

The 'two week rule' in head and neck cancer, 2000-2014; a systematic literature review

Steve Langton, MSc, FDSRCS, FDSRCPS, FRCS¹, Derrick Siau, MA, MB BChir, FRCS² and Clare Bankhead, BSc, MSc, DPhil³

¹Royal Blackburn Hospital, Blackburn, UK; ²Wythenshawe Hospital, Manchester, UK; ³Department of Primary Care Health Sciences, University of Oxford, UK

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ABSTRACT

Background: The UK fast-track system for suspected cancer – the ‘two-week rule’ (TWR) - states that for suspected cancer there should be a maximum of 14 days between primary care referral and secondary care specialist consultation. This approach is valued by patients, ensures a ‘universal standard’ of diagnosis and speeds up the overall cancer management pathway. However, it can be argued that the rule has had little or no effect on survival, diagnoses cancer in only a small proportion of referrals and is expensive.

Objectives: To conduct a systematic review on the effectiveness of the TWR in head and neck cancer.

Methods: Electronic searches of a several databases including: Medline, Embase, Cochrane Database of Systematic Reviews CINAHL and CANCERLIT were conducted up to the end of 2014. This search was supplemented by searching conference proceedings and contacting experts. Retrospective and prospective studies that included at least one of the following: **conversion rate** (proportion of TWR referrals diagnosed with cancer – positive predictive value) or **detection rate** (proportion of diagnosed cancers referred via the TWR - sensitivity) were included. Two reviewers assessed studies for inclusion and extracted data independently. Heterogeneity was assessed by inspection of forest plot confidence interval overlap and calculation of I^2 . Random-effects meta-analysis was undertaken

Results: 17 studies were included; all reported conversion rate; 10 of these also reported detection rate. Meta-analysis indicated an overall pooled conversion rate of 8.8% (95% CI 7.0%-10.7%) and a pooled detection rate of 40.8% (95% CI 25.7% – 55.8%) Subgroups

analysing maxillofacial (OFMS) and otolaryngology (ENT) units showed no significant difference in conversion rate (8.3% and 8.8%; $p = 0.73$). Subgroup analyses of 'early' studies (< 2008) and 'late' studies (2008 – 2014), showed a significant reduction in conversion rates from 10.6% to 6.6%, $p = <0.0001$. These 'early' and 'late' subgroups showed a significant increase in detection rate (35.0% to 49.7%, $p = 0.0008$).

Conclusions: The conversion and detection rates are similar to those for a number of other cancer sites that rely on a list of signs/symptoms for referral and were similar in ENT and maxillofacial units.

There is evidence to support the view that TWR conversion rates are falling whilst detection rates are rising, due to increasing referrals.

The influence of the TWR on outcomes, particularly survival is not well known.

Keywords: Fast-track cancer referral, two-week rule, head and neck cancer

INTRODUCTION

The two week rule (TWR), sometimes referred to as the 'two week wait', was introduced by the UK government in 1999 for breast cancer and in 2000 for all other cancers. The rule states that there should be a maximum 14 day wait from referral by a primary care practitioner to being seen by a secondary care specialist.

In the early 1990s inadequacies in UK cancer care were being identified and were the subject of much comment. The media described a so-called 'cancer lottery' in which the chances of successful cancer treatment depended on being referred to an appropriate specialist rather than a non-

specialist^{1,2}. In 1995 the first EURO CARE studies were published³. These studies indicated that outcomes for some cancers in the UK were worse than in a number of other European countries. In response, the UK government introduced the TWR in the document *The New NHS Modern, Dependable*⁴ and the policy was put into effect, initially for breast cancer in April 1999 and for all other cancers by December 2000.

However, the TWR has been subject to considerable debate. Those in favour point out that the rule is valued by patients, ensures a 'universal standard' of treatment and is important in speeding up the overall cancer management pathway. Opponents of the system argue that the rule has had little or no effect on survival, diagnoses cancer in only a small proportion of referrals and is expensive. In June 2001, Jones, Rubin and Hungin⁵, writing in *the British Medical Journal*, pointed out that there was no good evidence that delays in weeks in diagnosing cancer translated into improved staging or survival and suggested that the predictive values of symptoms of cancer were 'poorly defined'. Subsequently, Jiwa and Saunders⁶ identified that the proportion of people referred via the TWR diagnosed with cancer *decreased* from 1999 to 2005 and suggested the 'tick box' system of referral, using a list of key symptoms⁷ may not, in isolation, be adequate. Many studies, across a broad range of cancers, have examined *conversion rate* (positive predictive value) – the proportion of TWR referrals that have cancer and *detection rate* (sensitivity) – the proportion of cancers that were referred via the TWR. For a number of cancer types, including breast⁸, gastro-intestinal⁹ and colorectal¹⁰, the conversion rarely exceeds 10%.

In head and neck cancer a short review including six studies up to 2008 was carried out by Kumar et al¹¹ but a number of studies have been published since that time and an updated review would seem appropriate. The principal aim of this systematic review is, therefore, to assess the effectiveness of the TWR in the diagnosis of head and neck cancer for the period

2000 – 2014 by collating evidence from all studies fulfilling appropriate inclusion criteria, examining *conversion rate* and *detection rate*.

METHODS

Types of studies

Prospective and retrospective cohort studies, audits and conference abstracts were included. Studies were required to report specifically on the UK National Health Service TWR; studies in other countries were excluded. Case reports, economic evaluations and qualitative studies were excluded.

Types of intervention

The single intervention in this review is fast-track referral via the UK TWR from primary care to secondary care, using the agreed national guidelines⁷ for patients with suspected head and neck cancer. This includes referrals from both primary care doctors and dentists.

Types of outcome

The primary outcomes in this review are: *conversion rate* – the proportion of TWR referrals who do have cancer (positive predictive value) and *detection rate* – the proportion of diagnosed cancers that were referred via the TWR (sensitivity).

Search methods

The following databases and registers were searched: MEDLINE (Ovid), EMBASE (Ovid), Scopus, Google Scholar, CANCELIT, Web of Science (v5.13), CINAHL, CENTRAL (Cochrane

Central Register of Controlled Trials) and www.clinicaltrialsregister.eu and www.theses.com, from 1999 to month 6 2014

Additionally, reference lists of identified studies were searched, an author search was made using information from identified studies, a citation index search, using *Thomson Scientific*, the 'find similar' facility of databases, conference proceedings of British Association of Oral and Maxillofacial Surgeons (BAOMS) and British Academic Conference in Otolaryngology (BACO) and expert consultation was undertaken.

