; Dalhaus et al 2014; Redaniel et al 2015). There is evidence to indicate that primary care practitioners also greatly value information sharing in the care of cancer patients (Dalhaus et al, 2014). The importance of such communication in relation to head and neck surgery was emphasised in a questionnaire study of English primary and secondary clinicians by Bethell et al (2015) and this study strongly supports this view.

In this study specialists in both countries considered that primary care knowledge of head and neck cancer was not extensive, which has been demonstrated in several studies (Appelbaum et al 2009; Lau et al 2018). However, in agreement with other studies (Mansell et al 2011) there was little consensus on the value or type of education that might be helpful. Interestingly, Mansell's systematic review,

which included studies that employed lectures, a training session or internet/video sessions, found that no educational intervention produced a long-term positive outcome.

This study found that in the Netherlands patients were, in many instances, seen more rapidly in secondary care than in England. In some other countries, such as Denmark, cancer cases attend secondary care in typically 2 or 3 days (Olesen et al, 2009). It is known that patients often consider quality of care to be related to rapidity of diagnosis and treatment (Malmström et al, 2018). However, it is by no means certain that waiting time reductions of a few days translate into superior outcomes for head and neck cancer (McGurk et al 2005) although a shorter interval may lead to reduced patient anxiety (Ndukwe et al 2010).

Clinicians in both countries identified good aspects of their respective systems. The Dutch specialists emphasised rapidity of referral and a close relationship with GPs. The English specialists felt that their system was patient-centred, quick and that targets provided a means to achieve 'focus'. In a qualitative study on the referral of colorectal cancer by Redaniel et al (2015) participants also commented on the benefits of the TWR/NICE guideline system, including speed of referral and reduction of patient anxiety.

4.8.3 Reflexivity

Mays and Pope (2000) suggest that *'reflexivity means sensitivity to the ways in which the research process have shaped the collected data'* and this may include prior experience, personal and intellectual biases, personal characteristics and the 'distance' between participants and the researcher.

In relation to this study there are several aspects that may have shaped the research findings. Firstly, my own experience as a head and neck cancer surgeon may have influenced both study concept and study design; indeed, it is certainly the case that much of my interest in the subject of effective suspected cancer referral as a whole is influenced by my professional experience. Secondly, reflecting on the interviews, I gained an 'impression' that the Dutch participants presented their system 'in a good light' – as one might if a colleague from another country was visiting one's own establishment – whilst the English surgeons often spoke as if 'gossiping with a colleague'. Thirdly, it is probably reasonable to

say that whilst the 'distance' between interviewer and participants in both countries was minimal, English interviews may have been influenced by the fact that several participants were known to me from previous professional encounters.

4.8.4 Strengths and limitations

This study is, to my knowledge, the first study to examine and compare the views of specialist surgeons in head and cancer in two European countries, with different survival outcomes for the disease, on their referral systems. Previous work looking at clinicians' views on cancer referral has focused on single countries (Redaniel at al 2015; Dalhaus 2014; Tudor Car et al 2016) including limited published work in relation to head and neck cancer (Bethell et al 2015) although some international qualitative work has studied patients' views (MacArtney et al 2017; Malmström et al 2018) A cancer such as head and neck is seen only very rarely in primary care, perhaps only once or twice in an entire GP's career. Therefore, the views of specialists on the referral of the condition are valuable as they will receive many referrals every week of their working lives and have an in-depth understanding of the process. However, the perspective of both primary care practitioners and patients could possibly be valuable.

The sample in this study is relatively small (12 interviews in each country) but it was judged that data saturation was achieved in both countries following the interviews. The sample in England included interviews in Yorkshire, Lancashire, Greater Manchester, Merseyside and Cheshire. Clinicians in the Netherlands were interviewed in many different parts of the country. Participants in both countries worked in a range of large cities and smaller towns and clinicians in academic and non-academic roles were interviewed.

The study was restricted to two countries. Studying further countries with different health systems may shed further light on the primary to specialist referral process for suspected head and neck cancer.

4.9 Conclusions

The overall objective of this study was to compare the systems of head and neck cancer referral in the Netherlands and England from the point of view of the secondary care clinicians and attempt to identify aspects that might enhance the early diagnosis of head and neck cancer. The most prominent theme was

primary care-specialist communication. Interestingly, this was identified by the English clinicians as the aspect most lacking in the English referral system and by the Dutch clinicians as the most useful feature of their system. Other important themes included speed of referral (often much quicker in the Netherlands), the lack of ability to identify the urgency of referrals in England (good communication in the Netherlands allowed professional discussion to assist with this aspect), the large number of referrals that do not have cancer (particularly in England) and very variable views on the need for education in primary care in both countries. Specialists in the Netherlands were very satisfied with their system and while English specialists identified many good points in the TWR system there was an overall view that improvements could be made.

4.9.1 Implications for practice and research

It is suggested, in the light of this study, that improved direct communication between primary and secondary care is a factor likely to improve efficiency and effectiveness in head and neck cancer referral and, possibly, outcomes in England. It is also, of course, arguable that better communication might alone improve other aspects of the referral system identified in this study – speed of referral, the quality of referrals, unnecessary referrals and assist with educating GPs. However, with increasing pressure on primary and secondary care, any such system would need to be carefully piloted to ensure safety, effectiveness and practicality. Nevertheless, it is arguable that improved efficiency of the referral system, reducing unnecessary referrals, might prove cost-effective. I suggest that these aspects require further research, for all types of cancer.

4.10 Sources of support

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4.11 Related publication

Langton S, Rijken JA, Bankhead CR, Plüddemann A and Leemans CR (2019) *Referrals for head and neck cancer in England and the Netherlands: an international qualitative study of the views of secondary-care surgical specialists* British Journal of Oral and Maxillofacial Surgery 57 116-124

Chapter 4 references

Alho O-P, Teppo H, Mäntyselkä P and Kantola S (2006) *Head and neck cancer in primary care: presenting symptoms and the effect of delayed diagnosis of cancer cases* Canadian Medical Association Journal 174 779–784

Applebaum E, Ruhlen TN, Kronenberg FR, Hayes C Peters ES (2009) *Oral cancer knowledge, attitudes and practices A survey of dentists and primary care physicians in Massachusetts* Journal of the American Dental Association140 461-467

Bethell GS and Leftwick P (2015) *Views of general practitioners and head and neck surgeons on the referral system for suspected cancer: a survey* Journal of Laryngology and Otology 129 893-897

Butler J, Foot C, Bomb M, Hiom S Coleman M et al (2013) *The International Cancer Benchmarking Partnership: An international collaboration to inform cancer policy in Australia, Canada, Denmark, Norway, Sweden and the United Kingdom* Health Policy 112 148-155

Colorafi KJ and Evans B *Qualitative descriptive methods in health science research* Health Environments Research Journal 9 16-25

Commonwealth Fund (2020) *International Profiles of Health Care Systems* available at: https://www.commonwealthfund.org/international-health-policy-center/countries (accessed August 2020)

Coyne E and Borbasi S (2009) *Living the experience of breast cancer treatment; the younger woman's perspective* Australian Journal of Advanced Nursing 26 6-13

Dahlhaus A, Vanneman N, Guethlin C, Behrend J, Siebenhofer A (2014) *German general practitioners' views on their involvement and role in cancer care: a qualitative study* Family Practice 31 209-214

Edvardsson K, Gavare R, Ivarsson, I et al (2011) *Sustainable practice change: Professionals' experiences with a multisectoral child health promotion programme in Sweden* BMC Health Services Research 11 61

Forbes LJL, Warburton F, Richards MA et al (2014) *Risk factors for delay in symptomatic presentation: a survey of cancer patients* British Journal of Cancer 111 582-588

Gatta G, Botta L Sánchez MJ (2015) *Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study* European Journal of Cancer 51 2130-2143

Goy J, Hall SF, Feldman-Stewart D et al (2009) *Diagnostic delay and disease stage in head and neck cancer: A systematic review* Laryngoscope 119 889-898

Guest G, Namey E, Taylor J et al (2015) *Comparing focus groups and individual interviews: findings from a randomized study* International Journal of Social Research Methodology 20 693-708

Hamilton, W (2012) *Emergency admissions of cancer as a marker of diagnostic delay* British Journal of Cancer 107 1205-1206

Hammarberg K, Kirkman M and de Lacey S (2016) *Qualitative research methods: when to use them and how to judge them* Human Reproduction 31 498-501

Kvamme OJ, Olesen F and Samuelsson M (2001) *Improving the interface between primary and secondary care: a statement from the European Working Party on Quality in Family Practice (EQuiP)* British Medical Journal Quality and Safety 10 128

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Lau K, Wilkinson J and Moorthy R (2018) *A web-based prediction score for head and neck cancer referrals* Clinical Otolaryngology 43 1043-1049

MacArtney J, Malmström M, Nielsen TO et al (2017) *Patients' initial steps to cancer diagnosis in Denmark, England and Sweden: what can a qualitative, cross-country comparison of narrative interviews tell us about potentially modifiable factors?* BMJ Open 2017;7:e018210. doi:10.1136/bmjopen-2017-018210

Malmström M, Rasmussen BH, Bernhardson B-M, Hajdarevic S, Eriksson LE, Andersen RS and MacArtney JI (2018) *It is important that the process goes quickly, isn't it? A qualitative multi-country study of colorectal or lung cancer patients' narratives of the timeliness of diagnosis and quality of care* European Journal of Oncology Nursing 34 82-88

Mansell G, Shapley, M, Jordan JL, Jordan K (2011) *Interventions to reduce primary care delay in cancer referral* British Journal of General Practice DOI: 10.3399/bjgp11X613160

Mays N and Pope C (2000) *Assessing quality in qualitative research* British Medical Journal 320 50-52

McGurk M, Chan C, Jones J et al (2005) *Delay in diagnosis and its effect on outcome in head and neck cancer* British Journal of Oral and Maxillofacial Surgery 43 281-284

Miles M, Huberman M and Saldana J (2014) *Qualitative data analysis: a methods sourcebook* (3rd Ed.) Thousand Oaks Ca: Sage

Morrison J, Gillespie S and Mackenzie IZ (2003) *'Two week wait' standards for suspected gynaecological malignancy. On target, but missing the point* Journal of British Menopause Society 9 170-172

Ndukwe N, Borowski DW, Lee A, Orr A, Dexter-Smith S and Agarwal KA (2010) *The two-week rule for suspected colorectal cancer: Patient experience and psychological impact International Journal of Healthcare and Quality Assurance 25 (1) 75-85*

Neal RD (2009) *Do diagnostic delays in cancer matter?* British Journal of Cancer 109 S9-S12

NHG Standaarden (2017) available at: https://www.nhg.org/nhg-standaarden (accessed August 2020)

NICE (2015) *Suspected cancer: recognition and referral* available at: https://www.nice.org.uk/guidance/ng12/chapter/1-recommendations

Oderkirk J, Ronchi L and Klazinga N (2013) *International comparisons of health system performance among OECD countries: Opportunities and data privacy protection challenges* Health Policy 112 9–18

Pengiran Tengah DSNA, Byrne PO and Wills AJ (2003) *Urgent 2-week referrals for CNS/brain tumours: a retrospective audit* Clinical Oncology 15 (1) 7-9

Pope C, Mays N (eds.) (2006) *Qualitative research in healthcare* London BMJ Books

Potter S, Govindarjulu S, Shere M, Braddon F and Greenwood R (2007*) Referral patterns, cancer diagnoses and waiting times after the introduction of the two-week wait rule for breast cancer: a prospective cohort study* British Medical Journal 335 288 – 290

Quaife SL, Winstanley K, Robb KA et al (2015) *Socioeconomic inequalities in attitudes towards cancer: an international cancer benchmarking partnership study* European Journal of Cancer Prevention. 24(3):253-260

Redaniel MT, Ridd M, Martin RM, et al (2015) *Rapid diagnostic pathways for suspected colorectal cancer: views of primary and secondary care clinicians on challenges and their potential solutions* BMJ Open 5:e008577. doi: 10.1136/bmjopen-2015-00857

Ritchie J and Spencer L (1994) *Qualitative data analysis for applied policy research* in Bryman A and Burgess RG *Analysing qualitative data* New York: Routledge

Rose PW, Rubin G, Perera-Salazar R et al (2015) *Explaining variation in cancer survival between 11 jurisdictions in the International Cancer Benchmarking Partnership: a primary care vignette study* British Medical Journal Open 5: e007212

Sandelowski M (2000) *Whatever happened to qualitative description?* Research in Nursing and Health 23 483-505

Sandelowski M (2010) *What's in a name? Qualitative description revisited* Research in Nursing and health 33 77-84

Seoane J, Takkouche B, Varela-Centelles P, Tomás I and Seoane-Romero J (2012) *Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis* Clinical Otolaryngology 37 99-106

Silverman D (2000*) Doing qualitative research; a practical guide* Thousand Oaks Ca: Sage Publications

Srivastava A and Thomson SB (2009) *Framework analysis: a qualitative methodology for applied policy research* Journal of Administration and Governance 4(2) 72-79

Thorne K, Hutchings HA and Elwyn G (2006) *The effects of the two-week rule on NHS colorectal diagnostic services: a systematic literature review* BMC Health Services Research 6 43

Thorne K, Hutchings HA and Elwyn G (2009) *The two-week rule for NHS gastrointestinal cancer referrals: a systematic review of effectiveness* The Open Colorectal Cancer Journal 2 27-33

Tudor Car L, Papachruistou N, Urch C et al (2016) *Preventing delayed diagnosis of cancer; clinicians' views on main problems and solutions* Journal of Global Health 6 1-10

Van Boven K, Uijen AA, van de Wiel N, Oskam SK Schers HJ and Assendelft WJJ (2017) *The diagnostic value of the patient's reason for encounter for diagnosing cancer in primary care* Journal of the American Board of Family Medicine 30 806-812

CHAPTER 5: A comparison of primary care doctors and dentists in the referral of oral cancer: a systematic literature review

5.1 Abstract

Background

Oral cancer is referred to specialist care by both primary care doctors and dentists. Studies have reported varying proportions referred by each professional group but have also noted that dentists more frequently refer oral cancer patients following routine check-ups when the patient is not experiencing symptoms. Furthermore, it has been reported that there may be differences in the stage on presentation for patients referred by primary care dentists and doctors, with dentists referring patients at an earlier stage. However, in the UK approximately half the adult population do not receive regular dental care.

Aim and objectives

To conduct a systematic review on studies that compare primary care doctors and dentists in the referral of oral cancer with a focus on three main aspects: (1) the proportion of diagnosed oral cancers referred by each primary care profession (2) the differences in stage on presentation for oral cancers referred by each profession (3) difference in delay (professional and patient) for oral cancers referred by each profession. As a secondary objective, proportion of patients referred as 'incidental findings', when reported.

Methods

Electronic searches: Medline, Embase, Scopus, Google Scholar, Web of Science, CINAHL.

Other searches: Browsing the reference lists in initially-identified studies; author searching (in relation to initially-identified studies); citation index search; browsing the 'find similar' sections of many electronic databases; professional contacts; expert consultation; conference proceedings; Research Registry (https://www.researchregistry.com) and database of theses (EThOS - Electronic Theses Online Service).

Selection criteria: Studies that compare primary care doctors primary care dentists (i.e. the study included comparative data between both professions) in oral cancer referral were considered for this review. Studies were required to include one or more of the following: (1) proportion of diagnosed cancers referred by each profession (2) stage on presentation (3) delay.

Data collection/analysis: Two reviewers assessed studies for inclusion and collected data independently. Heterogeneity was assessed by inspection of forest plot confidence interval overlap and calculation of I^2. Random-effects meta-analysis was undertaken when I^2 was over 60%.

Results

22 studies from 10 countries were included, a total of 4953 oral cancers. The percentage of medical referrals ranged from 13% to 86%, the percentage of dental referrals from 15% to 80%. Random-effects meta-analysis indicated a combined relative risk of medical referral to dental referral of 1.36 (95%CI 0.99 to 1.86). For UK-based studies, the relative risk was also 1.36 (95% CI 1.05 to 1.76). There was considerable heterogeneity for all studies and for a sub-group of UK studies: I^2 96.4% (95% CI 95.4 to 97.1) and 81.0% (95% CI 63.3 to 90.1) respectively. Several studies showed a lower stage for dentally referred cancers; the combined risk of dentists/GPs referring early (stage 1 and 2) disease was 1.37 (95% CI 1.17 to 1.60) and one cause may be the much higher number of cases referred by dentists in the absence of symptoms. No studies demonstrated a statistically significant difference in delay.

Conclusions

Oral cancer is referred by both GPs and dentists, typically about 50% from GPs, 40% from dentists although there is a wide range, probably depending on local circumstances. Both groups require appropriate skills in oral examination, recognition of oral cancer and pre-cancer and knowledge of the risk factors. Several studies show a lower stage for dentally referred cancers, possibly partly explained by the number of cases referred in the absence of symptoms by dentists. Effectively, those that attend the dentist regularly are a select population gaining a regular 'screen' for oral cancer, yet it is likely that this is not delivered to those with the highest risk. In the light of this review, it is suggested that further work is required in the identification of high-risk individuals, methods of accessing such people, both for possible screening and preventive interventions, cost-benefit studies and assessment of the use of 'allied healthcare professionals' for oral cancer/pre-cancer screening examinations

5.2 Introduction

This chapter presents a systematic review comparing primary care doctors and dentists in the referral of oral cancer to specialist care.

Oral cancer stage at diagnosis has a major influence on survival (Mehanna et al 2010; Mao et al 2004) and cancers that are larger and have spread to the lymph nodes have a much poorer prognosis. Three year crude survival for stage 1 and 2 (early) disease is approximately 80% whilst for stage 3 and 4 (advanced) disease the rate is less than 50% (Cancer Research UK 2018[a]). Unfortunately, approximately 50% of oral cancers present at advanced stage 3 or 4, despite the accessibility of the mouth to relatively easy examination (Stefanuto et al 2014).

Oral cancer is unique amongst malignancies in that it is referred to specialist care by both primary care doctors and dentists, which is very unlikely for other types of cancer (Ford et al 2013). Proportions referred by each group vary across studies. A study of 200 oral cancer patients in the UK (Crossman et al 2016) reported that 57% were referred from their GP, 32% by their dentist, 2% via a hospital emergency department and 9% unknown, whilst in a Canadian series 65% of oral cancers were referred from a dentist (Holmes et al 2003). In the UK, both medical and dental primary care practitioners are provided with a list of 'guideline' symptoms and signs to assist in the referral of oral cancer (NICE 2004; NICE 2015). Several authors note the importance of utilising these guidelines in conjunction with thorough history and examination – '*the principles of good medical practice are paramount'* (Rubin et al 2015). However, one study (Meskin 1994) found that only 18% of family physicians carried out an examination of the mouth on at least half their patients.

Further differences between the referrals from each group of practitioners have been reported. In one study (Holmes et al 2003) 47% of dentist-diagnosed oral cancers were identified during a non-symptom driven visit whilst all medical referrals were symptom driven. In the same study, the non-symptom diagnoses were at a statistically significant better (lower) average clinical and pathological stage (1.7 and 1.6 respectively) than lesions detected during a symptom-directed examination (2.6 and 2.5 respectively). It would seem, therefore, that 'routine examination' of the oral soft tissues at a dental

check-up has importance in the early diagnosis of oral cancer and dental practitioners are in a good position to carry out such examination (McCann et al, 2000). However, English NHS data for 2017-18 indicated that only 50.9% of adults had visited an NHS dentist in the previous 2 years (NHS Digital 2018) and it is probable that those at highest risk of oral cancer are least likely to attend regular dental consultations (Donaldson et al 2008).

5.3 Aim and objectives

The overall aim of this systematic review is to compare primary care doctors and dentists in the referral of oral cancer, focusing on three main objectives: (1) the proportion of diagnosed cancers that were referred by each profession (2) differences in stage on presentation for referrals from each profession (3) differences in delay (professional and patient).

5.4 Methods

5.4.1 About systematic reviews and choice of study design

Systematic reviews collate evidence from primary studies to provide an answer to a defined research question. In contrast to other types of review, such as the 'invited review' or 'journalistic review', in which evidence is not selected in any standardised, objective or clearly stated way, systematic reviews are carried out in a clear, systematic manner. They aim to answer clear questions, have precise objectives and methodology and are conducted in a rigorous, explicit and reproducible manner (Greenhalgh 2010).

Systematic reviews have several advantages. They are useful in synthesising a number of individual studies, which may have conflicting results. By summarising all the studies on a specific question, they examine a broader range of findings than the results of perhaps one or two studies. They can be used to determine whether findings are generalisable across different populations and by using explicit and rigorous methodology, including searching the 'grey' and unpublished literature, bias is limited. Summary of outcomes in a meta-analysis can increase the power and precision of results (Juhl 2018; Akobeng 2005). Systematic reviews are increasingly advocated as a useful and concise way of keeping

up to date with current literature; it has been suggested that up to 20 articles per day would otherwise need to be read by a typical clinician wishing to keep abreast of relevant developments (Young 2005).

Systematic reviews are not without disadvantages. For example, the increased power of a systematic review can result in even small biases causing an apparent 'effect' (Glassziou et al 2001). However, for this study, a systematic review was considered to have a number of advantages, including:

- Evaluation of dental and medical referral across a broad range of studies.
- Increase the power of the outcomes, by meta-analysis (where possible).
- Explore the findings in relation to different study environments (for example, different countries and different referral systems).

5.4.2 Types of Studies

Studies that examined the referral of oral cancer and included outcomes to compare primary care doctors ('general practitioner'/'GP'/'primary care physician') and primary care dentists, i.e. the study included data for both professions, were considered for this review. They were required to include one or more of the following outcomes:

(1) Proportion/percentage of diagnosed cancers referred by each profession.

(2) Stage on presentation for each profession.

(3) Presentation delay in relation to each profession.

Studies were required to report on diagnosed oral cancers, rather than suspected cancer referrals. Scoping indicated that most studies were likely to be case series but other designs were acceptable, provided that they reported one or more of the required outcomes. Case reports, economic studies and qualitative studies were excluded. Rare types of intra-oral malignancy (such as lymphoma) were excluded.

5.4.3 Search Methods

The following electronic resources were searched: MEDLINE, EMBASE, Scopus, Google Scholar, Web of Science, CINHAL to May 2019. Further resources included: browsing the reference lists in initially identified studies, author searching, citation index search, browsing the 'find similar' sections of many electronic databases. In an attempt to identify on-going studies the Research Registry (https://www.researchregistry.com) and database of theses (EThOS - Electronic Theses Online Service) were examined. Search terms included: mouth neoplasms, oral cancer and mouth cancer in combination with primary health care, primary care, general practitioner, GP, physicians, dentist, general dental practitioner and GDP. The search strategy is given in Appendix 6, page 244.

5.4.4 Selection of studies

Following elimination of duplicates, abstracts were assessed to identify papers that included a comparison of primary care doctors and dentists in the referral of oral cancer by a single reviewer (SL). Abstracts indicating that the study did not fulfil the inclusion criteria - for example, qualitative studies or commentaries - were excluded at this stage. For the remaining studies, copies of the full papers were obtained and assessed by two reviewers for inclusion in the systematic review according to the pre-defined criteria.

5.4.5 Data extraction

Data were extracted by 3 independent reviewers. This was followed by a formal discussion to cross-check the data and to resolve any discrepancies by jointly re-examining the relevant paper and arriving at an agreement.

The following data were extracted:

Basic study information

- First author
- Title
- Publication year
- Reference

Study characteristics

- Country
- The type of study (prospective, retrospective, conference abstract, audit, letter)
- Type of unit in which the study was carried out
- Study size

Results and outcomes

- Percentages of diagnosed oral cancers referred by primary care doctors and dentists respectively
- Stage data for oral cancers referred by primary care doctors and dentists respectively
- Data on delay ('patient' and 'professional') for oral cancers referred by primary care doctors and dentists respectively

Other

- Authors' main conclusions

5.4.6 Study quality and bias (tables 5.1 and 5.2)

In order to give a 'picture of overall quality' of included studies in this review both *risk of bias* and *methodological quality* have been taken into consideration.

The Cochrane Handbook for Systematic Reviews (Higgins 2011; Cochrane Consumers and Review Group 2013) differentiate between 'bias' and 'quality'. The handbook notes that *'a study may be performed to the highest standards yet still have an important risk of bias'* (and conversely, may be unbiased even if there are flaws in methodology) but indicates that the key consideration, overall, is the extent to which the included studies should be 'believed'. Nevertheless, it is also noted that *'an emphasis on risk of bias overcomes ambiguity between the quality of reporting and the quality of the underlying research'*. Therefore, the Handbook advises it is *'important to assess the risk of bias in all studies'.* Bias is different to random error. Random error - in effect, imprecision - gives different estimates of effect in multiple studies but since the errors are both overestimations and underestimations, the average would give a 'correct' answer, its accuracy reflected in the confidence intervals. Bias, on the other hand, gives an error consistently in the same 'direction' and synthesis of multiple studies with the same bias would give an error in that direction.

Given the types of study included it was evident that the application of one of the many checklists for bias in 'classical' designs such as randomised controlled trials or diagnostic studies (Moher et al, 2001; Whiting et al 2003) was not possible. Therefore, another method of assessing bias was sought, consistent with the type of studies included. A concise bias assessment tool was developed by Hammer et al (2009) and includes evaluation in 5 categories (figure 5.1). This tool was considered appropriate for the studies in this review.

For the assessment of study quality, the *methodological index for non-randomised studies* ('MINORS') index (Slim et al 2003) was used. In developing this index, the authors noted that the development of randomised trials in surgery is challenging and hence many studies in surgery are observational. MINORS is a 12-item checklist, 8 items are for non-comparative studies and 4 additional items for comparative studies. Items are 'scored' 2 (reported and adequate), 1 (reported but inadequate) and 0 (not reported) and although numerical scales for study quality have been questioned (Cochrane Handbook 2011), the scale has been used to give an assessment of study quality in a number of systematic reviews (Elkhadem, Mickan and Richards, 2014; Langton, Siau and Bankhead, 2016). The results in this review are presented as a table to give a general view of quality.

Table 5.1 Evaluation of bias – Hammer checklist

Type of Bias	Assessment(s)	Risk (Low/Unclear/High)
SELECTION	Clear inclusion/exclusion criteria?	
	Does the sample represent the target population?	
INFORMATION	Is there evidence of bias in the collection of information?	
MEASUREMENT	Outcome measure(s) appropriate?	
	Objective measured outcome?	
	Outcome accurately measured?	
CONFOUNDING	Were potential confounders identified and measured?	
OTHER	Was the statistical analysis appropriate?	

Adapted from Hammer et al (2009) *Avoiding bias in observational studies* Deutsches Artzenblatt International 106 664-668

Table 5.2 Evaluation of study quality – the 'MINORS' scale

MINORS item	Notes
1. A clearly stated aim	The question should be precise and relevant in the light of the available literature
2. Inclusion of consecutive patients	All patients fit for inclusion (satisfying the inclusion criteria) have been included in the study during the study period
3. Prospective collection of data	Data were collected according to a protocol established before the beginning of the study
4. Endpoints appropriate to the aim of the study	Unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be addressed on an intention-to-treat basis
5. Unbiased assessment of the study endpoint	Blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise reasons for not blinding should be stated
6. Follow-up period appropriate to the aim of the study	The follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events
7. Loss to follow up less than 5%	All patients should be included in the follow-up. Otherwise, the proportion lost to follow-up should not exceed the proportion experiencing the major endpoint
8. Prospective calculation of study size	Information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event and the information about the level for statistical significance and estimates of power when comparing the outcomes

From: Slim et al (2003) *Methodological index for non-randomised studies (MINORS): development and validation of a new instrument* ANZ Journal of Surgery 73 712-716

5.4.7 Missing data

Attempting to obtain missing and/or unclear data, several authors were contacted by email. However, this met with very limited success because the required outcome had not been measured or the authors did not respond.

5.4.8 Synthesis and analysis of data

Data synthesis and analysis was carried out with MedCalc© software version 19.1. Forest plots were generated for relative risk of dental and medical referral. I^2 and associated 95% confidence intervals were calculated. Due to the differences in the ways stage and delay data were reported in the studies,

statistical meta-analysis of stage data included 4 studies and the other results were reported as a synthesised narrative and table.

5.4.9 Subgroups

Analysis of subgroups of studies undertaken in the UK was planned for each outcome, if data were available, to identify the effect of studies carried out within the same system of medical care.

5.4.10 Heterogeneity

There are several potential sources of clinical and methodological heterogeneity in this review. Studies from different countries may have study populations that differ in important ways – for example, in oral cancer rates, access to health professionals and willingness to consult a health professional. Different types of primary to specialist referral systems may be in place and, even within the same country, the local facilities (such as the presence of a university dental school with a large oral surgery department, where relevant specialists consult) may influence referral patterns. Referral patterns may, of course, have changed over the years, and this may be reflected in studies carried out at different times.

Several methods exist to identify statistical heterogeneity. A simple method is the examination of confidence intervals on a forest plot, assessing the overlap; less overlap indicates greater heterogeneity. Heterogeneity tests examine the null hypothesis that all studies measure the same effect. The chi-squared test generates a p value but is considered poor at detecting heterogeneity if the included studies are limited in size and number. On the other hand, it over-detects if the number of studies is high (Ionnidis et al 2007). Similarly, the Cochrane-Q has low power when few studies are included and excessive power when there are many studies, especially if they are large (Higgins et al 2003).

The I^2 test (Higgins et al 2003) takes the view that the fact that heterogeneity 'exists' is of less importance than the extent to which it influences the conclusions of a meta-analysis. I^2 can be calculated if the studies are of variable type, size and outcome data and can be used to investigate subgroups. Higgins suggested that for I^2, 'as a rule of thumb', up to 25% indicates 'low' heterogeneity; 50% - 75% 'moderate' heterogeneity and over 75% 'high' heterogeneity. However, I^2 is not perfect; caution is

advisable when few events are included in the meta-analysis and hence confidence intervals are important (Thorlund et al 2012).

In this review, heterogeneity was estimated by: (1) generation of forest plots and inspection of the 95% confidence intervals (2) calculation of I^2, estimating the percentage of variation caused by heterogeneity.

5.4.11 Publication bias

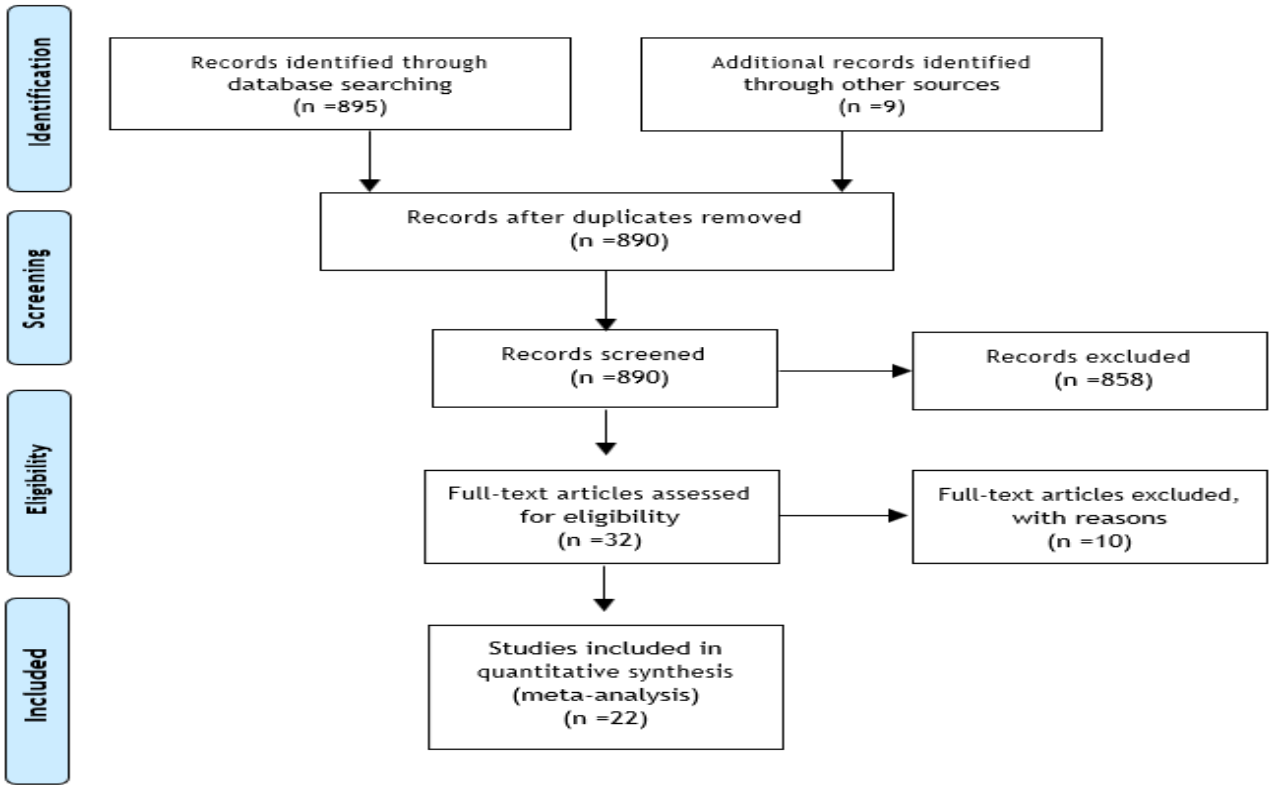
Publication bias – whether a study is more likely to be published should it report a perceived 'good' or 'favourable' outcome - was considered in relation to the included studies. Given the types of study in this review, it was considered unlikely that publication bias would be an important factor.

5.5 Results

5.5.1 Search outcome

The results of the literature search are described in the Prisma flow diagram (figure 5.1).

Figure 5.1 Prisma flow diagram of search outcome



Note: 'reasons for exclusion' are given in table 5.4

5.5.2 Description of included studies (table 5.3)

22 studies were included in the review. All 22 studies included data on proportion (percentage) of diagnosed oral cancers that were referred by primary care doctors (possibly referred to as 'general practitioner', 'GP' or 'primary care physician') and dentists. 8 studies compared medical and dental oral cancer referrals in relation to stage on presentation (or an aspect of 'stage' such as primary cancer size). 10 studies included comparative data on delay. 8 studies originated from the UK, 2 from each of USA, Australia and Denmark and 1 from each of Ireland, Canada, Netherlands, Finland, Thailand, Israel, Japan and Argentina. 15 studies were retrospective case series, 1 a prospective case series, 3 were questionnaires, 2 used a combination of case series analysis and patients interviews and 1 patient interviews alone. Overall, 4953 oral cancers were included and the number of oral cancers in each study ranged from 20 to 1841

5.5.3 Description of excluded studies (table 5.4)

10 studies were excluded at the 'eligibility' stage. Of these, 6 studies focused on oral cancer knowledge or diagnostic skills of the dental and medical practitioners, 2 studies included suspected oral cancer referrals, rather than diagnosed cancers, in 1 paper the referral sources were unclear and 1 paper reported stage in relation to regularity of dental care, rather than comparing primary care doctors and dentists.

