Investigating the toxicity and safety of radiotherapy for pancreatic cancer

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Abstract

The current level of understanding of the relationship of gastrointestinal toxicity with irradiation of the stomach, duodenum, and small bowel hampers the potential of radiotherapy to contribute effectively to achieving disease control for patients diagnosed with pancreatic cancer. The work in this thesis aimed to further this understanding through compilation and examination of existing informative data, and robust analysis of this relationship within a large cohort of patients treated with radiotherapy to the pancreas, and within a new clinical trial of stereotactic radiotherapy (SBRT).

A systematic literature review was undertaken and publications were identified that found dose-volume parameters for the stomach (V_{20Gy}, $V_{50Gy,}$ D_{2cm^3}), duodenum (V_{25Gy}-V_{55Gy}) and small bowel (V_{40Gy}, $V_{50Gy,}$ D_{2cm^3}) to be predictive of toxicity in pancreatic cancer. Parameters were fitted for the Lyman-Kutcher-Burman normal tissue complication probability model for the duodenum, using published cohort dose-volume histograms and the associated incidence of toxicity. Results were consistent with previous analyses, showing a dependence on exposure to high dose and small volume effect.

Published small bowel dose-volume histogram data was incorporated into meta-analysis and showed that, for rectal cancer, a significant volume effect exists for all clinically relevant doses (5 Gy to 50 Gy). This was not seen in data regarding irradiation for gynaecological cancer, where a volume effect was only observed at higher doses (40 Gy and over). This difference is thought to be primarily due to the concomitant chemotherapy used in the treatment of these malignancies.

Analysis of the toxicity outcomes for patients treated in the phase-II trials ARCII and SCALOP identified stomach dose-volume parameters predictive of acute gastrointestinal toxicity on multivariable analysis, alongside patient sex and the concomitant chemotherapy regimen utilised. Use of a statistical technique novel to radiotherapy dose-volume analysis was explored (canonical correlation) but was not shown to be superior to existing techniques.

Pre-trial radiotherapy quality assurance for the SPARC clinical trial of pre-operative SBRT was undertaken and found evidence of over-generous clinician contouring in definition of the primary tumour target volume. This was shown to have implications for modelled risk of treatment toxicity, however contouring improved with education and feedback from peers.

In conclusion, intensification of pancreatic cancer radiotherapy is likely to be safe and acceptable for patients, provided that dose to the neighbouring organs of the upper gastrointestinal tract is managed. This may be achieved through accurate target definition and optimisation of the treatment process with control of patient motion and image-guided intensity-modulated radiotherapy or SBRT. Concomitant chemotherapy is shown to be an important modifier of the radiotherapy dose-volume-toxicity relationship.

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List of abbreviations

3D-CRT	3D-conformal radiotherapy
5FU	5-fluorouracil
BD	Bis die (twice daily); Bile duct
BED	Biologically effective dose
BMI	Body mass index
BRPC	Borderline resectable pancreatic cancer
CECT	Contrast-enhanced CT
Chemo	Chemotherapy
CI	Confidence interval
CRT	Chemoradiotherapy
CRUK	Cancer Research United Kingdom
CSM	University of Oxford Centre for Statistics in Medicine
CT	Computed tomography
CTAAC	Cancer Research UK Clinical Trials Award and Advisory Committee
CTC	National Cancer Institute Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
CTV_M	Clinical target volume for margin-directed boost
DI	Discordance index
DLT	Dose-limiting toxicity
D_{max}	Max dose
D_{mean}	Mean dose
D_x	Dose received by x volume of a structure
DVH	Dose-volume histogram
ECOG	Eastern Cooperative Oncology Group
EGFRi	Epithelial growth factor receptor inhibitor
EORTC	European Organisation for Research and Treatment of Cancer
EQD_2	Equivalent dose in 2-Gy fractions
ESPAC	European Study Group for Pancreatic Cancer
FDG	Fluorodeoxyglucose
FOLFIRINOX	Folinic acid-5-fluourouracil-irinotecan-oxaliplatin
GEMCAP	Gemcitabine-capecitabine
GERCOR	Groupe Coopérateur Multidisciplinaire en Oncologie
gEUD	Generalised equivalent uniform dose
GI	Gastrointestinal
GMI	Geographical miss index
GTV	Gross tumour volume
HCC	Hepatocellular carcinoma
HPB	Hepato-pancreato-biliary
HR	Hazard ratio
IMRT	Intensity-modulated radiation therapy
IPD	Individual patient data
LAPC	Locally advanced pancreatic cancer
LKB	Lyman-Kutcher-Burman
m	Parameter reflecting gradient of response curve at TD_{50} in LKB model
MDACC	MD Anderson Cancer Centre
MDT	Multi-disciplinary team
MRC	Medical Research Council

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
n	Parameter reflecting volume effect in LKB normal-tissue endpoint risk model
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NTCP	Normal tissue complication probability
OAR	Organs at risk
OCTO	Oncology Clinical Trials Office
OCTRU	Oxford Clinical Trials Research Unit
OIRO	CRUK/MRC Oxford Institute for Radiation Oncology
ORR	Objective response rate
PA	Para-aortic
PET	Positron emission tomography
PS	Performance status
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PTV	Planning target volume
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
QDS	Quater die sumendum (four times daily)
REC	Research Ethics Committee
RIOC	Radiotherapy and Imaging Trials Oversight Committee
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RTQA	Radiation therapy quality assurance
RTTQA	Radiation Therapy Trials Quality Assurance
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiation therapy
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SPARC	A phase- trial of pre-operative stereotactic radiotherapy for pancreatic cancer
SPC	Summary of Product Characteristics
SSAT	Society for Surgery of the Alimentary Tract
SSO	Society of Surgical Oncology
$TD_{50(x)}$	Tolerance dose for a 50% risk of outcome for irradiation of structure x
TPS	Treatment planning system
UGI	Upper gastrointestinal
UKCRN	UK Clinical Research Network
V_{xGy}	Volume of structure receiving x Gy

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Publications

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Holyoake D L, Aznar M, Mukherjee S, Partridge M, Hawkins M A. Modelling duodenum radiotherapy toxicity using cohort dose-volume-histogram data. *Radiother Oncol.* 2017;3:431–437.

Holyoake D L, Robinson M, Grose D, et al. Conformity analysis to demonstrate reproducibility of target volumes for Margin-Intense Stereotactic Radiotherapy for borderline-resectable pancreatic cancer. *Radiother Oncol.* 2016;121:86-91.

Holyoake D L, Ward E, Grose D, et al. A phase-I trial of pre-operative, margin intensive, stereotactic body radiation therapy for pancreatic cancer: the 'SPARC' trial protocol. *BMC Cancer.* 2016;16:728.

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These presentations contain material produced as part of the preparation of this thesis:

Meta-analysis of toxicity and small bowel radiotherapy dose-volume: *omnibus consequentia*
Poster at ESTRO 37, Barcelona April 2018

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Trial-in-progress poster, ASCO GI January 2018
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Analysis of on-trial quality assurance for the SPARC clinical trial using novel peer-review methodology
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Stomach Dose-Volume Parameters and Clinical Factors Predict Acute Toxicity in Pancreatic Cancer Chemoradiotherapy
Poster at ASTRO Annual Meeting, San Diego September 2017
Holyoake DL, Partridge M, Hurt C, Mukherjee S, Hawkins MA. International Journal of Radiation Oncology Biology Physics. 2017;99:E155-E.

Dosimetric parameters predict toxicity in chemoradiotherapy for pancreatic cancer
E-poster at ESTRO 35, Turin April 2016
Holyoake D, Wilson J, Partridge M, Brunner T, Mukherjee S, Hawkins M. Radiother Oncol. 2016;119:S597-S8.

Conformity analysis to demonstrate reproducibility of method for definition of target volumes for Margin-Intense Stereotactic Radiotherapy for Borderline-Resectable Pancreatic Cancer
Oral Presentation at BIR SABR Event, Belfast November 2015
Poster at ESTRO 35 (Turin, April 2016) and NCRI (Liverpool, November 2016)
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1. Chapter One. Introduction – Pancreatic cancer, radiotherapy and toxicity

1.1. Pancreatic cancer

Pancreatic cancer comprises 3% of cancer diagnoses per year in the United Kingdom, but is responsible for 5% of cancer deaths, making it the fourth commonest cause of cancer death in this country [1]. The individual prognosis is particularly bleak, and the 5-year survival expectation of 3% is the worst of all common cancers. Furthermore, despite improvements in outcomes for many common cancers, the survival expectation of pancreatic cancer has barely changed in the last four decades [1]. While the majority of mortality is due to metastatic disease, therapies aimed at improving local control remain important, as 50% of patients present with localised disease. Of these, 30% will be locally advanced tumours (unresectable without distant metastases) and up to 20% will be surgically resectable [1]. After radical resection only, around one third of patients will experience recurrent disease locally [2].

1.2. Radiotherapy in the treatment of pancreatic cancer

The role of radiotherapy in the radical treatment of pancreatic cancer is not well established in the UK, and it is the subject of continuing debate due to conflicting trial results regarding the potential benefits [3]. Improved survival for patients treated with chemoradiotherapy, compared with those treated with chemotherapy alone, has been shown by some robust clinical investigations such as that of Huguet et al. [4]. This retrospective analysis of 181 patients with locally advanced pancreatic cancer found median progression-free survival with chemoradiotherapy was 10.8 months compared with 7.4 months for chemotherapy alone (p = 0.005), and median overall survival was 15.0 versus 11.7 months, (p = 0.0009). Loehrer et al. also showed improved survival for the addition of radiotherapy to gemcitabine

chemotherapy for patients with locally advanced pancreatic cancer (11.1 compared with 9.2 months, $p = 0.017$) in a prospective randomised study of 74 patients, but this clinical trial did not reach predetermined accrual targets [5]. Contrastingly, Chauffert et al. randomised 119 locally advanced pancreatic cancer patients to chemoradiotherapy or chemotherapy alone and found that patients treated with chemoradiotherapy had significantly shorter overall survival (8.6 versus 13.0 months, $p = 0.03$) [6]. Even meta-analyses of clinical trials have differed in their overall conclusions as to the existence of a significant survival benefit for radiotherapy [7, 8]. A significant proportion of patients who present with localised tumours quickly go on to develop metastatic disease. Therefore, there is a rationale for using radiotherapy for loco-regional consolidation only for patients who do not progress on primary systemic therapy [9]. The large phase-III randomised trial LAP-07 has now concluded and suggests that the benefits of radiotherapy in this approach may be limited to an increased rate of local control [10] without any improvement in overall survival [11, 12].

A key reason for the limited effectiveness of radiotherapy for pancreas cancer is likely to be that the dose that has been delivered is insufficient, and poor rates of objective response (in the region of 5%–25%) are seen when treating with prescribed doses of less than 60 Gy (Table 1-1). A recent study using published clinical outcomes of chemoradiotherapy in locally advanced pancreatic cancer has suggested that there is a strong dose-response relationship, in which dose escalation leads to improved rates of objective response (pathological complete response or partial response by RECIST) [13]. The model fitted to the data used in this study suggests that treatment with a biologically effective dose of around 80 Gy would be required to achieve a 50% response rate. Non-randomised data has also shown a significant improvement in outcomes for patients treated with higher doses, where the threshold above which an advantage was shown was 61 Gy in one study [14] and 70 Gy in another [15]. However, the dose that can be delivered to pancreatic tumours has historically been

constrained by the toxicity that results from attempts at dose escalation with conventional radiotherapy techniques.

Publication	N	Dose [Gy]	Dose/fraction [Gy]	ORR [%]	Chemotherapy
Ishii 1997	20	50.4	1.8	10	5-FU
Ceha 2000	44	72	2.0	27	-
Andre 2000	32	45	1.8	16	5-FU + Cis
Boz 2001	42	59.4	1.8	23	5-FU
Wolff 2001	42	30	3.0	24	Gemcitabine
Safran 2001	44	50.4	1.8	26	Paclitaxel
Epelbaum 2002	20	50.4	1.8	20	Gemcitabine
Ashmalla 2003	20	63.8	1.1	30	Paclitaxel
Okusaka 2004	42	50.4	1.8	21	Gemcitabine
Morganti 2004	15	39.6	1.8	7	5-FU
	15	50.4	1.8	13	5-FU
	20	59.4	1.8	5	5-FU
Cohen 2005	55	59.4	1.8	9	MMC + 5-FU
Murphy 2007	74	36	2.4	15	Gemcitabine
Saif 2007	20	50.4	1.8	20	Capecitabine
Hong 2008	41	45	1.8	24	Gem + cis
Crane 2009	82	50.4	1.8	26	Bev + cape
Sudo 2011	34	50.4	1.8	12	S-1

Table 1-1. Tumour response rates achieved with chemoradiotherapy for LAPC. N = number of patients, ORR = objective response rate. Adapted from Moraru et al. [13].

1.3. Radiotherapy toxicity

Radiotherapy is part of the treatment of around 40% of patients who are cured of cancer and most radiotherapy is given with curative intent [16]. Radiotherapy is secondary only to surgery in this respect, but has the advantage of being non-invasive and organ-sparing in most cases, and the modelled demand for this increasingly technical cancer treatment outstrips supply [17]. Unfortunately, almost all effective medical interventions cause some degree of side effects, and this is particularly true of anti-cancer treatments including radiotherapy.

Side effects which emerge during or shortly after therapy are called acute toxicity, while those with an onset after ninety days are defined as late effects, which can continue to worsen (or may only emerge) many years after treatment was delivered (Figure 1-1). Acute effects tend

to arise in tissues with high rates of cell turnover, such as the skin, mucosa and bone marrow, and they usually resolve once the tissue repopulates. Late effects can affect all tissues and are usually irreversible and progressive [18].

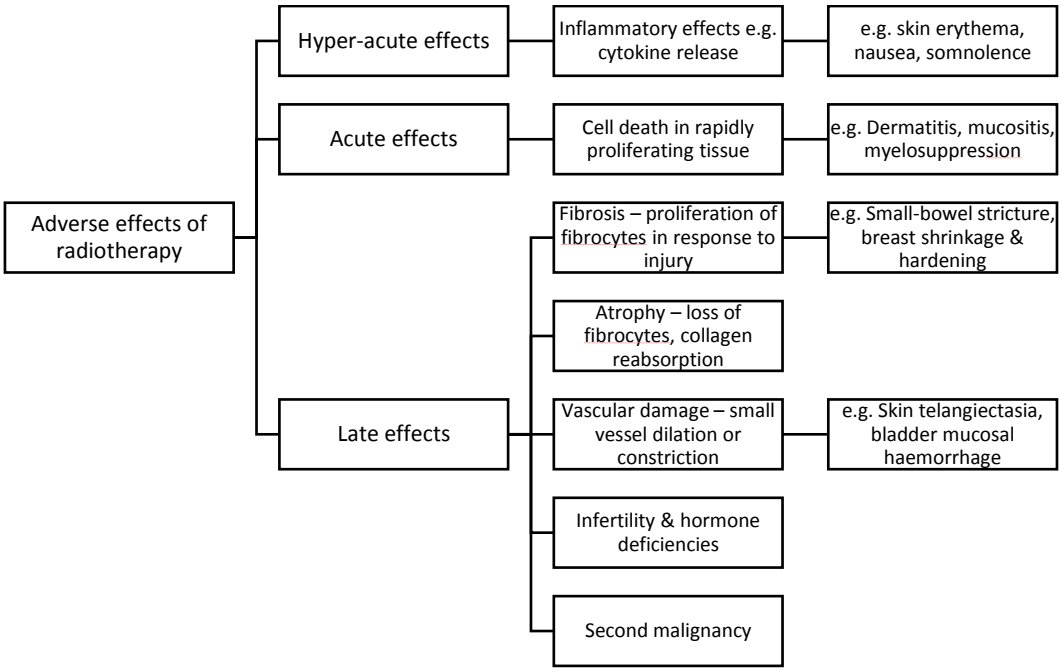


Figure 1-1. The toxicity of radiotherapy. Adapted from Barnett et al. [19].

The aim in radiotherapy treatment is to achieve 'local tumour control', long-term prevention of survival of cancer cells within the treated field. The likelihood of achieving this at a given prescribed dose is referred to as the 'tumour control probability' (TCP). A dose-response relationship exists for most tumour types, in which dose escalation will lead to better probability of tumour control. Unfortunately the same dose-response relationship exists for normal tissues, where the risk and severity of side effects also increases with dose. Normal tissues tend to exhibit a sigmoid dose-response curve featuring a threshold below which no apparent toxicity occurs (Figure 1-2) [20]. At these doses, all damage is repaired, or all killed cells are replaced by repopulation such that no tissue dysfunction results. However, the curve for many critical normal tissues features a steep section for the doses relevant in clinical

cancer therapy, and as a result, attempts to deliver increased dose to the tumour often therefore increase toxicity [21, 22]. The risk of radiotherapy side effects is the main factor determining the dose prescribed for most radical cancer treatments. While a sufficient dose can still be safely delivered to achieve high rates of local control for some malignancies, such as squamous-type cancers in the head and neck, anus and cervix cancers, the TCP for many cancers is disappointingly low.

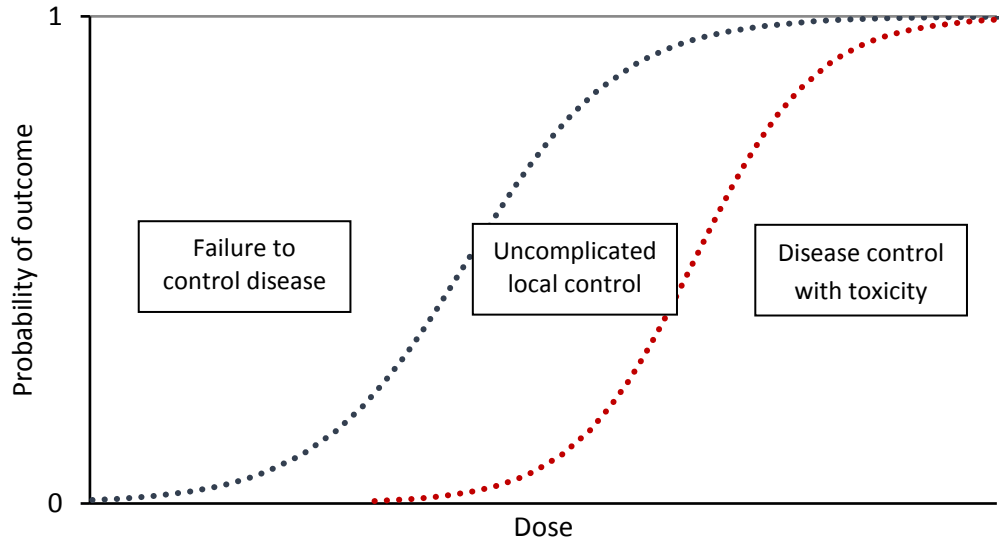


Figure 1-2. Dose–response curves for radiotherapy outcomes showing the typical sigmoidal curve. As radiation dose increases, the probability of tumour control (blue curve) increases. However, when normal tissue is included in the radiation field, the probability of normal tissue damage also increases (red curve). The difference between the two probabilities, at a given dose, is termed the therapeutic ratio. The text in the boxes describes the outcome expected for most patients if treated at that dose region. Adapted from Barnett et al. [19].

The total therapeutic dose that can be delivered is therefore limited by the tolerance of the normal tissues that will also be irradiated. Treatment can only hope to be successful if a satisfactory probability of tumour control can be achieved at a dose with an acceptable rate of side effects [20] (Figure 1-2). The ideal scenario would be to achieve 'uncomplicated tumour control', where the tumour does not recur and the patient is left with no toxicity whatsoever. In reality, there is usually an acceptance by the patient and the treating clinician

of a certain degree of risk of a potential side effect (such as a 5% risk at 5 years after treatment) in return for a given chance of disease control [23].

1.3.1. Volume effects in radiotherapy toxicity

The risk and severity of toxicity increases not only with dose but also with increased irradiated volume of normal tissue, as the amount of damaged tissue increases and the amount of undamaged tissue decreases. The tolerated dose is, consequently, dependent on the volume of the organ receiving that dose, and the tolerated volume is dependent on the dose (Figure 1-3). The relationship between dose-volume and toxicity is not straightforward, and also varies between different types of tissue and for different types of toxicity outcomes [24]. Some toxicity is dependent on gross (ie macroscopic) damage, such as ulceration or bleeding, while other symptoms of toxicity can be due to abnormal function and microscopic pathological changes without evidence of gross abnormalities. For toxicity outcomes dependent on the development of anatomical/structural damage to an organ, such as bleeding or ulceration, there tends to be little effect of volume on the risk of toxicity, whilst pronounced volume effects are usually seen for functional effects.

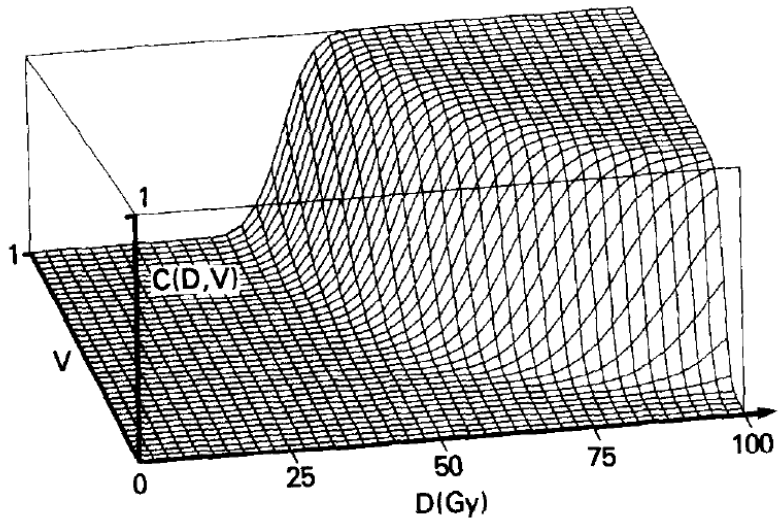


Figure 1-3. Plot of 'complication response function' C(D,V) ie risk of normal tissue complication according to dose and proportional volume of organ irradiated, in this case for the heart.
Taken from Lyman et al. [25].

For late-onset normal-tissue toxicity outcomes, the magnitude of the effect of volume on the risk of tissue dysfunction depends on the structural organisation of the organ into 'functional subunits' [24]. Some tissues are organised in a 'serial' fashion where the function of the organ requires the whole to be free of significant damage, and where toxicity results even if just a small portion of the organ is irradiated beyond the tolerated threshold. Examples include the spinal cord (when considered in terms of its length along the spinal canal rather than in cross-section), where even a small segment of irreparable radiation damage will result in transverse myelitis, preventing the upwards or downwards transmission of nerve signals, and resulting in impaired function for tissue beyond the lesion. For these tissues, the volume effect is small and large volumes can be irradiated provided the dose is kept below that threshold at which damage can subsequently be repaired. However, if the tolerance is exceeded there is a relatively small impact of the volume of this lesion on the risk of organ dysfunction.

This behaviour is in contrast with tissues considered to be organised in a 'parallel' fashion, with a multitude of effectively independent and replicated functional subunits. Examples include the nephrons of the kidney or the lobules of the liver, in which blood is filtered of circulating toxins or absorbed nutrients, and the acini of the lung, where gas exchange takes place [26]. These tissues usually have a large functional reserve and will tolerate loss of a small portion of their whole without suffering any significant impairment of resting physiological function. Thus, small volumes of high doses can be tolerated even if the irradiated proportion of tissue is rendered entirely non-functional. However, the volume effect is important in these tissues, where large volumes of low doses are tolerated poorly and can lead to a major reduction in overall organ function with a subsequent high risk of toxicity for the patient.

To further complicate this scenario, most organs are not homogenous in architecture, and a simple partial volume measurement is insufficient when the critical radiosensitive structures are not evenly distributed [27]. Furthermore, in the same way that cancer cells within a tumour will demonstrate heterogeneity in their radiosensitivity, there may be a degree of heterogeneity in the radiosensitivity of functional subunits within a patient, which will appear to reduce the gradient of the dose-response curve for the patient as a whole [28].

The importance of the volume effect and intrinsic radiosensitivity of a tissue can be incorporated into mathematical models such as the Lyman-Kutcher-Burman (LKB) model, to predict the risk of toxicity (Normal Tissue Complication Probability, NTCP) associated with exposure to any given dose or partial volume [29]. The LKB model utilises three parameters to describe the properties of the normal tissue in response to irradiation: TD_{50}, the equivalent homogenous dose which engenders a 50% risk of the normal tissue complication occurring, reflecting radiosensitivity; *m*, which describes the steepness of the dose-response curve at the TD_{50}; and *n*, a weighting for volume [30]. This final parameter is related to the descriptions of tissue FSU architecture described above, where tissues with 'serial' architecture have low values for *n,* and tissues with parallel architecture have higher values for *n*. To use the LKB model, the heterogeneous irradiation described by the DVH is first reduced to a single parameter of equivalent fractional irradiation (effective volume, V_{eff}) that would result in the same NTCP. Another related concept is that of the 'generalised Equivalent Uniform Dose' (gEUD), a dose at which uniform irradiation of the whole organ would result in the same NTCP as the real heterogeneous dose distribution [31], which is calculated using a similar volume parameter to that used in the LKB model (*a*, where $a = 1/n$).

1.3.2. Clinical research into normal effects of radiotherapy

Much of our current understanding of clinical normal tissue toxicity and organ tolerance comes from data such as that compiled by Emami et al. [32] and the subsequent QUANTEC project [33]. In comparison with the development of new systemic agents, few prospective radiotherapy dose escalation trials take place, partly due to the difficulty of monitoring for the development of late toxicity, when these symptoms can continue to progressively worsen for decades after the original exposure [34]. Randomised trials in which patients are treated with prospectively altered exposure of normal tissue to differing dose-volume profiles would be neither ethical nor practical, and as such, the evidence base is observational, using clinically-delivered treatment plans. This has the effect of limiting the variation seen in the parameters being studied and therefore increases the likelihood of analyses failing to demonstrate a relationship between dose-volume and toxicity when one truly exists.

The complexity of normal tissue reactions and their dependence on multiple variables in radiotherapy delivery, such as dose, dose per fraction, treatment scheduling and overall treatment time, means that much specific detail must be collected. Ideally, this should be done prospectively if we are to further our understanding of these relationships [35]. The clinical study of radiotherapy effects on normal tissues began almost as soon as the phenomenon was discovered, when skin erythema was even used as a measure of dose or exposure [36]. The field has undergone considerable evolution to refine the use of comprehensive multi-point toxicity grading systems, such as the National Cancer Institute CTCAE (NCI Common Terminology Criteria for Adverse Events) [37] and RTOG/EORTC (Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer) scales [38]. Difficulty can arise in attempting to collate results across different toxicity scales or tools, but some efforts have been made to overcome this challenge such as the development of the Standardised Total Average Toxicity score [39]. A new era is also seeing

the emerging use of patient-reported outcomes in the assessment of radiotherapy toxicity [40, 41].

A further complication is that the symptoms of radiotherapy toxicity can often mimic disease progression and vice-versa, even on direct visualisation, or imaging (as is seen with pseudo-progression after treatment for glioblastoma [42]). Disease progression or patient death may censor the true risk of late toxicity [19]. Therefore, detailed clinical disease outcomes are required to interpret data regarding apparent treatment toxicity. Late side effects may be considered less of a concern for patients with a very poor prognosis, for whom acute toxicity and detriment to quality of life will likely be prioritised. As cancer survival rates improve, however, late effects are of increasing importance [42].

1.3.3. Mechanisms of radiation effects on normal tissues

Radiotherapy principally causes harm to living cells, whether healthy or malignant, through damage to DNA. Double-strand breaks, the most destructive lesions, can result in chromosomal breakage or aberrant recombination leading to mitotic collapse and cell death in the first few cell divisions after irradiation [43, 44]. Many acute radiotherapy toxicity effects occur primarily due to the early depletion by death of relatively radiosensitive functional parenchymal cells, an explanation known as the 'target-cell hypothesis' [45]. In a high turnover tissue such as in the haematopoietic system and in the epithelial surfaces of the skin and gastrointestinal tract, these are frequently dividing and being replaced. The stem-cell compartment of these tissues has greater capacity for DNA repair, is less radiosensitive, and is often able to respond with compensatory increased proliferation (also called 'accelerated repopulation'), such that these acute side effects may begin to improve – or even resolve – as a course of fractionated radiotherapy continues [46, 47].

Some radiation toxicity can begin very rapidly, such as skin erythema, fatigue, nausea, and somnolence. The onset of these is often before significant cell death is likely to have occurred, and therefore these must be explained by other mechanisms. It is thought that DNA damage triggers production of cytokines and induction of an inflammatory process, somewhat akin to wound healing, but which itself can contribute to organ or tissue dysfunction [48, 49].

Late radiotherapy effects were historically thought to develop slowly due to two factors: firstly, the infrequent division – and, as such, infrequent death – of the parenchymal cells in the tissues in which they are seen, and the time taken for sufficient cell loss to result in tissue dysfunction; secondly, due to the slow development of vascular damage resulting from death of vascular endothelial cells [45]. However, it is now evident that late effects also develop slowly through a complex, active, ongoing process. Mediators such as transforming growth factor beta drive a chronic inflammatory reaction that promotes proliferation and differentiation of fibroblasts and results in excessive collagen deposition [50]. Direct vascular damage and activation of the coagulation cascade contributes to tissue ischaemic injury [51], while in a cycle of dwindling positive feedback, tissue atrophy contributes to the regression of its own blood supply [52]. *Consequential* effects, meanwhile, are defined as a particular subtype of late toxicity that develops via a separate mechanism, that is, as a direct result of severe, acute damage [53, 54].

Unfortunately, while animal models have contributed much to our current understanding of these processes [55], the accuracy in their translation to the clinical syndromes experienced by our patients may be limited. The complexity of the underlying mechanisms contributing to the outward manifestation of radiotherapy toxicity is demonstrated by two clinical examples, emphasising the active contribution of the host in the response to the damage that has been delivered. Firstly, there is a lack of correlation in many patients between the severity of acute

and late side effects [56, 57] and, secondly, there is an apparent degree of independence of different types of late effect in the same type of tissue after the same treatment is given to two areas of the body in the same patient [58]. A proposed revision of the classification of normal-tissue reactions has suggested division of effects into *cytocidal* – those due to direct cell killing; *functional* – due to non-lethal changes in cell behaviour through altered signalling, protein transcription or function; and *secondary* – describing those effects that occur in response to the original injury, such as inflammation and fibrosis [59].

1.3.4. Patient factors influencing radiotherapy toxicity

It has long been observed that the severity of toxicity differs between patients even after identical treatments are given [20]. The range of variation in radiosensitivity among individuals has an approximately normal distribution [60], and it is the incidence of reactions suffered by the patients with increased sensitivity that limits the dose prescribed for all [61]. As described earlier in the setting of functional subunits of normal tissue, variation in intrinsic radiosensitivity between individuals has the effect of flattening the apparent dose-response relationship for a group of patients, which will be made up of multiple steeper dose-response curves (Figure 1-4).

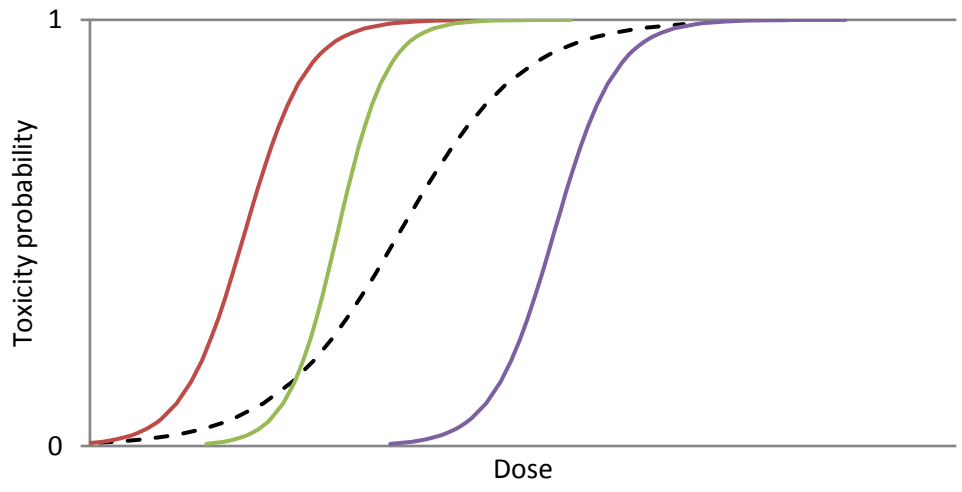


Figure 1-4. Illustration of hypothetical dose-response curves for three individual patients from a cohort, with an average dose-response curve showing apparently shallower relationship for the cohort overall.

There is thought to be a significant genetic contribution to variation in susceptibility, beyond the rare genetic conditions that cause extreme radiation sensitivity such as ataxia-telangiectasia. Results of the genome-wide search for the mechanisms of this may yet lead to further understanding of the nature of radiotherapy toxicity and the variation between individuals [62].

For patients with impaired baseline function, the reserve of an organ or tissue to tolerate further insult is reduced and the risk of toxicity is increased [42]. This phenomenon appears to be particularly true in the presence of systemic vascular disorders such as diabetes [63] and hypertension [64], and in patients with systemic connective tissue disorders.

Perhaps unsurprisingly, radiotherapy toxicity tends to be exacerbated in both frequency and severity by the concurrent administration of toxins such as alcohol, tobacco smoke [65] and cytotoxic chemotherapy, the specific influence of which will be examined in more detail in Chapters Two and Three of this thesis.

1.3.5. Radiation effects on the normal tissues of the gastrointestinal tract

The gastrointestinal (GI) tract essentially consists of a continuous tube from an entrance at the mouth to an exit at the anus, but each section of this tube has a different and specific function. As a result, the clinical complications that result from exposure of each section to ionising radiation also differ. The risk of gastrointestinal injury remains the most important dose-limiting factor in radiotherapy for abdominal tumours. The development of acute toxicity may lead to treatment interruption or cessation with a subsequent compromise of chances of cure [55]. Late intestinal radiation toxicity leads to a significant burden of long-term morbidity [66] with an impaired quality of life.

Acute toxicity consisting of mucosal inflammation and ulceration in the oral cavity and pharynx affects almost all patients receiving radiotherapy for head and neck cancer, and similar is seen for the oesophagus as a result of treatment of thoracic malignancy such as non-small cell lung cancer. This causes pain, and difficulty with eating, which can often be severe. Medical intervention – even hospital admission – may be required to maintain nutritional intake and prevent harmful excessive weight-loss [67, 68].

The specific radiation effects on the stomach, duodenum, and small bowel will be discussed in detail in Chapter Two. The effect of irradiation on the rectum and/or anus during radiotherapy for pelvic tumours, such as prostate cancer, is also due to mucosal inflammation but with a different range of clinical manifestations. Patients commonly suffer from urgency and frequency of bowel opening, tenesmus, pain, incontinence, mucus discharge and/or rectal bleeding. These symptoms can be mild and self-limiting, or they can be severe or long-standing such that the patient requires medical intervention [69]. The symptoms of radiotherapy toxicity due to treatment of rectal cancer can overlap with the effects of surgery or the tumour. The specific effect of radiotherapy itself can be observed, for example, in the Swedish rectal cancer study of preoperative short-course radiotherapy, where bowel frequency, urgency, incontinence and impaired social life were all significantly higher in patients receiving radiotherapy than in patients who had surgery alone [70]. In a trial of postoperative treatment, patients randomised to receive radiotherapy also suffered increased incidence of bowel frequency (80% vs 23%), loose/liquid stool (60% vs 23%) and faecal incontinence (60% vs 8%), sometimes requiring use of a pad (47% vs 0%) [71].

These specific symptoms of bowel dysfunction can have wider implications for the patient, such as disturbance of sleep, disruption of sexual function, and the inability to work or travel.

The potential risk of social withdrawal, anxiety and depression means that of all late effects, bowel symptoms have possibly the greatest effect on quality of life [72]. After pelvic radiotherapy, up to 90% of patients will have some degree of permanent change in bowel habit, of whom 50% will suffer a resulting reduction in quality of life, while up to 20% will have experienced serious complications at subsequent 20-year follow-up [73].

The study of GI toxicity is made more difficult by the wide range of symptoms that patients can suffer, and the imperfect methods that are available with which to assess and record symptoms [73]. Additionally, it is thought that the unskilled application of insensitive tools is likely to systematically underestimate the true incidence of side effects [35]. Patient-reported outcome measures may be adapted for use in recording radiotherapy toxicity [74, 75] and can be shown to be more sensitive than existing methods [76], although even these tools may produce inaccurate results due to patient embarrassment and fear of stigmatisation [73].

While the risk of bowel toxicity is affected primarily by dose, fractionation, dose-volume and concomitant therapy, great variation occurs between patients due to the complex interaction of patient and treatment factors [73]. The mechanisms of radiation toxicity in the GI tract are complex [55] and are not simply due to cell death, though this remains important [77]. Symptoms result from interacting effects on multiple cell and tissue types including the vasculature [78], the enteric nervous system [79] and even gut flora [80]. Symptoms may correlate imprecisely with structural or pathological changes [47] and this (mostly unexplained) disconnect raises concern that animal models, while useful [81], may not accurately represent the radiotherapy reactions of the human GI tract [66].

1.4. Toxicity resulting from radiotherapy for the treatment of pancreatic cancer

As described in the opening to this introductory chapter, the radiotherapy dose that can be prescribed when treating pancreatic cancer has been constrained by the limited radiotherapy tolerance of the upper GI organs that will unavoidably be irradiated. The duodenum is particularly at risk due to its universal proximity to the pancreas, as shown in Figure 1-5, but symptoms arising from damage to the stomach and small bowel are also common. When attempts have been made to increase the delivered dose, significant toxicity has resulted.

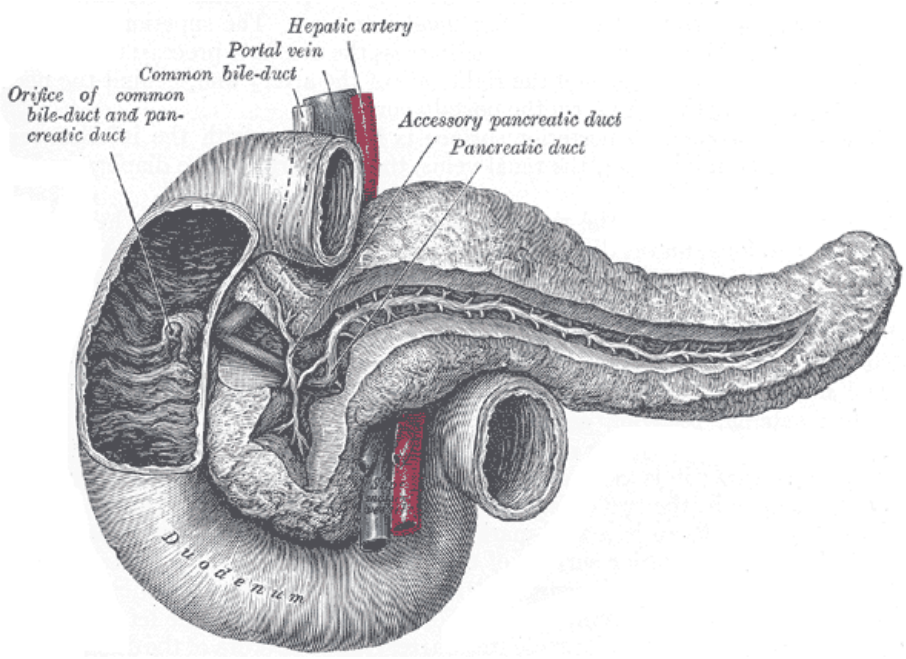


Figure 1-5. The duodenum and the pancreas. From [82].

A number of publications have described cohorts of patients with pancreatic cancer treated with radiotherapy, such that the typical patterns of toxicity that result are well characterised. Unfortunately, these analyses have mostly been retrospective analyses of patients from a single institution.

For example, Nakamura et al. examined the data regarding 40 patients with locally advanced pancreatic cancer treated with concurrent chemoradiotherapy with low-dose gemcitabine (250 mg/m^2 weekly) [83]. Their patients were treated with 54 Gy in thirty fractions over six weeks to a planning volume that encompassed the primary tumour and the elective nodal regions ('retropancreatic space between the root of the celiac trunk and superior mesenteric artery'). Grade ≥ 2 acute GI toxicity (anorexia, nausea, vomiting, and mucositis) was seen in 33% of patients, with Grade ≥ 3 upper GI bleeding seen in 20% and which mostly occurred within 2–7 months after radiotherapy. Median follow-up was 16 months and no further upper GI bleeding was seen after 12.1 months. Their analysis to examine the dosimetric parameters of the luminal organs at risk of the proximal GI tract that were postulated to be related to GI toxicity is discussed in more detail in Chapter Two of this thesis.

The largest published patient series that I was able to identify comprises 215 patients with locally advanced pancreatic cancer analysed by Habermehl and colleagues [84]. For these patients the median prescribed dose was 52 Gy in 1.8 Gy fractions, delivered using 3D conformal planning, with concomitant weekly gemcitabine at 300 mg/m^2. Haematological toxicity led to gemcitabine omission or reduction in 63% of patients but no radiation toxicity of Grade ≥ 3 was observed, and one patient who suffered duodenal ulceration was found to have tumour infiltration which was subsequently resected.

Studies in which radiotherapy dose has been prospectively increased would offer a useful insight into the dose-response effect on toxicity; unfortunately, these investigations are uncommon. McGinn at al. treated patients with locally advanced pancreatic cancer with concurrent chemoradiotherapy with 'full-dose' gemcitabine (1000mg/m^2) [85]. The total prescribed radiotherapy dose was increased by raising the dose per fraction while keeping the number of fractions and course duration constant – at fifteen daily fractions over three weeks

– from a starting point of 24 Gy in 1.6 Gy fractions. The target volume was the gross tumour plus a 1 cm margin and conformal fields were used. Acute dose-limiting toxicity was encountered at the final planned dose level, 42 Gy in 2.8 Gy fractions, consisting of Grade 4 vomiting for one patient and gastro-duodenal ulceration for another. Two further patients went on to suffer late GI toxicity requiring surgical intervention, and the investigators therefore selected a lower dose (36 Gy in 2.4 Gy fractions) to evaluate further in a subsequent multi-institution phase II study [86]. Twenty patients with resectable tumours were treated, where it proved very well tolerated and only one patient suffered Grade 3 GI toxicity. This comparably low rate of toxicity has been ascribed to the combination of the smaller resectable tumours and the omission of elective nodal irradiation resulting in smaller irradiated volumes.

The outcomes data for these patients were incorporated into a cohort of seventy-four patients with pancreatic cancer treated with this, and similar regimens, analysed by Murphy et al., among whom moderately severe GI toxicity (Grade 3) occurred in 22% of patients [87]. Half of these events were upper GI bleeding, while nausea, vomiting and diarrhoea were also common, and isolated events included choledochoduodenal fistula, small bowel obstruction and colonic stricture – each requiring surgery. Huang et al. later reported the retrospective analysis of toxicity outcomes for a cohort of forty-six patients with locally advanced pancreatic cancer treated with radiotherapy and concurrent full-dose gemcitabine, including patients treated within the aforementioned early-phase clinical trials. Erlotinib, an EGFR tyrosine kinase inhibitor, had also been given to 39% of the patients for whom the radiotherapy dose schedule was 2 Gy per fraction, with a total dose range of 30 – 38 Gy. Most patients were treated with 3D conformal radiotherapy, and intensity-modulated radiation therapy (IMRT) was used in only six patients when dose constraints could not otherwise be met. After a median follow-up of 36 months, the observed rate of severe (CTCAE v.4: Grade ≥ 3) toxicity was high (22% acute, 17% late, overall 37%), and higher among the patients receiving erlotinib

(32% vs 44%, p = 0.02). The toxicity events included nausea, vomiting or diarrhoea (10 patients), duodenal ulcer (3), upper GI bleeding (4) and small bowel obstruction [88].

Kelly et al. retrospectively examined the treatment records and radiotherapy plans for 106 patients with locally advanced pancreatic cancer treated with concomitant chemoradiotherapy, where the prescribed dose for most patients (74%) was 50.4 Gy in 28 fractions but some received dose escalation up to a maximum dose of 70.4 Gy in 1.8 Gy fractions. Dose escalation was delivered using IMRT and a duodenum dose-volume constraint of $V_{60Gy} < 5$ cm^3 was applied, achieved in 89% of patients. Concomitant chemotherapy comprised 5-FU/capecitabine for 82%, with the addition of erlotinib or cetuximab (an anti-EGFR monoclonal antibody) for 24% of these, while the other 18% received gemcitabine. The rate of duodenal toxicity was 23%: four patients suffered multiple events, in which case the highest-grade event was recorded, with the nature of all toxicity events confirmed by endoscopy. In addition, four patients had asymptomatic Grade 1 duodenal changes detected on endoscopy. All Grade ≥ 2 events were duodenal bleeding without perforation, which was treated using argon laser coagulation and no surgical interventions were required. The actuarial rate of Grade ≥ 2 duodenal toxicity was 14% at one year and 19% at two years, the median time to toxicity being 5.4 months. One patient suffered a Grade 4 duodenal toxicity and one patient died eleven months after radiotherapy, with a large duodenal ulcer, but also with extensive progressive disease thought to have contributed to their deterioration [89].

Cattaneo et al. reported toxicity outcomes for sixty-one patients with stage III/IV pancreatic carcinoma who were treated with relatively hypofractionated chemoradiotherapy after induction chemotherapy. The prescribed dose was 44.25 Gy in fifteen fractions over three weeks to the tumour and regional nodes for most patients, but twenty-three patients were treated as part of a phase I trial in which they also received an integrated boost to a total dose of up to 58 Gy. All but two patients received concomitant capecitabine or 5-fluorouracil (5-

FU) chemotherapy, all were treated with IMRT, and 4D-computed tomography (CT) was used in planning for 64% of patients. The authors reported that 33% of patients suffered Grade 2–3 acute GI toxicity, including nausea/vomiting, diarrhoea, weight loss and anorexia (8% were Grade 3). They also reported incidences of acute or late 'anatomical toxicity' – referring to visible damage to the stomach or duodenum mucosa on endoscopy, of which Grade 2–3 occurred in 11.5%, Grade 3 in five patients. The median time to emergence of this form of toxicity was 3.8 months (range 0.6–10.2 months). Median follow-up was nineteen months and there was no Grade 4–5 toxicity seen. The investigators went on to analyse the relationship of toxicity with radiotherapy planning and found that dose-volume to the stomach and duodenum was predictive of adverse outcomes. Again, these results are examined in more detail in Chapter Two [90].

1.4.1. Data on radiotherapy toxicity from randomised controlled studies

The analyses describe in detail the toxicity observed following chemoradiotherapy for pancreatic cancer. However, the observed symptoms overlap with those of toxicity from the systemic element of therapy and also those of the disease itself. To control for these confounds, prospective trials in which patients are randomised and only some receive radiotherapy would offer the best scenario in which to ascertain definitively the specific toxicities of pancreatic cancer radiotherapy. In the recent LAP-07 study, it was observed that the occurrence of adverse toxicity events was not significantly different between patients randomised to chemoradiotherapy or those who continued chemotherapy alone, other than for an increased incidence of nausea (seen in six patients compared with none, $p = 0.008$) [12].

Prior to the release of these results, a meta-analysis of randomised trials had found that among ten studies (n = 713) reporting Grade 3–4 non-hematologic toxicities, these were higher in patients treated with chemoradiotherapy, compared with those receiving

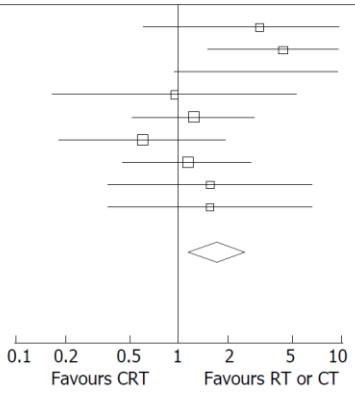
chemotherapy or radiotherapy alone (OR = 1.71; 95% CI: 1.16–2.53, $p < 0.01$) (see Table 1-2). Unfortunately, the authors did not examine toxicity in more detail and did not compare toxicity for radiotherapy or chemoradiotherapy compared with chemotherapy alone [7].

Table 1-2. Results of meta-analysis of non-haematological toxicity in patients treated with chemoradiotherapy (CRT) compared with radiotherapy (RT) or chemotherapy (CT) alone. Taken from Chen et al. [7].

Review: Radiotherapy plus chemotherapy in patients with locally advanced pancreatic cancer
Comparison: 01 CRT *vs* RT or CT
Outcome: 11 3-4 grade treatment related non-hematologica toxicity

Study or sub-category	CRT *n/N*	RT or CT *n/N*	OR (fixed) 95%CI	Weight %	OR (fixed) 95%CI
Moertel *et al*[11]	9/13	5/12		4.06	3.15 [0.61, 12.31]
Childs *et al*[20]	24/32	13/32		8.24	4.38 [1.51, 12.74]
Moertel *et al*[14]	40/169	0/26		1.68	16.95 [0.95, 267.86]
GITSG *et al*[21]	3/22	3/21		6.73	0.95 [0.17, 5.32]
Cohen *et al*[13]	17/55	13/49		24.10	1.24 [0.53, 2.91]
Sun *et al*[16]	6/26	10/30		18.12	0.60 [0.18, 1.97]
Chauffert *et al*[6]	12/59	11/60		22.04	1.14 [0.46, 2.83]
Ding *et al*[19]	5/25	4/29		7.52	1.56 [0.37, 6.60]
Sun *et al*[17]	5/25	4/29		7.52	1.56 [0.37, 6.60]
Total (95%CI)	426	287		100.00	1.71 [1.16, 2.53]

Total events: 121 (CRT), 63 (RT or CT)
Test for heterogeneity: $\chi^2 = 10.73$, df = 8 ($P = 0.22$), $I^2 = 25.4\%$
Test for overall effect: Z = 2.71 ($P = 0.007$)



Further details are available from some of the individual publications included in this meta-analysis. In the GITSG paper from 1988, 43 patients with locally advanced pancreatic cancer received 'SMF' chemotherapy (5-FU, streptozocin and mitomycin) with or without radiotherapy to a dose of 54 Gy in thirty daily fractions. The incidence of nausea and vomiting was not higher in the chemoradiotherapy arm compared with the chemotherapy-only arm – 'controllable' symptoms were seen in 73% compared with 81%, and 'intractable' symptoms in 5% versus 14%. Mild diarrhoea was also not increased (41% versus 48%), but the one patient admitted to hospital with severe diarrhoea had received radiotherapy [91]. Chauffert et al. reported increased incidence of CTC v3 Grade 3–4 toxicity in patients receiving chemoradiotherapy compared with chemotherapy alone (65.5% versus 40%; $p = 0.008$) [6]. The rate of digestive tract toxicity (nausea, vomiting, or diarrhoea) was 29.1% in the

chemoradiotherapy group compared with 11.1% in the induction chemotherapy patients. The findings of Loehrer et al. [5] were also incorporated in the meta-analysis of Chen et al., though this publication is not included in the forest plot shown above. In their study, a higher incidence of 'very severe' (Grades 4 and 5: 41% versus 9%) but not 'moderately severe' toxicity (Grades 3 and 4: 77% versus 79%) was seen in patients receiving radiotherapy in addition to gemcitabine. The authors reported the detailed toxicity outcomes for the two trial arms (Table 1-3), though they did not describe any statistical assessment regarding specific symptoms because they felt that "discrimination from disease-related symptoms was frequently not possible".