Hand searching (index) was undertaken of the *Journal of Laryngology and Otology* and *British Journal of Oral and Maxillofacial Surgery*

Search Strategy

The following terms were used in the search:

2 week, 14 day, fourteen day, rule, wait, referral, standard, urgent referral, fast track, early detection of cancer, head and neck, oral cancer, laryngeal cancer, pharyngeal cancer, mouth neoplasms.

Selection of Studies

Retrospective and prospective studies were considered that included at least conversion rate or detection rate. 2 reviewers assessed studies for inclusion and extracted data independently. Differences were resolved by discussion. Papers identified from all the above methods were assessed and duplicates were eliminated. Abstracts were studied by 2 reviewers to 'shortlist' papers that were about the TWR in relation to head and neck cancer.

Abstracts that clearly demonstrated that the study did not fulfil the inclusion criteria, for example, qualitative studies or commentaries, were eliminated at this stage. For the remaining studies, copies of the full papers were obtained.

Data extraction

Data were extracted by two reviewers independently as follows: first author, title of article, date of publication, location of study in the UK, type of study (prospective, retrospective, audit, conference abstract), type of unit in which the study was carried out (maxillofacial, ENT, 'head and neck', other), type of participants (general 'head and neck' or a subgroup such as 'oral'), duration of the study (months), dates between which the study was carried out, number of TWR referrals during the study period, number of TWR referrals diagnosed with cancer, *conversion rate* – the proportion (percentage) of TWR referrals that are diagnosed with cancer, the *detection rate* – the proportion of all cancers that were referred via the TWR.

Study quality

A methodological index for assessment of the quality of non-randomised studies (MINORS) was developed by Slim et al¹², which was applied to the included studies.

On the MINORS scale, items are 'scored' 2 (reported and adequate), 1 (reported but inadequate) and 0 (not reported). Previous workers¹⁰ have used the index to calculate an approximate assessment of study quality (0-5 = poor; 6-10 = fair; 11-16 = good). However, the use of numerical scales for study quality has been questioned¹⁴. Therefore, the studies

in this review were assessed using the MINORS scale with the results presented in the form of a table to give the reader an overall view of study quality.

In assessing study quality, consideration was also given to length (time) of the study. As it is established that there is a seasonal variation in cancer presentation^{15, 16, 17} it was considered that studies of less than 12 months duration were at greater risk of bias.

Missing Data

All studies included conversion rate as an outcome but not all studies included detection rate; it was not possible to obtain the relevant missing data. Outcomes for conversion and detection were analysed separately.

Heterogeneity

There are a number of potential sources of clinical and methodological heterogeneity.

Patients in the study populations will differ. Head and neck cancer predominates in the lower social classes, has strong associations with different levels of tobacco and alcohol use.

A number of different anatomical sites are classified as 'head and neck cancer' and different studies may contain different proportions of the various types.

For this review, heterogeneity was assessed by (1) generating forest plots and inspecting the confidence intervals (2) calculating I^2 and calculating the confidence intervals for I^2 which expresses, as a percentage, the proportion of variation in the study estimates due to heterogeneity.

Subgroup analysis

Subgroups were planned as follows:

1. Subgroups of 'early' studies conducted up to 2008 and 'late' studies after 2008

2. Subgroups of studies conducted in ENT units and those in oral and maxillofacial units (OMFS)

Data synthesis and analysis

Data synthesis was performed using *StatsDirect 3*[®] software. Forest plots were generated for conversion rate and detection rate (when reported) across the studies. The software estimated statistical heterogeneity, calculating I^2 values together with their confidence intervals. The software automatically calculated fixed-effects and random-effects meta-analyses. Random-effects analysis does not assume a common effect size and, bearing in mind the differing subjects and interventions in the studies, the random-effects method was utilised in this review.