5.5.4 On-going studies

No on-going studies were identified

5.5.5 Study quality and risk of bias (tables 5.5 and 5.6)

Most studies in this review are retrospective cohort studies, although three studies derived data from questionnaires (Wildt 1995, Kerdpon 2001 and Crossman 2016) and one from patient interviews (Scott 2005). Retrospective cohort studies rely on previously collected information, in this case from case records and therefore depend on accuracy of collection and recording and therefore are prone to information bias (Althubaiti 2016), although this is difficult to quantify in most of the studies in this review. Selection bias (Tripepi et al 2010) may also be a factor – for example in the type of unit

collecting the information. One further bias in relation to delay is recall bias (Sedgwick 2012); for example, if the recording of delay depends on patients remembering when symptoms first became evident.

A pragmatic approach was adopted in relation to study quality. Of the included studies, 3 focused specifically on dental/medical referral of oral cancer (Amsel 1983, O'Sullivan 2001 and Holmes 2005). However, most other studies examined oral cancer referral or early diagnosis in relation to a broader range of factors, in which the required outcomes for this review were variables included in the study. Furthermore, studies ranged from 10-year population-based studies including almost 2000 patients to small, audit-type studies (Piggott 2015). 'MINORS' scores are given in table 5.5. Studies scoring over 11 are generally considered to be of 'good' quality.

Bias was assessed using the checklist devised by Hammer et al (2009), described in the 'methods' section. The single-author assessment of bias is shown in table 5.6. No studies were assessed as having a high risk of bias. The studies using a patient questionnaire were judged to have a higher risk due to the possibility of recall bias.

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Table 5.3 - Included studies (ordered by date of publication)

FIRST AUTHOR, YEAR & REFERENCE (1)	SETTING	COUNTRY	STUDY SIZE (oral cancers)	STUDY TYPE	% GP and DENTIST REFERRALS	STAGE DATA ('early' stage 1 &2; 'late' stage 3&4 unless specified)	DELAY DATA	OTHER	AUTHORS' MAIN CONCLUSIONS
Amsel (1983) *The dentist as a referral source of first episode head and neck cancer patients* Journal of American Dental Association 106 195-197	Cancer centre	USA	231 (157 staged)	Retrospective case series	GP 41% Dentist 38% Other 20%	GP: 67% 'early' SEER 1& 2 33% 'late (SEER 3 and above) Dentist 86% 'early', 14% late	(Mean duration of symptoms) 28 weeks physician 21 weeks dentist	Cancers by intra-oral site	Professional and public education needed.
Scully (1986) *Sources and patterns of referrals of oral cancer; role of general practitioners* British Medical Journal 293 599-602	Oral medicine unit	UK	58	Retrospective case series	GP 28% Dentist 41% Other 20%	GP referrals by stage: **1** 40%; **2** 33%; **3** 27%; **4** 0% Dental referrals by stage: **1** 62%; **2** 38%; **3** 0%; **4** 0%	Median delay consultation-referral: 31 days GP 40 days dentist	Assessment of incidence at various sites	Need for public awareness.
Schnetler (1992) *Oral cancer diagnosis and delays in referral* British Journal of Oral and Maxillofacial Surgery 30 210-213	3 maxillofacial units	UK	96	Retrospective case series/questionnaire	GP 52% Dentist 41% Other 7%	Median size of primary 2cm – same for GP and dentist referrals	Duration of cancer 2.5 months for both GP and dentist referrals.	Practitioner diagnosis; Referrals by intra-oral site.	Need for education; opportunity for dentist to screen at check-ups.
Jovanovic (1992) *Delay in diagnosis of oral squamous carcinoma; areport from the Netherlands* Oral Oncol. European Journal of Cancer 32B 37-38	University hospital oral and maxillofacial surgery department	Netherlands	50 (41 analysed)	Retrospective case series	GP 66% Dentist 29% Other 5%	No comparison	GP: 0-4 weeks 22 (82%) 5-16 weeks 4 (15%) Over 16 weeks 1 (4%) Dentist: 0-4 weeks 8 (67%) 5-16 weeks 3 (25%) Over 16 weeks 1 (8%)	Of 50 patients, 7 oral cancers detected at routine dental examination	Importance of regular dental check-up.
Dimitroulis (1992) *Referral patterns of patients with oral squamous cell carcinoma, Australia* Oral Oncology, European Journal of Cancer 28B 23-27	Oral surgery unit (academic)	Australia	51	Retrospective case series	GP 24% Dentist 49% Other 28%	GP by stage**: 1** 16.7%; **2&3** 8.3%; **4** 75% Dentist by stage: **1** 20%; **2&3** 40%; **4** 40% Note: study did not separate stage 2 &3	Clinicians' delay assessed but no inter-professional comparison.	Delay (professions not compared) General factors (smoking, drinking etc) 11 cases (22%) identified as 'incidental' findings	Need for public awareness Professional education.

FIRST AUTHOR, YEAR & REFERENCE (1)	SETTING	COUNTRY	STUDY SIZE (oral cancers)	STUDY TYPE	% GP and DENTIST REFERRALS	STAGE DATA ('early' stage 1 &2; 'late' stage 3&4 unless specified)	DELAY DATA	OTHER	AUTHORS' MAIN CONCLUSIONS
Wildt (1995) *Delay in the diagnosis of oral squamous cell carcinoma* Clinical Otolaryngology 20 21-25	Head and neck department	Denmark	167	Questionnaire	GP 45% Dentist 35% Other 21%	No comparison	No comparison	Difference between sexes; old and young	Professional delay needs to be monitored.
Gorsky (1995) *Referral delay in diagnosis of oral/oropharyngeal cancer in Israel* Oral Oncology, European Journal of Cancer 31B 166-168	Dental School	Israel	543 oral cancers 225 analysed	Retrospective	86% GP 14% dentist	GP 55% early, 45% late Dentist 81% early, 19% late	No difference between professions	Sites diagnosed by each profession (no correlation)	Significant correlation between stage and referral profession.
Pinholt (1997) *Oral cancer: a retrospective study of 100 Danish cases* British Journal of Oral and Maxillofacial Surgery 35 77-80	Maxillofacial unit	Denmark	100	Retrospective case series	GP 13% Dentist 80% Other 7%	No comparison	8% of dentist referrals 6% of GP referrals	Presenting complaints, alcohol, tobacco, site of cancer Patient delay	Variability in tolerance of symptoms by patients.
Hollows (2000) Delays in the referral and treatment of oral squamous cell carcinoma British Dental Journal 188 262-265	Maxillofacial unit	UK	100	Retrospective case series	GP 56% Dentist 36% Other 8%	'No significant difference'	Mean practitioner delay 8.4 days GP 14.5 days dentist	Mean patient delay To GP: 25 weeks To GDP: 22 weeks	Most of the delay is patient delay. Opportunistic oral screening by dentist advocated.
Kerdpon (2001) *Factors relating to delay in diagnosis of oral squamous cell carcinoma in southern Thailand* Oral Oncology 37 127-131	University hospital head and neck clinic/dental clinic radiotherapy clinic	Thailand	161	Questionnaire	GP 83% Dentist 15% 2% other	No comparison	Healthcare professional not a predictor of patient delay	Many factors associated with delay assessed including sex, age, religion, residence, marital status and occupation; the only one related to delay was herbal treatment prior to referral.	Patients are a partial cause of the delay in diagnosing oral cancer. Education of public in prevention needed. Professional education to reduce professional delay.
Kantola (2001) *Detection of tongue cancer in primary care* British Journal of General Practice 51 106-111	University hospital	Finland	75 tongue cancer	Retrospective case series	GP 81% Dentist 19%	No comparison	GP 64% referred at first visit; Dentist 71% referred at first visit		Professional delay associated with worse outcome.
O'Sullivan (2001) Variations in the source of referral of oral cancer: a population-based study European Journal of Cancer Oral Oncol 37 S49	Academic unit	Ireland	388	Retrospective case series	GP 67% Dentist 15% Other 18%	No comparison	Not included	Comparison by site	Problem of low attendance at dentist by high-risk groups.

FIRST AUTHOR, YEAR & REFERENCE (1)	SETTING	COUNTRY	STUDY SIZE (oral cancers)	STUDY TYPE	% GP and DENTIST REFERRALS	STAGE DATA ('early' stage 1 &2; 'late' stage 3&4 unless specified)	DELAY DATA	OTHER	AUTHORS' MAIN CONCLUSIONS
Holmes (2003) *Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis?* Journal of Oral and Maxillofacial Surgery 61 285-291	Maxillofacial unit	USA	51	Retrospective case series and patient interviews	GP 22% Dentists 65% (of these, 47% no symptoms).	Mean pathological stage dental = 1.72; mean stage from GP = 3.25 79% dental referrals 'early' (stage 1 & 2) 28% GP referrals 'early')	Included but no comparison.	Patients who saw specialist *initially* more likely to have appropriate care initiated. Non-symptom driven diagnosis in 18 cases (15 dentist, 1 denturist 2 maxillofacial surgeons) - associated with significantly smaller lesion and lower stage	'Non-symptom driven' diagnosis is associated with lower stage, more likely by dentist.
Onizawa (2003) *Factors associated with diagnostic delay of oral squamous cell carcinoma* Oral Oncology 39 781-788	Maxillofacial unit	Japan	152, 144 analysed for referral source	Retrospective case series	GP: 20% Dentist: 59% Other 21%	No comparison	(defined as over 6 days) 51.7% physician 55.3% dentist	5 patients diagnosed in the absence of symptoms	Importance of the 'initial' professional emphasised; diagnostic difficulty of small lesions.
McLeod (2005) *Oral cancer: Delays in referral and diagnosis persist* British Dental Journal 198 681-684	Maxillofacial unit	UK	195 oral cancers; 120 analysed	Retrospective case series	GP 65% Dentist 27% 8% other	No comparison	GP 40% delayed over 2/52 Dentists 50% over 2/52	Comparison with earlier work	Delay in referral not improved since before TWR More needs to be done to transfer guidelines to everyday practice.
Scott (2005) *The idiosyncratic relationship between diagnostic delay and stage of oral squamous cell carcinoma* Oral Oncology 41 396-403	University maxillofacial unit/psychology department	UK	240	Patient interviews	19% GP 22% GDP Other 59% (50.4% referrals from OTHER surgeons) Of those where source stated GP 46%, dentist 54%, other 20%	GP: 41% 'early' 59% late Dentist: 57% early, 43% late	Not defined in relation to each primary care profession	Cancer identified at routine check-up ('incidental' finding) more likely to be at early rather than late stage	Professional training and public education needed.
Morelatto (2007) *Diagnostic delay of oral squamous cell carcinoma in two diagnostic centers in Córdoba Argentina* Journal of Oral Pathology and Medicine 36 405-408	Oral pathology/oncology university hospital	Argentina	70	Retrospective case series	GP 30% Dentist 43% Other 27%	No comparison	No comparison	Symptoms, treatment, overall delay	Professional education need, public awareness.

FIRST AUTHOR, YEAR & REFERENCE (1)	SETTING	COUNTRY	STUDY SIZE (oral cancers)	STUDY TYPE	% GP and DENTIST REFERRALS	STAGE DATA ('early' stage 1 &2; 'late' stage 3&4 unless specified)	DELAY DATA	OTHER	AUTHORS' MAIN CONCLUSIONS
Rogers (2007) *An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma* Oral Oncology 43 648-655	Regional maxillofacial unit, university hospital	UK	559, 504 analysed for referral source	Retrospective case series	GP 49% Dentist 43% Other 8%	No comparison	Primary care professional – no correlation with delay	Patients referred from doctors and dentists were had similar levels of socio-economic deprivation.	Reasons for delay are 'complex'.
Groome (2011) A population-based study of factors associated with early versus late stage oral cancer cavity diagnoses Oral Oncology 47 642-647	Head and neck department, university hospital	Canada	2033 (1841 analysed for professional referral source)	Retrospective case series	GP 66% Dentist 24.7% Other 9.5%	No comparison	No comparison	Dentists more likely to detect on (asymptomatic) screen than doctors (15% vs 1.4%)	Oral cancer being referred by both doctors and dentists. Targeted patient education Improved medical and dental school training Need for opportunistic oral examination
Piggott (2015) *Comparison of the diagnostic yield of medical and dental referrals an oral and maxillofacial 2 weeks rule clinic* National Journal of Maxillofacial Surgery 6 52-54	Maxillofacial unit	UK	20 oral cancers	Prospective case series	GP 70% Dentist 30%	No comparison	No comparison	Use of referral form ppv GP = 12.5% ppv dentist = 10%	Need for education, need for education in developing world (where dentists less common).
Crossman (2016) *Role of general practice in the diagnosis of oral cancer* British Journal of Oral and Maxillofacial Surgery 54 218-212	Public health	UK	161 oral cancers (questionnaire sent to 200)	Questionnaire	GP 56% Dentist 32% Other 12%	No comparison	No comparison	Symptoms that led to diagnosis Delay in relation to symptoms Reasons for delay	Interventions to promote prompt identification by GP & opportunistic screening of high-risk patients recommended.
Kaing (2016) *Referral patterns for oral squamous cell carcinoma in Australia* 61 29-34	Teaching hospital and dental school	Australia	101	Retrospective case series	GP 52% Dentist 43% Other 5%	No comparison	GP: mean delay 5.3 months, median delay 2.4 months Dentist: mean 5.8 months, median 3 months	*Consultations prior to referral:* GP: mean 2.7, median 2; GDP mean 2.9, median 3	Need for public oral cancer awareness. Oral cancer screening should be routine in dental practice.

Table 5.4 - Excluded Studies

FIRST AUTHOR, YEAR & REFERENCE	SETTING (authors)	COUNTRY	STUDY SIZE (n patients)	% GP and DENTIST REFERRALS	STAGE DATA	DELAY DATA	OTHER	AUTHORS' MAIN CONCLUSIONS	REASON FOR EXCLUSION
Elwood (1985) *Factors influencing early diagnosis of cancer of the oral cavity* Canadian Medical Association Journal 133 651-656	Cancer centre	Canada	160	Not included	70% stage 1 or 2 'regular dental care' 40% stage 40% stage 1 or 2 'not regular' (p=0.002)	No difference	Greater proportion of early lesions in patients with higher socio-economic status	Suggestion that impact of oral cancer might be reduced by more regular dental care.	Stage data related to regular dental care, not GP/dentist referral
Kowalski (1994) *Lateness of diagnosis of oral and oropharyngeal carcinoma: factors related to the tumour, the patient and health professionals*	Head and neck services in 3 hospitals	Brazil	336 oral cancer patients	Not clear in text of study	GP 27% 'early' (stage 1 & 2) Dentist 14% 'early'	Not included	None in relation to comparison of GP/dentist	Need for early diagnosis	Numbers referred by each profession not clear in text
Yellowitz (1995) *Assessing physicians' and dentists' cancer knowledge opinions and practices* Journal of American Dental Association 126 53-60	Dental School	USA	N/A	Not included	Not included	Not included	Knowledge and opinions of each group	Dentists performed more examinations, physicians saw more high-risk patients	Study compares knowledge opinions and practices; no required outcomes
Macpherson (2003) *The role of primary healthcare professionals in oral cancer prevention and detection* British Dental Journal 195 277-281	Dental public health	Scotland	357 GPs 331 dentists	NOT INCLUDED	NOT INCLUDED	NOT INCLUDED	Examination habits, confidence and detection, potential malignant lesion diagnossis	Need for continuing primary care education programmes	Study compares knowledge; no required outcomes
Carter (2007) *Oral cancer awareness of general medical and general dental practitioners* British Dental Journal 203 E10	Dental Schools	UK	238 GPs; 133 dentists	NOT INCLUDED	NOT INCLUDED		Oral cancer awareness for each group	Need for education of GPs	Study compares awareness and knowledge of oral cancer; no required outcomes
Sardella (2007) *Accuracy of referrals to a specialist oral medicine unit by general medical and dental practitioners and the educational implications* Journal of Dental Education 71 487-491	Oral Medicine	Italy	678 oral cancer referrals	Doctors (all types) 47% dentists 53%	NOT INCLUDED	NOT INCLUDED	% Correct diagnosis GDP 40% Other doctors 33%	Better education needed	Studies referrals, not diagnosed cancers
Borhan-Mojabi (2012) *Evaluating degree of knowledge on oral cancer among general practitioners and dentists in Qazvin* Journal of Evaluation in Clinical Practice 18 498-501	Oral Medicine	Iran	152	NOT INCLUDED	NOT INCLUDED	NOT INCLUDED	Professional knowledge/awareness of each group	Insufficient knowledge in each group; education needed	Study compares awareness and knowledge of oral cancer; no required outcomes

FIRST AUTHOR, YEAR & REFERENCE	SETTING (authors)	COUNTRY	STUDY SIZE (n patients)	% GP and DENTIST REFERRALS	STAGE DATA	DELAY DATA	OTHER	AUTHORS' MAIN CONCLUSIONS	REASON FOR EXCLUSION
Alami (2013) *Knowledge of oral cancer among recently graduated medical and dental professionals in Amman, Jordan* Journal of Dental Education 77 10	Cancer centre	Jordan	112 physicians and dentists	NOT INCLUDED	NOT INCLUDED	NOT INCLUDED	Knowledge and opinions of each group	Need for education in both undergraduate curricula	Study compares knowledge; no required outcomes
Hassona (2016) *Factors influencing early detection of oral cancer by primary health-care practitioners* Journal of Cancer Education	Maxillofacial unit	Jordan	165 GPs 165 dentists	NOT INCLUDED	NOT INCLUDED	NOT INCLUDED	Diagnostic ability assessed on a 28-item survey instrument	Need for continuing primary care education programmes	Study compares 'diagnostic ability'; no required outcomes
Roy (2018) *The two-week wait – a qualitative analysis of suspected head and neck cancer referrals British Dental Journal 225 159*-163	Maxillofacial unit	UK	141 cancer referrals	55% GP 45% dentist	NOT INCLUDED	NOT INCLUDED	PPV of referrals overall; quality of referrals	The UK TWR pathway for head and neck cancer is used inappropriately.	Studies referrals, not diagnosed cancers

Table 5.5 Study quality

MINORS ITEM → STUDY ↓	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of study size	MINORS quality assessment
Amsel (1983)	2	2	1	2	2	2	2	0	13
Scully (1986)	2	2	1	2	2	2	2	0	13
Dimitroulis (1992)	2	2	1	2	2	2	2	0	13
Jovanovic (1992)	2	2	1	1	2	2	2	0	12
Schnetler (1992)	2	2	1	2	1	2	2	0	12
Gorsky 1995)	2	2	1	2	2	2	2	0	13
Wildt (1995)	2	2	1	1	2	2	2	0	12
Pinholt (1997)	2	2	1	1	2	2	2	0	12
Hollows (2000)	2	2	1	2	2	2	2	0	13
Kantola (2001)	2	2	1	1	2	2	2	0	12
Kerdpon (2001)	2	2	1	1	1	2	2	0	11
O'Sullivan (2001)	2	2	1	1	2	2	2	0	12
Holmes (2003)	2	2	1	2	2	2	2	0	13
Onizawa (2003)	2	2	1	1	2	2	2	0	12
McLeod (2005)	2	2	1	1	2	2	2	0	12
Scott (2005)	2	2	2	2	1	2	2	0	13
Morelatto (2007)	2	2	1	1	2	2	2	0	12
Rogers (2007)	2	2	1	1	2	2	2	0	12
Groome (2011)	2	2	1	1	2	2	2	0	12
Piggott (2015)	2	2	2	1	2	1	2	0	12
Crossman (2016)	2	2	1	1	1	2	2	0	11
Kaing (2016)	2	2	1	1	2	2	2	0	12

KEY: 2 (reported and adequate), 1 (reported but inadequate) and 0 (not reported)

Study quality assessment method adapted from: Slim KA, Nini E, Forestier D, Kwiatkowski, Panis Y, and Chipponi J (2003)

Table 5.6 Assessment of bias (Single author evaluation)

STUDY	**SELECTION BIAS** Were there clear inclusion/exclusion criteria, does the sample represent the target population?	**INFORMATION BIAS** Evidence of bias in collection of information?	**MEASUREMENT BIAS** Was the outcome measure appropriate? Was there an objective measuring outcome? Was the outcome measured accurately?	**CONFOUNDING** Were potential confounders identified and measured?	**OTHER BIAS** Was the statistical analysis appropriate?
Amsel (1983)	◊	◊	◊	◊	◊
Scully (1986)	◊	◊	◊	◊	◊
Dimitroulis (1992)	◊	◊	◊	◊	◊
Jovanovic (1992)	◊	◊	◊	◊	◊
Schnetler (1992)	◊	◊	◊	◊	◊
Gorsky (1995)	◊	◊	◊	◊	◊
Wildt (1995)	◊	◊	◊	◊	◊
Pinholt (1997)	◊	◊	◊	◊	◊
Hollows (2000)	◊	◊	◊	◊	◊
Kantola (2001)	◊	◊	◊	◊	◊
Kerdpon (2001)	◊	◊	◊	◊	◊
O'Sullivan (2001)	◊	◊	◊	◊	◊
Holmes (2003)	◊	◊	◊	◊	◊
Onizawa (2003)	◊`	◊	◊	◊	◊
McLeod (2005)	◊	◊	◊	◊	◊
Scott (2005)	◊	◊	◊	◊	◊
Morelatto (2007)	◊	◊	◊	◊	◊
Rogers (2007)	◊	◊	◊	◊	◊
Groome (2011)	◊	◊	◊	◊	◊
Piggott (2015)	◊	◊	◊	◊	◊
Crossman (2016)	◊	◊	◊	◊	◊
Kaing (2016)	◊	◊	◊	◊	◊

KEY: ◊ = low risk of bias ◊ = unclear risk of bias ◊ = high risk of bias

Assessment of bias method adapted from: Hammer et al (2009)

5.5.6 Referral source, diagnostic stage and delay

5.5.6.1 Percentages of cases referred by primary care medical and dental practitioners (table 5.7)

There was a wide range of percentages of cases referred by each profession across 22 studies. Medical referrals ranged from 13% (Pinholt 1997) to 83% (Kerdpon 2001), whilst dental referrals ranged from 15% (Kerdpon 2001) to 80% (Pinholt 1997). Most oral cancers were referred by primary care doctors and dentists – the mean percentage referred by combined 'other' mechanisms (not usually specified but likely to include emergency hospital presentations and referrals from other hospital departments) was 12.2%, range 0 to 31%.

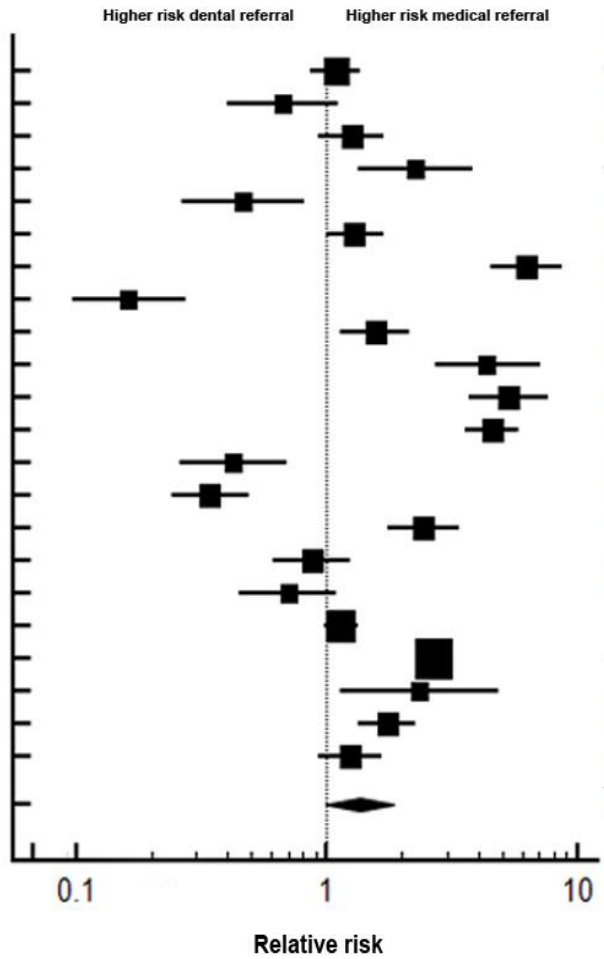
Table 5.7 - Numbers in each study and percentages referred by GPs and dentists

Study (chronological order)	Study size (oral cancers)	Percentage medical referrals (95% CI)	Percentage dental referrals (95% CI)
Amsel (1983)	231	41 (34.6 – 47.6)	38 (31.7 – 44.6)
Scully (1986)	58	28 (17.0 - 4 1.3)	41 (29.3 – 54.7)
Schnetler (1992)	96	52 (41.6 – 62.3)	41 (31.1 -51.5)
Jovanovic (1992)	41	66 (49.6 – 80.0)	29 (15.9 – 45.2)
Dimitroulis (1992)	51	24 (13.2 – 38.0)	49 (34.7 – 63.4)
Wildt (1995)	167	45 (37.3 - 52.9)	35 (27.8 – 42.8)
Gorsky (1995)	225	86 (80.1 - 90.3)	14 (9.8 – 19.2)
Pinholt (1997)	100	13 (7.1 – 21.2)	80 (70.8- 87.3)
Hollows (2000)	100	56 (45.7 – 65.9)	36 (26.6 -46.2)
Kantola (2001)	75	81 (70.29 – 89.1)	19 (10.9 – 29.7)
Kerdpon (2001)	161	83 (76.3 – 88.5)	15 (9.9 -21.5)
O'Sullivan (2001)	388	67 (62.1 – 71.7)	15 (11.6 – 19.0)
Holmes (2003)	51	22 (11.6 – 35.8)	65 (50.4 – 77.8)
Onizawa (2003)	144	20 (13.8 – 27.5)	59 (50.5 – 67.1)
McLeod (2005)	120	65 (55.8 -73.5)	27 (19.3 -35.9)
Scott (2005)	240	19 (14.2 – 24.5)	22 (16.9 – 27.8)
Morelatto (2007)	70	30 (19.6 – 42.1)	43 (31.2 – 55.4)
Rogers (2007)	504	49 (39.2 – 58.8)	43 (33.3 – 52.7)
Groome (2011)	1841	66 (63.8 – 68.1)	25 (23.0 – 27.0)
Piggott (2015)	20	70 (63.6 – 76.4)	30 (23.6 – 36.4)
Crossman (2016)	161	56 (50.9 – 61.1)	32 (27.3 – 36.8)
Kaing (2016)	101	52 (44.4 – 59.6)	43 (35.5 – 50.5)

5.5.6.2 Meta-analysis: relative risk of dental or medical referral (figure 5.2, figure 5.3)

Meta-analysis was undertaken for the relative risk of medical and dental referral for all studies *(figure 5.2)* and UK studies (*figure 5.3)*. Considerable heterogeneity was evident in all studies (I^2 = 96.4%, 95% CI 95.4 to 97.1), slightly less for studies carried out in the UK (I^2 = 81.0%, 95% CI 63.3 to 90.1).The overall pooled (random effects) risk ratio for medical compared to dental referral was 1.36 (95%CI 0.99 to 1.86); for UK studies the pooled risk ratio was almost identical, 1.36 (95% CI 1.05 to 1.76).

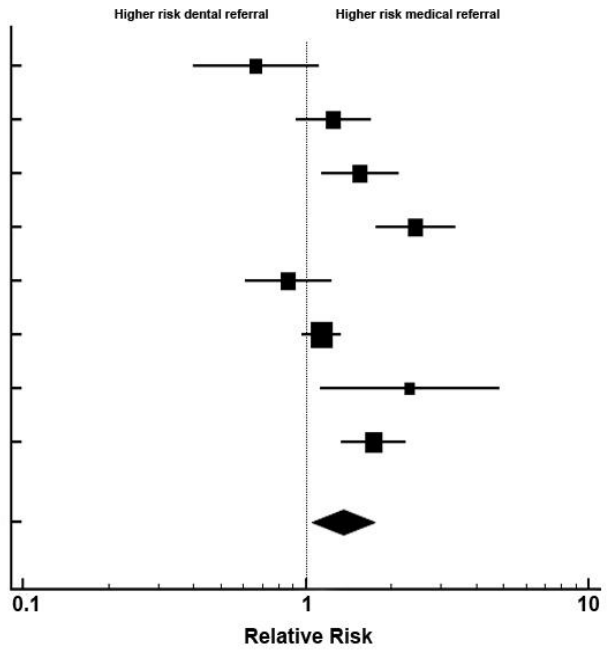
Figure 5.2 Forest plot for relative risk of medical/dental referral (all studies)



Study	Relative risk	95% CI	Medical referrals	Dental referrals	Weight fixed
Amsel (1983)	1.08	0.86 to 1.35	95	88	5.77
Scully (1986)	0.67	0.40 to 1.12	16	24	1.09
Schnetler (1992)	1.25	0.92 to 1.70	50	40	3.16
Jovanovic (1992)	2.25	1.33 to 3.80	27	12	1.07
Dimitroulis (1992)	0.46	0.26 to 0.81	12	26	0.92
Wildt (1995)	1.29	0.99 to 1.68	75	58	4.1
Gorsky (1995)	6.23	4.47 to 8.67	193	31	2.67
Pinholt (1997)	0.16	0.097 to 0.27	13	80	1.1
Hollows (2000)	1.56	1.14 to 2.13	56	36	2.98
Kantola (2001)	4.36	2.68 to 7.08	61	14	1.25
Kerdpon (2001)	5.32	3.69 to 7.68	133	25	2.17
O'Sullivan (2001)	4.54	3.54 to 5.83	259	57	4.7
Holmes (2003)	0.42	0.26 to 0.69	14	33	1.22
Onizawa (2003)	0.34	0.24 to 0.49	29	85	2.36
McLeod (2005)	2.44	1.76to 3.37	78	32	2.78
Scott (2005)	0.87	0.61 to 1.23	46	53	2.36
Morelatto (2007)	0.70	0.45 to 1.10	21	30	1.46
Rogers (2007)	1.14	0.97 to 1.34	198	174	11.17
Groome (2011)	2.67	2.45 to 2.91	1215	455	39.44
Piggott (2015)	2.33	1.13to 4.83	14	6	0.55
Crossman (2016)	1.73	1.33 to 2.25	90	52	4.26
Kaing (2016)	1.23	0.92 to 1.65	53	43	3.42
Total (random effects)	**1.36**	**0.99 to 1.86**			

I^2 (inconsistency) **96.4%** (95% CI 95.4 to 97.1) therefore random-effects meta-analysis undertaken. Combined risk ratio of medical to dental referral **1.36** (95%CI 0.99 to 1.86).

Figure 5.3 Forest lot for relative risk of medical/dental referral (UK studies)



Study	Relative risk	95% CI	Medical referrals	Dental referrals	Weight fixed
Scully (1986)	0.67	0.40 to 1.12	16	24	3.86
Schnetler (1992)	1.25	0.92 to 1.67	50	40	11.13
Hollows (2000)	1.56	1.14 to 2.13	56	36	10.5
McLeod (2005)	2.44	1.76 to 3.37	78	32	9.82
Scott (2005)	0.87	0.61 to 1.23	46	53	8.34
Rogers (2007)	1.14	0.97 to 1.34	198	174	39.39
Piggott (2015)	2.33	1.13 to 4.83	14	6	1.95
Crossman (2016)	1.73	1.33 to 2.25	90	52	15.01
Total (random effects)	**1.36**	**1.05 to 1.76**			

I^2 (inconsistency) **81.0%** (95% CI 63.3 to 90.1) therefore random-effects meta-analysis undertaken. Combined risk ratio of medical to dental referral **1.36** (95% CI 1.05 to 1.76)

5.5.6.3 Stage of oral cancer on referral - comparison between referrals from primary care doctors and dentists (table 5.8, figure 5.4)

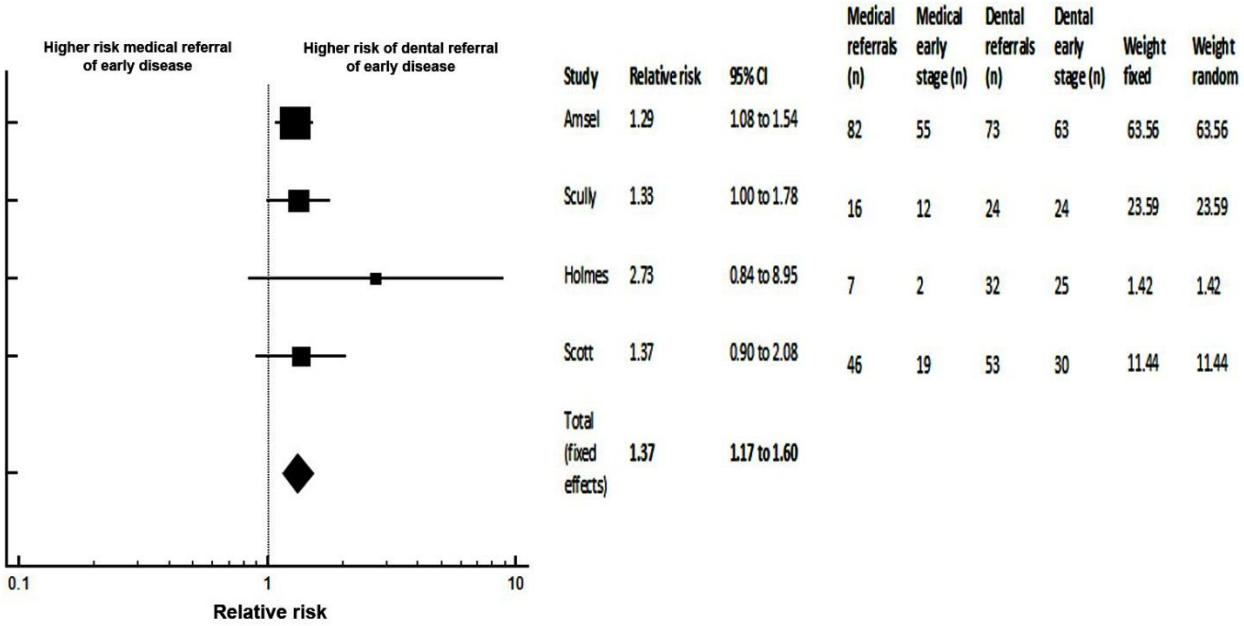
8 studies compared oral cancer referrals from primary care doctors and dentists in relation to stage on referral. Stage data were reported in several different ways including comparing primary tumour (T) stage, specific groupings of T stage, overall stage and nodal involvement, which precluded formal meta-analysis of all studies. However, 5 studies (Holmes 2003; Amsel 2003; Schnetler 1992; Dimitroulis 1992; Gorsky 1995) did show a statistically significant difference in relation to stage on presentation, all demonstrating a greater proportion of early (stage 1 and 2) disease being referred by dentists. Furthermore, one study (Holmes 2003) showed an increased proportion of patients with metastatic node disease for cancers referred by primary care doctors. 3 studies showed no statistically significant difference between doctors and dentists in relation to stage on referral (Jovanovic 1992; Hollows 2000; Scott 2005). Meta-analysis (fixed effects) was undertaken for 4 studies Holmes 2003; Amsel 1983; Scully 1986; Scott 2005) reporting data similarly. The combined risk of dentists/GPs referring early (stage 1 and 2) disease was 1.37 (95% CI 1.17 to 1.60), I^2 0.0% (95% CI 0.0 to 78.3).