	Gemcitabine (n = 35)		Gem + RT (n = 34)	
Toxicity grade	3	4	3	4
Weight loss			2	
Anorexia	1		6	
Nausea	3		8	2
Vomiting	3		7	2
Diarrhoea	1		2	
Melaena			2	
Abdominal pain			1	1

Table 1-3. Gastrointestinal toxicity symptoms observed in Loehrer et al. [5].

1.4.2. The influence of chemotherapy agents on pancreatic cancer radiotherapy

The optimal systemic cytotoxic regimen to use in combination with radiotherapy to treat pancreatic cancer remains debated. Historical practice utilised 5-FU [92, 93]. More recently, gemcitabine has grown in popularity due to evidence for significant activity as a single agent, with a persisting overall survival benefit after surgical resection [2], and superior survival compared with 5-FU as a single-agent in metastatic disease [94].

Gemcitabine remains recommended for patients with metastatic disease who may not be suitable for modern combination regimens [95]. This agent is a potent radiosensitiser and

many studies have demonstrated the feasibility of its combination with radiotherapy in treating pancreatic cancer. A meta-analysis has attempted to definitively compare gemcitabine-based with 5-FU-based concomitant chemoradiotherapy, but could only draw upon three randomised trials [96, 97] and one retrospective study [98]. A significant advantage in 12-month survival was shown for gemcitabine-based chemoradiotherapy (relative risk = 1.54, 95% CI 1.05–2.26, p = 0.03) but the benefit in survival rate at 6 and 24 months did not reach significance [99]. Importantly, the rates of severe acute toxicity were higher in patients treated with gemcitabine chemoradiotherapy, where the risk ratio for RTOG Grade ≥ 3 GI bleeding was 4.26 (95% CI [1.25, 14.48]), p = 0.02.

Again, further details regarding toxicity incidence can be found in the reports for the component studies of the meta-analysis. Li et al. had randomised thirty-four patients to receive either 5-FU (n = 16) or gemcitabine (n = 18) alongside 3D-conformal radiotherapy (50.4–61.2 Gy at 1.8 Gy per fraction) [96]. They found rates of RTOG Grade 3–4 toxicity were similar between the two arms for anorexia (33% versus 31%), nausea (33% versus 31%), and vomiting (17% versus 19%). GI haemorrhage occurred in two patients, one from each study arm. Percentage weight loss was analysed and was similar between the gemcitabine and 5-FU groups (4.6% vs 5.8%). Wilkowski and colleagues reported on ninety-five patients with locally advanced pancreatic cancer treated within a multi-centre phase II randomised trial of chemoradiotherapy using either concomitant 5-FU or gemcitabine and cisplatin together [97]. Gross disease was treated to 50 Gy and regional nodes to 45 Gy, all in twenty-five daily fractions using 3D-conformal planning. Significant differences in overall or progression-free survival were not seen, but GI toxicity was higher in patients treated with concomitant gemcitabine-cisplatin: RTOG Grade ≥ 3 upper GI 20% vs 0%, lower GI 10% vs 4%, CTC Grade ≥ 3 diarrhoea 10% vs 3%, weight loss 3% vs 0%, and nausea 13% vs 0%.

Crane and colleagues conducted the retrospective study that was included in the meta-analysis and analysed outcomes for 114 patients with locally advanced pancreatic cancer treated with chemoradiotherapy [98]. Fifty-three patients received gemcitabine, and sixty-one received infusional 5-FU, alongside 3D-planned hypofractionated radiotherapy (30 – 33 Gy in ten to eleven fractions, at 3 Gy per fraction) to the tumour and regional lymph nodes. In patients receiving gemcitabine, there was significantly more severe acute toxicity (23% versus 2%, $p < 0.001$) and a higher incidence of hospital admission (32% versus 7%, $p = 0.002$), with the most common reasons being nausea, vomiting, or dehydration (71%) and abdominal pain (18%). Two patients treated with gemcitabine-RT suffered severe late effects – one with duodenal ulcer, the other with small bowel obstruction.

Two further studies have been published reporting randomisation of patients between 5-FU or gemcitabine chemoradiotherapy. Brasiunene and Juozaityte report on randomisation of nineteen patients prescribed a radiotherapy dose of 50 Gy in twenty-five fractions. They found GI toxicity was similar in both arms, though the severity of events was not specified: nausea/vomiting was seen in 30% of 5-FU patients and 22% of gemcitabine patients, diarrhoea in 10% and 11% respectively [100]. Mukherjee and colleagues conducted a much larger multi-centre phase II trial in which patients were randomised to receive either gemcitabine or capecitabine – an oral prodrug converted to 5-FU preferentially in irradiated tumour cells, and which could thus potentially improve the therapeutic ratio of radiosensitisation [101]. The details of this study are discussed in much greater depth in Chapter Six, but rates of moderately severe GI toxicity were low – CTC v3 Grade ≥ 3 was seen in 16% of patients receiving gemcitabine, and 0% of those treated with capecitabine. The specific symptoms reported were diarrhoea, nausea/vomiting and anorexia, in equal proportions. For comparison, the rate of GI toxicity during induction chemotherapy was 9%, consisting mainly of diarrhoea [102].

1.5. Advancing pancreatic cancer radiotherapy

Modern radiotherapy techniques, such as intensity-modulated radiotherapy and image-guided radiotherapy offer the capability to modulate the delivery of dose precisely in time and space with increasing precision and accuracy. As a result, it may be possible to widen the therapeutic ratio – that is, to reduce the degree or likelihood of side effects that occur for a given probability of achieving tumour control [103].

Intensity-modulated radiotherapy (IMRT) is a process in which the radiotherapy field is constrained and attenuated by multiple collimators. These are interleaved tongues of shielding that move independently of each other to create a constantly variable aperture for the beam. In 'conformal' radiotherapy this ability is used to shape the external border of the field to follow that of the target. In IMRT, the collimators are programmed to move across the field during the exposure, to partially obstruct and therefore modulate the delivered dose. When multiple beams are then combined from different angles, the dose to each three-dimensional portion (voxel) of the target volume can be controlled [104]. This can be used to improve the homogeneity of the dose across a target, or to deliver an intentionally heterogeneous dose to a target, such as an 'integrated boost' technique. IMRT can also improve the conformality of the high dose region to the shape of the target volume, including the ability to sculpt complex 3D dose distributions with concavities, or even voids, enabling better avoidance of organs at risk and potentially a reduction in resulting toxicity [105]. Although the volume of non-target tissue irradiated to high doses is reduced, the integrated delivered dose to the patient usually remains the same [106] and the volume of normal tissue receiving low dose may be increased, with uncertain implications [107]. There is therefore a need for the development of dose-volume constraints and normal tissue complication probability (NTCP) models that can be used to take these consequences into consideration to optimise the balance of toxicity risk for the patient.

Image-guided radiotherapy (IGRT) refers to the use of any number of imaging modalities to improve the accuracy of radiotherapy delivery by reducing or correcting for errors in the radiotherapy target definition and localisation. The commonest application of IGRT is in the use of regular imaging of the patient immediately before treatment is given, to verify their position and location relative to that intended for delivery of the planned treatment and to correct for any discrepancy. In radiotherapy planning, the intention is to ensure adequate dose coverage of the clinical target volume (CTV – the region the clinician wants to treat) despite all anticipated motion and deformation relative to the original position when treatment was planned. A planning target volume (PTV) is thus derived by adding margins to the CTV that are calculated to encompass this variation [108]. When IGRT is implemented as described above, this can reduce the size of the component of the CTV-PTV margin that is required to correct for inter-fractional movement. This approach should enable the reduction of the size of volumes being irradiated, with subsequent reduction in dose to the organs at risk and a potential reduction in risk of toxicity. The volume treated to a high dose and the delivered total integrated dose should both be reduced, and in most cases this reduction will considerably outweigh the additional radiation exposure attributed to the additional imaging [109].

IGRT and IMRT techniques are usually combined to achieve cumulative benefits in the conformity of high dose to the tumour volume. Thus, both techniques reduce the highest dose received by any normal tissue and they also reduce the volume of the normal tissue irradiated to that dose [110]. Reducing the volume of an organ receiving a harmful dose can, therefore, enable a reduction in toxicity for the same likelihood of tumour control. Alternatively, and more helpfully in most tumour sites where current disease control outcomes are poor, reduction in normal tissue volume can enable ‘isotoxic dose escalation’,

that is, an increase in the prescribed or treated dose to the tumour achieved within the same accepted risk or severity of side effects [111]. The increase in dose and subsequent improvement in tumour control that may be possible can usually be modelled in planning studies before being verified in clinical trials [112].

1.5.1. The potential benefits of IMRT and IGRT in pancreatic cancer treatment

Planning studies have illustrated the potential reduced dose to the kidneys and small bowel [113] that can be achieved through the use of IMRT in the delivery of radiotherapy for pancreatic cancer and the effective clinical implementation of this technique has also been demonstrated.

Two reports of the use of IMRT to treat pancreatic cancer were published together in 2004. Ben-Josef et al. reported the treatment of fifteen pancreatic cancer patients (eight with unresectable disease, seven after tumour resection) with radiotherapy and concurrent capecitabine chemotherapy. The region including draining lymph nodes was treated to 45 Gy while the tumour, or tumour bed, received a simultaneous integrated boost to a total dose of 54 Gy, in 25 daily fractions. GI toxicity was low: Grade 1-2 nausea/vomiting was seen in 53% but only 1 patient (7%) had a Grade 3 event (gastric ulcer) [114]. Milano and colleagues reported the outcomes of 25 patients with pancreatic and biliary cancers treated with IMRT, of whom 14 had unresectable pancreatic tumours, where the regional lymph nodes were treated to 45 Gy and the primary tumour to 59.4 Gy [115]. An embedded planning study showed that IMRT plans reduced the volume of organs at risk exceeding tolerance dose compared with optimal 3D-conformal plans, significantly for the kidneys and liver but not for the small bowel. Toxicity levels were also felt to be acceptable in this investigation, with RTOG Grade ≥ 3 upper GI toxicity seen in 25% of patients and lower GI in 4%. Three Grade 3 acute events were seen, comprising one case of cholecystitis and two of symptomatic hypovolaemia

requiring intravenous fluids, and two Grade 4 events occurred: one duodenal fistula and one paralytic ileus, while no patients suffered Grade ≥ 3 late toxicity.

Multiple publications have since reported the use of IMRT to treat pancreatic cancer, and authors have reinforced the potential benefits both in sparing organs at risk and the reduction in toxicity [116, 117]. Moreover, a systematic review has collated results of thirteen such studies, and demonstrated that the incidence of toxicity is significantly reduced, compared with seven selected publications in which 3D-conformal radiotherapy (3D-CRT) was used. Acute toxicity data were incorporated for a total of 446 IMRT patients and 747 3D-CRT patients: Grade ≥ 3 nausea and vomiting was seen in 7.8% in IMRT and 13.4% in 3D-CRT ($p < 0.001$), diarrhoea Grade ≥ 3 incidence was 2.0% vs 11.6% ($p < 0.001$). Late toxicity data were available for 381 IMRT and 207 3D-CRT patients: Grade ≥ 3 GI toxicities were mostly GI bleeding/duodenal ulcer and were seen in 5.0% of patients versus 10.6% ($p = 0.017$) [118].

1.5.2. Radiotherapy dose escalation using IG-IMRT

Beyond the possible reduction of toxicity, IMRT offers the promise to achieve dose escalation in the treatment of pancreatic cancer, and thus potentially to improve disease control within manageable levels of toxicity and acceptable risks of harm.

Crane et al. published the first results of attempting to use IMRT to enable radiotherapy dose escalation in locally advanced pancreatic cancer within a phase-I clinical trial. Patients with unresectable pancreatic cancers were treated with 33 Gy in 11 fractions to the tumour and regional lymphatics with concomitant gemcitabine. Unfortunately, all three patients treated at the first dose level suffered a dose-limiting toxicity), namely myelosuppression and upper GI toxicity [119]. Although the gemcitabine dose was subsequently reduced, the next two patients treated in the study also suffered a dose-limiting toxicity and the trial was therefore

closed. It seemed that delivery of high radiotherapy dose to the large volumes required to cover the regional lymph nodes remained excessively toxic, even when IMRT was used. In contrast, Landry et al. reported low toxicity in a series of nine patients with locally advanced pancreatic cancer treated, using IMRT to between 49.5 and 60 Gy to the tumour and 50.4 Gy to the regional nodes (using either 1.8 Gy per daily fraction or 1.5 Gy per fraction twice daily). Infusional 5-FU was used and only one patient suffered any RTOG Grade 3 toxicity (nausea) [120].

Bai et al. conducted a feasibility study of using IMRT to deliver a sequential boost to the tumour and hence achieve dose escalation when treating locally advanced pancreatic cancer. 21 patients were recruited of whom 16 completed radiotherapy, with concomitant gemcitabine or 5-FU. No patients suffered dose-limiting toxicity (Grade ≥ 3 nausea, vomiting or diarrhoea) and as a result, the highest dose level was reached and delivered for seven patients (30 Gy in fifteen fractions to tumour and regional nodes, followed by 30 Gy in ten fractions to the primary tumour only [121].

As described above, image-guided radiotherapy can be used to enhance precision and to support the use of reduced planning margins to reduce the volume of the target that must be irradiated. Fuss et al. used ultrasound to correct for setup error before radiotherapy for 41 patients with pancreatic cancer (17 resected, 24 unresectable) but in fact did not reduce their PTV margins. The mean prescribed dose was 55 Gy, with most patients receiving 5-FU/capecitabine. Incidence of toxicity was low, with Grade ≥ 3 upper GI toxicity seen in 7.3% and lower GI in 4.9% [122].

To reduce irradiated volumes with the aim of achieving safe dose escalation, Ben-Josef et al. used active breathing control techniques to reduce the planning margins required to account

for the motion of the tumour with respiration. Treatment fields were also intended to cover gross disease only (not uninvolved lymph nodes), for patients with unresectable pancreatic cancer treated using IMRT with concurrent gemcitabine in a prospective phase I/II trial. All radiotherapy was delivered in 25 daily fractions, from a starting dose of 50 Gy, and the dose per fraction was increased until a total dose of 57.5 Gy was reached at which three of eight patients had suffered a dose-limiting toxicity (defined as GI toxicity Grade ≥ 3, neutropenic fever, or deterioration in performance status to ≤3). In total, eleven of the fifty treated patients suffered a dose-limiting toxicity. These comprised anorexia, nausea, vomiting, and/or dehydration in seven cases, duodenal bleed in three patients and one case of duodenal perforation. The authors used a logistic regression model to demonstrate a dose-dependent increase in likelihood of dose-limiting toxicity, and suggested a dose of 55 Gy in 25 fractions should be taken forward for further assessment as it resulted in an acceptable rate of severe toxicity (24%) [123].

A randomised controlled clinical trial aiming to prove the benefit to patient survival outcomes of the moderate radiotherapy dose escalation that can be achieved using IMRT is currently recruiting patients in the UK. Patients in the SCALOP-2 trial (NCT02024009, ISRCTN50083238) will be randomised to receive either a standard dose (50.4 Gy in thirty fractions) or a regimen delivering up to 60 Gy in thirty fractions.

1.5.3. Stereotactic radiotherapy

While image-guidance and intensity modulation began to change radiotherapy delivery to the body, intracranial radiotherapy had been revolutionised by the adoption of 'stereotaxic' three-dimensional co-ordinate techniques originating in neurosurgery. The principles were used to treat small targets to ablative doses with high precision, initially with specialised equipment featuring multiple cobalt sources, and later using linear accelerators. The two

approaches came together in the practice of stereotactic body radiotherapy (SBRT), sometimes known as stereotactic ablative body radiotherapy (SABR).

Stereotactic radiotherapy usually employs a 'hypofractionated' schedule, meaning that the prescribed dose is split into fewer fractions than for conventional radiotherapy. Though any cut-off is somewhat arbitrary, the definition of SBRT usually implies the entire treatment is delivered in eight fractions or fewer, in contrast to conventional fractionation in which treatment courses commonly comprise up to 37 daily fractions. Hypofractionation was originally used in stereotactic radiotherapy for mainly practical reasons. Early stereotactic radiosurgery required the use of a rigid frame fixed directly to the patient's skull, and so treatment was constrained to the time period for which the frame could reasonably be left in place. Doses were delivered in a single fraction, or three fractions given over twenty-four hours. Even with the advent of frameless stereotaxy, practical advantages to hypofractionation remain considerable, with the requirement for fewer appointments and lower summed treatment time being beneficial both to patients in terms of convenience and quality of life, and for busy radiotherapy departments in terms of managing service demand. However, and perhaps more importantly, there are also potential radiobiological advantages to hypofractionation.

'Conventional' fractionation usually refers to the practice of accumulating the prescribed dose in small fractions of around 2 Gy, in order to exploit a difference in the survival and repair characteristics of the tumour compared with normal tissues. The total physical dose that can be delivered is usually limited by the risk of subsequent late toxicity. For a given total physical dose, tissues are more likely to show a significant effect if that dose is given in fewer large fractions than many small fractions. However, while fraction size usually has a large influence over the risk of late effects in normal tissues, it usually has less effect over the likelihood of

tumour control. This is hypothesised to reflect that in healthy cells the DNA damage sustained by smaller exposures can be repaired, but large exposures exceed the repair capacity and lead to cell death. In most tumour cells the DNA repair functions are dysfunctional, and the way in which a given physical dose is delivered is of less consequence. Of course, the reality is likely far more complex than this over-simplification [124].

The behaviour of a tissue or tumour in the face of changes in fractionation is well described by the linear-quadratic model, although this model actually arose to describe in-vitro cell survival in response to single-fraction irradiation under the hypothesis that the lethal event was induction of a double-strand DNA break [125]. Such survival is closely modelled by curves comprising a linear dose-response element, denoted alpha, and a quadratic dose-response element, denoted beta. The higher the ratio of alpha to beta, the straighter the line on a graph of surviving fraction against dose (ie the more linear the dose-response). The lower the alpha-beta ratio, the more sharply such a line curves downwards, as survival decreases rapidly with increased dose per exposure. The probability of clinical outcomes can be modelled in a similar fashion, where the Tumour Control Probability for most tumours has a high alpha-beta ratio, and outcome is related to dose-per-fraction in a linear fashion, while late effects have a low alpha-beta ratio, and outcome is more highly dependent on dose-per-fraction.

The overall effect is that if significant exposure to normal tissues cannot be avoided, as was historically the case, delivering external beam radiotherapy in a large number of small dose fractions should yield the highest 'therapeutic ratio', reducing the risk of important (late) toxicity for a given likelihood of tumour control. Thus, the use of small fractions became standard clinical practice. However, two things have since changed to challenge this convention. Firstly, it has become apparent that for some tumours, including several common malignancies such as breast and prostate cancer, the response to fractionation is not different

to that of late effects from normal tissue, ie the alpha-beta ratio is similarly low, and in this scenario conventional fractionation offers little advantage. Secondly, the ability of modern radiotherapy to improve the conformality of high dose deposition to the target, and thereby reduce the dose to normal tissues, has also reduced the imperative to rely on fractionation to limit late toxicity. There has, therefore, been a recent trend for increasing fraction size in the treatment of such cancers, with the benefits of reduced fraction number being managed against acceptable levels of tumour control and late toxicity [126, 127].

The effect of fraction size on the risk of acute toxicity is usually less than that for late toxicity, and these symptoms show greater dependence on total physical dose (ie they are characterised by a high alpha-beta ratio). The risk of acute toxicities is therefore usually not increased in hypofractionated radiotherapy and, in fact, it is likely to be a lower than for an 'equivalent' conventionally fractionated treatment if a lower total physical dose is delivered.

Controversies persist over the accuracy of the linear-quadratic model at very small fraction numbers, and the balance of effects of the shortened overall treatment time on the processes of repopulation, redistribution, and reoxygenation [128]. Overall, however, it is clear that the use of high dose-per-fraction achieves a higher biologically effective dose for a given physical dose in terms of tumour control probability (with the effect most pronounced in tumours with lower alpha-beta ratio), but also increased risk of late effects in the proportion of normal tissue exposed to the treatment dose [129].

Very hypofractionated SBRT was initially established in the treatment of peripheral lung tumours, where it was not difficult to achieve a favourable therapeutic ratio [130]. For small tumours in this location, the signal to noise ratio for the imaging required to guide patient positioning is high. These tumours can usually be easily seen against surrounding lung tissue

even on a crude cone-beam CT, and the surrounding tissue has a parallel functional architecture, where even severe damage to a small volume of tissue can be tolerated without compromise of function. In contrast, when normal tissues with serial architecture are located close to the tumour, exposure of even a small volume of that tissue to such a high dose will likely result in toxicity to the patient [131]. In this scenario, such as is the case for the pancreas, high-quality imaging and robust techniques for management of intra-fraction motion are required to support the use of small planning margins, and limit the exposure of normal tissue and thus the risk of toxicity.

The evidence to date regarding the use of SBRT in the treatment of pancreatic cancer is reviewed in detail in Chapter Six, which describes a clinical trial of preoperative SBRT for pancreatic cancer. This trial employs such imaging and motion management, and also utilises intensity-modulation techniques to escalate dose to clinically defined target regions, while maintaining the dose to normal tissue within accepted tolerances.

1.6. Summary

In summary, although the evidence for the role for radiotherapy in the radical treatment of pancreatic cancer has been conflicting, it may be because of the failure thus far to deliver sufficient dose to the tumour. Dose escalation may improve the response rate to chemoradiotherapy in pancreatic cancer, but the radiotherapy dose that can be safely prescribed has been limited by the tolerance of the surrounding normal tissue. Attempts at an escalation of dose to large target volumes, with insufficient conformality due to the limitations of historical radiotherapy techniques, have caused unacceptable toxicity. The choice of a concomitant chemotherapy drug may also be important: gemcitabine appears to be more effective at the cost of increased toxicity. IMRT appears to reduce the toxicity of treatment at conventional doses and may enable dose escalation, particularly if the irradiation

of uninvolved nodes can be omitted, and image guidance can be used to reduce planning margins and improve treatment accuracy. Stereotactic radiotherapy offers the promise of even higher effective doses achieved through higher precision, but it may have unacceptable risks of severe toxicity.

Data contributing to our understanding of the relationship of dose-volume and toxicity in the upper GI tract – that is, the stomach, duodenum and small bowel – are limited, and better modelling of the risk of adverse effects might enable tumour control rates to be safely increased in pancreatic cancer.

1.7. Aims of this thesis

Aim 1. To conduct a systematic review of the evidence regarding the relationship of dose-volume and toxicity in the stomach, duodenum and small bowel.

The QUANTEC systematic review in 2010 reported that data on radiation-induced stomach or duodenum toxicity were insufficient [132]. They recommended that more studies should make use of available 3D CT-planning dose-volume data and attempt to understand the effect of concurrent administration of chemotherapy, the standard of care for treatment of GI cancers. Since this report, a number of publications have sought to address the shortfall and a contemporary review is appropriate. The findings of multiple studies can be collated to identify the most robust and consistent results and identify remaining gaps in our knowledge. Hypothesis: Since the publication of the QUANTEC review, significant data has been added to this field and our understanding of this relationship in these organs has progressed, allowing us to better understand the nature of the volume effects in these tissues and set new and refined radiotherapy dose-volume constraints for these organs.

The results of the work towards this aim are described in Chapter Two of this thesis.

Aim 2. To conduct a meta-analysis of published DVH data to explore and model the relationship of dose-volume and toxicity in the stomach, duodenum and small bowel.

Hypothesis: Published dose-volume data describing the radiotherapy exposure to the organs of the proximal GI tract in patients treated in clinical trials and other cohorts with rigorous data describing toxicity outcomes can be used to inform our understanding of the causes of adverse events in these patients and to enable refinement of predictive models.

The results of the work towards this aim are described in Chapters Three, Four and Five of this thesis.

Aim 3. To analyse the radiotherapy dose-volume-toxicity relationship in data from two clinical trials of radical chemoradiotherapy for locally advanced pancreatic cancer.

Two recent prospective clinical trials of chemoradiotherapy in locally advanced pancreatic cancer (ARCII [133]and SCALOP) provide an opportunity to examine the dose-volume toxicity relationship for the organs of the upper GI tract in treating this disease, using detailed, comprehensive, robustly collected and rigorously quality-assured individual patient radiotherapy and toxicity data.

Hypothesis: The dose-volume relationship for the stomach, duodenum and small bowel in radical chemoradiotherapy for pancreatic cancer can be modelled, and dose-volume constraints can be derived in order to guide radiotherapy delivery for future patients.

The results of the work towards this aim are described in Chapter Six of this thesis.

Aim 4: To implement a robust and objective method of defining a target volume to receive dose escalation in the SPARC trial, and assess the quality of reproduction of such a target through pre-trial and on-trial radiotherapy quality assurance.

For patients with borderline-resectable pancreatic cancer (BRPC), defined by a limited extent of vascular invasion [95], the rate of positive surgical margins is more than 50% [134] and there is increased interest in neoadjuvant strategies that may reduce the high risk of subsequent disease relapse [135]. Preoperative stereotactic body radiotherapy (SBRT) for patients with BRPC aims to improve the chances of achieving clear resection margins and reduce local recurrence. This may in turn improve chances of long-term survival. The safety and ability to dose-escalate this intervention will be tested in a phase-I clinical trial (SPARC).

In the SPARC trial, a 'margin-intense' radiotherapy concept will be utilised. Pre-operatively a region is defined where the tumour is in contact with adjacent vasculature. This contact is the reason for the tumour being defined as borderline-resectable, because it is difficult to successfully remove the tumour here without leaving cancer cells behind. In margin-intensified radiotherapy one dose is prescribed to the main tumour target while a simultaneous integrated boost technique is used to deliver additional dose to this region thought to be at the highest risk of positive resection margins. The aim is to maximise the likelihood of achieving tumour cell sterilisation in a small volume but which is of critical significance. The whole tumour is still treated to a dose hoping to achieve tumour control, lest the operation not proceed as planned. Other clinicians have explored this technique, but target definitions for the boost volume have varied and sometimes lacked reproducibility [136-139]. A systematic method has been devised for the consistent definition of the target volume for the simultaneous integrated boost, namely the tumour-vascular contact

responsible for the definition of the patient as BRPC, and denoted CTV_M (Clinical Target Volume: Margin). A stepwise protocol with atlas was produced and the contouring by treating clinicians on a pre-trial test case assessed using conformity analysis techniques.

Hypothesis: a systematic method of defining the margin-intensified target volume will produce consistency in its derivation by clinicians on pre-trial test cases and trial patients.

The work regarding the SPARC clinical trial is described in Chapter Seven of this thesis.

2. Chapter Two. A systematic review of published evidence regarding the relationship of gastrointestinal radiotherapy toxicity with dose and volume delivered to the stomach, duodenum and small bowel

2.1. Introduction

Radiotherapy dose escalation may improve the response rate to the treatment of some abdominal malignancies, such as pancreatic cancer [13] but toxicity from the proximal GI tract is the major dose-limiting factor, as was introduced in Chapter One. A better understanding of the radiotherapy tolerance of the GI organs, including a more accurate and comprehensive library of radiotherapy dose-volume constraints, would inform radiotherapy planning, and could potentially reduce toxicity risk or enable safe dose escalation.

Unfortunately, the data contributing to our understanding of the relationship of dose-volume and toxicity in the upper GI tract (stomach, duodenum and small bowel) has historically been very limited. In their landmark publication on normal-tissue tolerance, Emami et al. [32], cite data from Gallagher et al. [140], but otherwise relied on clinical judgement for their recommendations. The authors of the QUANTEC systematic review also found that data on stomach or duodenum toxicity remained insufficient to make recommendations, and found only six studies reporting an analysis of toxicity outcomes and small bowel dose-volume [141].

The work described in this chapter aimed to identify and review published analyses of the relationship of dose-volume and risk of toxicity, and to collate results of dose-volume thresholds and associated toxicity risk, to guide treatment planning. The normal tissue

structures studied in this review make up the region of the upper GI tract: from the gastro-oesophageal junction to the terminal ileum, namely the stomach, duodenum and small bowel (Figure 2-1). This chapter compiles the clinical evidence currently available, in order to reassess the previous conclusions and derive updated guidance.

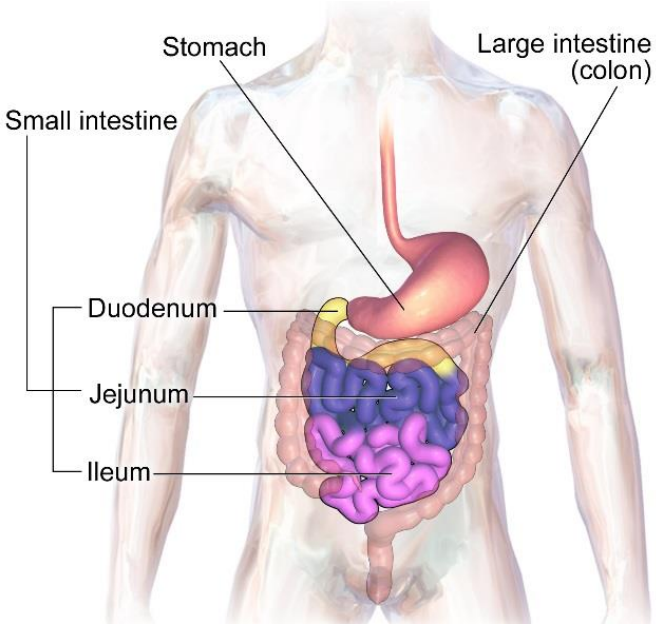


Figure 2-1. The organs of the gastrointestinal tract [6].

2.2. Methods

Search strategy

The SCOPUS **[http://www.scopus.com]**, EMBASE **[http://www.elsevier.com/online-tools/embase],** and MEDLINE **[http://www.ncbi.nlm.nih.gov/pubmed]** electronic databases were searched systematically using appropriate subject headings, key words, and synonyms. Search terms included *pancreatic cancer/neoplasm, stomach, gastric, duodenum, small bowel, ileum, jejunum, toxicity and radiation/radiotherapy*. The full search strings used are included in Appendix A. Results were limited to those published in English since 2002. The

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations were followed where possible [142].

The PROSPERO register of systematic reviews was checked, and no protocols that would overlap with this work were identified. A protocol for a review of clinical risk factors for late intestinal toxicity was found; however, this planned specifically to exclude consideration of radiation dose-volume factors [143].

Eligibility criteria

Studies were eligible for inclusion in the review if they fulfilled each of the following criteria:

- Population of interest: reports of studies of the treatment of malignancy in adult humans including males or females with radiotherapy to the abdomen or pelvis. *In-vitro* or animal studies were excluded.
- Intervention/comparison of interest: reports of studies using fractionated external beam radiotherapy, excluding papers describing stereotactic or intra-operative radiotherapy.
- Outcomes and risk factor of interest: reports analysing dose-volume data for the duodenum, stomach and small bowel, with related toxicity outcomes, measured and recorded using either objective or patient-graded outcomes. Reports of only dosimetric radiotherapy planning comparisons without clinical data were excluded.
- Study type: prospective trials, and prospective or retrospective case series or cohorts.

Data extraction

The data extracted comprised: nature of data collection (prospective or retrospective); study design (case series, prospective cohort or clinical trial); patient numbers; median duration of follow-up; type of cancer; treatment intention (radical, adjuvant, or palliative); toxicity

assessment method used (e.g. National Cancer Institute Common Toxicity Criteria) and timing of toxicity assessment (acute and/or late).

The radiotherapy treatment data collected comprised: median or mean dose, minimum and maximum doses prescribed; details of any boost (concomitant or sequential); number of fractions; dose per fraction; details of any concurrent chemotherapy; radiotherapy technique used (simple fields, 3D-conformal, IMRT or VMAT).

2.3. Results

Search results

The search results were reviewed by one author (DH). A total of 1422 results were returned (EMBASE 632, MEDLINE 299, SCOPUS 498), and 952 unique results remained after de-duplication. After screening by title, 495 relevant articles were selected for review of abstracts. Ninety-three publications were selected for assessment in full, not including three additional relevant papers identified from relevant review articles. Of these 96 papers, findings from 28 were included in this publication (Figure 2-2).

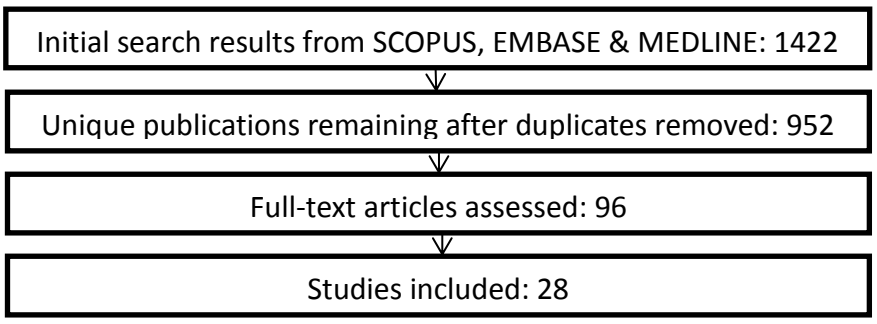


Figure 2-2. PRISMA flow diagram depicting the results of publication identification and inclusion

Stomach

Six papers, including one abstract, reported analysis of the relationship of toxicity with the radiotherapy dose and volumes received by the stomach. Two of these studies investigating pancreatic cancer chemoradiotherapy toxicity were described in Chapter One.

Nakamura et al. analysed dosimetric parameters against two toxicity endpoints: acute GI toxicity Grade ≥2 ('anorexia, nausea, vomiting, and upper GI mucositis') and, separately, upper GI bleeding Grade ≥3. They found stomach mean dose and stomach V_{30Gy}–V_{50Gy} all showed significant relationships with acute GI toxicity, most strongly for the D_{2cm3} (the highest dose received by at least 2 cm^3 of stomach), with an optimal predictive threshold of 53.6 Gy, below which no patients suffered toxicity [144]. Cattaneo et al. also found that multiple stomach dose-volume parameters were associated with acute GI toxicity (grade 1 or higher nausea, vomiting, diarrhoea, abdominal pain, anorexia and weight loss). Only borderline statistical significance was seen, however, with the best predictor being the V_{20Gy} (p = 0.058), and the optimal threshold for dividing patients into high or low risk being 31% [90]. Two other research groups identified predictive dose-volume parameters through retrospective analysis of the treatment of liver tumours. Feng et al. found that D_{max} was significantly higher among the 14% of patients who suffered gastric bleeding, with a greatly increased risk of gastric bleed among the cirrhotic patients [145]. Yoon et al. analysed patients receiving radiotherapy for hepatocellular carcinoma, among whom Grade ≥ 2 acute GI toxicity was seen in 30% and Grade 3 in 9%. Endoscopy after radiotherapy revealed gastritis in 16% of patients and gastric ulcer in 9%. The stomach D_{max}, D_{3ml}, D_{5ml}, D_{10ml}, and V_{10Gy}–V_{30Gy} were all significant predictors of toxicity, but only V_{25Gy} remained significant on multiple regression [146]. Studying records for patients treated for oesophageal cancer, Juloori et al. found mean dose to stomach (D_{mean}) was significantly related to incidence of anorexia (seen in 25.9% of their patients) [147]. Predictive parameters and optimal risk thresholds are collated in Table 2-1.

Three of the six publications fitted parameters to the Lyman-Kutcher-Burman (LKB) NTCP model, which models the risk of toxicity using the integrated organ DVH. In 2003, Pan et al. analysed the risk of GI bleeding after liver tumour irradiation, and LKB values derived for the stomach were: TD_{50} = 62 Gy (69% CI interval 53–71 Gy), *m* = 0.30 (0.23–0.39), *n* = 0.07 (0.03–0.16) suggesting a small volume effect and dependence on high point dose [148]. These results are considered in more detail in Chapter Three, in comparison with those derived by fitting this model using published DVH and toxicity data. Feng et al. derived similar values, of *n* = 0.10 and *m* = 0.21 [145]. For non-cirrhotic patients TD_{50} was 56 Gy, but for cirrhotic patients a greatly increased risk of gastric bleed was reflected in a lower TD_{50} of 22 Gy. Juloori et al. also derived a low value for the volume parameter (*n*) of ~0.2, but did not report values for TD_{50} or *m* [147].

Duodenum

Nine publications were found that had analysed the dose-volume toxicity relationship for the duodenum. Five of these used data regarding chemoradiotherapy for pancreatic cancer, and for which the patient cohort and treatment details were described in Chapter One.

Murphy et al. highlighted the possible importance of the duodenum DVH (measured using the gEUD, generalised Equivalent Uniform Dose), although the association did not achieve statistical significance. In addition, they found no significant associations with the specific duodenal dosimetric parameters they tested (V_{20Gy}–V_{40Gy}, D_{1cm3} $D_{5cm3,}$ and D_{10cm3}) [87]. Specific parameters have subsequently showed significant associations with relevant toxicity, including D_{2cm3} and D_{mean} (Nakamura et al. [144]), V_{20Gy}–V_{35Gy} (Huang et al. [88]), and V_{55Gy} (Kelly et al, [89]). As referred to previously, Cattaneo et al. also analysed dosimetric parameters against an adverse outcome endpoint which they call ‘anatomical’ toxicity [90]. This was

defined as visible damage to the mucosa on endoscopy, was carried out in all patients in their study for whom such toxicity was suspected, and correlated with the duodenum V_{40Gy} and V_{50Gy} (with the optimal cut-off values 16% and 26% respectively). Nakamura et al. constructed a combined gastro-duodenum structure for which they also derived dose-volume parameters, and found the V_{50Gy} for this structure (cut-off 33 cm^3) to be the best predictor of upper GI bleeding [144]. Cattaneo et al. also found that parameters for a similar combined stomach-duodenum structure (V_{40Gy} and V_{45Gy}) were associated with toxicity, but the associations shown on univariate analysis were not confirmed to be significant on multivariate analysis. Again, predictive thresholds with associated risks are collated in Table 2-1.

Three studies had analysed duodenal dosimetry in the setting of liver tumour irradiation. Pan et al. derived LKB parameters for the duodenum (TD_{50} = 180 Gy (69% CI ~ 100 to > 200 Gy), *m* = 0.49 (0.36–0.61) and *n* = 0.12 (0.09–0.30)) [148]. The other two publications both identified the same parameter (V_{35Gy}) to be a significant predictor of toxicity. Kim et al. reported a 12% rate of Grade ≥ 3 gastroduodenal toxicity (epigastric discomfort, dyspepsia, or upper GI bleeding) among cirrhotic patients treated for hepatocellular carcinoma, and derived a threshold of 5% for a combined gastro-duodenum structure [149]. Yoon et al. saw similar rates of toxicity, with erosive duodenitis in 17% and duodenal ulcer in 16% in their patients, and identified similar predictive dosimetric parameters. They found that the duodenum V_{20Gy}–V_{35Gy} and the $D_{3cm3,}$ D_{5cm3}, and D_{10cm3} were predictors of toxicity on univariate analysis, with duodenum V_{35Gy} the only factor remaining significant on multiple regression [146].

Of three studies investigating para-aortic lymph node irradiation for gynaecological cancers [150-152], only one identified a duodenal dosimetric parameter predictive of toxicity: Verma et al. reported that no patients suffered duodenal toxicity for whom the V_{55Gy} was below a threshold of 13.9% [152].

Table 2-1. Dose-volume thresholds for stomach, duodenum, and combined structures, with associated toxicity risk.

LAPC = locally advanced pancreatic cancer, HCC = Hepatocellular carcinoma, UGB = upper GI bleed, GI = gastrointestinal, Gr = grade, StoDuo = combined stomach-duodenum structure

Reference (patients)	Cancer, RT dose	Concurrent chemo	Toxicity outcome	Structure	DVH parameters	Risk comparison
Nakamura 2012 [144]	LAPC 54 Gy in 30 #	Gemcitabine	Acute UGI (Gr ≥2)	Duodenum	D_{mean} 46.1 Gy	19% vs 57%
					D_{2cm3} 55.5 Gy	21% vs 58%
				Stomach	D_{2cm3} 53.6 Gy	0% vs 57%
					V_{50Gy} 16 cm3	9% vs 61%
			UGB (Gr ≥3)	StoDuo	V_{50Gy} 33 cm^3	0% vs 44%
Huang 2012 [88]	LAPC 36 Gy in 15 #	Gemcitabine Gem + erlotinib	GI (Gr ≥3)	Duodenum	V_{35Gy} 20%	0% vs 41%
					V_{25Gy} 45%	8% vs 48%
Cattaneo 2013 [90]	LAPC 44 ± 15 Gy, in 15 #	Capecitabine or 5-FU	GI (Gr ≥2)	Stomach Duodenum	V_{20Gy} 31% V_{40Gy} 16%, V_{45Gy} 2.6%	Not specified
Kelly 2013 [89]	LAPC 50.4 Gy in 28 #	Gemcitabine ± 5-FU/cape ± EGFRi	Duodenal (Gr ≥2)	Duodenum	V_{55Gy} 1 cm^3	9% vs 47%
Kim 2009 [149]	HCC 36 Gy in 12 #	None	Gastro-duodenal (Gr ≥3)	Gastro-duodenum	V_{35Gy} 5%	4% vs 48%
Yoon 2013 [153]	HCC 33 Gy in 11 #	None	Gastro-duodenal (Gr ≥2)	Duodenum Stomach	V_{35Gy} 5.4% V_{25Gy} 6.3%	9.4% vs 45.9%
Verma 2014 [152]	Gynae (PA nodes) 64 Gy in 25 #	Platinum agents (55 %)	Duodenal (Gr ≥2)	Duodenum	V_{55Gy} 13.9%	7.4% vs 48.6%

Small bowel

Eighteen publications were identified which reported analysis of the dose-volume toxicity relationship for the small bowel (Table 9-1), not including six studies that found no evidence to support such a relationship [150, 154-158]. Six of the eighteen had been included in the QUANTEC review. Analysing rectal cancer chemoradiotherapy outcomes, Baglan et al. [159], Tho et al. [160], Gunnlaugsson et al. [161], and Robertson et al. [162] each reported that all of the small bowel DVH parameters they tested (V_{5Gy}–V_{40Gy}) were significantly associated with risk of acute toxicity. For radiotherapy for gynaecological malignancies, Roeske et al. [163] found intestinal cavity V_{45Gy} predictive, and Huang et al. [164] identified $V_{15.8Gy}$ ($V_{39.6Gy}$ for postoperative patients) as the most strongly predictive metrics.

Studies published since QUANTEC have mostly repeated the earlier findings. Further work by Robertson et al. later confirmed the V_{15Gy} to be the strongest predictor of toxicity among an expanded patient cohort, with a volume threshold of 130 cm^3 below which the risk of acute Grade ≥ 3 diarrhoea was 11% [162]. This DVH parameter has since been shown to be associated with the risk of acute toxicity in four other studies of rectal cancer [165-168]. A novel result was that of Chen et al., who showed that while conventional toxicity scales such as CTC are normally employed, the V_{15Gy} also predicted the risk of patient reported symptoms [165]. Alongside V_{15Gy}, Arbea et al. found that V_{10Gy} (volume threshold 92.6 cm^3) and V_{50Gy} (4.4 cm^3) [166], while Reis et al. found V_{5Gy} (291.9 cm^3) [168] also predicted risk of diarrhoea. Banerjee et al. found that among their patients, all of V_{15Gy}–V_{45Gy} were associated with a risk of small bowel toxicity [167]. In gynaecological cancers, both Chi et al. [169] and Rath et al. [170] have repeated the finding of Roeske et al. that an intestinal cavity V_{45Gy} best predicted toxicity. Ray et al. found slightly lower doses were most important (V_{35Gy}, V_{40Gy}) and though Chopra et al. found similar parameters (V_{15Gy}, V_{30Gy}, and V_{40Gy}) significant on univariate analysis, only V_{15Gy} (275 cm^3) remained significant on multivariate analysis [171].

In the treatment of patients with anal cancer, DeFoe et al. saw Grade 3 toxicity in 27.6%, and found small bowel dose-volume thresholds of V_{30Gy} ≤310 cc and V_{40Gy} ≤70 cc were predictive of Grade ≥ 3 GI toxicity on univariate analysis [172]. In their study of patients treated for pancreatic cancer, Nakamura et al. found the small bowel DVH parameters significantly predictive of toxicity included V_{30Gy} (310 cm^3), V_{40Gy} (17 cm^3), and V_{50Gy} (10 cm^3) [144]. Having analysed toxicity in the largest cohort included in this review, Fiorino et al. reported intestinal cavity V_{20Gy}–V_{50Gy}, and predicted acute GI toxicity after prostate cancer radiotherapy, with V_{45Gy} most significant [173].

In summary, in the treatment of rectal cancer, small bowel threshold dose-volumes from V_{5Gy} to V_{50Gy} predicted toxicity, while in radiotherapy for gynaecological malignancies the predictive dose-volumes were V_{15Gy} to $V_{40Gy,}$ or V_{45Gy} if individual bowel loops were not contoured.

Publications with negative findings

Six publications identified in the systematic search did not find a significant relationship between small bowel dose-volume and toxicity, including studies of radiotherapy for prostate cancer [156], pancreatic cancer [157], rectal cancer [158], cervical cancer [155], gynaecological cancer in para-aortic lymph nodes [150], and adjuvant radiotherapy after surgery for endometrial cancer [154].

Table 2-2. Publications reporting no association between small bowel volume parameters and GI toxicity

Reference	Cancer site	N =	Concurrent chemo	RT dose (Gy)	Toxicity outcome	OAR examined
Beriwal 2007 [154]	Endometrium	47	None	45–50.4 Gy (1.8 Gy per #)	Acute & late small bowel	Small bowel
Chinnachamy 2012 [155]	Cervix	21	Cisplatin	50 Gy in 25 #	Acute bowel	Small bowel
Cox 2011 [156]	Prostate	239	None	45 Gy in 25 #	Acute GI Grade ≥ 3	Small bowel
Ito 2006 [157]	Pancreas	42	Gemcitabine	50.4 Gy in 28 #	Acute GI	Small bowel
Poorvu 2013 [150]	Gynae (PA nodes)	53	Cisplatin	54 Gy in 30 # (41–65 Gy)	Acute & late GI	Duodenum & small bowel
Xu 2015 [158]	Rectum	63	Oxaliplatin-capecitabine	50 Gy in 25 #	Acute lower GI	Small bowel

(R = retrospective, P = prospective, NS = not specified, OAR = organ(s) at risk, # = fractions)

2.4. Discussion

Appraisal of literature results

Until recently, the evidence base for understanding the relationship between stomach and duodenum dose-volumes and toxicity has been extremely limited. For the stomach, the results of a small number of quality analyses are available. From these we can draw some overall conclusions but there are also some potentially conflicting findings. Regarding the

duodenum, multiple independent publications have now shown the importance of the dose-volume received by this structure in determining the risk of toxicity from radiotherapy for upper abdominal tumours. For the small bowel, papers published since the QUANTEC review have mostly replicated the findings of their predecessors. However, the data from the treatment of a range of tumour types enable a clearer picture to be seen of the differences in the relationship between toxicity and dose-volume in different clinical settings.

Stomach

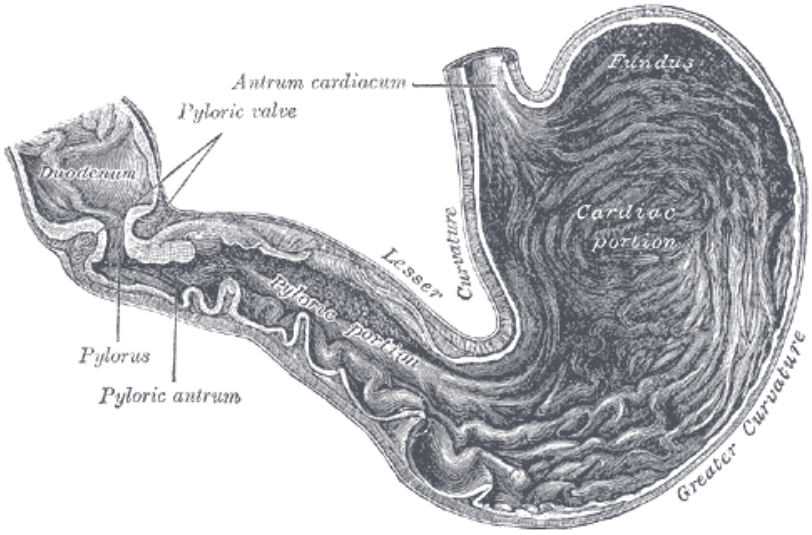


Figure 2-3. Interior of the stomach [82]

The stomach is the section of the digestive tract that reaches from the cardiac orifice of the lower oesophageal sphincter to the pyloric sphincter, which demarcates its transition to the duodenum. The stomach lies in the upper left abdomen surrounded by the diaphragm above, the spleen behind, and with the left kidney and splenic flexure of the colon below. It is also somewhat mobile [82]. When empty and contracted, folds of excess mucosa are visible as rugae (see Figure 2-3), which help permit dramatic expansion to accommodate ingested meals [174]. Food material is mechanically and chemically digested by mixing with strongly acidic

gastric fluid, which contains fat-digesting lipase, to render it into a soupy liquid known as chyme. This is permitted through the pyloric valve into the small intestine [175].

Irradiation of the stomach causes loss of appetite, nausea and vomiting within hours [176], and symptoms can be severe leading to measurable reductions in quality of life [177]. The mechanism of action is thought to involve 5-HT_3 secretion by enterochromaffin cells. Emesis is associated with increases in excreted serotonin metabolites [178], and prophylactic use of 5-HT_3 receptor antagonist drugs has been shown to reduce vomiting [179]. Afferent vagal neural impulses are transmitted to the brainstem, from where signals are generated to expel the stomach contents through vomiting [180]. Mucosal inflammation subsequently develops over days, with symptoms of dyspepsia and gastritis (upper abdominal discomfort and sensation of excess acid). Ongoing death of parietal and chief cells may lead to submucosal fibrosis and functional impairment with prolonged gastric emptying and reduced acid secretion [181]. The mucin-secreting surface columnar cells lining the stomach have a short lifespan of around three days, and are regularly replaced by the daughters of precursor cells. These precursor cells are killed by low doses of radiotherapy, and lack of replacement of the surface columnar cells leads to rapid denudation of the gastric mucosa. This can result in acute ulceration, but rarely perforation, as the connective tissues deep to the mucosa remain intact [181].

There is now evidence from several studies that the incidence of acute GI toxicity in radiotherapy for various malignancies, including pancreatic cancer and liver tumours, is dependent on the dose and partial volume of stomach that is irradiated. Therefore, during the radiotherapy planning process for tumours of the upper abdomen, this structure should be contoured and efforts should be made to reduce exposure where possible. Evidence suggests that there may be specific relationships between particular symptoms and

dosimetric parameters, such as between gastric bleeding and D_{max} [145, 147], though a possible link shown between anorexia and D_{mean} [145] has not yet been independently validated. A broader range of parameters may also be important and some have shown significant associations on univariate analysis, including mean dose, maximum dose, and other partial dose-volume parameters between V_{20Gy}–V_{50Gy}. The attempt to identify individual metrics, which are able to predict toxicity independently, may be counter-intuitive when a large range of the stomach DVH appears to contribute to determining risk for patients. Where NTCP model parameters have been derived for gastric and duodenal haemorrhage, a consistent finding is the low value for *n,* suggesting that it is the maximum dose that is most important in determining the risk of adverse events, and that the risk of this toxicity is not affected greatly by the partial volume. This result is in keeping with those publications that have identified high dose parameters (eg V_{50Gy}, $D_{2cm3,}$ and Dmax) as the best predictors of adverse events, but in contrast with those that had suggested lower doses ($V_{20Gy,}$ V_{25Gy}) as most important.