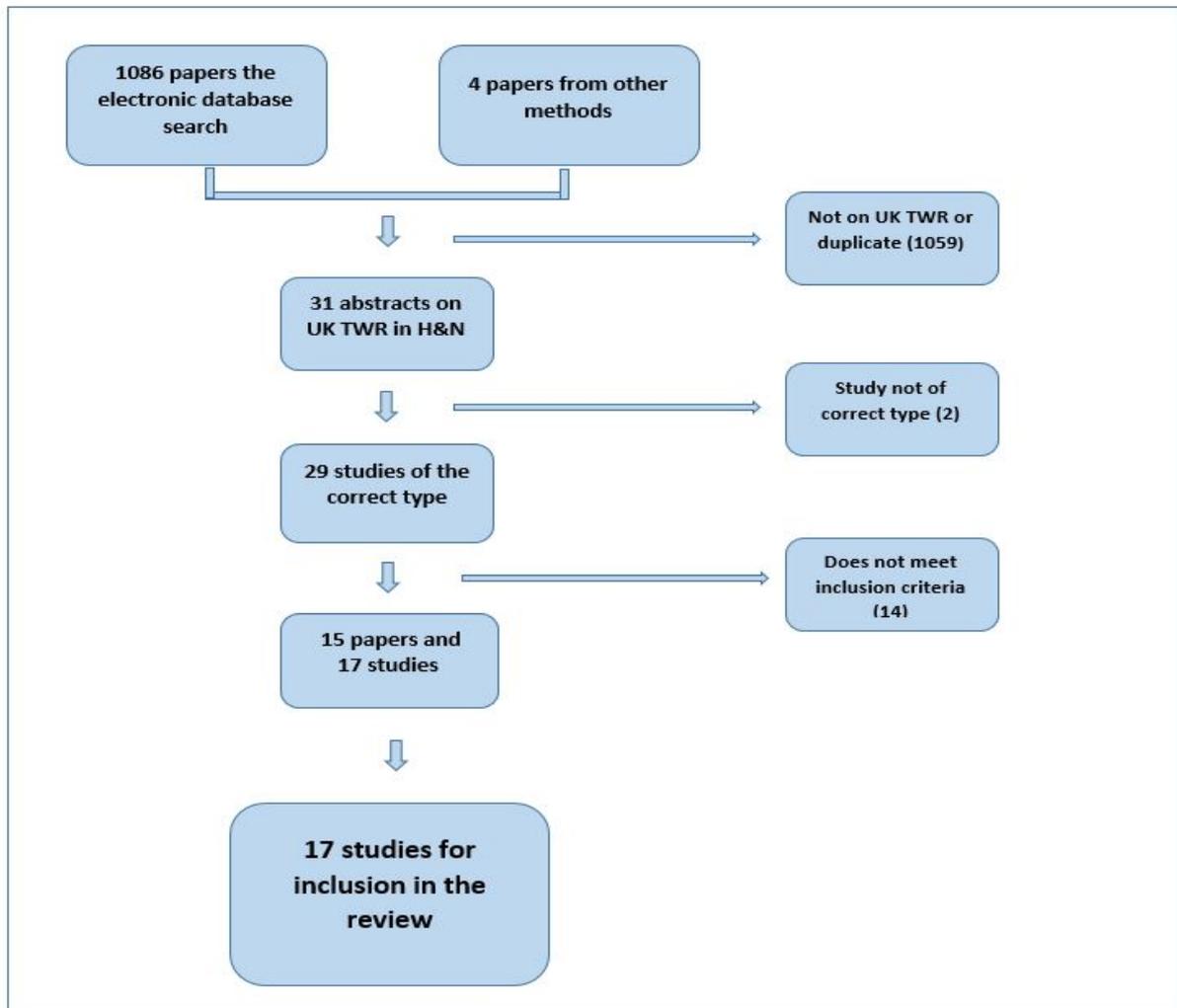
Publication bias

We considered whether papers in this review were more likely to be published should 'good' or 'positive' outcomes be reported. Would a paper be more likely to be published (or published rapidly) should it show the TWR to be highly effective or, conversely, highly ineffective? Given the types of study included, which are not controlled trials, it was considered that publication bias was unlikely to be a significant factor in this review.

RESULTS

1086 papers for potential inclusion were identified by the electronic searches, 4 papers by other methods. Scrutiny of the abstracts revealed 31 papers on the UK TWR on head and neck cancer; 2 were not of the type specified in the protocol. The complete papers were retrieved and scrutinised for inclusion by two reviewers and a consensus was agreed for the

inclusion of papers in the review. 14 papers did not meet the pre-specified inclusion criteria; however, 2 papers included two *separate* audits reporting appropriate outcomes^{18,19}. As a result, 17 studies were included in this review as shown in the 'Prisma' flow diagram.



Description of included studies

The characteristics of the included studies are shown in *table 1*

17 studies met the inclusion criteria²⁰⁻³⁴. Of these all reported conversion rate (positive predictive value); 10 reported both conversion rate and detection rate (sensitivity). 12 studies were published full journal articles whilst 5 were published conference abstracts. 15 studies were retrospective and 2 prospective. 7 studies were carried out in OMFS units, 9

were undertaken in ENT units and one was undertaken jointly between ENT and OMFS in the same hospital. 12 studies studied 'head and neck cancer' whilst 5 (all OMFS units) looked at 'oral cancer'. Length of study varied from 3 months to 36 months (mean 12.4 months). The number of TWR referrals examined ranged from 40 to 1079. Studies were all published in English and were undertaken in a broad range of UK localities. 8 studies were published between 2002 and 2008 and 9 studies were published between 2009 and 2013.

Characteristics of excluded studies

14 studies were excluded at the final stage of selection when full articles were assessed. Six studies did not report at least one of the pre-specified outcomes³⁵⁻⁴⁰. Three articles were commentaries on other papers^{4,42,43} and one was a short letter with insufficient information⁴⁴. Kennedy et al⁴⁵ reported both of the specified outcome measures but was undertaken in Scotland where the TWR does not apply as it does in the rest of the UK.

Hodgson et al⁴⁶ also reported the specified outcome measures. However, the authors did not study a consecutive cohort of TWR referrals to their unit but examined all referrals for suggestion of malignant disease and then selected 'a random subgroup of 241 patients'. Because of this slightly unusual method this study was excluded.

On-going studies

No on-going studies were identified.

Study Quality (table 2)

Evaluation of study quality was undertaken using the MINORS scale (table 2). Using the criteria previously used by Elkhadem, Mickan and Richards¹⁰, 4 studies are classified as being of 'fair' quality and 13 of 'good' quality.

Effects of the Intervention

OVERALL CONVERSION RATE (positive predictive value)

All 17 studies reported conversion rate. 4028 TWR referrals were made and 360 cancers were diagnosed. Conversion rate ranged from 2.2% to 14.6%. Inspection of the forest plot indicated low to moderate heterogeneity. I^2 was calculated to be 72.6% (95% confidence interval 52.1% - 82.0%) and random-effects meta-analysis was undertaken. The pooled conversion rate (positive predictive value) was 8.8% (95% CI = 7.0% to 10.7%).

OVERALL DETECTION RATE (sensitivity)

10 studies reported detection rate. 912 cancers were diagnosed. 280 of these cancers had been referred via the TWR. Detection rate ranged from 13.6% to 80.3%. Random-effects meta-analysis was undertaken and the pooled detection rate was 40.8% (95% CI = 26.7% to 55.8%).

SUBGROUP ANALYSES

Subgroups were analysed in relation to: (1) ENT and maxillofacial units (2) 'Early' and 'late' studies

ENT units and OMFS units

9 studies were carried out in ENT units. 2212 TWR referrals were made, 183 cancers diagnosed.

Conversion rate ranged from 2.2% to 14.6%; the pooled conversion rate for this subgroup was 8.8% (95% CI = 6.0% to 12.0%). 7 studies were carried out in OMFS units, representing 738 TWR referrals and 59 cancers diagnosed. The conversion rate ranged from 6.0% to 11.1%, and the pooled conversion rate was 8.3% (95% CI = 6.4% to 10.4%). The difference between conversion rate in ENT and OMFS units

was not significant ($p=0.73$). The analysis for detection rate for maxillofacial and ENT units was not undertaken as only 2 OMFS studies reported detection rate.