Table 5.8 Stage of oral cancer on referral – studies comparing GPs and dentists

Study	Comparison dental/medical referral					Significance and conclusion
Amsel (1983)	Stage*	'Early' SEER<2		'Late' SEER>3		Early disease significantly more likely from dentist **p = 0.008**
	GP n=82	55 (67%)		27(33%)		
	Dentist n=73	63 (86%)		10 (14%)		
Scully (1986)	Stage	T_1	T_2	T_3	T_4	Early disease significantly more likely from dentist **p = 0.008**
	GP (n=16)	7 (44%)	5 (31%)	4 (25%)	0%	
	Dentist (n=24)	15 (62%)	9 (38%)	0%	0%	
Schnetler (1992)	**GP (n= 45); dentist (n 39)**	Median size of referred cancer 2cm both medical and dental; 'no statistical difference'** in node involvement.				'No significant difference' **
Dimitroulis (1992)	Stage	T_1	T_2&$_3$	T_4		Early disease significantly more likely from dentist **p= 0.049**
	GP (n=12)	2 (17%)	1 (8%)	8 (75%)		
	Dentist (n=25)	5 (20%)	10 (40%)	10 (40%)		
Gorsky (1995)	Stage	**Early (stage 1 & 2)**		**Late (stage 3 & 4)**		Early disease significantly more likely from dentist p= **0.006** *NOTE GP/dentist data only available for 225 of 543 patients. Excluded from meta-analysis as likely to be source of bias*
	GP (n=194)	107 (55%)		87 (45%)		
	Dentist (n=31)	25 (81%)		6 (19%)		
Hollows (2000)	**GP (n= 56); dentist n 36)**	'No statistical difference' in T stage for patients referred by dental or medical practitioners'				'No statistical difference'**
Holmes (2003)	Stage, node disease	**Average clinical stage**	**Average pathological stage**	**Early (stage 1 & 2) and late (stage 3 & 4)**	**Node disease**	Early disease significantly more likely from dentist **p=0.009** Node disease risk more likely in GP referrals **p=0.007**
	GP (n=7)	3.0 (SD 0.82)	3.25 (SD 0.96)	Early 2 (28%), late 5 (72%)	Higher risk node disease	
	Dentist (n=32)	1.94 (SD 1.05)	1.72 (SD 1.19)	Early 25 (79%), late 7 (21%)	Lower risk node disease	
Scott (2005)	Stage	**Early**		**Late**		No significant difference **p = 0.11**
	GP (n=46)	19 (41%)		27 (59%)		
	Dentist (n=53)	30 (57%)		23 (43%)		

**Classified using the Surveillance, Epidemiology and End Results (SEER) system (Funk et al., 2002) **author statement*

Figure 5.4 - Forest plot relative risk of medical/dental referral of early (stage 1 and 2) oral cancer (4 studies)



Study	Relative risk	95% CI	Medical referrals (n)	Medical early stage (n)	Dental referrals (n)	Dental early stage (n)	Weight fixed	Weight random
Amsel	1.29	1.08 to 1.54	82	55	73	63	63.56	63.56
Scully	1.33	1.00 to 1.78	16	12	24	24	23.59	23.59
Holmes	2.73	0.84 to 8.95	7	2	32	25	1.42	1.42
Scott	1.37	0.90 to 2.08	46	19	53	30	11.44	11.44
Total (fixed effects)	1.37	1.17 to 1.60						

I^2 (inconsistency) **0.0%** (95% CI 0.0 to 78.3) therefore fixed-effects meta-analysis undertaken.

Combined risk ratio medical/dental referral of early (stage 1 and 2) oral cancer **1.37** (95% CI 1.17 to 1.60)

5.5.6.4 Delay on presentation (table 5.9)

10 papers compared delay for referrals from primary care doctors and dentists (Amsel 1983; Scully 1986; Schnetler 1992; Jovanovic 1992; Pinholt 1997; Hollows 2000; Onizawa 2003; McLeod 2005; Rogers 2007; Kaing 2016). 'Professional' delay was assessed in 6 studies, 'appraisal period' (patient delay) was measured in 3 studies and the type of delay was not specified in 1 further study. There was no consistency in the method of assessment of delay across studies and formal meta-analysis was not possible. Overall, 2 studies reported no difference in delay whilst 7 reported slightly increased delay for dentists' referrals and one for GP referrals. No studies reported a difference of statistical significance.

Table 5.9 Delay – studies comparing GPs and dentists

Study (first author)	Delay data GP vs dentist	Type of delay (patient/professional)	Significant/p-value	Conclusion
Amsel (1983)	(Mean duration of symptoms) 28 weeks physician; 21 weeks dentist	Patient	N/A	Longer delay prior to presentation at GP compared to dentists
Scully (1986)	Median delay consultation-referral:31 days GP; 40 days dentist	Professional	N/A	Longer professional (primary-secondary referral) for dentist compared to GP
Jovanovic (1992)	0-4 weeks GP 82% 0-4 weeks dentist 67%	Professional	**p=0.31**	No significant difference
Schnetler (1992)	Duration of cancer 2.5 months for both GP and dentist referrals.	Patient	N/A	No difference in delay between oral cancer patients presenting to primary care doctor or dentist
Pinholt (1997)	8% of dentist referrals 6% of GP referrals	N/A	**p = 0.58**	Slightly longer delay overall for dental referrals, not significant
Hollows (2000)	Mean practitioner delay GP (n=56) 8.4 days (SD 17.6) Dentist (n=36) 14.5 days (SD 32.3)	Professional	**p = 0.24**	Slightly longer professional (primary-secondary referral) for dentist compared to GP
Ozinawa (2003)	(defined as over 6 days) 51.7% physician 55.3% dentist	Professional	**p = 0.74**	Longer professional delay for dentist compared to GP, not significant
McLeod (2005)	GP 40% delayed over 2/52 Dentists 50% over 2/52	Professional	**p = 0.34**	Longer professional (primary-secondary referral) for dentist compared to GP
Rogers (2007)	GP mean 22 days Dentist mean 22 days	Professional	N/A	No statistical difference in professional delay between professions
Kaing (2016)	GP mean delay 5.3 months; dentist 5.8 months	Patient	N/A	No difference GP/dentist

5.5.6.5 Other reported findings

Several studies reported on the number/proportion of oral cancer cases referred following 'incidental' or 'symptomless' identification at routine examination. In one Dutch study (Jovanovic 1992) 7 (14%) of a series of 50 cancers were diagnosed at routine dental examination. An Australian study of 51 oral cancers (Dimitroulis 1992) noted that 11 cases (22%) were identified as 'incidental' findings. A further study (Holmes 2003) found that of 51 oral cancers, 18 (35%) of cases were referred on a non-symptomatic basis. Non-symptomatic cases were associated with a significantly smaller lesion (p =

0.03) and cancer stage (p = 0.007). A UK study (Scott 2005) found that oral cancer identified at 'a routine check-up' was more likely to be at early stage (stage 1 & 2) than oral cancer referred following symptomatic presentation. Canadian research (Groome et al 2011) found that dentists were more likely to detect asymptomatic cases than primary care doctors (15% vs 1.4%, p< 0.001).

5.6 Discussion

5.6.1 GP and dentist referrals

This review confirms that both primary care doctors and dentists – in many different countries and settings - have an important role in the referral of oral cancer to specialist services. Meta-analysis of GP/dentist referral risk ratio indicated that approximately 14 oral cancers are referred from GPs for every 10 from a dentist although there was considerable variation between studies undertaken in different countries and, indeed, between studies in the same country. Subgroup analysis of UK studies similarly demonstrated varying proportions of dental and medical referrals, albeit with a smaller range.

The results of these meta-analyses do, of course, need to be interpreted in the light of the considerable heterogeneity that exists between studies undertaken in different countries with varying medical, dental and secondary care systems. The context of the study is also an important consideration. For example, one study in this review (Holmes 2003), which had a notably high proportion of dentally referred cancers, included referrals from two dental practitioners with a background of training in maxillofacial surgery. Another study (Scully 1986), again reporting a high proportion of dentally referred cancers, originated from a central London specialist academic oral medicine department, which may have a different referral 'profile' to a typical UK regional oral and maxillofacial or head and neck unit.

Why might patients present initially to one profession or the other? Studies analysing the presentation of lesions in different parts of the mouth have reported that a dentist was more likely to refer an oral cancer in relation to the areas related to the dentition or dentures (Schnetler 1992; Jovanovic et al 1992; Kerdpon 2001). Alternatively, an Australian study (Kaing 2016) has suggested that the fact that GP consultations attract a financial insurance rebate whilst dental consultations do not was a reason why there had been a shift towards initial oral cancer presentations to GPs. A UK study examining the role

of general medical practice in the diagnosis of oral cancer (Crossman et al 2016) suggested that *'evidence is emerging that patients with oral symptoms would rather see their GP than their dentist'*. This view was supported in a further study on early oral cancer detection in which over 70% of respondents considered it likely that they would consult a GP compared to 29% - 45% who would consult a dentist with symptoms of potential oral cancer (Eadie et al 2009). However, patients attending GPs with 'routine' dental problems is a common occurrence and, furthermore, socio-economically deprived patients, the social group more likely to present with oral cancer, are particularly prone to do this (Cope et al 2015).

Although studies have shown that patients do have variable views on whether they would first attend a primary medical or dental practitioner with a variety of oral-facial problems (Indermun et al 2017) one reason probably influencing the choice of practitioner first seen in relation to oral cancer – and possibly the 'elephant in the room' in relation to this issue – is access to dental services. In the UK, for the 2-year period to March 2018, 49.1% of adults had not seen an NHS dentist (NHS Digital 2018) This phenomenon is by no means restricted to the UK and typically impacts on people who have low income, are unemployed and lacking health insurance (Zabos et al 2002) factors also having established associations with oral cancer (Greenwood et al 2003; Auluck et al 2016).

5.6.2 Stage on presentation

As primary care doctors and dentists refer nearly all oral cancer, the question arises whether referrals from each group have different characteristics that may, potentially, translate into different outcomes.

Overall, studies in this review did not provide data on stage in a consistent format which made full statistical meta-analysis inappropriate. For example, one study grouped T_2 and T_3 cancers together as an 'intermediate' group, one study reported average clinical and pathological stage and another the median size of the referred cancer. However, the overall pattern was for either a report of 'no statistical difference' or an earlier stage for dentally referred cancers.

Several factors may account for the differences in stage on presentation between oral cancers referred by primary care doctors and dentists. One reason may be the proportion of oral cancers identified in the

absence of symptoms, as 'incidental' findings. Such diagnoses are made much more frequently by dentists, being very rare in primary care medical practice (Groome 2011) and evidence exists that an earlier stage on diagnosis is present with individuals who receive regular dental care (Elwood 1985). In the studies in this review, asymptomatic oral cancer diagnoses were reported in 5 studies (Holmes 2003; Jovanovic,1992; Dimitroulis 1992; Onizawa 2003; Groome 2011), comprising between 14% and 35% of cases. In these studies, all except one study reported all asymptomatic referrals being from dentists. In one study (Groome 2011)15% of dental referrals were asymptomatic compared to 1.4% of GP referrals.

Studies comparing GPs and dentists in knowledge of oral cancer, pre-malignant lesions, risk factors and oral examination skills and habits indicate dentists are more likely to examine the oral cavity routinely although in one study 94% of GPs did in response to oral soreness (Macpherson et al 2003; Carter and Ogden 2007)). On the other hand, some argue (Guggenheimer et al 1993) that *'the medical practitioner is the most likely resource'* for oral cancer screening as doctors are more likely to encounter at-risk patients because of co-existing medical conditions.

This review shows that in a range of different health systems a proportion of oral cancers are, effectively, diagnosed by an 'informal screening procedure' – usually a visit to a dental surgeon – and this, of course links to the rather broader and certainly more complicated question of whether a more systematic, evidence-based approach to screening would be effective. A Cochrane systematic review (Brocklehurst et al 2013) provided evidence of reduced mortality, a stage-shift towards earlier diagnosis and reduced costs. However, the reviewers considered that there was insufficient evidence to recommend population-based screening. The Global Oral Cancer Forum (Speight et al 2017) explored the question of screening for oral cancer in considerable detail and reported that accumulated evidence suggested that opportunistic screening of high-risk groups was cost effective but not practical in dental practice as few of the high-risk individuals attended regularly. To date, no screening program for oral cancer has been introduced into the UK (Cancer Research UK 2018[b]).

5.6.3 Differences in delay between medical and dental referrals

10 studies in this review reported on either 'patient delay' (sometimes referred to as 'appraisal period' delay) or 'professional delay' (practitioner delay). In common with stage of presentation data, there was inconsistency in the method of reporting. For example, studies reported 'mean duration of symptoms', 'mean professional delay', 'median delay' and 'duration of cancer'. Definitions of what period exactly represented delay also varied. For example, one study (Onizawa et al 2003) defined 'practitioner delay' as being over 6 days delay, whilst other studies (McLeod at al 2005) defined 'practitioner delay' as over 2 weeks and this inconsistency made statistical meta-analysis impractical. The overall pattern was one of slightly greater delay for dental referrals, although in no studies was a difference between medical and dental referrals of statistical significance reported. A slightly longer delay in dental referrals has been observed in previous work (Grafton-Clarke 2019). Several authors consider one explanation of the difference in delay is that dentists more commonly initiate a 'treatment trial', such as altering dentures prior to referring for secondary care opinion (Kaing et al 2016; Grafton-Clarke 2019). However, inappropriate initial treatment is not confined to dentists. A study of 779 patients with oral cancer (Shafer 1975) found 14.8% had initially received inappropriate management, with medical practitioners most often prescribing antibiotics and dentists extracting teeth or adjusting dentures (Scully 1986).

However, studies do not point towards a consistent relationship between delay, cancer stage and survival. One study (Scott et al 2005) found no correlation between delay and stage and suggests that 'the error is to assume that symptoms are related to the size of a tumour' – in other words, large oral cancers may remain asymptomatic and unnoticed by the patient. However, other work has reported that delayed referral correlated with both more advanced stage at presentation and poorer survival (Pitchers et al 2006). A meta-analysis found that diagnostic delay was a 'moderate' factor in stage on presentation (Seoane et al 2012) although studies on the relationship between delay and stage for oral cancer are not common (Seoane et al 2016).

5.6.4 Implications for practice and research

Implications for practice, policy and future referral pathways for oral cancer

In England – and indeed all parts of the UK – oral cancer incidence continues to increase rapidly, in contrast to several other European countries such as Italy, France and Germany, where incidence is beginning to fall (Miranda-Filho and Bray, 2020). Furthermore, it has a mortality of approximately 50%, a fact that reflects the high proportion of cases diagnosed at late stage (Grant et al 2010). Overall, as discussed in Chapter 2 of this thesis, most of the diagnostic delay is in the patient (or 'appraisal') interval. This, of course, implies that promotion of oral cancer awareness and symptom recognition amongst patients is an vital part of an oral cancer early diagnosis strategy (Macpherson 2018). Nevertheless, treatment delay in oral cancer is associated with poorer outcomes (Seoane et al 2012) and therefore rapid diagnosis and treatment pathways are essential components of improving outcomes.

In the light of this systematic review, how might this be achieved and what might be usefully considered for urgent referral pathways in the future? This review confirms an overall trend for a greater proportion of oral cancers to be referred by a GP rather than a dentist, in agreement with other work (Rodgers et al 2007). Nevertheless, both professions require an understanding of the signs and symptoms of oral cancer and the characteristics of the at-risk population – as Macpherson (2018) points out: *'the wider primary healthcare team therefore needs to be equipped to respond to patients presenting with signs and symptoms of the disease'.* Several studies have investigated primary care health care professionals' knowledge of oral cancer (Carter and Ogden 2007) and have recommended improved training in oral cancer diagnosis for these clinicians.

This review provides evidence that oral cancers may be referred at an earlier stage by dentists, probably as a result of routine dental examination, although those at highest risk are unlikely to attend a dentist regularly and therefore are less likely to benefit from such opportunistic diagnosis (Ford and Farah 2013). One obvious future approach would be to improve access to dental services for those at risk. However, such patients – often being heavy drinkers and smokers – frequently access primary medical care for reasons other than oral symptoms and this, as Ford and Farah (2013) suggest, may provide an

opportunity to develop opportunistic screening/diagnosis of oral cancer in general medical practice, possibly facilitated by allied health professionals. However, this would need to be considered in the light of practical and financial aspects.

One possible approach, defined in the most recent UK National Institute of Health and Care Excellence guidelines (NICE 2015) is increased co-operation between primary care doctors and dentists. The guidelines advise that lip lumps, erythroplakia or leukoerythroplakia (although not all oral symptoms, including persistent ulcers) are referred initially by GPs to a dentist for evaluation. The guideline has proved controversial and whilst some work suggests that increased GP-dentist collaboration is desirable (Crossman et al 2016), others consider that such an approach, whilst potentially reducing the secondary care workload, may result in diagnostic delay. This may be worsened by a lack of formal GP-dentist referral systems and insufficient access to dental care for many patients (Grimes et al 2017).

Implications for further research

This review suggests research is needed in several areas. Research is needed into how dental services might be provided for more of the population, specifically the socio-economically deprived 'irregular attenders' - who are often most at risk of oral cancer - and how they might be encouraged to attend the dentist. Clearly, this would need to also be evaluated in the light of economic studies. The most effective type of education in oral cancer for primary care practitioners (both dental and medical) is unclear and further research in this aspect may be useful. Additionally, research into the use of 'allied health professionals' in early oral cancer diagnosis may also prove valuable. Finally, further research into the benefits and practicalities of a screening programme for oral cancer, aimed at the at-risk population, is suggested. The lack of an oral cancer screening program in the UK continues to be a subject of interesting debate. It has certainly been pointed out that the mouth is accessible to simple examination and lesions are relatively easy to detect (Brocklehurst et al 2018). A systematic review (Walsh et al 2013) found 'conventional oral examination' (COE), across 10 studies, gave varying diagnostic accuracy, although sensitivity was at least 0.7 and specificity at least 0.9 in all studies, values of the order delivered by cervical cancer and breast cancer screening programmes. However, direct evidence for oral cancer in the form of a randomised trial is lacking and in its absence a screening programme is

very unlikely to be implemented. The only RCT (to date) on oral cancer screening - a large 15 -year study carried out in India with non-medical staff undertaking the examinations - demonstrated a 24% mortality reduction for high risk individuals but not in lower risk people (Sankaranarayanan et al 2005). Unfortunately, the study suffered from marked attrition bias and therefore further research is required to demonstrate clear benefits.

5.6.5 Strengths and weaknesses

This review provides insight into the referral of oral cancer to specialist care by primary care doctors and dentists, focusing on the proportions referred by each specialty, the differences in stage on presentation and difference in delay, across 22 studies from 12 countries.

However, the included studies did not present data – such as stage – in a consistent format, making formal meta-analysis of some outcomes inappropriate. The long-standing problem of different definitions and methods in studies on early cancer diagnosis research has been addressed by the Aarhus statement' (Weller et al 2012) although this review includes studies undertaken up to 30 years before the Aarhus guidelines were produced. Studies from different countries, and even within the same country, will be influenced by the local systems for referral and organisation of both primary and secondary services. Such differences, together with changes in systems over time, have almost certainly been sources of considerable heterogeneity. The wide range of countries involved does, of course, mean that transferability needs to be interpreted with caution.

5.7 Related publication

Langton S, Cousin GCS, Bankhead CR and Plüddemann A (2020) *A comparison of primary care doctors and dentists in the referral of oral cancer: a systematic literature review* British Journal of Oral and Maxillofacial Surgery doi.org/10.1016/j.bjoms.2020.06.00

Chapter 5 references

Akobeng AK (2005) *Understanding systematic reviews and meta-analysis* Archives of Disease in Childhood 90 845-848

Alami A El Sabbagh R and Hamdan A (2013) *Knowledge of oral cancer among recently graduated medical and dental professionals in Amman, Jordan* Journal of Dental Education 77 1356-1364

Althubaiti A ((2016) *Information bias in health research: definition, pitfalls, and adjustment methods* Journal of Multidisciplinary Healthcare 9 211-217

Amsel Z, Strawitz J and Engstrom P (1983) *The dentist a source of first episode head and neck cancer patients* Journal of the American Dental Association 106 195-197

Auluck A, Walker BB, Hislop G et al (2016) *Socio-economic deprivation: a significant determinant affecting stage of oral cancer diagnosis and survival* BMC Cancer 16 569

Borhan-Mojabi K Moradi A and Yazdabadi A (2011) *Evaluating the degree of knowledge on oral cancer among general practitioners and dentists in Qazvin* Journal of Evaluation in Clinical Practice 18 498-501

Brocklehurst P, Kujan O, Glenny A, Oliver R, Sloan P et al (2013) *Screening programmes for the early detection and prevention of oral cancer* Cochrane Database Syst Rev 2013; CD004150

Brocklehurst P and Speight P (2018) *Screening for mouth cancer: The pros and cons of a national programme* British Dental Journal 225 815-819

Cancer Research UK (2018)[a] *Mouth and oropharyngeal cancer - survival* available at: https://www.cancerresearchuk.org/about-cancer/mouth-cancer/survival (accessed August 2018)

Cancer Research UK (2018)[b] *Screening mouth cancer* available at: https://www.cancerresearchuk.org/about-cancer/mouth-cancer/getting-diagnosed/screening (accessed August 2020)

Carter L and Ogden G (2007) *Oral cancer awareness of general medical and general dental practitioners* British Dental Journal 203(5) E10

Cochrane Consumers and Communication Review Group (2013) *Guide for authors on assessing study quality* Available at: https://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/StudyQualityGuide_May%202013.pdf (accessed August 2020)

Cope AL, Wood F, Francis NA et al (2015) *General practitioners' attitudes towards the management of dental conditions and use of antibiotics in these consultations: a qualitative study* BMJ Open 2015 5: e008551. doi:10.1136/ bmjopen-2015-008551

Crossman T *et al* (2016) *Role of general practice in the diagnosis of oral cancer* British Journal of Oral and Maxillofacial Surgery 54 208–212

Dimitroulis G, Reade P, Wiesenfield D (1992) *Referral patterns of patients with oral squamous cell carcinoma, Australia* European Journal of Cancer Part B: Oral Oncology 28 (1) 23-27

Donaldson AN et al (2008) *The Effects of Social Class and Dental Attendance on Oral Health* Journal of Dental Research SAGE 87(1) 60–64

Eadie D, MacKintosh, MacAskill et al (2009) *Development and evaluation of an early detection intervention for mouth cancer using a mass media approach* British Journal of Cancer 101 S73-S79

Elkhadem, A., Mickan, S. and Richards, D. (2014) *Adverse events of surgical extrusion in treatment for crown-root and cervical root fractures: a systematic review of case series/reports* Dental Traumatology 30(1) 1–14

Elwood JM and Gallagher RP (1985) *Factors influencing early diagnosis of cancer of the oral cavity* Canadian Medical Association Journal 133 651-656

Ford PJ and Farah CS (2013*) Early detection and diagnosis of oral cancer: Strategies for improvement* Journal of Cancer Policy 1 e2–e7

Funk GF et al (2002) *Presentation, treatment, and outcome of oral cavity cancer: A national cancer data base report* Head & Neck 24(2) 165–180

Glasziou P, Irwig L, Bain C et al (2001) *Systematic reviews in health care* Cambridge University Press

Grant E, Silver K, Bauld L et al (2010) *The experiences of young oral cancer patients in Scotland: symptom recognition and delays in seeking professional help* British Dental Journal 208 465-469

Gorsky M and Dayan D (1995) *Referral delay in diagnosis of oro/oropharyngeal cancer in Israel* European Journal of Cancer B Oral Oncol 31B 166– 168

Grafton-Clarke C, Chen K and Wilcock J (2019) *Diagnosis and referral delays in primary care for oral squamous cell cancer: a systematic review* British Journal of General Practice 69 e112-e126

Greenhalgh T (2010) *How to read a paper: the basics of evidence-based medicine Wiley*-Blackwell BMJ Books

Greenwood M, Thomson P, Lowry R *et al* (2003) *Oral cancer: Material deprivation, unemployment and risk factor behaviour - An initial study* International Journal of Oral Surgery 32 74-77

Grimes D, Patel J and Avery C (2017) *New NICE referral guidance for oral cancer; does it risk delay in diagnosis?* British Journal of Oral and Maxillofacial Surgery 55 404-406

Groome PA, Rohland SL, Hall SF, Irish J, MacKillop, WJ and O'Sullivan B (2011) *A population-based study of factors associated with early versus late stage oral cavity cancer diagnoses* Oral Oncology 47 642-647

Guggenheimer J Weissfeld J and Kroboth F (1993) *Who Has the Opportunity to Screen for Oral Cancer?* Cancer Causes and Control 4 (1) 63-66

Hammer GP, du Prel J-P and Blettner M (2009) *Avoiding bias in observational studies* Deutsches Ärzteblatt International 106(1) 664-668

Hassona Y Scully C Shahin A Maayta W Sawair F (2016) *Factors Influencing Early Detection of Oral Cancer by Primary Health-Care Professionals* Journal of Cancer Education 31 285-291

Higgins JPT, Thompson SG, Deeks JJ and Altman DG (2003) *Measuring inconsistency in meta-analyses* British Medical Journal 327 557-560

Higgins JPT, Green S editors (2011) *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration

Hollows P, McAndrew PG and Perini MG (2000) *Delays in the referral and treatment of oral squamous cell carcinoma* British Dental Journal 188 262-265

Holmes JD *et al* (2003) *Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis?* Journal of Oral and Maxillofacial Surgery 61(3) 285–91

Ionnidis J, Patsopoulos N and Evangelou E (2007) *Uncertainty in heterogeneity estimates in meta-analyses* British Medical Journal 335 914-918

Indermun S, Isaacs Q and Mulder R (2017) *Participants' preferred choice of practitioner for orofacial symptoms* South African Dental Journal 72 315-322

Jovanovic A, Kostense PJ, Schulten EAJM, Snow GB, Van Der Waal I (1992) *Delay in Diagnosis of Oral Squamous Cell Carcinoma; A report from the Netherlands* European Journal of Cancer. Part B: Oral Oncology 28(1) 37-38

Juhl CB and Lund H (2018) *Do we really need another systematic review?* British Journal of Sports Medicine 52 1408-1409

Kaing L, Manchella S, Love C, Nastri A and Wiesenfeld D (2016) *Referral patterns for oral squamous cell carcinoma in Australia: 20 Years progress* Australian Dental Journal 61 29-34

Kantola S, Jokinen K , Hyrynkangas K, Mäntyselkä P, and Alho OP (2001) *Detection of tongue cancer in primary care* British Journal of General Practice 51 106-111

Kerdpon D and Sprilung H (2001) *Factors related to advanced stage oral squamous cell cancer in Southern Thailand* Oral Oncology 37 216-221

Kowalski L Franco E Torloni H Fava A de Andrade Sobrinho J et al (1994) *Lateness of diagnosis of oral and oropharyngeal carcinoma: factors related to the tumour, the patient and health professionals* European Journal of Cancer Part B, Oral Oncology 30B (3) 167-173

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Macpherson LMD, McCann MF, Gibson J et al (2003) *The role of primary healthcare professionals in oral cancer prevention and detection* British Dental Journal 195 277-281

Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316

McCann MF, MacPherson LM, Gibson J (2000) *The role of the general dental practitioner in prevention and detection of oral cancer; a review of the literature* Dental Update 27 404-408

McLeod NMH, Saeed N and Ali E (2005) *Oral cancer: Delays in referral and diagnosis persist* British Dental Journal 198 681-684

Mehanna H, West CML, Nutting C and Paleri V (2010) *Head and neck cancer – part 2: treatment and prognostic factors* British Medical Journal 341 721-725

Meskin LH (1994) *Oral cancer – the forgotten disease* Journal of the Amerian Dental Association 125 1042

Miranda-Filho A and Bray F (2020) *Global patterns and trends in cancers of the lip, tongue and mouth* Oral Ocology 102 104551

Moher D, Schulz KF and Altman D (2001) *The CONSORT statement: revised recommendation for improving the quality of reports of parallel-group randomized trials* Journal of the American Medical Association 285 1987-1991

Morelatto RA, Herrera MC, Fernandez EN et al (2007) *Diagnostic delay of oral squamous cell carcinoma in two diagnosis centers in Cordoba, Argentina* Journal of Oral Pathology and Medicine 36 405-408

Netuveli G, Sheiham A and Watt RG (2006) *Does the "inverse screening law" apply to oral cancer screening and regular dental check-ups?* Journal of Medical Screening 13 47-50

NHS Digital (2018) *NHS Dental Statistics for England, 2017-18, Second quarterly report* available at: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-dental-statistics/nhs-dental-statistics-for-england-2017-18-second-quarterly-report (accessed August 2020)

NICE (2004) *Improving Outcomes in Head and Neck Cancers – The Manual* available at: https://www.nice.org.uk/guidance/csg6 (accessed August 2020)

NICE (2015) *Suspected cancer: recognition and referral* available at: https://www.nice.org.uk/guidance/ng12 (accessed August 2020)

O'Sullivan EM *Variation in the sources of referral of oral cancer: a population-based study* European Journal of Cancer Oral Oncology 37 S49

Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T et al (2003) *Factors associated with diagnostic delay of oral squamous cell carcinoma* Oral Oncology 39 781-788

Piggott L (2015) *Comparison of the diagnostic yield of medical and dental referrals an oral and maxillofacial 2 weeks rule clinic* National Journal of Maxillofacial Surgery 6 52

Pinholt EM, Rindum J and Pindborg JJ (1997) *Oral cancer: a retrospective study of 100 Danish cases* British Journal of Oral and Maxillofacial Surgery 35 77-80

Pitchers M and Martin C (2006) *Delay in referral of oropharyngeal squamous cell carcinoma to secondary care correlates with a more advanced stage at presentation, and is associated with poorer survival* British Journal of Cancer 94(7) 955-958

Rodgers J, Macpherson LMD, Smith GLF et al (2007) *Characteristics of patients attending rapid access clinics during the West of Scotland Cancer Awareness Programme oral cancer campaign* British Dental Journal. 202(11):E28

Rogers S, Pabla R, McSorley A, Lowe D, Brown J et al (2007) *An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma* Oral Oncology 43 648-655

Roy S and Anjum K (2018) *The two-week wait – a qualitative analysis of suspected head and neck cancer referrals* British Dental Journal 225 159-163

Rubin G, Berendsen A, Crawford SM et al (2015) *The Lancet Oncology Commission The expanding role of primary care in cancer control* Lancet Oncology 16 1231–72

Sankaranarayanan R, Ramadas K, Thomas G et al. Trivandrum Oral Cancer Screening Study Group (2005) *Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial* Lancet 365 1927–1933

Sardella A, Demarosi F, Lodi G, Canegallo L, Rimondi L and Carrassi A (2007) *Accuracy of Referrals to a Specialist Oral Medicine Unit by General Medical and Dental Practitioners and the Educational Implications* Journal of Dental Education 71 487-491

Schnetler JFC (1992) *Oral cancer diagnosis and delays in referral* British Journal of Oral and Maxillofacial Surgery 30 210-213

Scott, SE Grunfeld, EA and McGurk M (2005) *The idiosyncratic relationship between diagnostic delay and stage of oral cell carcinoma* Oral Oncology 41 396– 403.

Scully C, Malmos D, Levers BG, Porter SR and Prime SS (1986) *Sources and patterns of referrals of oral cancer: role of general practitioners* British Medical Journal 293 599-601

Sedgwick P (2012) *What is recall bias?* British Medical Journal BMJ 2012;344:e3519

Seoane J, Alvarez-Novoa P, Gomez I et al (2016) *Early oral cancer diagnosis: The Aarhus statement perspective. A systematic review and meta-analysis* Head and Neck 38 E2182-E2189

Seoane J, Takkouche B, Varela-Centelles P, Tomás I and Seoane-Romero J (2012) *Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis* Clinical Otolaryngology 37 99-106

Shafer WG (1975) *Initial mismanagement and delay in oral cancer* Journal of the American Dental Association 90 1262-1264

Slim KA, Nini E, Forestier D, Kwiatkowski, Panis Y, and Chipponi J (2003*) Methodological index for non-randomized studies (MINORS):* development and validation of a new instrument ANZ Journal of Surgery 73 712-716

Speight PM, Epstein J, Kujan O et al (2017) *Screening for oral cancer - a perspective from the Global Oral Cancer Forum* Oral and Maxillofacial Pathology 123 680-687

Stefanuto P, Doucet JC and Robertson C (2014) *Delays in treatment of oral cancer: a review of the current literature* Oral and Maxillofacial Surgery 117 424-429

Thorlund K, Imberger G, Johnston BC, Walsh M, Awad T, et al. (2012) *Evolution of Heterogeneity (I2) Estimates and Their 95% Confidence Intervals in Large Meta-Analyses* PLoS ONE doi: 10.1371/journal.pone.0039471

Tripepi G, Jager KJ, Dekker FW et al (2010) *Selection Bias and Information Bias in Clinical Research* Nephron Clinical Practice 115 94-99

Walsh T, Liu JLY, Brocklehurst P et al (2013) *Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults* DOI: 10.1002/14651858.CD010173.pub2

Weller D, Vedsted P, Rubin G et al (2012) *The Aarhus statement: improving design and reporting of studies on early cancer diagnosis* British Journal of Cancer 106 1262-1267

Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM et al (2003) *The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews* BMC Medical Research Methodology 3, 25 (2003). https://doi.org/10.1186/1471-2288-3-25

Wildt J, Bundgaard T, Bentzen SM (1995) *Delay in the diagnosis of oral squamous cell carcinoma* Clinical Otolaryngology 20 21-15

Yellowitz J and Goodman H (1995) *Assessing physicians' and dentists' oral cancer knowledge, opinions and practices* Journal of the American Dental Association 126 53-60

Zabos G, Northridge M, Ro M, Trinh C, Vaughan R *et al* (2002) *Lack of Oral Health Care for Adults in Harlem: A Hidden Crisis* American Journal of Public Health 92 49-52

CHAPTER 6: Prioritisation of approaches to the early diagnosis of oral cancer: a Delphi study of UK experts

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6.1 Abstract

Background

There are many possible methods and approaches that may improve the early diagnosis of oral cancer – several have been described in this thesis - including screening, patient education, improving social inequalities and improved access to dental care, education of medical students and professionals, improving rapid specialist referral and communication and focus on at-risk individuals. As resources for healthcare are finite, it would seem reasonable to prioritise the various methods.