Duodenum

The duodenum is the first part of the small bowel (or small intestine), beginning where the stomach ends at the pyloric sphincter, and ending when the jejunum begins at the suspensory muscle of the duodenum (also known as the Ligament of Treitz). The name is derived from the Latin for the number twelve, a historical measurement of its approximate length (in fingers' breadth) in humans, but which is now usually measured at around 20–40 cm. Its path is contorted in three dimensions (see Figure 2-4), curving upwards and backwards initially, before descending in a wide crescent around the head of the pancreas and looping back up to the abrupt duodenojejunal flexure, making "somewhat of the shape of an imperfect circle…its termination not far removed from its starting point" [82]. It can be anatomically divided into four parts, namely superior, descending, horizontal, and ascending. Alternatively, these

sections may be referred to as D1 to D4. Not simply an inert tube connecting the stomach to the rest of the small intestine, the main functions of the duodenum are to continue the breakdown of ingested foodstuff and begin the absorption of nutrients. Alkaline mucous secreted by Brunner's glands neutralises persisting stomach acid, and lubricates and protects the mucosal surface, while bile acid from the liver and digestive enzymes from the pancreas are released into the intestinal lumen through the Ampulla of Vater [175].

Manifestations of irradiation of the duodenum include inflammation, with or without ulceration, and stenosis due to fibrosis. Stenosis may lead to symptoms of gastric outlet obstruction with nausea, vomiting and reduced appetite, or early satiety. Ulceration, if severe, can lead to bleeding or fistula formation, both potentially life-threatening events.

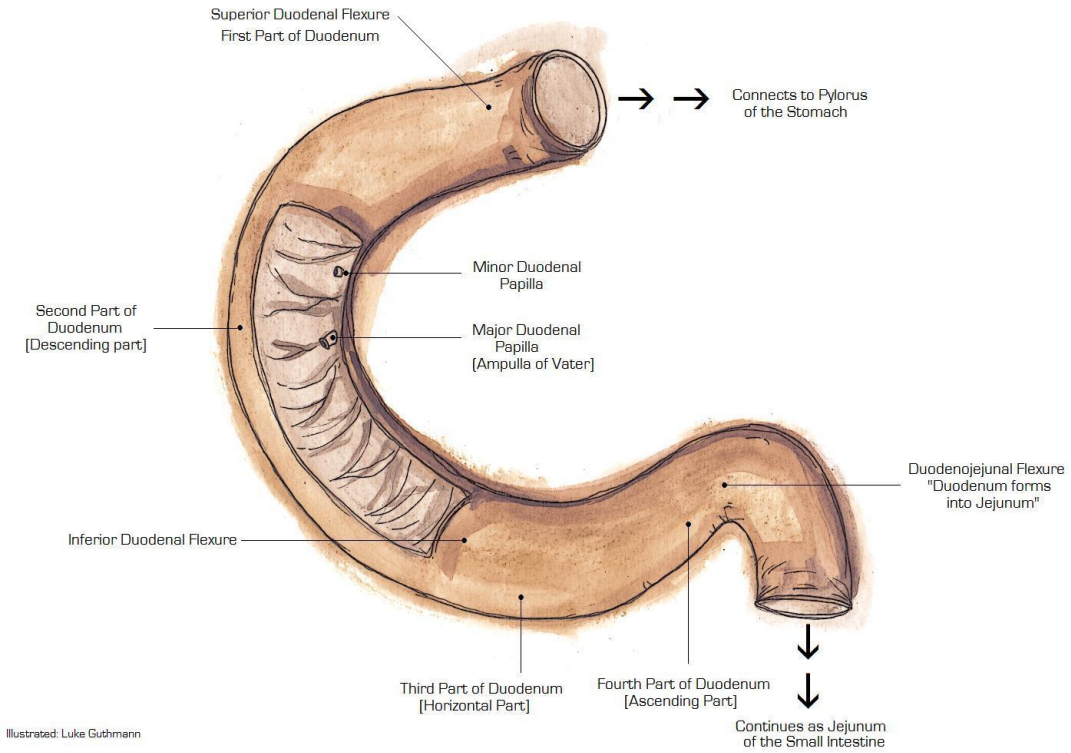


Figure 2-4. Anatomical illustration of the duodenum [182]

Duodenal toxicity is a common complication of radiotherapy for pancreatic cancer. A dose-dependency relationship has been observed and has been the limiting factor in attempting to escalate treatment dose. Observed duodenal toxicity rates appear to be acceptable (in the region of 5–10%) when duodenum doses remain less than 55 Gy, but rise to affect one third of patients when the dose exceeds this level [183]. Morganti et al. treated fifty patients with unresectable disease with an escalating radiotherapy dose and found that radiation dose correlated significantly with the incidence of toxicity (p = 0.02). The prescribed dose was 39.6 Gy for the first fifteen patients and 50.4 Gy in the next fifteen patients, among which the incidence of toxicity was 0%. In contrast, a dose of 59.4 Gy was prescribed in the remaining twenty patients, among whom 58.2% suffered toxicity [184].

Duodenal toxicity is also observed following abdominal radiotherapy for other malignancies, such as irradiation of para-aortic lymph nodes for treatment of cervical cancer, where Kodaira et al. reported milder stomach/duodenum toxicity (Grade 1-2) in 26.8% of ninety-seven patients treated with a mean dose of 50.4 Gy [185]. Following para-aortic irradiation after nephrectomy for renal cancer, Kjaer and colleagues saw stenosis or bleeding in the duodenal or small bowel in a third of patients treated with 50 Gy in 20 fractions [186].

Multiple studies have now identified duodenum dose-volume parameters predictive of toxicity. Most of these are found in the high-dose region of the DVH, particularly when analysed in relation to ulceration or GI bleeding, but the importance of the volume of duodenum receiving lower doses (in the region of 20–25 Gy) has also been identified (Table 2-1). The importance of the mid-range doses is also reinforced by data from two publications regarding liver tumour irradiation that independently identified duodenum V_{35Gy} as predictive of toxicity. Many publications were able to derive cut-off volumes which can inform radiotherapy planning to minimise risk for patients, and risk of toxicity is likely to be low if the

dose-volume exposure can be kept below the identified thresholds: duodenum – V_{25Gy} < 45%, V_{40Gy} (or 16%), V_{45Gy} < 2.6%, and V_{55Gy} < 1 cm^3; combined 'StoDuo' structure – V_{40Gy} < 52 cm^3 and V_{50Gy} < 33 cm^3.

Small bowel

The small bowel, or small intestine, refers to the part of the gastrointestinal tract between the pyloric valve of the stomach and the beginning of the colon. It is around seven metres long on average, and comprises three sections – the duodenum, jejunum and ileum. Distal to the duodenum, the small bowel is attached to the posterior abdominal wall by the mesentery, a fan-shaped flexible sheet which allows a large degree of motion while maintaining vascular, lymphatic and neural connections [82]. The main function of the small bowel is the ongoing digestion of food material (chyme) and absorption of liberated nutrients [175]. Absorption is facilitated by the large surface area provided by the texture of the mucosa, which is not smooth but instead made up of countless villi, finger-like projections each containing capillaries and lymphatics, and further enhanced by microvilli, projections of the epithelial cell surface membrane itself. The wall of the small bowel is also not smooth, and encircling folds (valvulae conniventes or plicae circulares) help control the transit speed of chyme and further increase surface area. The division between the jejunum and ileum is poorly defined but a gradual transition takes place, which means the proximal jejunum is quite distinct from the distal ileum. The diameter of the lumen gradually reduces, the muscular wall becomes thinner, vascularity is reduced, and the circular folds of the mucosa become fewer. The ileum is further distinguished from other sections of small bowel by the presence of Peyers Patches, nodular aggregations of lymphoid tissue [82].

The clinical effects of radiotherapy on the small bowel are better known than for those on the stomach or duodenum, due to the more prevalent use of radiotherapy in the treatment of

cancers of the pelvis than for cancers of the upper abdomen. The effects can be collectively labelled radiation enteritis, or radiation enteropathy, and overlap with those of radiation proctitis (radiation damage to the rectum) to contribute to the condition known as pelvic radiation disease. Acute toxicity is typified by the symptomatic inflammation of the mucosa, with onset one to three weeks after treatment commences [76]. The main feature is increased motility, with cramping discomfort and diarrhoea, and malabsorption and weight loss can result. The pathological changes include intestinal crypt micro-abscess formation and arteriolar swelling [50]. Epithelial denudation due to depletion of mucosal cells brings the risk of ulceration and sepsis due to the loss of an effective barrier against infection [187].

Before the age of routine cross-sectional soft-tissue imaging in radiotherapy planning, Emami et al. had limited evidence to draw upon when they attempted to define dose-volume constraints for the small bowel [32]. The authors complained of scarce dosimetry values and of variability in methods of defining partial volume (by length or by volume), but published a TD5/5 (tolerated dose with 5% risk of events at 5 years) of 50 Gy based on clinical experience (see Table 2-3). They did commend the work of Gallagher et al. for calculating the dose delivered to volumes of small bowel visualised on orthogonal radiographs, showing that the severity of acute effects correlated with the volume of small bowel irradiated and that late effects correlated with prescription dose and volume receiving over 45 Gy [140].

Table 2-3. Normal tissue tolerance to therapeutic radiation: Small intestine. TD5/5 = tolerance dose leading to 5% risk of complication (obstruction, perforation/fistula) at five years. From Emami et al. [32].

Risk of complication at five years	**TD5/5**			**TD50/5**		
Volume of small bowel irradiated	Whole	2/3	1/3	Whole	2/3	1/3
Dose threshold	40		50	55		60

Several subsequent publications examined small bowel dose-volume using radiographic films, and demonstrated relationships with acute [188-190] and with late [191] GI toxicity. The

uptake of computerised radiotherapy planning has since enabled more comprehensive analysis of dose distributions in three dimensions. The QUANTEC review [141] was able to consider results of six publications, and concluded that a threshold dose and volume exists above which the risk of acute toxicity escalates, which is $V_{15Gy} \geq 120$ cm^3 for individually contoured small bowel, or $V_{45Gy} \geq 195$ cm^3 if an encompassing peritoneal space structure has been defined [159-161, 163, 164, 192].

As mentioned, the papers published since the QUANTEC review have mostly replicated the findings of their predecessors. However, the evidence for a threshold effect of around 15 Gy appears to have been eroded, as metrics from the full width of the clinical small bowel DVH have repeatedly and independently been shown to predict toxicity. It can now also be more clearly seen how the predictive DVH parameters differ according to the tumour site (Table 9-1, Appendix A). In rectal cancer chemoradiotherapy, all of V_{5Gy} to V_{50Gy} have been shown to be important predictors of the risk of acute toxicity, usually specified as diarrhoea. The most repeated finding remains the importance of the V_{15Gy}, reported in all nine publications here, consistent with the conclusions of Robertson et al. [162] as adopted by QUANTEC. However, the impression that 15 Gy is a threshold dose, above which the irradiated volume matters less, appears to disregard the evidence for the importance of the volume of small bowel irradiated by doses at the higher end of the DVH, such as V_{30Gy} and $V_{40Gy;}$ which were each also found to be significant predictors in five studies. As dose escalation becomes more popular in the treatment of rectal cancer, with the intent of improving pathological Complete Response rates [193], the importance of high-dose thresholds (such as $V_{50Gy} < 4.44$ cm^3, shown by Arbea et al. [166]) may become even more apparent. In radiotherapy for gynaecological cancer, the range of parameters from V_{15Gy} to V_{50Gy} have shown significant associations with toxicity, while the most repeated finding is that of V_{45Gy}, with a threshold volume of 180–195 cm^3, contoured as 'intestinal cavity' or 'single small bowel structure', not as individual loops of small bowel.

The reasons for the apparent difference in the dose-volume-toxicity response between studies of rectal cancer and those of gynaecological malignancies cannot be precisely defined, due to the presence of major confounding factors. These include the effect that the primary disease may have on the incidence and evolution of toxicity symptoms over time, and the difference in concomitant chemotherapy agents that are usually used in treating these conditions. Radiotherapy for rectal cancer is usually given preoperatively, with the rectal tumour remaining in situ, and with concomitant fluoropyrimidine chemotherapy, which is usually 5-FU or capecitabine. Conversely, radiotherapy for gynaecological cancers is more often given postoperatively and concomitant platinum-based drugs are favoured, with fluoropyrimidines rarely used. There appears to be only a very small number of studies that offer insight by acting as controls for some of these variables, and which may help to shed light on the interactions between these factors. These will be reviewed in more detail in this following discussion.

Rectal tumours and gynaecological cancers will both often cause symptoms that overlap with those that are usually included in a definition of small bowel radiotherapy toxicity, such as change in bowel habit (usually diarrhoea and/or frequency of bowel opening) and abdominal discomfort or pain. When treatment is given preoperatively, with the disease remaining in situ, there is a risk that symptoms attributed to treatment toxicity could in fact be due to disease effects, a situation that could be missed if symptoms at baseline are not recorded and considered in the analysis of toxicity events. Likewise, the surgical interventions for resection of rectal or gynaecological tumours can also leave patients with persistent symptoms that could themselves complicate the recording and understanding of radiotherapy toxicity, while the modification of the small bowel dose-volume toxicity relationship by surgery would likely be different in different cancers.

When pelvic radiotherapy is delivered postoperatively there is likely to be a greater volume of small bowel falling into the treatment field [140]. Some studies have shown increased toxicity if radiotherapy is given after abdominal or pelvic surgery [140, 164, 173], though a similar number of studies have not seen this association [161, 163, 192]. Outside of randomised studies, however, there are likely to be other confounding factors, particularly the stage of the primary disease, that will drive the sequencing of therapy and hinder comparisons of outcomes in such patients. Robertson et al. repeated the finding that preoperative chemoradiotherapy appeared to be less toxic than postoperative (risk of Grade ≥ 3 diarrhoea 18% vs 28%; $p = 0.31$), and showed that while the same small bowel dose-volume parameters were predictive of toxicity, regardless of the sequencing of surgery, the predictive ability was not as strong in postoperative patients. Huang et al. found that, in gynaecological cancer patients, different small bowel dose-volume parameters were best predictors of toxicity in patients with no prior surgery (Group 1 – $V_{40\%}$, equivalent to 15.8 Gy) to those who had undergone prior surgery (Group 2 – $V_{100\%}$, equivalent to 39.6 Gy) [164]. Unfortunately, however, there were other differences between these patient groups, including the balance of disease type and the proportion of patients who received concomitant chemotherapy. 74% of group 1 were cervical cancer patients who received 5-FU, compared with 45% in group 2, ($p = 0.011$).

The expected toxicities of the chemotherapy drugs used to treat these cancers also overlap with those of radiotherapy. Fluoropyrimidine agents frequently cause diarrhoea as well as nausea, vomiting and abdominal discomfort in patients treated for rectal cancer [194]. Platinum drugs, such as cisplatin and oxaliplatin, can also cause nausea and vomiting, loss of appetite and diarrhoea [195]. A small number of randomised studies of radiotherapy with or without concomitant chemotherapy have been conducted which can indicate the degree of

exacerbation of GI-specific pelvic radiotherapy toxicity by the relevant chemotherapy agents commonly used in this analysis.

Two large randomised studies, which both opened in 1993, went on to show significantly increased toxicity with the addition of 5-FU and leucovorin chemotherapy to preoperative radiotherapy (45 Gy in 25 daily fractions) for resectable rectal cancer. The Fédération Francophone de Cancérologie Digestive (FFCD) study 9203 randomised 733 patients, and found that Grade ≥ 3 acute toxicity increased from 2.7% to 14.6% [196]. The European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921 recruited 1011 patients [197]. The authors reported that the addition of chemotherapy led to a highly significant increase in acute Grade ≥ 2 diarrhoea, from 17.3% to 34.3%, and led to a greater number of patients having their radiotherapy interrupted (twelve versus five patients) or even suspended (nine versus one) [198].

The method of delivery of these drugs is important and infusional 5-FU/leucovorin regimens have been adopted in routine clinical practice, as their toxicity appears to be lower than that of bolus schedules [199]. Intriguingly, however, when used in combination with postoperative radiotherapy, the rates of GI toxicity are higher with infusional rather than bolus regimens [200]. Toxicity outcomes are further altered when capecitabine is used in place of 5-FU in chemoradiotherapy for rectal cancer, as shown by Hofheinz et al. in a randomised trial of 392 patients [201]. Diarrhoea was the most common adverse event in both groups, but while rates of diarrhoea during chemotherapy were almost identical between groups, the side effect was significantly more common during chemoradiotherapy in the capecitabine group (45% vs 32%, $p = 0.009$), suggesting capecitabine may exacerbate the effect of radiotherapy on the small bowel more potently. In the treatment of cervical cancer, the addition of cisplatin chemotherapy to radical radiotherapy increases the risk of Grade ≥ 3 GI toxicity from 5% to

14%, but this mostly consists of vomiting [202]. In one study, the combination regimen of cisplatin/5-FU caused Grade ≥ 3 bowel or rectal abnormalities in 9% of patients, compared with 1% in those receiving radiotherapy alone [203]. In another, this resulted in the experience of diarrhoea in 10% of patients, compared with 6% in those receiving radiotherapy alone [204].

Unfortunately, there appears to have been no analysis of the relationship between dose-volume and toxicity to organs at risk in the studies mentioned above. While the degree that concomitant chemotherapy increases the risk of toxicity is quite clear, the interaction of chemotherapy with small bowel radiotherapy dose-volume and toxicity remains unknown. Insights can be gained, however, from tentative comparison of data from separate studies.

The addition of fluoropyrimidine chemotherapy appears to increase the risk of toxicity for a given volume of small bowel irradiated. For example, for the same volume irradiated, a higher rate of toxicity is reported in the rectal cancer chemoradiation [167] versus cervical cancer chemoradiation [205] – 10% vs 5% respectively. Correspondingly, the volume of small bowel that can be safely irradiated to a given dose is also reduced when 5-FU is added. For example, a 5% risk was observed for a V_{40Gy} of 150 cm^3 [171] in the treatment of cervical cancer compared with a risk of 10% for a V_{40Gy} of 71 cm^3 in the treatment of rectal cancer with concomitant chemoradiotherapy [192]. However, for both of these comparisons, the differing disease type is a confounding factor, and there is no data to show how the response to changing radiotherapy dose-volume is modified by the addition of the radio-sensitising chemotherapy.

Adding irinotecan and cetuximab to capecitabine also appears to increase the rate of toxicity for a given volume of small bowel irradiated: incidence of 18% when $V_{15Gy} \leq 125.5$ cm^3 [168]

compared with 11% $V_{15Gy} \leq 130$ cm^3 for 5-FU alone [162]. It follows that the tolerance volume for a given dose is also reduced when these drugs are being used. For example, three threshold volumes of V_{40Gy} can be compared: Chopra et al. saw a 5% risk when 150 cm^3 was irradiated; Robertson et al. saw a 10% risk when only 71 cm^3 was irradiated, with concomitant 5-FU [171, 192]; and when gemcitabine (a potent radiosensitiser) was used in the treatment of pancreatic cancer, the tolerance V_{40Gy} was even smaller (17 cm^3) for a higher observed risk (15%) [144]. The findings of Huang et al. may be consistent with this. They found that a lower dose was important in non-surgical compared with postoperative patients ($V_{40\%}$ (15.8 Gy) vs $V_{100\%}$ (39.6 Gy)), but a significantly larger proportion of these received concomitant chemotherapy (74% vs 45%, p = 0.011) and the use of chemotherapy was itself an independent predictor of toxicity among the whole cohort [164]. The confound to this interpretation is that it may be the surgery itself that alters the important DVH parameters in risk of toxicity – surgery is likely to reduce bowel loop mobility within the abdominal cavity [206] and may lead to 'fixed' loops, possibly leading to greater accumulated dose than if their position varied throughout a fractionated course [207].

A further potentially confounding issue in dose-volume analysis is the use of different methods for delineation of the structure concerned. This is of particular concern for the small bowel, in which individual loops can be outlined, or a peritoneal or abdominal cavity structure can be used as a surrogate. The former approach is recommended by recent RTOG guidance [208] but the latter technique is commonplace, particularly in gynaecological radiotherapy, partly as a way to compensate for inter-fraction variation in bowel loop filling and position. Tolerance threshold volumes for any given parameter will understandably be larger for the cavity structures, but different parameters might be more or less important for each technique: Huang et al. [164] and Chopra et al. [171] exclusively contoured individual loops of small bowel, and were also the only studies to identify V_{15Gy} as important in gynaecological

radiotherapy. Two groups of researchers have directly compared the two approaches within the same patients. In rectal neoadjuvant chemoradiotherapy, Banerjee et al. found that the same parameters were significant for both contouring methods (V_{15Gy} and V_{25Gy}) [167], while Chi et al. found that only an Intestinal Cavity DVH parameter (IC V_{45Gy}) had significant association with acute toxicity from adjuvant radiotherapy for endometrial cancer [169]. Again, the possible influence of surgery is a confounding factor here.

Overall, these results suggest that it may be incorrect to attempt to harmonise dose-volume constraints across tumour sites, and that it remains more appropriate to derive and set indication-specific constraints for radiotherapy planning.

Late effects

Survival rates are improving for many malignancies, meaning that late toxicities are increasingly important. Unfortunately, such late events have been collated and analysed in only three publications identified in the literature search [150, 154, 171]. This shortage of studies is presumably due to the increased costs that would be involved in comprehensive long-term follow-up, and of these three reports only one (Chopra et al.) found significant associations with small bowel dose-volume [171].

Late bowel toxicity can overlap with unresolved acute symptoms, but more commonly has a latency of many months and can sometimes only appear years after treatment. Pathological appearances are of mucosal atrophy, intestinal wall fibrosis and microvascular sclerosis causing chronic ischaemia, and may be irreversible and progressive. These changes manifest most commonly as pain or bloating after meals, but diarrhoea, urgency or frequency of bowel opening can also occur due to altered transit, dysmotility and/or malabsorption. At worst,

they may be complicated by obstruction, bleeding, perforation or fistula [209]. Gastrointestinal ulceration from denudation of the mucosa tends to develop several months after radiotherapy as a result of fibrosis of the tissue, with resultant ischaemia and it comes with the risk of significant haemorrhage or perforation [209]. There is thought to be a relatively low alpha-beta ratio of 4 Gy, suggesting the risk of late effects is likely to be increased if large doses per fraction are used [18]. Other features of late toxicity, driven by intestinal wall fibrosis and chronic ischaemia resulting from microvascular sclerosis, may only appear a number of years after radiotherapy. Symptoms can include diarrhoea, urgency or frequency of bowel opening, and when severe they can be life threatening or necessitate surgical intervention [210, 211]. Risk of toxicity is increased in patients who smoke [65], in those with pre-existing conditions such as diabetes, vascular disease or inflammatory bowel disease, and in those with lower body mass index (BMI) [55].

Historical estimates of tolerance parameters for late-effects of the small bowel include TD5/5 of 50 Gy for partial irradiation (one third of the volume of the small bowel), and 40 Gy for whole-organ irradiation. Estimates of TD50/5 (50% risk at five years) are 60 Gy for partial-organ and 55 Gy for whole-organ exposure [32]. The authors of the QUANTEC review found evidence consistent with these estimates, noting that rates of small bowel obstruction or perforation from 2% to 9% were observed after irradiation to the order of 50 Gy [141]. Further published data from analysis of pelvic radiotherapy for cervical cancer suggests the important dose-volume parameters associated with risk of late complications are similar to those identified for acute side effects (V_{15Gy}, V_{30Gy}, V_{40Gy} [171]).

Chronic radiation enteropathy is a condition that is not well understood, and can present in many ways including post-prandial pain, acute or intermittent small bowel obstruction, nausea, anorexia, weight loss, bloating, diarrhoea, steatorrhoea and malabsorption of

selected or multiple nutrients [212]. Prevalence of specific syndromes such as lactose intolerance, small bowel bacterial overgrowth and bile acid malabsorption is high among these patients, who benefit from investigation and treatment by a clinician with relevant specialist expertise [213]. Given this complexity, it is to be expected that any apparent relationship with dose-volume parameters would be harder to elucidate.

Intensity-Modulated Radiation Therapy

Intensity-Modulated Radiation Therapy (IMRT) is gaining popularity in abdominal and pelvic radiotherapy as a means to reduce dose exposure to the healthy GI tract. As reviewed here, multivariate analyses have confirmed significant associations between acute GI toxicity and dose-volumes for both the stomach and duodenum as low as 25 Gy. However, no relationship between toxicity and volumes irradiated to doses below 20 Gy has been observed. This would suggest that a low-dose threshold does exist, below which radiotherapy damage can be adequately repaired without leading to significant toxicity. This would explain the reduced toxicity that can be achieved by IMRT, which can reduce high dose to organs at risk despite an increased 'low-dose bath' [118, 214]. The same cannot be said of the small bowel, where three publications have shown that even V_{5Gy} is significantly associated with the risk of acute toxicity [159, 168, 192]. Despite this, the ability of IMRT to reduce the high dose to the bowel [215] appears to be sufficient to enable reduced acute and late bowel toxicity in pelvic radiotherapy [216-219] when this technique is employed.

Limitations

Important limitations in this review include data heterogeneity and the risk of bias. Reporting bias and publication bias mean that positive associations are likely to be over-represented, as investigations that find no relationship between dose-volumes and outcomes may be less likely to be successfully published. Though six such reports were found by the systematic

search, two of these 'negative' studies were published only as abstracts [155, 156], a much higher proportion than that observed among 'positive' analyses.

The groups of patients for comparison in these studies have been defined retrospectively, and as such may be subject to confounding differences in their underlying disease or other aspects of their treatment. The diverse range of underlying disease stages, treatment indications, concomitant chemotherapy regimens, and radiotherapy schedules and delivery techniques (within studies as well as between studies) also introduces potentially confounding factors.

2.5. Conclusions

From a review of ninety-six published studies, we can conclude that there is substantial evidence for the importance of the dose-volume received by the stomach, duodenum and small bowel in predicting the risk of toxicity. Adverse events can potentially be managed if these organs are defined accurately during the planning process, and tolerance constraints are achieved.

For the stomach and duodenum, derived LKB model parameters suggest 'serial' type tissue behaviour, and most data suggest that the risk of toxicity depends on volumes receiving high doses. Stomach dose thresholds predicting an increased risk include: V_{20Gy} 31%, V_{25Gy} 6.3%, V_{50Gy} 16 cm^3, and D_{2cm3} 53.6 Gy, and also for a combined gastro-duodenum structure V_{35Gy} 5% and V_{50Gy} 33%. Duodenum thresholds include: V_{25Gy} 45%, V_{35Gy} 5–20%, V_{40Gy} 16%, V_{45Gy} 2.6%, V_{55Gy} 13.9%, D_{mean} 46.1 Gy, and D_{2cm3} 55.5 Gy.

The small bowel dose-volume parameters predictive of toxicity vary according to the tumour site being treated. In the treatment of rectal cancer, predictive dose-volumes include not only the established V_{15Gy} (volume 120–275 cm^3) but also V_{5Gy} (291.9–500 cm^3), V_{10Gy} (92.6–300 cm^3)

to V_{40Gy} (71–125 cm^3) and V_{50Gy} (4.44 cm^3). In radiotherapy for gynaecological malignancies, the predictive dose-volume parameters are: V_{15Gy} 275 cm^3, V_{30Gy} 190 cm^3, V_{40Gy} 150 cm^3, and V_{45Gy} 180–195 cm^3 (if individual bowel loops are not contoured). Small bowel dose-volume thresholds for pancreas cancer radiotherapy are: V_{40Gy} 17 cm^3 and V_{50Gy} 10 cm^3, and for anal cancer: V_{30Gy} 310 cm^3 and V_{40Gy} 70 cm^3. Unfortunately, sufficient published data could not be found in order to untangle the confounding factors of disease type, effects of concomitant chemotherapy and timing of radiotherapy in relation to surgery. This highlights the requirement for more work in this field to collate and analyse radiotherapy dose-volume and toxicity data from prospective clinical trials, in order to better understand the mechanistic relationships of the effects of radiotherapy on normal tissue in interaction with other clinical factors.

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3. Chapter Three. Modelling duodenum radiotherapy toxicity using published cohort dose-volume histogram data

3.1. Introduction

Irradiation of the duodenum may result in severe, even life-threatening toxicity, such as ulceration with the risk of bleeding, fistula formation and fibrosis, all of which can lead to stenosis with possible gastric outlet obstruction. The duodenum was not mentioned specifically in the 1991 review of dose-volume by Emami et al. [32], and QUANTEC [141] referred to only one publication reporting specific duodenal toxicity outcomes, with no dose-volume histogram (DVH) data available [220]. As described in Chapter Two, several studies have since shown that the risk of toxicity is associated with an increased volume of duodenum irradiated, using data from the treatment of pancreatic cancer [88-90, 144], liver tumours [146] and para-aortic lymph node irradiation for gynaecological malignancies [152]. The key results are summarised in Table 3-1.

Table 3-1. Published duodenum dose-volume parameters predictive of toxicity, with derived dose-volume parameters or volume thresholds (as either absolute or proportional volumes of the duodenum), and associated comparison of proportional incidence of specified toxicity between those patients whose radiotherapy plans achieved or did not achieve this threshold value.

Reference	Cancer site	Concurrent chemotherapy	Duodenum DVH parameters	Risk comparison
Huang 2012 [88]	LAPC	Gemcitabine ± erlotinib	V_{25Gy} 45%	8% vs 48%
Nakamura 2012 [144]	LAPC	Gemcitabine	D_{mean} 46.1 Gy D_{2cm3} 55.5 Gy	19% vs 57% 21% vs 58%
Cattaneo 2013 [90]	LAPC	Capecitabine or 5-FU	V_{40Gy} 16% V_{45Gy} 2.6%	Not specified
Kelly 2013 [89]	LAPC	Gemcitabine ± 5-FU/capecitabine ± EGFRi	V_{55Gy} 1 cm^3	9% vs 47%
Yoon 2013 [146]	HCC	None	V_{35Gy} 5.4%	9% vs 46%
Verma 2014 [152]	Gynae (PA nodes)	Platinum agents (55%)	V_{55Gy} 13.94%	7% vs 49%

DVH: dose-volume histogram; LAPC: locally advanced pancreatic cancer; GI: gastrointestinal; $D_{mean:}$ mean dose to a structure; D_{2cm3}: dose to at least 2 cm^3 of a structure; V_{xGy}: volume of structure receiving at least x Gy; 5-FU: 5-fluorouracil; EGFRi: epidermal growth factor receptor inhibitor; HCC: hepatocellular carcinoma; Gynae: gynaecological malignancies; PA: para-aortic.

These publications have each identified specific features of the DVH that show an association with increased risk. To enable the prospective estimation of risk for subsequent patients, or to inform treatment planning, derivation is then required of parameters for an NTCP model, such as that of Lyman-Kutcher-Burman [221], which was described in the introduction. One study, published as an abstract by Pan and colleagues, has used individual patient data to derive values for the three parameters of the LKB model for the duodenum, using the endpoint of GI bleeding following irradiation for liver tumours [148]. However, a major potential limitation of findings derived from a single cohort of patients is their external generalisability. Results derived using data from multiple institutions and treatment protocols may be more indicative of the true underlying properties of the tissue or organ of interest, and may be more universally applicable [222].

Two existing publications have described attempts to derive NTCP model parameters for the duodenum using published toxicity data: Prior and colleagues used published DVH data for the small intestine and duodenum [223] while Elhammali et al. derived LKB parameters for the duodenum using an assumed radiation exposure – homogenous irradiation of 5% of the duodenum by the prescription dose [224]. Both studies also included data from both standard and hypofractionated radiotherapy. The radiobiology and pathology of upper GI toxicity is poorly understood, and the mechanisms for normal tissue damage and repair in standard fractionation potentially follow different pathways than those of extreme hypofractionation.

The intention in this analysis was to analyse published DVH data regarding only conventionally fractionated radiotherapy, supplemented with data derived from individual patient outcomes from two prospective clinical trials of chemoradiotherapy for locally advanced pancreatic cancer, namely ARCII and SCALOP.

The aims of this work were: firstly to derive an updated NTCP model for duodenal toxicity in conventional fractionated radiotherapy using available published duodenum DVH data, secondly to test model predictions in two prospective trials delivering chemo-radiation in pancreatic cancer, and thirdly further revise the model incorporating prospective trial data.

3.2. Materials and methods

3.2.1. Updating the current NTCP model using published DVH data

A comprehensive literature search was conducted as described in Chapter Two, to identify publications describing clinical treatment of adult humans with conventionally-fractionated radiotherapy and which reported duodenal DVH parameters and incidence data for toxicity attributable to upper GI irradiation. Further suitable publications were identified through existing reviews, and results were examined systematically by the author. All DVH values for the duodenum were extracted with the associated proportional incidence of toxicity experienced by that patient cohort.

3.2.2. Extraction of DVH data for prospective clinical trial cohorts

The planning CT scans, radiotherapy plans, and individual patient outcomes were available for the two additional clinical trials, SCALOP and ARCII. Patients in the SCALOP study (NCT 01032057, n = 74) with stable or responding disease after twelve weeks of induction gemcitabine and capecitabine chemotherapy were randomised to receive either gemcitabine or capecitabine alongside 50.4 Gy in 28 fractions [100]. Patients in the single-arm open-label ARCII study (EudraCT 2008-006302-42, n = 23) received concomitant chemoradiotherapy with gemcitabine, cisplatin and nelfinavir (a hypoxia modifier). Radiotherapy was delivered in two phases: 50.4 Gy in 28 daily fractions was prescribed to the primary tumour and elective lymph nodes, followed by a sequential boost to the primary tumour of 9 Gy in five fractions [131].

The eligibility criteria, patient disease characteristics and treatment outcomes for the two trials have been published previously [100, 131]. In both studies, effects of toxicity events were prospectively recorded and graded according to CTCAE, using v3 [272] in SCALOP, and v4 [37] in ARCII, and both studies recorded baseline toxicity symptoms at trial entry. In ARCII, clinical assessments were performed weekly during chemoradiotherapy, six to eight weeks after chemoradiotherapy, and three-monthly thereafter until twelve months after trial entry. In SCALOP, the assessments were monthly during induction chemotherapy, weekly during chemoradiotherapy, two weeks following chemoradiotherapy completion, and three months and six months later. For both trials, the prophylactic use of a proton-pump inhibitor or histamine receptor blocker and appropriate anti-emetics during radiotherapy were mandatory, except where contra-indicated.

		Combined	ARCII	SCALOP
N		91	21	70
Age, mean (range)		64.0 (43.4–78.8)	64.5 (43.4–78.8)	63.8 (45.9–77.9)
Sex	Male	50 (54.9%)	11 (52.4%)	39 (55.7%)
	Female	41 (45.1%)	10 (47.6%)	31 (44.3%)
BMI, mean (range)		23.9 (16.4–44.4)	23.6 (17.4–34.2)	24.0 (16.4–44.4)
ECOG performance status	0	45 (49.5%)	7 (33%)	38 (54.3%)
	1	39 (42.9%)	10 (47.6%)	29 (41.4%)
	2	7 (7.7%)	4 (19.0%)	3 (4.3%)
Tumour volume [cm^3], mean (range)		35.9 (1.4–114.2)	29.8 (6.6 – 74.0)	37.7 (1.4–114.2)
Tumour location	Body	5 (5.5%)	4 (19.0%)	1 (1.4%)
	Head	74 (81.3%)	13 (61.9%)	61 (87.1%)
	Neck	12 (13.2%)	4 (19.0%)	8 (11.4%)
Concomitant chemotherapy	Gem			36 (51.4%)
	Cape			34 (48.6%)
Baseline upper GI toxicity		33 (36.3%)	5 (23.8%)	28 (40%)
Baseline Grade ≥ 2 nausea or vomiting		2 (2.2%)	1 (4.8%)	1 (1.4%)
Baseline Grade ≥ 2 Abdominal pain		5 (5.5%)	0	5 (7.1%)
Baseline Grade ≥ 2 Weight loss		3 (3.3%)	0	3 (4.3%)
Baseline diarrhoea		12 (13.2%)	2 (9.5%)	10 (14.3%)

Table 3-2. Collated patient characteristics including incidence of baseline toxicity symptoms

	Combined	ARCII	SCALOP
Grade 0 Upper GI Toxicity	17 (18.7%)	3 (14.3%)	14 (20.0%)
Grade 1 Upper GI Toxicity	36 (39.6%)	7 (33.3%)	29 (41.4%)
Grade 2 Upper GI Toxicity	26 (28.6%)	8 (38.1%)	18 (25.7%)
Grade 3 Upper GI Toxicity	12 (13.2%)	3 (14.3%)	9 (12.9%)
Grade ≥ 2 Upper GI Toxicity	38 (41.8%)	11 (52.4%)	27 (38.6%)
Grade ≥ 2 Nausea or vomiting	27 (29.7%)	12 (57.1%)	15 (21.4%)
Grade ≥ 2 Anorexia	13 (14.3%)	3 (14.3%)	10 (14.3%)
Grade ≥ 2 Abdominal pain	13 (14.3%)	3 (14.3%)	10 (14.3%)
Grade ≥ 2 Weight loss	8 (8.8%)	1 (4.8%)	7 (10%)
Grade ≥ 2 GI bleeding	9 (9.9%)	0 (0%)	9 (12.9%)
Grade 0 diarrhoea	44 (48.4%)	7 (33.3%)	37 (52.9%)
Grade 1 diarrhoea	28 (30.8%)	10 (47.6%)	18 (25.7%)
Grade 2 diarrhoea	12 (17.1%)	0 (0%)	12 (17.1%)
Grade 3 diarrhoea	7 (7.7%)	4 (19.0%)	3 (4.3%)
Grade ≥ 2 diarrhoea	19 (20.9%)	4 (19.0%)	15 (21.4%)

Table 3-3. Acute toxicity incidence in ARCII, SCALOP and a combined cohort

In SCALOP, the GTV was defined as 'tumour visualised on planning CT scan along with lymph nodes > 1 cm diameter', and the planning target volume (PTV) was defined as 'the GTV plus a margin of 20 mm -in the superior-inferior direction, and a margin of 15 mm in other directions'. All patients were treated to 50.4 Gy in 28 daily fractions in a single phase with three-dimensional conformal radiotherapy.

In ARCII, radiotherapy was delivered in two phases. The first encompassed the primary tumour and draining lymph node regions (peripancreatic and aorto-caval nodes, plus common bile duct nodes for head of pancreas tumours). This was followed by a sequential boost to the primary tumour PTV (also defined as the GTV plus 20 mm in the cranio-caudal axis and 15 mm in all other directions). Phase 1 was delivered using IMRT and Phase 2 using 3D-conformal planning. The use of intravenous-contrast and oral water contrast (100–200 mL-) in the acquisition of treatment-planning sectional imaging was specified in both studies. No dose-volume constraints for the stomach or duodenum were specified in either study. Radiotherapy for all patients in the ARCII study was planned using Varian Eclipse (Varian

Medical Systems, Palo Alto USA). Two patients in the ARCII study underwent re-imaging and re-planning due to weight loss during radiotherapy. Deformable registration of the planning CT and dose cubes for summation of the two partial courses was conducted using Mirada RTx (Mirada Medical, Oxford, UK). Doses were recalculated to reflect the delivered dose for patients who did not complete their prescribed treatment course. SCALOP was a national multi-centre study, hence radiotherapy was planned using a variety of treatment planning systems. However, the quality of radiotherapy delivery was enforced through an extensive and robust system of pre-trial assessment and on-trial monitoring [225, 226].

The stomach, duodenum, and small bowel were segmented retrospectively according to the RTOG atlas and guidance [208]. Where these structures had been contoured previously by treating clinicians – as was the case in all ARCII patients and in nine SCALOP patients – they were modified or replaced as necessary. Particular care was taken to identify the pyloric sphincter correctly, to indicate the junction of the stomach and duodenum, and to contour the full length of the duodenum up to the duodenojejunal flexure, which is suspended by the ligament of Treitz. Radiotherapy planning CT scans and dose-cubes were anonymised and imported into CERR, and absolute cumulative dose-volume data were exported in 5-Gy bins using a custom in-house MATLAB tool.

Where the GI tract normal structures had not previously been contoured, as was the case for the majority of SCALOP patients, they were defined post-hoc by the author, and reviewed with a radiologist and a radiation oncologist with an interest in GI oncology. The SCALOP trial had undertaken a prospective radiotherapy quality assurance review during the trial, including the approval of pre-trial benchmark test cases of contouring and planning which were required before centres were permitted to treat patients in the study [225].

Median DVH statistics for the SCALOP and ARCII patients were derived from the individual patient DVH data, for each 5-Gy bin for which data was extracted. For consistency, a cubic spline was then fitted to this data to derive a continuous DVH using the same method as was applied to the published trial data. The data describing these two studies was then added to the model-fitting process alongside the data taken from the published studies, weighted in the same manner, according to the number of patients in each trial.

3.2.3. Equivalent dose calculation and LKB model fitting

To facilitate comparisons between studies, the reported duodenum dose-volume parameters were converted to the equivalent dose in twenty-five fractions ($EQD_{25\#}$), chosen for being both median and mode among the source cohorts, using an alpha-beta ratio of four [227, 228]. For the majority of studies, all treatment was delivered in a fixed and consistent number of fractions but there were some cohorts with mixed numbers of fractions delivered. Verma et al. report that in 7% of their patients, a sequential rather than integrated boost was used, though more detail is not provided [152]. In the study by Poorvu et al., sequential dose escalation was titrated to tolerance by normal-tissue constraints, hence in conversions to $EQD_{25\#}$ the reference number of fractions for each partial dose-volume in the study was different for each dose level [150]. All source data values are shown in Table 3-7.

Cubic splines were fitted to the published DVH data using a Microsoft Excel macro, to recreate continuous distributions. An example spline fit is shown in Figure 3-1.

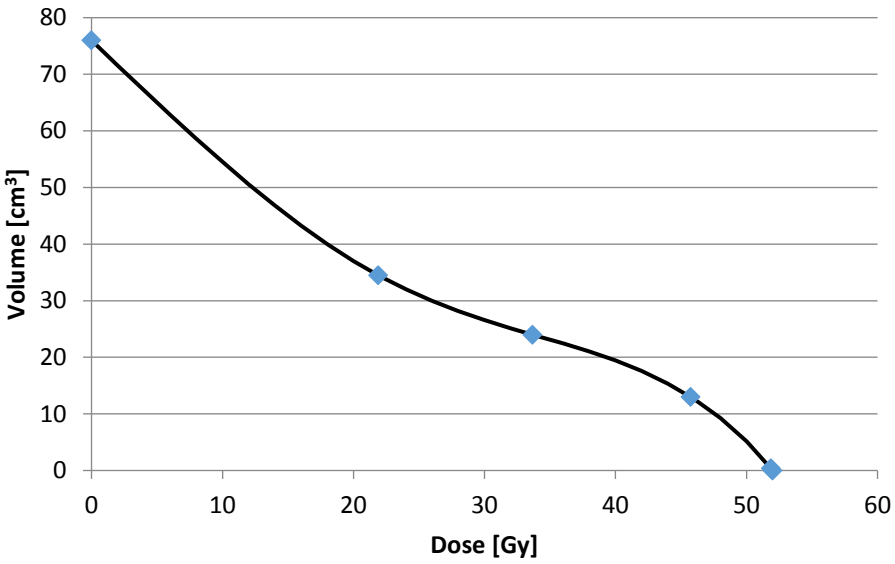


Figure 3-1. Visualisation of cubic spline fitted to reported data to reconstruct a continuous DVH.

Each reconstructed DVH was sampled at 5-Gy intervals to derive the effective volume (V_{eff}) using the following expression [30]:

$$V_{\text{eff}} = \sum_j \left[\left(\frac{D_j}{D_{\max}} \right)^{\frac{1}{n}} \Delta V_j \right] \quad (1)$$

where D_j and ΔV_j are the dose and volume of the j^{th} element on the DVH, $D_{\max}$ is the maximum dose, and n is the LKB tissue architecture parameter.

The standard form of the LKB model was adopted [221]:

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-\frac{t^2}{2}} dt \quad (2)$$

where u is a function of the 'steepness' parameter m [221]:

$$u = \frac{D_{\max} - \text{TD}_{50}(V)}{m \cdot \text{TD}_{50}(V)} \quad (3)$$

The 50% tolerance dose to a sub-volume of the organ $\mathrm{TD}_{50}(V)$ is found by applying a power law volume effect [221]:

$$\mathrm{TD}_{50}(V) = \frac{\mathrm{TD}_{50}(1)}{{V_{\mathrm{eff}}}^{n}} \quad (4)$$

Values of *n*, *m*, and $\mathrm{TD}_{50}(1)$ (the 50% tolerance dose for irradiation of the whole organ) were found by simultaneously minimising the least square error between the LKB model prediction and all observed clinical outcomes. The non-linear Levenberg-Marquardt search technique was used, and confidence intervals on the fit values obtained were estimated using the leave-one-out method.

The model was firstly fitted using only the published DVH data sources, initially with an unconstrained fit of all three parameters (DuoLKB1). As the resulting value for *n* fell slightly below the confidence intervals for the value derived by Pan et al. (0.09–0.30) [148], the model was fitted again with *n* constrained to ≥ 0.09 (DuoLKB2). For models DuoLKB1 and DuoLKB2, each data source was treated with equal significance, while for model DuoLKB3 the contribution of each source was then weighted according to the number of patients included in that treatment cohort, with an unconstrained fit. The model values were then used to predict the rate of toxicity expected in the two new clinical trial datasets (ARCII and SCALOP). Finally, the model was then fitted again including the average DVH data for the two new data sources, with each data point again weighted to reflect the number of patients per cohort (DuoLKB4). Therefore eight datasets were used for fitting models 1-3, and ten datasets for model 4.

3.3. Results

The literature search identified 170 results, among which were six publications that reported duodenum dose-volume data and relevant toxicity outcomes and could therefore be included in this analysis [89, 90, 150-152, 229] (see Table 3-6). Two of the studies reported data separately for separate cohorts treated using different variants of the same treatment protocol. In the analysis by Cattaneo et al., thirty-eight of the sixty-one patients were treated to a dose of 44.25 Gy in fifteen fractions ('cohort I'), while the other twenty-three patients also received a simultaneous, integrated boost to a total dose in the range of 48–58 Gy ('cohort II') [5]. Xu et al. reported that thirty-five of the seventy-six patients were treated to a dose of 45 Gy in twenty-five fractions while the other forty-one received a boost to 55 Gy in twenty-five fractions [151]). Where separate sub-groups were described within a study, these patient cohorts were considered separately for model fitting. Eight datasets were therefore used for fitting models DuoLKB1-3, and ten datasets for model DuoLKB4.

Cohort	Patients	Toxicity incidence	V_{0Gy}	V_{10Gy}	V_{20Gy}	V_{30Gy}	V_{40Gy}	V_{50Gy}	V_{60Gy}
Cattaneo I	38	17%	69.0	51.6	35.7	22.9	15.2	6.2	0.0
Cattaneo II	23	8%	76.0	54.5	37.0	26.6	19.5	5.1	0.0
Kelly	106	8%	65.0	62.5	59.0	53.4	44.7	25.2	0.0
Poorvu	53	7%	71.0	54.4	38.7	24.4	12.5	3.7	0.0
Xia	33	0%	70.0	49.7	31.1	15.9	5.7	1.1	0.0
Xu 'low'	35	3%	83.0	69.0	55.3	42.3	28.3	1.0	0.0
Xu 'high'	41	4%	83.0	72.1	61.6	52.2	41.0	4.0	0.0
Verma	105	8%	70.0	61.3	52.0	41.9	30.3	16.8	1.6
ARCII	23	14%	68.5	68.3	67.3	60.3	51.9	33.7	0.0
SCALOP	74	12%	92.6	77.0	68.9	60.2	46.3	8.8	0.0

Table 3-4. Selected values from the reconstructed duodenum DVH for each cohort used in the model fitting.

The analysis included treatment data for a total of 531 patients with a median of sixty-eight patients (range 23–106) per cohort. Median follow-up duration ranged from six to thirty-two months (median sixteen months) and the observed rate of Grade ≥ 3 GI toxicity ranged from

0%–14% (median 8%). Selected values from the reconstructed duodenum DVH for each cohort are shown in Table 3-4. The LKB model parameter values derived using the different model fits are detailed in Table 3-5, along with the SSE achieved. Comparisons of least square error values for each model do not necessarily indicate relative 'quality' of model fit achieved, as each model was derived using different constraints, and model DuoLKB4 using a different dataset.

Model	*n*	*m*	TD_{50} (1) [Gy]	SSE
DuoLKB1	0.068 (0.060-0.076)	0.36 (0.30-0.43)	125.9 (63.1-188.7)	0.0160
DuoLKB2	0.090 (0.090-0.090)	0.39 (0.32-0.46)	141.8 (36.7-246.9)	0.0161
DuoLKB3	0.070 (0.061-0.079)	0.46 (0.40-0.52)	183.8 (122.1-245.5)	0.0163
DuoLKB4	0.193 (0.147-0.239)	0.51 (0.47-0.55)	299.1 (242.1-356.1)	0.0208

Table 3-5. Results of LKB model fitting.
Mean values for parameters are shown with 95% confidence intervals estimated by refitting all data using the leave-one-out method (in each refitting of DuoLKB2 the optimal value for parameter n was precisely 0.09). SSE = residual sum squared error; DuoLKB1 = Unconstrained, unweighted; DuoLKB2 = Constraint: n > 0.09, unweighted; DuoLKB3 = Unconstrained, weighted; DuoLKB4 = Unconstrained, weighted, data from ARCII & SCALOP included.