‘Early’ studies (conducted between 2001 and 2008) and ‘late’ studies (conducted 2009-2014)

10 studies were carried out in the early period and 7 in the later period. The pooled conversion rate from the fixed effect meta-analysis was 10.6% (95% CI 9.4% to 11.8%) in the early group, and was 6.6% (95% CI 4.2% to 9.6%) in the late group. The difference between the ‘early’ and ‘late’ studies is significant ($p < 0.0001$).

DISCUSSION

This systematic review found a pooled TWR referral conversion rate for head and neck cancer of 8.8% (95% CI 7.0% - 10.7%). This rate of cancer diagnosis is similar to that reported in several other specialties including gastro-intestinal^{47, 9, 48}, breast⁸, colo-rectal¹⁰, CNS⁴⁹ and gynaecology⁵⁰. The pooled detection rate of 40.8% (95% CI 26.7% to 55.8%) suggests that for the included studies approximately two thirds of UK head and neck cancers were diagnosed via routes other than the TWR system. Rates of this order are often described as ‘poor’^{5, 6, 11}.

However, defining exactly what is ‘poor’ (or, indeed ‘acceptable’, ‘good’, ‘outstanding’ or any other category) is not easy. In the light of this review, we would suggest several questions need to be addressed, including the following:

- Is a conversion rate of the order of 10%, or a detection rate of 40%, acceptable? If so, why? If not, why not?
- If improvement is needed, how can this be achieved?
- What are the implications for the secondary care services? Does the TWR direct resource (such as doctors, nurses and clinical time) away from other important services?
- What are the economic implications?

- Does the policy improve mortality and morbidity?
- What are the other benefits? What is the evidence that patients benefit from the system, for example, psychologically? Is there a high level of anxiety at being referred via the TWR?

Analysis of the 'early' and 'late' subgroups for conversion rate in this review suggests that a *drop* has occurred over the years the TWR has been in effect (10.6% 'early' 6.6% 'late', $p < 0.001$). This has also been a finding in several other studies^{8, 9, 51}. However, subgroup analysis indicated the pooled detection rate, or proportion of all cancers diagnosed via the TWR, *increased* from 35% to 47.9%. A falling conversion rate with an increasing detection rate reflects an increasing number of TWR referrals. In short, our meta-analysis indicates that over the years more head and neck patients are being referred but proportionally less are actually being diagnosed with cancer.

The increase in TWR referrals has important implications. Pullyblank, Silvant and Cook⁵² comment on the potential for the TWR numbers to 'overwhelm' the system; indeed Potter⁸ noted a 42% increase in such referrals between 1999 and 2005 and Rai and Kelly⁴⁸ commented on a 60% increase in TWR referrals from 2001 to 2004. They argue that in some specialties, a doubling of waiting time for *routine referrals* is a result of the resource required to implement the TWR. However, it can certainly be argued that if a patient presents with a symptom that suggests an approximately 10% chance of having malignancy, then urgent specialist assessment is very appropriate.

How might the diagnostic 'yield' of the TWR be improved? Several authors, studying a number of cancer types, have focused on the guidelines themselves. The guidelines were not developed in an evidence-based manner but as a consensus view⁴⁸. Jones et al⁵ argue that simple 'guideline symptoms' alone are insufficient indicators of potential cancer. On the other hand, head and neck cancer is a common presentation in neither general medical nor dental practice and several authors^{53, 54} have commented on the need for clear guidelines together with an 'education programme'. However, exactly what type of education is required to improve the quality of TWR referrals remains unclear.

Subgroup analysis in this review demonstrated very little difference in diagnostic accuracy rates between OMFS units and ENT units (conversion rates 8.3% & 8.8% respectively, $p=0.73$). It was not possible to identify specifically which patients had been referred by doctors or dentists although it is likely that the vast majority of referrals from dentists will be sent to OMFS as these patients are likely to be oral cancers.

Whilst there is most certainly evidence that patients value a fast-track referral for suspected cancer⁵⁵, perhaps the most important question is whether the system has an influence on survival. However, this has been questioned; Hanna et al⁵⁶ argue that the TWR *in isolation* is unlikely to have an influence simply because it only addresses a small portion of the overall cancer 'pathway'. Unfortunately, very little research to date has examined the effect of fast-track referral on cancer survival.

In June 2015, updated UK guidelines for cancer referral⁵⁷ were issued by NICE; the effect on cancer referral effectiveness remains to be seen.

Strengths and Weaknesses of this Review

This review provides – with greater power than the individual studies - information on two measures of effectiveness of the two-week rule in head and neck cancer, conversion rate and detection rate. Subgroup analysis was also performed, providing evidence for firstly, changes over the period that the TWR has been in existence and, secondly, comparing two groups of surgeons that treat head and neck cancer.

However, a pragmatic view was taken of the types of study included – no randomised controlled trials exist. Although all studies fulfilled the pre-specified criteria for inclusion, and showed little evidence of bias, only 10 of 17 reported *both* outcome measures. 5 studies were published conference abstracts and limited methodology was available. For several analyses considerable heterogeneity was evident and the potential inconsistency needs to be considered when making conclusions. Due to the variation in rate of presentation of head and neck cancer, results from studies that involve a short period need to be interpreted with caution.

Conflict of Interest

There are no conflicts of interest

Ethics statement/confirmation of patient permission

There is no identifiable patient information in this paper

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Table 1 CHARACTERISTICS OF INCLUDED STUDIES (PCA = published conference abstract)