Aim of Study

The overall aim of this study was to prioritise the methods of improving the early diagnosis of oral cancer by developing an expert consensus view on the priority of the various methods.

Methods

This study used the Delphi method to gather a consensus opinion from a panel of experts on early oral cancer diagnosis. Items for the initial questionnaire were identified from a broad range of published literature, including published reviews and systematic reviews. Participants were selected from two groups: (1) UK-based senior academics (2) consultants in dental public health. The Delphi process involved 2 rounds and questionnaires were delivered on-line using JISC online surveys. For the first round, participants were requested to rate the effectiveness of each approach to early oral cancer diagnosis using a 7-point Likert scale. Results from the first round were summarised and presented to the experts for further item ranking and comment, thus developing a final ranking of the items.

Results

Response rate for the first round was 13/14 (92%) and of these 13/13 (100%) responded in the second round.

Following the two rounds of Delphi questionnaires, the two methods given highest priority were ‘fast-track referral systems’ with 81.8% of experts agreeing this was ‘high priority’, the remainder placing it in the ‘intermediate’ category and ‘rapid diagnosis, such as ‘one stop’ clinic in secondary care’, placed ‘high priority’ by 72.7% and ‘intermediate’ by the remaining 27.3%. ‘Education of medical and dental students’, ‘improved primary-secondary communication’ and ‘primary care education (doctors and dentists)’ were also considered high priority by a clear majority of respondents. At the opposite end of the priority scale, ‘screening agents in dental practice’ and ‘general population screening for oral cancer’ were considered ‘low priority’ by 100% and 90.9% of experts respectively. Other methods were placed in ‘the middle ground’, either dividing opinion relatively evenly across all three priority categories or being placed in the ‘intermediate’ category by a majority of experts.

Conclusions

This Delphi study has developed a priority ranking for the effectiveness of the methods of encouraging early diagnosis of oral cancer. The methods considered to be of highest priority were fast-track referral systems and ‘one-stop’ diagnosis clinics although several other methods were considered of high priority by the experts in this study. Further research should continue on methods of early diagnosis of oral cancer, even if ranked low in this study. It is likely that a ‘multi-measure’ approach to early oral cancer diagnosis will be most effective and research on how to deliver this may prove valuable.

6.2 Background

This chapter presents the results of a Delphi study of expert opinion on the priority of the various methods of encouraging early oral cancer diagnosis.

Previous chapters of this thesis and associated published work have focused on several methods and aspects of the urgent referral of oral cancer. These include the effectiveness of the current English 'fast track' TWR system of referral and its relationship to socio-economic deprivation (Langton et al 2019[a]), the potential for close professional communication and system flexibility to enhance urgent referral (Langton et al 2019[b]) and how regular dental care might improve early referral of oral cancers, particularly if asymptomatic (Langton et al 2020).

However, the causes of late oral cancer presentation, discussed in earlier chapters, are complex, involving many factors and therefore there are several methods and systems other than urgent referral that might, potentially, be effective in encouraging earlier oral cancer diagnosis. Scoping reviews of the literature indicate that suggested approaches include primary care education (Greenwood et al 2001), general population screening (Sankaranarayanan 2005) public awareness campaigns (Hassona et al 2014), examination by 'allied health professionals' (General Dental Council 2009) and more general measures such as addressing social inequalities (Conway et al 2008).

How, then – given the inevitable resource limits on any health system - might the methods be prioritised? Furthermore, how do the methods identified in this thesis 'rank' in relation to other methods? In this chapter, the question of prioritisation of the methods of encouraging early oral cancer diagnosis is addressed by a Delphi study of expert opinion.

6.3 Delphi studies

6.3.1 About Delphi studies

The Delphi technique (sometimes referred to as Delphi 'process' or 'procedure') is a method of developing a consensus opinion amongst experts through a series of iterative questionnaires with controlled feedback to the participants. The technique was originally developed by the Rand

Corporation of California in the 1950s with a view to avoiding counterproductive group dynamics on decision-making committees where it was considered that the consensus view may be dominated by a small number of individuals (Goodman 1987; Boulkedid et al 2011). There are many variants of the Delphi study – some differing considerably from the original technique – and there is no universally agreed method of conducting such a study (Dufresne 2017).

Four features characterise a Delphi study and distinguish the technique from other consensus methods, such as nominal group technique (NGT), 'brainstorming' and focus groups. These include: (1) anonymity, (2) iteration with controlled feedback, (3) statistical group response and (4) expert input (Goodman 1987).

Anonymity of participants (to each other) encourages opinions that are not influenced by peer pressure. However, it can also be argued that anonymity encourages 'snap judgements', as respondents are not accountable to other participants, as they usually are when on a committee (Sackman 1975).

Iteration is achieved by successive 'rounds' of questionnaires; information is incorporated into each successive questionnaire, thus informing the participants of the on-going group view.

Statistical 'group response' provides a statistical summary of the participants' views, for example by reporting percentage scores, allowing participants to see how their view ranks within the group (Goodman 1987).

Delphi studies use a panel of experts, although there is some debate about what an 'expert' actually is and how one might be identified (Hasson et al 2000). However, in most Delphi studies it is usual to recruit a panel who have extensive relevant knowledge or who are, at least, informed advocates in relation to a specific issue (Goodman 1987). Hohmann (2018) suggests: *'knowledgeable people should be identified through literature and conference abstract searches for those who have contributed to the subject of interest.'* Very often, participants are sampled purposively in order to save time, resource and ensure that the expert panel is appropriate (Dufresne 2017).

6.3.2 Delphi process

The initial questionnaire is developed in relation to the research question and is then piloted to ensure that satisfactory responses are elicited by the questions. In the first round, participants provide answers which are ranked for future rounds. In subsequent rounds, participants are provided with a summary of the outcomes from the previous round – 'controlled feedback' – and asked to respond to the analysed outcomes. The process is repeated until a consensus is achieved (Goodman 1987; Dufresne 2017). The level of agreement is variable, depending on a number of factors including participant 'burnout' and available resources. However, there is no universally recognised method of identifying the end point of a Delphi study (Dufresne 2017).

6.3.3 Advantages and disadvantages

The Delphi technique has a number of advantages including being a convenient and concise way of organising a 'committee', reducing peer pressure on participants who can express views in an entirely non-adversarial way, allowing participants to re-consider opinions in the light of group rankings and, as responses are all of the same weight, no single person can 'force the issue'.

However, there is no clearly-defined methodology, reliability is questionable (different panels may come to different conclusions if asked the same question), participant discussion is precluded and a consensus does not necessarily represent the 'right' answer, just the opinion of the experts on what is important in relation to the issue in question (Goodman 1989; Dufresne 2017; Hohmann 2018).

6.3.4 When are Delphi studies used?

Typically, the Delphi design is employed when there is uncertainty in a given field, a judgement is required or where there is no 'true' answer – for example in policymaking (Dufresen 2017; Hohmann 2018).

6.3.5 Choice of the Delphi method for this study

This study aims to prioritise the diverse methods of encouraging earlier oral cancer diagnosis and, specifically, the priority of a fast-track referral system – the principal focus of this thesis - in relation to the other methods of encouraging early diagnosis.

As described in previous sections, many questions in relation to the complex problem of earlier oral cancer diagnosis remain unanswered. The Delphi design, as noted above, is considered useful when a 'judgement' is required and with this in mind it is used here to develop an expert consensus on the priority, in terms of effectiveness, of the various methods.

6.4 Aim and objectives

The overall aim of this study is to prioritise the methods of encouraging earlier diagnosis of oral cancer by expert consensus.

Objectives include:

1. A focus on the priority given to fast-track referral systems in relation to other methods.
2. To explore the priority rankings further in the light of the 'free comments' made by the expert panel members.
3. To explore the priority of methods identified in the studies included in this thesis (in the view of the expert panel)

6.5 Methods

6.5.1 Ethical approval

Ethical approval for the study was obtained from the Medical Sciences Interdivisional Research Ethics Committee of the University of Oxford, CUREC reference R66073/RE001. (see Appendix 1 p.214)

6.5.2 Generation of item list

The item list for this study's questionnaire was considerably influenced by data from earlier research in this thesis. The first study (Chapter 3; Langton et al 2019[1]) examined the effectiveness of protocol-driven 'fast-track' referrals and therefore both the concepts of 'fast-track' referral and 'protocols' were included. In the second study (Chapter 4; Langton et al 2019[2]), primary to secondary communication was the most prominent theme and therefore this was included as a questionnaire item. Several important items were identified through the systematic review (Chapter 4; Langton et al 2020). These included improving access to dental care, improving education in oral cancer for primary care doctors and dentists, and the need to focus on high-risk individuals, all of which were included in the questionnaire. A theme that was evident throughout the thesis – and indeed in much of the literature in the theoretical framework - was the influence of socio-economic inequalities and therefore the 'need to address inequalities' was included. Other items were supported by a broad range of published literature, including systematic reviews (Massano et al 2006; Van der Waal et al 2011; Ford et al 2013). Further items were included from scoping, including screening (Brocklehurst and Speight 2018) and 'one stop' cancer diagnosis clinics (NHS England 2018).

Therefore, the initial questionnaire (Table 6.1; Appendix 5) included 13 items, each an 'approach' to improving the early diagnosis of oral cancer. For clarity, these were divided into 3 groups: 'patients', 'primary care' and 'secondary care':

Table 6.1 Items for Delphi questionnaire

PATIENTS	PRIMARY CARE	SECONDARY CARE	OTHER
Screening for oral cancer	Primary care (doctor and dentist) education and symptom/sign knowledge improvement	Rapid diagnostic systems (such as one-stop clinics)	Respondents' inclusions if not listed.
Patient education and sign/symptom awareness	Screening methods (e.g. mucosal staining agents)	Improved primary care-secondary care communication	
Address social inequalities	Involvement of other professional groups in screening		
Improve access to regular dental care	Protocol-driven referrals		
	Fast-track referral systems for suspected cancer		
	Focus on high-risk individuals		
	Education at medical/dental school in oral cancer		

The Delphi questionnaires were developed and delivered on-line using JISC online surveys (https://www.jisc.ac.uk/online-surveys). The on-line questionnaires were piloted by professional colleagues to ensure that questions and responses were understandable, appropriate and satisfactorily worded and also to confirm that the online system 'worked'.

6.5.3 Participant identification

Participants were selected from two groups, using the principles described by Hohmann (2018) – see section 6.3.1. These included:

(1) UK-based senior academics who had, from their publication record, contributed to the evidence base on early oral cancer diagnosis (2) consultants in dental public health, with a role in commissioning oral cancer services. In the second group, 'snowballing' was also employed.

The study was restricted to UK-based experts as aspects such as the referral system and the structure of primary care services will be similar. Potential participants were contacted, in the first instance, by

email, informed of the nature and purpose of the study and invited to participate. Potential participants were issued with appropriate information sheets in order to decide whether they wished to participate in the study.

6.5.4 Consent

For this study no written consent was undertaken. Participants were informed that responding to the questionnaire implied consent to take part in the study and have their de-identified responses included in the study results. Data were kept in password-protected digital format, to which only I had access. Participants were advised that they had the right to withdraw from the study at any time.

6.5.5 Data collection

The Delphi questionnaires were delivered on-line using JISC online surveys: (https://www.jisc.ac.uk/online-surveys). The first-round questions and image captures of the web-based questionnaire are included in the appendices of this thesis.

6.5.6 Delphi procedure

The study was conducted as a 2-round Delphi process.

The first round was available for 4 weeks. Non-responding participants were sent a reminder email at weekly intervals. Participants who completed round 1 were invited to undertake round 2, which was administered similarly, being available for 4 weeks, with participants sent reminder emails weekly.

For the first round, participants were requested to rate the *effectiveness* of each approach to early oral cancer diagnosis using a 7-point Likert scale where 1 indicates low effectiveness and 7 indicates high effectiveness. Open comments on each item together with suggestions for items that may have been overlooked were invited, together with the opportunity to make general comments.

Responses to the first questionnaire were initially categorised according to the proportion of respondents ranking the approach 6 or 7 on the Likert scale of effectiveness, a method used similarly in

previous Delphi studies (Plüddemann et al 2010). Based on this categorisation, in accordance with the protocol, three *priority* groups were developed: 'high priority', 70% or more respondents ranking the approach 6 or 7 on the Likert scale, 'intermediate priority', 50% to 69% and 'low priority', less than 50%. In the light of the responses to the first round, the second questionnaire was developed.

For the second round, also available online for 4 weeks, participants were provided with the results of the first-round questionnaire. Results from the first questionnaire, using the above categorisation, classified all methods as low priority (table 6.3). .

Therefore, following discussion with my supervisors, the round 1 responses were 're-calibrated' according to the percentage of respondents scoring the method 5 (fairly high effectiveness), 6 (high effectiveness) or 7 (very high effectiveness) on the Likert scale as follows: 'high priority', 50% or more respondents; 'intermediate priority', 30% to 49.9% and 'low priority' 29.9% or less.

The respondents were informed of the method used to develop 'high', 'moderate' and 'low' priority groups and asked whether they agreed or disagreed with the placement of all items in the low priority group. Respondents who disagreed all methods were 'low priority' were then asked whether they agreed with the priority of the item in the re-classification and, if not, into which category it should be placed General comments were also invited at this stage. The final responses were reviewed at a focus meeting between myself and my supervisors. The round 1 questionnaire and image of the web application is given in Appendix 5, p219; images of the round 2 questionnaire are in Appendix 5, p220.

6.6 Results

6.6.1 Response rates and demographics of experts

Response rate for the first round was 13/14 (92%) and of these 13/13 (100%) responded in the second round. The mean age of the respondents was 56.4 years and the mean time since medical or dental qualification 33.3 years. 10 (77%) respondents were male and 3 (23%) female. 8 (62%) respondents

were academics in the fields of oral and maxillofacial surgery, oral medicine or oral pathology and 5 (38%) were dental public health consultants (table 6.2)

Table 6.2 Response rates and demographics

VARIABLE	OUTCOME
Response rate (round 1)	13/14 = 92%
Response rate (round 2)	13/13 = 100%
Mean age	56.4 years
Mean time qualified	33.3 years
Male	10/13 = 77%
Female	3/13 = 23%
Senior academics (maxfac/oral surgery/medicine/pathology)	8/13 = 62%
Dental Public Health	5/13 = 38%

The experts are listed (with their permission) in Appendix 5c

6.6.2 Round 1 questionnaire

Overall, the level of consensus for the effectiveness of methods in this round (table 6.3) was in the 'middle ground' for many items. For example, items 5 ('patient education on signs/symptoms'), 6 ('screening of high-risk individuals'), 8 ('primary care education') and 10 ('rapid diagnosis, such as one-stop clinic in secondary care'), over 69% of respondents awarded a Likert score of 3 (fairly low), 4 (intermediate) or 5 (fairly high), whilst for item 13 ('improve access to dental services for all'), 84.4% awarded one of these scores. There was strong consensus for the ineffectiveness of items 1 ('general population screening for oral cancer') and 2 ('screening agents in dental practice'), with these items scoring Likert 1 or 2 for 84.7% and 69.3% respectively. There was little consensus regarding methods that were considered highly or very highly effective. No items achieved the protocol-specified

consensus of over 70% Likert 6 or 7 denoting 'high priority' or 50-69% denoting 'intermediate priority' (table 6.4). Two suggestions for additional methods were received; neither was judged to differ significantly from pre-defined ones and therefore do not appear in the second round.

Table 6.3 Percentage of respondents awarding Likert scores of effectiveness for each oral cancer early diagnosis method (round 1)

Item number	METHOD	LIKERT SCORE (%)							
		Very Low (1)	Low (2)	Fairly low (3)	Inter-mediate (4)	Fairly high (5)	High (6)	Very high (7)	Don't know
1	General population screening for oral cancer	38.5	46.2	7.7	0	7.7	0	0	0
2	Screening agents in dental practice (e.g. mucosal stains)	38.5	30.8	7.7	15.4	7.7	0	0	7.7
3	Protocol driven referrals	0	23.1	0	46.2	0	15.4	0	15.4
4	Screening undertaken by 'allied health professional'	7.7	23.1	15.4	30.8	7.7	7.7	7.7	0
5	Patient education on signs/symptoms	15.4	7.7	15.4	23.1	30.8	7.7	0	0
6	Screening of high-risk individuals	7.7	7.7	15.4	30.8	23.1	0	15.4	0
7	Address social inequalities in the population as a whole	23.1	15.4	7.7	7.7	30.8	15.4	0	0
8	Primary care education (doctors and dentists)	7.7	0	15.4	30.8	23.1	23.1	0	0
9	Education of medical/dental students	7.7	7.7	23.1	7.7	30.8	23.1	0	0
10	Rapid diagnosis, such as 'one stop' clinic in secondary care	0	7.7	15.4	7.7	30.8	15.4	7.7	15.4
11	Improved direct primary-secondary communication	0	15.4	7.7	15.4	30.8	7.7	15.4	7.7
12	Fast-track referral systems	0	15.2	7.7	23.1	23.1	15.4	15.4	0
13	Improve access to dental services for all	0	7.7	30.8	0	53.6	7.7	0	0

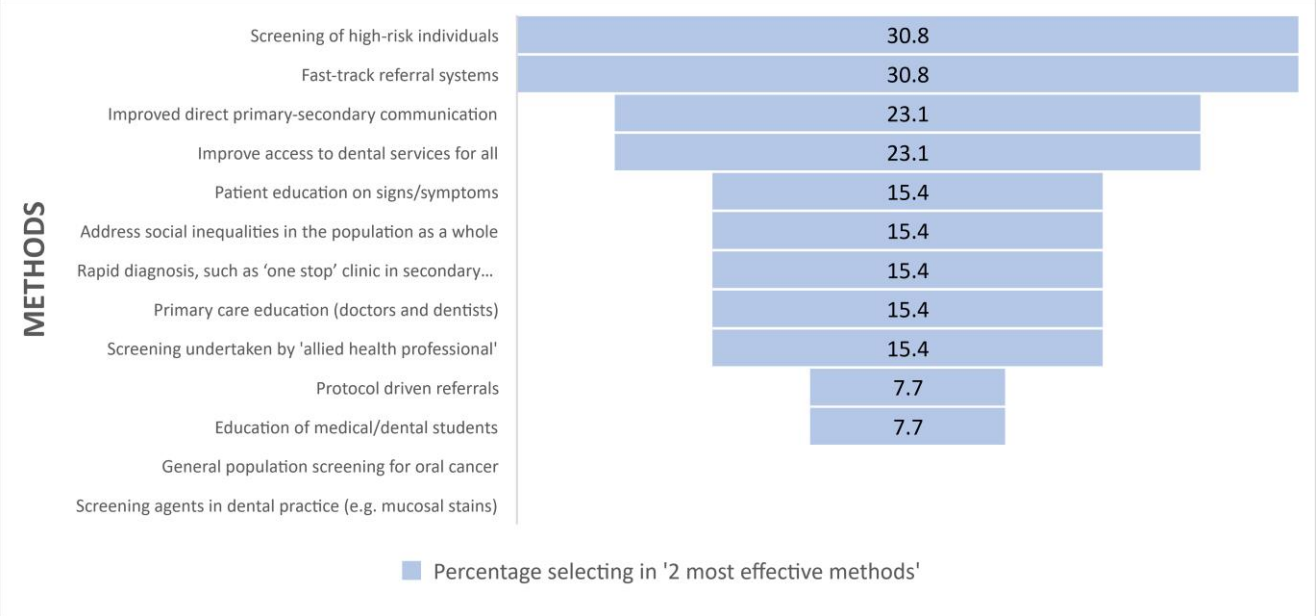
Table 6.4 Percentage of respondents scoring 6 or 7 on Likert scale (high or very high effectiveness) round 1

METHOD	% 6 or 7 Likert (high or very high effectiveness)
Fast-track referral systems	30.8
Education of medical/dental students	23.1
Rapid diagnosis, such as 'one stop' clinic in secondary care	23.1
Improved direct primary-secondary communication	23.1
Primary care education (doctors and dentists)	23.1
Protocol driven referrals	23.1
Screening of high-risk individuals	15.4
Address social inequalities in the population as a whole	15.4
Screening undertaken by 'allied health professional'	15.4
Improve access to dental services for all	7.7
Patient education on signs/symptoms	7.7
General population screening for oral cancer	0

Screening agents in dental practice (e.g. mucosal stains)	0

Participants were also asked to name which two approaches they considered the most effective. There was no strong consensus regarding the most effective methods. The highest-scoring methods were 'screening high-risk individuals' and 'fast-track referral systems', both methods being included by just under 31% of respondents whilst 'general population screening for oral cancer' and 'screening agents in dental practice' were included by no respondents. The responses are indicated in figure 6.1.

Figure 6.1 Percentage including method as one of 'two most effective methods' of encouraging early diagnosis



Participants were also asked for suggestions on other methods of encouraging early diagnosis. No method was suggested by more than one participant and included: well man/woman checks by a GP, tele-dentistry for suspicious lesions, 'empowering clinicians in service development', visits to schools and instruction on oral self-examination.

6.6.3 Round 2 questionnaire

In the second-round questionnaire the results of round 1 (table 6.3) were presented to the respondents, indicating that no method had attained 70% or greater of Likert 6/7 score ('high priority') or over 50% (intermediate priority). 2 respondents agreed that all methods should be considered 'low priority'

(15.4%), whilst 11 (84.6%) disagreed. The *priority* classification under the revised criteria, described in the methods section, are shown in table 6.5. Agreements and disagreements with these categories are shown in table 6.6.

Table 6.5 Percentage of respondents scoring 5, 6 or 7 on Likert scale – revised classification

METHOD	% scoring 5, 6 or 7	Priority
Improve access to dental services for all	61.3	High
Fast-track referral systems	53.9	High
Improved direct primary-secondary communication	53.9	High
Rapid diagnosis, such as 'one stop' clinic in secondary care	53.9	High
Education of medical/dental students	53.9	High
Primary care education (doctors and dentists)	46.2	Inter
Address social inequalities in the population as a whole	46.2	Inter
Screening of high-risk individuals	38.5	Inter
Patient education on signs/symptoms	38.5	Inter
Screening undertaken by 'allied health professional'	23.1	Low
Protocol driven referrals	15.4	Low
Screening agents in dental practice (e.g. mucosal stains)	7.7	Low
General population screening for oral cancer	7.7	Low

Table 6.6 Agreement/disagreement with round 1 priority and suggested category if disagreement (round 2)

LOW PRIORITY ROUND 1				
Method	**R1 'priority classification'**	**% Agree**	**% Disagree, intermediate**	**% Disagree, high**
General population screening for oral cancer	Low	90.9	9.1	0
Screening agents in dental practice (e.g. mucosal stains)	Low	100	0	0
Protocol driven referrals	Low	0	81.8	18.2
Screening undertaken by 'allied health professional'	Low	36.4	45.5	18.2
INTERMEDIATE PRIORITY ROUND 1				
Method	**R1 'priority classification'**	**% Agree**	**% Disagree, low**	**% Disagree, high**
Patient education on signs/symptoms	Intermediate	81.8	0	18.2
Screening of high-risk individuals	Intermediate	36.4	27.3	36.4
Address social inequalities in the population as a whole	Intermediate	72.7	18.2	9.1
Primary care education (doctors and dentists)	Intermediate	27.3	18.2	54.5
HIGH PRIORITY ROUND 1				
Method	**R1 'priority classification'**	**% Agree**	**% Disagree, low**	**% Disagree, intermediate**
Education of medical/dental students	High	63.6	0	36.4
Rapid diagnosis, such as 'one stop' clinic in secondary care	High	72.7	0	27.3
Improved direct primary-secondary communication	High	63.6	9.1	27.3
Fast-track referral systems	High	81.8	0	18.2
Improve access to dental services for all	High	36.4	36.4	27.3

Of the methods specified in the revised criteria to be of low priority, there was agreement that 'general population screening for oral cancer' (90.9% agreement) and 'screening agents in dental practice' (100% agreement) were of 'low priority'. There was a 100% disagreement that 'protocol driven referrals' was a 'low priority' method, the majority (81.8%) moving this to 'intermediate priority' and 18.2% to 'high priority'. 'Screening undertaken by allied health professional' divided opinion, with 36.4% agreeing this was a 'low priority' method, 45.5% re-categorising as 'intermediate priority' and 18.2% as 'low priority'.

Of the methods classified as 'intermediate priority', a majority agreed that 'patient education on signs/symptoms' and 'address social inequalities in the population' were in this category (81.8% and 72.7% respectively). 'Screening high-risk individuals' divided opinion relatively evenly, with 27.3%, 36.4% and 36.4% classifying the method 'low', 'medium' and 'high' priority respectively. A majority (72.7%) disagreed 'primary care education' was an 'intermediate priority' method, 54.5% considering it 'high priority' method with 27.3% re-classifying in the 'low priority' category.

Five methods were classified in the revised criteria as 'high priority'. There was agreement that 'fast-track referral systems', 'rapid diagnosis such as one stop clinics', 'improved direct primary-secondary communication' and 'education of medical/dental students' were 'high priority' by 81.8%, 72.7%, 63.6% and 63.6% respectively. Of those reclassifying these 4 methods, all except 'improved direct primary-secondary communication' were transferred to 'intermediate'; for the latter category 9.1% considered this method 'low priority'. 'Improve access to dental services for all' divided opinion; 36.4% agreed this was high priority, whilst 27.3% and 36.4% re-classified 'intermediate' and 'low' respectively.

6.6.4 Comments

Comments were invited in both rounds 1 and 2. These included comments on the individual items and 'overall' comments in both rounds 1 and 2 (table 6.7). Comments were of several types and included qualifying statements (*'Effectiveness would depend on the method and quality of education'; 'This assumes that there is room for improvement'),* further information on the choice of score (*'In the absence of a good screening test - v low specificity'; 'May result in less cases in future but will not increase "early detection" ')*, evidence-based statements (*'Good evidence that AHPs are as effective as dentists - so effectiveness will depend on the type of screening – e.g. population or high risk')* and personal experiences (*'I score this highly mainly because I trained just such a team so I know it can work. Unfortunately, without the correct infrastructure it falls apart. So; it is effective but only under very specific circumstances'*).

Table 6.7 Comments

CATEGORY/METHOD	COMMENT
Population screening	*'Never going to work'* *'In the absence of a good screening test - v low specificity'* *'If visual with good lighting and environmental circumstances good. Dental surgery-based screening, in my view would be comparatively more effective'.*
Screening of high-risk individuals	*'Improves specificity and cost-effectiveness'* *'There will be variation in understanding of 'high risks' between participants of this Delphi survey'*
Address social inequalities in the population	*'May result in less cases in future but will not increase "early detection" '* *'This would need to be a system-wide, long term intervention to make a difference to early oral cancer diagnosis'*
Improve access to dental services for all	*'Improving access doesn't necessarily include improving service uptake. Those groups at risk of oral cancer are often those who might not attend'* *'GDPs well-placed to diagnose premalignant and early cancers. Evidence is that cost and non-availability of dentists deter people from attending. Improve dental access, and this will increase oral mucosal checks'*
Primary care education (doctors and dentists)	*'Effectiveness would depend on the method and quality of education'* *'Originally scored this higher but they already have "education" do we then displace something else essential that they must learn?'*
Screening agents in dental practice	*'Sensitivity and specificity of screening agents not good enough at present'* *'I am not aware of evidence base of their effectiveness'*
Screening undertaken by 'allied health professional'	*'Good evidence that AHPs are as effective as dentists - so effectiveness will depend on the type of screening – e.g. population or high risk'* *'I score this highly mainly because I trained just such a team so I know it can work. Unfortunately, without the correct infrastructure it falls apart. So; it is effective but only under very specific circumstances.'*
Protocol driven referrals	*'Hopefully "Mouth Cancer Toolkits" in primary care will improve quality of referrals'* *'As long as this is coupled with primary care education. Early identification of signs/symptoms and rapid referral is effective - but we know primary care dentists and doctors miss lots of early warning signs'* *'This would depend on the protocol. Inclusion of a full oral examination, regardless of the any 'dental' intervention, in my view is likely to be effective.'*
Fast-track referral systems	*'If linked to early detection and referral protocols that work'* *'No question! Absolutely'* *'If easy access, good relationships between primary and secondary care, and feedback'* *'What we've had for some time'* *'We have to accept a low conversion rate and have the capacity to deal with this effectively'*
Education of medical/dental students	*'Depends on quality'* *'Long lag time. Plus, average GDP only sees 1-2 cancers in their careers'*
Rapid diagnosis, such as 'one stop' clinic in secondary care	*'I hold weekly USC clinic. Conversion rate 6%. Hopefully with improved referral protocol this will increase'*
Improved direct primary-secondary communication	*'This assumes that there is room for improvement. In my view there is always room for improvement.'*
GENERAL COMMENTS round 1	*'Very little research into what is effective; need some demonstration pilots'* *'Any patient facing material would need to be carefully researched as to the content / nuance of the approach'* *'I think odds of early diagnosis of cancer may increase if there were multiple interventions sustained over a time. However, a plan for ongoing robust evaluation of such approach will be required.'* *'Hardly fun for those involved in the classical at-risk groups and since the "oral sex gives you oral cancer" misrepresentation tough to do for the HPV risk groups without some additional training for the personnel'*
GENERAL COMMENTS round 2	*'Individual service variation will influence the use of AHP/CNS[9] which can be valuable. Student education and social standard improvement are important but not specific to oral cancer'.* *'Education of primary care dentists and medics - value added if it had said their teams. Staff may work and live in lower deprived areas, thus spread knowledge in social circles. Further, it may change out of hours service perceptions to what constitutes a dental emergency. Currently a painful ulcer would not lead to an appointment'*

[9] *AHP = allied health professional; CNS = clinical nurse specialist*

6.7 Subgroups

2 subgroups were analysed: (1) Academic oral surgeon/pathologist/medicine (2) Dental public health experts. For each group, the proportion rating an item as 'high priority' was calculated. The results are shown in table 6.8.

Both groups considered a wide range of items to be of 'high priority'. 'Fast track referral systems' was considered 'high priority' by 100% of dental public health respondents and 75% of academics, and a majority of both groups included 'rapid diagnosis, such as 'one stop' clinic in secondary care' in this category. 60% of dental public health experts considered 'improve access to dental services for all' high priority, whilst this was only 'high priority' for 25% of academics.

Table 6.8 Subgroups: percentage of (a) dental public health (b) academic oral surgery/pathology/medicine respondents rating item as 'high priority' following final round

METHOD	% RESPONDENTS RATING ITEM 'HIGH PRIORITY' AFTER FINAL ROUND
DENTAL PUBLIC HEALTH (n=5)	
Fast-track referral systems	100
Improve access to dental services for all	60
Rapid diagnosis, such as 'one stop' clinic in secondary care	60
Improved direct primary-secondary communication	40
Education of medical/dental students	40
Address social inequalities in the population as a whole	40
Primary care education (doctors and dentists)	40
Screening of high-risk individuals	20
Protocol driven referrals	20
ACADEMIC ORAL SURGERY/MEDICINE/PATHOLOGY (n=8)	
Fast-track referral systems	75
Education of medical/dental students	75
Rapid diagnosis, such as 'one stop' clinic in secondary care	75
Improved direct primary-secondary communication	75
Primary care education (doctors and dentists)	50
Improve access to dental services for all	25
Screening of high-risk individuals	25
Screening undertaken by 'allied health professional'	25
Patient education on signs/symptoms	13

Note: only items gaining at least one 'high priority' evaluation included

6.8 Discussion

6.8.1 General points

The overall objective of this study was the prioritisation of the many methods of potentially encouraging the earlier diagnosis of oral cancer. Following the two rounds of Delphi questionnaires, the two methods

given highest priority were 'fast-track referral systems' with 81.8% of experts agreeing this was 'high priority', the remainder placing it in the 'intermediate' category and 'rapid diagnosis, such as 'one stop' clinic in secondary care', placed 'high priority' by 72.7% and 'intermediate' by the remaining 27.3%. 'Education of medical and dental students', 'improved primary-secondary communication' and 'primary care education (doctors and dentists)' were also considered high priority by a clear majority of respondents. At the opposite end of the priority scale, 'screening agents in dental practice' and 'general population screening for oral cancer' were considered 'low priority' by 100% and 90.9% of experts respectively. The remaining six methods would appear to be in 'the middle ground', either dividing opinion relatively evenly across all three priority categories or being placed in the 'intermediate' category by a majority of experts.

However, the overall picture is more complicated than suggested by this relatively simple classification would suggest and several insights are given by the experts' comments. For example, whilst it was agreed that education for both students and clinicians was generally beneficial, this, of course, depends upon the quality of the education. Furthermore, both GPs and dentists are only likely to see perhaps one or two oral cancers in a career and, as one expert pointed out, in a congested student curriculum including oral cancer education was challenging. One expert suggested that a plan for sustained implementation of multiple methods might be the best approach. Another expert pointed out that there was a paucity of research on what exactly was effective and opined that further research on this aspect was needed.

6.8.2 Relationship to findings in other studies in this thesis

One objective of this study was to explore the priority, in the view of the experts in this study, of the methods of encouraging early diagnosis identified in other studies in this thesis. The first study suggests that the influence of the existing TWR urgent referral system on achieving earlier stage oral cancer diagnosis may be limited, yet such a method was considered of high priority by this group of experts. Some further insights into the experts' views on the TWR system are revealed by the comments. These included general strong support ('*No question! Absolutely'*) and an acceptance that relatively low positive predictive values are inevitable ('*We have to accept a low conversion rate and have the*

capacity to deal with this effectively'). However, much support for the urgent referral system was 'conditional', for example: '*As long as this is coupled with primary care education'*.