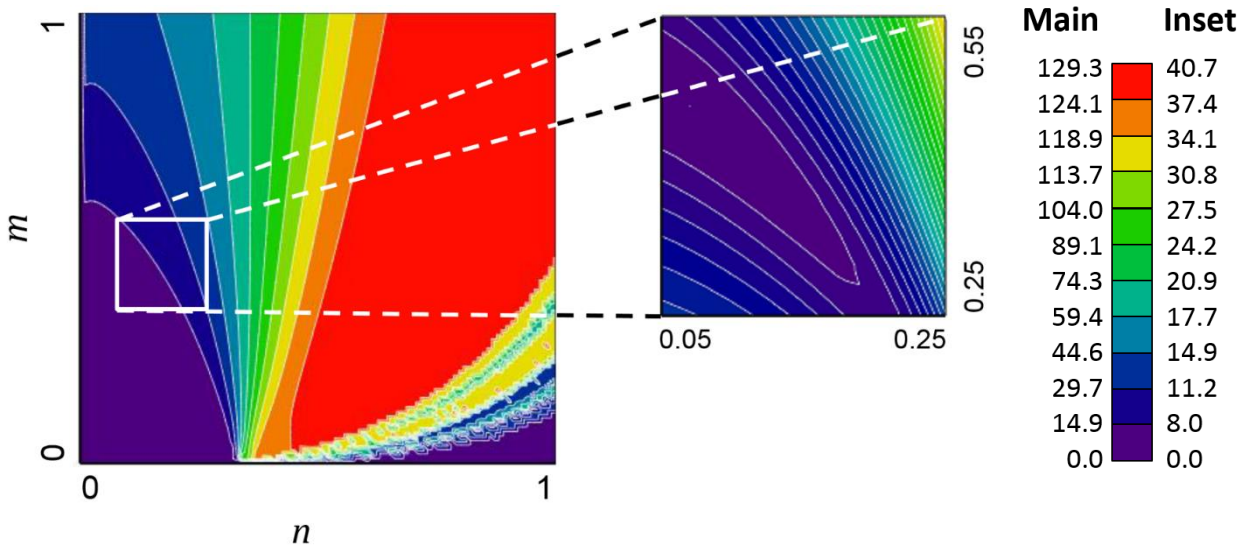


Figure 3-2. Plot of solution space for model DuoLKB2 (TD_{50} (1) value of 142 Gy).
Low cost (favourable) solutions in purple and the high cost (unfavourable) solutions in red. A subset of solution space is shown (inset). The colour bar shows the value of the cost function (note a different scale for the inset plot for clarity)

The solution space for DuoLKB2 (LKB function with a TD_{50} (1) value of 142 Gy) is visualised in Figure 3-2. This shows that there is some degeneracy in the fit of values of *n* and *m,* with a shallow 'valley' in solution space corresponding to the region of optimised values. Figure 3-3 (a) shows a plot of the four models (DuoLKB1–4) and the model derived by Pan et al. Confidence limits are shown for the unconstrained model, derived using leave-one out cross-validation. Figure 3-3 (b) shows the model derived when incorporating the clinical trial datasets (DuoLKB4), along with 95% confidence estimates for this curve, demonstrating the uncertainty that exists outside of the observed data range.

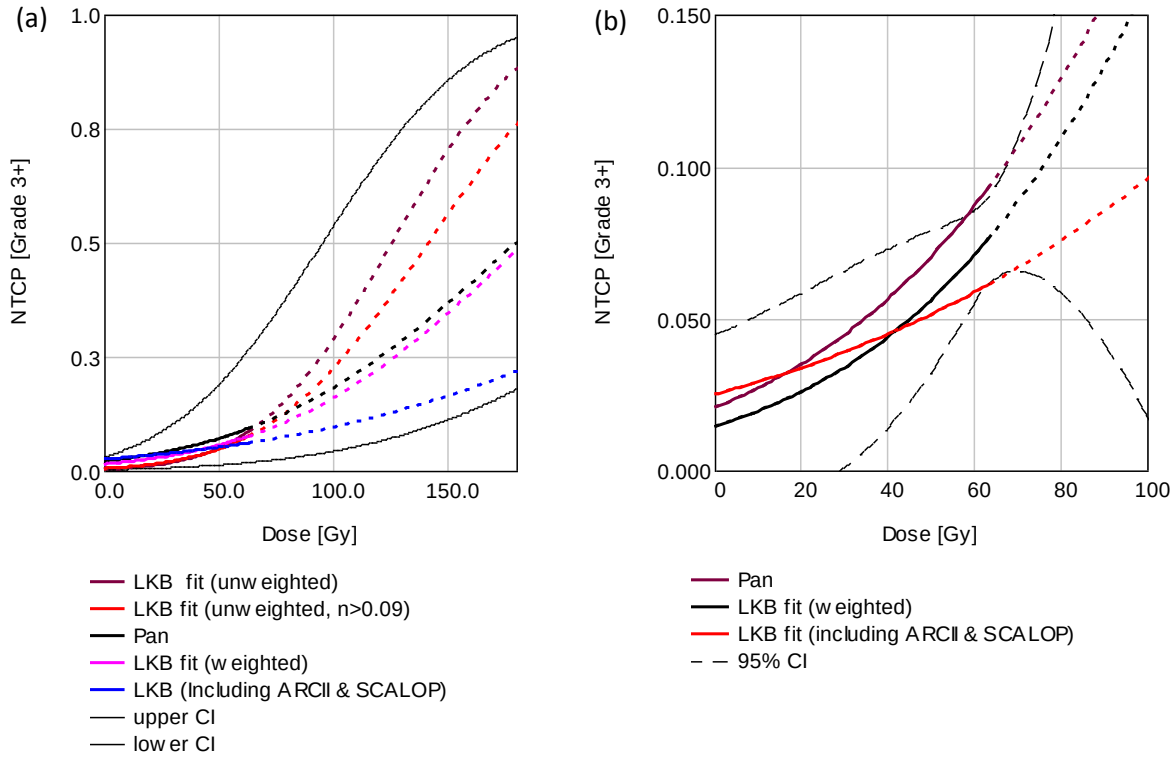


Figure 3-3. NTCP model of grade ≥3 duodenal toxicity fitted to published data
(a) unconstrained fit (DuoLKB1), fit with constraint n ≥ 0.09 (DuoLKB2), fit weighted according to cohort size (DuoLKB3), weighted fit including ARCII and SCALOP data (DuoLKB4), and the model parameters as published by Pan et al. Confidence intervals for the fitting process show the envelope of solutions given using a leave-one-out error estimation. Curves are shown by dotted lines where the model extrapolates beyond the region supported by the data.

(b) NTCP model of duodenal toxicity published by Pan, and those fitted to published data either excluding (DuoLKB3) or including (DuoLKB4) the ARCII and SCALOP trials, weighted according to cohort size. 95% confidence intervals are shown for the fit excluding the ARCII and SCALOP trials.

The variable on the x-axis is the 'reference dose' as used in the Kutcher 'effective volume' dose reduction approach.

The proportional incidence of Grade ≥ 3 gastrointestinal toxicity observed in the SCALOP trial was 8.1%, and the values predicted by the three models DuoLKB1, 2, and 3 were 7.4%, 7.6%, and 7.0% respectively. For the ARCII trial, the observed toxicity incidence was 14.3%, while the incidence predicted by the model fits were 8.9%, 9.1%, and 7.8% respectively.

3.4. Discussion

Six publications have been identified with clinical duodenum DVH data that have been used to fit the LKB model and derive parameter values that have consistency with those derived by existing publications using individual patient data. The derived values were especially similar to previous results when the sources were weighted according to the number of patients in each cohort, as highlighted in Figure 2. These parameters have then been used to predict toxicity within two clinical trials of pancreatic cancer chemoradiotherapy, with accurate results for one study but not the other. It is felt likely that the particular chemotherapy combination used in the ARCII trial (concurrent gemcitabine, cisplatin, and nelfinavir) explains the observed toxicity in this study being higher than was predicted by the model. When the data from these clinical trials is incorporated into the model fit, the values are less consistent with existing literature, however this comprises the largest meta-analysis of this type to have been conducted. This model (DuoLKB4) is based on the pooled data accrued in the treatment of over 500 patients, and it is therefore the model that is suggested be adopted for clinical practice.

The values derived for the parameter *n* suggest a small volume effect for the toxicity endpoint. Low values of *n* increase the dependence of the outcome on the maximum dose received by the tissue and are seen for tissues (or endpoints) where the functional subunits are arranged in a serial manner, as was described in Chapter One. The results of this meta-analysis therefore suggest that toxicity in the duodenum behaves in the manner expected of a serially

structured organ, where the maximum exposure dose is more important than the affected volume of the organ at risk. This is logical, as the common clinical events used to denote toxicity in the component studies in this analysis, such as bleeding or ulceration, are likely to only occur when a sufficient threshold dose is achieved to cause a high proportion of cell death and result in physical damage to the mucosa. Only a small proportional or absolute volume of the duodenum needs to have been irradiated to this dose. This finding is consistent with most previous published findings regarding the upper GI tract.

While results of dosimetry-toxicity analysis have differed between studies, the importance of high dose to the duodenum is clear (Table 3-1), and the predictive significance of the V_{55Gy} has been reproduced by independent investigators [89, 152]. Only Huang et al. have reported that toxicity was associated with larger proportional irradiation by a lower dose (predictive threshold V_{25Gy} 45%) [88]. Similarly while there is variability in the values that have been derived for the LKB model by the various publications considered here, there is some consistency in the ranges of results observed, and the results of the meta-analysis are closer to those found in studies of individual patient data [148] than in the two other attempted meta-analyses [223, 224]. This is attributed to the use of collated rather than assumed volume data, and the exclusion of possibly confounding hypofractionated radiotherapy data.

During their original development of the LKB model, Kutcher and Burman published model parameters for many tissues based on clinical tolerance data developed by Emami et al. [29]. The duodenum was not among these tissues, but values reported for ulceration or perforation in the stomach were n = 0.15, m = 0.14, $TD_{50}(1)$ = 65 Gy and for obstruction or perforation of the small bowel were n = 0.15, m = 0.16, $TD_{50}(1)$ = 55 Gy. Pan and colleagues later derived LKB model values for the duodenum using retrospective analysis of 92 patients treated for liver tumours with conformal radiotherapy [148]. The patients received either 1.5 Gy twice

daily with intrahepatic arterial chemotherapy, or 1.8 – 3.0 Gy four times per day without chemotherapy. Thus, for analysis these doses were converted to effective doses at 2 Gy per fraction (EQD_{2Gy}). The LKB values derived were n = 0.12 (0.09–0.30), m = 0.49 (0.36–0.61) and TD_{50} (1) = 180 Gy (69% CI ≈100 to > 200 Gy), suggesting a small volume effect and shallow dose-NTCP curve. In our model fitting process, when the value of n was constrained to ≥ 0.09, the other fitted values also shifted closer to those of Pan et al., but with no change in the goodness of fit, suggesting these values are equally appropriate to the data. Interestingly, the values for DuoLKB3 – with free fitting for parameter values, but with data sources weighted according to patient numbers – were even closer to those of Pan et al.

LKB parameters for the duodenum have also been derived by Murphy et al. using data from a cohort of 73 patients treated with single-fraction SBRT for inoperable pancreatic cancer (n = 0.12, m = 0.23, and TD_{50} (1) = 24.6 Gy) [230]. While the authors acknowledged that comparing single-fraction treatment with conventional fractionation regimens is challenging, the EQD_{2Gy} for 24.6 Gy in a single fraction is 117.3 Gy (alpha-beta 4 Gy), a value not dissimilar to those established by other authors and ourselves.

In their meta-analysis Prior et al. incorporated published duodenum DVH and toxicity data from four studies (two using conventional fractionation (used in this investigation) and two using hypofractionated radiotherapy, and encompassing 312 patients [223]. A model was derived partly using small bowel homogenous irradiation tolerance data from Burman et al. [29]. They were unable to derive a value for n, and this may explain the difference between the LKB values they have fitted (m = 0.21 ± 0.05 and TD_{50} (1) = 60.9 ± 7.9 Gy) and ours.

Elhammali et al. collated toxicity data from 16 human studies – and two canine studies – involving a total of 1160 patients and used regression analysis to show that dose was the only

significant predictor of toxicity among the studies they analysed [224]. The authors went on to derive LKB parameters n = 0.38–0.63, m = 0.48–0.49, and TD_{50} (1) = 35–95 Gy; however, as the majority of publications they examined did not report treatment DVH data, the authors had resorted to an assumption that across all studies 1–5% of the duodenum was exposed to the prescription dose. Their values for n are higher and their values for TD_{50} (1) are considerably lower than those found in other studies (including ours). The assumption of volume made by the authors is not likely to reflect the true exposure of the duodenum in these patients, particularly when some cohorts included single-fraction intraoperative radiotherapy and others were preclinical animal studies. These further particularities limit the applicability of these results to conventional clinical external beam irradiation.

A key limitation of this study is the persistently small number of studies that provide suitable data, and their somewhat heterogeneous range of clinical conditions and treatment schedules. However, these results are potentially strengthened by the addition of data derived directly from the complete DVH for the individual patients treated in the SCALOP and ARCII trials, and the coherent use of similarly fractionated studies. One publication that was found and reviewed provided DVH data only for a combined stomach-duodenum structure [149] and these values were not incorporated into the model fitting, while Pan et al. reported only mean dose for the duodenum [148]. While there is some degeneracy of the parameter values derived in the model fitting there is also a shallow 'valley' as shown in Figure 1 where the fit is optimised. The confidence intervals for the parameter values are broad, and the proportion of each of the models that is extrapolated beyond the observed data should be interpreted with caution. It is acknowledged that the spline-fitting method that has been used to recreate the DVH from reported data points may lack precision when few data are provided. Further uncertainty exists in the conversion of the varying dose-fractionation schedules, and

in the influence of the differing chemotherapy drugs and combination regimens on the behaviour of duodenal radiotherapy toxicity.

For an organ to be studied rigorously, it must be defined consistently. Detailed guidance on the delineation of the duodenum has now been published in the recent RTOG upper GI atlas, but the authors of this guideline noted that the fourth part of the duodenum was frequently missed by the contributing clinicians, meaning that existing data relating to this organ may be affected by this inconsistency in anatomical delineation [208]. While the duodenum is less mobile than other parts of the small bowel, large inter-fractional variations in volume still occur, which can lead to significant differences in delivered dosimetry compared with that which is planned [231-233]. Very few publications have investigated the delivered or accumulated dose to upper GI organs [234], and the data used here rely on planned dose as a surrogate.

A perceived benefit of the LKB model includes the rational interpretation that can be made of the parameter values, relating to tissue architecture, dose-response gradient and tolerance dose. However, the LKB model originates from an era of simple radiotherapy field arrangements, with more homogenous dose distribution across target structures and normal tissues. Consequently, the DVH-reduction step may be inappropriate for the modern era of highly modulated radiotherapy dose depositions because the detail of the shape of the DVH will be obscured [235]. Furthermore, for the duodenum, as for the other hollow organs in the GI tract, the tissue of interest itself comprises only a thin layer surrounding a variable amount of contents and the dose-volume concept appears of limited application. Dose-surface maps can achieve a more accurate description of the dose received by the relevant parts of the structure, though are not straightforward to render for complex curved organs such as the duodenum [236]. Ideally, these tools would also be used to record delivered rather than

simply a planned dose, and doing so may allow more accurate modelling of toxicity in hollow or tubular organs [237].

There are subtle differences in the toxicity endpoints that were defined by the source publications utilised here, but which have had to be pooled to facilitate the analysis. Also, many of the relevant symptoms that indicate radiation toxicity (nausea, vomiting, anorexia, abdominal pain) could arise from damage to the other tissues of the abdomen, particularly the stomach and small bowel, even if the duodenum were entirely spared, or could result from systemic therapy or the underlying disease. Some analyses have confined their study to outcomes with physical evidence of toxicity, such as ulceration or bleeding in the organ of interest, proven using endoscopy. To the author, this seems an oversimplification that may overlook other features of duodenal toxicity that also cause patient morbidity, and which may impair outcomes if they were to impede the delivery of a prescribed course of radiotherapy.

3.5. Conclusions

Parameters for the LKB model for the duodenum have been successfully derived using reconstructed DVH data from a set of publications reporting clinical toxicity outcomes after irradiation of upper abdominal tumours, which show some consistency with values derived using individual patient data. These parameters can be used to understand the dependence of toxicity in this organ on dose and volume and potentially predict toxicity risk in a patient cohort, but work in this field is restricted by the limited availability of source data and its heterogeneity, and by the complexity of the outcome of interest.

Acknowledgement

Dr Mike Partridge assisted in generation of the LKB model parameters and figures.

Reference	Clinical data	Patients	mFU, [m]	Cancer site	Radiotherapy dose schedule ($EQD_{25\#}$ where applicable)	Chemotherapy	Radiotherapy technique	Toxicity scale	Grade ≥ 3 toxicity	Duodenum dose-volume data available
Cattaneo 2013 [90]	NS	61	19	LAPC	45 Gy ± 15 Gy boost in 15 # ($EQD_{25\#}$ = 51.9 Gy ± 17.1 Gy)	Capecitabine or 5-FU	IMRT	CTCAE v3	12%	D_{mean}, V_{20Gy}, V_{30Gy}, V_{40Gy}, V_{45Gy}
Kelly 2013 [89]	Retro	106	12	LAPC	50.4 Gy in 28 # ($EQD_{25\#}$ = 49.0 Gy)	Gemcitabine ± 5-FU/cape ± EGFRi	3D-CRT (75) /IMRT (31)	CTCAE v4	8%	D_{mean}, V_{40Gy}, V_{45Gy}, V_{50Gy}, V_{55Gy} V_{60Gy}
Xia 2013 [229]	Prosp	33	6	Pancreas	PTV: 50 Gy, GTV: 70 Gy in 20 # ($EQD_{25\#}$ = PTV: 53.1 Gy, GTV: 75.0 Gy)	None	Tomo	NS	0%	D_{1cc}, D_{5cc}, D_{10cc}
Poorvu 2013 [150]	Retro	53	17	Gynae	54 Gy in 30 # ($EQD_{25\#}$ = 51.6 Gy)	Cisplatin	IMRT	CTCAE v4	7%	V_{55Gy} & V_{60Gy}
Xu 2014 [151]	Retro	76	19	Gynae (PA nodes)	45 Gy ± 10 Gy boost in 25 #	Platinum agents (86%)	IMRT	CTCAE v4	4%	D_{mean}, D_{max}, V_{35Gy}, V_{40Gy}, V_{50Gy}, V_{55Gy}, D_{2cc}, D_{5cc}
Verma 2014 [152]	Retro	105	32	Gynae	64 Gy in 25 #	Platinum agents (55%)	IMRT	RTOG	8%	D_{Max}, D_{2cc}, D_{5cc}
Mukherjee 2013 [102]	Prosp	74	12	LAPC	50.4 Gy in 28 # ($EQD_{25\#}$ = 49.0 Gy)	Gemcitabine (51%) or capecitabine (49%)	3D-CRT	CTCAE v3	8%	Access to full individual patient DVH data
Wilson 2016 [133]	Prosp	23	14	LAPC	59.4 Gy in 33 # ($EQD_{25\#}$ = 55.4 Gy)	Gemcitabine, cisplatin & nelfinavir	3D-CRT/ IMRT	CTCAE v3	14%	Access to full individual patient DVH data
Kim 2009 [149]	Retro	73	11	HCC	36 Gy in 12 #	None	3D-CRT	CTC v2	12%	'StoDuo' D_{mean}, D_{max}, V_{25Gy}, V_{40Gy}
Pan 2003 [148]	Retro	92	7.6	Hepatic	1.5 Gy per # BD with chemo or 1.8 – 3 Gy per # QDS without	Hepatic arterial chemotherapy	3D-CRT	N/A	16%	D_{mean}

Table 3-6. Details of publications and clinical trial cohorts with duodenum DVH data available, including those used in this analysis.
mFU [m] = median follow-up [months]; # = number of radiotherapy treatment fractions; NS = not specified; Retro = retrospective; Prosp = prospective; LAPC = locally advanced pancreatic cancer; 5FU = 5-fluorouracil; cape = capecitabine; IMRT = intensity modulated radiotherapy; 3D-CRT = 3D conformal radiotherapy; Tomo = TomoTherapy; CTC = National Cancer Institute Common Toxicity Criteria; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PA: para-aortic; RTOG = Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria, StoDuo = combined stomach & duodenum; $EQD_{25\#}$ = Equivalent Dose in 25 #, using α/β ratio = 4; BD = twice daily; QDS = four times per day

Reference		Cattaneo 2013 [90]			Kelly 2013 [89]			Xia 2013 [229]	Poorvu 2013 [150]	Xu 2014 [158]			Verma 2014 [152]
Data		Mean (SD)			Mean (SD)			Mean (SD)	Mean (range)	Mean / median (range)			
Cohort	Group 1 (SIB)	Group 2	Weighted average	G0-1 toxicity	G2-5 toxicity	Weighted average				High dose	Low dose	All patients	
Patients	23	38	61	90	16	106		25	53	41	35	76	105
Volume [cm³]	69 (36.4)	76 (58)	*73.4*							73.9 (21.2-148.4)	94.3 (26.2-174.9)	83.2 (21.2-174.9)	
D_{Mean} [Gy]	21 (6.5)	22 (7.2)	*21.6*	36 (14)	44 (9)	*41*							
V_{20Gy} [cm³]	33 (23.7)	34.5 (18.8)	*33.9*										
V_{30Gy} [cm³]	19.5 (15.4)	24 (15.9)	*22.3*										
V_{35Gy} [cm³]										47.5 (0.3-100.9)	36.2 (0-90.7)	41.2 (0-100.9)	
V_{40Gy} [cm³]	11 (9.8)	13 (11.9)	*12.2*	46 (34)	44 (24)	*46*				41.4 (0-90.0)	28.3 (0-77.3)	34.5 (0-90.0)	
V_{45Gy} [cm³]	3.5 (3.2)	0.4 (1)	*1.6*	42 (33)	41 (23)	*42*							
V_{50Gy} [cm³]				34 (30)	34 (23)	*34*				4.0 (0-21.9)	1.0 (0-20.0)	2.6 (0-21.9)	
V_{55Gy} [cm³]				2 (11)	5 (10)	*2*			1.5 (0-14.2)	0.8 (0-10.6)	0	0.4 (0-10.6)	
V_{60Gy} [cm³]				0.3 (1.4)	1.7 (3.0)	*0.5*			0.4 (0-7.6)				
D_{10cc} [Gy]								33.39 (1.53)					
D_{5cc} [Gy]								38.91 (1.41)		48.8 (31.1-57.3)	34.0 (0-51.9)	42.0 (0-57.3)	
D_{2cc} [Gy]										50.1 (31.3-58.3)	34.9 (0-52.3)	43.1 (0-58.3)	59.6
D_{1cc} [Gy]								47.38 (1.19)					57.6
D_{Max} [Gy]										53.8 (38.0-63.2)	37.3 (0-53.3)	46.2 (0-63.2)	63.4

Table 3-7. Duodenum DVH data extracted from publications described in Table 3-6.
The data indicated in italic typeface has been calculated to represent the whole clinical cohort, if values for a sub-cohort were reported.

4. Chapter Four. Meta-analysis of the relationship between toxicity and small bowel dose-volume in rectal cancer radiotherapy

4.1. Introduction

4.1.1. Toxicity arising from irradiation of the small bowel in radiotherapy for abdominal and pelvic malignancies

Abdominal and pelvic radiotherapy inevitably risks irradiating some volume of the small bowel, resulting in symptoms of acute toxicity such as diarrhoea, nausea, vomiting, abdominal discomfort and fatigue, as was reviewed in Chapter Two. Almost all patients receiving pelvic or abdominal radiotherapy experience some form of GI symptoms [238]. In treatment of cervical cancer with chemoradiotherapy using cisplatin, the most common adverse effects include diarrhoea, malaise and nausea, though severe toxicity is uncommon [239]. Among patients receiving preoperative rectal cancer chemoradiotherapy, Grade ≥ 2 acute GI toxicity is seen in around 20% of patients, and Grade ≥ 3 in 10% [240]. Symptoms are usually noticed during the second week of treatment (when tissue damage and inflammation is at a maximum), and characteristically will peak by the fourth to fifth week of treatment (when histological changes are stable or slowly improving) [241]. Toxicity causes treatment to be suspended, altered, or even terminated prematurely, in up to 5% of patients [198], and failure to deliver treatment per protocol may have implications for efficacy in achieving tumour control.

As discussed in Chapter Two, Nakamura et al. found that the risk of acute GI toxicity and GI bleeding due to chemoradiotherapy for pancreatic cancer is associated significantly with small bowel dose-volume parameters. Thus, a greater understanding of the radiation tolerance of

this tissue is vital to facilitate safe delivery of radiotherapy and possibly enable dose escalation. The small bowel is the major dose-limiting organ in pelvic radiotherapy, and while it is believed dose escalation may be able to improve disease response in rectal cancer [242], a better understanding of the tolerance of the surrounding organs at risk is required for this to be implemented safely.

4.1.2. Evidence that small bowel dose-volume predicts GI toxicity

The published evidence regarding the relationship of radiation dose-volume and toxicity in the small bowel was reviewed in Chapter Two. In total, eighteen studies identified in the literature search reported significant relationships between the risk of GI toxicity and irradiation of the small bowel.

It was shown that the range of small bowel dose-volume measures from V_{5Gy} to V_{50Gy} have been found to be predictors of the risk of acute toxicity. In the treatment of rectal cancer, V_{15Gy} has been highlighted as the most repeated finding, reported by nine publications. However, doses at the higher end of the DVH were also frequently shown to be important, such as V_{30Gy} and V_{40Gy}, which were each found to be significant predictors in five studies.

This findings mostly come from retrospective case-control studies, comparing the treatment that was given to those patients within a defined cohort who suffered toxicity with that which was given to those who did not. Importantly, all of the studies identified in the literature search used data from patients treated in a single centre, sometimes by a single clinician. This would potentially further increase the risk of a systematic difference in patients or treatment relative to other centres, and thus limit the external validity of the findings. Many (eight) of the studies used clinical data collected retrospectively, increasing the risk that their conclusions could have been affected by bias.

The aim of this work was to conduct a systematic meta-analysis of the available published literature, to consider evidence of a persisting dose-volume effect for small bowel irradiation across patient data sourced from multiple publications.

4.2. Method and materials

4.2.1. Studies for analysis

Three of the publications identified in the systematic literature search – presented in Chapter Two of this thesis – reported DVH and toxicity data in a consistent manner suitable for incorporation in formal inverse-variance meta-analysis. This comprised: mean volumes of small bowel irradiated for cohorts of patients separated according to whether or not they experienced moderately severe acute small bowel or lower GI toxicity (patients with worst toxicity Grade 0–2 versus worst toxicity Grade ≥ 3) [167, 192, 243]. Summary characteristics for these papers are shown in Table 4-1, where it can be seen that each study used similar definitions of acute toxicity outcomes. Each was a study of treatment in the same clinical scenario: radical treatment of rectal cancer with conformal external beam radiotherapy in combination with concomitant 5-FU chemotherapy and a treatment schedule of 1.8 Gy per fraction.

Table 4-1. Key parameters of studies included in this meta-analysis

Publication	N	Treatment indication	Radiotherapy schedule	Toxicity outcome	Toxicity scale
Baglan et al. 2002 [243]	40	Neoadjuvant	50.4 Gy @ 1.8 Gy/# (range 45–72 Gy)	Small bowel toxicity	CTC v2
Robertson et al. 2008 [192]	96	Neoadjuvant 53% / Adjuvant 47%	45 Gy @ 1.8 Gy/#	Small bowel toxicity	CTCAE v3
Banerjee et al. 2013 [167]	67	Neoadjuvant	50.4 Gy @ 1.8 Gy/#	Diarrhoea	RTOG

N = number of patients in study; # = number of fractions; CTC = National Cancer Institute Common Toxicity Criteria; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RTOG = Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria.

4.2.2. Analysis technique

The Review Manager (*RevMan)* computer program, a piece of software developed and maintained by the Cochrane Review group [244] was used to carry out the meta-analysis calculations and generate figures including forest plots and funnel plots. Mean difference, inverse-variance, fixed-effect analysis was chosen with 95% confidence intervals. The treatment effect was defined as the difference in volume of small bowel receiving each dose between cohorts of patients with Grade ≥ 3 toxicity, compared with those without. This was calculated for each dose level from 5 Gy to 40 Gy, in 5-Gy bins. Leave-one-out sensitivity analysis was conducted by repeating the analysis with each of the studies omitted.

4.2.3. Heterogeneity and bias

The studies included in the meta-analysis were assessed for bias and heterogeneity using tools recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* [245], while acknowledging the relevant differences that apply to non-randomised studies such as those studies examined here. The domains and criteria specified in The Cochrane Collaboration's *Tool for Assessing Risk* of *Bias* have been used to assess the risk of bias affecting the results within the publications themselves. Funnel plots (plots of standard error in the treatment effect against the absolute treatment effect) were generated using the *RevMan* tool [244] and have been used to look for evidence of bias affecting the inclusion of studies in the meta-analysis, and for heterogeneity between studies [246]. Heterogeneity of study methodology was evaluated by collating reported descriptions of patient details and treatment delivery. Heterogeneity of results was evaluated using Chi-squared and I^2 parameters.

4.3. Results

4.3.1. Meta-analysis

For each of the doses examined, the small bowel volume irradiated to that dose was significantly greater for patients who suffered Grade ≥ 3 toxicity compared with those who did not, as shown in Table 4-2 and Figure 4-1. Figure 4-3 shows the forest plots and analysis results as produced in RevMan.

The absolute difference in irradiated volume is largest for the lowest dose-volume parameter and decreases with increasing dose. However, relative to the volume irradiated in the patients who did not suffer Grade ≥ 3 toxicity, the difference in volume irradiated in the patients who had toxicity actually **increases** with increasing dose, as shown in Figure 4-2. The results of the leave-one-out sensitivity analysis are reported in Table 4-3.

Table 4-2. Results of meta-analysis including absolute and relative differences in volume of small bowel irradiated to threshold dose VxGy, between patients with Grade 0–2 and those with Grade ≥ 3 toxicity.

DVH parameter	Absolute difference [cm^3]	95% Confidence interval	Relative difference
V_{5Gy}	299	225–373	81%
V_{10Gy}	275	206–343	131%
V_{15Gy}	212	164–261	170%
V_{20Gy}	198	152–243	189%
V_{25Gy}	184	142–227	219%
V_{30Gy}	148	109–186	219%
V_{35Gy}	138	100–175	227%
V_{40Gy}	128	92–164	240%

DVH = dose-volume histogram.

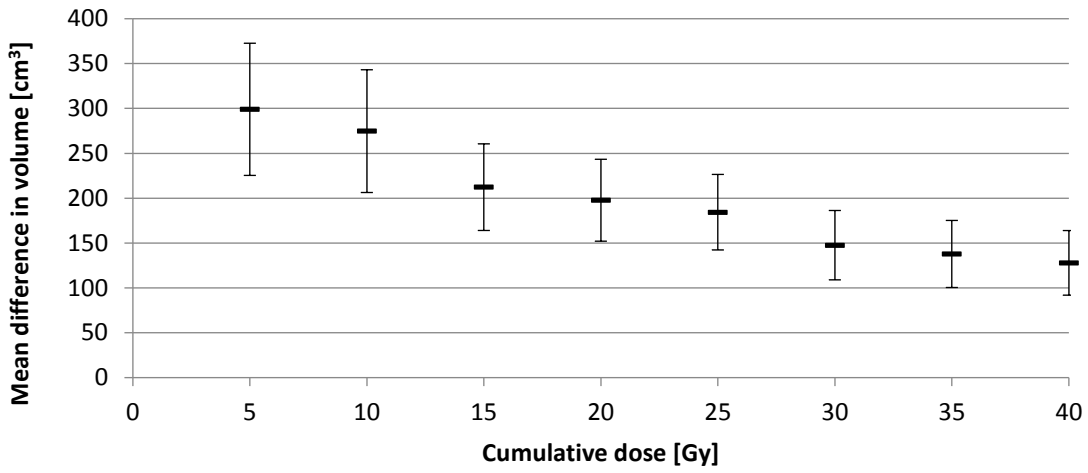


Figure 4-1. Mean difference in volume of small bowel irradiated to specified dose levels between patients with Grade 0–2 and those with Grade ≥ 3 toxicity by inverse-variance fixed-effect meta-analysis (error bars indicate 95% confidence intervals)

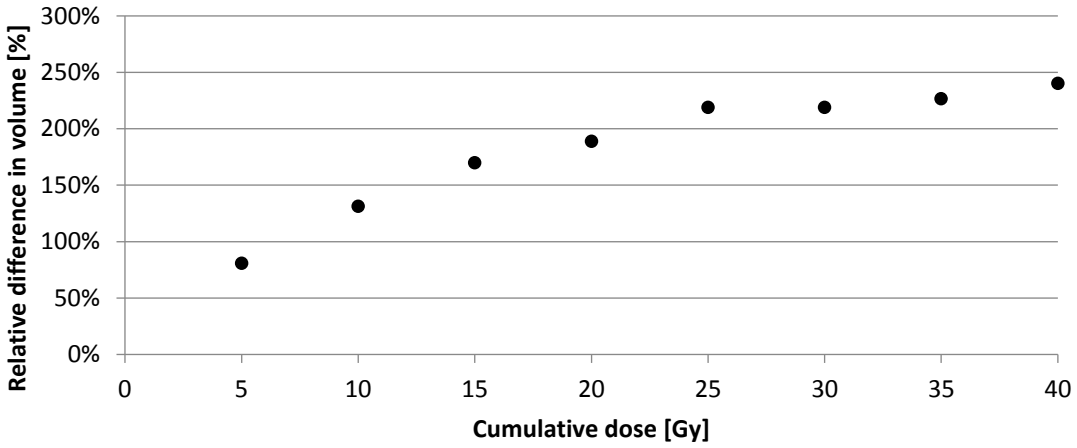


Figure 4-2. Mean relative difference in small bowel volume [%] between patients with Grade 0–2 and those with Grade ≥ 3 toxicity, weighted according to number of patients in each published cohort

Table 4-3. Results of leave-one-out (LOO) sensitivity testing for fixed-effects meta-analysis.

LOO Round	**1**	**2**	**3**
Studies	Banerjee et al. 2013 & Robertson et al. 2008	Baglan et al. 2002 & Robertson et al. 2008	Baglan et al. 2002 & Banerjee et al. 2013
Participants	163	136	107
Parameter	Mean absolute difference in small bowel volume [cm^3] (95% confidence interval)		
V_{5Gy}	285 (204–367)	236.05 (133–339)	364.06 (274–454)
V_{10Gy}	274 (197–351)	197.78 (102–293)	331.92 (250–413)
V_{15Gy}	230 (164–297)	166.60 (110–223)	244.75 (189–301)
V_{20Gy}	216 (153–280)	152.29 (100–205)	231.89 (178–285)
V_{25Gy}	198 (141–254)	141.03 (91–191)	216.70 (167–266)
V_{30Gy}	141 (91 –190)	120.93 (74–168)	180.04 (134–226)
V_{35Gy}	130 (82–177)	113.68 (69–159)	168.98 (124–214)
V_{40Gy}	122 (76–167)	103.69 (60–148)	156.76 (114–200)

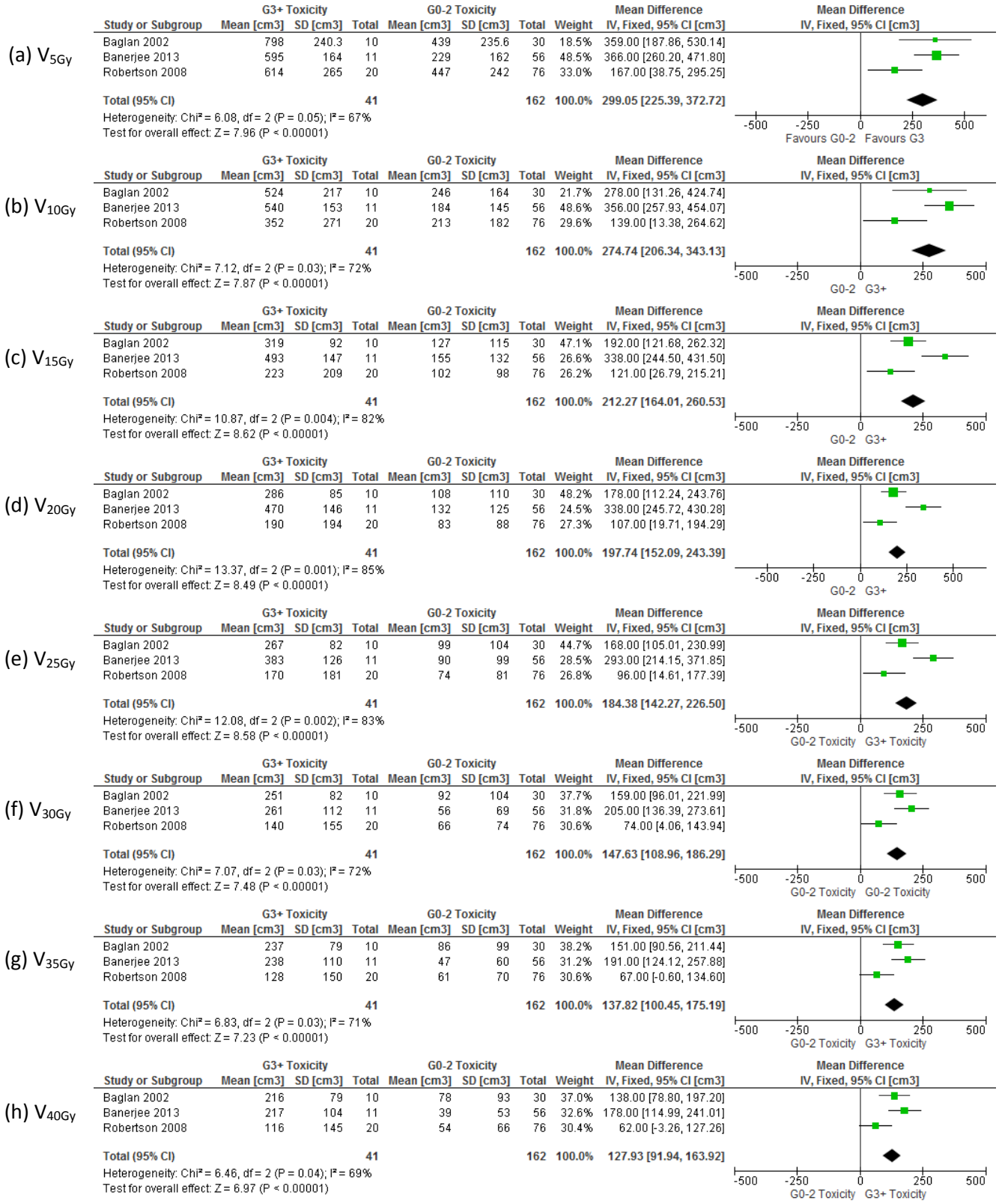


Figure 4-3. Forest plots for mean difference in small bowel volume in relation to incidence of clinically significant acute toxicity (grade 0-2 vs grade ≥ 3) in the radical treatment of rectal cancer with concomitant chemoradiotherapy
(a) V_{5Gy} (b) V_{10Gy} (c) V_{15Gy} (d) V_{20Gy} (e) V_{25Gy} (f) V_{30Gy} (g) V_{35Gy} (h) V_{40Gy}

4.3.2. Assessment of study methodology

The results of the assessment of study methodology are detailed in Table 4-4. The implications of the results are considered in the discussion.

Table 4-4. Details of study methodology utilised in the three publications. Where possible the text of the publication has been quoted.

	Baglan 2002	**Robertson 2008**	**Banerjee 2013**
Subject source	'Forty consecutive patients … limited to only those patients treated by one of the authors'	'Consecutive patients … treated by single radiation oncologist'	Patients with neoadjuvant chemoradiation for rectal cancer between 2008 and 2010.
Disease definition	'Rectal adenocarcinoma'	'Rectal cancer'	'Rectal adenocarcinoma'
Treatment indication	29 (72.5%) postoperative, 9 (22.5%) preoperative, 2 (5%) for local recurrence (all curative).	'Curative intent'	[All patients] 'treated with curative intent neoadjuvant chemoradiation'
Imaging	Planning CT with oral small bowel contrast. Entire abdomen and pelvis imaged in 24 patients, and pelvis alone imaged in 16.	Diluted barium before helical planning CT. Images obtained at 3- or 5-mm through pelvis only or abdomen and pelvis.	
Patient positioning	37 (93%) treated prone on a vacuum bag. All planned and treated with full bladder.	93 (96%) treated prone on a vacuum bag. All planned and treated with full bladder.	37 patients (55%) treated prone.
Radiotherapy	45 Gy in 25 # ± '5.4–27 Gy boost to reduced field when small bowel could be excluded from the boost field. Median total 50.4 Gy (range: 45–72 Gy). Only RT for recurrence used total dose greater than 54 Gy.'	All patients: minimum dose 45 Gy in 25 #. Small bowel excluded from lateral fields after 45 Gy. Consistent plan technique for all but 7% where other field arrangements were necessary.	'Patients were excluded if they received a radiation dose greater than 50.4 Gy, or treatment to nonstandard pelvic fields'
Chemotherapy	'22 (56%) 5-FU alone, 17 (44%) 5-FU and leucovorin. 5-FU by bolus in 12 (31%) and by infusion in 27 (69%).'	'81 Continuous infusional 5-FU (1 with Irinotecan); 7 Bolus 5-FU/Leucovorin; 4 Capecitabine; 3 Bolus 5-FU; 1 None'	'Only patients receiving continuous infusional 5-FU chemotherapy were included.'
Small bowel contouring	'Opacified and unopacified - individual loops of small bowel were contoured on each CT slice'	'Small bowel loops on every slice… both opacified and non-opacified loops'	'Individual loops contoured from the inferior extent of small bowel to 1.5 cm above the field'
DVH data collection	'A small bowel DVH was calculated for the initial pelvis field receiving 45 Gy.'	'A small bowel DVH was calculated retrospectively for the initial pelvic treatment to 45 Gy'	'Absolute DVH data were exported from [TPS]'.
Toxicity data collection	Scored retrospectively	Acute diarrhoea was scored prospectively	Maximal acute toxicity by retrospective review of notes.
Toxicity grading scale	National Cancer Institute Common Toxicity Criteria	National Cancer Institute Common Terminology Criteria for Toxicity v3.0	Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria for lower GI tract.
Toxicity definition	Acute small bowel toxicity	Acute diarrhoea (liquid stool analysed separately)	Acute lower GI

4.3.3. Heterogeneity and bias

Risk of bias (within study results)

The results of the assessment of risk of bias in the results reported within the studies themselves are detailed in Table 4-5. The implications of the results are considered in the discussion.

Table 4-5. Results of assessment using the domains and criteria specified in 'The Cochrane Collaboration's tool for assessing risk of bias' [245].

	Baglan 2002	**Robertson 2008**	**Banerjee 2013**
Selection bias risks			
Allocation concealment	N/A – Non-Randomised Study (but see below under blinding).	N/A – Non-Randomised Study (but see below under blinding).	N/A – Non-Randomised Study (but see below under blinding).
Performance bias risks			
Blinding of participants and personnel	Low-risk – Though treatment delivery was altered partly dependent on the exposure of interest, the data collected pertains only to the treatment phase prior to this alteration.	Low-risk – Though treatment delivery was altered partly dependent on the exposure of interest, the data collected pertains only to the treatment phase prior to this alteration.	Low risk – DVH data were determined after treatment delivered; hence these data were not able to influence treatment delivery or toxicity assessment.
Detection bias risks			
Blinding of outcome assessment	Unclear risk – No blinding, and while outcome [DVH data] is unlikely to be influenced by lack of blinding, the group allocation (toxicity status) was determined retrospectively and could be at risk of bias.	Low risk – No blinding, but the outcome measurement [DVH data] is unlikely to be influenced by lack of blinding, and the group allocation (toxicity status) was determined prospectively.	Unclear risk – No blinding, and while outcome [DVH data] is unlikely to be influenced by lack of blinding, the group allocation (toxicity status) was determined retrospectively and could be at risk of bias.
Attrition bias risks			
Incomplete outcome data	Low risk – no missing data.	Low risk – no missing data.	Low risk – no missing data.
Reporting bias risks			
Selective reporting	High risk – 'possible volume effect for higher dose could not be evaluated, because small bowel was routinely shielded after a dose of 45 Gy, and few patients had small bowel receiving doses above 40 Gy.'	Unclear risk – Insufficient information to permit judgement of 'Low risk' or 'High risk.'	High risk – evidenced by statement 'Initial analyses demonstrated [variable] to be unrelated to toxicity; therefore, subsequent analyses were foregone.'
Other bias risks			
Other sources of bias	Low risk of confounding factors, despite heterogeneity – 'Univariate analysis of patient- and treatment-factors…revealed no other significant associations with acute small bowel toxicity.'	Low risk of confounding factors – Preoperatively treated patients and postoperatively treated patients were assessed separately.	High risk of confounding factor – patient sex – all patients who suffered outcome were female ($p = 0.000$). Other clinical parameters assessed were not different between groups.

Risk of bias (for study inclusion)

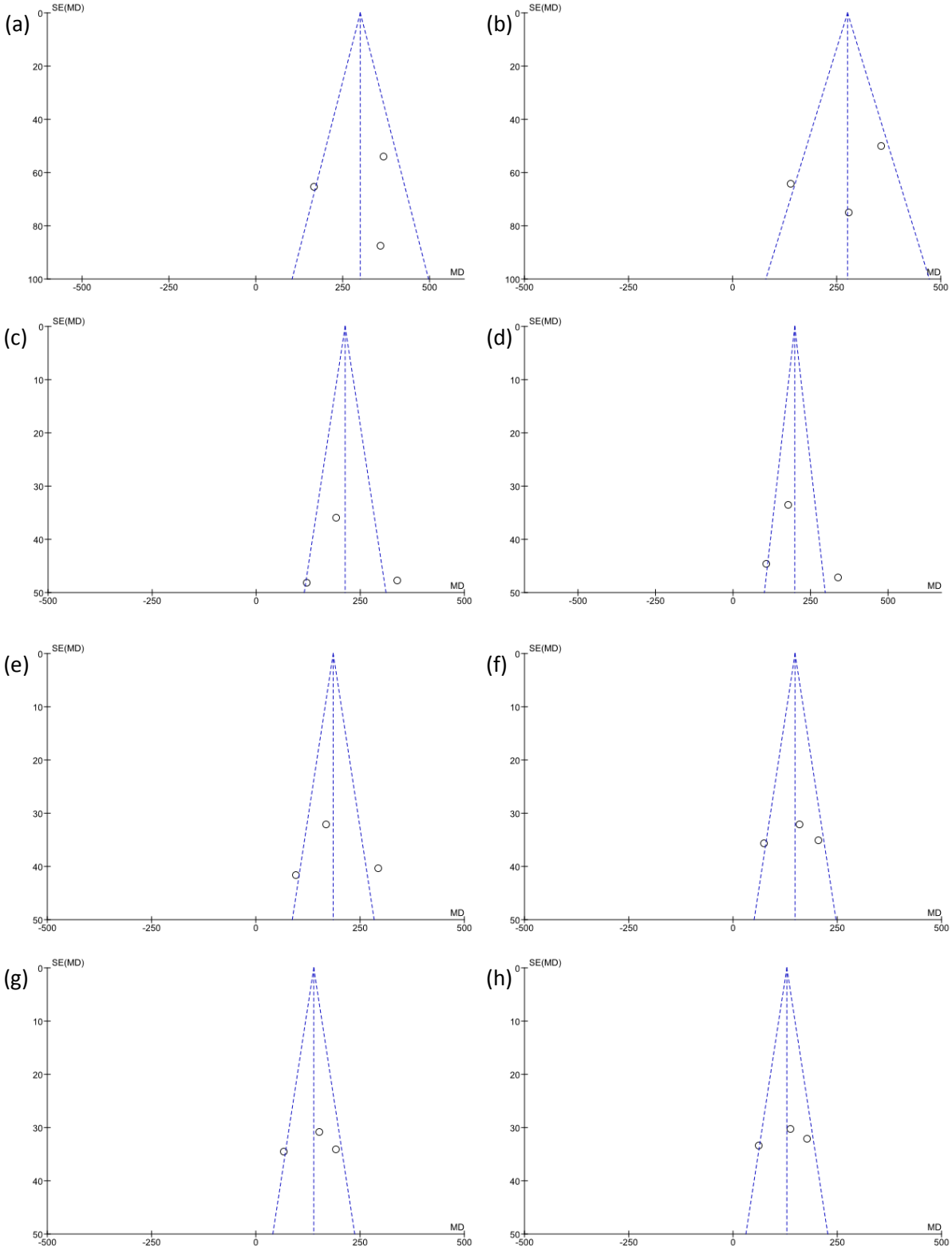


Figure 4-4. Funnel plots of standard error against mean difference in small bowel cumulative dose-volume for patients with grade 0-2 compared with those with grade ≥ 3 toxicity
(a) V_{5Gy} (b) V_{10Gy} (c) V_{15Gy} (d) V_{20Gy} (e) V_{25Gy} (f) V_{30Gy} (g) V_{35Gy} (h) V_{40Gy}. MD = mean difference (in irradiated small bowel volume), plotted on the x-axis; SE(MD) = standard error of the mean difference, plotted on the y axis.

Figure 4-4 shows the funnel plots generated for each comparison. The markers represent the three studies in the meta-analysis. The effect size seen in each study (difference in small bowel volume irradiated for each dose level) is indicated on the horizontal axis, and standard error for this value on the vertical axis. The vertical scale is reversed such that the markers for studies with the more precise estimates of effect size – usually those with greatest numbers of participants – are found towards the top.

In the absence of publication bias, a symmetrical triangular distribution of markers is expected, where smaller studies with associated reduced precision of effect size are lower on the vertical axis and further scattered either side of the summary effect size (due simply to sampling variation). Publication bias is indicated if there is an absence of markers low down on the vertical axis and close to the intercept (zero effect) where the implication is that small studies that have failed to show a significant result have not been published, or could not be identified for inclusion in the meta-analysis. Here, the distribution of markers appears to adopt this symmetrical triangular shape, apart from for the comparison of V_{5Gy} and $V_{10Gy.}$

In the absence of heterogeneity of effect size, 95% of markers are expected to lie within the triangular region. With only three studies, it is difficult to assess this condition for each individual comparison. However, we can potentially examine the overall result across all of the comparisons where we find that, in total, only thirteen markers of twenty-four (54%) lie within the triangles and eleven lie outside their bounds.

Heterogeneity

Table 4-6 contains the results of Chi-squared testing for heterogeneity in effect size across the three studies. The results show significant heterogeneity in effect size ($p \leq 0.05$) for all dose-volume comparisons. Further, I^2 values of between 67% and 85% were seen, lying within the

range of 50% to 90% specified by the Cochrane Handbook that 'may represent substantial heterogeneity' [245].

Table 4-6. Heterogeneity results for effect size across publications in each small bowel dose-volume comparison.

DVH Parameter	Chi-squared	*P* value	I^2
V_{5Gy}	6.08	0.05	67%
V_{10Gy}	7.12	0.03	72%
V_{15Gy}	10.87	0.004	82%
V_{20Gy}	13.37	0.001	85%
V_{25Gy}	12.08	0.002	83%
V_{30Gy}	7.07	0.03	72%
V_{35Gy}	6.83	0.03	71%
V_{40Gy}	6.46	0.04	69%

4.4. Discussion

4.4.1. Meta-analysis

The results of the meta-analysis indicate that, for all tested dose levels, an association exists between small bowel volume and acute toxicity in which patients who suffered toxicity had larger irradiated small bowel volumes (Figure 4-3). The absolute difference in mean small bowel volume exposure is largest for the lowest doses, and the differences become smaller with increasing dose (Figure 4-1). However, larger absolute volumes of tissue are exposed to lower dose, while the relative difference in volume between the groups is actually higher as dose increases (Figure 4-2), suggesting the volume of small bowel irradiated is increasingly important as the dose increases. The range of values for the mean difference between patient groups seen in the leave-one-out analysis lies within the confidence intervals of the original analysis (Table 4-3). This suggests two things: firstly that the assumed distribution of the difference utilised for the significance testing is reasonable; and secondly, the overall result of the meta-analysis is not dependent on the inclusion of any one particular study.