FIRST AUTHOR & REFERENCE	DATE OF PUBLICATION	LOCATION OF STUDY	TYPE OF STUDY	TYPE OF UNIT	TYPE OF PARTICIPANT	PERIOD OF STUDY -MONTHS	DATES DATA COLLECTED	NUMBER OF TWR REFERRALS	TWR REFERRALS DIAGNOSED	% TWR REFERRALS DIAGNOSED CANCER	TOTAL CANCERS DIAGNOSED	DIAGNOSED CANCERS VIA TWR	% TWR SEEN 2/52
Williams (2002) <i>An audit of two week wait referrals for head and neck cancer</i> Annals of the Royal College of Surgeons (Supplement) 84 304-306	2002	Bristol	Prospective	OMFS	Head and neck	9	05.2001 - 01.2001	100	11	11.0%	NA	NA	98%
Lyons (2004) <i>Audit of referrals for head and neck cancer – the effect of the 2-week, fast track referral system</i> Clinical Otolaryngology 29 143-145	2004	Southend	Retrospective	Otolaryngology	Head and neck	12	1.10.2000 - 30.09.2001	171	25	14.6%	85	29.4%	95%
Shah (2004) <i>Fast-track referrals for oral lesions: A prospective study</i> British Journal of Oral and Maxillofacial Surgery 44 207-208	2005	Bristol	Retrospective	OMFS	Oral	32	05.2001 - 12.2003	150	9	6.0%	27	33.3%	98%
East (2005) <i>Is the two week rule of any benefit to patients with oral cancer?</i> British Journal of Oral and Maxillofacial Surgery 43 511-512	2005	Middlesbrough	Retrospective	OMFS	Oral	6	08.2003 - 01.2004	48	3	6.3%	22	13.6%	NA
Singh (2006) <i>The two-week wait cancer initiative on oral cancer; the predictive value of urgent referrals to an oral medicine unit</i> British Dental Journal 11 717-720	2006	Central London (King's College)	Prospective	Oral Medicine	Oral	12	08.2003 - 08.2004	76	6	7.9%	NA	NA	86%
Duvvi (2006) <i>Two-week rule for suspected head and neck cancer. A study of compliance and effectiveness</i> Journal of Evaluation in Clinical Practice 12 591-594	2006	Warrington	Retrospective	Otolaryngology	Head and neck	12	01.01.2003 - 31.12.2003	187	19	10.2%	31	61.3%	96%
Hobson (2008) <i>Outcomes for patients referred urgently with suspected head and neck cancer</i> Journal of Laryngology and Otology 122 1241-1244	2008	Stockport	Retrospective	Otolaryngology	Head and neck	12	01.01.2005 - 31.12.2005	177	22	12.4%	39	56.4%	96%
McKie (2008) <i>The 2-week rule for suspected head and neck cancer in the United Kingdom: referral patterns, diagnostic efficacy of the guidelines and compliance</i> Oral Oncology 44 851-856	2008	Newcastle upon Tyne	Retrospective	Otolaryngology and OMFS	Head and neck	36	01.01.2004 - 31.12.2006	1079	118	10.9%	552	21.4%	97%
Ahmad (2011) <i>'Two week rule' referrals for suspected head and neck cancer: An audit of clinical effectiveness</i> Irish Journal of Medical Science 180 (Supplement) S90	2011	Central London (St. George's)	Retrospective (PCA)	Otolaryngology	Head and neck	3	01.2010 - 03.2010	114	6	5.3%	NA	NA	NA
Haikel - audit 1 (2011) <i>The effect of increasing two-week wait referrals for head and neck cancer in East Kent</i> Annals of the Royal College of Surgeons of England (Supplement) 93 217-220	2011	East Kent	Retrospective	Otolaryngology	Head and neck	5	01.02.2005 - 30.06.2005	163	17	10.4%	57	29.8%	98%
Haikel - audit 2 (2011) <i>The effect of increasing two-week wait referrals for head and neck cancer in East Kent</i> Annals of the Royal College of Surgeons of England (Supplement) 93 217-220	2011	East Kent	Retrospective	Otolaryngology	Head and neck	6	01.04.2007 - 30.09.2007	542	53	9.8%	66	80.3%	98%
Miller - audit 1 (2012) <i>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)</i> 63-68	2012	Newcastle upon Tyne	Retrospective	OMFS (General Hospital)	Oral	12	04.2008 - 03.2009	63	7	11.1%	NA	NA	90%
Miller - audit 2 (2012) <i>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)</i> 63-68	2012	Newcastle upon Tyne	Retrospective	OMFS (Dental Hospital)	Oral	12	01.2010 - 12.2012	49	3	6.1%	NA	NA	88%
Madhvani (2012) <i>The efficacy of two-week suspected cancer referral pathway to the oral and maxillofacial surgery department</i> British Journal of Oral and Maxillofacial Surgery 50 (supplement) S47-S48	2012	Northwest London Hospitals	Retrospective (PCA)	OMFS	Head and neck	6	04.2011 - 10.2011	252	20	7.9%	NA	NA	NA
Joshi (2012) <i>Is the 2 week wait system an efficient method of detecting head and neck cancer?</i> Clinical Otolaryngology 37 (Supplement 1) 47	2012	King's Lynn	Retrospective (PCA)	Otolaryngology	Head and neck	12	08.2010 - 07.2011	362	8	2.2%	17	47.1%	99%
Davey (2012) <i>Clinical audit of the 2-week wait referral system for head and neck cancer</i> Clinical Otolaryngology 37 (Supplement 1) 83-84	2012	Brighton	Retrospective (PCA)	Otolaryngology	Head and neck	12	08.10 - 07.11	446	27	6.0%	NA	NA	95%
Kayhanian (2013) <i>Diagnostic efficacy of the two week wait referral system for suspected head and neck cancer in the United Kingdom</i> European Journal of Cancer 49 (Supplement) S330-331	2013	Luton	Retrospective (PCA)	Otolaryngology	Head and neck	12	01.2012 - 12.2012	50	6	12.0%	16	37.5%	98%

Table 2 **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	<u>MINORS quality assessment</u>
Williams	2	2	2	1	2	1	2	0	12
Lyons	2	2	0	2	2	2	2	0	12
Shah	2	2	2	2	2	2	2	0	14
East	2	2	0	2	2	1	2	0	11
Singh	2	2	0	1	2	2	2	0	11
Duvvi	2	2	0	2	2	2	2	0	12
Hobson	2	2	0	2	2	2	2	0	12
McKie	2	2	0	2	2	2	2	0	12
Ahmad	2	2	0	1	2	0	2	0	9
Haikel (audit 1)	2	2	0	2	2	0	2	0	10
Haikel (audit 2)	2	2	0	2	2	1	2	0	11
Miller (audit 1)	2	2	0	1	2	2	2	0	11
Miller (audit 2)	2	2	0	1	2	2	2	0	11
Madhvani	2	2	0	1	2	1	2	0	10
Joshi	2	2	0	2	2	2	2	0	10
Davey	2	2	0	1	2	2	2	0	11
Kayhanian	2	2	0	2	2	2	2	0	12