The importance of primary-secondary professional communication was an important theme in the international qualitative study. Communication was classified as high priority by almost two thirds of the experts and of intermediate priority by the remainder, providing further evidence that improvement in this aspect might be useful and that further research should be considered.

The potential value of access to regular dental inspection in encouraging earlier diagnosis was demonstrated in the systematic review, and this received strong support in this study, particularly from experts with a background in public health: *'GDPs well-placed to diagnose premalignant and early cancers. Evidence is that cost and non-availability of dentists deter people from attending. Improve dental access, and this will increase oral mucosal checks'.* It was also noted that such examinations might be carried out by 'allied health professionals' (AHPs).

6.8.3 Comparison with existing literature

Several studies have explored the various ways in which early diagnosis of oral cancer could be encouraged (Gómez et al 2010; Mehrotra et al 2011) and other work has examined the priorities for early detection of cancer in general (Badrick et al 2019). However, as far as I am aware this is the first work to attempt to prioritise early diagnosis methods for oral cancer. Many studies have examined oral cancer early detection 'in general' although most acknowledge that efforts to achieve this aim have met with limited success (Awan 2014).

In this study, the experts considered that fast-track referral systems for suspected oral cancer and rapid diagnosis clinics to be the two methods of highest priority, yet it is known that urgent referral systems deliver a positive predictive value of the order of 8-10% (Langton et al 2016) and there is some evidence that their influence on improving the stage on diagnosis may be limited (Langton et al 2019). One-stop clinics for diagnosis are recommended in some national guidelines on oral cancer (Madera et al 2019) although the evidence for effectiveness is not extensive. However, such clinics have been shown to be feasible and affordable for other cancers, such as breast (Delaloge et al 2016). Interestingly, in

subgroups of 'academics' and dental public health specialists most agreed that fast-track referral and one-stop diagnostic clinic were of high priority although there were differences in the perceived effectiveness of 'dental care for all'

General population screening and use of oral 'staining' methods were identified as low priority methods. There has been, to date, one randomised controlled trial of the effectiveness of general population screening, involving 130,000 subjects. The authors suggested that such an approach was only effective for high-risk individuals, such as smokers (Sankaranarayanan et al 2005). Oral stains, including toluidine blue and chemoiluminescence agents are known to have low sensitivity and specificity (Shukla et al 2018).

Much work has focused on medical and dental primary care practitioners' knowledge of oral cancer and diagnostic signs/symptoms and many such studies conclude that there is scope for knowledge improvement (Appelbaum et al 2009; Wade et al 2010). Similar conclusions have been reached in relation to undergraduate knowledge and awareness (Carter & Ogden 2007). The experts in this Delphi study considered these 'professional education methods' to be of intermediate or high priority. However, as several respondents noted, effectiveness is likely to be strongly influenced by the quality of the educational measures.

6.8.4 Strengths and weaknesses

This Delphi study provides an evaluation of experts' views on the priority of the various methods of encouraging the early diagnosis of oral cancer. It involves experts from two broad groups – senior academics in the 'oral specialties' and consultants in dental public health, typical of those involved in the development of policy documents and advising policymakers. Although the Delphi panel was relatively small, the response rate was high.

Although the study gives insight into how such early diagnosis might be prioritised in terms of perceived effectiveness, a Delphi study – by design – represents the subjective view of experts in the field and the results do need to be interpreted in this light. Murphy et al (1998) consider that Delphi studies need to be viewed as a method to use established knowledge effectively and *'one cannot judge it on the same*

basis as a concrete measurement'. The Delphi process aims to achieve a consensus view using feedback and reiteration over a number of rounds. This study included two rounds and although there were changes in opinion in some categories, for many items there was little from the first to second rounds (table 6.4). Therefore, it was judged unlikely that a third round would have made a marked difference. Furthermore, as Hamilton et al (2015) point out, the process is 'a balance between maintaining recruitment and allowing change'.

The study focuses 'effectiveness' and does not, of course, address other issues, for example economic aspects and cost-effectiveness.

6..8.5 Implications for policy, practice and research

The experts in this Delphi survey support the concept of a fast-track referral system for oral cancer, which, of course has been in place in the UK for approximately 20 years (*'What we've had for some time'*, as one respondent noted). Several other early diagnosis methods received strong support including 'one stop' clinics for diagnosis (which one respondent had established) and improved direct primary-secondary care communication, together with improved education for practitioners and students. Nevertheless, there remain many aspects – even amongst the more-strongly supported items – for which the evidence-base is weak. For example, there is little evidence on the outcome benefits of urgent suspected cancer policy, 'one-stop' diagnosis clinics for oral cancer and exactly what type of education improves cancer outcomes. It would seem logical that these subjects require further research.

Several items in this survey divided opinion evenly, notably 'screening of high-risk individuals' and 'improve access to dental services for all'. These are the subjects of considerable debate, particularly in relation to addressing social inequalities yet providing an effective and affordable service. Satisfactory solutions are yet to be identified (Speight et al 2017; Harris 2016) and these areas also need further research.

6.9 Conclusions

This Delphi study has developed a priority ranking for the effectiveness of the methods of encouraging early diagnosis of oral cancer. It has the potential to assist with future policy decisions and also to guide

further research. The methods considered to be of highest priority were fast-track referral systems and one-stop referral systems although several other methods were considered of high priority by the experts in this study and also might be useful for policy development. Research should continue on methods of early diagnosis of oral cancer, even if ranked low in this study. It is likely that a 'multi-measure' approach to early oral cancer diagnosis will be most effective and research in how to deliver this effectively and efficiently could prove valuable.

Chapter 6 references

Applebaum E, Ruhlen TN, Kronenberg FR, Hayes C Peters ES (2009) *Oral cancer knowledge, attitudes and practices A survey of dentists and primary care physicians in Massachusetts* Journal of the American Dental Association 140 461-467

Awan KH (2014) *Oral cancer: early detection is crucial* Journal of International Oral Health 6(5) i-ii

Badrick E, Cresswell K, Ellis P et al 2019 *Top ten research priorities for detecting cancer early* (2019) Lancet Public Health 4 e551

Boulkedid et al (2011) *Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review* PLoS ONE 6:e20476

Carter L and Ogden G (2007) *Oral cancer awareness of general medical and general dental practitioners* British Dental Journal 203(5) E10

Conway DI, Petticrew M, Marlborough H et al (2008) *Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies* International Journal of Cancer 122 2911-2819

Delaloge S, Bonastre J Borget I et al (2016) *The challenge of rapid diagnosis in oncology: diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic* European Journal of Cancer 66 131-137

Dufresne K (2017) *The Delphi technique* available at: https://www.students4bestevidence.net/blog/2017/11/15/the-delphi-technique/ (accessed August 2020)

Ford PJ and Farah CS (2013*) Early detection and diagnosis of oral cancer: Strategies for improvement* Journal of Cancer Policy 1 e2–e7 https://doi.org/10.1016/j.jcpo.2013.04.002

General Dental Council (2009) *Scope of Practice* available at: https://dentallawandethics.co.uk/wp-content/uploads/2016/03/GDC-Scope-of-practice.pdf (accessed August 2020)

Gómez I, Warnakulasuriya S, Varela-Centelles PI, López-Jornet P, Suárez-Cunqueiro M, Diz-Dios P and Seoane J (2010) *Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay?* Oral Diseases 16 333-342

Goodman CM (1987) *The Delphi technique: a critique* Journal of Advanced Nursing 12 729-734

Greenwood M and Lowry RJ (2001) *Primary care clinicians' knowledge of oral cancer: a study of dentists and doctors in the North East of England* British Dental Journal 191 510-512

Hamilton W, Stapely S, Campbell C et al (2015) *For which cancers might patients benefit most from expedited symptomatic diagnosis? Construction of a ranking order by a modified Delphi technique* BMC Cancer 15 820

Harris RV (2016) *Do 'poor areas' get the services they deserve? The role of dental services in structural inequalities in oral health* Community Dental Health 33 164-167

Hasson F, Keeney S and McKenna HP (2000) *Research guidelines for the Delphi Survey Technique* Journal of Advanced Nursing 32 1008-1015

Hassona Y, Scully C, Ghosh MA et al (2014) *Mouth cancer awareness and beliefs among dental patients* International Dental Journal 65 15-21

Hohmann E, Cote MP and Brand JC (2018) *Research pearls: expert consensus-based evidence using the Delphi method* Arthroscopy 34 3278-3282

Langton S, Lowe D, Rogers SN, Pludemann A and Bankhead C (2019[a]) *The impact of the UK 'two-week rule' on stage-on-diagnosis of oral cancer and the relationship to socio-economic inequalities* Journal of Cancer Policy 20 1-8

Langton S, Rijken JA, Bankhead CR, Plüddemann A and Leemans CR (2019[b]) *Referrals for head and neck cancer in England and the Netherlands: an international qualitative study of the views of secondary-care surgical specialists* British Journal of Oral and Maxillofacial Surgery 57 116-124

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Langton S, Cousin GCS, Plüddemann A et al (2020) *Comparison of primary care doctors and dentists in the referral of oral cancer: a systematic review* British Journal of Oral and Maxillofacial Surgery 58 898-917

Madera M, Franco J, Solà et al (2019) *Screening and diagnosis of oral cancer: a critical quality appraisal of clinical guidelines* Clinical Oral Investigations 23 2215-2226

Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316

Massano J, Regateiro F, Januário (2006) *Oral squamous cell carcinoma: Review of prognostic and predictive factors* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 102 67-76

Mehrotra R and Gupta DK (2011) *Exciting new advances in oral cancer diagnosis: avenues to early detection* Head and Neck Oncology 3 33-40

Murphy MK et al (1998) *Consensus development methods and their use in clinical guideline development* Health Technology Assessments 2(3) 1-88

NHS England (2018) *New 'one stop shops' for cancer to speed up diagnosis and save lives* available at: https://www.england.nhs.uk/2018/04/new-one-stop-shops-for-cancer-to-speed-up-diagnosis-and-save-lives/

Pluddemann A, Heneghan C, Thompson M et al (2010) *Prioritisation criteria for the selection of new diagnostic technologies for evaluation* BMC Health Services Research 10(1) 109

Sackman H (1975) *Delphi Critique: Expert Opinion, Forecasting and Group Process* (Lexington Books) Lexington Massachusetts

Sankaranarayanan R, Ramadas K, Thomas G et al. Trivandrum Oral Cancer Screening Study Group (2005) *Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial* Lancet 365 1927–1933

Shukla A, Singh NN, Adsul S et al (2018) *Comparative efficacy of chemiluminescence and toluidine blue in the detection of potentially malignant and malignant disorders of the oral cavity* Journal of Oral and Maxillofacial Pathology 22 442

Speight PM, Epstein J, Kujan O et al (2017) *Screening for oral cancer - a perspective from the Global Oral Cancer Forum* Oral and Maxillofacial Pathology 123 680-687

Van der Waal I, de Bree R, Brakenhoff R et al (2013) *Early diagnosis in primary oral cancer: is it possible?* Medicina Oral Patalogia Oral y Cirugia Oral 18 e33-e37

Wade J, Smith H, Hankins M et al (2010) *Conducting oral examinations for cancer in general practice: what are the barriers?* Family Practice 27 77-84

CHAPTER 7: Summary, discussion and conclusions

7.1 Overview of the thesis findings

7.1.1 Literature review and questions

The literature review in this thesis examined the evidence that led to the conclusion that UK cancer outcomes were genuinely worse than the best in Europe, focusing firstly on cancer in general and subsequently oral cancer. The studies originally identifying UK cancer outcome deficiencies have weaknesses but subsequent work has indicated that the relatively poor outcomes – including those for oral cancer - are probably genuine. The causes of relatively poor oral cancer outcomes are multiple and complex and a range of solutions is probably needed. However, late presentation is likely to be one important cause and, although for oral cancer most delay occurs in the patient interval, it is probable that system delay also influences outcome.

As part of an effort to reduce late presentation, the UK government introduced the guideline driven and target enforced 'two-week rule' system in 2000. However, for oral cancer little is known about whether the system has improved mortality or stage on diagnosis and there is limited work on how the system might be improved.

From the literature review, the questions addressed by studies in this thesis were developed: Firstly, does the urgent suspected cancer system result in an earlier stage on diagnosis for oral cancer? Secondly, how does the English referral system compare to that in other countries with better outcomes? Thirdly, oral cancer is unique in having a 'double referral base' from both primary care doctors and dentists. Are there differences in the oral cancer referrals from each profession that might provide insight into how earlier diagnosis of oral cancer might be delivered? Fourthly, urgent referral systems are one of several methods of potentially improving early oral cancer diagnosis. How might the methods be prioritised and where might an urgent suspected cancer system rank in relation to other methods?

7.1.2 Summary of findings from the studies

The first study in this thesis addressed the question whether the TWR/NICE guidance referral system had resulted in an earlier stage of oral cancer at diagnosis. As a secondary aim, the results were analysed in relation to socio-economic deprivation. Although stage on diagnosis steadily improved for the period studied, 'Joinpoint' analysis showed, overall, no significant change in trend in relation to the introduction of the urgent suspected cancer system. This was also the case for 'more' and 'less' deprived social groups, and, although the 'more' deprived showed more rapid improvement, the 'deprivation gap' persisted throughout the study. Notably, the number of presenting oral cancers per year increased markedly throughout the study period.

The second, qualitative, study compared urgent head and neck cancer (of which oral cancer is one type) in England and the Netherlands. Several themes were identified, some describing similarities in the experiences of the secondary care specialists in each country. However, differences were evident including a more rapid, flexible system in the Netherlands, some criticism of a 'tick box' referrals in England and, most prominently, much closer communication between primary and specialist care in the Netherlands.

The third study, a systematic review, examined the differences between primary care doctors' and dentists' referrals for oral cancer. This study showed that typically, about 50% of such referrals came from GPs, 40% from dentists. However, although there was no statistically significant difference in delay between the two professions, there was evidence of dentists referring oral cancer at an earlier stage and 14-35% of cases were referred, by dentists but not doctors, in the absence of symptoms.

The fourth study, a Delphi study of experts' views, aimed to prioritise the various ways of encouraging early oral cancer diagnosis, focusing on the ranking of fast-track referral systems compared to other methods. Fast-track referral systems were considered of high priority by a majority of experts although other methods such as one-stop diagnosis systems and practitioner education were also considered important. It would seem likely that a 'multi-measure' approach to early oral cancer referral and diagnosis would be most effective.

7.2 Discussion

7.2.1 Does the current English urgent referral system, the TWR, 'work' for oral cancer?

There is little doubt that diagnosing oral cancer at an earlier stage would improve overall outcomes, yet it seems that achieving this, in practice, presents something of a challenge. To what extent does the TWR urgent referral system help achieve earlier oral cancer diagnosis? Even within the studies in this thesis there is some element of 'conflict'. For example, on one hand a group of experts consider that urgent referral systems should be of the highest priority, yet when the stage on diagnosis is examined in a time-series study, the TWR system appears to have had no statistically significant influence on the change in trend in reducing late stage diagnosis.

This does not mean that the urgent referral system has had no benefit at all. There is evidence to indicate that patients value rapid diagnosis of suspected cancer (Ndukwe 2010) and it certainly represents an effort to implement a 'universal standard' for all, addressing the 'post code lottery' described in Chapter 1. Nevertheless, research in this thesis – although restricted to one area of England - suggests that the TWR system, in terms of diagnostic stage improvement for oral cancer, has had limited benefit.

Why might this be the case? One contributing factor might be the proportion of all oral cancer cases that are diagnosed by the TWR system. There is evidence that only approximately 40% of head and neck cancer cases present to secondary care as TWR referrals, the majority reaching specialist treatment services via a variety of methods, including 'general' referrals and emergency presentations (Langton et al 2016). Another possible explanation for the lack of influence on the rate of improvement in stage on presentation might be that many cases of suspected cancer were already being referred urgently prior to the inception of the TWR system. The concept of the importance of early diagnosis and treatment for many types of cancer is, of course, not new (MacArthur et al 1984; MacAdam et al 1979) and includes oral cancer (Boyle et al 1959; Shedd et al 1967). Indeed, some published work has suggested that the speed of referral was no different for oral cancer cases before and after the TWR system was introduced (East et al 2005). Alternatively, perhaps it is simply the fact that delays of a few weeks in the referral and treatment of oral cancer have less influence than the delay prior to presentation to a medical

professional. Furthermore, different cancers (of course) have different symptoms and signs but, as discussed in Chapter 2, certain types have highly characteristic, if not invariable, presentation features - for example, a lump in breast cancer or post-menopausal bleeding in the case of uterine cancers. On the other hand, some cancers often present with vague symptoms, indistinguishable from many other conditions; examples include pancreas and ovary (Foot and Harrison 2011). The diagnosis of cancers with vague symptoms is probably less influenced by a relatively rigid symptom/sign driven system such as the TWR. For oral cancer, the signs and symptoms can be either relatively 'straightforward' such as an obvious non-healing ulcer on the tongue or, alternatively, vague and typical of many other conditions including bad breath or a loose tooth (Cancer Treatment Centers of America 2020). Therefore, it would seem unlikely - unless every patient with a complaint of 'bad breath' or 'mouth ulcer' is submitted to an urgent referral pathway – that a system such as the TWR, in isolation, can be relied on to detect every case of symptomatic oral cancer. Furthermore, as demonstrated in the systematic review, not all cases of oral cancer present symptomatically and these will not be diagnosed by a system based on symptom recognition alone.

7.2.2 International differences in referral systems – a cause of outcome differences? Could England 'do it better'?

If it is accepted that the TWR system, guideline-driven and target-enforced, is unlikely alone to diagnose every oral cancer in a 'timely manner', how might the English system of suspected oral cancer referral be improved?

The second, qualitative, study gives some insight into the differences between the English and Dutch systems of urgent head and neck cancer referral that might shed light on aspects with potential to influence improvements. In the Netherlands suspected cancer referral is more flexible, without specific targets, than the system in England, yet 1-year oral cancer survival rates are consistently better in the Netherlands. Obviously, many factors could influence this outcome, for example greater patient awareness and hence reduced delay in presenting at primary care.

Nevertheless, Dutch specialists focused on two aspects of their referral system that may encourage earlier diagnosis: firstly, a strong culture of direct primary to specialist communication and secondly

marked flexibility in the speed of referral, for example same-day referral if, following a professional telephone discussion, it appeared that a case might be particularly urgent. Both direct inter-professional communication and speed of referral were considered by many English surgeons in the study to be deficient in the TWR system (*'everything comes through on day 13 and management think that represents success'* as one English participant in the qualitative study suggested). The 'two-week rule' is, of course, a 'cornerstone' of the policy to ensure timely treatment yet this study suggests that it may be possible that similar or better outcomes can be achieved with a system that is somewhat more flexible and, arguably, responsive.

7.2.3 Other approaches to encourage early diagnosis of oral cancer? Possible insights from comparing doctors and dentists

The TWR protocol-driven system for oral cancer is, in itself, limited – apart from the possible lack of influence on stage on diagnosis, it has a positive predictive value in the order of 8-9% and a specificity of just over 40%. So, what else might be done – or what other approach(es) might be considered, in addition to the TWR system - to encourage earlier referral to specialist care? Oral cancer is referred to specialist care not only by primary care doctors but also in considerable numbers by dentists. The systematic review showed that whilst there is little or no difference in delay between the two professions, several included studies confirmed two interesting findings: firstly, that oral cancer may, overall, be referred at an earlier stage by dentists and secondly that between 14% and 35% of cancers from dentists are referred in the absence of patient-perceived symptoms. This suggests that routine dental examination (in effect, an 'informal screen') may have value in the diagnosis of early oral cancer, although to be of most benefit this would need to include those most at risk of the disease, including the socio-economically deprived who, unfortunately, are least likely to attend a dentist regularly.

One suggested practical implementation, which appeared in one political party's manifesto in the 2019 general election, was to end 'band 1' dental check-up charge (£22.70 at the time of writing). The manifesto item addressed the problem of oral cancer and noted the importance of regular dental inspection:

'Scrapping band one dentistry charges will give everyone a free teeth MOT with their dentist……dentists are often first health professionals to detect signs of oral cancers. Given these cancers currently claim more lives than testicular and cervical cancers combined – and are killing twice as many as those killed in car accidents in England, this policy could play a key role in screening and early detection.' (Labour Party 2019).

One recurring theme throughout this thesis is the influence of socio-economic inequalities. In the first study, the socio-economic gap for late diagnosis of oral cancer persisted throughout the study, although was observed to be reducing. For many years it has been well-established that large social inequalities exist in both cancer incidence and mortality (Kogevinas et al 1997) and 'the socio-economic gap' for head and neck cancers, including oral, is one of the greatest of all cancer types (Spedea et al 2010). Although smoking and excessive alcohol consumption are considered to have a major influence on socio-economic differences in head and neck cancers (Huisman et al, 2005), other factors, such as different probabilities of viral infection, education (with associated skills in preventing health damage) and material living standards may contribute (Merletti et al 2009).

7.2.4 Priority of the various methods of encouraging early oral cancer diagnosis

The initial motivation for undertaking the Delphi study was to attempt to identify what priority experts gave to urgent suspected cancer referral systems compared to the other methods of encouraging early diagnosis of oral cancer. In a sense this represented a 'real world' question, bearing in mind that firstly, for many clinical or health policy questions, evidence is incomplete. Secondly, decisions regarding the course of action when faced with a problem (in this case how to construct policy to diagnose a cancer earlier) often need to be made in the face of incomplete evidence. After two Delphi rounds, fast track referral systems – in other words the system currently in place in England – received strong support although, overall, it is likely that complementing the existing TWR system with other methods, such as 'one-stop' specialist clinics would be more effective in encouraging early oral cancer diagnosis.

7.2.5 Earlier diagnosis or 'prevention first'?

The first study demonstrated a rapid and continuing rise in the number of presenting oral cancers in Merseyside. This reflects the national trend; as described in Chapter 1, oral cancer presentations have increased by 135% in the last 20 years. Despite the steady improvements in stage on diagnosis of oral cancer that have been demonstrated in this thesis, it is clear that in the face of increasing incidence of oral cancer, prevention of the disease needs to be of high priority in the overall strategy. The influence of HPV vaccination for boys (implemented in the UK in 2019) - in addition to that for girls, introduced 2008 (Public Health England 2018) - on oral cancer incidence remains to be fully evaluated at present.

7.3 Strengths and weaknesses of the thesis

This thesis critically examines the evidence that led to the development of the UK Cancer Plan, focusing on the development of the urgent referral policy which has been in place – albeit with some minor modifications – for approximately 20 years. The thesis includes a range of study types: a time series cohort study, a qualitative study, a systematic review and a Delphi study of expert opinion. It provides insights into the system for urgent referral of oral cancer, including evaluation of its effectiveness, how the system might be improved and experts' views on the prioritisation of the various methods for the early diagnosis of oral cancer.

However, the topic of timely diagnosis of oral cancer is very broad and has many facets, certainly more than could reasonably be included in a thesis. Several areas of the subject, examples include economic studies and patient experience studies, have not (by design) been incorporated in this thesis, which aims to provide an insight – perhaps a 'snapshot' - into a number of important areas whilst accepting that within the constraints of a thesis many other important questions remain unanswered. As described in the literature review, it is unlikely that all the findings in this thesis can be directly transferred to other cancer types, as much published work would suggest that in most instances different cancers need to be considered separately. Nevertheless, concepts such as professional communication in cancer diagnosis may well apply across several types.

The time-series study suggested that the TWR may not be effective in improving the stage on diagnosis of oral cancer. However, it was carried out in one area of England that has a particularly high incidence of oral cancer and a high level of socio-economic deprivation. Therefore, the results may or may not reflect the position in other parts of the country – or the country as a whole.

The qualitative study compared the views of secondary care specialists on the referral of head and neck cancers, although England was compared with only one country, the Netherlands. Comparing further countries and the views of other groups – notably GPs and patients - could possibly give a 'broader picture'.

The systematic review included 22 studies from 10 countries. However, there was marked heterogeneity between studies. Synthesis of outcomes – notably in relation to cancer stage – was complicated by diverse staging methods in the included studies.

The Delphi study was relatively small, with 13 experts completing both rounds of the study and although there was strong consensus that an urgent referral system was of high priority, this was the view of one group of experts; a different result is possible if the same questions were asked of a different group of experts.

7.4 Implications for policy

*'Billions of dollars are spent each year on producing research but to what extent does all this research actually serve to improve health outcomes?' (*Andermann, 2016)

'Even the highest quality evidence will have no impact unless it is incorporated into decision-making for health.' (Andermann, 2016)

This thesis is, of course, an evaluation of a government policy. How, broadly speaking, might research be incorporated into policy? Consider the view of Sanderson (2002) who suggests that research can inform policy in four ways:

(1) By identifying problems or needs that may require policy intervention

(2) By identifying solutions that are likely to prove effective

(3) By identifying objectives that can be measured to evaluate policy

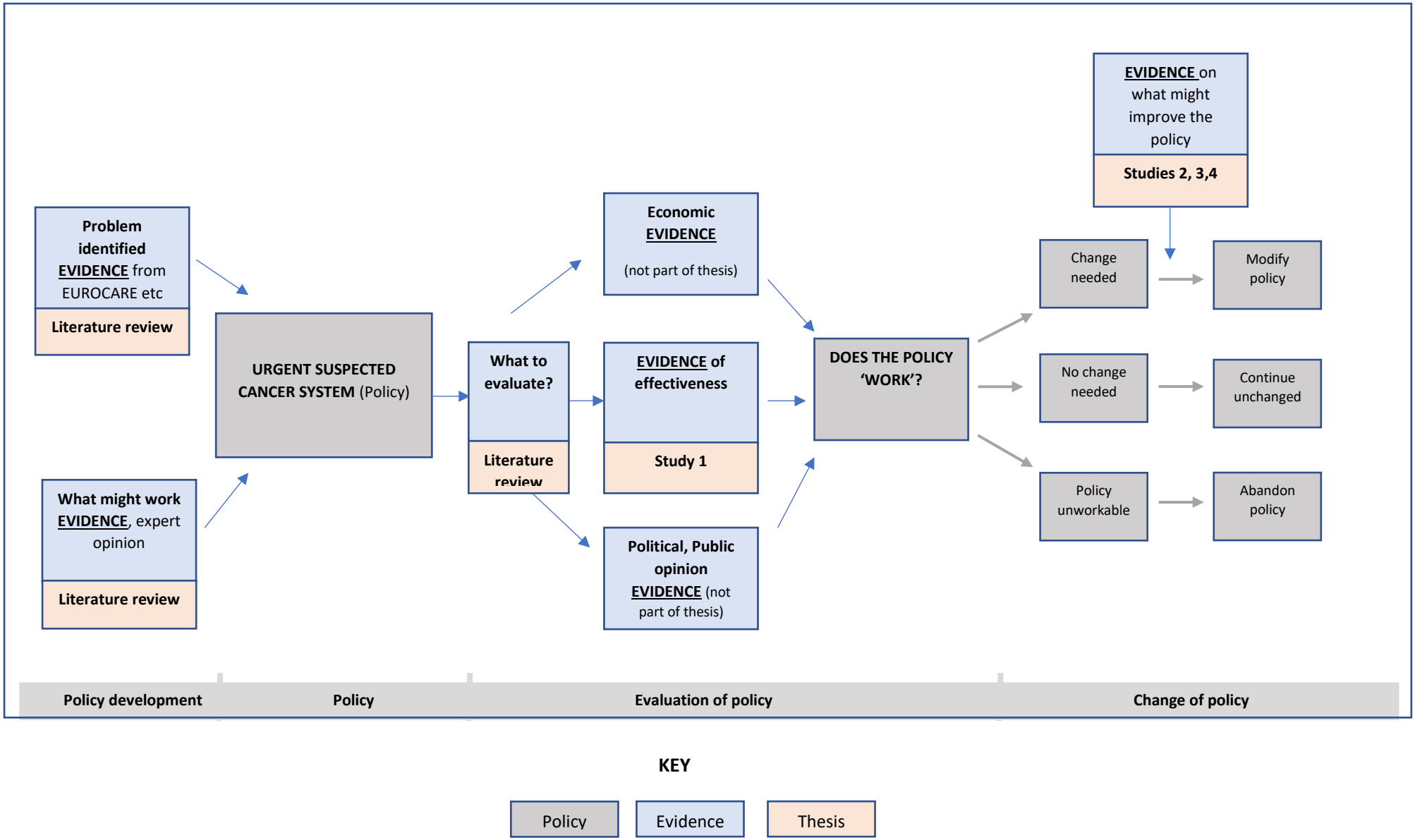
(4) By evaluating the effectiveness of policy

In this thesis, the literature review focuses on the identification of a 'problem' (poor UK cancer outcomes) and what might prove effective in resolving the problem. Study 1 (time series study) focuses on evaluating the effectiveness of a policy, the urgent suspected cancer referral system and studies 2, 3 and 4 on what might improve the policy. These aspects are illustrated in figure 7.1.

Clearly not all influences on policy are studied given the practical limits of a thesis – for example, economic studies - although they are, of course, central to policy development and evaluation.

Whilst some findings do have, potentially at least, benefits for the earlier diagnosis of oral cancer, the relationship between evidence and policy is complex and the process of 'knowledge to action' is far from straightforward. The topic has been the subject of a very large volume of published work (Parkhurst, 2017, Parkhurst et al 2018, Greenhalgh and Russell 2006) and it is agreed there are no direct, straightforward solutions to what is without doubt a 'complex practice' (Flitcroft et al 2011; Reid et al 2017; Smits et al 2018) – as Greenhalgh (2015) points out: *'Knowledge to action: there is no tooth fairy'*.

Figure 7.1 – Thesis and links to evidence-based policy influences defined by Sanderson (2002)



Accepting that 'knowledge to policy action' is challenging it can, nevertheless, be argued that the UK urgent cancer policy – as part of the 2000 Cancer Plan - was implemented as a response to evidence, in the form of the EUROCARE studies, that appeared to show UK outcomes were inferior to the European best. However, as noted in previous sections of this thesis, the studies are far from perfect and it was only many years after the 2000 Cancer Plan introduction that there was convincing evidence that the UK outcomes for cancer were, genuinely, worse than the best in Europe.

What might have prompted the government to act and introduce policy such as a fast-track cancer system, when there was limited evidence about its likely effectiveness and, indeed, at the time of its introduction no certainty that UK cancer outcomes were genuinely worse than in other European countries? Shepherd and Rudd (2014) give some insight. They consider that policy debate can be broadly classified as 'rational' - based, for example on measuring costs and outcomes - and 'irrational' which include cognitive biases, external pressures, political necessity, and public engagement. As Bourne (2014) points out: *'policy windows are often underpinned by a mixture of political, evidence-based and personal momentum'*. Considering UK cancer policy, it is possible that in publishing the EUROCARE studies, 'facts' about UK poor cancer performance had been made public (to the whole of Europe, not just the UK, of course), these 'facts' were hardly likely to be ignored by opposition politicians, the subject of 'cancer' focused public opinion and, possibly most importantly, the subject was reported (and exaggerated) with enthusiasm by the media – examples are given earlier in this thesis. Therefore, it seems that urgent suspected cancer policy – and, of course, the 2000 Cancer Plan – was possibly developed with a view to addressing both practical and pressing political problems.

Should the policy for urgent oral cancer referral continue in its present form? One finding in this thesis was that the TWR system may have limited effect, in its current form, on the stage on diagnosis of oral cancer although it is not entirely clear whether this would apply in all parts of England, particularly those with different socio-economic structures and oral cancer incidence. It would also be important to evaluate the economic implications of the TWR policy. There is no doubt that UK urgent referral policy consumes considerable resource, although it could also be argued that this is offset by diagnosing cancers earlier (if this is actually achieved), with reduced treatment costs.

Unfortunately, economic analysis of cost/benefit for urgent cancer diagnosis lags considerably behind the analysis of screening benefits (Hamilton 2016). There have been a small number of studies on the cost of diagnosis, for a limited number of cancer types, such as colorectal (Tappenden et al 2009) but fewer on cost-benefit and none, as far as I am aware, for any type of head and neck cancer. Between 2011 and 2014 suspected cancer referrals (all types) increased by approximately 10% per year with 1.36 million referrals made in 2013-14 (NICE 2015) and one estimate is that early diagnosis of cancer in the UK, at that time, cost in the order of £1 billion per year (Hamilton 2015).

However, for oral cancer, a situation exists where there has been very little work on the clinical benefits of an early diagnosis policy (notwithstanding the first study in this thesis) and even less on exactly how much the system costs in relation to benefits. Perhaps a clearer insight into these aspects, provided by high-quality evidence, would be of further value to policymakers. The first (time series) study in this thesis also emphasised the rapid increase in oral cancer cases, implying the need for effective prevention policy.

From the studies, several further findings might prove useful in policy development. The qualitative study suggested that effective referral may be achieved with a less 'protocolised' and more flexible policy; yet again, the economic implications of this would need to be evaluated.

The systematic review in this study provides evidence that 'informal screening' at conventional dental examination might improve the early detection of oral cancer, particularly for asymptomatic lesions. It would seem that those least likely to attend the dentist regularly are those most at risk of oral cancer and therefore policy to provide basic dental care to all social groups could be useful, if it could be practically implemented – once again - in the light of the practical and economic implications.

In the Delphi study, urgent referral systems were supported by experts but several methods were considered effective and it is possible a policy that embraces multiple measures is likely to prove most effective.

Oral cancer campaigns

Given the increasing UK incidence, its mortality and the fact that many cases are a result of preventable causes, described previously in this thesis, what might be done to encourage prevention and early diagnosis through the media and prevention campaigns?

A systematic review by Austoker et al (2009) examined evidence for the effectiveness of interventions to promote awareness of cancer (of several types). Some evidence was identified that individual-level interventions were effective but only in the short term. 'Community interventions' (for example, in leisure centres) had limited effectiveness and, whilst national campaigns, again, had some limited effectiveness, the overall conclusion of the review was that more work was needed to define exactly the requirements for a successful cancer campaign.

What is known in relation to oral cancer? Macpherson (2018) provides an comprehensive description on what has been attempted and how successful such efforts have been. There is some evidence that national campaigns, such as 'mouth cancer action month' (NHS 2019) result in improved awareness but less so amongst the high-risk population, in contrast attracting large numbers of low risk 'worried well'. A multi-intervention campaign in the West of Scotland (WoSCAP) aimed to improve oral cancer awareness and encourage patients with suspicious signs/symptoms to seek professional advice as quickly as possible. The outcomes of the campaign, described in Chapter 1 of this thesis, did show some benefits but overall demonstrated a mixed picture of effectiveness.