4.4.2. Assessment of study methodology

The assessment of study methodology indicates a number of potential sources of bias within the studies, and potential causes of heterogeneity in results between studies (Table 4-4). Regarding patient selection, these studies are all retrospective analyses of patient treatment rather than prospective clinical trials or cohorts. This introduces the risk of bias in how these cohorts were collated; however, the strict use of a consecutive patient list (as by Baglan et al. and Robertson et al.) or the selection of patients according to clear objective criteria (as per Banerjee et al.) should minimise this risk. The patients themselves appear to be homogeneous in diagnosis, and relatively homogeneous in treatment indication. The patients in Banerjee et al. were all treated postoperatively, but the cohorts of Baglan et al. and Robertson et al. contain a mixture of pre- and post-operatively irradiated patients. While Baglan et al. found there was no significant difference in the risk of toxicity between these groups, Robertson et al. found that preoperatively treated patients had a lower incidence of Grade ≥ 3 acute diarrhoea. They also found that diarrhoea was not significantly related to small bowel dose-volume for the postoperative group, suggesting it may not be appropriate to analyse these patients as a mixed cohort with those receiving preoperative radiotherapy.

In all the studies, there was a split of patients treated either prone or supine, but for Banerjee et al. more patients were treated supine (55%) than for the Baglan et al. (7%) or Robertson et al. (3%) cohorts. In terms of treatment planning, a major shortcoming of the Banerjee et al. paper is that the authors provide no details regarding the acquisition of the radiotherapy planning imaging in terms of scan extent or CT slice thickness. There is heterogeneity in the use of planning imaging by Baglan et al. and Robertson et al., where some patients had imaging of their pelvis only, while for others the scan included both abdomen and pelvis. The authors then specify that the small bowel was contoured on each CT slice, meaning that total small bowel volumes will be dependent on the extent of the CT scan. Furthermore, while the

reason for the differing scan extents in different patients is not explained, it is possible that it reflects an underlying difference in disease, or that treatment and is a potentially significant confound. In the studies of Baglan et al. and Robertson et al. the delivered treatment was actually altered depending on the patient small bowel anatomy itself, and the prescription dose was escalated for each patient provided the small bowel could be spared. However, the dose-volume data that were used for the analysis against toxicity outcomes was taken from an earlier phase of therapy, before this personalisation of dose was implemented.

All three studies were internally consistent in their use of an objective toxicity scale, though the scales used were different in each publication. Baglan et al. used the CTC v2, Robertson et al. used CTCAE v3, and Banerjee et al. used the RTOG acute lower GI scale. While CTC v2 and CTCAE v3 are almost identical, the two have only limited commonality with the RTOG scale, as shown in Table 4-7. However, although the finer points of the wording vary between these systems, the definition of Grade 3 toxicity is fundamentally consistent and objective, being indicated by the requirement for hospital-based intervention. In summary, the use of the different toxicity scales is unlikely, therefore, to mean that the patient groups defined by the three different studies are not comparable.

Table 4-7. Comparison of toxicity grading scales CTC v2, CTCAE v3, and RTOG acute lower GI toxicity

	CTC v2	**CTCAE v3**	**RTOG**
1	Increase of < 4 stools per day over pre-treatment; Mild pain, not interfering with function	Increase of < 4 stools per day over baseline	Increased frequency or change in quality of bowel habits not requiring medication
2	Increase of 4–6 stools per day, or nocturnal stools; Moderate pain, interfering with function but not with ADLs	Increase of 4 – 6 stools per day over baseline; IV fluids indicated < 24hrs; not interfering with ADL	Diarrhoea requiring parasympatholytic drugs/ rectal or abdominal pain requiring analgesics
3	Increase of ≥ 7 stools per day or incontinence or need for parenteral support for dehydration; Severe pain, severely interfering with ADLs	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; interfering with ADL	Diarrhoea requiring parenteral support/ abdominal distension
4	Physiologic consequences requiring intensive care or hemodynamic collapse; Disabling pain	Life-threatening consequences (e.g. hemodynamic collapse)	Obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain requiring tube decompression or bowel diversion

4.4.3. Risk of bias assessment

Risk of bias (within studies)

Assessment for bias within the publications highlighted several areas with a high risk of bias (Table 4-5). The risk of performance bias (where patients are managed differently according to their exposure to the risk) is low, as the small bowel DVH data were not determined until after the treatment was completed. Although in Baglan et al. and Robertson et al. there was a second phase of treatment that was altered dependent on the patient anatomy, the data analysed in the study was derived from the first phase, as discussed in section 4.4.2.

The risk of detection bias (in which assessment of outcome is affected by knowledge of exposure) is more difficult to assess because neither Baglan et al. nor Banerjee et al. specify whether the DVH or toxicity data were collated first. The retrospective assessment of treatment records is prone to being influenced by bias if the individual inspecting the data sources and collating the outcome has not been blinded to the DVH status of the subjects. Robertson et al., assessed toxicity prospectively, and subsequently calculated small bowel DVH data. This arrangement should be less susceptible to bias, since the extraction of DVH data for the contoured small bowel is an objective process, although the contouring of the small bowel itself is operator-dependent and would be at risk of bias if the said operators were not blinded to the outcome status for the patient. Both Baglan et al. and Banerjee et al. appear to be at high risk of reporting bias: Baglan et al. report that planned analysis of exposure to higher doses was not possible due to insufficient data, while Banerjee et al. admit that planned analyses were foregone and for which data is not reported.

The risk of bias due to confounding differences between the patient groups other than the exposure of interest appears to be highest for Banerjee et al., where all the patients who suffered Grade ≥ 3 toxicity were female. The other studies did not find an association between

patient sex and toxicity. As previously mentioned, Robertson et al. identified that preoperatively treated patients had a lower incidence of diarrhoea than postoperatively treated patients, and so these two groups were assessed separately to control for this.

Risk of bias (for study inclusion in the analysis)

Results of funnel plots

Though the small number of studies limits interpretation of the funnel plots, we can see that there is the approximately triangular shape that would be expected, and that shape is approximately symmetrical, apart from for the V_{5Gy} comparison (Figure 4-4). This result does not suggest evidence of the form of publication or reporting bias where only studies with significant results are published. However, the failure to demonstrate this with these few data also does not mean this issue has not affected this analysis. We cannot reasonably assess whether 95% of each set of three markers lie within the triangular region, but the fact that only 54% of the total of twenty-four markers lie inside the triangles does suggest that there is heterogeneity in the effect size between the studies. This impression is consistent with the results of formal heterogeneity testing, where there was significant variation in effect size between the studies.

Assessment of risk of publication bias

Other evidence suggests a high risk of publication bias in terms of the identification of relevant studies and access to data for inclusion in the meta-analysis. The three studies that have been included all individually reported positive findings of an association of dose-volume with toxicity, and so it is perhaps unsurprising that the meta-analysis of these three trials found the same result. While several papers have reported not finding any association between dosimetric parameters and small bowel volumes and toxicity [150, 154-158], these studies

were more likely to have been published in abstract form only (two of the six negative papers, 33%) compared with studies reporting positive findings (one of eighteen, 6%). None provided sufficient DVH data in a form that could be included in this analysis. While Xu et al. reported DVH data, their toxicity outcome group definition was into Grade 0–2 versus Grade ≥ 3 [158]). Two of the studies included in this meta-analysis were also published by the same institution [192, 243] where all patients were treated by a single clinician, and there may be a persisting reason why their results may not be externally applicable.

4.4.4. Suitability of source data

Mean-difference inverse variance meta-analysis assumes the summary data describes a symmetrical Gaussian (normal) distribution. The individual patient datasets for these studies were not available in order to assess the normality or symmetry of their distribution, and these attributes were not described in the published manuscripts. The fact that all three publications have reported the mean, and either standard error or variance, and that they have themselves used parametric statistical tests to analyse their data, suggests that they were satisfied their data was appropriately distributed for the use of these tests.

4.5. Conclusions

The results indicate a persistent overall association of small bowel volume with acute toxicity in rectal cancer chemoradiotherapy for all of the tested dose levels (V_{5Gy} to V_{40Gy}), where patients who suffered toxicity had larger irradiated small bowel volumes from three studies consistent in major treatment and methodological factors. This effect persisted on leave-one-out sensitivity analysis.

Conventionally, meta-analysis is conducted using data from randomised controlled trials. When such trials do not exist, the use of data acquired in observational non-randomised

studies is necessary; however, the results are understood to be at greater risk of being affected by bias, heterogeneity and confounds.

Unfortunately, not only were there very few studies providing suitable data for inclusion in this analysis, but the availability of study data for this analysis also appears to have been affected by publication bias. The studies themselves were shown to be at risk of bias affecting their results, and there was evidence for heterogeneity of size of effect of exposure between the studies.

Despite this, the overall impression from this analysis is that not only is there a true effect of volume on toxicity, but also this effect is significant for both low doses and high doses, especially when the relative difference in volume is considered. This finding is consistent with the results of the informal cross-trial comparisons that will be presented in Chapter Five, where broader criteria for data inclusion were applied, and which are contrary to the concept that the volume receiving 15 Gy or more is the most important predictive parameter as has sometimes been suggested [162].

To resolve the problems identified in this analysis should not be insurmountable. However, it will require concerted efforts from researchers and clinicians to:

1) achieve consistent application of consensus guidelines on data acquisition, such as for the definition and measurement of organ volumes,

2) enable prospective collection of detailed objective toxicity outcomes,

3) ensure publication of important negative findings and,

4) allow data sharing between institutions in order to facilitate analyses of larger multi-centre clinically annotated patient cohorts.

5. Chapter Five. Analysis of published small bowel dose-volume and toxicity data

5.1. Introduction

The association of the irradiated small bowel volume with the resultant risk of toxicity has been demonstrated by multiple single-centre observational studies, as reviewed in Chapter Two. For this thesis, a formal meta-analysis has been conducted using small bowel DVH data from three publications regarding rectal cancer chemoradiotherapy (Chapter Four). This showed that there was a statistically significant association between irradiated small bowel volume and acute bowel toxicity for all of the tested dose levels (V_{5Gy} to V_{40Gy}).

Several of the papers identified in the literature search described in Chapter Two reported small bowel DVH data for their patient cohorts, but these could not be included in the formal meta-analysis described in Chapter Four due to differences in the way patient toxicity was classified, or the way the irradiated bowel volumes were measured or reported. A number of alternative meta-analysis methods were therefore selected in order to make use of the data as was available, with the caveat that the interpretation of the results should be limited by the heterogeneous nature of the collated publications.

One of the pitfalls of analysis of radiotherapy data is that a potentially limitless number of parameters can be extracted or derived from a DVH, and it would be misleading to examine each parameter individually, as there is an increased risk of positive findings due to chance alone. In situations such as this, dimensionality-reduction techniques such as Principal Component Analysis may be useful [247]. These tools seek to reduce the number of free

parameters and limit the problems of multiple statistical testing, while preserving as much as possible of the variation and associated relationships (Figure 5-1).

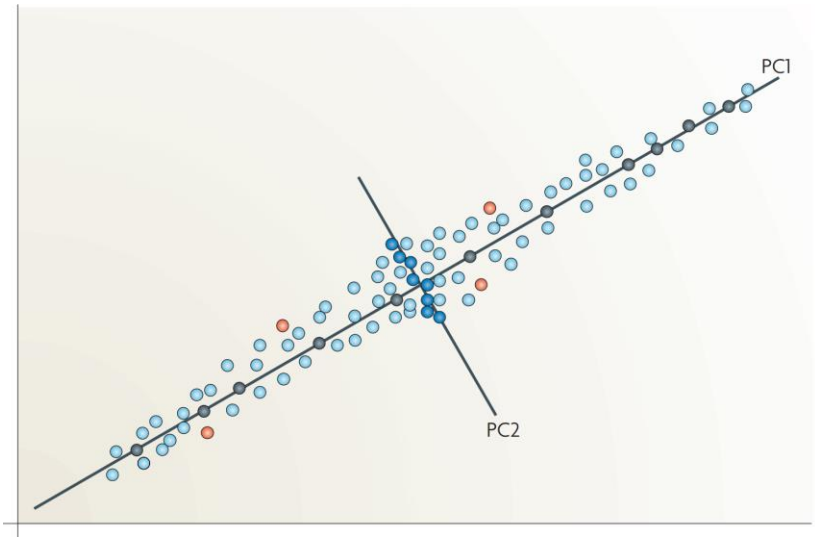


Figure 5-1. An illustration of the concept of Principal Components Analysis. Between them, Principal Component 1 (black circles) and Principal Component 2 (deep blue circles) capture most of the information in the original data. From Clarke et al. [248]

Canonical correlation analysis is one particular dimensionality-reduction technique, which is specifically intended for use when a set of predictive variables are known or suspected to be interrelated, such as measurements of length of different parts of the human body [249]. This also applies for the use of clinical radiotherapy DVH parameters, where each parameter is not independent of the others due to the limited degree of spatial modulation of dose that can be achieved. Further, in the case of absolute volumes, the volume receiving any particular dose cannot be larger than the total dose of the organ or tissue that has been contoured in that example, and in the case of a cumulative DVH, a volume receiving a particular dose can never be smaller than the volume that receives a higher dose.

In the work described in this chapter, the aim was to conduct exploratory cross-trial analyses using small bowel DVH data from a wider range of publications than could be utilised in the

analysis in Chapter Four, using several different methods. The first approach would be to pool data from studies that provide irradiated bowel volume data for patients in cohorts according to whether or not they experienced toxicity, in a similar manner to that conducted in Chapter Four, with the aim to confirm or challenge the findings of that analysis. The second approach would be to use data from studies where the small bowel DVH data were reported for a group of patients along with a toxicity incidence rate for this group, with the aim to visualise and analyse the quantitative relationship between small bowel volume and risk of toxicity. The final aim was to explore the potential role of canonical correlation in the reduction of a DVH for modelling of the relationship with toxicity risk.

5.2. Method and materials

5.2.1. Studies for analysis

As part of the systematic literature search described in Chapter Two, publications were identified that reported small bowel DVH values for patient cohorts treated with conventionally fractionated radiotherapy (ie dose per fraction < 4 Gy) (see Table 5-5). This included the three publications regarding radiotherapy for rectal cancer that were analysed in the formal meta-analysis described in Chapter Four. Several other papers in the literature search reported DVH data in a similar way, with patient cohorts divided into groups according to grade of toxicity (Table 9-2, Appendix B). However, this was done according to different criteria or thresholds for these three studies, such as comparing patients with Grade 0–1 toxicity to those with Grade ≥ 2. Of these, one paper provided median and IQR statistics for their patient cohorts rather than mean and variance [160], and one reference did not report the number of patients in each cohort [164]. For two of these publications, figures were provided showing DVH values but the values themselves were not reported. Additionally, while it has been possible to derive values for the purpose of this thesis using plot digitisation (see section 5.2.2), no measures of variance could be obtained and none were included in the

report [161, 168]. As such, these publications could not be included in the formal meta-analysis and other methods of appraising the data were adopted (see Section 5.2.3).

In some of the studies identified in the literature search, the investigators had contoured the abdominal or peritoneal cavity to act as a surrogate for the location of the small bowel [170, 173, 250-252]. Justification for this approach is twofold. Firstly, it takes much less time than contouring loops of bowel individually, and it is therefore a more realistic prospect for implementation in a busy radiotherapy department. Secondly, much of the bowel is mobile within the abdomen, and contouring of the peritoneal cavity represents the potential space into which the small bowel may move during a course of radiotherapy. It has also been shown that dose-volume parameters for these planning structures can be predictive of toxicity outcomes in the same way as contoured individual bowel loops [167, 169]. However, the recent RTOG consensus guidelines have recommended that the small bowel loops be contoured individually [208], and we have not included data in our analysis from publications that did not define the organs-at-risk structure as the contoured loops of bowel.

5.2.2. Extraction and handling of data from publications

Plot digitisation

Two publications included graphs of the cumulative DVH for the small bowel but did not provide values [161, 168]. The graphs each showed data points representing individual patients and a median DVH, calculated separately for those patients who did or did not suffer significant toxicity. To derive values for the DVH parameters from these studies, digital versions of the figures were analysed using a plot digitisation programme (Plot Digitizer [253]) as shown in Figure 5-2, and the values derived are contained in Table 5-1 and Table 5-2.

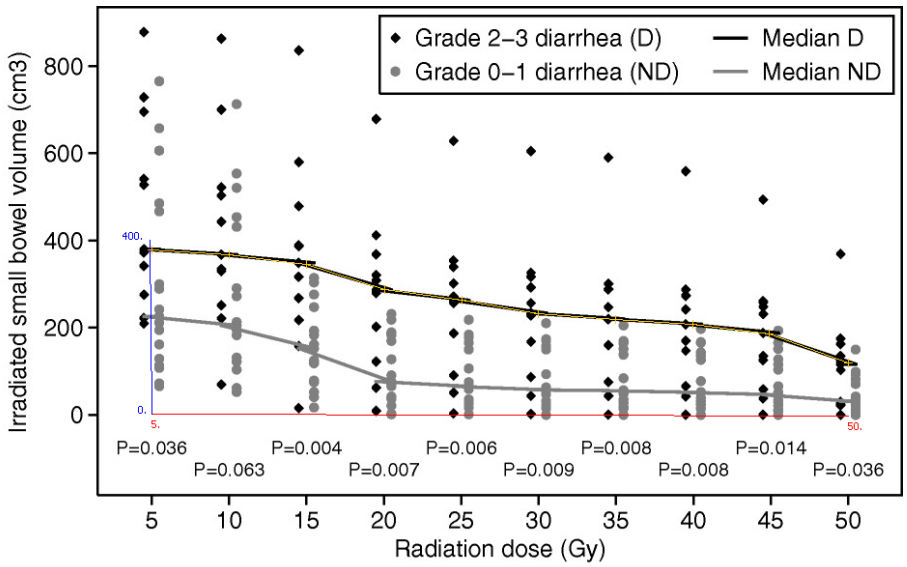


Figure 5-2. Cumulative DVH for small bowel from Gunnlaugsson (2007) [161] showing the median for the Grade 2–3 group marked using Plot Digitizer

Dose-volume parameter [Gy]	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}
Median small bowel volume [cm³]										
Grade 0–1 toxicity	225	203	152	78	65	59	57	52	48	33
Grade 2–3 toxicity	379	368	347	289	264	234	221	209	188	121

Table 5-1. Median absolute dose-volume parameters of small bowel, for patient cohorts separated according to severity of toxicity (Grade 0–1 vs Grade 2–3), as derived from Gunnlaugsson et al. [161] using plot digitisation

Dose-volume parameter [Gy]	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}
Median small bowel volume [cm³]									
All patients	385	297	155	91	76	63	51	41	15
Grade 0–1 toxicity	262	199	94	63	52	45	34	27	13
Grade 2–3 toxicity	452	356	197	109	88	72	60	49	16

Table 5-2. Median absolute dose-volume parameters for all patients, and for cohorts separated according to severity of toxicity (Grade 0–1 vs Grade 2–3), as derived from Reis et al. [168] using plot digitisation

Conversion of relative volume or dose parameters to absolute values

Almost all of the publications utilised in this analysis reported DVH data using absolute dose, but Huang et al. reported volumes of small bowel irradiated by percentages ($V_{10\%}$ etc) of the prescription dose (most often 50.4 Gy) [164]. This was, therefore, converted to equivalent absolute dose to enable comparison with other studies. Almost all of the publications also reported data in terms of absolute volume of an organ or tissue (in cubic centimetres or millilitres) irradiated to a given dose, but Chen et al. [254] report data for a cumulative DVH using only relative volumes (percentages). The relative volumes were therefore converted into plausible absolute volumes (Table 5-3) using a suitable expected value for the total contoured organ volume (283 cm^3). This value was taken from Chopra et al., who had analysed the same treatment indication as Chen et al. (adjuvant treatment after hysterectomy for cervical cancer) and reported the outlined small bowel volume ranged from 12–712 cm^3 (mean 283 cm^3 and median 257 cm^3) [171].

	DVH parameter	V_{25Gy}	V_{35Gy}	V_{45Gy}	V_{50Gy}
Reported relative volume	IMRT	78%	35%	12%	4%
	'Box-RT'	93%	75%	64%	53%
Converted absolute volume [cm^3]	IMRT	221	99	34	11
	'Box-RT'	263	212	181	150

Table 5-3. Irradiated small bowel DVH data from Chen et al. [254] converted from relative to absolute volume

Toxicity scale grading system alignment

The majority of publications providing data included in this analysis have used versions of the NCI EORTC/ CTCAE system to assess and classify the severity of adverse events among their patients. The first iteration of CTC was published in 1994, and CTCAE v4 has been in use since 2009 [37]. Minor modifications have been made to GI toxicity definitions during this evolution, but the grade scores for each symptom or outcome are roughly equivalent. Most commonly, the definitions of lowest and highest grades were altered, such as the change in

threshold from Grade 1–2 being changed from two episodes of vomiting in 24 hours to three, or the removal of Grades 4–5 for nausea in v4 (see Table 9-9, in Appendix B).

Almost all publications that did not use the NCI CTC scales used the RTOG toxicity grading scales instead. The RTOG *Acute Radiation Morbidity Scale* is used specifically to assess and record acute radiotherapy toxicity, and outcomes are combined into groups representing the expected toxicity from irradiation of specific organ systems, ie upper GI or lower GI [38]. The upper GI toxicity outcomes comprise anorexia, nausea, vomiting, abdominal discomfort or pain, haematemesis, melaena, ileus, bleeding, obstruction and perforation. The lower GI toxicity outcomes comprise bowel frequency, diarrhoea, mucous discharge, rectal discomfort, obstruction, bleeding, fistula and perforation. The RTOG *Cooperative Group Common Toxicity Criteria* can be used to report toxicity outcomes that are not part of the Radiation Morbidity Scale, and can be used to specify the severity of specific symptoms [255].

The basic structure used in the CTC and RTOG systems is the same, with a score of zero referring to 'no toxicity' and a score of five indicating 'death due to toxicity', while the criteria for each grade are also approximately equivalent within the range. Relevant excerpts of CTC version 4 and the RTOG scales are included in Table 9-10 and Table 9-11 in Appendix B.

One study reporting small bowel dose-volume data had used neither the CTC nor RTOG criteria, but instead had collected patient-reported outcomes using a Bowel Problems Scale [165]. This was taken from a tool utilised primarily in prostate cancer radiotherapy patients, but which had also been used to detect toxicity in patients receiving chemoradiotherapy for rectal cancer [74]. The scale includes a question on diarrhoea in which patients self-reported the frequency of symptoms in the preceding week on a 5-point Likert scale: 'not at all' (score 1), 'occasional' (score 2), 'fairly frequent' (score 3), 'frequent' (score 4), or 'very frequent'

(score 5) [256]. For the purpose of this analysis these scores were translated to an approximately equivalent CTC grade (Table 5-4).

PROM grade	1	2	3 or 4	5
Symptom frequency	Not at all	Occasional	Fairly frequent or frequent	Very frequent
Equivalent CTC grade	0	1	2	3
Severity criterion	No symptoms	Requires no treatment	Requires treatment	Requires hospital treatment

Table 5-4. Alignment of 'Bowel Problems Scale' from Clark et al. [256] with approximately equivalent CTC grade.

Missing data

Where studies reported data values for cohorts of patients, but not for the overall study cohort, weighted averages were derived for comparison with other cohorts. This was done for ten publications [157-161, 164, 167, 192, 254, 257] and the values derived are provided in Appendix B (Table 9-2).

Some of the studies reported only a small number of DVH parameters for their patients. As described in Chapter Three, cubic splines were fitted to these data points to derive continuous DVH curves from which missing values could be imputed. The imputed values, which were used for the purposes of logistic regression modelling and canonical correlation analysis only, are also provided in Table 9-3 (Appendix B).

5.2.3. Analysis methods

Average effect size across studies

Nine studies reported volumes of small bowel (contoured as individual loops) for their patients divided into cohorts according to incidence of a particular grade of toxicity [157-161, 164, 167, 168, 192]. The weighted average of the effect size was calculated, where this was defined as the difference between the average volume of small bowel irradiated for each group.

Other cross-trial analyses and comparisons

For studies in which patients were not split into cohorts according to toxicity incidence but in which a measure of average small bowel dose-volume was reported (or could be calculated), along with a proportional incidence of toxicity, the data were visualised and analysed as described below.

Colour maps

Values for toxicity incidence were entered into cells of a matrix representing points of the small bowel cumulative DVH, to render a map of toxicity risk according to dose and volume, based on the method proposed by Jackson et al. [258]. The cells were then colour-labelled according to the rank of toxicity risk within the map. A colour map was produced using data from all studies described in Table 5-5, and an additional colour map was produced using data only from studies regarding treatment of anal or rectal cancer.

Comparisons of trial cohort data according to overall outcomes

Studies were then split into two approximately equal groups according to incidence of toxicity. The studies regarding the treatment of rectal cancer and those regarding the treatment of gynaecological cancers were examined separately, due to the gross differences in rates of toxicity observed between the reports regarding the two different tumour types.

Correlation analysis and modelling of trial cohort data

Lastly, toxicity incidence was analysed against dose-volume parameters for cohorts of patients in a similar manner to that which has been used by Semenenko and Li [222], and later Marks et al. [259]. Correlations between DVH parameters and risk were tested, and logistic regression was used to fit a predictive model to the available data points. The effect of using

differential rather than cumulative DVH data was also investigated. Cumulative DVH data from the published studies were converted into differential DVH data by subtracting from each value the volume that is receiving more dose than the specified range of interest, for example to derive the volume receiving between 5 and 10 Gy:

$$V_{5-10Gy} = V_{5Gy} - V_{10Gy} \quad (1)$$

Canonical correlation

Canonical correlation examines a sequence of pairs of variates and their correlation. Each pair consists of an independent variable, in this case a measurement of dose-volume, and the dependent variable, in this case a proportional incidence of toxicity. Coefficients are then derived for each predictive parameter of the set such that the correlation between the values of those parameters and the observed variable can be maximised. A new parameter is derived which is the weighted sum of the products of the values in the set and their coefficients, known as the 'canonical variate':

$$CV_x = a_1x_1 + a_2x_2 + a_3x_{3+} + \ldots + a_nx_n \quad (2)$$

Where CV_x = canonical variate of x; α_1 = coefficient for parameter 1; x_1 = value of parameter 1 etc.

Canonical correlation analysis was conducted using Rstudio (RStudio, Inc., Boston, MA [260]), a user interface for the R statistical analysis environment (R Core Team, Vienna, Austria [261]). Coefficients were derived for each cumulative DVH parameter, and the resultant summary statistic (the canonical variate) was labelled Vfactor. As necessary, patient cohorts were also

classified according to whether or not radiotherapy was delivered with concurrent chemotherapy was likely to worsen acute bowel toxicity, ie capecitabine/5-FU.

A generalised linear model was fitted to explore the interaction of the canonical variate and concomitant chemotherapy as independent variables in prediction of relevant toxicity:

$$y = A + B.Chemotherapy + C.Vfactor + D.Chemotherapy.Vfactor \quad (3)$$

Where: *A* = intercept, *B* = chemotherapy coefficient, *C* = Vfactor coefficient, *D* = interaction coefficient, *Chemotherapy* = value can be 0 or 1, *Vfactor* = canonical variate, *y* = log odds of predicted proportional risk of toxicity.

Studies of rectal cancer treatment were also analysed separately. All patients in these studies received concomitant chemotherapy, and so the model took the simplified form:

$$y = A + B.Vfactor \quad (4)$$

Equation 5 is then used to derive a value for the proportional toxicity incidence predicted by the model:

$$Predicted\ proportional\ incidence = \frac{e^y}{1+e^y} \quad (5)$$

The number of predictor parameters that can be included in a canonical correlation process is limited to n – 1, where *n* is the number of cases in the analysis.

5.3. Results

5.3.1. Data sources

Nineteen studies provided data for the meta-analysis, for which summary details are compiled in Table 5-5. These included ten studies concerning rectal cancer (a total of 659 patients), six studies of treatment for gynaecological malignancies (343 patients), two studies of pancreatic cancer (89 patients), and one study of anal cancer (seventeen patients).

Thirteen of the studies (68%) reported that toxicity data were collected prospectively while in the others toxicity was assessed retrospectively. The radiotherapy techniques used included simple fields, 3D-conformal, IMRT and helical arc therapy. It is assumed that as the actual organs-at-risk dose-volume data is available, the method that was used to plan and deliver the treatment should not otherwise have an effect on the relationship between dose-volume and outcomes. Four studies reported data on acute and late toxicity outcomes [117, 159, 171, 254] but all others collected only acute toxicity data. The median rate of Grade ≥ 3 toxicity was 16% (range 0% to 62%), while among rectal cancer cohorts, the median toxicity rate was 21% (range 4% to 35%), and among gynaecological cancer cohorts it was 3% (range 0% to 15%). The source DVH data values themselves are collated in Table 9-2 and Table 9-3, which can be found in Appendix B.

Table 5-5. (Following page) Summary details of papers reporting dose-volume and toxicity data for small bowel. (N = number of patients reported, Retro = retrospective data collection, Prosp = prospective data collection, mFU = median follow-up, NS = not specified, 5-FU = 5-fluorouracil, MMC = mitomycin-C, IMRT = intensity modulated radiotherapy, 3D-CRT = 3D conformal radiotherapy, CTC = Common Toxicity Criteria, CTCAE = Common Terminology Criteria for Adverse Events, RTOG = Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria, PROM = Patient-Reported Outcome Measures)

Reference	Data	N =	Cancer site	RT indication	RT dose schedule (range if reported)	Chemo	RT technique	Toxicity scale	Toxicity timing	Toxicity incidence
Baglan 2002 **[243]**	R	40	Rectum	Preoperative	50.4 Gy in 28 # (45–72 Gy)	5-FU	Open fields	CTC v2	Acute & late	25%
Banerjee 2013 **[167]**	R	67	Rectum	Preoperative	50.4 Gy in 28 #	5-FU	3D-CRT	RTOG	Acute	16%
Chen 2012 **[165]**	P	66	Rectum	Preoperative	50.4 Gy in 28 #	5-FU	3D-CRT	PROM	Acute	13%
De Ridder 2008 **[262]**	P	24	Rectum	Preoperative	50 Gy in 25 # (46–55.2 Gy)	None	Helical arc therapy	CTCAE v3	Acute	4%
Gunnlaugsson 2007 **[161]**	R	28	Rectum	Radical/ Preoperative	50.4 Gy in 28 # (n = 15) 50 Gy in 25 # (n = 13)	Oxaliplatin & 5-FU	3D-CRT	CTC v2	Acute	29%
Reis 2015 **[168]**	P	45	Rectum	Preoperative	50.4 Gy in 28 #	Cetuximab, capecitabine, irinotecan	3D-CRT	CTCAE v3	Acute	29%
Robertson 2008 **[192]**	P	96	Rectum	Preoperative 53% / Adjuvant 47%	45 Gy in 25#	5-FU	Open fields	CTCAE v3	Acute	21%
Tho 2006 **[160]**	P	41	Rectum	Preoperative	45 Gy in 25#	5-FU	3D-CRT	CTCAE v3	Acute	20%
Van der Voort 2012 **[257]**	R	189	Rectum	Preoperative	NS	NS	NS	CTCAE v4	Acute	16%
Xu 2015 **[158]**	P	63	Rectum	Preoperative	50 Gy in 25 #	Oxaliplatin & capecitabine	IMRT	CTCAE v3	Acute	35%
Chen 2007 **[254]**	P	68	Cervix	Adjuvant	50.4 Gy in 28 #	Cisplatin	Open fields 51%/ IMRT 49%	RTOG	Acute & late	0%
Chi 2012 **[169]**	P	32	Endometrial	Adjuvant	50.4 Gy in 28 #	Carboplatin (n = 1)	IMRT	CTCAE v3	Acute	0%
Chopra 2014 **[171]**	P	71	Cervix	Adjuvant	50 Gy in 25 #	Cisplatin	IMRT 65%/ 3D-CRT 35%	CTCAE v3	Acute & late	13%
Huang 2007 **[164]**	P	80	Mixed Gynae	Radical 61% / Adjuvant 39%	45 Gy in 25 # (39.6–50.4 Gy)	Cisplatin & 5-FU (63%)	Open fields	CTC v2	Acute	15%
Macchia 2014 **[263]**	P	60	Endometrial	Adjuvant	45 Gy in 25#	None	IMRT/ 3D-CRT	CTCAE v4	Acute	0% IMRT, 3% 3D-CRT
Martin 2005 **[264]**	P	32	Mixed Gynae	Adjuvant	50.4 Gy in 28 # (43–55.8 Gy)	Cisplatin (41%)	Open fields	CTC v2	Acute	7%
Abelson 2012 **[117]**	R	47	Pancreas	Adjuvant 62% / Radical 38%	50.4 Gy in 28 #	5-FU	IMRT	CTCAE v3	Acute & late	4%
Ito 2006 **[157]**	P	42	Pancreas	Radical	50.4 Gy in 28 #	Gemcitabine	3D-CRT	CTC v2	Acute	62%
Milano 2005 **[265]**	R	17	Anus	Radical	54 Gy in 30 # (45–59.4 Gy)	MMC & 5-FU	IMRT	RTOG	Acute	0%

5.3.2. Average effect size across studies

Absolute differences in irradiated small bowel volume between cohorts of patients with or without toxicity are shown in Table 5-6 (a), with a mean value weighted according to the cohort size, visualised in Figure 5-3. Individual cohort DVHs are included in Appendix B (Table 9-2 and Figure 9-1). The largest absolute difference was seen for the lowest dose parameter (V_{5Gy}, 177 cm^3), and the difference decreased sequentially as the dose increased. However, the largest **relative** difference was seen for the V_{40Gy} (141%), and the difference for the V_{5Gy} is in fact the smallest relative difference seen (55%), as shown in Table 5-6 (b).

(a) Absolute differences [cm^3] in small bowel volume between patients with or without toxicity

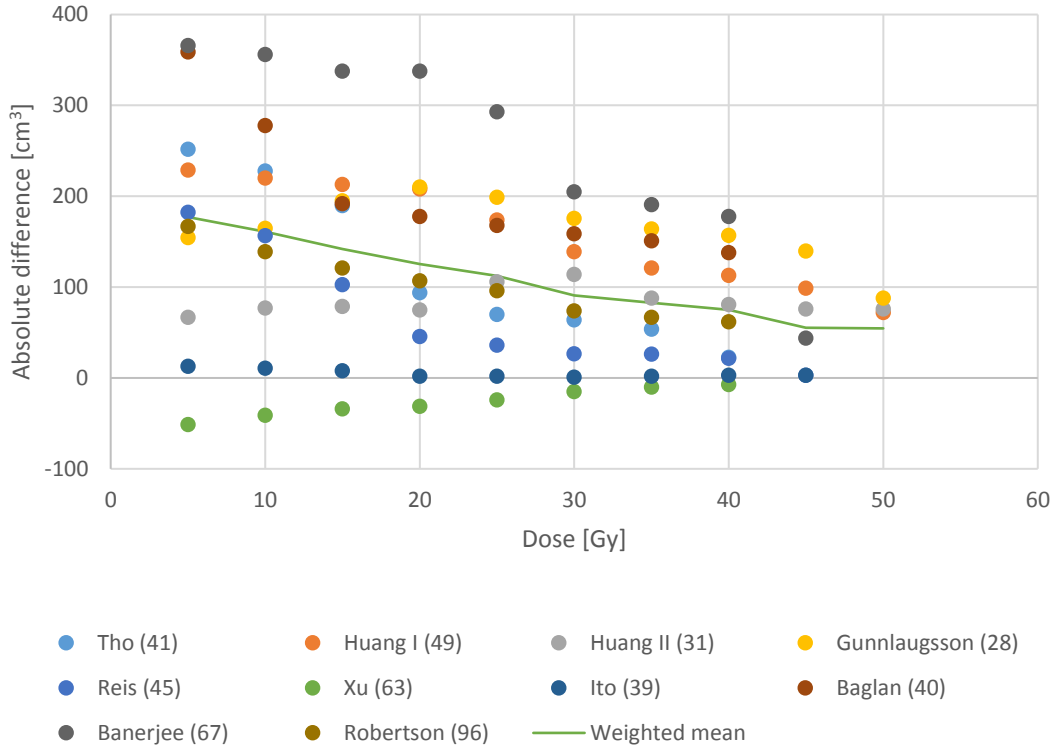
	n	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}
Tho 2006	41	252	228	190	94	70	64	54	23		
Huang 2007 – I	49	229	220	213	208	174	139	121	113	99	72
Huang 2007 – II	31	67	77	79	75	106	114	88	81	76	76
Gunnlaugsson 07	28	155	165	195	210	199	176	164	157	140	88
Reis 2015	45	182	157	103	46	36	27	26	22	3	
Xu 2015	63	-51	-41	-34	-31	-24	-15	-10	-7		
Ito 2006	39	13	11	8	2	2	1	2	3	3	
Baglan 2002	40	359	278	192	178	168	159	151	138		
Banerjee 2013	67	366	356	338	338	293	205	191	178	44	
Robertson 2008	96	167	139	121	107	96	74	67	62		
Weighted mean	499	177	161	142	125	112	91	83	75	55	55

(b) Relative differences in small bowel volume between patients with or without toxicity

	n	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}
Huang 2007 – I	49	61%	65%	70%	74%	82%	83%	86%	91%	89%	73%
Huang 2007 – II	31	19%	26%	29%	30%	61%	102%	96%	100%	107%	136%
Gunnlaugsson 07	28	69%	81%	129%	269%	307%	300%	289%	302%	292%	263%
Reis 2015	45	68%	79%	110%	72%	69%	59%	77%	81%	25%	
Xu 2015	63	-19%	-18%	-17%	-18%	-19%	-20%	-21%	-23%		
Ito 2006	39	8%	7%	6%	3%	4%	2%	5%	8%	9%	
Baglan 2002	40	82%	113%	151%	165%	170%	173%	176%	177%		
Banerjee 2013	67	160%	193%	218%	256%	326%	366%	406%	456%	191%	
Robertson 2008	96	37%	65%	119%	129%	130%	112%	110%	115%		
Weighted mean	458	55%	71%	96%	110%	126%	129%	136%	147%	116%	141%

Table 5-6. Differences in cumulative (a) absolute and (b) relative volume of small bowel irradiated at each dose level between patients with or without toxicity as defined in each study. Relative change for data from Tho et al. could not be included as the irradiated volume for the patients without toxicity was zero. Huang 2007 – I = Group I: no prior abdominal surgery; Huang 2007 – II = Group II: prior abdominal surgery

(a) Absolute difference in small bowel volume



(b) Relative difference in small bowel volume

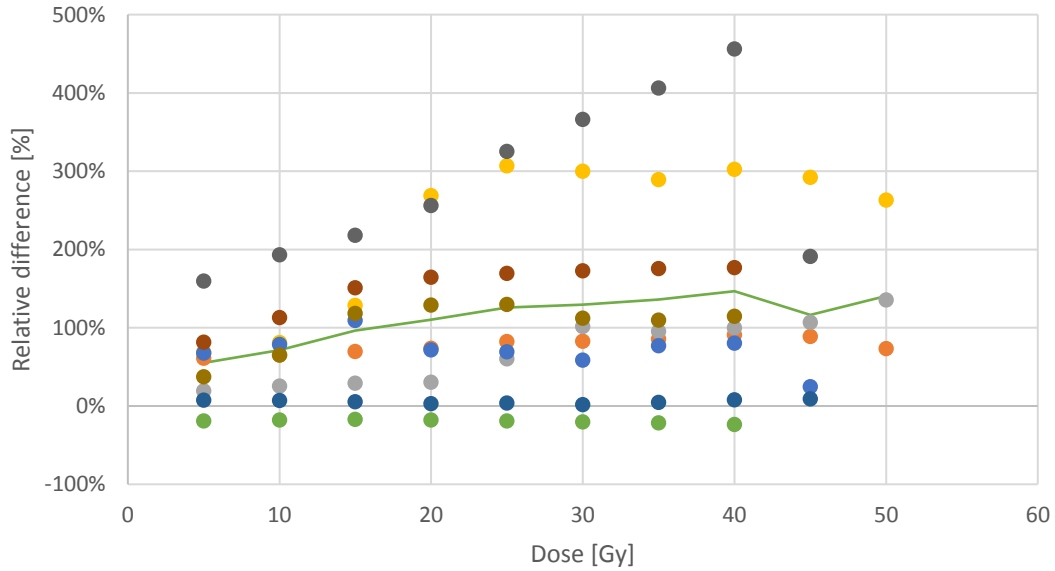


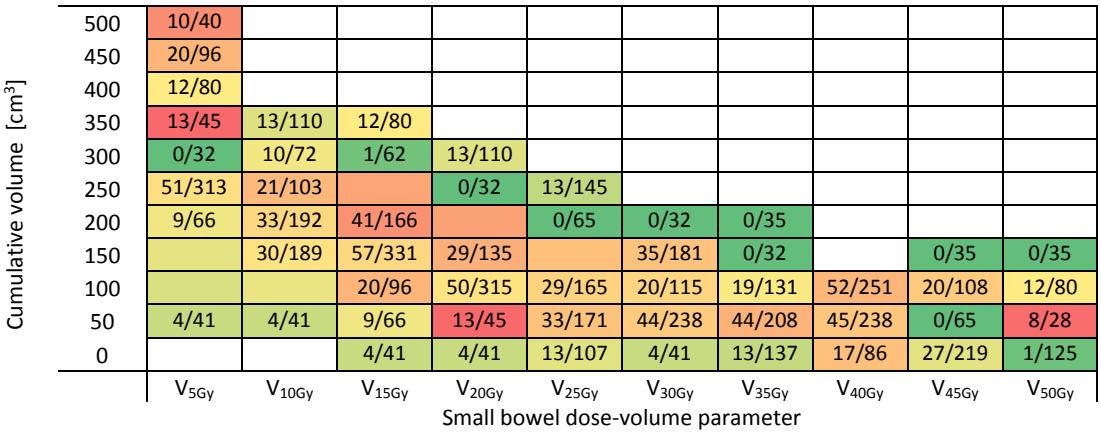
Figure 5-3. Difference in cumulative volume of irradiated small bowel between patients with low-grade and high-grade toxicity for each cohort and a weighted mean of these differences across studies contributing data at each dose level.
(a) Absolute difference in small bowel volume [cm³]. (b) Relative difference in small bowel volume [%]. The numbers in brackets specify the number of patients in each study/cohort. Huang I = patients without surgery; Huang II = postoperative patients.

5.3.3. Other cross-trial analyses and comparisons

Colour maps

The colour maps of toxicity incidence according to small bowel dose-volume show that when data from all studies are included (Figure 5-4a), there is not an obvious relationship between dose-volume and toxicity. However, when only data from studies regarding rectal or anal cancer are included (Figure 5-4b), it can be seen that the rate of toxicity increases along both axes, ie there is increasing risk with increasing volume of small bowel irradiated at a given dose, and with increasing dose received by a given volume.

(a) Data from all available studies



(b) Data from studies regarding treatment of rectal or anal cancer only

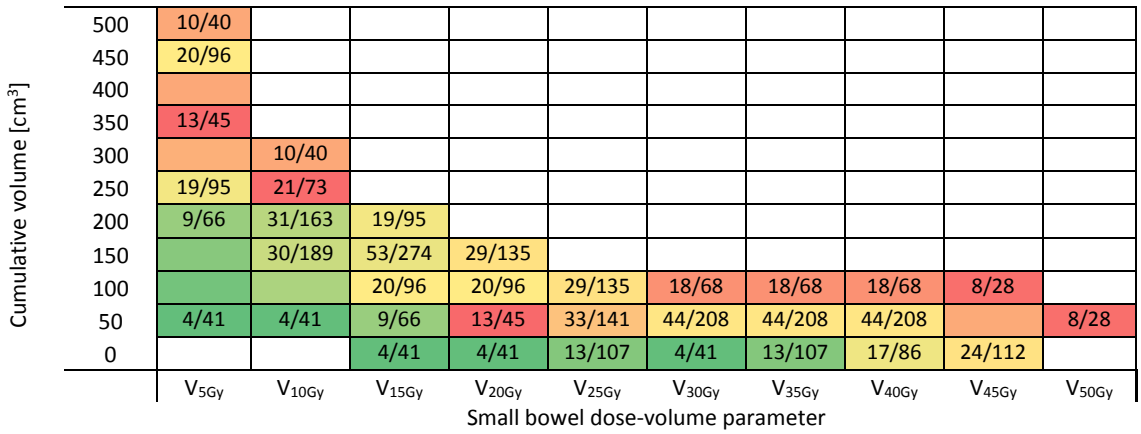
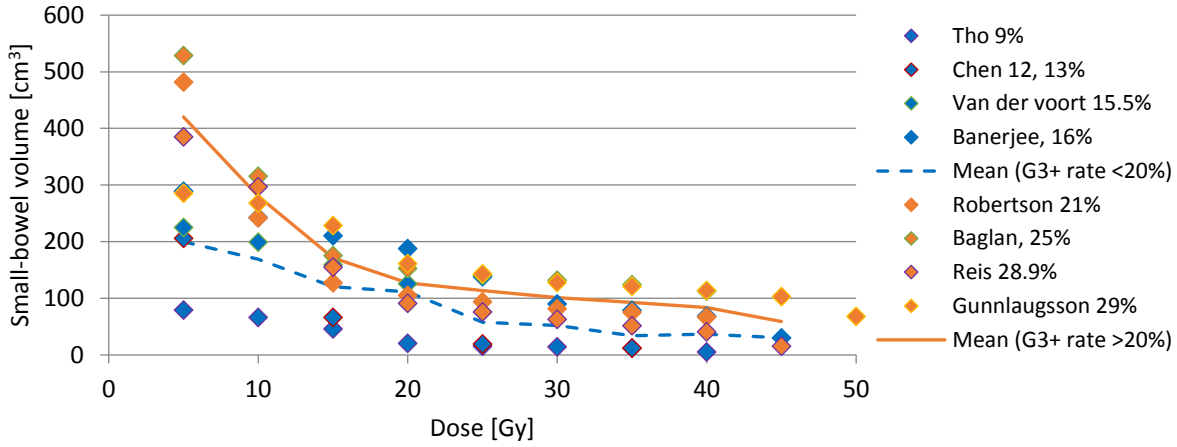


Figure 5-4. Colour maps of toxicity risk associated with irradiation of small bowel to indicated dose-volumes. (a) data from all available studies; (b) data from studies regarding treatment of anal or rectal cancer only. Values in cells indicate observed toxicity incidence for studies or cohorts whose DVH intersects in the relevant dose-volume range. Cells are colour-labelled according to rank, within each colour map. Cells not containing numerical values had no data available. Colour has been interpolated in gaps between cells with data.

Comparisons between trial cohort data according to overall toxicity incidence

Among rectal cancer studies, the irradiated small bowel volume was larger for studies with higher toxicity rates, for all dose values (Figure 5-5). However, this was not the case among studies of patients with gynaecological tumours, where the curves only separate at high dose, (ie V_{40Gy} and above). This can be seen more clearly when the data-points are removed (Figure 9-2, Appendix B). Figure 5-6 shows that, while the absolute difference in the mean DVH between rectal cancer studies with high and low toxicity is greatest for the low dose region (V_{5Gy} and V_{10Gy}), the relative differences are larger for the higher dose region (V_{35Gy} and V_{40Gy}).

(a) Rectal cancer publications (20% threshold)



(b) Gynaecological cancer publications (5% threshold)

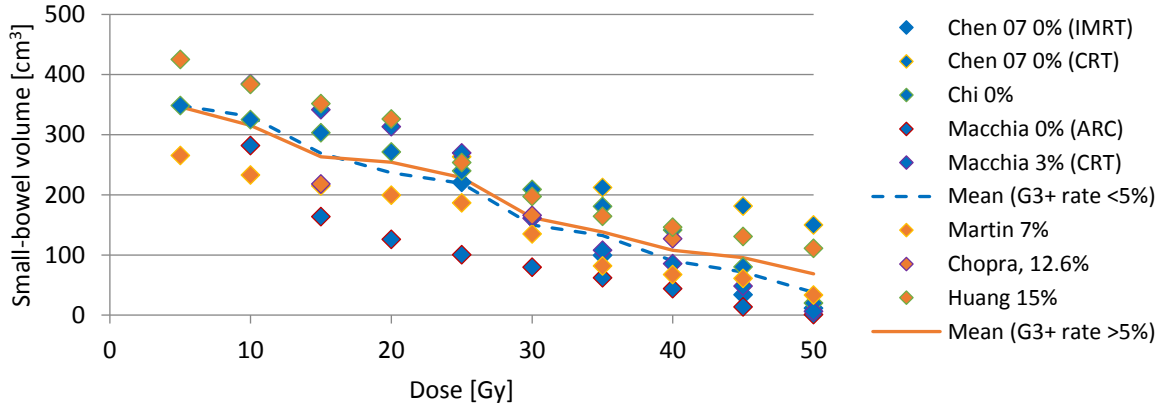
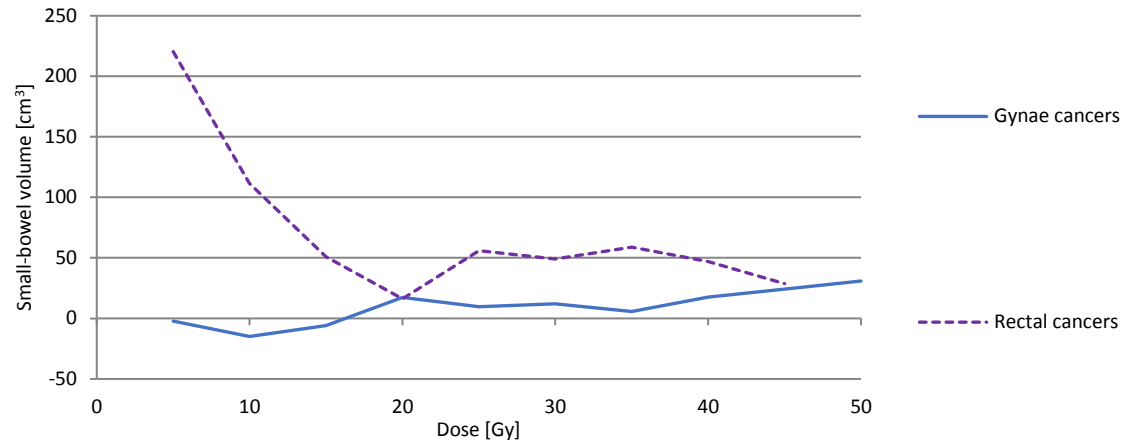


Figure 5-5. Individual small bowel cumulative DVH data and mean DVH for study populations/treatment cohorts with low (blue) and high (orange) incidence of Grade ≥ 3 acute GI toxicity, divided by median proportional incidence. (a) Rectal cancer publications (20% threshold) (b) Gynaecological cancer publications (5% threshold)

(a) Absolute difference in irradiated small-bowel volume



(b) Relative difference in irradiated small-bowel volume

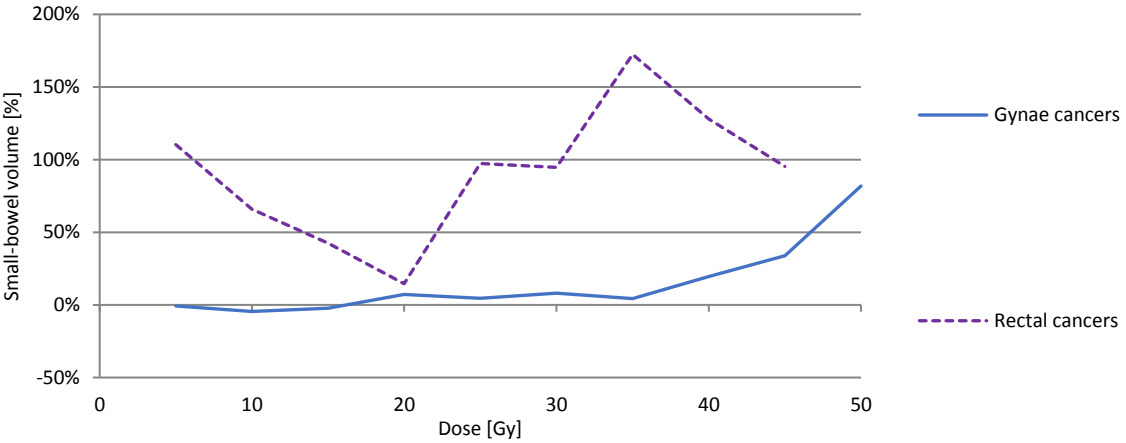


Figure 5-6. Differences in mean small bowel volume irradiated to each dose level between high and low toxicity cohorts for rectal cancer and gynaecological cancers. (a) Absolute difference. (b) Relative difference.