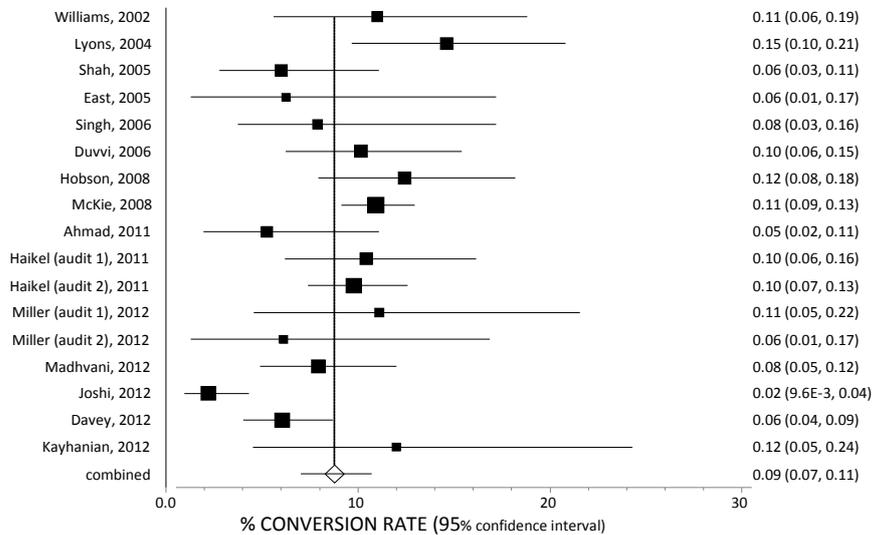
2 (reported and adequate), 1 (reported but inadequate) and 0 (not reported)

For "endpoints" if both conversion rate and detection rate were included = 2; if only one was reported = 1 For follow-up > 1year = 2, 6 months to 1 year = 1, less than 6 months = 0

OVERALL CONVERSION RATE (positive predictive value)

Study	Number in study	Conversions	Percentage	Lower CI	Upper CI	Weight
Williams, 2002	100	11	11.0%	5.6	18.8	5.1
Lyons, 2004	171	25	14.6%	9.7	20.8	6.3
Shah, 2005	150	9	6.0%	2.8	11.1	6
East, 2005	48	3	6.3%	13.1	17.2	3.4
Singh, 2006	76	6	7.9%	3	16.3	4.5
Duvvi, 2006	187	19	10.2%	6.2	15.4	6.5
Hobson, 2008	177	22	12.4%	8	18.2	6.4
McKie, 2008	1079	118	10.9%	9.1	12.6	8.7
Ahmad, 2011	114	6	5.3%	2	11.1	5.4
Haikel (audit 1), 2011	163	17	10.4%	6.2	16.1	6.2
Haikel (audit 2), 2011	542	53	9.8%	7.4	12.6	8.1
Miller (audit 1), 2012	63	7	11.1%	4.6	21.6	4.0
Miller (audit 2), 2012	49	3	6.1%	1.3	169	3.5
Madhvani, 2012	252	20	7.9%	4.9	12	7.0
Joshi, 2012	362	8	2.2%	1	4.3	7.6
Davey, 2012	446	27	6.1%	4	8.7	7.9
Kayhanian, 2013	50	6	12.0%	4.5	24.3	3.5

OVERALL CONVERSION RATE

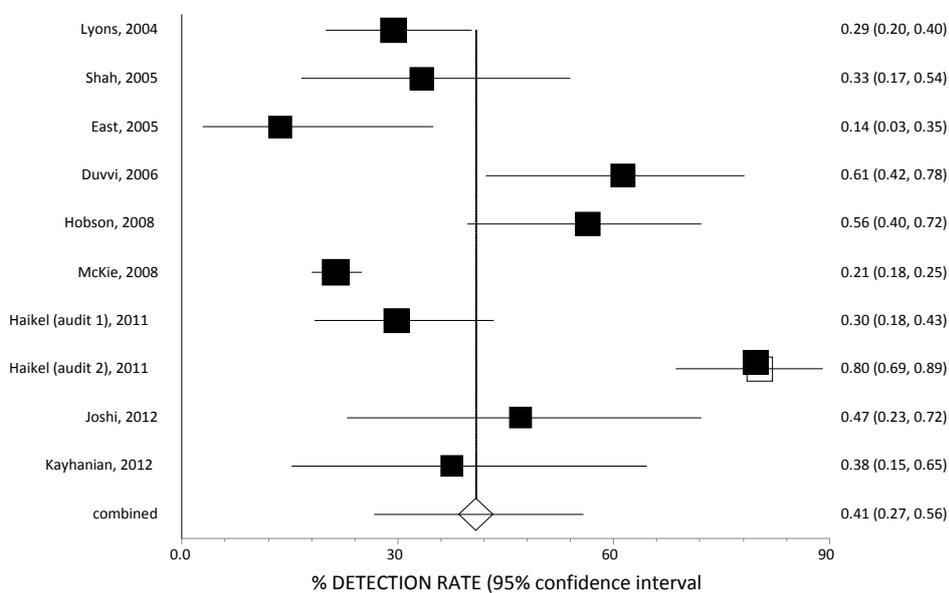


I^2 (inconsistency) = 72.6% (95% CI = 52.1% to 82%)

OVERALL DETECTION RATE (sensitivity)