The Delphi study in this thesis included 'patient education on signs and symptoms' yet only 18.2% of experts suggested this item was of high priority, the majority (81.8%) considered it to be of intermediate priority.

What is the future of oral cancer 'campaigns' and preventative information? One obvious method, briefly mentioned by Macpherson (2018) is the internet. A systematic review by Webb et al (2010) examined the use of the internet to promote health behaviour change and found that internet-based interventions using 'behavioural techniques' had greater effect, especially if accompanied by additional communication, such as text messages. An evaluation of healthcare information (in relation to

colorectal cancer) noted improved utilisation by those with extensive internet experience, which does raise the question of the effectiveness in relation to oral cancer for the socio-economically deprived. An evaluation of information quality on French language oral cancer information sites (Vivien 2017) concluded: '*the quality of general public French-speaking websites dedicated to oral cancer detection is very bad'.* However, a study in the Philippines (Dalanon et al 2020) noted an increasing use of oral cancer public information websites. Overall, as Macpherson (2018) points out *'many people now turn to the internet for health information'* and this may well be the future of oral cancer awareness campaigns.

Population based screening

What is the future for a possible screening programme? The arguments for an oral cancer screening programme have been discussed in section 2.6.7. The mouth is easy to examine, abnormalities are easily seen and oral cancer is preceded, in most cases, by a so-called 'oral potentially malignant disorder' (OPMD), usually a white patch (leukoplakia) or a red patch (erythroplakia) (Warnakulasuriya et al 2007). The existence of these pre-malignant lesions, in an easily accessible site suggests that screening for oral cancer might well be feasible. Furthermore, as mentioned in Chapter 5, a systematic review (Walsh et al 2013) found 'conventional oral examination' (COE), across 10 studies, gave varying diagnostic accuracy, although sensitivity was at least 0.7 and specificity at least 0.9 in all studies, values of the order delivered by cervical cancer and breast cancer screening programmes. However, the UK National Screening Committee specify very stringent criteria for the implementation of a screening programme (Brocklehurst and Speight 2018), one being the need for evidence of improved mortality from a randomised controlled trial (RCT). To date, only one RCT has been undertaken on oral cancer screening, a large 15-year study carried out in India with non-medical staff undertaking the examinations (Sankaranarayanan 2013). The results did show improved mortality for high risk groups but not for the 'general population'. Unfortunately, the study suffered from marked attrition bias (of over 95,000 subjects included in each arm, less than 20,000 completed the trial) and no screening programme exists in the UK or anywhere else in the world. Overall, it would seem unlikely that one

would be implemented the absence of sound RCT evidence, together with economic evidence, which presents a considerable challenge.

The key recommendations in relation to policy are given in table 7.1.

Table 7.1 Summary of key recommendations for policy

Finding in this thesis	**Where in thesis**	**Recommendation**
English/UK outcomes for oral cancer are probably genuinely worse than the best in Europe and have been for many years.	Chapter2, literature Review	Efforts to improve English/UK oral cancer outcomes are justifiable and should continue.
The causes of relatively poor outcomes are multiple and complex.	Chapter2, literature review	Policy needs to consider the broad range of factors influencing cancer outcomes.
Fast-track suspected cancer referral systems may have not changed the trend in late oral cancer presentation, although they have other benefits.	Chapter 3, time series study	This needs further research but the policy for urgent suspected cancer referral (probably for all cancer types, including oral) should be re-evaluated in the light of its effectiveness and cost-effectiveness.
Oral cancer is increasing rapidly	Chapter 3, time series study	A comprehensive policy for the prevention of oral cancer is needed.
Socio-economic discrepancies influence late presentation of oral cancer.	Chapter 3 time series study	Addressing relevant aspects of socio-economic inequalities may improve late presentation of oral cancer.
Improved direct communication between primary care and specialist practitioners may enhance several aspects of suspected oral cancer referral.	Chapter 4, qualitative study	Efforts to improve direct primary-secondary healthcare communication should be considered.
Regular dental check-ups may facilitate earlier diagnosis of oral cancer.	Chapter 5, systematic review	Efforts to deliver routine dental examination to all may improve early referral/diagnosis of oral cancer.
Urgent suspected oral cancer systems are supported by experts; however, a broad range of 'early diagnosis measures' are likely to prove helpful in improving early diagnosis.	Chapter 6, Delphi study	Early referral/diagnosis is likely to be enhanced by a policy that includes broad 'package' of measures.

7.5 Implications for research

The research implications derived from this thesis are broad.

The suggested areas where further research might be considered are shown in table 7.2

Table 7.2 Implications for research

Finding in this thesis	Where in thesis	Further research that might be considered
The causes of relatively poor outcomes for oral cancer (and indeed other types) are multiple and complex.	Chapter2, literature review	Solutions are likely to be multiple and complex; this should be reflected in research.
Late diagnosis is an important cause of poor oral cancer outcomes.	Chapter 2, literature review	Further research into the multiple causes of late presentation is needed.
Fast-track suspected cancer referral systems may have not changed the trend in late oral cancer presentation, although they have other benefits.	Chapter 3, time series study	Further research on effectiveness and cost-effectiveness of urgent suspected cancer referral systems is needed (and across a range of cancer types).
Oral cancer is increasing.	Chapter 3, time series study	Further research into exactly why this is the case and effective prevention is needed.
Socio-economic discrepancies influence late presentation of oral cancer.	Chapter 3 time series study	Further research on socio-economic equalities both in general and specifically how they affect oral cancer, together with effective solutions, is required.
The Netherlands has better 1-year survival for head and neck/oral cancer than England. The Dutch system is flexible, clinician led and responsive.	Chapter 4, qualitative study	Research into other countries' referral systems – particularly those with better 1-year survival than the UK - could prove valuable.
Regular dental check-ups may facilitate earlier diagnosis of oral cancer.	Chapter 5, systematic review	Research into how regular dental (oral) inspection can be delivered to all, including cost-effectiveness studies, is needed. Furthermore, research into how those most at risk of oral cancer could be targeted is needed.
A 'cornerstone' of early oral cancer diagnosis is the TWR, yet other methods of encouraging early diagnosis are considered important by experts.	Chapter 6, Delphi study	Further research into how other methods of encouraging early oral cancer diagnosis (e.g. practitioner education, 'one-stop' diagnosis in secondary care) could be delivered.

7.6 Overall conclusions

This thesis has addressed *'An evidence-based approach to the to the urgent referral of suspected oral cancer in England'* from several perspectives, using a range of study methodologies. The thesis studies aspects of a national policy for rapid referral and early diagnosis for only one type of cancer; nevertheless, the subject is broad, encompassing not only clinical outcomes but many other political and economic aspects and clearly within the limits of a thesis it is impossible to evaluate everything. Bearing this in mind, some areas that without doubt could influence the debate, such as economic studies and patient experience evaluations have, by design, been excluded for practical reasons.

Overall, the current system of urgent referral of oral cancer referral has benefits in ensuring a timely, universal standard that is carefully monitored. However, its effect in delivering an earlier stage of cancer may be limited. How might the system be enhanced? Overall, I would suggest that an urgent cancer referral system needs to be 'tailored' to the type of cancer in question and not only in terms of 'red flag' symptoms. What applies to one type of cancer cannot be simply transferred to oral cancer or indeed other cancers. In summary, the main points derived from the thesis are:

(1) The TWR-NICE urgent suspected cancer referral system has benefits but may have had limited influence on the change in stage at diagnosis of oral cancer in England.

(2) Systems such as the one in place in the Netherlands – more flexible and with better inter-professional communication than in England – may have features that help to deliver outcomes for head and neck/oral cancer better than those in England.

(3) In addition to rapid referral, other methods encouraging early diagnosis of oral cancer diagnosis need to be considered to obtain best effect. One important method may be implementing regular dental inspections for as many as possible but particularly for those at most risk.

(4) Studies in this thesis suggest that further methods, including improved primary-secondary care communication, practitioner education and addressing socio-economic inequalities may also be important in encouraging early oral cancer diagnosis.

(5) Prevention is an essential part of the overall strategy and a reduction in the incidence of oral cancer is very important

7.7 **Final thoughts – some reflections**

The learning experience

Without doubt, my DPhil has been an excellent learning experience. From a practical research point of view, I have undertaken four different types of study, including my first qualitative study and my first Delphi study and have improved my understanding - and ability to carry out – statistical analysis, at least within the context of the relatively limited research in the thesis. I have also organised and undertaken an international study and worked with researchers at other institutions. Although I have learnt that a DPhil is essentially an 'independent' activity on the part of the student, it requires interaction and co-operation with many different people.

What might I have done differently?

Getting started

I found that simply 'starting' my research for the thesis was something of a challenge – there seemed to be an endless road ahead, disappearing into the distance. One initial mistake, which I suspect may be common, was a failure to realise (initially, at least) that the DPhil process is a 'marathon', not a 'sprint' and, on reflection, I should probably have taken more time to read, plan and been in slightly less of a hurry to actually start my first study.

Challenges and 'hitting the rails'

It became evident early in my DPhil studies that doctoral research will almost inevitably result in challenges and difficulties at some point. One aspect that I found interesting – and challenging - was the identification of oral cancer stage data, as utilised in the first study in this thesis. Searching for a suitable source of data took a considerable amount of time and effort during the early part of my DPhil studies. Sources of national data were explored – unsuccessfully and with considerable disappointment- and it was only due to a 'personal contact' and the much-appreciated help from colleagues in Liverpool that I was able to gain access to suitable staging data.

At the early stage of this thesis, one planned study on the influence of alcohol and smoking on the predictive value of oral cancer referrals failed to gain ethical approval on the grounds that no funding was secured for the study. A decision was made to exclude this study from the thesis.

Study designs

'The best thesis is a finished thesis' (Taylor 2018)

On reflection, it would seem that one challenge in a DPhil is balancing the various options and study designs for addressing research questions with the practicalities of completing the research within the constraints of a research degree and thesis. The systematic review in this thesis does, of course, have the advantage of providing a more general overview of the differences between dental and medical oral cancer referrals and gives some insight into applicability of conclusions as different studies in different countries are included. Nevertheless, the question could reasonably have been addressed by a prospective cohort study of presenting oral cancers, although this might well have necessitated complex co-operation with more than one clinical unit and may well have taken a considerable time to complete. Perhaps such a study would be a useful next step.

Other studies that might have been usefully included in the thesis

In retrospect, one aspect that I think might have been usefully included was an economic or cost-benefit study. Economic questions 'appear' at many points in the thesis – for example, in relation to the cost-benefits of an early diagnosis programme or the financial implications of providing a basic dental service for all socio-economic groups. In relation to this, towards the end of my research I enjoyed an interesting paper by Whitty (2015) entitled *'What makes an academic paper useful for health policy'*, targeted at academics wishing to produce such research. Whilst it is, of course, obvious that the economic aspect of any policy is a central issue, Whitty explores this aspect in some detail explaining that the 'mindset' of many – if not most - policymakers 'thinking like economists' (indeed, many senior politicians have backgrounds in economics, from university onwards). He advises that without this component, the influence of research on policy is considerably reduced. A thesis is of course limited in

size and scope it is not possible to include 'everything' but evaluation of the economic questions following on from findings in the thesis might be included in future work.

What went well?

In contrast to the challenges experienced, there were also aspects that proved beneficial.

Collaboration and teamwork

It is very unlikely that I could have completed the time-series study or the international qualitative study without the help of my colleagues in Liverpool and Amsterdam respectively and, although the importance of collaboration is well-established, this was highlighted clearly during my research work for this thesis.

Publishing

Three of the four studies in this thesis were published during my studies. I found this very useful as the process necessitates evaluation and provides focus. Furthermore, comments from the journal referees stimulated considerable thought about the studies.

Writing up – from an early stage

I began to draft chapters from an early stage in my DPhil studies. Although much modification of early efforts took place (of course), it was a helpful exercise in 'organising thoughts' and ultimately reduced the writing burden in the final months.

Chapter 7 references

Andermann A, Pang T, Newton JN et al *Evidence for health II: overcoming barriers to using evidence in policy and practice* Health Research Policy and Systems14 17-24

Austoker J, Bankhead C, Forbes LJL et al (2009) *Interventions to promote cancer awareness and early presentation: systematic review* British Journal of Cancer 101 S31-S39

Bourne AW (2014) *How does policy change happen?* Available at: https://www.researchtoaction.org/2014/02/how-does-policy-change-happen

Boyle PE (1959) *The dentist's responsibility in diagnosis and treatment of cancer* Oral Surgery, Oral Medicine and Oral Pathology 12 771-776

Brocklehurst P and Speight P (2018) *Screening for mouth cancer: The pros and cons of a national programme* British Dental Journal 225 815-819

Cancer Treatment Centers of America (2020) *Oral cancer symptoms* available at: https://www.cancercenter.com/cancer-types/oral-cancer/symptoms

Chen CC, Yamada T and Smith J (2014) *An evaluation of healthcare information on the internet: the case of colorectal cancer prevention* International Journal of Environmental Research and Public Health 11 1058-107

Dalanon J, Esguerra R, Diano et al (2020) *Analysis of the Filipinos' interest in searching online for oral cancer* Asian Pacific Journal of Cancer Prevention 21 1121-1127

East SC, Stocker JL and Avery BS (2005) *Is the two-week rule of any benefit to patients with oral cancer?* British Journal of Oral and Maxillofacial Surgery 43 511-512

Flitcroft K, Gillespie J, Salkeld G et al (2011) *Getting evidence into policy: the need for deliberate strategies* Social Science and Medicine 72 1039-1046

Foot C and Harrison T (2011) *How to improve cancer survival* The King's Fund available at: https://www.kingsfund.org.uk/sites/default/files/How-to-improve-cancer-survival-Explaining-England-poor-rates-Kings-Fund-June-2011.pdf

Greenhalgh T (2015) *Knowledge to action: there is no tooth fairy* available at: https://www.cebm.net/2015/11/knowledge-to-action-there-is-no-tooth-fairy/

Greenhalgh T and Russell J (2006) *Reframing evidence synthesis as rhetorical action in the policy-making drama* Healthcare Policy 1 34-42

Hamilton W (2015) *Diagnosing symptomatic cancer in the NHS* British Medical Journal doi: 351:h5311

Hamilton, W, Walter FM, Rubin G and Neal RD (2016) *Improving early diagnosis of symptomatic cancer* Nature Reviews Clinical Oncology 13 740-749
https://www.nice.org.uk/guidance/ng12/resources/costing-statement-pdf-74145421

Huisman M, Kunst A, Bopp M et al (2005) *Educational inequalities in cause-specific mortality in middle-aged and older men and women in eight western European populations* Lancet 365 493-500

Kogevinas M, Pearce N, Susser M et al (1997) *Social inequalities and cancer* IARC Scientific Publications

The Labour Party *Labour to offer free dental check-ups for all* available at: https://labour.org.uk/press/labour-to-offer-free-dental-check-ups-for-all/

Langton SG, Siau D and Bankhead C (2016) *Two-week rule in head and neck cancer 2000-14: a systematic review* British Journal od Oral and Maxillofacial Surgery 54 120-131

Macadam DB (1979) *A study in general practice of the symptoms and delay patterns in the diagnosis of gastrointestinal cancer* Journal of the Royal College of General Ptractitioners 29 723-729

Macarthur C and Smith A (1983) *Delay in the diagnosis of colorectal* cancer British Journal of General Practice 33 159-161

Merletti F, Galassi C and Spadea T (2009) *The socioeconomic determinants of cancer* Environmental Health 10 (S1) 57

Ndukwe N, Borowski DW, Lee A, Orr A, Dexter-Smith S and Agarwal KA (2010) *The two-week rule for suspected colorectal cancer: Patient experience and psychological impact International Journal of Healthcare and Quality Assurance 25 (1) 75-85*

NHS (2019) *November is Mouth Cancer Action Month: If in doubt get it checked* available at: https://whh.nhs.uk/about-us/news-events-and-features/latest-news/november-mouth-cancer-action-month-if-doubt-get-it-checked (accessed November 2020)

NICE (2015) *Costing statement: suspected cancer* available at *https://www.nice.org.uk/guidance/ng12/resources/costing-statement-57211*

Parkhurst J (2017) *The Politics of Evidence* Routledge

Parkhurst J, Ettelt S and Hawkins B (2018) *Evidence use in health policy making* Palgrave Macmillan

Public Health England (2018) *Ten years on since the start of the HPV vaccine programme – what impact is it having?*available at: https://publichealthmatters.blog.gov.uk/2018/06/18/ten-years-on-since-the-start-of-the-hpv-vaccine-programme-what-impact-is-it-having/

Reid G, Connolly J, Halliday W et al (2017) *Minding the gap; the barriers and facilitators of getting evidence into policy when using a knowledge-brokering approach* Evidence and Policy 13 29-38

Sanderson, I (2002) *Evaluation, Policy Learning and Evidence-Based Policy Making* Public Administration 80 1-22

Sankaranarayanan R, Ramadas K, Thara S et al (2013) Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India Oral Oncology 49 314-321

Shedd DP, von Essen CF, Bevin AG et al (1967) *Ten year survey of oral cancer in a general hospital* American Journal of Surgery 114 844-852

Shepherd NG and Rudd JM (2014) *The Influence of Context on the Strategic Decision-Making Process: A Review of the Literature* International Journal of Management Reviews 16 340-364

Smits P, Denis J, Preval J et al (2018) *Getting evidence to travel inside public systems; what organisational brokering capacities exist for evidence-based policy*? Health Research Policy and Systems 16 122

Spadea T, Zengarini N, KunstA et al (2010) *Cancer risk in relationship to different indicators of socio-economic position in Turin, Italy* Cancer caoses and Control 21 1117-1130

Tappenden P, Chilcott J, Brennan A and Pilgrim H (2009) *Systematic review of economic evidence for the detection, diagnosis, treatment, and follow-up of colorectal cancer in the United Kingdom* International Journal of Technology Assessment in Health Care 25 470-478

Taylor LA (2018) *Twenty things I wish I'd known when I started my PhD* Nature DOI: 10.1038/d41586-018-07332-x

Walsh T, Liu JLY, Brocklehurst P et al (2013) *Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults* DOI: 10.1002/14651858.CD010173.pub2

Webb TL, Joseph J Yardley L et al (2010) *Using the Internet to Promote Health Behavior Change: A Systematic Review and Meta-analysis of the Impact of Theoretical Basis, Use of Behavior Change Techniques, and Mode of Delivery on Efficacy* Journal of Medical Internet Research 12(1):e4

Whitty CJM (2015) *What makes an academic paper useful for health policy?* BMC Medicine 13 301

APPENDICES

Guide to appendices

APPENDIX NUMBER		CONTENT	PAGE
1	……	Ethics approval letters	210
2	……	Two-week rule oral cancer guidelines (NICE 2004 and NICE 2015)	215
3	……	Qualitative study semi-structured questionnaire template	216
4	……	Systematic review data collection form	217
5	……	Screenshots – examples of online Delphi study	218
		Round 1 Delphi questionnaire	220
		Delphi expert panel members	221
6	……	Study protocols	222
7	……	Literature update system	258

Appendix 1 – Ethics approval letters

Study 1

MEDICAL SCIENCES INTER-DIVISIONAL RESEARCH ETHICS COMMITTEE

Research Services, University of Oxford, Wellington Square, Oxford, OX1 2JD
Tel: +44(0)1865 616577 Fax: +44(0)1865 280467
ethics@medsci.ox.ac.uk

UNIVERSITY OF OXFORD

Stephen Langton
Department for Continuing Education
University of Oxford
Rewley House
1 Wellington Square
Oxford, OX1 2JA

25th January 2017

To whom it may concern,

Study Title: Does the UK fast-track cancer referral system result in earlier stage diagnosis of oral cancer?

I am writing to confirm that this application has been reviewed by the Officer of the Oxford University Medical Sciences Inter-divisional Research Ethics Committee. This study does not require ethical approval because it will be analysing information previously collected in the course of normal care, and patients or service users will not be identifiable to the research team carrying out the analysis.

Yours Sincerely

H. Barnby-Porritt

Dr. Helen Barnby-Porritt
Research Ethics Manager, Medical Sciences

Study 2

medisch ethische toetsingscommissie

Van der Boechorststraat 7
postbus 7057
1007 MB Amsterdam

telefoon 020 444 5585
kamer H-565

www.vumc.nl/METc
METc@vumc.nl

J.A. Rijken
afd. KNO, ZH1C85

VUmc

onderwerp	ons kenmerk	datum
niet-WMO advies	2017.116	24 maart 2017

Geachte heer Rijken,

Het Dagelijks Bestuur van de Medisch Ethische Toetsingscommissie VU medisch centrum heeft uw onderzoek **Head and neck cancer fast-track referral in England and The Netherlands: an international qualitative study of secondary care specialists' views.** besproken in de vergadering van 07/03/2017.

Het onderzoek valt niet onder de reikwijdte van de Wet Medisch-wetenschappelijk Onderzoek met mensen (WMO).

Het oordeel is gebaseerd op de volgende documenten:

Sectie	Onderwerp	Versie
A1	aanbiedingsbrief	d.d. 22-2-2017
A1	commentaar METc	d.d. 24-3-2017
A1	commentaar METc	d.d. 7-3-2017
A1	reactie op commentaar METc	d.d. 22-3-2017
C1	onderzoeksprotocol	Ontvangen d.d. 22-2-2017
C1	onderzoeksprotocol	Versie 1 d.d. 22-2-2017
E11	informatiebrief	Ontvangen d.d. 22-2-2017 English
E11	informatiebrief	ontvangen d.d. 22-3-2017 NL
E2	toestemmingsverklaring	Ontvangen d.d. 22-2-2017 English
E2	toestemmingsverklaring	ontvangen d.d. 22-3-2017 NL
K6	overig sectie K	Confidentiality Agreement for the Transcription of Qualitative Data March 2017

202.000.235

Zelfstandig bestuursorgaan
De METc VUmc is een erkende onafhankelijke toetsingscommissie en geeft als zelfstandig bestuursorgaan (ZBO) oordelen die landelijk geldig zijn.

Het Dagelijks Bestuur van de Medisch Ethische Toetsingscommissie VU medisch centrum wijst u erop dat hoewel het ingediende onderzoek niet onder de reikwijdte van de WMO valt, andere wet- en regelgeving (mogelijk) wel van toepassing is, waaronder:

- WGBO (Wet Geneeskundige BehandelingsOvereenkomst);
- WBP (Wet Bescherming Persoonsgegevens), zie www.cbpweb.nl;
- Code Goed Gedrag (Gedragscode gezondheidsonderzoek: gebruik medische gegevens in wetenschappelijk onderzoek), zie www.federa.org;
- Code Goed Gebruik (Gedragscode Verantwoord omgaan met lichaamsmateriaal ten behoeve van wetenschappelijk onderzoek, 2011), zie www.federa.org;
- Reglement VUmc Nader gebruik lichaamsmateriaal, zie KwaliteitsNet VUmc, document 046913, versie 2;
- Overdrachtsovereenkomst van lichaamsmateriaal, zie http://www.vumc.nl/afdelingen/METc/wetgeving/lichaamsmateriaal/;
- Biobanken: Tijdelijke regeling 'de novo' biobanken (METc VUmc 2012), zie http://www.vumc.nl/afdelingen/METc/wmo-oordeel/soorten_onderzoek/tijdelijke_regeling_biobanken/;
- WBO (Wet Bevolkings Onderzoek), zie http://www.vumc.nl/afdelingen/METc/wetgeving/wetbevolkingsonderzoek/.

To whom it may concern

We are pleased to confirm that the Medical Research Involving Human Subjects Act (WMO) does not apply to the above mentioned study and that an official approval of this study by our committee is not required.

The Medical Ethics Review Committee of VU University Medical Center is registered with the US Office for Human Research Protections (OHRP) as IRB00002991. The FWA number assigned to VU University Medical Center is FWA00017598.

Met vriendelijke groet,
namens de Medisch Ethische Toetsingscommissie VU medisch centrum,

prof. dr. J.A. Rauwerda, voorzitter

c.c.: afdelingshoofd KNO prof.dr. C.R. Leemans

202.000.236

VUmc Medisch Ethische Toetsingscommissie

Study 4

MEDICAL SCIENCES INTER-DIVISIONAL RESEARCH ETHICS COMMITTEE

Research Services, University of Oxford, Wellington Square, Oxford, OX1 2JD
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ethics@medsci.ox.ac.uk

CONFIDENTIAL

Ref: R52175/RE001

Stephen Langton
2 Ravensdale Road
Bolton
BL1 5DN

5th July 2017

Dear Stephen

Research Ethics Approval - CUREC 1

Study title: Head and neck cancer fast-track referral in England and The Netherlands: an international qualitative study of secondary care specialists' views

The above application has been considered on behalf of the Medical Sciences Inter-divisional Research Ethics Committee (IDREC) in accordance with the procedures laid down by the University for Ethical Approval of all research involving human participants.

I am pleased to inform you that, on the basis of the information provided to the IDREC, the proposed research has been judged as meeting appropriate ethical standards, and approval has been granted for a period of **19 months**, commencing on **5th July 2017**. The reference number for this study is **R52175/RE001**.

This is **subject to:**

a) **it is your responsibility to comply with the requirements for administering any tests or questionnaires and, if in doubt, to contact the publisher of those tests or questionnaires.**

b) **if new research staff are engaged, the PI is responsible for ensuring they are suitably qualified by training and/or experience.**

I would like to remind you that your study may be selected for review by the MS IDREC during an annual audit.

Amendments

Should there be any subsequent changes to the study, which raise ethical issues not covered in the original application, you should submit details to the IDREC for consideration and approval. If there are significant alterations then the Committee will require a succinct letter explaining these. If your study received University Sponsorship through CTRG, then the amendment will first need to be submitted to CTRG for approval of continued Sponsorship.

Please do not hesitate to contact me if you have any queries.

Yours Sincerely

H. Barnby-Porritt

Dr. Helen Barnby-Porritt
Research Ethics Manager, Medical Sciences

MEDICAL SCIENCES INTERDIVISIONAL RESEARCH ETHICS COMMITTEE
Research Services, University of Oxford, Wellington Square, Oxford, OX1 2JD
Tel: +44(0)1865 616577 Fax: +44(0)1865 280467
ethics@medsci.ox.ac.uk

CONFIDENTIAL

Ref: R66073/RE001

Stephen Langton
Kellogg Colllege
60-62 Banbury Road
Oxford
OX2 6PN

12th November 2019

Dear Stephen,

Research Ethics Approval - CUREC 1

Study title: Prioritisation of approaches to the early diagnosis of oral cancer: a Delphi Study of UK experts

Short title: Experts' views on approaches to early oral cancer diagnosis

The above application has been considered on behalf of the Medical Sciences Interdivisional Research Ethics Committee (IDREC) in accordance with the procedures laid down by the University for Ethical Approval of all research involving human participants.

I am pleased to inform you that, on the basis of the information provided to the IDREC, the proposed research has been judged as meeting appropriate ethical standards, and approval has been granted for a period of **1 year**, commencing on **7th November 2019**. The reference number for this study is **R66073/RE001**.

This is **subject to:**

a) **you agreeing to follow Approved Procedure 04**
b) **you following the BPS guidelines for online research**
c) **the PI agreeing to comply with the requirements for administering any tests or questionnaires and, if in doubt, to contact the publisher of those tests or questionnaires**
d) **the PI ensuring that, where new research staff are engaged, they are suitably qualified by training and/or experience.**

I would like to remind you that your study may be selected for review by the MS IDREC for the purposes of monitoring and/or audit.

Amendments
Should there be any subsequent changes to the study, you should submit details to the MS IDREC for consideration and approval. Details of changes must be listed on an amendment form.

Please do not hesitate to contact me if you have any queries.

Yours Sincerely

H. Barby-Porritt

Dr. Helen Barnby-Porritt
Research Ethics Manager, Medical Sciences

Appendix 2 – NICE oral cancer referral guidelines 2004 and 2015

2a 2004 guidelines

Oral/lip cancer

- ≥ 3 weeks unexplained ulceration in the oral cavity
- Suspicious lump/mass on the lip or in the oral cavity
- A red or red and white patch in the oral cavity suggestive of leukoplakia or erythroleukoplakia
- Tooth mobility not associated with periodontal disease
- Poor healing ≥ 3 weeks post tooth extraction

2b 2015 update

Referral for suspected oral cancer

- **Consider a suspected cancer pathway referral** (for an appointment within 2 weeks) for oral cancer in people with either:
  - Unexplained ulceration in the oral cavity lasting for more than 3 weeks, or
  - A persistent and unexplained lump in the neck (new NICE recommendation for 2015).
- **Consider an urgent referral** (for an appointment within 2 weeks) for assessment for possible oral cancer by a dentist in people who have either:
  - A lump on the lip or in the oral cavity, or
  - A red or red and white patch in the oral cavity consistent with erythroplakia, or
  - Erythroleukoplakia (new NICE recommendation for 2015).
- **Consider a suspected cancer pathway referral by the dentist** (for an appointment within 2 weeks) for oral cancer in people when assessed by a dentist as having either:
  - A lump on the lip or in the oral cavity consistent with oral cancer, or
  - A red or red and white patch in the oral cavity consistent with erythroplakia, or
  - Erythroleukoplakia (new NICE recommendation for 2015).

Appendix 3 – Qualitative study semi-structured questionnaire template

1. **Could you describe the typical referral process of a suspected head and neck cancer patient to your out-patient clinic?**

(a) What are the good points?
(b) What areas could be improved?
(c) Can you describe some examples from your experience where things have gone well and not so well?

2. **Could you explain your view of the effectiveness of the system, overall, in identifying and referring potential head and neck cancer patients as early as possible?**

(a) What modifications in the referral system – if any are needed – would help improve efficient early diagnosis of head and neck cancer?

3. **What kind of information, both in quality and quantity, does the written referrals you receive, provide?**

(a) Would you like to see this changed, and if so how?

4. **We know only a small percentage of referrals have cancer. What do you think of this?**

(a) Is it necessarily part of the process?
(b) Can you describe how it influence your/the clinic's efficiency?
(c) Can you describe how this affects patients? (Do they welcome being seen or does it cause anxiety?)
(d) Does it need to be changed in any way? If so, what do you suggest?

5. **What is your experience of patients being referred where cancer is extremely/very unlikely?**

(a) (If this happens), why do you think this is?
(b) Could you describe some examples?

6. **Could you describe your view of the overall quality of suspected head and neck cancer referrals?**

(a) In what way(s) are they (good/poor/indifferent)? Please explain your view.

7. **Could you describe your view of the training needs, if any, of primary care practitioners, in the early referral of head and neck cancer?**

8. **Could you describe your experience of communication between primary and secondary care (in relation to head and neck cancer referral)?**

(a) How do you think this could be improved (if at all)

9. **What else might improve timing/quality of suspected head and neck cancer referrals?**

10. **Is there anything else on which you would like to comment in relation to fast-track referral of head and neck cancer?**

Appendix 4 - Systematic review data collection form

Item	Result

Basic study information

First author	
Title	
Publication year	
Reference	

Study characteristics

Country	
The type of study (prospective, retrospective, conference abstract, audit, letter)	
Type of unit in which the study was carried out	
Study size	

Results and outcomes

Percentages of diagnosed oral cancers referred by primary care doctors and dentists respectively	
Stage data for oral cancers referred by primary care doctors and dentists respectively	
Data on delay ('patient' and 'professional') for oral cancers referred by primary care doctors and dentists respectively	

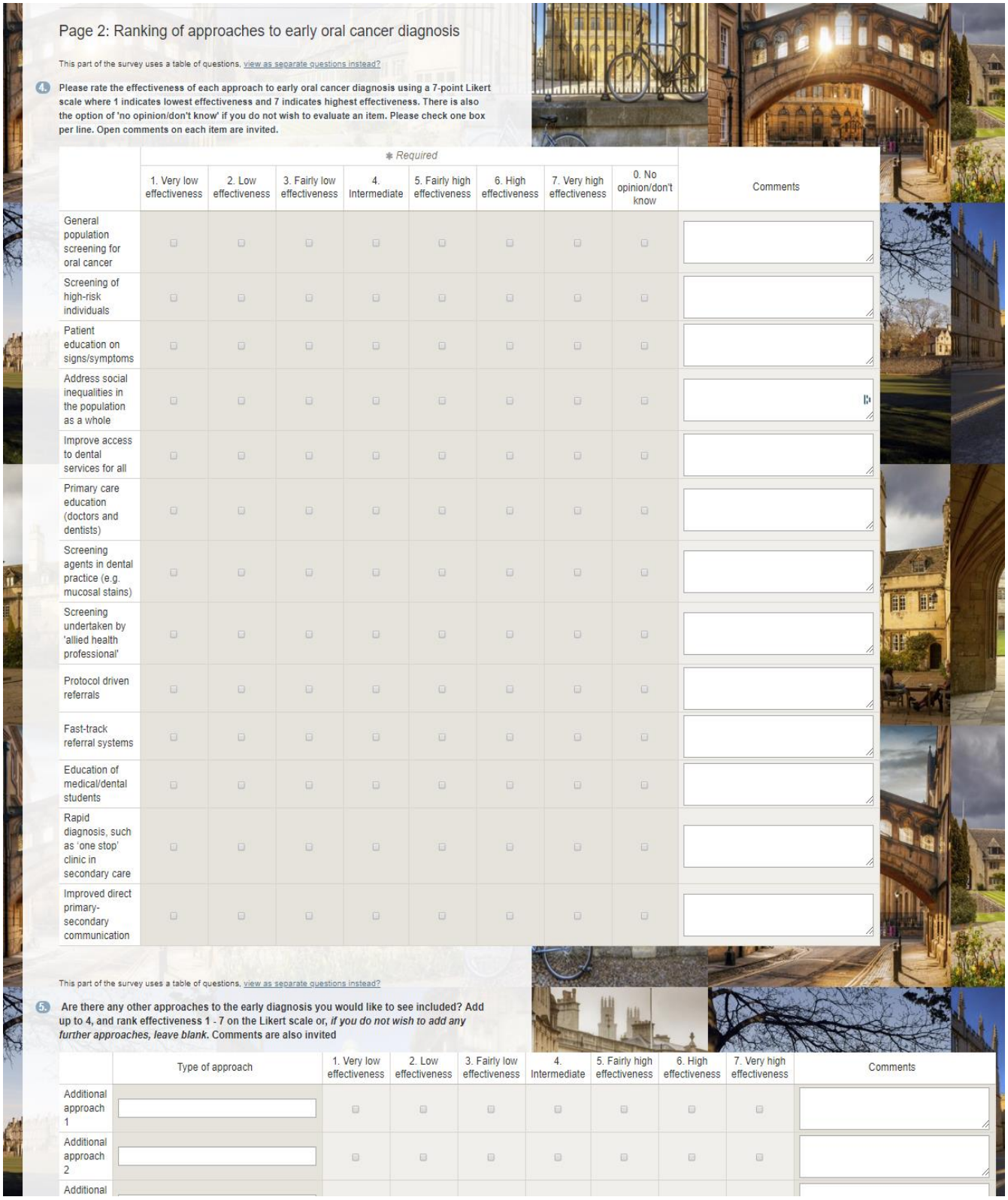
Other

Authors' main conclusions	

Appendix 5 – Delphi study

(a) Example 'screenshots' Delphi online questionnaire

Round 1



Page 2: Ranking of approaches to early oral cancer diagnosis

This part of the survey uses a table of questions, view as separate questions instead?