Analysis and modelling of trial cohort data

When cumulative DVH data from all available studies were examined, there was no significant correlation between any DVH parameter and the risk of Grade ≥ 3 toxicity. When the data were converted to differential DVH, two parameters showed significant negative correlations with outcome: $V_{30–35Gy}$, correlation -0.502, (95% CI -0.799 to -0.008), p = 0.048, and $V_{35–40Gy}$: correlation -0.548, (95% CI -0.821 to -0.072), p = 0.028. Tables of these correlation results are included in Appendix B (Table 9-4 and Table 9-5). Table 5-7 shows the results of the same analysis for cumulative DVH data, when taken only from studies describing the treatment of rectal cancer. This shows that several small bowel dose-volume parameters (V_{10Gy}, V_{30Gy}, V_{35Gy},

and V_{40Gy}) were significantly correlated with toxicity incidence if a threshold p-value of 0.05 is chosen. If a Bonferroni correction were used to account for multiple testing, a more stringent p-value threshold of 0.005 would apply (0.05 divided by 10 tested parameters). In this case only one parameter would remain significant, the V_{10Gy}. The results of univariate logistic regression modelling are shown in Table 5-8, including coefficients and statistical significance of the fit to the observed data for each DVH parameter. Figure 5-7 visualises the distribution of source data points for two parameters (V_{10Gy} and V_{40Gy}) with the logistic regression model overlaid.

Parameter	Correlation	95% CI		*P* value
V_{5Gy}	0.696	-0.018	0.940	0.055
V_{10Gy}	0.888	0.489	0.980	***0.003***
V_{15Gy}	0.687	-0.035	0.940	0.060
V_{20Gy}	0.523	-0.282	0.898	0.179
V_{25Gy}	0.627	-0.138	0.924	0.096
V_{30Gy}	0.719	0.031	0.945	**0.044**
V_{35Gy}	0.719	0.028	0.945	**0.045**
V_{40Gy}	0.723	0.038	0.946	**0.042**
V_{45Gy}	0.696	-0.018	0.940	0.056
V_{50Gy}	0.526	-0.284	0.898	0.181

Table 5-7. Correlation coefficients with 95% confidence intervals for small bowel DVH parameters from studies of rectal cancer treatment only, with risk of Grade ≥ 3 toxicity.
P values < 0.05 indicated in bold. P values < 0.005 indicated by italic typeface.

Parameter	B for VxGy	SE for B	Intercept	SE for intercept	*P* value for V_{xGy}
V_{5Gy}	0.0020	0.0008	-2.11	0.288	**0.017**
V_{10Gy}	0.0052	0.0018	-2.63	0.428	***0.004***
V_{15Gy}	0.0038	0.0023	-2.05	0.359	0.095
V_{20Gy}	0.0028	0.0023	-1.80	0.287	0.227
V_{25Gy}	0.0045	0.0028	-1.92	0.291	0.108
V_{30Gy}	0.0068	0.0034	-2.01	0.289	**0.046**
V_{35Gy}	0.0075	0.0035	-1.99	0.264	**0.034**
V_{40Gy}	0.0079	0.0036	-1.93	0.232	**0.026**
V_{45Gy}	0.0092	0.0043	-1.79	0.183	**0.033**
V_{50Gy}	0.0095	0.0064	-1.54	0.115	0.143

Table 5-8. Logistic regression model coefficients with standard error (SE) for each small bowel DVH parameter, with statistical significance of logistic regression model fit to risk of Grade ≥ 3 toxicity.
P values < 0.05 indicated in bold. P values < 0.005 indicated by italic typeface.

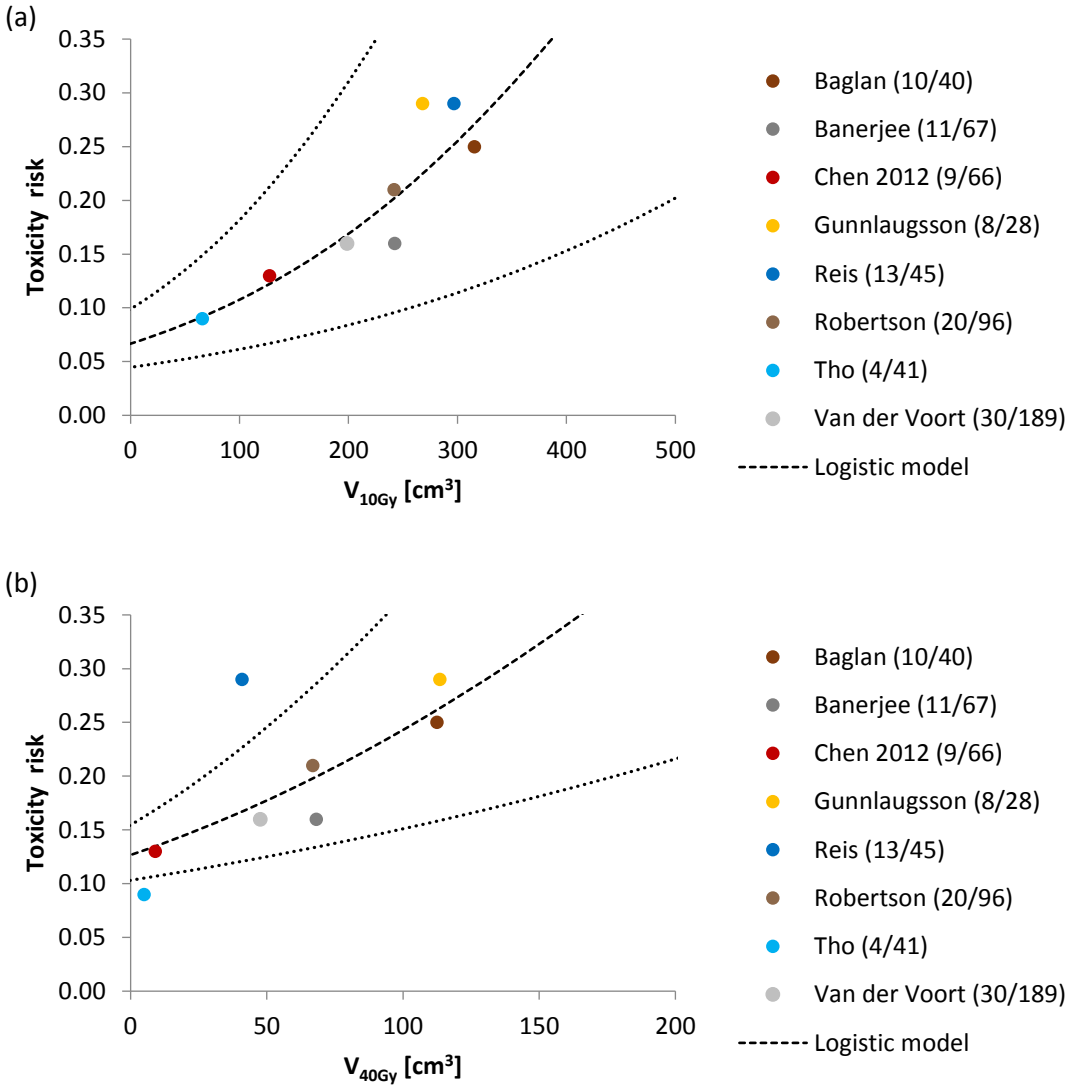


Figure 5-7. Plot of reported toxicity rate against small bowel (a) V_{10Gy} [cm³], (b) V_{15Gy} [cm³] and (c) $_{v40Gy}$ for studies of radiotherapy for rectal cancer with univariate logistic regression model (dashed line) and 69% confidence interval for model parameters (dotted lines).

5.3.4. Canonical correlation

Matrices of correlation between each small bowel DVH parameter among the source data are shown in Table 5-9 highlighting how, for cumulative DVH data (a), there is a positive correlation between almost all parameters. As would be expected, the parameters of the DVH closest to each other are most closely correlated with each other, and the strength of correlation falls as the distance between parameters on the horizontal axis of the charted DVH distribution (dose in Gy) increases. It can be seen that for the differential DVH data (b), this is

not the case, and the relationship between different parameters is not consistent, with more independence of DVH parameter values.

a) Cumulative absolute DVH values

	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}
V_{5Gy}	1	0.811	0.461	0.455	0.469	0.481	0.489	0.521	0.399	-0.112
V_{10Gy}		1	0.864	0.829	0.825	0.793	0.743	0.738	0.604	0.16
V_{15Gy}			1	0.986	0.973	0.915	0.832	0.805	0.704	0.365
V_{20Gy}				1	0.988	0.925	0.833	0.804	0.686	0.319
V_{25Gy}					1	0.954	0.862	0.831	0.739	0.377
V_{30Gy}						1	0.967	0.939	0.849	0.485
V_{35Gy}							1	0.988	0.888	0.53
V_{40Gy}								1	0.926	0.572
V_{45Gy}									1	0.768
V_{50Gy}										1

b) Differential absolute DVH values

	$V_{5–10Gy}$	$V_{10–15Gy}$	$V_{15-20Gy}$	$V_{20-25Gy}$	$V_{25–30Gy}$	$V_{30–35Gy}$	$V_{35–40Gy}$	$V_{40–45Gy}$	$V_{45–50Gy}$	$V_{\geq 50Gy}$
$V_{5–10Gy}$	1	0.816	-0.152	-0.303	-0.282	-0.321	-0.332	0.042	0.273	-0.388
$V_{10–15Gy}$		1	0.285	-0.322	-0.327	-0.351	-0.334	-0.027	0.055	-0.408
$V_{15-20Gy}$			1	-0.117	-0.247	-0.285	-0.179	-0.265	-0.215	0.229
$V_{20-25Gy}$				1	0.662	0.441	0.342	0.602	0.398	-0.039
$V_{25–30Gy}$					1	0.845	0.334	0.314	0.361	0.01
$V_{30–35Gy}$						1	0.515	0.239	0.351	0.098
$V_{35–40Gy}$							1	0.673	0.451	0.137
$V_{40–45Gy}$								1	0.718	0.087
$V_{45–50Gy}$									1	0.19
$V_{\geq 50Gy}$										1

Table 5-9. Correlation matrix of (a) cumulative and (b) differential small bowel DVH parameters with each other. A colour scale has been applied to visualise strength and direction of correlation. Green shading indicates positive correlation and red indicates negative correlation.

The variable derived by the canonical correlation process showed a very high correlation with incidence of Grade ≥ 3 toxicity when all available data were included (correlation coefficient -0.914, 95% confidence interval -0.970 to -0.766, p = 7.168e-07). Tables of the individual DVH values with derived canonical-correlation coefficients and Vfactor values are included in Table 9-6, Table 9-7 and Table 9-8 in Appendix B. Interestingly, while the derived coefficients are different for the cumulative and differential DVH data, as would be expected, the resultant

Vfactor values – and hence also correlation with outcome – for each cohort are the same, regardless of whether the cumulative or differential DVH data are used.

The coefficients for a generalised linear model using Vfactor and chemotherapy classification to predict toxicity were: Chemotherapy -1.68, Vfactor -16.9, Chemotherapy:Vfactor +14.9, and intercept -0.0676. The relationship between Vfactor and proportional incidence of Grade ≥ 3 GI toxicity was significant (p = 0.015), with the administration of concomitant chemotherapy a significant interacting variable (p = 0.032). The relationship between toxicity and chemotherapy alone was not significant (p = 0.101). When only studies of rectal cancer were included in the analysis, the correlation of Vfactor with toxicity was 1 (95% confidence interval 1 – 1), and coefficients for the simplified model were A = -2.55, B = 1.21. These models are plotted with the source data points in Figure 5-8.

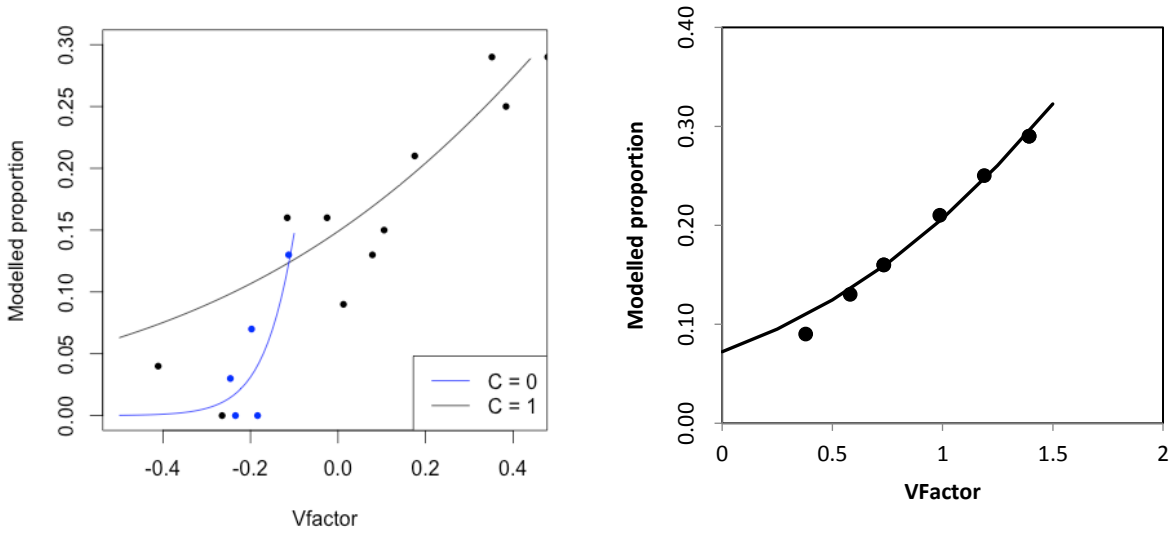


Figure 5-8. Plots of modelled proportional incidence of Grade 3 GI toxicity against -Vfactor with points marking data points derived from published studies.
Left hand panel: C = 1 indicates use of concomitant 5-FU/capecitabine, C = 0 indicates concomitant 5-FU/capecitabine chemotherapy not given. Right-hand panel: data from studies of rectal cancer only.

A Vfactor derived using only four DVH parameters – those that on their own showed statistically significant correlations with outcome, namely V_{10Gy}, V_{30Gy}, V_{35Gy}, and V_{40Gy} –

remained a highly significant predictor of toxicity, showing correlation with toxicity incidence of 0.909 (95% confidence interval 0.567–0.984, $p = 0.002$).

5.4. Discussion

5.4.1. Review of key results

A novel finding from the analysis undertaken here is that using the data from rectal cancer studies, several population-derived small bowel dose-volume parameters (V_{10Gy}, V_{30Gy}, V_{35Gy}, and V_{40Gy}) were found to be significantly predictive of toxicity incidence, in a univariate logistic regression model. For the parameter $V_{10Gy,}$ the p-value was sufficiently low that it would remain significant if a Bonferroni correction were applied to account for multiple testing. Analysis of published clinical data in this manner has not previously been reported for these treatments, although similar techniques have been proposed to model the toxicity of SBRT to the upper abdomen [266], and for fractionated treatment of other organs at risk including the parotid gland and lung [222].

When data from all available studies were used, there was no significant correlation between small bowel DVH parameters and the risk of toxicity, which is attributed to the underlying heterogeneity in the patients, their multimodal treatment, and in the method of dose-volume and toxicity data collection, and which will be discussed in more detail below. The results pertaining to rectal cancer therapy are, therefore, specific to this treatment paradigm and may not have broader generalisability.

Another important result is the replication of the finding in Chapter Four, that while the largest absolute differences in volume are seen at low doses, when such differences in dose-volume are recalculated as relative differences, the largest differences between patients with or without toxicity are seen for the higher dose regions. When examining the average effect size

across studies, the largest relative differences in small bowel volume between the cohorts of patients with or without toxicity were for the V_{30Gy}, V_{35Gy}, and V_{40Gy} (Figure 5-5). A similar signal was also apparent in the comparison of studies according to overall toxicity risk where the largest absolute differences in the average DVH for low or high toxicity studies were seen for the $V_{5Gy,}$ but the largest relative differences were seen for the V_{35Gy} and V_{40Gy}.

The importance of both high- and low-dose exposure to the small bowel has been demonstrated in both formal meta-analysis (Chapter Four) and in the analyses described here, and which is consistent with the conclusions made for the systematic review of the literature. Although the volume effect at doses below 5 Gy has not been tested in the published literature, the available data would not suggest that there is a threshold below which the small bowel can be irradiated, regardless of volume and without implication for risk of toxicity. As was mentioned in Chapter Two, this could in theory negate the intended benefit of techniques such as IMRT, which tend to reduce exposure of normal tissue to a high dose, but at the cost of increased volume irradiated to a low dose. However, as reduced toxicity has been demonstrated when pelvic IMRT is implemented, it appears the benefit of reduced high dose-volume outweighs the cost [216]. It has been shown here that the volume effect remains significant for the highest dose tested in these meta-analyses (V_{40Gy}). While several publications have reported evidence of a volume effect for the small bowel exposed to 50 Gy, there is also no evidence to suggest that a threshold dose exists above which the increased exposure does not increase the risk of toxicity.

Differences in effect according to tumour type

Consistent with the findings of the systematic literature review in Chapter Two, differences in the dose-volume-toxicity relationship for treatment of different abdominal-pelvic tumours

have been demonstrated here. For example, in both the colour-maps and in the modelling of the proportional toxicity risk according to DVH parameters, a relationship was only evident among the rectal cancer publications, with no such relationship apparent within the gynaecological cancer studies or when all data were pooled.

The colour maps of toxicity risk show that, within the rectal cancer studies, a strong relationship exists between toxicity and both dose and volume, where risk increases with increasing dose for a given volume and increasing volume irradiated to a given dose. This relationship was not consistent when all studies are included, but it can be seen that the trend is being 'disrupted' by a number of papers reporting very low rates, or zero toxicity, despite irradiated small bowel volumes being amongst the highest of the group. The pattern is clearer when studies regarding the treatment of endometrial cancer are removed (a condition for which patients usually do not receive concomitant chemotherapy but receive radiotherapy alone).

This evidence suggests, therefore, that in radiotherapy for gynaecological cancers, the relationship between small bowel dose-volume and toxicity is not as strong as that seen in the treatment of rectal cancer. As reviewed in Chapter Two, studies have shown that small bowel dose-volume does predict risk of toxicity in the treatment of endometrial cancer [169], cervical cancer [170, 171], and mixed cohorts of patients with gynaecological malignancies [163, 164, 250]. However, studies using data from treatment of patients with gynaecological cancers have generally identified fewer parameters with significant associations with outcome. Of all the studies of treatment of gynaecological malignancies identified in the literature search (nine), a greater number (three) and proportion (one third) reported having failed to show significant associations between small bowel dose-volume and toxicity. In comparison, from a total of ten studies reporting analysis of rectal cancer radiotherapy, only one was 'negative'.

As was also discussed in Chapter Two, it is challenging to elucidate if the difference in dose-volume relationship between different tumour sites is due to the nature of the primary condition, such as the effects of a rectal tumour remaining in situ, the effects or surgery, or the effect of concomitant chemotherapy administration. Sufficient data with which to disentangle these confounding factors was not identified in the literature search. To demonstrate the specific modifying effect of fluoropyrimidine chemotherapy, independently of tumour type and relation to surgery, would require DVH data reported separately for patients with each of both rectal cancer and gynaecological cancers, treated pre- or post-operatively and either with or without relevant chemotherapy regimens, and such data are not available.

Only one study was found that provided DVH data for patients receiving radiotherapy for rectal cancer without fluoropyrimidine chemotherapy, and only one small bowel DVH parameter (V_{15Gy}) was included in this report [262]. Hence, although it was possible to include this data point in the toxicity-risk colour maps, this publication can only make a small contribution to addressing the question regarding the modification of the radiotherapy dose-volume-toxicity relationship by chemotherapy. Interestingly, no publications were found that reported DVH data, or analysis of DVH data, from short course preoperative radiotherapy for rectal cancer, which is usually delivered without concomitant chemotherapy. Presumably this is because simple planning techniques are usually employed, without contouring of the organs at risk. Nonetheless, even if such data had been available, the significant difference in dose-per-fraction would make comparisons of data with conventionally fractionated chemoradiotherapy difficult. Likewise, no small bowel DVH data specifically for patients receiving postoperative radiotherapy after surgery for rectal cancer appears to have been published, and it was not possible to examine this factor in this meta-analysis.

The study by Huang et al. [164] was the only publication identified providing DVH data from radiotherapy for gynaecological malignancies where a large proportion of patients received concomitant fluoropyrimidine chemotherapy. It was observed that chemotherapy increased the risk of toxicity, and in the postoperative group, patients with toxicity were twice as likely to have received chemotherapy (60% vs 31%, $p = 0.108$). However, the small bowel DVH data were only reported for cohorts according to whether or not radiotherapy followed or preceded surgery, and *not* according to whether or not chemotherapy was given. As a result, the specific modifying effect of chemotherapy on the relationship of dose-volume with outcomes cannot be ascertained.

Other limitations

A key limitation to this work overall is the heterogeneity in the methods used to collect toxicity outcomes data and in the aspects of the clinical treatment that was delivered (within and across studies) that could not be controlled for. While it has been possible to divide the source publications into subgroups according to treated disease, with only two papers reporting data regarding pancreatic cancer and only one regarding anal cancer, no firm conclusions regarding these disease sites are possible. The studies reporting treatment of gynaecological malignancies were also an assortment of those regarding cervical cancer, endometrial cancer, or mixed populations of these and other tumour types. As mentioned, there was further heterogeneity in the treatment paradigm, with some studies describing preoperative radiotherapy, some describing postoperative therapy, others describing definitive treatment, and others describing mixed populations. At least nine different chemotherapy drugs or combinations were described, and the proportion of patients receiving those agents, and the adherence to the prescribed regimens, varied between studies. While only DVH data regarding small bowel outlined as 'individual loops' has been analysed, disregarding data pertaining to abdominal or peritoneal cavity or 'bowel bag' structures, there remain

differences in the manner in which the relevant tissue was contoured. For example, some groups only included loops of bowel that contained oral contrast. Furthermore, as it was discussed in relation to the studies analysed in Chapter Four, the absolute volume of small bowel that can be contoured for any patient is dependent on the extent of the imaging being used, but this was not specified by the majority of the publications.

While different methods and tools have been used for the collation and grading of toxicity symptoms, there are major key similarities between these, and it has been possible to translate grades between different scales. There was some further inconsistency in the definition of the relevant toxicity endpoint, where many studies used terminology such as 'lower GI toxicity' or 'small bowel toxicity', but without usually specifying the toxicity events or symptoms that constitute such a description. Others reported only the rate of any non-haematological toxicity, or conversely only the incidence of a single specific symptom ('diarrhoea' or 'watery stool' were both used). All studies except for one (Chen et al. [165]) relied on clinician-assessed toxicity, whereas potential benefits that may come from the use of patient-reported outcomes include greater breadth and sensitivity for the symptoms that trouble patients after their treatment for cancer [40].

Another variable in which heterogeneity exists was the definition of the time period constituting acute toxicity, which was not consistent between publications. For example, Baglan et al. [159] and Robertson et al. [192] only analysed toxicity occurring during the initial 25 fractions of radiotherapy, while Huang et al. [164] only included events occurring up to the delivery of 39 Gy. Other groups analysed events occurring during treatment [160, 161, 165, 168], or within a 90-day period from the start of radiotherapy [263], which is consistent with the RTOG/EORTC definition of acute toxicity [38], but many papers did not specify the observation period. Furthermore, the use of supportive medications such as anti-emetics and

anti-diarrhoeal drugs, in a prophylactic or reactive context, was not comprehensively recorded or reported, and as such the possible interaction with the effect of dose-volume cannot be ascertained.

Perhaps the most important limitation to consider in relation to this analysis is the significant risk of publication bias. As was reported in Chapter Two, six publications identified in the systematic search did not find a significant association between small bowel dose-volume and toxicity [150, 154-158]. Two of these studies did report DVH data suitable for inclusion in this analysis [157, 158], and in fact one of these found that patients without toxicity had higher volumes of irradiated small bowel [158]. However, two were published as abstracts only [155, 156] and, thus, there is reason to suspect that studies failing to show an association between DVH and toxicity were less likely to be published, and so their data will not have been available.

Finally, all of the studies providing data for this analysis comprise single institution cohorts of patients, leading to the risk of systematic differences in treatment or data collection between publications that could confound true differences. It has historically been difficult to compile multi-centre databases of radiotherapy dose distribution or dose-volume data for organs at risk. Open-source, manufacturer-independent tools such as the Computational Environment for Radiotherapy Research (CERR) [267] are intended to facilitate compilation of plans from different treatment platforms to enable consistent data extraction and enable large-scale analyses. Despite this, there remains an absence of collaborative analysis of large cohorts thus far, and efforts to achieve this – ideally using prospective and robust clinical trial data – should be supported and congratulated.

Canonical correlation

Canonical correlation does not appear to have been used in the analysis of radiotherapy data before now. Principal Component Analysis (PCA) has been used in clinical radiotherapy research and can be used to identify features of a dose-distribution that are most predictive of outcomes [268]. A potential advantage of canonical correlation over PCA is that all of the chosen DVH data can be incorporated into the derived parameter (the canonical variate), to a greater or lesser degree according to its apparent importance in association with the outcome, while in PCA only the 'important' data parameters are retained and the other data is discarded. Another advantage of canonical correlation is that the technique is expressly intended for use with data where the multiple predictive variables are interdependent.

A potential disadvantage of canonical correlation is that the canonical variate is difficult to interpret in terms of clinical applicability. PCA may identify regions of a DVH that have direct interpretability eg $V_{5–10Gy}$, which are straightforward for oncologists and dosimetrists to use in appraisal and optimisation of radiotherapy plans. However, a canonical variate could still be used to inform radiotherapy planning where facilities are available for inverse-planned IMRT. For example, it would seem feasible for a treatment planning system to attempt to optimise dose delivery in order to meet a constraint derived from multiple DVH parameters. An investigation of the implementation of canonical correlation coefficients to improve radiotherapy planning for patients with pancreatic cancer is presented and discussed in Chapter Six.

Another apparent disadvantage of canonical correlation is that the process has, in this case, derived negative coefficients for several DVH parameters, which would suggest these variables may have an inverse relationship with outcome. Negative coefficients for DVH

parameters are hard to accept as clinically plausible because we would not expect increased volumes of exposure to ever lead to a reduction in the likelihood of toxicity.

The behaviour of the canonical correlation process is interesting in itself. For example, it was found that the canonical variate derived for each subject/case in the analysis was the same, regardless of whether the original published cumulative DVH data is used or if the data were first converted to differential DVH data. This suggests that the process itself identifies the differences between the parameters and it is these, rather than the values themselves, that are important. Hotelling himself wrote:

> "The relations between two sets of variates with which we shall be concerned are those that remain invariant under internal linear transformations of each set separately….If measurements such as height to shoulder, and difference in height of shoulder and top of head, are replaced by shoulder height and stature, the invariant relations with other sets of variates will not be affected" [249].

A detailed analysis and discussion of the canonical correlation process itself is beyond the scope of this thesis, but the technique is evaluated further in the analysis of individual patient DVH data in Chapter Six.

5.5. Conclusions

Published cohort small bowel DVH data from multiple clinical studies have been analysed, and they illustrate the increasing risk of toxicity with both increased dose and volume of exposure during radiotherapy, with differences in the dose-volume-toxicity relationship apparent in the treatment of different tumour sites, but which are not easily explained, due to the presence of confounding factors.

Toxicity is shown to be associated with largest **absolute** differences in the volume of small bowel irradiated to low dose (V_{5Gy}), but with largest **relative** differences in volume irradiated to higher doses (V_{35Gy}-V_{40Gy}) in the treatment of rectal cancer, and doses of V_{40Gy}-V_{50Gy} in the treatment of gynaecological cancers. For studies of the treatment of rectal cancer, cohort-derived small bowel dose-volume parameters (V_{10Gy}, V_{30Gy}, V_{35Gy} and V_{40Gy}) were found to be significantly predictive of the toxicity incidence in that population in a univariate logistic regression model. Canonical correlation appears to be a useful means of integrating multiple DVH parameters in order to derive a single parameter, which correlates highly with outcomes, but this process requires further exploration before it can be utilised in the clinic.

Differences in toxicity incidence and in the dose-volume-toxicity relationship for the small bowel in the treatments of rectal and gynaecological cancers are likely to be due to the difference in the concomitant chemotherapy regimens normally utilised, specifically fluoropyrimidine or platinum agents, respectively. However, a lack of data is available to evaluate this or to control for the possible effects of the disease itself, the pre- or post-operative sequencing of radiotherapy, and the use of different radiotherapy techniques. Despite this, these findings strongly suggest that specific radiotherapy planning constraints should be used for each treatment indication, and that generic optimisation parameters for organs at risk regardless of disease and chemotherapy regimen would be inappropriate.

Future work would ideally attempt to disentangle these confounding factors using multi-centre prospectively collected radiotherapy and outcomes data. The use of dose escalation is becoming increasingly popular in the treatment of some pelvic tumours, such as locally advanced rectal cancer and anal cancer, and may provide an opportunity for a small bowel dose-volume effect at doses greater than 50 Gy to be studied. The effect of very-low dose

should also be examined, where the use of patient-reported outcome measures may possibly improve sensitivity to lower-grade toxicity.

Acknowledgement

I am grateful to Dr Daniel Lunn of the University of Oxford Statistics Consultancy Service for suggesting the use of canonical correlation.

6. Chapter Six. Predictors of toxicity in chemoradiotherapy for pancreatic cancer: analysis of individual patient data from the ARCII and SCALOP clinical trials

6.1. Introduction

As has been discussed in the preceding chapters, clinical data on the radiotherapy dose and volume tolerances for the stomach, duodenum and small bowel remain sparse. Through collating the published data, and applying both modelling and meta-analysis techniques, some firm conclusions have been made regarding the dose-volume-toxicity relationship for the duodenum and for the small bowel. However, it is clear that further analysis of individual patient data regarding delivery of radiotherapy involving these organs will be required in order to develop our understanding, and to enable safe intensification of treatment. Furthermore, as most analyses have comprised retrospective data from single institutions, this field would benefit from work utilising robust, multi-centre radiotherapy and outcomes data that has been prospectively collected.

In this chapter, toxicity outcomes are analysed in relation to clinical factors and dose-volume parameters for the GI organs at risk, in patients with locally advanced pancreatic cancer treated in two prospective phase-II clinical trials.

This analysis aimed to: 1) identify normal-tissue DVH parameters associated with an increased risk of toxicity, including exploration of canonical correlation, a novel method to integrate the whole DVH; 2) develop and validate predictive multivariable models for a personalised estimation of risk that might be utilised in the clinic; 3) investigate associations of toxicity and survival outcomes.

6.2. Methods

6.2.1. Patient data

The treatment given in the ARCII and SCALOP trials has been described in Chapter Three, along with the patient characteristics and toxicity incidence. For analysis against possible predictive variables, a single comprehensive toxicity endpoint of upper GI toxicity (UGIT) was defined, comprising symptoms encompassed by the RTOG definition: nausea, vomiting, abdominal pain, GI bleeding/perforation, bowel obstruction, and anorexia ± weight loss [38]. The maximal grade of any of these symptoms suffered by each patient during a period of three months (90 days) from the onset of chemoradiotherapy was identified. The maximal grade of acute diarrhoea was recorded separately. Where necessary (eg for logistic regression and ROC analysis) the toxicity outcome was dichotomised according to a threshold of Grade 2 or above, chosen because this grade indicates sufficient severity of symptoms to require medical intervention.

Two patients from the ARCII study were excluded from the analysis as they received only one radiotherapy fraction. For one patient, this was due to acute complications of disease progression (cholangitis and biliary sepsis), and the other experienced sudden unrelated medical comorbidity (acute confusional state). One other patient from the SCALOP study was excluded due to abnormal stomach dilatation on planning CT (stomach volume 2954 cm^3) caused by gastric outlet obstruction. Median stomach volume for the patients who were analysed was 361 cm^3 (interquartile range 255 cm^3 – 541 cm^3). Radiotherapy dose distribution data were not available for three patients from the SCALOP study. In total, ninety-one patients (seventy from SCALOP, twenty-one from ARCII) were included in the final analysis.

Disease and patient characteristics analysed included age, sex, performance status, BMI, tumour volume, and tumour location within the pancreas. Tumour volume was that of the

gross tumour volume (GTV) as contoured by the treating clinician, and calculated in CERR [267]. The centre of mass of the tumour was identified using a custom in-house MATLAB tool, and classified manually as lying within the head (including uncinate process), neck, or body of the pancreas according to the location relative to anatomical landmarks. In ARCII the Karnofsky scale [269] had been used to assess and record patient performance status, whereas in SCALOP the ECOG (Eastern Cooperative Oncology Group) scale [270] had been used. The ARCII KPS scores were therefore converted to the equivalent ECOG grade using a published comparison tool, which is reproduced in Appendix B [270]. For the SCALOP patients, weight loss during induction chemotherapy was calculated, in kilograms.

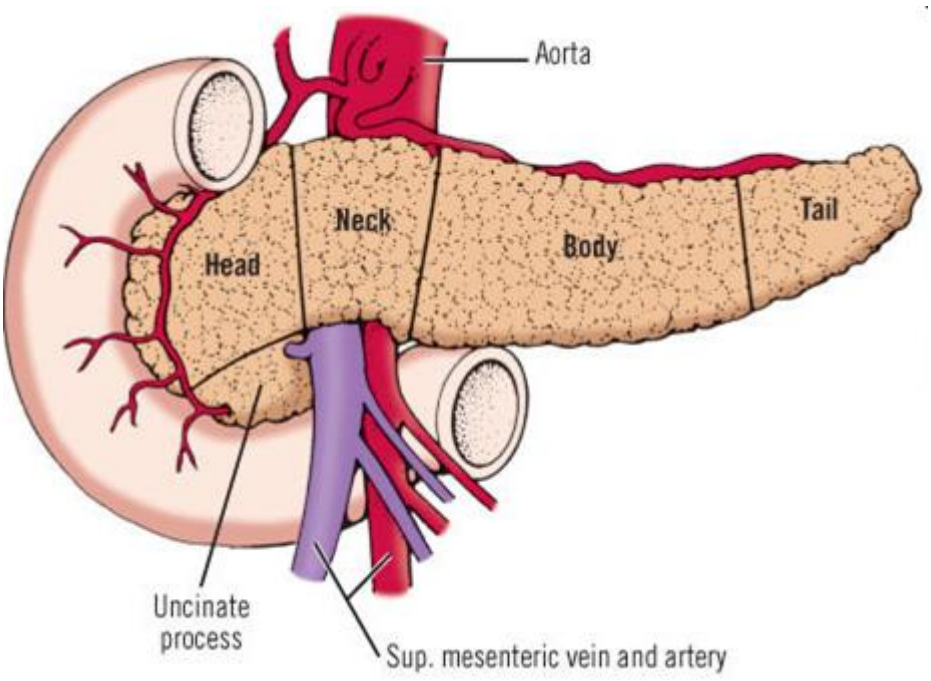


Figure 6-1. Anatomical subdivisions of the pancreas. From Skandalakis' Surgical Anatomy [271]

6.2.2. Radiotherapy data

Details of the radiotherapy planning protocol for the two studies and the extraction of radiotherapy data have been described in Chapter Three (section 3.2.2). The small bowel was contoured as individual loops, to a minimum inferior extent of the inferior limit of the

duodenum, or 15 mm inferior to the inferior limit of the treatment fields, whichever was lower. Differential and proportional/ relative DVH data were derived from the extracted data as necessary.

6.2.3. Statistics

Non-parametric tests were used for the analysis of associations and correlation using radiotherapy data. Differences in continuous variables between groups were assessed using the Mann-Whitney-Wilcoxon test, and differences in frequencies according to categories were assessed using the Chi-squared distribution. Spearman's rank was used for correlations between continuous variables, and Kendall Tau-b was used to test for correlations between continuous variables and dichotomous outcomes. Binary logistic regression was used to test and quantify relationships of predictive variables with the risk of incidence of dichotomised outcomes, and ordinal regression used to test for associations with grade of toxicity. Optimal risk thresholds for division of patients into groups according to continuous variables were derived using ROC analysis and ranked according to Youden's index (J = Sensitivity + Specificity – 1) [272]. Canonical correlation was investigated as a supplementary method to try and discover dose-volume parameters predictive of toxicity.

Factors showing significant associations on univariate analysis and those with a sound clinical rationale for relationships with toxicity were incorporated into multivariate logistic regression. Parameters considered for incorporating into a multivariate model were first examined for associations. Optimal models were selected by maximal classification accuracy, and the area under the curve (AUC) with a minimum Akaike Information Criterion. A backwards-stepwise model selection was used to identify predictive factors with significant contribution to the multivariable model (threshold for exclusion from the model $p > 0.1$). The models were 'offered' the clinical factors and parameters: sex (male vs female), age, performance status

(ECOG 0 vs ≥ 1), tumour location (centre of mass of tumour in head vs neck/body), tumour volume, chemotherapy regimen (SCALOP gemcitabine vs SCALOP capecitabine vs ARCII), stomach $V_{35–45Gy}$, and presence of baseline toxicity (Grade 0 vs ≥ 1).

6.2.4. Cross-validation

Internal cross-validation was used to estimate generalisability of the results to independent patients by testing the performance of the multivariable models on unseen data. A custom software tool was used to divide the combined cohort, comprising the pooled patients from the two trials (ninety-one patients), into even partitions. The allocation to partitions was randomised but with stratification according to clinical trial, so that in each partition the proportion of patients taken from the two studies was constant, and similar to that for the cohort as a whole. Two variants of the cross-validation technique were evaluated. In the first, in an attempt to more realistically simulate the external validation process, a partition of the cohort was initially set aside (twenty-one patients). The remainder of the cohort was then split into ten equal partitions of seven patients each. The model was then trained on nine-tenths of the remaining patients, and tested on the other one-tenth, on a rotational basis. Finally, the optimal model defined in this manner was tested on the patients initially set aside and this not part of the model training. Due to some concerns in the literature about the appropriateness of this method in a small cohort with resultant small partitions, an alternative method was also investigated in which the whole cohort was divided into five equal partitions, creating four partitions with eighteen patients and one with nineteen. The model was trained on four-fifths then tested on the remaining fifth of the patients, five times. In both variants the partitions were defined once, and these partitions were used thoughout (ie the pool of patients was not sampled again with each training/testing exercise). This means the data from each patient contributed equally to training and testing each model, rather than randomly being selected potentially for none or all of the training or test partitions.

6.2.5. Survival analysis

Overall survival and progression-free survival were charted using the Kaplan-Meier method, and compared between groups using log-rank (Mantel-Cox) testing. Patients who did not die or suffer disease progression during follow-up were censored at the last known follow-up in the clinical trial. Survival durations were measured in days from the start of chemoradiotherapy. In an attempt to address the potential confounding effect, the overall survival assessment was repeated excluding patients who suffered documented disease progression within the period of evaluation of acute toxicity (90 days from the start of chemoradiotherapy).

6.3. Results

6.3.1. Toxicity incidence, and clinical and radiotherapy data

CTCAE Grade ≥ 2 UGIT symptoms occurred in 38 patients (42%) overall. Grade ≥ 2 diarrhoea occurred in 19 patients (21%). Incidence rates of individual toxicity grades for each study were detailed in Chapter Three, Table 3-3. No Grade 4 or Grade 5 toxicity occurred. The risk of Grade ≥ 2 UGIT was higher among the ARCII cohort than among the SCALOP patients, but not significantly so ($\chi^2 = 1.267$, $p = 0.216$). The proportion of patients with performance status ≥ 1 ($\chi^2 = 2.837$, $p = 0.092$) (Figure 6-2), and those whose tumour centre of mass lay in the neck or body of the pancreas rather than the head ($\chi^2 = 6.773$, $p = 0.335$) (Figure 6-3), were also higher in the ARCII cohort but not significantly. Other clinical and treatment parameters were equivalent across the two cohorts (Chapter Three, Table 3-2).

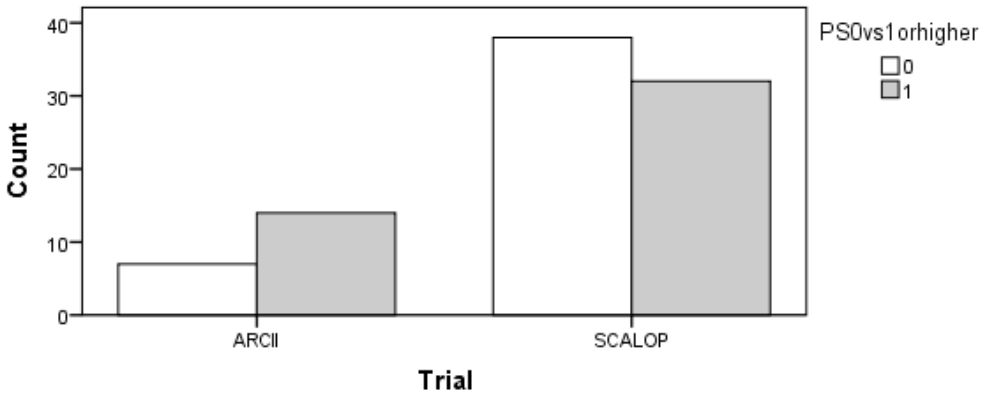


Figure 6-2. Performance status for patients in ARCII and SCALOP

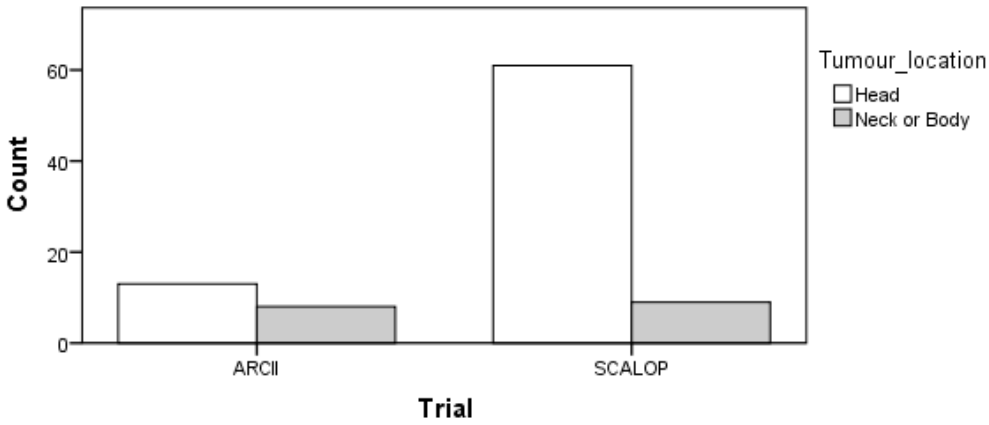


Figure 6-3. Classification of tumour location within the pancreas according to clinical trial.

6.3.2. Univariate analysis of toxicity against clinical and radiotherapy factors

On univariate analysis, the stomach cumulative V_{35Gy} (volume receiving 35 Gy or more) was significantly higher for patients with toxicity: median for patients with Grade 0–1 UGIT = 30.9 cm^3 (IQR 12.0–62.0), compared with median for patients with Grade ≥ 2 = 39.4 cm^3 (24.8–101.7), (p = 0.036). The stomach cumulative DVHs for the individual ARCII patients are shown in Figure 6-4, and the median DVH for two groups of patients defined according to the incidence of toxicity in Figure 6-5. The differential DVH parameter $V_{35Gy–40Gy}$ (volume receiving between 35 Gy and 40 Gy) was a more statistically significant indicator of toxicity (median 6.36 cm^3, IQR 1.89–18.4, vs 10.2 cm^3, 5.24–18.4) than

the cumulative DVH parameter V_{35Gy}. The largest difference between the patient cohorts, and strongest correlation with toxicity risk, was seen for differential DVH region $V_{35–45Gy}$ (median 12.9 cm^3 (IQR 3.56–23.4) vs 16.4 cm^3 (9.75–32.0), Kendall Tau-b 0.185, p = 0.033). On univariate logistic regression the stomach $V_{35–45Gy}$ was predictive of risk of UGIT Grade ≥ 2 (odds ratio 1.035, 95% CI 1.007-1.063, p = 0.014) (Figure 6-6). On univariate ordinal regression, stomach $V_{35–45Gy}$ was predictive of UGIT grade (1.023, 1.003–1.044, p = 0.022) and median stomach $V_{35–45Gy}$ for patients increased sequentially with toxicity grade as detailed in Table 6-1 and visualised in Figure 6-7.

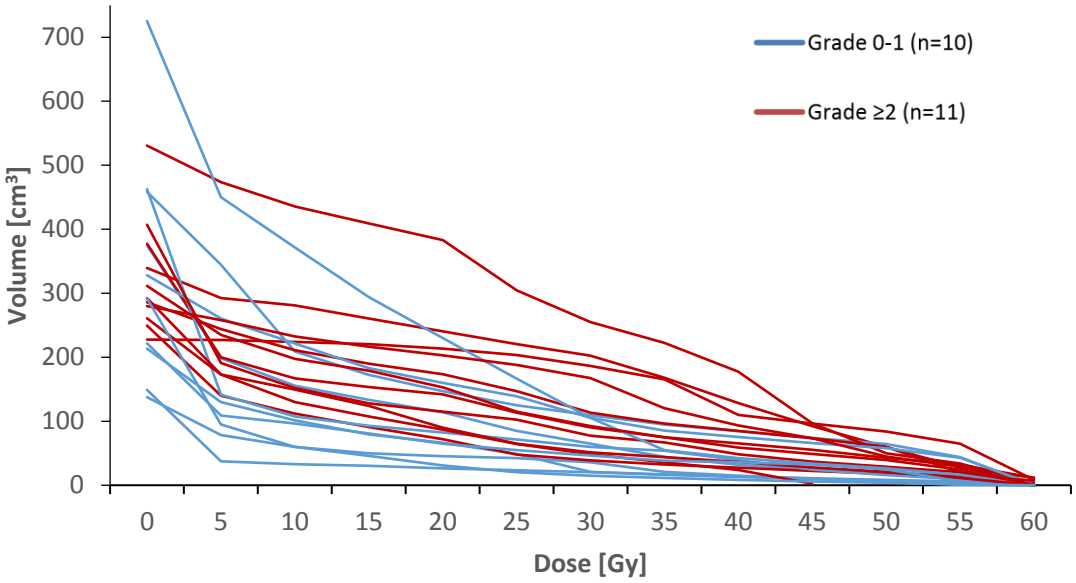


Figure 6-4. Stomach cumulative dose-volume histograms for the ARCII patients (n = 21) labelled according to highest grade of acute upper GI toxicity. Blue = Grade 0–1, Red = Grade ≥ 2

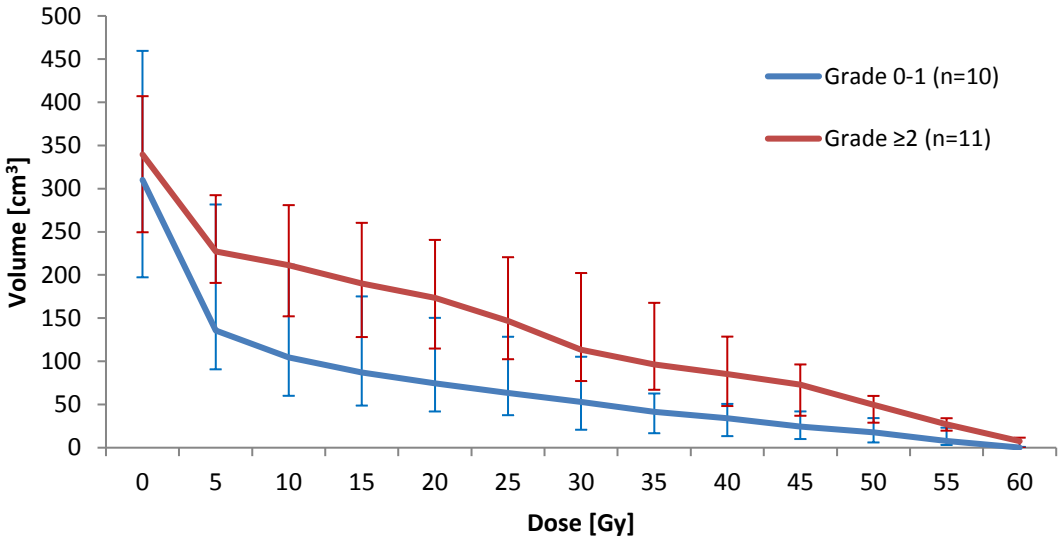


Figure 6-5. Median cumulative stomach dose-volume histograms for the ARCII patients (n = 21) divided into cohorts according to incidence of acute upper GI toxicity. Blue = Grade 0–1, Red = Grade ≥ 2. Error bars indicate interquartile range.

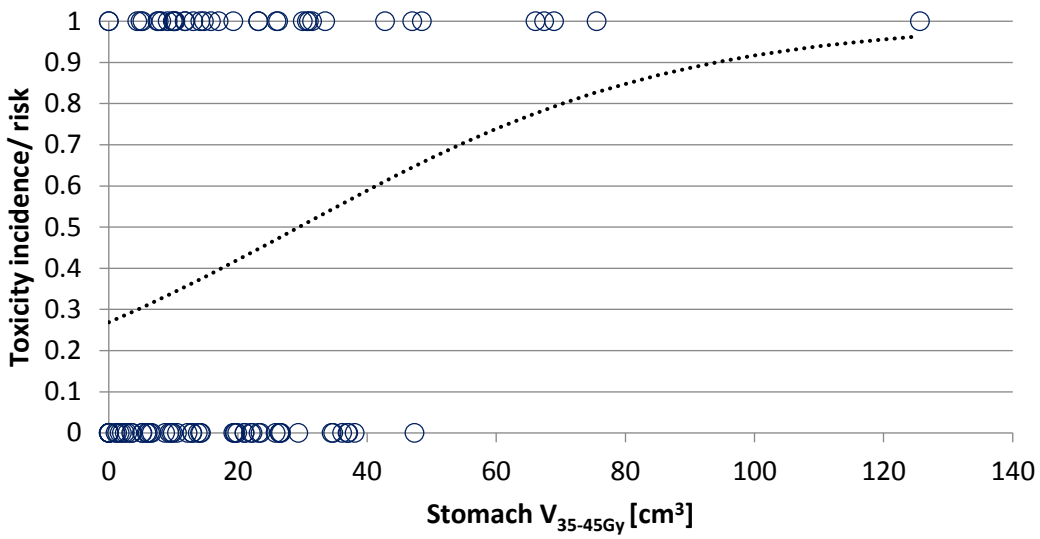


Figure 6-6. Plot of univariate logistic regression model (dotted line) for stomach $V_{35–45Gy}$ against risk of Grade ≥ 2 acute upper GI toxicity for the pooled cohort (n = 91), with observed patient data (blue circles).