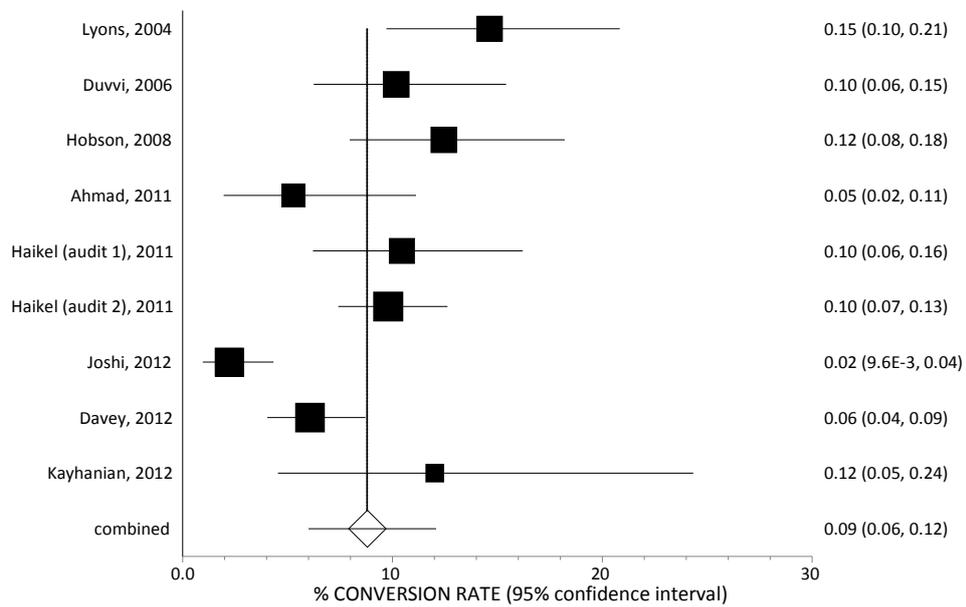
Study	Number of cancers	Detections by TWR	Percentage	Lower CI	Upper CI	Weight
Lyons, 2004	85	25	29.4%	20	40	10.8
Shah, 2005	27	9	33.3%	16.5	53.9	9.7
East, 2005	22	3	13.6%	29	34.9	9.4
Duvvi, 2006	31	19	61.2%	42.2	78.2	9.9
Hobson, 2008	39	22	56.4%	39.6	72.2	10.1
McKie, 2008	552	118	21.4%	18	25	11.3
Haikel (audit 1), 2011	57	17	29.8%	18.4	43.4	10.5
Haikel (audit 2), 2011	66	53	80.3%	68.7	89.1	10.6
Joshi, 2012	17	8	47.1%	23	72.2	8.9
Kayhanian, 2013	16	6	37.5%	15.2	64.6	8.8

OVERALL DETECTION RATE



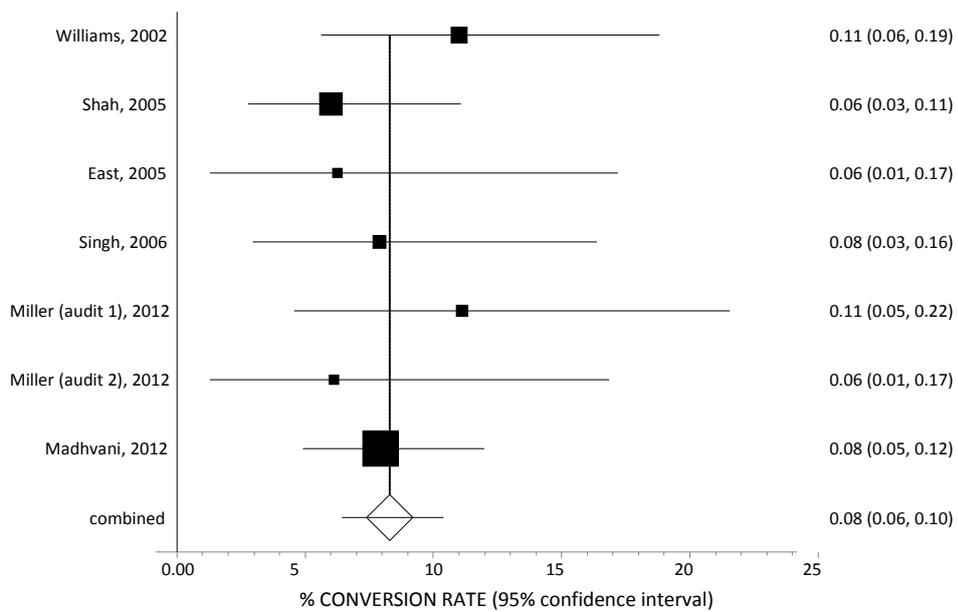
I^2 (inconsistency) = 92.8% (95% CI = 89.4% to 94.7%)

ENT UNITS CONVERSION RATE



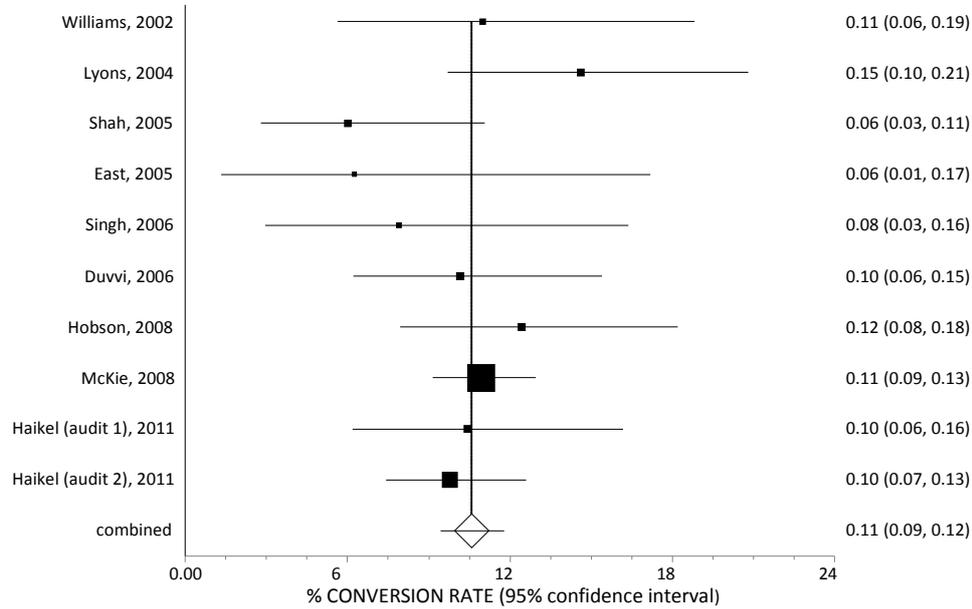
I^2 (inconsistency) = 83.2% (95% CI = 67.4% to 89.5%)