4. **Please rate the effectiveness of each approach to early oral cancer diagnosis using a 7-point Likert scale where 1 indicates lowest effectiveness and 7 indicates highest effectiveness. There is also the option of 'no opinion/don't know' if you do not wish to evaluate an item. Please check one box per line. Open comments on each item are invited.**

* *Required*

	1. Very low effectiveness	2. Low effectiveness	3. Fairly low effectiveness	4. Intermediate	5. Fairly high effectiveness	6. High effectiveness	7. Very high effectiveness	0. No opinion/don't know	Comments
General population screening for oral cancer	☐	☐	☐	☐	☐	☐	☐	☐	
Screening of high-risk individuals	☐	☐	☐	☐	☐	☐	☐	☐	
Patient education on signs/symptoms	☐	☐	☐	☐	☐	☐	☐	☐	
Address social inequalities in the population as a whole	☐	☐	☐	☐	☐	☐	☐	☐	
Improve access to dental services for all	☐	☐	☐	☐	☐	☐	☐	☐	
Primary care education (doctors and dentists)	☐	☐	☐	☐	☐	☐	☐	☐	
Screening agents in dental practice (e.g. mucosal stains)	☐	☐	☐	☐	☐	☐	☐	☐	
Screening undertaken by 'allied health professional'	☐	☐	☐	☐	☐	☐	☐	☐	
Protocol driven referrals	☐	☐	☐	☐	☐	☐	☐	☐	
Fast-track referral systems	☐	☐	☐	☐	☐	☐	☐	☐	
Education of medical/dental students	☐	☐	☐	☐	☐	☐	☐	☐	
Rapid diagnosis, such as 'one stop' clinic in secondary care	☐	☐	☐	☐	☐	☐	☐	☐	
Improved direct primary-secondary communication	☐	☐	☐	☐	☐	☐	☐	☐	

This part of the survey uses a table of questions, view as separate questions instead?

5. **Are there any other approaches to the early diagnosis you would like to see included? Add up to 4, and rank effectiveness 1 - 7 on the Likert scale or, *if you do not wish to add any further approaches, leave blank.* Comments are also invited**

	Type of approach	1. Very low effectiveness	2. Low effectiveness	3. Fairly low effectiveness	4. Intermediate	5. Fairly high effectiveness	6. High effectiveness	7. Very high effectiveness	Comments
Additional approach 1		☐	☐	☐	☐	☐	☐	☐	
Additional approach 2		☐	☐	☐	☐	☐	☐	☐	
Additional									

Round 2

p. 1 **Initial analysis**

Very many thanks for completing round 1 of this Delphi survey on the prioritisation of methods of encouraging early oral cancer diagnosis and welcome to round 2!

The protocol for this study specified that to rank as 'high' priority , 70% of more of respondents should have ranked the approach to early oral cancer diagnosis as a 6 or 7 on the Likert scale of effectiveness, 'intermediate' priority' 50-69% ranking 6 or 7 on the Likert scale and 'low priority' less than 50% ranking 6 or 7 on the Likert scale.

Using this classification, there was no consensus on 'high priority' and all methods of encouraging early oral cancer diagnosis were classified as 'low priority':

Method	% 6 or 7 Likert (high or very high effectiveness)
Fast-track referral systems	30.8
Education of medical/dental students	23.1
Rapid diagnosis, such as 'one stop' clinic in secondary care	23.1
Improved direct primary-secondary communication	23.1
Primary care education (doctors and dentists)	23.1
Protocol driven referrals	23.1
Screening of high-risk individuals	15.4
Address social inequalities in the population as a whole	15.4
Screening undertaken by 'allied health professional'	15.4
Improve access to dental services for all	7.7
Patient education on signs/symptoms	7.7
General population screening for oral cancer	0
Screening agents in dental practice (e.g. mucosal stains)	0

1 Do you agree that all the appoaches to encouraging early oral cancer diagnosis are 'low priority'? *

Yes

No

a If you responded 'no' which TWO methods of encouraging early oral cancer diagnosis are of highest priority?

General population screening for oral cancer

Screening of high-risk individuals

Patient education on signs/symptoms

Show all (13)

3 The following methods of encouraging early oral cancer diagnosis were classified as 'intermediate priority' in the re-classification. Do you agree with this or should the method be placed in a different category?

	Yes, I agree this is an 'intermediate priority' method	No, this should be a 'low priority' method	No, this should be a 'high priority' method
Patient education on signs/symptoms	0	0	0
Screening of high-risk individuals	0	0	0
Address social inequalities in the population as a whole	0	0	0
Primary care education (doctors and dentists)	0	0	0

+ Add question column

(b) Round 1 questionnaire (modified for web distribution, with sections for free comments)

LIKERT SCORE

Approach to improving early oral cancer diagnosis	1 Very low effectiveness	2 Low effectiveness	3 Fairly low effectiveness	4 Intermediate	5 Fairly high effectiveness	6 High effectiveness	7 Very high effectiveness
PATIENTS							
Population screening for oral cancer							
Patient education on signs/symptoms							
Address social inequalities							
Improve dental access							
PRIMARY CARE							
Primary care education (doctors and dentists)							
Screening agents (e.g. mucosal stains)							
Allied health professional screening							
Protocol driven referrals							
Fast-track referral systems							
Focus on high-risk individuals							
Education medical/dental students							
SECONDARY CARE							
Rapid diagnosis, such as 'one stop' clinic							
Improved direct primary-secondary communication							
RESPONDENTS ADDITIONS							

(c) Delphi expert panel (names included with permission)

Academics

Dr Gary Cousin, University of Central Lancashire

Professor Mark Greenwood, University of Newcastle-upon Tyne

Professor Michael Lewis, University of Cardiff

Professor David Mitchell, University of Leeds (Editor British Journal of Oral and Maxillofacial Surgery)

Professor Simon Rogers, Edge Hill University

Professor Richard Shaw, Liverpool University

Professor Paul Speight, Sheffield University

Professor Peter Thompson, University of Hong Kong (previously at Newcastle-upon Tyne)

Consultants in Dental Public Health

Dr Melanie Catleugh, Lancashire

Dr Yvonne Dailey, Liverpool

Dr Siobhan Grant, Public Health England

NAME WITHHELD at the request of the participant

Dr John Morris, Birmingham

Appendix 6 – Study protocols

STUDY PROTOCOL (study 1)

Does the UK fast-track cancer referral system result in an earlier stage diagnosis of oral cancer?

Date and Version No: v2.00 January 2017

Chief Investigator: Steve Langton, MSc (Oxford), BDS, MB, ChB, FDSRCS, FRCS (retired consultant Maxillofacial Surgeon and part-time DPhil student, University of Oxford)

Investigators: Professor Simon Rogers, Edge Hill University, Liverpool; Professor Derek Lowe Edge Hill University, Liverpool; Dr Annette Pluddemann, University of Oxford (supervisor): Professor Clare Bankhead, University of Oxford (supervisor)

Sponsor: University of Oxford

Funder: None

Chief Investigator Signature: 

Conflict of Interest There are no known conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

1. SYNOPSIS

Study Title	*'Does the UK fast-track cancer referral system result in an earlier stage diagnosis of oral cancer?'*
Study Design	Before-after cohort study
Study Participants	Patients diagnosed with oral cancer, 1992 -2012
Planned Sample Size	Approximately 1500
Planned Study Period	6 months

2. ABBREVIATIONS

CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
CUREC	Central University Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SCC	Squamous cell carcinoma (oral in this study)

3. BACKGROUND

The 'two-week rule' (TWR) or 'two-week wait' (TWW) fast-track cancer referral system was introduced by the UK government in 1999 for breast cancer and for all other cancers in 2000. The rule requires that all cases of suspected cancer referred to secondary care by a primary care clinician are assessed by a specialist within 14 days. The process is facilitated by a set of National Institute for Health and Care Excellence ('NICE') guidelines for primary care practitioners, one set for each cancer type. The 2004 guidelines (NICE 2004) were revised and updated in 2015 (NICE 2015).

The introduction of the TWR was, essentially, a UK government response to reported poor UK outcomes for cancer. In the 1990s, inadequacies in UK cancer care were being identified. In 1995, the first EUROCARE studies were published (Berrino, Sant, Verdecchia et al, 1995). These studies indicated that outcomes for some cancers in the UK were worse than the best-performing European countries. More recently, the EUROCARE-5 studies (Gatta et al 2015) indicated that for head and neck cancer, UK 5-year survival rates compare well with the best in Europe yet 1-year survival rates are still worse than a number of European countries, suggesting a higher incidence of cancers presenting at an

advanced stage in the UK. There is a broad consensus that the relatively poor UK performance in cancer is genuine (Hamilton, 2012).

The main purpose of the TWR is to improve cancer outcomes by facilitating diagnosis at an early stage when patients present with signs or symptoms suggesting possible cancer. Harrison and Foot (2012) note: *'for the two-week rule to be effective……the stage at which patients were identified should have fallen since its introduction'*.

For head and neck cancer, including oral cancer, studies clearly show the correlation between stage on diagnosis and outcome (Mehanna et al 2010; Mao, Hong and Papadimitrakopoulou 2004). However, whilst much published research has focused on the process of cancer referral via the TWR, there is relatively little evidence, for all cancer types, on whether the introduction of the TWR and NICE associated guidance has resulted in improved survival or whether cancer cases are presenting at an earlier stage. For oral cancer there is very little such evidence (Langton et al 2016). Data from the National Cancer Registration and Analysis Service (NCRAS) on oral cancer indicate that between 2006 and 2013 there was little difference in 1-year survival between TWR referrals and other 'routine' referrals (77% vs 78%) but emergency presentations did considerably worse (44%). During the same period, 34% of cases presented via the TWR system whilst 6% presented as emergencies. The proportion of oral cancers presenting via the TWR also steadily increased from 24% in 2006 to 33% in 2012 (NCRAS, 2016).

In addition to improving overall cancer survival, a key UK government health focus is the relationship of social inequalities and cancer (Cancer Research UK 2006; Department of Health, 2011). Socio-economic difference in survival from head and neck cancers are among the largest of any malignancies (Robertson and Greenlaw, 2010). Oral cancer has a well-established link to social deprivation and is known to have both increased incidence and poorer outcome for the more socially deprived (Thorne, Etherington and Birchall, 1998).

4. AIMS of STUDY

This study has two overall aims. Firstly, to evaluate the stage-on-presentation of oral cancers in Merseyside from 1992 to 2012, comparing the periods before and after the introduction of the TWR and NICE guidance in 2001 - has the stage on presentation of oral cancer improved since the system was introduced? Secondly, to study the relationship of stage-on presentation to social deprivation from 1992 to 2012, again comparing the periods before and after the introduction of the TWR in 2000. Has the 'social deprivation gap' in oral cancer changed since the TWR and associated guidance were implemented?

5. STUDY POPULATION

Patient data will be extracted from the Aintree (Liverpool) head and neck oncology database. Consecutive patients diagnosed with SCC oral cancer between January 1992 and December 2012 and either treated curatively or referred for palliation will be included. The data will include T, N, M staging using the American Joint Committee on Cancer (AJCC) stage groupings. Data will be provided in 'anonymous' form, including the relevant staging information but no personal information.

6. STUDY DESIGN

Cancers will be classified into group stages 1 to 4 using staging following clinical examination and CT/MRI scanning. Presenting cancers will be grouped into (a) 'early' presentations, comprising stage 1 and 2 cases and (b) 'late' presentations, comprising stage 3 and 4 cases.

Patient postcode will be used to derive Index of Multiple Deprivation (IMD) data. The overall IMD is conceptualised as a weighted area level aggregation of several specific dimensions of deprivation. In England, the IMD 2000 replaced the 1998 Index of Local Deprivation and was superseded by IMD 2004, IMD 2007, IMD 2010 and IMD 2015 (Smith et al 2015; Department for Communities and Local Government 2015). The spread of cases over two decades in this study presents a problem as to which version(s) of the IMD to use. The IMD 2000 assigned deprivation scores and ranks to 8414 areas, whereas later IMD assigned to over 32,000 areas. Therefore, IMD 2004 is used where possible as it incorporated data indicators relating to 2001, a year which is close to the centre of the time period studied. The IMD 2004 consists of seven domains (income deprivation, employment deprivation, health deprivation and disability, education skills and training deprivation, barriers to housing and services, living environment deprivation and crime) with each domain containing several indicators.

7. DATA ANALYSES

(a) Trends in stage on presentation

To determine any changes in the stage-on-presentation trend, particularly following the introduction of the TWR and the associated NICE guidance, *'Joinpoint'* Regression Program version 4.6.0.0 (Surveillance Research Program of the National Cancer Institute, Calverton, USA, 2018), will be used used to calculate the best-fitting line through years of data, employing an algorithm to determine whether a multiple-segmented line fits better than a straight line. Each line is connected by a 'joinpoint' which indicates a statistically significant ($p<0.05$) change in trend. The test of significance uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series. The software allows the user to specify several joinpoints to be tested, depending on the number of data points (0 joinpoints represents a straight line). Starting with the minimum number, the program adds further joinpoints, up to the maximum, if they are statistically significant. Each joinpoint can, therefore, be interpreted as a significant change in trend.

(b) Other analyses

The Chi-squared test will be used to test the association of patient groups with 'late' presentation. SPSS version 25 will be used for data management, for descriptive statistics and for the Chi-squared tests. Binary regression (STATA binreg procedure, rr link option) will be used to assess the association of clinical and demographic variables with 'late' (stage 3 or 4) presentation. It will also be used to assess the association of time period (1992-1998, 1999-2005, 2006-2012) with whether patients presented 'late' after adjustment for other factors as independent predictors and similarly the association with IMD deprivation status. Risk ratios and 95% confidence intervals will be estimated.

8. ETHICS

Ethical review was undertaken by the Medical Sciences Inter-Divisional Research Ethics Committee of the University of Oxford who confirmed that the study does not require ethical approval because it analyses information previously collected in the course of normal care.

9. DATA MANAGEMENT

9.1 Access to data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

9.2 Data recording and record-keeping

All data will be kept in password-protected digital format, in secure storage to which only the researchers will have access. A backup copy of data will be produced and stored separately from the main copy.

10. QUALITY ASSURANCE

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3 Approvals

The protocol and first-round questionnaire will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

11.5 Participant Confidentiality

Although it is anticipated the participants will be named in published work, they will not be identifiable in relation to specific views and comments. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

11. FINANCE AND INSURANCE

12.1 Funding

None

11.2 Insurance

Oxford University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

12. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

13. REFERENCES

Berrino F, Sant M, Verdecchia A et al (1995) *Survival of cancer patients in Europe: the EUROCARE study* IARC Scientific Publications 132 1-463

Gatta G, Botta L, Sánchez MJ, Anderson LA et al (2015) *Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study* European Journal of Cancer 51 2130-2143

Hamilton W (2012) *Emergency admissions of cancer as a marker of diagnostic delay* British Journal of Cancer 107 1205-1206

Harrison AJ and Foot, CS (2012) *Targets and prioritisation: the case of cancer in the English NHS* Quality in Primary Care 20 125-129

Langton S, Siau D and Bankhead CR (2016) *The 'two week rule' in head and neck cancer, 2000-2014; a systematic literature review* British Journal of Oral and Maxillofacial Surgery 54 120-131

Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316

Mehanna H, West CML, Nutting C and Paleri V (2010) *Head and neck cancer – part 2: treatment and prognostic factors* British Medical Journal 341 721-725

NCRAS (2016) *Routes to Diagnosis* available at: http://www.ncin.org.uk/publications/routes_to_diagnosis

NICE (2004) *Improving Outcomes in Head and Neck Cancers – The Manual* available at: http://www.nice.org.uk

NICE (2015) *Suspected cancer: recognition and referral* available at: https://www.nice.org.uk/guidance/ng12/chapter/1-recommendations

Robertson G and Greenlaw N (2010) Explaining the effects of socio-economic deprivation on survival in a national prospective cohort study of 1909 patients with head and neck cancers Cancer Epidemiology 34 682-688

Thorne P, Etherington D and Birchall MA (1998) *Head and neck cancer in the South West of England: Influence of socio-economic status* Clinical Otolaryngology and Allied Sciences 23 277

STUDY 2

STUDY PROTOCOL

Study Title: Head and neck cancer referral in England and the Netherlands: an international qualitative study of secondary care specialists' views

Ethics: (1) Confirmed by medisch ethische toetsingscommissie VU Amsterdam 24 maart 2017

(2) Research Ethics Approval - CUREC 1 – University of Oxford Ref: R52175/RE001 July 2017

Date and Version No: v3.2 July 2017

Chief Investigator:	**Steve Langton, MSc (Oxford), BDS, MB, ChB, FDSRCS, FRCS (Consultant Maxillofacial Surgeon and part-time DPhil student, University of Oxford)**
Investigators:	Dr Clare Bankhead, University of Oxford (supervisor); Dr Annette Pluddemann, University of Oxford (supervisor), Dr. J. Rijken, Professor R. Leemans (Free University of Amsterdam).
Sponsor:	University of Oxford
Funder:	British Association of Oral and Maxillofacial Surgeons Small Project Grant
Chief Investigator Signature:	

Conflict of Interest

There are no known conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

12. SYNOPSIS

Study Title	***'Head and neck cancer referral in England and the Netherlands: an international qualitative study of secondary care specialists' views'***
Study Design	Qualitative
Study Participants	Secondary care specialists in England and the Netherlands
Planned Sample Size	10 to 15 interviews from each country
Planned Study Period	12 to 18 months

13. ABBREVIATIONS

CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
CUREC	Central University Research Ethics Committee
ICF	Informed Consent Form
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

BACKGROUND AND RATIONALE

Cancer survival is considered by many to be a key indicator of the effectiveness of healthcare systems (De Angelis et al, 2014). It is known that the most important prognostic factor for many cancers is stage at diagnosis (Richards, 1999) and the early diagnosis of cancer is widely considered to be an important public concern (Moller et al 2015). Stage at diagnosis of head and neck cancer correlates well with survival (Mehanna et al 2010; Mao, Hong and Papadimitrakopoulou 2004).

In 1995, the first EUROCARE studies were published (Berrino, Sant, Verdecchia et al, 1995), comparing cancer survival in European countries. These studies indicated that outcomes for some cancers in the UK were considerably worse than the best in Europe. Some 19 years later, the fifth version of the Eurocare studies (EUROCARE-5) was published (De Angelis et al, 2014), indicating that although

improvements had been made in UK outcomes, in some areas these still lagged behind the best in Europe. Many consider that the relatively poor UK cancer outcomes are at least partly due to diagnostic delays resulting in a more advanced stage when cancer is identified (Neal 2009).

Data from the EUROCARE-5 studies indicate that for head and neck cancer UK 5-year survival outcomes compare well with the best in Europe yet 1-year survival still lags behind a number of other countries, including Holland (Gatta et al, 2015). This suggests that in the UK head and neck cancers may be presenting at a later stage than in some other European countries. However, determining exactly why diagnostic delay occurs is a complicated problem for all cancers and may have many components requiring a different solution (Hamilton, 2012).

In an attempt to reduce the delay in cancer diagnosis, following the early EUROCARE studies, the UK government introduced the UK fast-track referral system for all cancers, commonly known as 'the two week rule' (TWR). This was based on referral guidelines to assist primary care practitioners in referral of potential cancer for specialist care and all such referrals are required to be seen within 14 days. The initial sets of guidelines (one for each type of cancer) were introduced in 2005 (NICE 2005) and updated in 2015 (NICE 2015). However, the effectiveness of the system remains unclear and somewhat controversial (Hanna et al 2005; Hamilton 2009; Langton, Siau and Bankhead 2015; Rose et al 2015)

Certainly, the pathways to diagnosis are now known to be considerably more complex than was first believed (Walter et al, 2012). Furthermore, different types of cancer almost certainly need to be considered separately when examining diagnostic challenges (Lyratzopoulos et al, 2014) and published work on head and neck cancer fast-track referral is not extensive (Langton, Siau and Bankhead 2015).

In the UK, primary care has an important 'gatekeeping' function in providing access to specialist cancer care and recently has been, quite appropriately, the focus of much research on early cancer detection. This has included several qualitative studies exploring primary care practitioners' and patients' views (Green et al, 2015; Cook et al 2014; Banks et al 2014). However, there is limited qualitative work exploring the views of secondary care specialists on the process of early referral of cancer to specialist care and their perceived role in this respect.

The purpose of this study is, therefore, to gain an in-depth insight into the views of head and neck cancer specialists, in England and Holland, on their early cancer referral system and their perceived role in the system. The study aims to compare the views of specialists in England with those of specialists in Holland where a higher rate of 1-year survival was reported in the EUROCARE-5 studies. *In particular, the study aims to attempt to identify, through the views of the secondary specialists, differences in the system of fast-track cancer referral that might account for differences in survival.*

AIM AND OBJECTIVES

Aim/Research Questions	Objectives
This study will investigate the views of secondary care specialists in England and Holland focusing on their views and perceptions of the cancer referral system in their country. The overall aim is to identify themes (particularly those not readily defined by quantitative analysis), compare the findings from each of the countries and explore themes that may account for differences in survival.	*Objectives* include (but are not limited to): • A description of the system(s) for head and neck cancer that exists in the relevant country • The ways in which patients present to secondary care • The best features of the system – what do the specialists identify as parts of the referral system that work well? • The weak features of the system – how could the system in their country be improved?

STUDY DESIGN

5.1 Personal characteristics

The interviews will be conducted by Steve Langton, MSc (Oxford) BDS, MB, ChB, FDSRCS, FDSRCPS, FRCS, an experienced consultant head and neck cancer surgeon, who is also a past Clinical Director for Cancer Services in East Lancashire. This work is being conducted as part of a DPhil thesis at the University of Oxford and he has received basic training in qualitative methods at this University and at the University of Newcastle. He will be supervised in this work by Oxford academic staff with extensive experience in qualitative research methods.

5.2 Relationship with participants

It is likely that many of the English participants and some of the European participants will know or have some knowledge of the principal investigator

5.3 Study Design

A qualitative design is proposed to address these questions, utilising a combination of semi-structured interviews (to ensure a degree on consistency between countries) combined with an iterative approach to further question development as interviews progress. The qualitative design permits an 'open' approach to the questions allowing analysis in depth of the complex issues in referral of head and neck cancer to secondary care specialists.

5.4 Setting

The interviews are planned to take place at the workplace of the participants (or other place, at their convenience). The interviews will involve the participants and researcher only.

5.5 Data Collection

The interviews will be audio recorded; video recording is not planned for this study. Digital recording will be employed which will allow upload of the recording to a computer immediately after completion of the interview. A back-up copy of the audio file will be made at the same time and stored separately from the principal computer. All files will be stored securely and with appropriate password protection. The interviewer/investigator will take field notes throughout the course of the interview process to supplement the information derived from the interview recordings. It is expected that interview notes will assist with the refinement of subsequent interviews, provide clarification of the recorded interviews and assist with analysis of the data.

Following completion of the interview process, transcription of the interviews will take place to facilitate analysis. It is planned to employ the services of a professional transcriber. Transcripts of the interviews will also be stored in a secure, password-protected manner.

Prior to analysis, transcripts will be made available to the participants for the purpose of comments and/or correction to ensure accuracy of information.

PARTICIPANT IDENTIFICATION

Study Participants

The proposed participants are surgical specialists treating head and neck cancer in England and Holland.

In the first instance, 10-15 interviews in each country are planned.

Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Established specialist (not a trainee) undertaking surgery for cancer of the head and neck.
- Specialists with a background in both maxillofacial and ENT surgery are eligible

Exclusion Criteria

- Unwilling or unable to consent
- Trainees in head and neck cancer surgery are ineligible

STUDY ACTIVITIES

7.1 Sampling

For the purposes of this study, a combined method of purposive and convenience sampling is proposed, using national lists of head and neck cancer surgeons and to make initial contact by email, seeking a willingness to be involved in the study. The principal investigator has undertaken surgical training in the Netherlands and it is believed that a satisfactory number of participants can be recruited from these areas. However, should insufficient participants be recruited initially, snowball sampling will be considered. The participants will need to be able to speak English

7.2 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific activities are undertaken.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; any risks involved in taking part. It will be

7.1 Sampling

For the purposes of this study, a combined method of purposive and convenience sampling is proposed, using national lists of head and neck cancer surgeons and to make initial contact by email, seeking a willingness to be involved in the study. The principal investigator has undertaken surgical training in the Netherlands and it is believed that a satisfactory number of participants can be recruited. However, should insufficient participants be recruited initially, snowball sampling will be considered. The participants will need to be able to speak English.

7.2 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific activities are undertaken.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtains the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

7.3 Subsequent Visits

It is anticipated that there will be a single interview per participant.

7.4 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. (In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of Consent; withdrawn participants will be replaced

The reason for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file.

7.5 Definition of End of Study

The end of study is the date of the last interview of the last participant.

ANALYSIS

The Number of Participants

We have used the principles defined by Morse (2000) in estimating the sample size likely to achieve saturation. Given the relatively narrow scope of the study, the clarity of the topic and the likelihood of obtaining good quality data, we estimate that initially 10 - 15 interviews will be undertaken in each country.

Data Analysis

For this study, the transcriptions obtained from the interview process will be subjected to content analysis. It is proposed that data coding will be undertaken by the principal investigator (SL) in a systematic manner. The data will be subject to several readings in order to develop an in-depth understanding of developing themes and subtleties – so-called *data intimacy* (Saldaña , 2011) which, it is believed, will provide a greater understanding of the important issues. It is anticipated that as themes develop, a coding tree will be produced to provide organisation and structure to the themes and data.

New themes will be added as required during and/or following the definitive interview process. It is proposed that data analysis will start at an early point in the study – the initial analysis could facilitate the identification of developing themes and concepts that had not been previously considered. Following transcription, it is planned that the data will be analysed with the help of *NVivio.* The findings will be reported to the participants in order to obtain feedback and comment.

DATA MANAGEMENT

Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Data Recording and Record Keeping

The interviews will be audio recorded; video recording is not planned for this study. Digital recording will be employed which will allow upload of the recording to a computer immediately after completion of the interview. A back-up copy of the audio file will be made at the same time and stored separately from the principal computer. All files will be stored securely and with appropriate password protection. The interviewer/investigator will take field notes throughout the course of the interview process to supplement the information derived from the interview recordings. It is expected that interview notes will assist with the refinement of subsequent interviews, provide clarification of the recorded interviews and assist with analysis of the data.

Following completion of the interview process, transcription of the interviews will take place to facilitate analysis. It is planned to employ the services of a professional transcriber, trained in the appropriate transcription process, to perform this work. Whilst it is recognised that transcription of qualitative data by an investigator does have some benefits, such as a more intimate understanding of the interview data and is, indeed, preferred by some researchers (Ziebland and McPherson, 2006) professional typing skills are preferred for this study. Transcripts of the interviews will also be stored in a secure, password-protected manner.

Prior to analysis, transcripts will be made available to the participants for the purpose of comments and/or correction to ensure accuracy of information.

QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

FINANCE AND INSURANCE

Funding

British Association of Oral and Maxillofacial Surgeons small project grant awarded

Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Oxford University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

14. REFERENCES

1. Banks J, Walter FM, Hall N, Mills K et al (2014) *Decision making and referral from primary care for possible lung and colorectal cancer: a qualitative study of patient experiences* British Journal of General Practice DOI 10.3399/bjgp14X682849
2. Berrino F, Sant M, Verdecchia A et al (1995) *Survival of cancer patients in Europe: the EUROCARE study* IARC Scientific Publications 132 1-463
3. Brockbank S, Miller N, Owen S and Patterson JM (2015) *Pretreatment information on dysphagia: exploring the views of head and neck cancer patients* Journal of Pain and Symptom Management 49 (1) 89 - 97
4. Coar L and Sim J (2006) *Interviewing one's peers: methodological issues in a study of health professionals* Scandanavian Journal of Primary Health Care 24 251-256
5. Cook N, Thomson G and Dey P (2014) *Managing risk in cancer presentation, detection and referral: a qualitative study of primary care staff views* BMJ Open 2014 Jun 12;4(6):e004820. doi: 10.1136/bmjopen-2014-004820.

6. Dahlhaus A, Vanneman N, Geuthlin C, Behrend J and Siebenhofer A (2014) *German general practitioners' views on their involvement and role in cancer care: a qualitative study* Family Practice 31 (2) 209 - 214
7. De Angelis R, Sant M, Coleman MP, Francisci S et al (2014) *Cancer survival in Europe 1999-2007 by country and age: reults of EUROCARE-5 – a population-based study* Lancet Oncology 15(1) 23-24
8. Department of Health (1997) The New NHS. Modern. Dependable: London available at: https://www.gov.uk/government/publications/the-new-nhs
9. Gatta G, Botta L, Sánchez MJ, Anderson LA et al (2015) *Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study* European journal of Cancer 51 2130-2143
10. Green T, Atkin K and Macleod U (2015) *Cancer detection in primary care: insights from general practitioners* British Journal of Cancer 112 S41-S49
11. Hamilton W (2009) *Five misconceptions in cancer diagnosis* British Journal of General Practice 59 441-447
12. Hamilton, W (2012) *Emergency admissions of cancer as a marker of diagnostic delay* British Journal of Cancer 107 1205-1206
13. Hanna SJ, Muneer A and Khalil KH (2005) The 2-week wait for suspected cancer: time for a rethink? International Journal of Clinical Practice 59 1334-1339
14. Langton S, Siau D and Bankhead CR (2016) *The 'two week rule' in head and neck cancer, 2000-2014; a systematic literature review* British Journal of Oral and Maxillofacial Surgery 54 120-131
15. Lyratzopoulos G, Wardle J and Rubin G (2014) *Rethinking diagnostic delay in cancer: how difficult is the diagnosis?* British Medical Journal 2014 Dec 9;349:g7400. doi: 10.1136/bmj.g7400
16. Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316
17. Mehanna H, West CML, Nutting C and Paleri V (2010) *Head and neck cancer – part 2: treatment and prognostic factors* British Medical Journal 341 721-725
18. Morse JM (1995) The significance of saturation *Qualitative Health Research* 5(3), 147-149
19. Morse JM (2000) Determining sample size *Qualitative Health Research* 10 3-5
20. Neal RD (2009) Do diagnostic delays in cancer matter? *British Journal of Cancer* 101 S9-S12
21. NICE (2005) *Referral guidelines for suspected cancer* available at: https://www.nice.org.uk/guidance/cg27
22. (NICE 2015) *Suspected cancer: recognition and referral* available at: https://www.nice.org.uk/guidance/ng12
23. Richards MA, Wolfe CD, Tilling K et al (1999) *Variations in the management and survival of women under 50 with breast cancer in the South East Thames region* British Journal of Cancer 73 751-757
24. Rose PW, Rubin G, Perera-Salazar R et al (2015) Explaining variation in cancer survival between 11 jurisdictions in the International Cancer Benchmarking Partnership: a primary care vignette survey BMJ open 5, no. 5 (2015): e007212.
25. Saldaña J (2011) Fundamentals of Qualitative Research *Oxford University Press*
26. Tong A, Sainsbury P and Craig J (2007) Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups *International Journal for Quality in Health Care* 19 (6) 349-357
27. Walter F, Webster A, Scott S and Emery J (2012) *The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis* Journal of Health Services Research and Policy 17(2) 110-8
28. Ziebland S and McPherson A (2006) *Making sense of qualitative data analysis: an introduction with illustrations from DIPEx (personal experiences of health and illness)* Medical Education 40 405-414

15. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.0	December 2015	Steve Langton	First draft protocol
2	2.0	March 2016	Steve Langton	Modifications to include Netherlands in study
3	3.0	July 2016	Steve Langton	Restructuring to standard Oxford format
4	3.11	May 2017	Steve Langton	Minor changes, VU Amsterdam logo added, details of Netherlands ethical approval
5	3.2	July 2017	Steve Langton	UK ethical approval

STUDY PROTOCOL

A comparison of primary care doctors and dentists in the referral of oral cancer: a systematic literature review

Date and Version No: v3.00 April 2019

Chief Investigator: Steve Langton, MSc (Oxford), BDS, MB, ChB, FDSRCS, FRCS (retired consultant Maxillofacial Surgeon and part-time DPhil student, University of Oxford)

Investigators: Mr Gary Cousin, University of Central Lancashire; Dr Annette Pluddemann, University of Oxford (supervisor): Professor Clare Bankhead, University of Oxford (supervisor)

Sponsor: University of Oxford

Funder: None

Chief Investigator Signature: 

Conflict of Interest There are no known conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

A comparison of primary care doctors and dentists in the referral of potential oral cancer: a systematic literature review

PURPOSE OF THIS SYSTEMATIC REVIEW

The purpose of this systematic review is to compare primary care doctors and dentists in the referral of oral cancer with specific reference to proportion of diagnosed oral cancers diagnosed by each profession, stage on diagnosis of oral cancers referred by each profession and diagnostic delay in relation to each profession.

THE RESEARCH QUESTION

Population: Primary care doctors and dentists

Intervention: Referral of oral cancer to specialist care

Comparison: Primary care doctors with primary care dentists

Outcomes: Papers that compare primary care doctors/general practitioners (GPs) in one or more of the following:

(1) Proportion of diagnosed oral cancers referred to a secondary specialist unit by each profession.
(2) Stage (or aspects of stage, such as primary cancer size) on presentation.
(3) Delay in presentation.

Study designs: Cohort studies, published audits and published conference abstracts are eligible for inclusion. Case reports and economic evaluations are excluded.

BACKGROUND

Description of the condition

Oral cancer is the sixth most common cancer in the world (Warnakulasuriya, 2009) and approximately 6500 cases are diagnosed per year in the UK (Crossman et al 2016). The incidence of oral cancer is projected to rise by 33% in the UK from 2014 to 2035, with 20 cases per 100,000 people in 2035 (Cancer Research UK 2017).