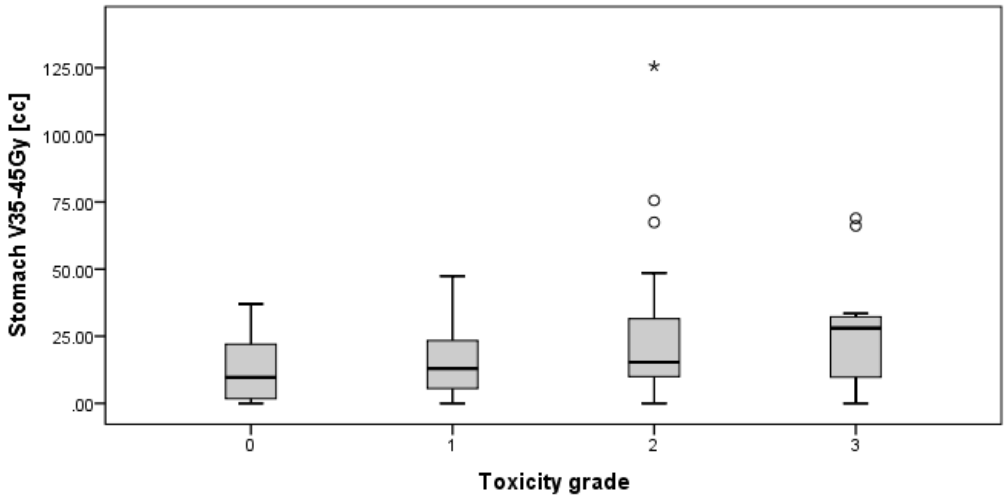


Figure 6-7. Box and whisker plot of stomach $V_{35–45Gy}$ against maximal grade of acute upper GI toxicity for the pooled cohort (n = 91).

Table 6-1. Stomach $V_{35–45Gy}$ according to grade of acute upper GI toxicity, for the pooled cohort (n = 91)

Toxicity grade		**0**	**1**	**2**	**3**
Stomach	Median	9.70	12.93	15.31	28.02
$V_{35–45Gy}$ [cm^3]	IQR	1.72–22.00	5.54–23.37	9.95–31.51	9.74–32.26

As a predictor of the risk of UGIT Grade ≥ 2, the AUC for the stomach $V_{35–45Gy}$ was 0.632 (0.516–0.747). Toxicity incidence was 33/66 (50%) for patients with $V_{35–45Gy}$ above the optimal discriminatory threshold of 7.1 cm^3, and 5/25 (20%) below, with a sensitivity of 0.892 and specificity 0.377. The volume threshold with second-highest Youden index was 30 cm^3, for which the risk was 13/20 (65%) above and 25/71 (35%) below. Duodenum dose-volume parameters did not predict risk or severity of toxicity in any cohort (Table 9-13, Appendix C).

Table 6-2 shows the results of univariate logistic regression for risk of UGIT Grade ≥ 2 for clinical factors. Risk of UGIT was higher in patients with ECOG performance status greater than zero, but the difference was not significant (odds ratio 1.661, 95% CI 0.717–3.852, p = 0.235). For patients in the SCALOP study, significant predictors of risk and severity of UGIT included the amount of weight loss during induction chemotherapy (odds ratio 1.199, 95% CI 1.040–1.382) and the allocated concomitant chemotherapy drug, where risk was highest for

patients in the gemcitabine arm (odds ratio 3.632, 95% CI 1.300–10.151). Increasing age was a significant predictor of toxicity risk and severity only for the ARCII cohort, odds ratio 1.344 (95% CI 1.015–1.780). Table 6-3 shows the odds ratios for significant ordinal regression relationships.

On multivariate analysis, GTV size and the presence of diarrhoea symptoms at baseline were significant predictors of the risk of Grade ≥ 2 diarrhoea within 90 days from the commencement of chemoradiotherapy. Small bowel DVH parameters did not show association with risk or severity of diarrhoea (Table 9-13, Appendix C).

Table 6-2. Collated results of univariate logistic regression of clinical factors against risk of Grade ≥ 2 UGIT, showing odds ratio (with 95% confidence intervals) and p-values

	Combined cohort	***p***	**ARCII**	***P***	**SCALOP**	***p***
Age	1.01 (0.96–1.06)	0.807	**1.34 (1.02–1.78)**	**0.039**	0.97 (0.91–1.03)	0.289
BMI	0.97 (0.88–1.07)	0.535	1.08 (0.86–1.36)	0.498	0.95 (0.84–1.06)	0.333
Tumour size	1.01 (1.00–1.03)	0.144	1.01 (0.96–1.06)	0.753	1.01 (1.00–1.04)	0.098
ECOG PS (0–1 vs 2)	1.96 (0.41–9.32)	0.397	3.38 (0.29–39.32)	0.332	0.79 (0.07–9.14)	0.849
Male sex[1]	0.59 (0.26–1.37)	0.220	0.56 (0.10–3.15)	0.507	0.61 (0.23–1.60)	0.314
Tumour location[2]	1.80 (0.72–4.45)	0.207	4.80 (0.68–33.80)	0.115	1.23 (0.42–3.58)	0.711
Baseline UGI toxicity	1.54 (0.65–3.66)	0.328	1.50 (0.20–11.54)	0.697	1.73 (0.65-4.63)	0.272
Weight loss on induction					**1.20 (1.04–1.38)**	**0.012**
Chemotherapy agent[3]					**3.63 (1.30–10.15)**	**0.014**

Results in bold typeface Indicate significance at p < 0.05 level; [1]Risk is lower for males, in both studies, [2]Head of pancreas vs other part of pancreas; [3]Gemcitabine vs capecitabine, risk is highest for gemcitabine arm. BMI = Body Mass Index; ECOG = Eastern Cooperative Oncology Group; PS = Performance status

*Table 6-3. Statistically significant results for univariate ordinal regression. *Gemcitabine vs capecitabine, severity grade is higher for gemcitabine. 95% CI = 95% confidence intervals; $V_{35–45Gy}$ = volume of organ receiving between 35 and 45 Gy.*

		Odds ratio	**95% CI**	***p***
Pooled cohort	Stomach $V_{35–45Gy}$ [cm^3]	1.023	1.003–1.044	0.022
ARCII	Age [years]	1.159	1.019–1.318	0.024
SCALOP	Concomitant Chemotherapy*	3.56	1.43–8.85	0.006
	Weight loss [kg]	1.172	1.046–1.314	0.006

6.3.3. Multivariate modelling of toxicity risk

Age, tumour volume, and stomach $V_{35–45Gy}$ were not significantly different for men or women (Table 6-4). Patients with performance status ≥ 1 were more likely to have symptoms of toxicity at baseline (Figure 6-8), but no other categorical variables showed significant associations (Table 6-6). Stomach $V_{35–45Gy}$ was highest in ARCII, (median 21.0, IQR 10.6–30.1) next highest in the gemcitabine arm (14.5, 7.9–28.7) and lowest in the capecitabine arm (9.8, 2.9–22.3), and was significantly different between these groups (Kruskal-Wallis test, χ^2 = 7.197, p = 0.027). GTV volume was non-significantly larger (p = 0.160) in SCALOP patients (median 31.7 cm^3, IQR 21.4–45.3 cm^3) compared with those in ARCII (median 27.3 cm^3, IQR 14.1–41.6 cm^3). Overall, stomach $V_{35–45Gy}$ was significantly correlated with GTV volume (Spearman's correlation 0.211, p = 0.044), as seen in Figure 6-9.

Table 6-4. Continuous variables according to patient sex. Median values with inter-quartile range are reported. P-value indicates result of Mann-Whitney U test (M-W U). N = number of patients; GTV = Gross Tumour Volume; Stomach $V_{35–45Gy}$ = volume of organ receiving between 35 Gy and 45 Gy

	N	Age	GTV volume	Stomach $V_{35–45Gy}$
Male	40	64.9 (57.0–70.3)	31.7 (19.2–47.8)	18.3 (5.2–26.7)
Female	51	65.5 (57.7–69.5)	27.9 (19.9–42.7)	13.1 (6.7–26.0)
M-W U		992.5	960.0	1002.0
***p*-value**		0.795	0.604	0.854

Table 6-5. Categorical variables according to patient sex. P-value indicates result of Chi-squared testing.

	ECOG PS		Tumour location		Baseline toxicity		Trial/chemo*		
	0	≥ 1	Head	Neck/body	None	Present	ARCII	Cape	Gem
Male	25	25	40	10	33	11	11	17	22
Female	20	21	34	7	25	12	10	17	14
Chi-squared	0.013		0.127		0.663		0.945		
p-value	0.908		0.722		0.718		0.624		

**Trial/chemo = concomitant chemotherapy regimen, considered as three categories – 1) ARCII 2) SCALOP capecitabine 3) SCALOP gemcitabine.*

Table 6-6. P-value results of Chi-squared testing for associations of categorical variables thought to be possible predictors of toxicity

	Sex	ECOG PS	Tumour location	Baseline toxicity	Trial/chemo*
Sex	-	0.908	0.722	0.718	0.624
ECOG PS		-	0.827	**0.001**	0.234
Tumour location			-	0.515	**0.033**
Baseline toxicity				-	0.081
Trial/chemo*					-

**Trial/chemo = concomitant chemotherapy regimen, considered as three categories – 1) ARCII 2) SCALOP capecitabine 3) SCALOP gemcitabine.*

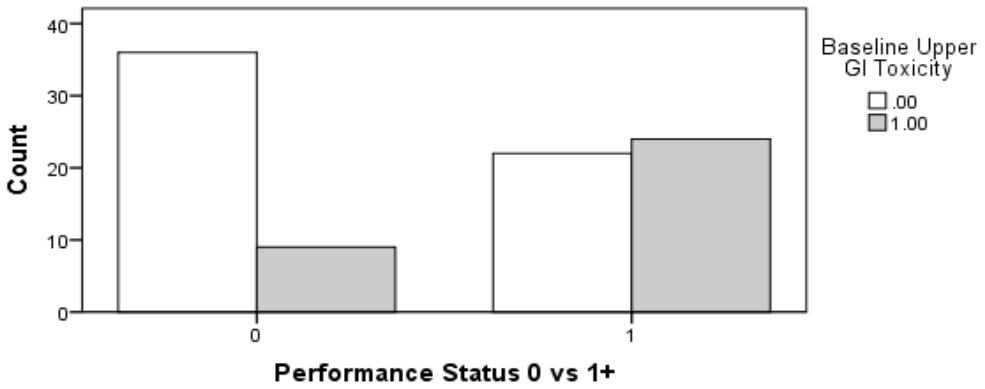


Figure 6-8. Presence or absence of upper GI toxicity symptoms at baseline according to ECOG performance status

The optimal multivariate model incorporated patient sex, chemotherapy regimen (gemcitabine vs capecitabine vs ARCII regimen) and stomach $V_{35–45Gy}$ as a continuous variable. This achieved overall predictive accuracy of 71.4% and AUC of 0.745. Model coefficients are detailed in Table 6-7. Age, performance status, tumour volume and tumour location were not retained in the model. Figure 6-10 shows a plot of observed against predicted proportional incidence of toxicity for three evenly sized groups divided by predicted risk and the ROC curve for the same model.

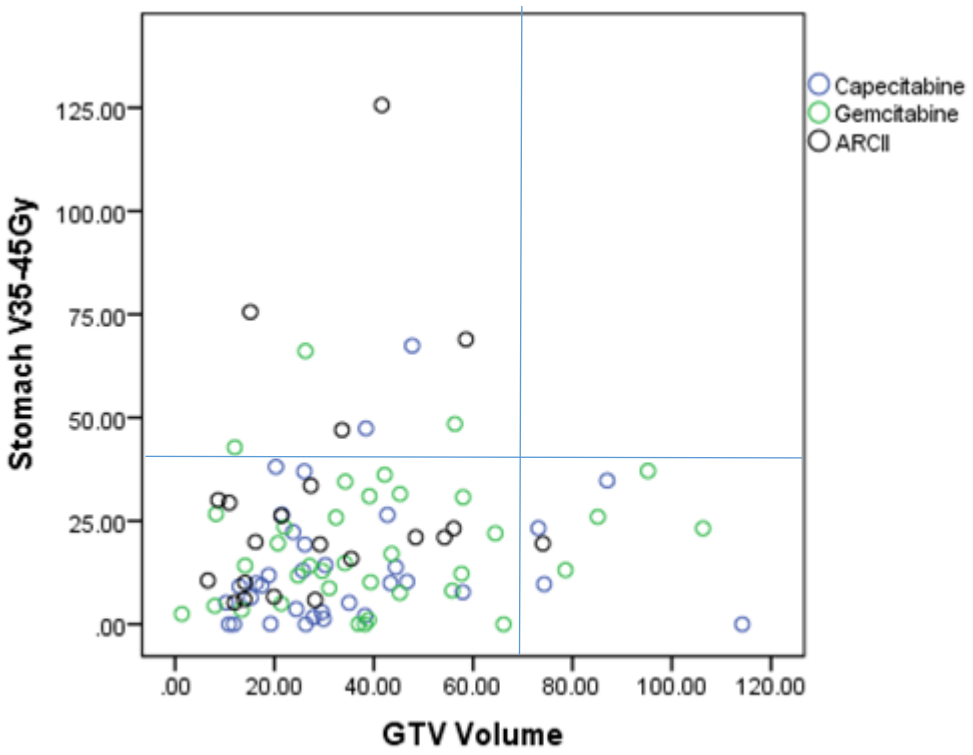


Figure 6-9. Scatter plot, showing relationship of GTV volume [cm³] with stomach $V_{35–45Gy}$ [cm³] with individual patients labelled by clinical trial cohort. The highest 10th centile groupings for each parameter are indicated.

	Coefficient	SE	*p*	Odds ratio	95% CI
Chemo = Gemcitabine	1.350	0.559	0.016	3.859	1.291–11.533
Chemo = ARCII	1.022	0.636	0.108	2.779	0.799–9.665
Sex = Female	0.782	0.481	0.104	2.185	0.851–5.613
Stomach $V_{35–45Gy}$ [cm³]	0.033	0.015	0.025	1.034	1.004–1.064
Constant	-2.163	0.603	0.000	0.115	

Table 6-7. Multivariable logistic regression model coefficients. SE = standard error; 95% CI = 95% confidence intervals; $V_{35–45Gy}$ = volume of organ receiving between 35 and 45 Gy.

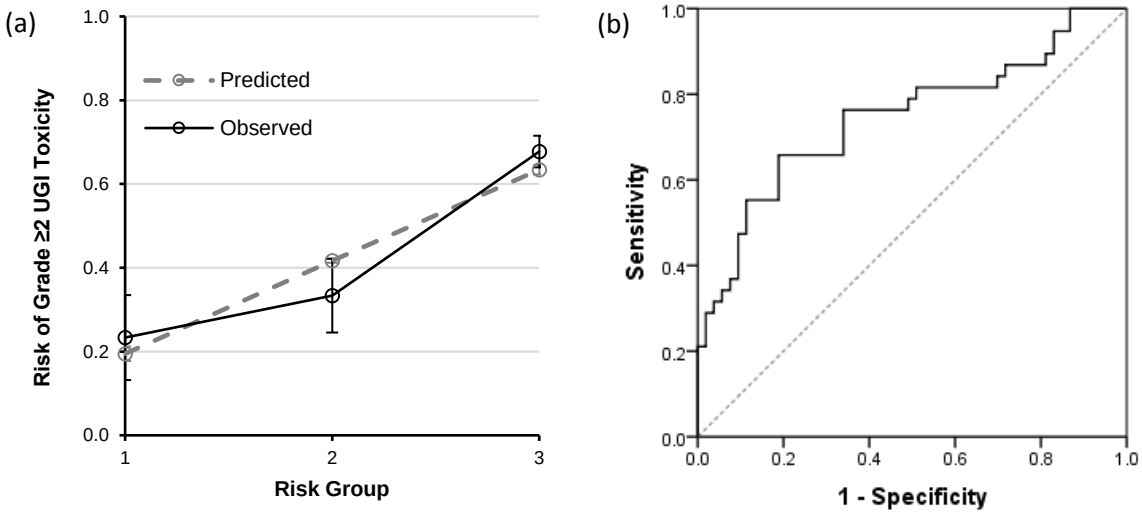


Figure 6-10. (a) Plot of observed proportional incidence of acute UGI toxicity Grade ≥ 2 among three evenly-sized cohorts divided according to risk (low, medium, high) as predicted by multivariable logistic regression model. (b) ROC curve for multivariable model

Table 6-8. Canonical correlation coefficients for stomach dose-volume histogram parameters

DVH parameter	Coefficient
V_{0Gy}	0.00009
V_{5Gy}	0.00059
V_{10Gy}	-0.00096
V_{15Gy}	0.00283
V_{20Gy}	-0.00396
V_{25Gy}	0.00096
V_{30Gy}	-0.00095
V_{35Gy}	0.00722
V_{40Gy}	-0.00390
V_{45Gy}	-0.00055
V_{50Gy}	-0.00031

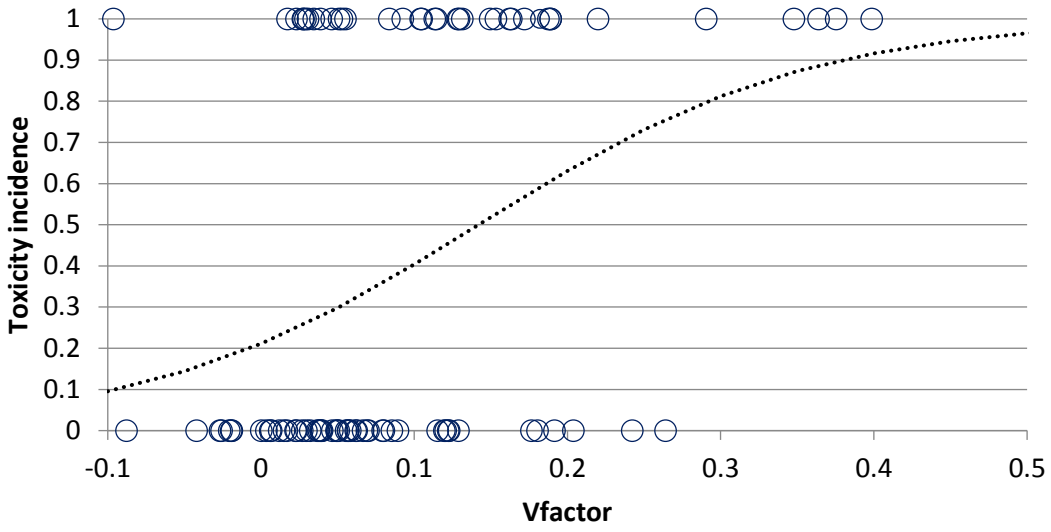


Figure 6-11. Plot of univariate logistic regression model of stomach Vfactor (dotted line) against risk of Grade ≥ 2 acute upper GI toxicity for the pooled cohort (n = 91), with observed patient data (blue circles)

The canonical correlation technique was only investigated using the stomach DVH data, as the other organs at risk did not show a relationship with toxicity on conventional analysis. A canonical dose-volume-factor was derived using the 5-Gy DVH bins V_{0Gy} – V_{50Gy} (selected as the parameters V_{55Gy} and V_{60Gy} did not contain data for the SCALOP patients). This 'Vfactor' achieved very high correlation with incidence of toxicity: Kendall Tau-b parameter = 0.291, $p < 0.001$. The regression model parameters were: intercept = -1.240 (standard error 0.365), coefficient for 'Vfactor' = 8.179 (SE 2.631), $p = 0.002$. The coefficients for the DVH parameters are specified in Table 6-8, and the model is plotted with the observed data in Figure 6-11.

6.3.4. Cross-validation

As described in the methods, two variants of internal cross-validation were explored. In the first variant, twenty-one patients were first set-aside. The model was then trained on nine-tenths of the remaining patients, and tested on one-tenth, on a rotational basis. The mean AUC on the training sets was 0.764 (Standard Deviation 0.023 and range 0.722–0.807), while the mean AUC on each unseen test cohort was 0.722, SD 0.192 range 0.417–1. The optimal

model identified during this process was then tested on the as-yet unseen twenty-one patients, in which the AUC was 0.491.

In the second variant of this exercise, the cohort was simply split into five partitions and the model was trained on four-fifths then tested on the remaining fifth of the patients, five times. The mean AUC on the training sets was 0.736 (SD 0.035) and on the test partitions was 0.598 (SD 0.188) (Table 6-9). The predictive factor most frequently retained in the model was the chemotherapy group (retained in four models), followed by the stomach $V_{35–45Gy}$ (3 models) and sex and GTV volume (2 models each).

Table 6-9. Results of five-fold internal cross-validation. The performance of the model trained on the whole cohort is included for comparison. The significant predictors retained in the final model are indicated, with a summary count of how often each predictor was retained. AUC = area under the curve; ECOG PS = Eastern Co-Operative Group performance status; GTV = gross tumour volume; Chemo = chemotherapy group (SCALOP gemcitabine vs SCALOP capecitabine vs ARCII); SD = standard deviation.

Model*	Accuracy (training)	Accuracy (test)	AUC all	AUC train	AUC test	Sex	ECOG PS	GTV Volume	Chemo	Stomach $V_{35–45Gy}$
1	69.9	55.6	0.685	0.704	0.844		Y	Y		Y
2	71.2	44.4	0.722	0.793	0.403	Y		Y	Y	
3	72.6	33.3	0.665	0.732	0.462	Y				Y
4	72.6	55.6	0.711	0.740	0.538				Y	Y
5	68.1	73.7	0.716	0.709	0.744				Y	Y
Mean	70.9	52.5	0.700	0.736	0.598	2	1	2	3	4
SD	1.9	15.0	0.024	0.035	0.188					
Whole cohort	71.4	-	0.745			Y			Y	Y

* The model number denotes the partition that was omitted for training, then used for testing

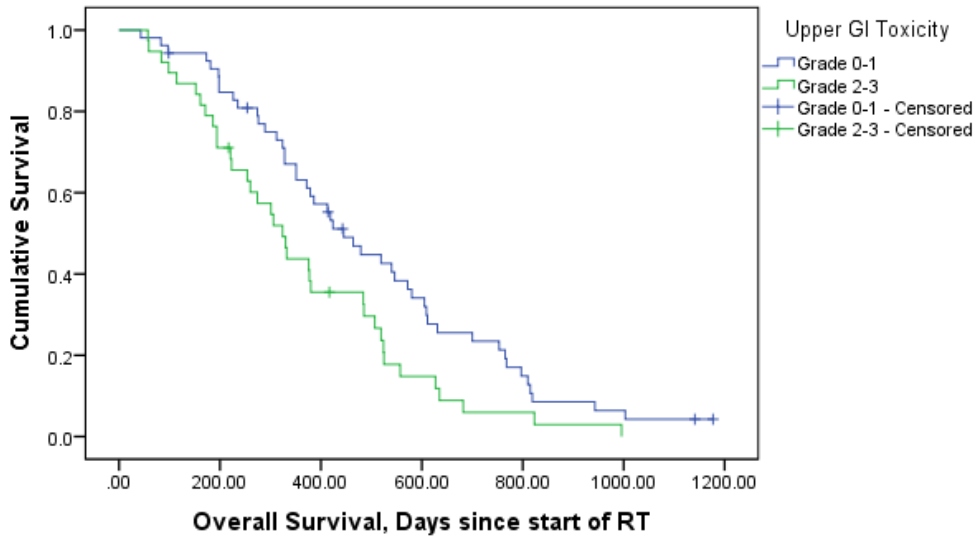
The canonical correlation method was also tested through five-fold internal cross-validation in the same manner. The canonical variate was tested alone without other clinical parameters. The results are detailed in Table 6-10. The model performance on the validation partition was consistently lower than on the training set.

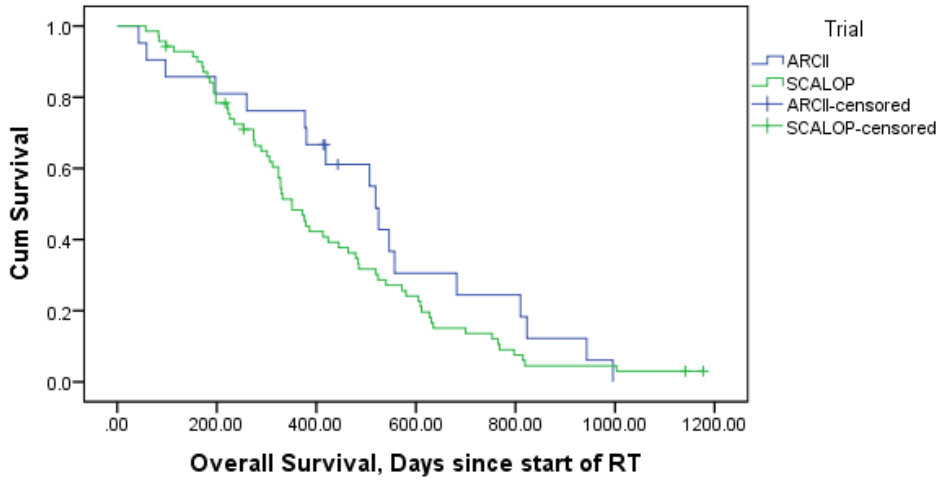
Table 6-10. Results of five-fold internal cross-validation of canonical-correlation models using stomach Vfactor. AUC = area under the curve on receiver operating characteristic (ROC) analysis; SD = standard deviation.

Test partition	Training AUC	Validation AUC
Partition 1	0.752	0.649
Partition 2	0.737	0.442
Partition 3	0.802	0.477
Partition 4	0.721	0.477
Partition 5	0.691	0.679
Mean	0.741	0.545
SD	0.041	0.110

6.3.5. Survival analysis

Overall survival was significantly worse in patients who experienced Grade ≥ 2 UGIT (median 10.8 months (95% CI 11.9–17.7) vs 14.8 months (8.5–13.1), log-rank 5.637, $p = 0.018$) (Figure 6-12). This was the only categorical division tested that showed a statistically significant difference between groups. The same result was seen when patients who had progressive disease within 90 days were excluded from the analysis, which was the case for three patients from ARCII and three from SCALOP. Survival was non-significantly better for patients in ARCII compared with those in SCALOP ($p = 0.187$), and in patients with a performance status of 0 compared with others ($p = 0.423$) (Figure 6-12). Survival was not different for male or female patients. Patients with acute Grade ≥ 2 UGIT were not less likely to complete radiotherapy: 41/53 patients (71.1%) received all fractions compared to 27/38 (77.4%), $\chi^2 = 0.466$, $p = 0.495$.





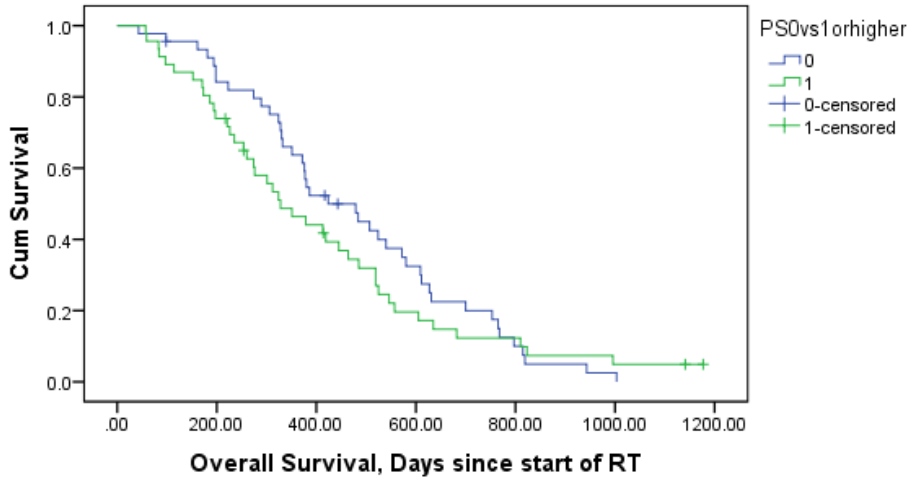


Figure 6-12. Kaplan-Meier plots of overall survival in days since start of chemoradiotherapy for (a) patients with or without Grade ≥ 2 UGI toxicity (b) patients in ARCII compared with those in SCALOP (c) patients with ECOG PS = 0 compared with others.

On exploratory analysis of survival according to the incidence of toxicity among subgroups, the finding of worse survival in patients with toxicity was statistically significant in the SCALOP cohort but not in the ARCII trial. Within SCALOP, it was significant only in the gemcitabine arm and not the capecitabine arm (Figure 6-13). The association of survival with UGIT remained significant in female patients, and, although the direction of association persisted in male patients, it was no longer statistically significant. The association also remained significant among patients with a performance status of 0, but not among the others.

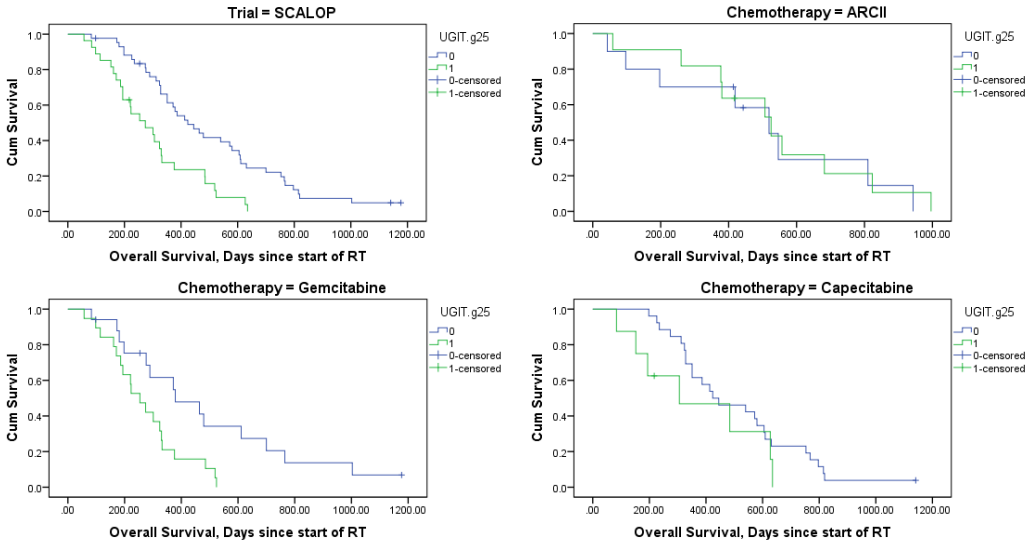


Figure 6-13. Overall survival according to incidence of acute upper GI toxicity Grade 2–5 in subgroups of the patient cohort (a) SCALOP trial (b) ARCII trial (c) SCALOP patients randomised to gemcitabine concomitant chemotherapy (d) SCALOP patients randomised to capecitabine concomitant chemotherapy

Progression-free survival (PFS) was also worse for patients with any acute UGI toxicity, but the difference was not statistically significant: 6.1 months (95% CI 4.1–8.2) compared with 8.2 months (6.6–9) (p = 0.052). No other differences in PFS between groups were seen.

6.4. Discussion

Acute upper GI toxicity has been analysed for two prospective trials of chemoradiotherapy for locally advanced pancreatic cancer, and demonstrated patient-related factors influencing risk and severity of acute GI toxicity. Further, it has been shown that this complication of treatment itself is associated with worse overall survival.

Stomach dose-volume was predictive of toxicity risk, and thresholds for risk have been derived that could be used to inform radiotherapy planning for subsequent patients. Several studies have reported similar associations of radiotherapy dose-volume parameters with the risk of toxicity incidence. However, this is the first analysis in chemoradiotherapy for pancreatic cancer to show how the increasing volume of stomach irradiated to a particular dose can predict increasing grade of severity of resultant toxicity, using ordinal regression. The slightly higher predictive performance of a differential DVH parameter is noted, compared with those taken from a conventional cumulative DVH. It is reasonable to expect that a more specific measurement of the delivered treatment may show clearer associations with outcomes, and may be of more utility in prospective treatment planning. Relative (proportional) volume parameters were also investigated, and showed significant associations with outcome, but due to the smaller differences in measurements between patients, these parameters led to modelling regression results that were not straightforward to interpret and utilise clinically. It is worth noting that duodenum dose-volume was not associated with toxicity, although several studies have found such an association in patients receiving chemoradiotherapy for pancreatic cancer, as was discussed in Chapter Two.

The incidence of toxicity was different between the two clinical trials making up this pooled cohort; however, the specific causal relationship for this is difficult to interpret, due to the possible confounding differences between the treatments delivered in the two studies. Not

only did the patients receive different concomitant chemotherapy administered with radiotherapy, but in ARCII the radiotherapy treatment field was also larger in order to irradiate the draining lymph nodes. Additionally, the prescription dose to the tumour itself was higher, while the SCALOP patients had also received induction chemotherapy and only those without progressive disease went on to receive chemoradiotherapy. Despite this heterogeneity, it was possible to show that patient sex and stomach dose-volume remained significant contributors to overall risk in the multivariable model for the pooled cohort. It is not clear why females were at greater risk of toxicity than men, and there were no significant associations between sex and other factors such as age, PS, tumour size/location, or presence of baseline symptoms (Table 6-4 and Table 6-5). In the SCALOP cohort, the degree of weight loss during the induction phase of systemic chemotherapy was associated with an increasing risk of acute toxicity following concomitant radiotherapy, although the mechanism for this relationship is not clear. The risk of both acute and late GI toxicity after pelvic radiotherapy has previously been shown to be higher in women with low body weight [65, 164], however low BMI itself was not associated with the risk of acute toxicity in our dataset.

Tumour size was not found to be a significant predictor of toxicity on univariate analysis, nor was it incorporated in the final multivariable model. Tumour size was highly correlated with stomach dose-volume, but it was not mutually exclusive for retention in multi-variable models with the stomach $V_{35–45Gy}$, which would be expected if the two parameters were simply acting as surrogates for each other. In the event of actual dose-volume data being unavailable, tumour size is likely to be more important as a predictor of toxicity by acting as a surrogate, or indicator, for the volume of normal tissue that is likely to be irradiated by a 'standard' plan for that tumour type. Stomach dose-volume is here associated with an increased risk of toxicity, independently of tumour size. It can be seen in the scatter plot (Figure 6-9) that there remains variation in each parameter in relation to each other. It can be seen that while GTV

volume and stomach $V_{35–45Gy}$ are correlated, a large GTV need not mean high volume of stomach treated to the dose in question, nor vice versa. None of the nine patients (10^{th} centile) with the largest GTV were among the nine patients with the largest volumes of stomach receiving 35–45 Gy.

A model intended to predict clinical outcomes is of little utility if it correctly classifies all cases in the cohort on which it is trained, but fails to predict outcomes for independent but otherwise comparable cases. Predictive modelling of radiotherapy toxicity can be prone to such overfitting, with disappointing results on external data [273]. Internal validation is a tool intended to estimate the generalisability (external applicability) of a predictive model by testing its ability to correctly classify an unseen sample of cases, and it is considered an essential part of model development [274]. In cross-validation, a model should not have been trained on the cases on which it is tested and should be attempting to classify these cases unseen, based on parameters and predictive factors optimised on the training partition. Rotational k-fold cross-validation, as has been investigated here, aims to reduce the susceptibility to random bias.

This work is the first in pancreatic cancer to undertake internal cross-validation in an attempt to evaluate generalisability and to restrain potentially over-optimistic estimates of prospective model performance. Unfortunately, our results indicate a degree of overfitting may have occurred, with model performance on unseen data that is poorer than on training cohorts, and this has been recognised to be a possible drawback of using stepwise predictor selection methods [275]. In the five-fold analysis, the mean training AUC (0.736) indicates a 'fair' ability to correctly classify the training cases and appears reasonably stable across the five-fold training sets (range 0.704–0.793), while in the ten-fold analysis, the average training AUC was higher (0.764) with a tighter range (0.722–0.807). However, the performance of the

models on the test cohorts was lower than on the training sets and also showed far greater variation. For the five-fold validation, the mean test AUC of 0.598 suggested poor or limited external generalisability, with the range (0.462–0.744) also showing that, unfortunately, some models performed worse than chance on the test cohorts.

Overall, this would suggest that the incidence of toxicity remains difficult to predict among individual patients, due to factors that have not been encompassed by this analysis – despite strong univariate associations being observed and the ability to derive a multivariable model with high fit to the observed data.

The canonical correlation technique derived a stomach dose-volume parameter that showed highly significant predictive ability for risk of toxicity. The coefficients derived for each of the DVH parameters in the canonical correlation model using all of the data (Table 6-8) show that the V_{35Gy} is given the greatest weighting. This means it has the greatest influence on the resultant Vfactor for each patient, and which is therefore consistent with the results of the analyses which did not incorporate canonical correlation. Unfortunately, the canonical correlation method also appears to have suffered from overfitting, evidenced by the fact that while the model performance in training was, on average, better than that achieved by the optimal multivariable model, the performance on validation partitions was worse.

The stomach canonical correlation parameters performed no better than chance when faced with unseen data, and hence were not included in the multivariable model building. It is likely that overfitting is due to the high number of predictive parameters being incorporated into the canonical variate relative to the number of patients in the analysis. Furthermore, canonical correlation is conventionally used to establish relationships between a set of

multiple predictive parameters with a set of multiple outcomes, while in this work only one outcome was used, providing the model with the opportunity to overfit to the observed data.

In external validation, a model is tested on an entirely separate cohort. An external cohort is not always available, or in some cases it is felt that significant underlying difference(s) exist between the available cohorts, as is the case here. In this situation, an alternative approach that can be used is to combine the cohorts, and then immediately remove a proportion of the cases, selected at random, for independent testing of a model derived on the remaining portion. The results of this method (the ten-fold cross-validation with a hold-out portion) indicated that this approach appeared to be inappropriate for this small sample size. The model performance on each rotational assessment showed huge variability due to the very small test partition, and the performance of the model on the partition that was set aside was very poor, falling toward the lower extreme of the range demonstrated in rotational cross-validation. It is possible that, simply due to chance, the patients in the withheld partition were harder to classify correctly than the average for the cohort, leaving the remainder comparatively easier to predict. This could explain why the mean test performance in the ten-fold internal validation for the remainder was apparently better than that seen in the five-fold analysis, when all patients were included in either training or test.

It has been described that when sample size is small, the technique of random splitting to simulate external validation may increase risk of bias and it appears in this case that it has added little information beyond that achieved through internal cross-validation, other than to have possibly demonstrated this risk [276]. True external validation of these findings is required and is hoped to be conducted using data from an ongoing randomised study investigating chemoradiation in locally advanced pancreatic cancer.

The association between toxicity and survival does not appear to be explained by any single factor, such as the failure to complete radiotherapy. Instead, it may represent a combination of effects that are not individually significant. For multiple clinical factors (tumour size, age, BMI, PS, recent weight loss, baseline symptoms), it is expected that the direction of effect that is associated with risk of toxicity would be correlated with worse outcomes overall (Table 6-2).

This analysis has focused exclusively on acute GI toxicity, since for patients with locally advanced pancreatic cancer, the prognosis is so poor that late toxicity cannot be considered a clinical priority. In ARCII, the median overall survival was 17.4 months, with median progression-free survival only 5.5 months. In SCALOP, the median overall survival was 15.2 months in the capecitabine group and 13.4 months in the gemcitabine group. Both trials were designated as phase-II studies, and for which the trial data collection period was for a maximum of 12 months. Even then, only 57% of SCALOP patients had data available for the final toxicity assessment at 52 weeks, while only 67% of ARCII patients were still 'on-study' at 12 months.

Previous analyses of relationships between GI dose-volumes and toxicity in chemoradiotherapy for pancreatic cancer have been reviewed in Chapter Two, and are summarised again in Table 9-14 (Appendix B). In only two of these five studies has stomach dose-volume been shown to predict toxicity, while four of the five found duodenum dose-volume predictive of toxicity. The stomach parameters found to be predictive have not yet been replicated, being the V_{50Gy} (with 16 cm^3 being the optimal threshold to separate patients into high or low risk) and D_{2cm^3} (threshold 53.6 Gy) in the analysis conducted by Nakamura et al. [83], and the V_{20Gy} (threshold 31%) in the analysis by Cattaneo et al. [90]. Recently Shinoto et al. have reported their analysis of dose-volumes parameters predicting risk of gastric ulcer after carbon-ion chemoradiotherapy for pancreatic cancer, though the values themselves may

not be directly comparable with those from conventional photon chemoradiotherapy [277]. The result of the analysis described here has therefore again failed to replicate previous findings, but interestingly has shown that the dose region lying between those highlighted by the previous investigators is important. This is consistent with the concept that all of the organ DVH is potentially important in its relation to different components of toxicity, but that the parameters that will be emphasised by any individual study depends on the specifics of the patients, the radiotherapy delivery and the toxicity endpoints chosen.

It is important to note that the toxicity rates observed among the patients in ARCII and SCALOP are similar to those that have been seen in these previous studies of pancreatic chemoradiotherapy. Considering the ARCII study specifically, the rate of Grade 3 GI toxicity among these patients (14.3%) is very similar to that seen in the phase-I study of this treatment regimen (16.7%) [278]. The rate of Grade ≥ 3 diarrhoea (19%) is approximately similar to that seen in other small studies using nelfinavir alongside radiotherapy for rectal cancer, with capecitabine (16.7%) [279] or without (10.0%) [280].

Stomach dose-volume parameters have also been shown to predict toxicity risk in radiotherapy for other malignancies in which, interestingly, the results were more similar to those of this analysis (Table 9-14). In the treatment of hepatic tumours, the combined 'gastroduodenum' V_{35Gy} [149] and the stomach V_{25Gy} [153] have been shown to predict Grade 3 and Grade ≥ 2 gastroduodenal toxicity respectively, and stomach D_{max} has shown an association with gastric bleeding [145].

Unfortunately, this analysis must be considered to have a number of limitations. Due to the number of parameters assessed in any DVH analysis, there is an elevated risk of type I error, while in the absence of a power calculation negative results may be due to insufficient power,

or alternatively due to insufficient variation in the independent factors. Neither of these two clinical trial protocols enforced radiotherapy planning constraints for either the stomach or duodenum, potentially allowing the dose-volume parameters to vary considerably between patients. However, the near-ubiquitous proximity of the duodenum to tumours of the head of the pancreas may mean that there is less scope for plans to spare this structure, and that there is more similarity in dose-volume distributions between patients. Despite this comprising the largest prospective pancreas radiotherapy trial dataset analysed to date, the sample size remains relatively small and the method of pooling data from two trials to increase total numbers does increase heterogeneity and risk of confounds.

Analysis of any toxicity endpoints is potentially restricted by the complex relationship of patient symptoms with the underlying pathological effects of treatment and the disease itself. It is possible, in conflating multiple symptoms to derive a single toxicity endpoint, that the detail of a specific relationship with a specific symptom is obscured. The challenge in investigating multiple toxicity endpoints is of increased risk of spurious findings. Patient-reported outcome measures may potentially represent an improvement over conventional methods of toxicity recording, but no tool is yet established for the assessment of upper abdominal radiotherapy toxicity. Conversely, while endpoints of unequivocal physical damage (such as ulceration seen on endoscopy) may be less susceptible to subjectivity and reporting bias, these severe events represent only a small proportion of the morbidity associated with treatment. The GI organs are highly mobile and deformable, which can lead to significant increase in dose to the stomach compared with the planned dose, even if breath-hold methods are implemented [281], and, as has been discussed, ideally outcomes would be analysed against the delivered dose [234]. Neither gating nor tracking were used for delivery of radiotherapy in the studies analysed here, and planning margins were used to account for respiratory motion. Shinoto et al. have noted that, relative to the resting exhale phase, most

of the movement of the intra-abdominal organs is downwards. This brings the distal stomach (usually lying superior to the PTV) inferiorly into the high-dose irradiated volume of space, while much of the duodenum actually moves away from the targeted volume, an observation that they think may explain the absence of duodenal ulceration in their study [277].

6.5. Conclusions

In chemoradiotherapy for locally advanced pancreatic cancer, the volume of stomach irradiated to moderately high dose (35–45 Gy) predicts incidence and severity of acute toxicity. For the patients analysed, if $V_{35–45Gy}$ was kept below 30 cm^3, the risk of Grade ≥ 2 toxicity was 35% or less, and if kept below 7.1 cm^3, the risk was 20% or less. Small bowel and duodenum dose-volumes were not significantly associated with toxicity outcome, but risk of toxicity was higher for patients with poorer performance status at baseline, though not significantly so. In ARCII patients, age predicted risk and severity of toxicity, and in SCALOP the toxicity risk and severity was greater for patients treated with concomitant gemcitabine than with capecitabine, and for those who suffered more weight loss during their induction chemotherapy treatment. Tumour size and the presence of diarrhoea symptoms at baseline were significant predictors of risk of Grade ≥ 2 diarrhoea.

The optimal multivariate model for prediction of acute upper GI toxicity incorporated the stomach $V_{35–45Gy,}$ the concomitant chemotherapy regimen (ARCII regimen vs gemcitabine vs capecitabine) and patient sex. Age, performance status, tumour volume and tumour location were not retained in the model. The model achieved a strong overall predictive accuracy of 71.4% and AUC of 0.745, however, the model performance on internal cross-validation was rather disappointing, suggesting the model was overfitting and that external generalisability may be limited. Canonical correlation appeared to be a promising tool with which to

incorporate information from a wider region of the DVH for organs at risk into a predictive model, but also appeared to suffer from overfitting.

The incidence of acute toxicity is shown to be associated with worse overall survival, and though the reasons for this are not uncertain, it may be due to the confounding associations with other clinical factors likely to contribute to poorer outcomes such as age, tumour size, and performance status.

These results and these models could be immediately utilised in two ways. Firstly, the result that stomach dose-volume predicts toxicity suggests that the stomach should always be contoured for patients due to undergo chemoradiotherapy for pancreatic cancer (and potentially for other tumours of the upper abdomen or lower thorax). In this way, the DVH data can be examined so that efforts can be made to avoid this organ at risk with the aim of reducing the likelihood of acute upper GI toxicity. Secondly, the multivariate model can be used to predict the individual risk for patients undergoing such treatment: to help inform patient expectations and potentially warn treating clinicians to be prepared to respond with supportive treatments more promptly for those patients who are forecast to be at higher risk.

Acknowledgements

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7. Chapter Seven. Target definition for margin-intense pre-operative stereotactic body radiation therapy for pancreatic cancer and preliminary results of SPARC, a phase-I trial

7.1. Introduction

Radical surgical resection represents the only chance of long-term disease control in pancreatic cancer, but it was possible for just 8% of UK patients diagnosed between 2006–2010 [282]. In Europe, standard practice for resectable disease is surgery followed by chemotherapy, but 50% of these patients will suffer local recurrence [2] suggesting that further improvement in multi-modal therapy is required to improve the likelihood of tumour control.

A failure to consistently achieve microscopic surgical clearance is a factor in the high rates of disease relapse, because alongside tumour size, grade and lymph node metastases, microscopic resection margin involvement (R1 status) has been shown repeatedly to predict long-term survival [283, 284]. Survival for patients with positive margins may actually be little better than for those with unresectable disease [285].

Accurate assessment of resection margins requires a comprehensive examination of the surgical specimen, and rates of detection of margin involvement are higher when a standardised protocol is used [286]. Despite centralisation of surgery and improved preoperative investigations, positive margins were reported in > 35% of patients in the largest

multi-national adjuvant trial in pancreatic cancer (ESPAC-3, involving over 1000 patients), which again reinforced that patients with positive margins face a poor prognosis [287].

Borderline-resectable pancreatic cancer (BRPC) is a radiological definition to classify tumours that can be surgically excised but with likely requirement for vascular reconstruction and particularly high risk of positive resection margins [288]. In UK high-volume specialist surgical centres, the rate of microscopic positive margin status (R1) for patients undergoing pancreatectomy with vein resection was 62.9% (144/230), and almost half of these were due to disease at the infiltrated mesenteric vessels [289]. The most widely accepted definition of BRPC is published by the National Comprehensive Cancer Network [95] (see Box 1), following the first publication of the concept by Mehta et al. [290].

- Venous involvement of the superior mesenteric vein or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing safe resection and reconstruction
- Gastro-duodenal artery encasement up to hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis
- Tumour abutment of the superior mesenteric artery (SMA) not to exceed greater than 180° of the circumference of the vessel wall.

Box 1. NCCN definition of borderline-resectable pancreatic cancer

An alternative definition of BRPC proposed by the MD Anderson Cancer Centre has not been as widely recognised [291]. Whichever definition is used, it is essential that a multidisciplinary team should to assess whether a patient is a potential candidate for resection and the probability of attaining negative resection margins [291, 292].

The management of BRPC is controversial, and there is increasing interest in preoperative strategies that may improve outcomes [293]. Theoretical advantages over adjuvant treatment include a greater chance of delivering treatment as intended, as adjuvant treatment is often not completed – in ESPAC-3, only 68% of patients completed chemotherapy

[287]. Potential drawbacks of a neoadjuvant approach include the need to confirm the diagnosis of cancer with a biopsy prior to initiating treatment, the possible over-treatment of resectable disease, and the likely need for placement of a stent to relieve biliary obstruction while awaiting surgery. In practice many patients who present with localised disease develop metastases shortly after diagnosis, and if this occurs during induction therapy these patients can be spared inappropriate and futile surgery [291].

Preoperative chemotherapy or radiotherapy aims to treat the tumour in situ, hoping to achieve tumour regression and facilitate curative resection. This has become standard of care for some tumour sites, but is not yet established in pancreatic cancer, despite potential advantages over postoperative treatment [294]. This is likely due to limited historical effectiveness of standard radiotherapy dose schedules, where complete tumour response is only seen in around 5% of patients [295], though a larger proportion of patients (35%) may benefit from sufficient tumour regression to achieve resectability [296]. Further evidence in support of neoadjuvant treatment suggests that patients who successfully complete upfront chemoradiotherapy and go on to have resection tend to have high rates of clear resection margins [297, 298] and reduced rates of local recurrence [299, 300].

As was described in the introduction to the thesis, stereotactic body radiation therapy (SBRT) combines rigorous immobilisation and image-guidance with hypofractionation, to reduce radiotherapy-planning margins and treat small, targeted volumes with greater accuracy and precision, supporting safe delivery of much higher biologically effective dose. It has been shown to be a highly-effective local treatment option in unresectable pancreatic cancer with high rates of local control (over 90%) achieved using treatment delivered in a single exposure [301-304]. When treatment was delivered in three to five fractions, lower rates of toxicity were seen while maintaining impressive disease control (local control rates of 50-85%) [305-

311]. Treatment has been shown to remain safe when used after induction chemotherapy regimens [311, 312].

The specific goal in treating BRPC with preoperative radiotherapy is to improve the chances of achieving clear resection margins, reduce the risk of local recurrence, and achieve long-term survival similar to that for patients with initially resectable tumours. Neoadjuvant treatment has been shown to be deliverable and effective in BRPC, such as in a series of 160 patients described by Katz et al., among whom 78% completed preoperative therapy and restaging and 41% underwent pancreatectomy, with a 94% rate of clear margins [313].