OMFS UNITS CONVERSION RATE



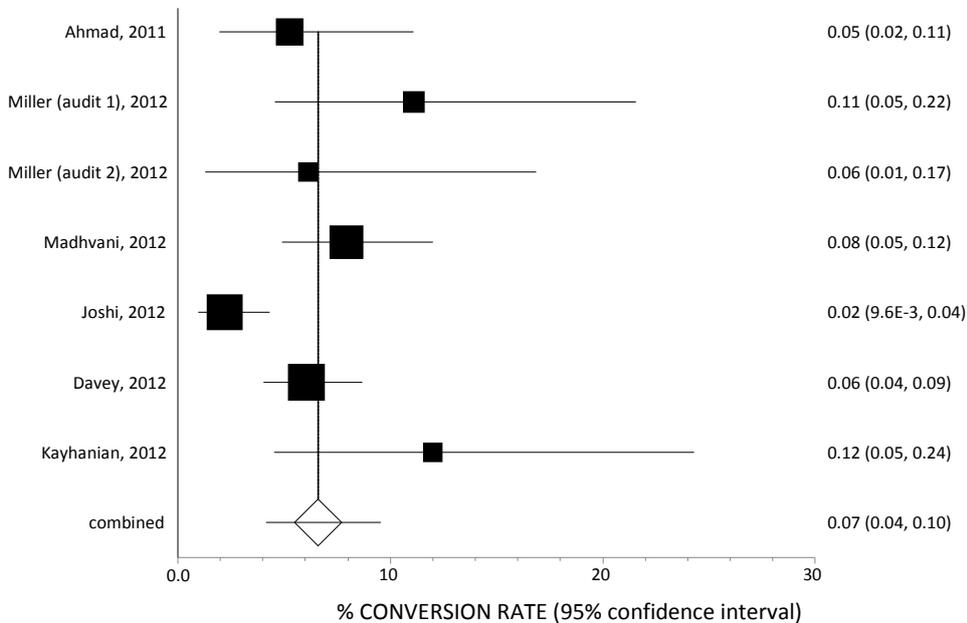
I^2 (inconsistency) = 0% (95% CI = 0% to 58.5%)

'EARLY' STUDIES CONVERSION RATE



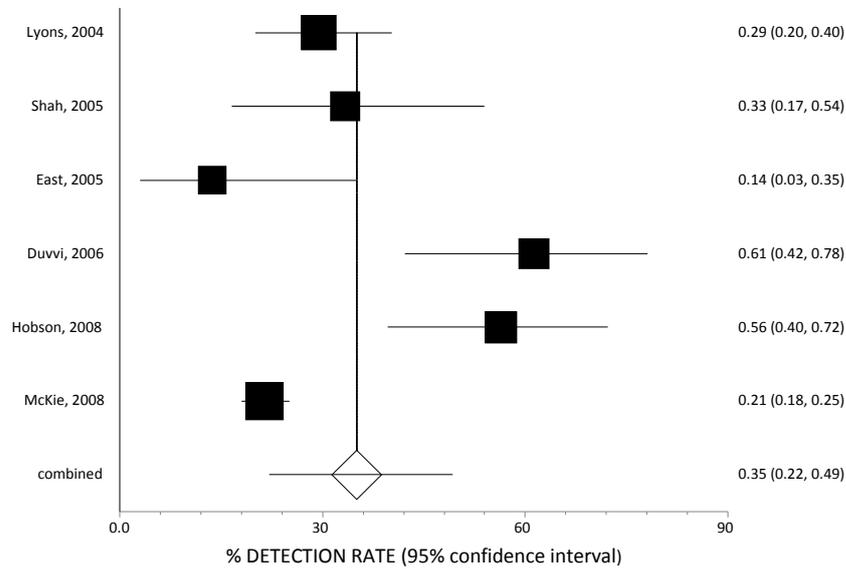
I^2 (inconsistency) = 0% (95% CI = 0% to 52.7%)

'LATE' STUDIES CONVERSION RATE



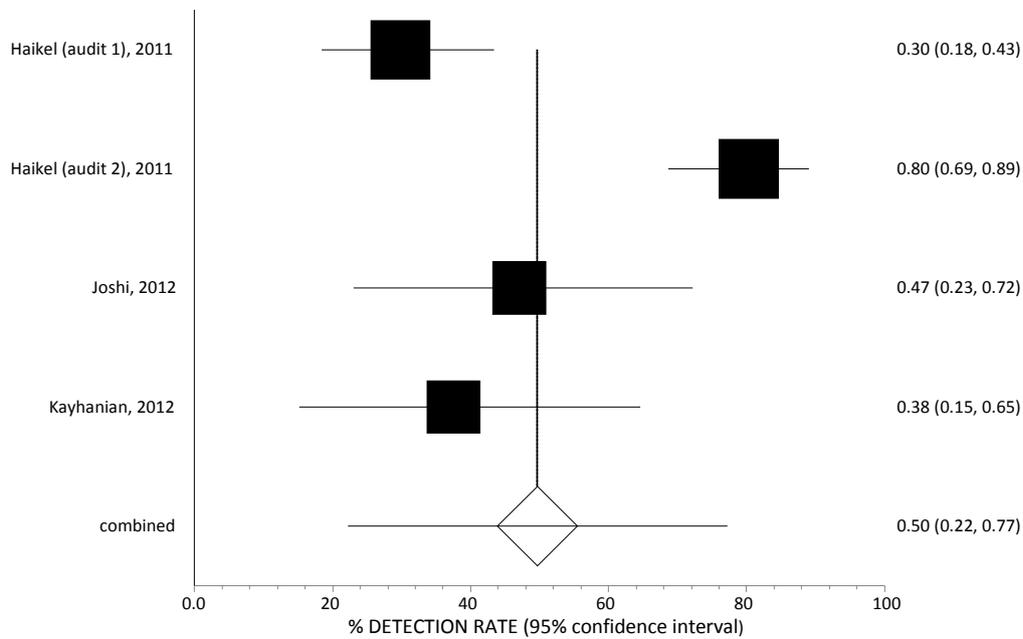
I^2 (inconsistency) = 69.6% (95% CI = 9.1% to 84.3%)

'EARLY' STUDIES DETECTION RATE



I^2 (inconsistency) = 69.6% (95% CI = 9.1% to 84.3%)

'LATE' STUDIES DETECTION RATE



I^2 (inconsistency) = 87.9% (95% CI = 74.7% to 92.7%)