The survival of oral cancer is poor, with overall 5-year survival rates in the order of 50%, having remained much the same for the past 50 years, despite advances in both surgery and radiotherapy (Crossman et al 2016; Stefanuto et al 2014).

Poor survival rates are thought to be closely related to advanced stage at presentation (Gomez et al 2009). Disease stage at presentation has a major influence on survival (Mehanna et al, 2010; Mao, Hong and Papadimitrakopoulou 2004). Cancers that are larger and have spread to the lymph nodes have a much poorer prognosis. Two-year crude survival for stage 1 (early) disease is approximately 90% whilst for stage 4 (advanced) disease the rate is less than 50% (South West Cancer Intelligence Unit, 2001). Unfortunately, approximately 50% of oral cancers present at advanced stage 3 or 4,

which many consider difficult to explain given the accessibility of the mouth to relatively easy examination (Stefanuto et al 2014).

The most common treatment methods are surgery and radiotherapy. For small tumours, single modality treatment is often effective and has a high cure rate, with relatively low morbidity. Advanced tumours require much more extensive treatment, often employing combined surgery and radiotherapy or radio-chemotherapy. The side effects of this extensive treatment are often very severe (Mehanna, West, Nutting and Paleri, 2010).

In common with other types of head and neck cancer, 75% or more of oral cancers are caused by a combination of cigarette smoking and heavy alcohol consumption (Hashibe et al, 2007; Blot, McLaughlin, Winn et al 1988). The risk for smokers is 10 times or more the risk for non-smokers. High alcohol consumption and smoking operate synergistically; heavy drinkers and smokers have a risk of developing oral cancer over 30 times that of individuals who neither drink nor smoke (Blot McLaughlin, Winn et al, 1988). Excessive alcohol consumption is of particular importance in relation to oral and pharyngeal cancers – an increased risk of over six times has been identified in those consuming over 12 units of alcohol per day (Bagnardi, Blangiardo, La Vecchia and Corrao, 2001)

Human papilloma virus subtypes 16 and 18 (HPV-16, HPV-18), is becoming increasingly recognised as a risk factor for oral cancer and are believed to be sexually transmitted. Many such patients do not smoke or drink excessively and often present relatively young, at 30-50 years of age (Sudhof et al, 2011). There is evidence that HPV related head and neck cancers may have better survival rates than other types (Fakhry, Westra, Sigui, Li et al, 2008). Low socio-economic status is associated with an increased risk of oral cancer (Ford and Farah 2013).

It is considered that 91%-93% of oral cancer cases are preventable (Cancer Research UK, 2016).

Description of the intervention

Oral cancer is unique in that it is referred to specialist care by both primary care doctors *and* dentists, which is most unlikely for other types of cancer (Ford and Farah 2013). Proportions referred by each group vary across studies. Crossman et al (2016) in a study of 200 oral cancer patients in the UK, reported that 57% were referred from their GP, 32% by their dentist, 2% via a hospital emergency department and 9% unknown (missing data), whilst in another series 65% of oral cancers were referred from a dentist (Holmes 2003).

Important differences between the referrals from each group of practitioners have been reported. For most cancers, only a minority are diagnosed through a screening programme (usually colorectal, breast and cervical, in high-income countries). However, in one study 47% of dentist-diagnosed oral cancers were identified during a non-symptom driven visit (Holmes et al 2003), whilst all medical referrals were symptom-driven. It would seem clear, therefore, that routine examination of the mouth has importance in the early diagnosis of oral cancer and dental practitioners are in a good position to carry out routine soft tissue examination of the oral cavity (McCann et al, 2000). However, English NHS data for 2014 – 2015 indicated that only 55.7% of adults had visited an NHS dentist in the previous 2 years (NHS 2015) and it is probable that those at highest risk of oral cancer are least likely to attend regular dental consultations (Donaldson et al 2008).

In the UK, primary care practitioners are provided with a list of 'guideline' symptoms and signs to assist in the referral of all cancer types, including oral cancer (NICE 2004, NICE 2015). Several authors note the importance of utilising these guidelines in conjunction with thorough history and examination – '*the principles of good medical practice are paramount'* (Rubin et al 2015) However, a study by Meskin (1994) indicated only 18% of physicians carried out an examination of the mouth on half their patients.

Differences do, of course, exist in the training of primary care doctors and dentists and this may well influence their management of oral cancer. However, it is evident that both groups of practitioners have an important role in prevention, early detection and referral and therefore require appropriate knowledge of the condition, an understanding of the risk factors and the skill to examine the oral cavity.

How the intervention might work

There is an established link between stage at presentation of oral cancer and survival (Gomez et al 2009; Mehanna et al, 2010; Mao, Hong and Papadimitrakopoulou 2004). Oral cancers are referred to specialist care by both primary care doctors and dentists but scoping has identified that (1) there is considerable variation in the reported proportions referred by doctors and dentists (2) there are reported differences in the stage on presentation of oral cancers referred by each group of professionals (3) there are differences in the presentation delay, both 'patient' and 'professional'.

Why it is important to do this review

It has been suggested that effective primary medical care/dental management of oral cancer has two main aims: Firstly, ensure that suspected oral cancer is referred in a timely manner and, secondly, ensure that those at high risk of developing the condition are identified and appropriately advised and managed (Conway et al 2002)

It is known that all or nearly all medical oral cancer referrals are in response to symptoms yet in one study almost half dental oral cancer referrals were 'incidental' findings at routine visits and cancers referred by dentists were diagnosed at an earlier stage (Holmes et al 2003). Therefore, it is hoped that this review might shed further light on the referral process for oral cancer and the value of routine regular dental/oral examination in screening for the disease.

OBJECTIVES

The overall main objective is to compare primary care doctors and dentists in the referral of oral cancer focusing on (1) the proportion of diagnosed cancers that were referred by each profession (2) differences in stage on presentation for referrals from each profession (3) differences in delay (professional and patient).

METHODS

Criteria for considering studies for this review

Types of studies

Studies that examine the referral of oral cancer, including both primary care doctors ('general practitioner'/'GP'/'primary care physician') and primary care dentists will be considered for this review. They are required to include one or more of the following outcomes:

(4) Proportion/percentage of diagnosed cancers referred by each profession
(5) Stage on presentation for each profession
(6) Presentation delay in relation to each profession

Following scoping searches, it is anticipated that many studies will be cohort studies but other designs are eligible, providing one or more of the specified outcomes are included. Case reports, qualitative studies and economic studies will not be part of this systematic review.

Types of intervention

The broad intervention is the referral oral cancer, comparing primary care doctors with dentists.

Types of Outcome Measures

It is anticipated that outcome measures will include:

Proportion of diagnosed cancers that were referred by primary care doctors and dentists.

Stage on presentation data for primary care doctors and dentists.

Delay (including 'patient delay' and 'professional delay' for primary care doctors and dentists.

Quality assessment

Papers will be selected for inclusion by 2 independent researchers. Abstracts of identified studies will be scrutinised to make an in initial assessment of design and relevance. We shall then read the full text of selected articles independently to assess eligibility for inclusion. Disagreements regarding study inclusion will be resolved by discussion in order to reach a consensus view on whether to include the study in the review or not.

Search Methods

The following resources will be searched:

Main Databases

- MEDLINE
- EMBASE
- CENTRAL (Cochrane Central Register of Controlled Trials)

Other Databases

- Scopus
- Google Scholar
- Web of Science
- CINAHL

To identify further studies the following resources (at least) will be searched:

- Browsing the reference lists in initially-identified studies
- Author searching (in relation to initially-identified studies)
- Citation index search (such as *Thomson Scientific*)
- Browsing the 'find similar' sections of many electronic databases
- Professional association contact (including British Association of Head and Neck Oncologists - BAHNO)
- Expert consultation
- Databases of theses (EThOS (Electronic Theses Online Service)
- Conference proceedings (including those of the British Association of Head and Neck Oncologists (BAHNO), British Academic Conference in Otolaryngology (BACO) and the British Association of Oral and Maxillofacial Surgeons ((BAOMS).
- Hand searching – including the journals of the above Associations

Search Strategy

The following search strategy will be applied to MEDLINE and EMBASE (using the *Ovid* 'front end')

1. Mouth Neoplasms/
2. oral cancer.mp.
3. mouth cancer.mp
4. 1 or 2 or 3
5. Primary Health Care/
6. primary care.mp.
7. General Practitioners/
8. general practitioner.mp.
9. GP.mp.
10. Physicians/
11. physician.mp
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Dentists/
14. dentist.mp.
15. general dental practitioner. mp
16. GDP.mp.
17. 13 or 14 or 15 or 16
18. 4 and 12 and 17

The search strategy will be appropriately modified for other databases (for example 'Oral Cancer/' in Embase is 'Mouth Neoplasms/' in Medline)

For Web of Science and Google Scholar separate searches will be made using the following phrases:

Referral of oral cancer

Dentist and oral cancer

Doctors and oral cancer

Physician and oral cancer

Primary care and oral cancer

GP and oral cancer

A decision on a 'desist' strategy for this review was be made using a method such as 'law of diminishing return' or 'stopping rules' described by Booth (2010).

Data extraction

Two researchers will independently extract data from the selected papers into a predefined electronic data spreadsheet. Data will be cross-checked by both reviewers and agreement reached, by discussion, on any discrepancies.

The following data will be extracted for each study:

General data: Main author, year of publication, language abstract/full text

Trial characteristics: Study design, duration.

Study population: Where the study was carried out, number in trial.

Outcome measures: as described above,

Data analysis

The main results of all included studies will be reported, including background information for individual papers.

Assessment of risk of bias in included studies

Risk of bias will be assessed by two independent researchers. A risk of bias table will be completed for each study. Disagreements between researchers will be resolved by discussion to reach a consensus view.

Heterogeneity

Clinical heterogeneity

Studies will be assessed for clinical heterogeneity and evaluation of at least the following:

- Variability between participants Intervention
- Outcomes (including those in addition to the main outcome measures described above)

Methodological heterogeneity

Methodological heterogeneity will be assessed by examining variability in the designs of the studies.

Statistical heterogeneity

Scoping searches indicate that statistical heterogeneity is unlikely to be evaluated, given the types of study involved.

Declarations of Interest

None

Sources of Support

None

REFERENCES

1. Cancer Research UK (2017) *available at*: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oral-cancer (*accessed January 2018*)
2. Conway DI, Macpherson LMD, Gibson J and Binnie VI (2002) Oral cancer: prevention and detection in primary dental healthcare Primary Dental Care 9 119-123
3. Crossman T, Warburton F, Richards MA, Smith H, Ramirez A and Forbes LJL (2016) *Role of general practice in the diagnosis of oral cancer* British Journal of Oral and Maxillofacial Surgery 54 208-212
4. Donaldson AN, Everitt B, Newton T, Steele J, Sherriff and Bower E (2008) *The Effects of Social Class and Dental Attendance on Oral Health* Journal of Dental Research 87 60-64
5. Ford P and Farah C (2013) *Early detection and diagnosis of oral cancer: Strategies for improvement* Journal of Cancer Policy 1 e2-e7
6. Gómez I, Seone J Varella-Centelles P et al (2009) Is diagnostic delay related to advanced-stage oral cancer? A meta-analysis European Journal of Oral Science 117 541-456
7. Holmes JD, Dierks EJ, Homer LD and Potter BE (2003) *Is detection of oral and oropharyngeal squamous cell carcinoma by a dental health care provider associated with a lower stage at diagnosis?* Journal of Oral and Maxillofacial Surgery 61 285-291
8. Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316
9. McCann MF, Macpherson LMD, Gibson J (2000) *The role of the general dental practitioner in detection and prevention of oral cancer: a review of the literature* Dental Update 27 404-8.
10. Mehanna H, Paleri V, West CML, Nutting C (2011) *Head and neck cancer – part 1 Epidemiology, presentation and prevention* Clinical Laryngology 36 65-68
11. Mehanna H, West CML, Nutting C and Paleri V (2010) *Head and neck cancer – part 2: treatment and prognostic factors* British Medical Journal 341 721-725
12. Meskin LH (1994) *Oral cancer – the forgotten disease* Journal of the American Dental Association 125 1042-1045
13. NHS (2015) *Dental Statistics England 2014/15* The Health and Social Care Information Centre, Leeds Available at: hscis.gov.uk/catalogue/PUB18129.
14. NICE (2004) Improving Outcomes in Head and Neck Cancers – The Manual available at: http://www.nice.org.uk
15. NICE (2015) *Suspected cancer: recognition and referral* available at: https://www.nice.org.uk/guidance/ng12/chapter/1-recommendations
16. Stefanuto P, Doucet J-C, Robertson C (2014) *Delays in treatment of oral cancer: a review of the current literature* Oral and Maxillofacial Surgery 117 424-429
17. Warnakulasuriya S (2009) *Global epidemiology of oral and oropharyngeal cancer* Oral Oncology 45 309–16

STUDY PROTOCOL

Prioritisation of approaches to the early diagnosis of oral cancer: a Delphi study of UK experts

Date and Version No:	v1.00 August 2019
Chief Investigator:	Steve Langton, MSc (Oxford), BDS, MB, ChB, FDSRCS, FRCS (retired consultant Maxillofacial Surgeon and part-time DPhil student, University of Oxford)
Investigators:	Dr Clare Bankhead, University of Oxford (supervisor); Dr Annette Pluddemann, University of Oxford (supervisor).
Sponsor:	University of Oxford
Funder:	None
Chief Investigator Signature:	
Conflict of Interest	There are no known conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

14. SYNOPSIS

Study Title	*'Prioritisation of approaches to the early diagnosis of oral cancer: a Delphi study of UK experts'*
Study Design	Delphi questionnaire study
Study Participants	UK experts on early diagnosis of oral cancer
Planned Sample Size	Approximately 12
Planned Study Period	3 months

15. ABBREVIATIONS

CI	Chief Investigator
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
CUREC	Central University Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
REC	Research Ethics Committee
SOP	Standard Operating Procedure

16. BACKGROUND

Oral cancer is the sixth most common cancer in the world (Gomez et al 2010) and approximately 6500 cases are diagnosed per year in the UK (Crossman et al 2016). The survival of oral cancer is poor, with overall 5-year survival rates in the order of 50%, having remained much the same for the past 50 years despite advances in both surgery and radiotherapy (Stefanuto et al 2014).

For head and neck cancer, including oral cancer, studies clearly show the correlation between stage on diagnosis and outcome (Mehanna et al 2010; Mao et al 2004). Furthermore, treatment of stage 1 and 2 cancers is considerably less extensive than for more advanced disease; for example, sentinel node biopsy may preclude the need for neck dissection in early oral cancers and complex reconstruction, with associated morbidity, may often be avoided (Schilling et al 2015). It is, therefore, clear that early diagnosis of oral cancer is highly desirable.

However, the reasons for late presentation – in all cancer types - are multiple, complex and often require diverse solutions (MacArtney et al 2017). Potentially, delay may be influenced by patients,

primary care, specialist care or 'the system' including referral management and rapid diagnosis procedures.

What, then, are the possible causes late oral cancer presentation? Many studies indicate that patient delay (or 'appraisal period') – the time between noticing a symptom and seeking professional help – is responsible for most of the overall 'delay pathway'. A UK study by McGurk et al (2005), including two cohorts of 319 and 160 oral cancers, found that patients accounted for delay in 81% and 78% of cases respectively, with a mean delay of 3 months. Yet how patient delay for oral cancer should be approached is unclear. In a study of 115 oral cancer patients, approximately half the patients interpreted their symptoms as something minor that would resolve spontaneously and nearly all the patients stated they would have obtained professional advice had they been more aware of oral cancer (Rogers et al 2007).

Public knowledge of oral cancer and the associated risk factors is poor and this has changed little over many years (Lowry and Craven 1999). Furthermore, efforts to improve public knowledge and awareness of oral cancer have had mixed benefits. In an American Dental Association oral cancer campaign (Stahl et al 2004) a majority of dentists agreed that public awareness of oral cancer was improved by the campaign and the study concluded: *'health promotion interventions aimed at consumers and dentists invariably will result in the detection of oral cancers at early and curable stages'.* However, an alternative view is given by Stefanuto (2014): *'Patients cannot be relied upon to present for examination. Some oral cancers and precancerous lesions may be asymptomatic and even though most are symptomatic patients may misrepresent their symptoms'.* Delay is also influenced by socio-economic deprivation (Johnson et al 2011) and access to primary care, including dental services (Holmes 2009).

Studies on professional delay and oral cancer have, again, produced mixed results. An early UK study by Scully et al (1986) found a median delay between primary care consultation and specialist referral of 31 days. A 2007 study in Liverpool identified a mean primary care practitioner delay of 22 days, although 78% of the 325 patients included were referred the same day as presentation (Rogers et al 2007).

The causes of professional delay in relation to oral cancer are complex. It might be assumed that because of the ease of access to the mouth, examination would be relatively simple. However, in a study in Scotland of 357 GPs and 331 dentists, on the role of primary care professionals in oral cancer prevention and detection, Macpherson et al (2003) reported that the majority (85%) of GPs and 63% of dentists felt 'less than confident' in oral cancer detection, with 70% of GPs identifying lack of training as an important barrier. This study concluded that education to improve primary care practitioners' diagnostic skills for oral cancer was needed.

Professional delay can, of course, also occur in secondary care. A study by Patel and Brennan (2012) identified a median delay of 37 days from date of biopsy to date of surgery for oral cancer. The 2000 UK 'two-week rule' focused on the need for urgent referral of cancer, specifying a maximum primary care-specialist assessment review interval of 14 days and providing primary care practitioners with list of 'red flag' signs and symptoms. The UK target for treatment is 31 days from formal diagnosis and 62 days from primary care referral; these targets should be achieved for 85% of patients. Unfortunately, the target has been consistently failed since 2013 and approximately 1 in 7 cancer patients (of all

types) wait over 62 days for treatment. The proportion of head and neck cancers meeting the 62-day target has steadily fallen from 2012 to 2017 (Nuffield Trust 2017).

There is no program for oral cancer screening in the UK - or indeed anywhere else in the world - (Cancer Research UK 2019). A paper from the Global Oral Cancer Forum (Speight et al 2017) provides a comprehensive and detailed analysis of the problem. The authors point out that the mouth is easy to examine, abnormalities are readily identified and oral cancer is preceded, in most cases, by a so-called 'oral potentially malignant disorder' (OPMD), usually a white patch (leukoplakia) or a red patch (erythroplakia) (Warnakulasuriya et al 2007). Unfortunately, no controlled trials on improved mortality in response to oral cancer screening - studies would need to be very large indeed - and the lack of controlled studies is cited by the UK National Screening Committee as a reason for not supporting a screening program. Similar conclusions have been reached in the USA (Wanrnakulasuriya et al 2015; Moyer 2014).

It is clear, therefore, that there are many possible methods and approaches that may improve the early diagnosis of oral cancer including screening, patient education, improving social inequalities and improved access to dental care, education of medical students and professionals, improving rapid specialist referral and communication and focus on at-risk individuals. However, budgets for any form of healthcare are not without limits and it is clearly important that the methods used for early oral cancer diagnosis are both efficient and effective (Abel 2016). Therefore, it would seem appropriate to prioritise the many approaches to the early diagnosis of oral cancer.

17. AIMS

Overall aim	**Objectives: prioritisation of the following 'approaches' to early oral cancer diagnosis**
The overall aim of this study is to prioritise the methods for improving the early diagnosis of oral cancer by gaining an expert consensus on the relative effectiveness of each approach.	**Patients** Screening for oral cancer; Patient education and sign/symptom awareness; Address social inequalities; Improve access to regular dental care **Primary care** Primary care (doctor and dentist) education and symptom/sign knowledge improvement; Screening methods (e.g. mucosal staining agents); Involvement of other professional groups in screening; Protocol-driven referrals; Fast-track referral systems for suspected cancer; Focus on high-risk individuals; Education at medical/dental school in oral cancer **Secondary care** Rapid diagnostic systems (such as one-stop clinics); Improved primary care-secondary care communication **Experts' (respondents') suggestions if not included above**

18. STUDY DESIGN

5.1 Delphi study design

This study will use the Delphi method to gather a consensus opinion from a panel of experts on early oral cancer diagnosis. The Delphi method is a structured process that develops a consensus expert opinion on a specific question. The process is iterative and includes sequential questionnaires that constitute each 'round'. Each round is refined by controlled feedback based on the previous round. Originally used by the US military, the method is now applied to many settings including finance, civic planning and healthcare (Thangeratinam and Redman 2005). The respondents will take part anonymously in that expert panel members are unaware of the identity of other panel members. The Delphi method is considered to avoid counterproductive group dynamics where the consensus view is dominated by a small number of individuals (Boulkedid et al 2011).

5.2 Generation of item list

Items for the initial questionnaire have been identified from a broad range of published literature, including published reviews and systematic reviews (Massano et al 2006; Van der Waal et al 2011; Ford and Farah 2013) and developed into a survey questionnaire (appendix 1) following discussions amongst the authors. The initial questionnaire includes 13 items, each an 'approach' of improving the early diagnosis of oral cancer. For convenience, these are divided into 3 groups: 'patients', 'primary care' and 'secondary care'. The 'items' are as follows:

(a) Patients

Screening for oral cancer

Patient education and sign/symptom awareness

Address social inequalities

Improve access to regular dental care

(b) Primary care

Primary care (doctor and dentist) education and symptom/sign knowledge improvement

Screening methods (e.g. mucosal staining agents)

Involvement of other professional groups in screening

Protocol-driven referrals

Fast-track referral systems for suspected cancer

Focus on high-risk individuals

Education at medical/dental school in oral cancer

(c) Secondary care

Rapid diagnostic systems (such as one-stop clinics)

Improved primary care-secondary care communication

(d) Other ways of improving early diagnosis (respondents' inclusions if not listed)

5.3 Data collection

The Delphi questionnaires will be delivered online and will be administered with JISC software03

5.4 Delphi procedure (data collection and analysis)

The study is a 2-round Delphi process.

The on-line study will available for up to 4 weeks and participants will be sent a reminder email at weekly intervals if they have not completed the questionnaire. Only participants who complete round 1 will be invited to undertake round 2.

For the first round, participants will be requested to rate the effectiveness of each approach to early oral cancer diagnosis using a 7-point Likert scale where 1 indicates low effectiveness and 7 indicates high effectiveness. Open comments on each item together with suggestions for items that may have been overlooked are invited, together with the opportunity to make general comments.

Responses to the first questionnaire will be categorised according to the proportion of respondents ranking the approach 6 or 7 on the Likert scale, a method used in previous Delphi studies (Plüddemann et al 2010). Based on this categorisation, three groups will be developed: 'high effectiveness', 70% or more respondents ranking the approach 6 or 7 on the Likert scale, 'moderate effectiveness', 50% to 69% and 'low effectiveness', less than 50%.

In the light of the responses to the first round, the second questionnaire will be developed. Participants will be provided with the results of the first-round questionnaire. The respondents will be informed of the method used to develop 'high', 'moderate' and 'low' effectiveness groups and asked whether they agree or disagree with the placement of the item in its group; should they disagree, respondents will be asked in which group they consider the item should be placed and to provide brief explanatory comments. General comments will also be invited at this stage. The final responses will be reviewed at a focus meeting of the authors before final analysis and publication.

19. PARTICIPANT IDENTIFICATION

6.1 Selection of participants

Participants will be selected from two groups: (1) UK-based individuals who have contributed significantly to the evidence base on early oral cancer diagnosis (2) consultants in public health who have a role in commissioning cancer services. This study is restricted to UK-based experts as aspects such as the referral system and the structure of primary care services will be essentially uniform. Potential participants will be contacted, in the first instance, by email, informed of the nature and purpose of the study and invited to participate.

20. STUDY ACTIVITIES

7.1 Consent

Participants will be informed that responding to the questionnaire implies consent to take part in the study and have their de-identified responses included in the study results. Data will be kept in password-protected digital format, to which only the researchers will have access.

7.2 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of consent; withdrawn participants will be replaced

The reason for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file.

7.3 Definition of end of study

The end of study is the date of the second questionnaire completion by the last participant.

21. DATA ANALYSIS

8.1 Number of participants

There are no 'hard and fast' rules regarding panel size for a Delphi study and although a minimum panel size of 7 was suggested by Linstone (1978), panel sizes from 4 to 3000 have been noted (Thangaratinam & Redman 2005). The decision on panel size is to an extent pragmatic, including factors such as time and expense constraints and expert availability (Hassan et al 2000). Scoping suggests approximately 12 experts will be recruited for this study.

8.2 Data analysis

Initial data analysis will take place following the first-round questionnaire (as described in section 5) and will include analysis of the Likert scores for each pre-specified approach to oral cancer diagnosis together with any additional approaches suggested by participants. Additional comments will be analysed with a view to presenting the results as a narrative. Subsequent data analysis will take place following the second-round questionnaire and the development of consensus. Both quantitative analysis of the data and narrative analysis of the comments will be undertaken.

22. DATA MANAGEMENT

9.1 Access to data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

9.2 Data recording and record-keeping

All data will be kept in password-protected digital format, in secure storage to which only the researchers will have access. A backup copy of data will be produced and stored separately from the main copy.

23. QUALITY ASSURANCE

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures

24. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.3 Approvals

The protocol and first-round questionnaire will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

11.5 Participant Confidentiality

Although it is anticipated the participants will be named in published work, they will not be identifiable in relation to specific views and comments. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

25. FINANCE AND INSURANCE

12.1 Funding

None

11.2 Insurance

Oxford University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

26. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

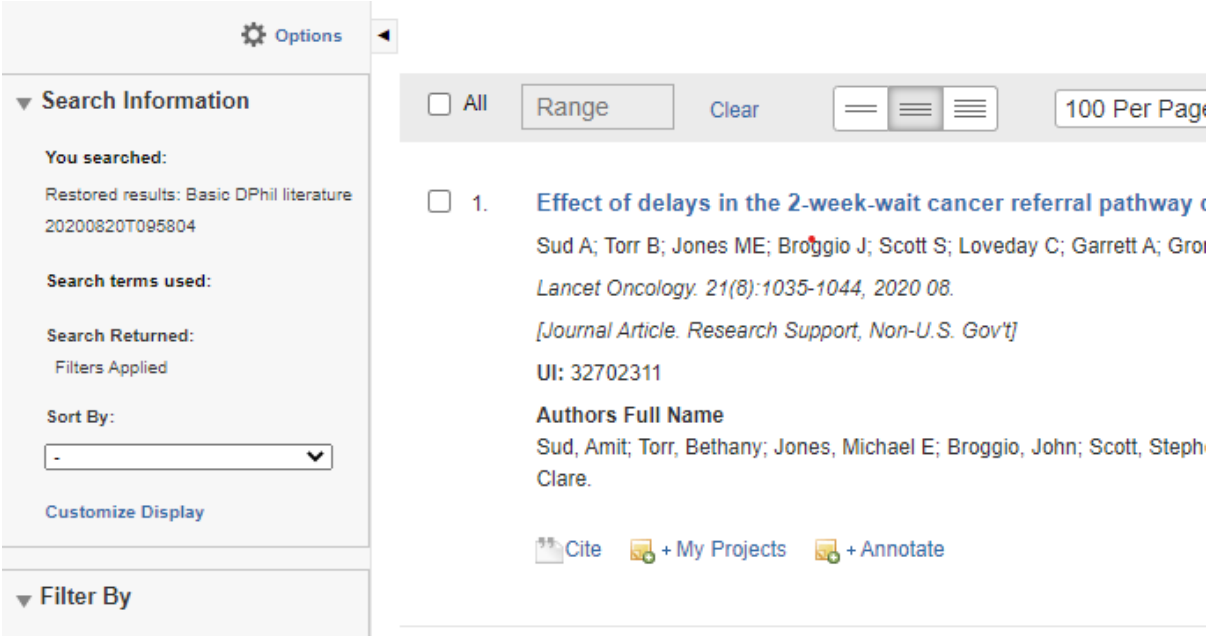
27. REFERENCES

1. Abel L (2016) *Catching it early: netting the costs of earlier cancer diagnosis* available at: https://www.phc.ox.ac.uk/news/blog/catching-it-early-netting-the-costs-of-earlier-cancer-diagnosis
2. Boulkedid et al (2011) Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review PLoS ONE 6:e20476
3. Crossman T, Warburton F, Richards MA et al (2016) *Role of general practice in the diagnosis of oral cancer* British Journal of Oral and Maxillofacial Surgery 54 208–212
4. Ford PJ and Farah CS (2013*) Early detection and diagnosis of oral cancer: Strategies for improvement* Journal of Cancer Policy 1 e2–e7
5. Gómez I, Warnakulasuriya S, Varela-Centelles PI, López-Jornet P, Suárez-Cunqueiro M, Diz-Dios P and Seoane J (2010) *Is early diagnosis of oral cancer a feasible objective? Who is to blame for diagnostic delay?* Oral Diseases 16 333-342
6. Hassan F, Keeney S & McKenna H Research Guidelines for the Delphi Survey Technique Journal of Advanced Nursing 32 1008-1015
7. Holmes JD *et al* (2003) *Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis?* Journal of Oral and Maxillofacial Surgery 61(3) 285–91
8. Johnson NW et al (2011) *Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions* Advances in Dental Research 23 237-246
9. Linstone HA (1978) *The Delphi technique. Handbook of futures research* Westport CT Greenwood

10. Lowry RJ and Craven MA (1999) *Smokers' and drinkers' awareness of oral cancer: a qualitative study using focus groups* British Dental Journal 187 668-670
11. MacArtney J, Malmström M, Nielsen TO, Evans J, Bernhardson B-M, Hajdarevic S, Chapple A, Eriksson LE, Locock L; Rasmussen BH, Vedsted P, Tishelman C, Andersen RS and Ziebland S (2017) *Patients' initial steps to cancer diagnosis in Denmark, England and Sweden: what can a qualitative, cross-country comparison of narrative interviews tell us about potentially modifiable factors?* BMJ Open 2017;7:e018210. doi:10.1136/bmjopen-2017-018210
12. Macpherson LMD, McCann MF, Gibson J et al (2003) *The role of primary healthcare professionals in oral cancer prevention and detection* British Dental Journal 195 277-281
13. Mao L, Hong WK and Papadimitrakopoulou VA (2004) *Focus on head and neck cancer* Cancer Cell 5 311-316
14. Massano J, Regateiro FS, Januário G et al (2006) *Oral squamous cell carcinoma: Review of prognostic and predictive factors* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology 102 67-76
15. McGurk M, Chan C, Jones J et al (2005) *Delay in diagnosis and its effect on outcome in head and neck cancer* British Journal of Oral and Maxillofacial Surgery 43 281-284
16. Mehanna H, West CML, Nutting C and Paleri V (2010) *Head and neck cancer – part 2: treatment and prognostic factors* British Medical Journal 341 721-725
17. Moyer VA (2014) *Screening for oral cancer: US preventative services task force recommendation statement* Annals of Internal Medicine 160 55–60
18. Nuffield Trust (2017) *Cancer waiting times: how has NHS performance changed over time?* Available at: https://www.nuffieldtrust.org.uk/news-item/cancer-waiting-times-how-has-nhs-performance-changed-over-time
19. Patel UA and Brennan TE (2012) *Disparities in head and neck cancer: assessing delay in treatment initiation* Laryngoscope 122 1756-1760
20. Pluddemann A, Heneghan C, Thompson M et al (2010) *Prioritisation criteria for the selection of new diagnostic technologies for evaluation* BMC Health Services 10 109
21. Rogers S, Pabla R, McSorley A, Lowe D, Brown J et al (2007) *An assessment of deprivation as a factor in the delays in presentation, diagnosis and treatment in patients with oral and oropharyngeal squamous cell carcinoma* Oral Oncology 43 648-655
22. Rogers SN, Hunter R and Lowe D (2011) *Awareness of oral cancer in the Mersey region* British Journal of Oral and Maxillofacial Surgery 49 176-181
23. Schilling C et al (2015) Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer European Journal of Cancer 52 2777-2784
24. Scully C, Malmos D, Levers BG, Porter SR and Prime SS (1986) *Sources and patterns of referrals of oral cancer: role of general practitioners* British Medical Journal 293 599-60
25. Speight PM, Epstein J, Kujan O et al (2017) *Screening for oral cancer - a perspective from the Global Oral Cancer Forum* Oral and Maxillofacial Pathology 123 680-687
26. Stahl B, Meskin LH and Brown LJ (2004) *The American Dental Association's oral cancer campaign: the impact on consumers and dentists* Journal of the American Dental Association 135 1261-1267
27. Stefanuto P, Doucet JC and Robertson C (2014) *Delays in treatment of oral cancer: a review of the current literature* Oral and Maxillofacial Surgery 117 424-429
28. Thangaratinam S and Redman CWE (2005) *The Delphi Technique* The Obstetrician and Gynaecologist 7 120-125
29. Van der Waal et al (2011) *Early diagnosis in primary oral cancer: is it possible?* Medicina Oral Patalogica Oral y Cirugia Bucal 1;16(3):e300-5
30. Warnakulasuriya S, Fennell N, Diz P et al (2015) An *appraisal of oral cancer and pre-cancer screening programmes in Europe: a systematic review* Journal of Oral Pathology and Medicine 44 559-570
31. Warnakulasuriya S, Johnson NW, van der Waal I (2007) *Nomenclature and classification of potentially malignant disorders of the oral mucosa* Journal of Oral pathology and Medicine 36 575-580

Appendix 7: Literature update system: keeping up to date

In order to keep informed about the current literature throughout my thesis, I established several Ovid 'AutoAlerts' which provided literature updates via email, automatically. Examples are shown for reference.



Ovid Results AutoAlert: Delay and oral cancer 2015 on

OA Ovid AutoAlert <autorun@ovid.com>
To

Reply

Follow up.

Your autoalert was checked against the latest changes but no relevant documents were found.

Total documents retrieved: 0

Results Generated From:

Ovid MEDLINE(R) <1946 to December Week 1 2017>
Ovid MEDLINE(R) <August Week 3 2017 - December Week 1 2017> (updates since 2017-12-06

#	Search History	Results
1	delay.mp.	2635
2	Delayed Diagnosis/	229
3	delayed diagnosis.mp.	316
4	patient delay.mp.	8
5	presentation delay.mp.	1
6	1 or 2 or 3 or 4 or 5	2854
7	Mouth Neoplasms/	418
8	oral cancer.mp.	221
9	7 or 8	461
10	6 and 9	6
11	limit 10 to updaterange="medl(20171206103935-20171213084907]"	0