The radiotherapy in the SPARC trial employs a margin-intense strategy where the whole tumour is treated to a minimum dose, and a simultaneous integrated boost is used to deliver additional dose to the margin of tumour around structures, such as the superior mesenteric artery, superior mesenteric vein or portal vein (Figure 7-1). These are the areas thought to be at highest risk of positive surgical margins [314]. Retrospective institutional studies have demonstrated the feasibility of such an approach with standard fractionated radiotherapy [315, 316] or moderate hypofractionation [311, 317, 318]. For SBRT, a systematic method of defining the margin at risk has not been defined.

Prospective dose escalation aims to establish the maximum tolerated dose for this treatment paradigm for subsequent definitive investigation of efficacy. Once the maximum tolerated dose is established, this could then be appropriately integrated or compared with optimal systemic treatment.

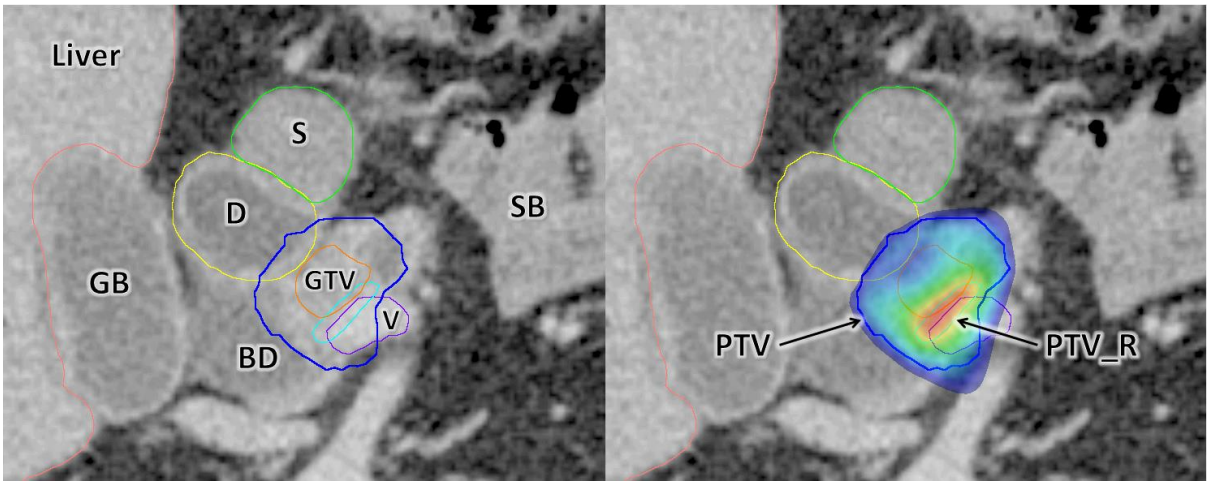


Figure 7-1. Axial contrast-enhanced CT of patient with borderline-resectable pancreatic cancer demonstrating SPARC radiotherapy planning. Left-hand image – delineated structures: (clockwise from left) GB = gall bladder, D = duodenum, S = stomach, SB = small bowel, V = vessel in contact with tumour, GTV = Gross Tumour Volume, BD = bile duct. Right-hand image – radiotherapy plan dose colourwash demonstrating dose levels delivered to PTV_R (light blue contour), PTV (dark blue) and PTV overlapping with duodenum.

SPARC incorporates a comprehensive radiotherapy quality assurance (RTQA) programme to ensure consistency in target definition and radiotherapy delivery. This includes a radiotherapy manual with atlas, and pre-trial contouring and planning test cases. These must be completed satisfactorily by recruiting centres followed by attendance at a workshop, and both of these interventions have previously been shown to reduce variation in target volume definition [319-321].

The aim of the work in this chapter was: 1) to evaluate the novel method that was designed for the definition of the target structures in the SPARC trial, through analysis of the pre-trial test cases; 2) to further investigate the implications of this for the safety of the trial radiotherapy in terms of NTCP; and finally 3) to assess the quality of target-definition for the patients treated on the study. Preliminary results regarding trial recruitment and treatment outcomes are also presented.

7.2. Methods and materials

7.2.1. Study design

The SPARC trial is a phase-I dose escalation study using the rolling-six design [322]. The trial opened in April 2015 and will recruit up to 24 patients. Details of the trial design and intended definitive analysis have been published [323].

7.2.2. Participants

The inclusion and exclusion criteria for the SPARC trial are reproduced in Table 9-15 (Appendix D). In response to a slow rate of initial recruitment, some changes were made to the eligibility criteria by the Trial Management Group. The original eligibility criteria specified that the patient's tumour must strictly meet the NCCN definition of borderline-resectable. Patients were excluded if there was any suspicion of metastatic disease, if there was a concern that they may not be fit for surgical resection, or if they had already received chemotherapy for their localised pancreatic cancer. Since the study was initially designed, primary chemotherapy has become more common practice [324], and many patients considered for recruitment were rendered ineligible for this reason. As the primary endpoint of the study was the assessment of the safety and tolerability of the intervention, the patient eligibility criteria for the study were revised to the current version included here, with the aim of improving patient recruitment.

7.2.3. Radiotherapy

Patients are assigned to the appropriate SBRT dose level (Table 7-1). All patients receive five daily fractions of SBRT. It is expected that a maximum of four dose levels (including one de-escalated dose level) will be needed to establish the maximum tolerated dose.

Table 7-1. Radiotherapy dose levels for the SPARC trial

Radiotherapy dose level	Tumour (PTV)				Area at risk of R1 (PTV_M)			
	Dose/# [Gy]	Total dose [Gy]	BED [Gy_{10}]	EQD_2 [Gy]	Dose/# [Gy]	Total dose [Gy]	BED [Gy_{10}]	EQD_2 [Gy]
Level -1	6	30	50	40	8	40	72	60
Level 1	6	30	50	40	9	45	88	71.5
Level 2	6.5	32.5	56	45	9.5	47.5	92	77.2
Level 3	7	35	62	50	10	50	100	83.3

BED [Gy_{10}] = biologically effective dose for acute reacting tissues ($\alpha/\beta = 10$), EQD_2 = equivalent dose in 2-Gy fractions, # = fraction, R1 = microscopic positive margin status

A contrast-enhanced CT is used at radiotherapy planning to visualise tumour and normal tissues, particularly blood vessels, and should be taken in the exhale position. Tumour motion during respiration is then quantified using 4D-CT, and the use of motion mitigation techniques are mandated (such as gating or abdominal compression) if tumour motion is recorded to be greater than 5 mm. If gating is not used, an internal target volume is derived on 4D-CT to ensure tumour coverage throughout the breathing cycle. To create the PTV, a further 3 mm symmetrical margin is added to account for other positional uncertainties. On-line volumetric (CT) image verification is mandated to support the use of these narrow planning margins.

Radiotherapy planning dose-volume constraints are set for the organs at risk, and are detailed in Table 9-16 (Appendix D). In the event of overlap or close proximity between treatment target structures and defined organs at risk, the recommended practice is to respect the organs-at-risk constraints as the priority, even if this leads to a reduction in the proportional volume of the target structure that is treated to the prescription dose [325].

The target region for the margin-directed boost is defined following discussion with a radiologist and/or hepato-pancreato-biliary surgeon to identify the vascular structures that are responsible for the tumour being classified as borderline resectable according to the NCCN criteria.

The radiotherapy planning structure for the boost is generated in a stepwise manner (see Figure 7-2)**:**

a) The vessel(s) eg superior mesenteric artery, superior mesenteric vein, or portal vein should be outlined for that length that is in contact with the tumour. This structure is denoted *VesselContact*.

b) This structure is then expanded **circumferentially** by 3 mm (ie anterior/posterior and laterally but not cranio-caudally). The resulting structure is denoted *Vessel+3mmC*. The GTV is also expanded circumferentially by 3 mm to produce *GTV+3mmC*.

c) A Boolean operator is used to define the region that lies in both *Vessel+3mmC* **and** *GTV+3mmC*, and the resultant structure is denoted the *Boost Volume*.

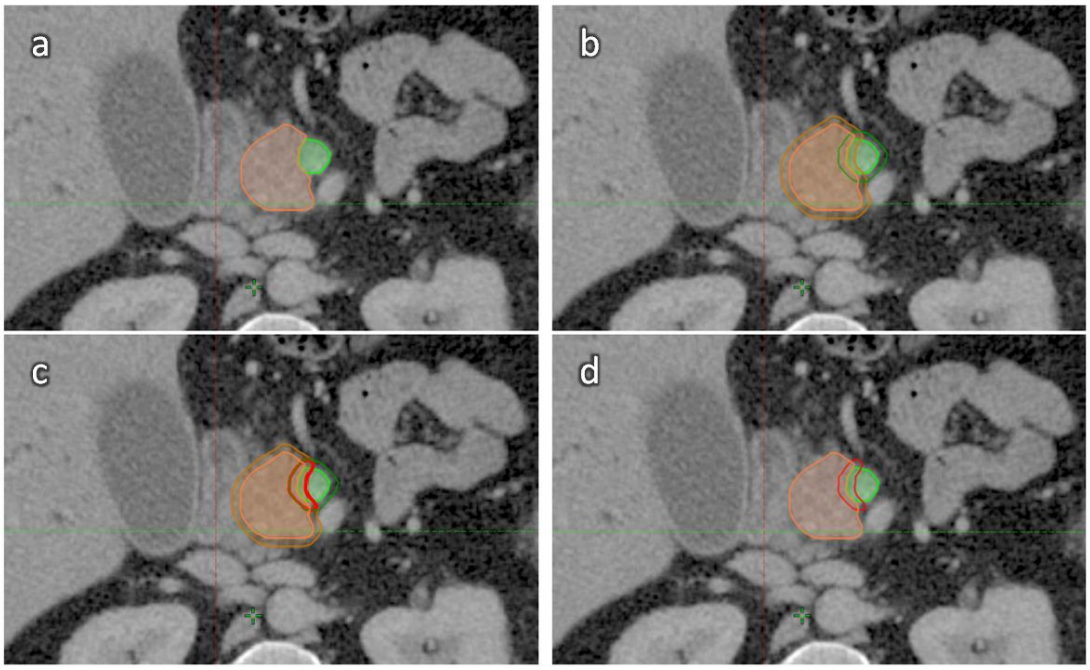


Figure 7-2. Definition of target volumes for SPARC trial. Orange = GTV, Green = VesselContact, Red = Boost volume.

7.2.4. Radiotherapy quality assurance (RTQA)

Pre-trial RTQA

Each treating centre completed pre-trial test cases of contouring and treatment planning before patients could be registered and treated within SPARC. A suitable test case of BRPC

was selected, and a set of reference structures were defined by a team of two expert clinical oncologists and one radiologist, on an intravenous contrast-enhanced CT scan. A contemporaneous ^{18}FDG-PET (fluorodeoxyglucose-Positive Emission Tomography) scan was used to help interpret CT appearances, but the GTV was contoured to define the extent of gross tumour as evident on the CT scan.

Eight clinical oncologist investigators specialising in pancreatic cancer were provided with the CT and PET scans, along with radiologist reports, and asked to follow the written instructions for the delineation of the target structures within the radiotherapy guidance for the SPARC trial protocol. Structure sets were imported into the Eclipse radiotherapy treatment planning system (Varian, Palo Alto, CA). Submitted structures were assessed qualitatively by the RTQA team and classified as acceptable or unacceptable for treatment to proceed. Descriptive parameters (volume, centre of mass) and conformity indexes were calculated:

$$\text{Dice coefficient} = \frac{2 \times (A \cap B)}{A + B}$$

$$\text{Geographical miss index} = \frac{B - (A \cap B)}{B}$$

$$\text{Discordance index} = 1 - \left(\frac{(A \cap B)}{A}\right)$$

A denotes the investigator structure and *B* the reference structure. $A \cap B$ denotes the intersection of *A* and *B* (equivalent to Boolean operator '*A* AND *B*').

A radiotherapy plan was produced based on the reference set of target structures, to deliver 35 Gy to the primary tumour PTV and 50 Gy to the margin at risk (the highest dose level in the SPARC trial). Next, this plan was used to reproducibly create further plans for each set of investigator target structures, and cumulative DVH statistics were extracted describing target coverage and exposure of organs at risk.

Normal Tissue Complication Probability (NTCP) for risk of upper GI bleed in the duodenum was modelled using the LKB model within the Biological Evaluation Module of the treatment planning system, adopting parameters derived by Pan et al. (TD_{50} = 180 Gy, m = 0.49, n = 0.12, α/β ratio = 3 Gy) [148]. Shapiro-Wilk testing did not show evidence of deviation from normality in the distribution of the results, hence Pearson product-moment correlation testing and 2-tailed paired t-tests were performed using RStudio [260], and a threshold of $p < 0.05$ was defined as significant.

On-trial RTQA

Approval by the RTQA team before radiotherapy treatment commenced was mandatory for the contours and plans for the first three patients recruited in each trial centre. Subsequent contour sets and plans were reviewed as soon as it was convenient. Where possible, a web-conferencing format took place to enable prompt review, feedback and potential revision [326].

7.2.5. Outcome measures and definitions

The primary endpoint of the SPARC study is the maximum tolerated dose, defined as the highest level of SBRT at which no more than one of six patients, or zero of three patients, experiences a dose-limiting toxicity. The definition of dose-limiting toxicity and other adverse events is included in Table 9-17 (see Appendix D).

Secondary outcomes that will be recorded and analysed include surgical resection rate, resection margin status rates, rate of pathological complete response, late SBRT toxicity, efficacy, and long-term safety. Tumour marker CA19-9 levels are scheduled to be tested at defined time-points: baseline (trial entry), end of SBRT, prior to surgery, and one- three- and six-months post-surgery. This assay is non-specific for pancreatic cancer but is raised in many pancreatic cancer patients and if it raised at baseline it can be used as an indicator of disease

response to treatment. The test results are derived in the treating institution, and the results are not verified centrally.

7.3. Results

7.3.1. RTQA analysis

Pre-trial RTQA

The reference and submitted investigator contours for the GTV and boost volume are visualised in Figure 7-3. Only two of the eight submitted GTV contours were approved as acceptable, while all but two of the boost volume contours were considered acceptable. Reference and mean investigator volumes for GTV were 2.1 cm^3 and 6.03 cm^3 (95% CI 3.92–8.13 cm^3) respectively, and for boost volume were 1.1 cm^3 and 1.25 cm^3 (1.02–1.48 cm^3), as shown in Figure 7-4.

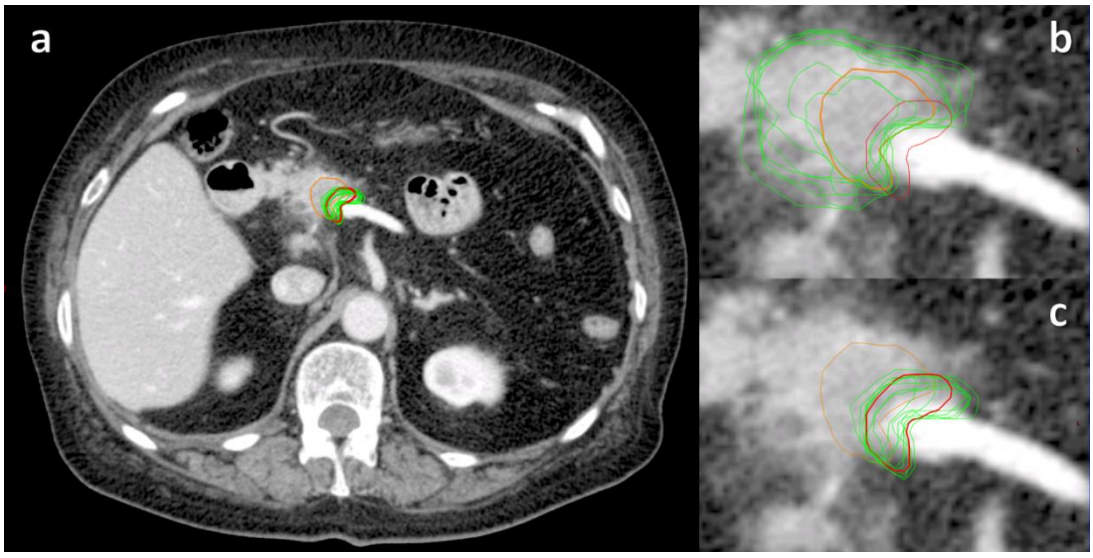


Figure 7-3. Reference (orange = GTV, red = boost volume) and investigator contours (green) of boost volume (images a and c) and GTV (image b) on contrast-enhanced axial CT of patient with borderline-resectable pancreatic carcinoma

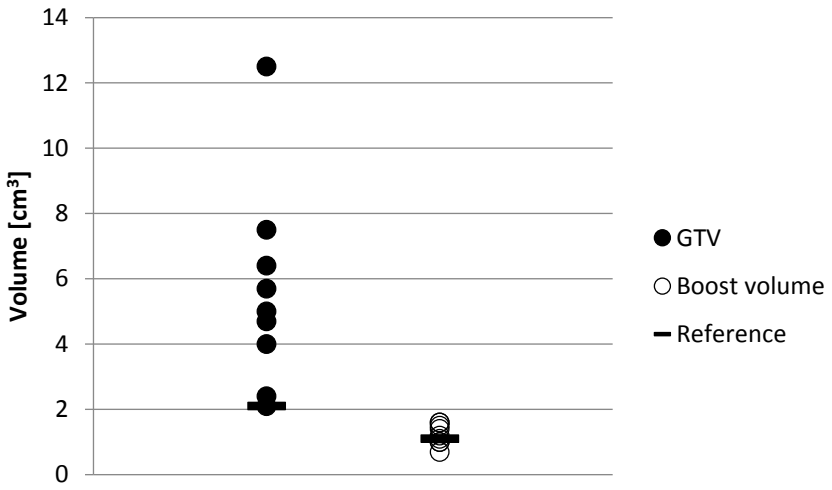


Figure 7-4. Volume [cm³] of investigator target structures compared with reference definition. Solid circles = GTV; hollow circles = boost volume; horizontal bar = volume of reference contour.

Conformity indices are detailed in Table 7-2 and charted in Figure 7-5. Correlation coefficient for GTV volume with the discordance index was 0.93 (0.65–0.99, $p < 0.001$), and for GTV with the geographical miss index was -0.06 (-0.73 to 0.68, $p = 0.899$).

	Dice coefficient	**Geographical miss index**	**Discordance index**
GTV (95% CI) [cm³]	0.47 (0.38–0.56)	0.17 (0.10–0.23)	0.65 (0.56–0.75)
Boost volume [cm³]	0.61 (0.52–0.70)	0.33 (0.23–0.43)	0.39 (0.28 0.49)
***p* value**	0.01	0.005	0.001

Table 7-2. Mean conformity indices (with 95% confidence intervals) for submitted contours in relation to the reference contour. p-value derived from 2-tailed paired t-tests.

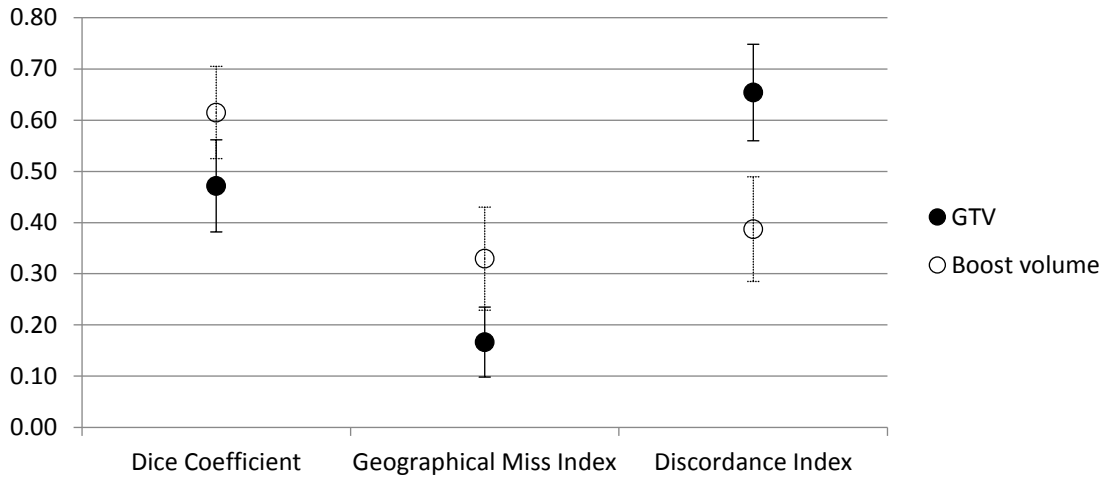


Figure 7-5. Mean conformity indices for investigator target structures when assessed against reference (error bars show 95% confidence interval)

Treatment plans based on the investigator contours were able to meet planning constraints for target coverage and avoidance of organs at risk, but were associated with an increased modelled risk of duodenal bleed: risk for the plan based on reference target structures was 2.95%, while mean risk using investigator structures was 3.93% (3.63%–4.22%). Risk of duodenal bleed was correlated with delineated tumour volume (correlation coefficient 0.74, 95% CI 0.15–0.94, $p = 0.02$) and with discordance index (0.83, 0.29–0.97, $p = 0.01$) (Figure 7-6).

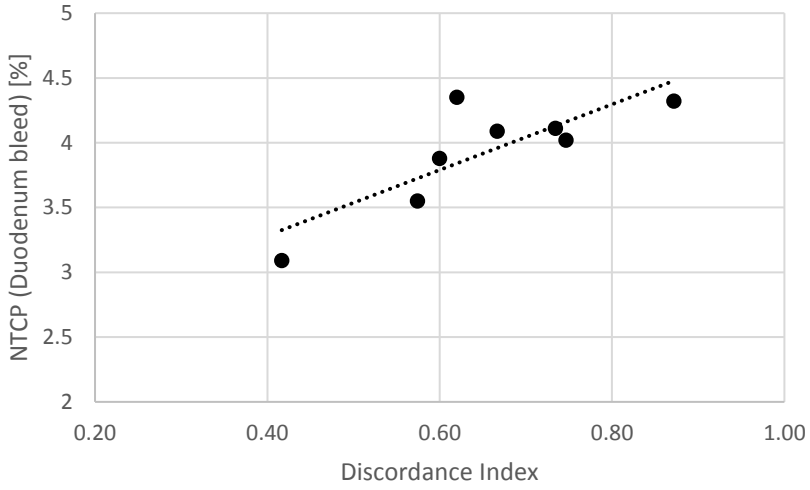


Figure 7-6. NTCP (risk of duodenal bleed) according to discordance index. Black dots indicate discordance index scores for submitted GTV contours compared with reference. Dotted line shows linear regression model fit.

On-trial RTQA

The submitted target contours for the first eleven patients recruited to the study were analysed. In two of the eleven cases, the primary GTV was found to be unacceptable, in one case the boost volume was found to be unacceptable and in one case both were considered unacceptable (Figure 7-7).

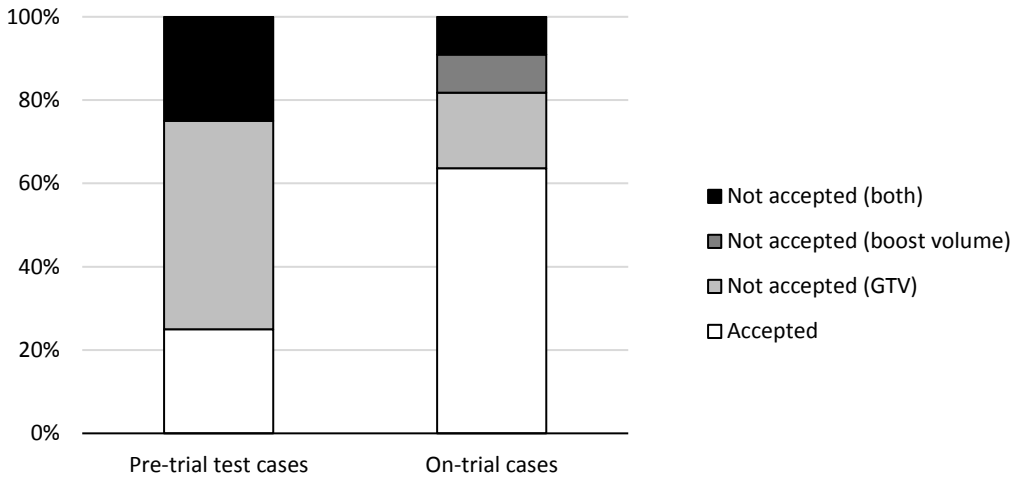


Figure 7-7. Comparison of approval rates of target structures in pre-trial test cases and on-trial treatment cases

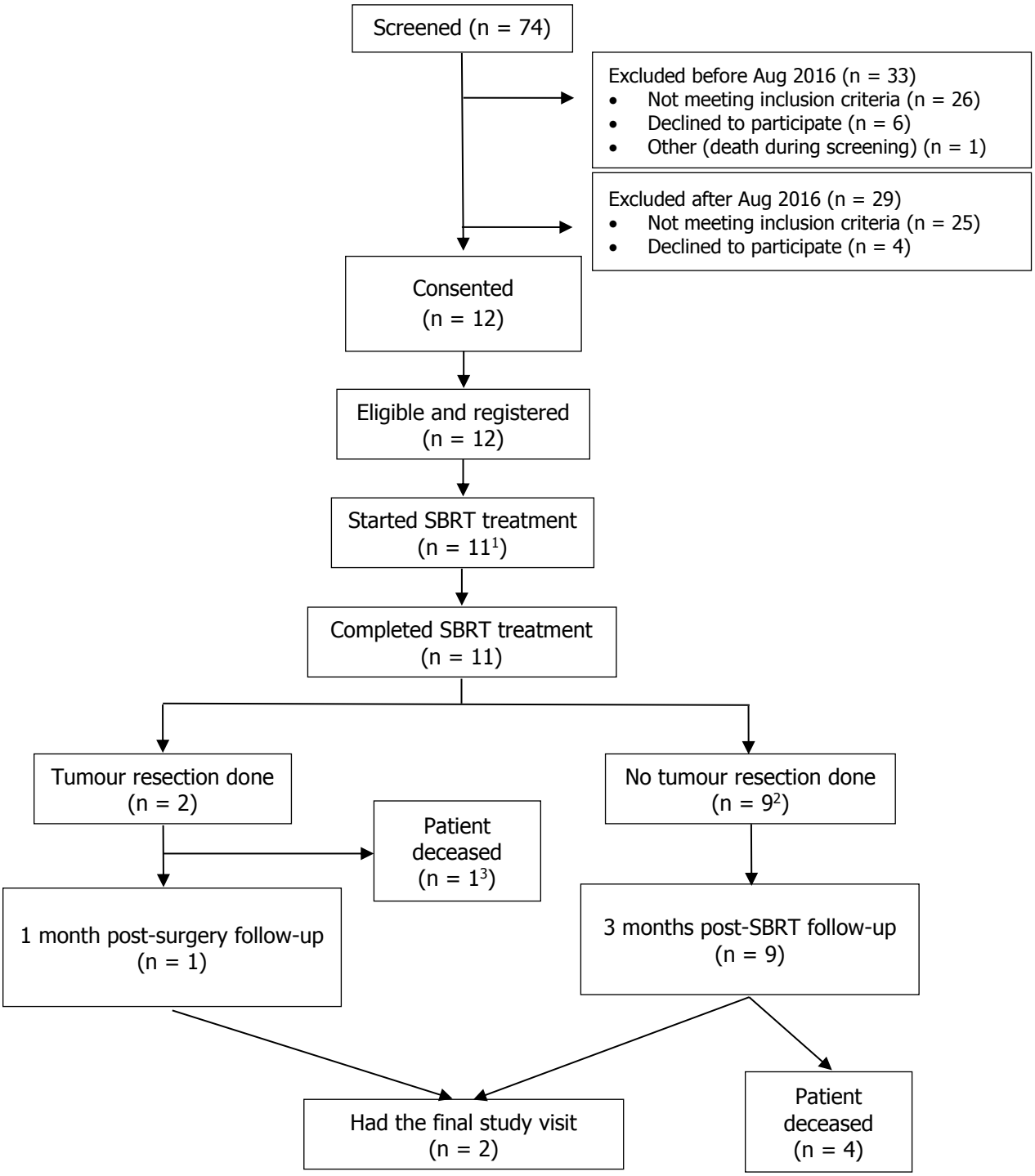
7.3.2. Patient screening and recruitment

The SPARC trial first opened on 12th April 2015 and the first patient was registered on 10th December 2015. For the purpose of this thesis, a data lock was applied on 31st August 2017, and results describe the data acquired up to that date, by which point twelve patients had entered the study. Four patients were recruited between April 2015 and August 2016, the point at which the revised eligibility criteria were implemented, a rate of one patient every four months. Eight patients were then recruited during the following year, a rate of one patient approximately every six weeks. After the change in the eligibility criteria, the proportion of patients screened who were recruited did not change notably (68% afterwards compared with 70% previously).

Seventy-four patients were recorded as having been screened for recruitment, of which 16% were registered. There were various reasons why patients were not able to take part. Thirteen patients had pancreatic cancer of the appropriate stage but were not fit to undergo surgery due to general condition or significant comorbidity. Two patients were found to have a second malignancy. For twelve patients, completed staging showed that the primary tumour was too advanced for resection. Five patients presented with a primary tumour of suitable stage but either non-local lymph nodes or visceral metastases were present, and eight patients appeared to be suitable but did not have histological or cytological confirmation of pancreatic carcinoma. Five patients were identified as potentially suitable during time periods in which recruitment was paused, while monitoring patients who had already received radiotherapy. There were three such periods, spanning a total of 122 days. Ten patients declined to take part despite being suitable.

The course of the screened and registered patients is shown in the following CONSORT diagram (Figure 7-8). One registered patient suffered locally progressive disease before radiotherapy was planned, and has been omitted from subsequent analyses.

Figure 7-8. CONSORT diagram showing patient throughput among the potential 74 patients screened. (Diagram produced by Gavin Reilly, Centre for Statistics in Medicine, University of Oxford).



[1] Patient SP-C2-109 withdrew before commencing SBRT treatment
[2] SP-C1-102 went on surgery but no tumour removed. SP-C2-106 tumour found to be adhered to IVC during surgery, no tumour removed
[3] SP-C2-111 was unable to complete trial visits post-surgery due to complications, patient died nine weeks after surgery.

7.3.3. Patient characteristics

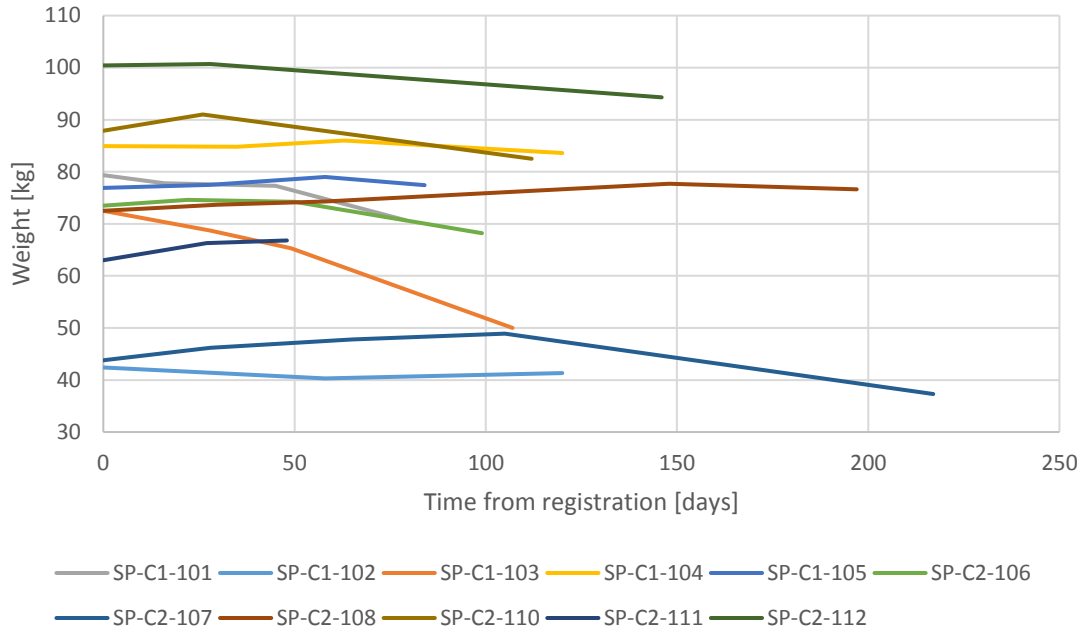
Age (years)	Median 69 (IQR 58–73)
Sex	6 male, 5 female
Age, according to sex	Median 71 (IQR 67–72) vs 63 (57–72)
Weight (kg)	Median 73 (IQR 67–82)
Performance status	PS 0 = 4 patients, PS 1 = 7 patients

Table 7-3. Basic demographic information for SPARC patients registered up to data-lock of 31st August 2017.

Demographic information for the registered patients is shown in Table 7-3. The median age for female patients is lower, but the inter-quartile ranges are similar. Patient weight recorded at each physical assessment is shown in Figure 7-9. Eight patients lost weight and three patients gained weight during their time on the trial. The largest decrease in weight recorded was for patient SP-C1-103, who had lost 22.5 kg at the last recorded assessment (107 days from baseline). The largest increase was for patient SP-C2-108, who had gained 5.2 kg at 148 days. The average change was a fall of 4.0 kg (5.7%) according to the last recorded measurement. Three patients lost 10% or more of their body weight.

No patients with performance status outside of the eligibility criteria (ECOG score 0–1) were registered for the study, and no patient performance status score greater than 2 was recorded at any point on the study. The commonest co-morbid conditions recorded at baseline included hypertension (three patients) and diabetes (also three patients). Five patients were suffering from abdominal pain at time of registration, and other conditions possible attributable to the underlying disease process included indigestion/heartburn/gastric reflux (recorded in four patients) and pancreatic exocrine insufficiency/pancreatitis (four patients). Modal Charlson comorbidity index was five (range three to six) [327].

(a)



(b)

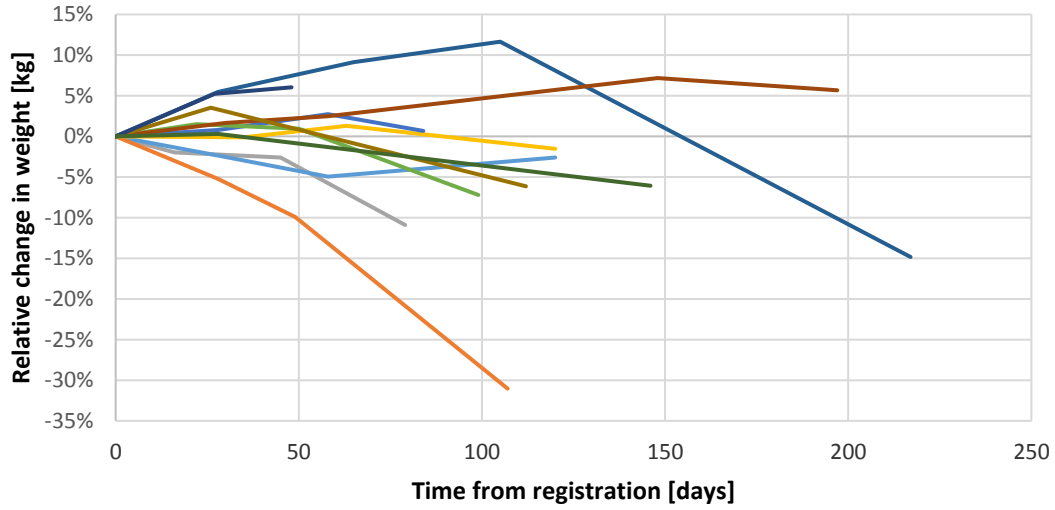


Figure 7-9. (a) Patient weight as recorded from time of registration; (b) Change in patient weight compared with baseline, as a proportion of baseline weight.

7.3.4. Disease characteristics

All patients underwent CT scan at baseline and after radiotherapy. Two patients underwent MRI after RT, before planned surgery. For both patients, the MRI showed metastatic disease that had not been detected on CT scan, and for one patient, the T-stage increased from T2 to

T3. No patients underwent PET imaging at staging. The staging for the registered patients is shown in Table 7-4. The most common T-stage was T3 (6 patients, 55%), and the majority of patients (73%) did not have nodal disease evident at baseline CT. As would be expected, no patients with confirmed metastatic disease were registered. Mean tumour size at baseline was 29 mm diameter, range 14–40 mm. For patients with a repeat CT scan after SBRT, the mean tumour size was 31 mm (range 10–55 mm) and the mean change in tumour size was an increase of 2.6 mm as shown in Figure 7-10. The range was from a decrease of 4 mm to an increase of 21 mm in size. For three patients the tumour increased in size, for three it stayed the same size, and for three patients the tumour reduced in size. The T-stage remained stable for all but two patients, where for one patient it rose from T3 to T4, and for one patient the reverse occurred.

T stage	Count	N Stage	Count	M Stage	Count
T1	0	N0	8	M0	11
T2	3	N1	3	M1	0
T3	6				
T4	2				

Table 7-4. TNM stage at baseline for patients registered for the SPARC clinical trial up to 31st August 2017.

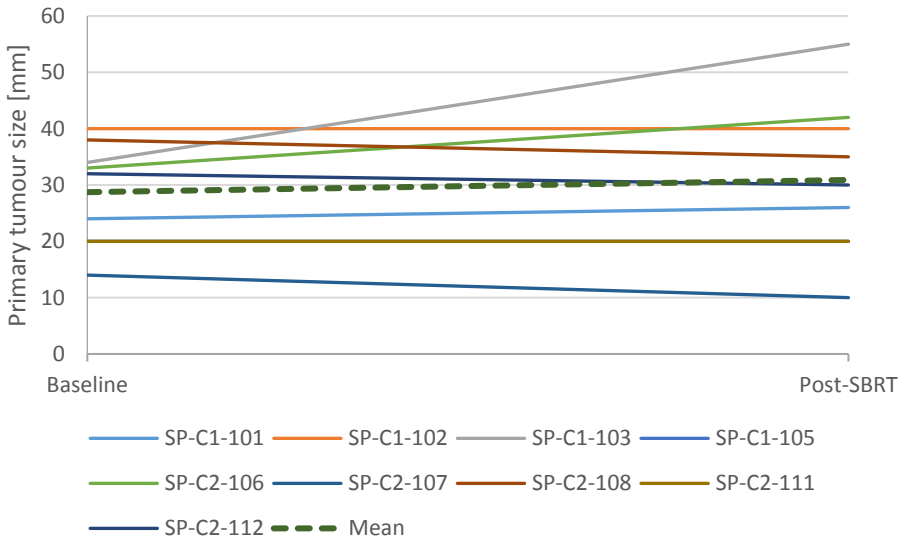


Figure 7-10. Tumour size (largest diameter in mm) on baseline and post-SBRT CT scan.

Serum CA19-9 levels are charted in Figure 7-11. All but one patient had a baseline CA19-9 recorded before the start of SBRT, and the median value was 259 units/ml (IQR 78–993). The recording of subsequent values varied between patients. Four patients had a lower CA19-9 at the final available measurement, relative to baseline (values in Table 9-18, in Appendix D), but for all other patients, the latest recorded CA19-9 was higher than that at baseline. Of those with CA19-9 results for before SBRT, the level on the first test result taken after starting SBRT was higher for six patients and lower for four patients, taken at an average of nine days (range seven to fifteen). The average change in CA19-9 from before to immediately after radiotherapy was a relative increase of 32% (range from a fall of 29% to an increase of 254%).

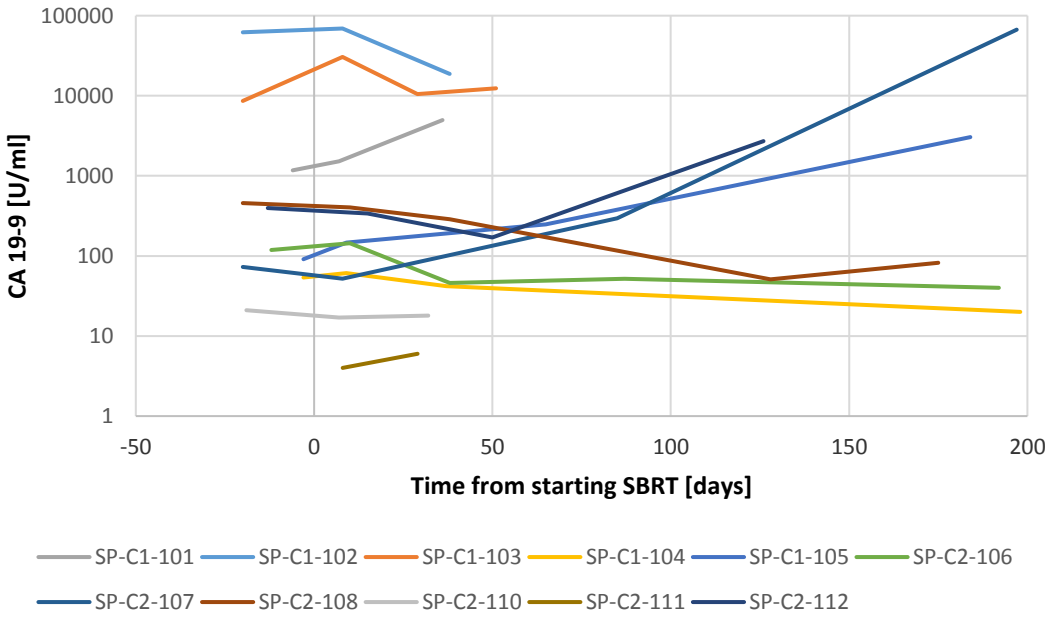


Figure 7-11. CA19-9 levels for patients treated in the SPARC trial. Vertical axis uses a logarithmic scale (base 10).

7.3.5. Treatment

Radiotherapy

SBRT was delivered as intended for all patients, with no delays, modifications or reductions. Five patients were treated at dose-level one (30 Gy to the tumour PTV and 45 Gy to the boost volume), and six at dose-level two (32.5 Gy to the tumour and 47.5 Gy to the boost volume).

Surgery

Two patients underwent tumour resection following SBRT (SP-C2-107 and SP-C2-111). Patient SP-C2-107 underwent a pancreaticoduodenectomy, 52 days following the completion of radiotherapy. On histological examination the tumour was confirmed as pancreatic ductal adenocarcinoma and with clear resection margins (R0). The size of the tumour was 25 mm, with evidence of perineural invasion but not lymphovascular invasion. Substantial response to chemoradiotherapy was seen with an estimated 80% resolution of viable tumour. Twenty-five lymph nodes were examined but none showed evidence of involvement by malignancy, hence final staging was ypT3N0.

Patient SP-C2-111 went to the operating theatre for planned surgery 40 days post-SBRT. Restaging CT after SBRT had shown increased soft tissue surrounding the head of the pancreas, though this was thought to indicate changes in response to radiotherapy rather than tumour progression. During surgery, tissues were reported to be friable and prone to bleed, and marked fibrotic tissue was found between the pancreas, duodenum and vessels, though which was negative for tumour involvement on intra-operative frozen section examination. The operation was prolonged by difficulty in completing a satisfactory vascular reconstruction after resection of the tumour itself, and the patient required further surgery the following day to close the abdominal wound. Unfortunately, the patient did not recover from his surgery and died 49 days following his initial operation. The resected specimen again confirmed

pancreatic ductal adenocarcinoma, but with conspicuous perineural and lymphovascular space invasion in this case. There was again evidence of regression in response to prior therapy, judged as Grade 2 on the scale used by the College of American Pathologists, but tumour was found within 0.5 mm of the vascular groove of the pancreatic specimen, and within the adventitia and media of the portal vein itself, extending to the longitudinal transected ends. One of twenty-four examined lymph nodes was found to be involved, and the summary staging was ypT3N1, R1.

The reasons for the other patients not having resection surgery are shown in Figure 7-12. For four patients, surgical resection of the primary tumour did not take place due to evidence of metastatic disease on restaging imaging. For two patients (SP-C1-103 and SP-C2-112) restaging showed local progression, which rendered the patients' tumours no longer suitable for attempted resection (SP-C1-103 also had new metastatic disease, in the form of peritoneal nodules). For three patients (SP-C1-102, SP-C2-106 and SP-C2-110) the tumour was found at laparotomy to be too locally advanced for resection to proceed. For two of these patients (SP-C1-102 and SP-C2-106), palliative gastro-duodenostomy was performed, and for the third (SP-C1-102), a suspicious lesion was found in the liver and confirmed to be metastatic adenocarcinoma. One patient did not proceed to the operating theatre due to anaesthetic safety concerns.

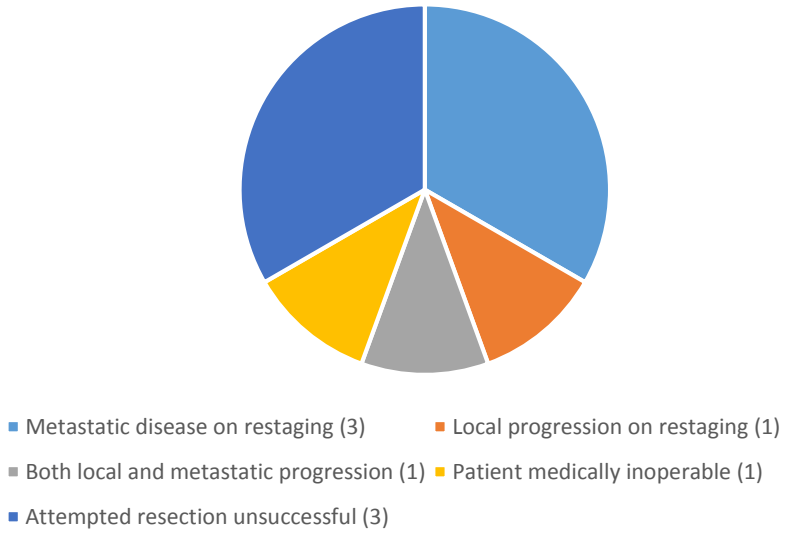


Figure 7-12. Reasons for patients not undergoing resection of tumour, of first 11 patients registered.

Systemic therapy

Of the six patients registered for the study since the change to eligibility criteria permitting the use of prior systemic therapy, five received FOLFIRINOX (folinic acid, 5-FU, irinotecan, and oxaliplatin) multi-agent chemotherapy before registration for SPARC. Four patients completed six cycles of therapy, one received seven, and two patients required dose-reductions. Four patients had stable disease on reassessment after chemotherapy, while one suffered progressive disease despite therapy, and this is the patient who was registered for the study but did not receive any SBRT (SP-C2-109). No patients received any other anti-cancer therapy prior to trial entry. One patient received systemic therapy after SBRT, being treated with three cycles of FOLFIRINOX.

None of the patients who were unable to proceed to surgery due to the presence of metastatic disease had received induction chemotherapy prior to joining the study, and none of the patients who did receive induction chemotherapy were found to have metastatic disease at restaging between SBRT and planned surgery.

Concomitant medications

The patients received eight different concomitant medications on average (not including systemic anti-cancer therapy). The commonest included proton-pump or histamine inhibitors to reduce stomach acid secretion (82%), anti-emetics (73%), opioid/opiate analgesia (73%) and pancreatic enzyme supplementation (64%). Over a third of patients were also treated with an anti-depressant.

7.3.6. Adverse outcomes

Up to the data lock on 31st August 2017, no dose-limiting toxicities or suspected unexpected serious adverse reactions had occurred in SPARC, and no patient deaths were thought to have been caused by SBRT.

In all, sixty-six adverse events (including five serious adverse events and three serious adverse reactions) were reported. One patient completed their participation in the study without any documented adverse events. Of the eight serious adverse outcomes, seven were classified as CTCAE Grade 3, and one was Grade 4. The Grade 4 SAE was wound dehiscence, suffered by patient SP-C2-111 (as described in section 7.3.5). Two adverse events (one Grade 1 anorexia, and one Grade 1 nausea) but no SAE were classified as 'Definitely related [to SBRT]'. The Grade 4 SAE was considered to be 'Probably related' while one occurrence of Grade 3 anorexia and one Grade 3 GI haemorrhage were each classified as 'Possibly related'.

Side effects considered to be part of the spectrum of upper GI radiotherapy toxicity (namely nausea, vomiting, anorexia, weight loss, abdominal pain, indigestion/heartburn) are detailed in Table 7-5. Adverse events classified as 'Probably not related' or 'Definitely not related' are not included, while events without classification of likely causality are included. The column totals do not sum as individual patients may experience multiple symptoms. The overall

cumulative incidence rate of any upper GI toxicity events is 45% (5 patients out of 11), and of Grade ≥ 2 events is 18% (2/11).

	CTCAE grade			Any grade	Grade ≥ 2
Adverse event	**1**	**2**	**3**		
Anorexia	1		1	2	1
Nausea	2			2	
Vomiting		1		1	1
Abdominal pain					
Weight loss					
Heartburn/indigestion	1			1	
Any	3	1	1	5	2

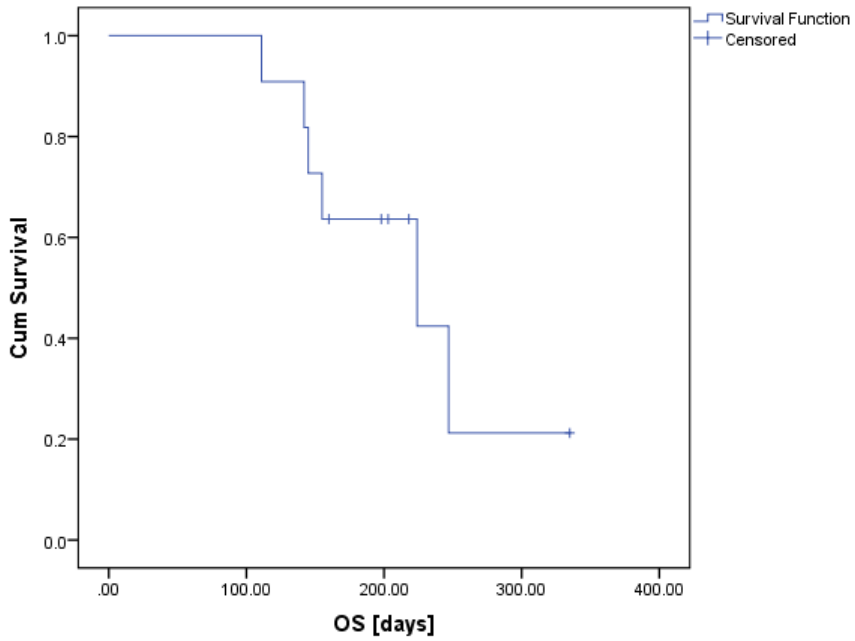
Table 7-5. Worst grade of symptoms or adverse events considered 'upper GI toxicity' experienced by patients in the SPARC trial up to the data-lock of 31st August 2017.

7.3.7. Disease outcome and survival

As discussed, several patients showed local or distant disease progression (or both) after SBRT but before surgery was intended to take place, and others were found on attempted resection to have disease that was now considered inoperable. For four patients the first site of progression was local, for three patients it was distant metastases, while for one patient both local progression and metastatic disease were diagnosed simultaneously.

Six patients have died since receiving SBRT. Median overall survival was 198 days, or twenty-eight weeks. Median progression-free survival was seventy-one days, or ten weeks. For patients who were found to be inoperable during attempted surgical resection, the date of surgery is recorded as the date of progression. For both assessments, time was from date of registration and patients were censored at 31st August 2017, or at end of trial participation if this was sooner.

(a)



(b)

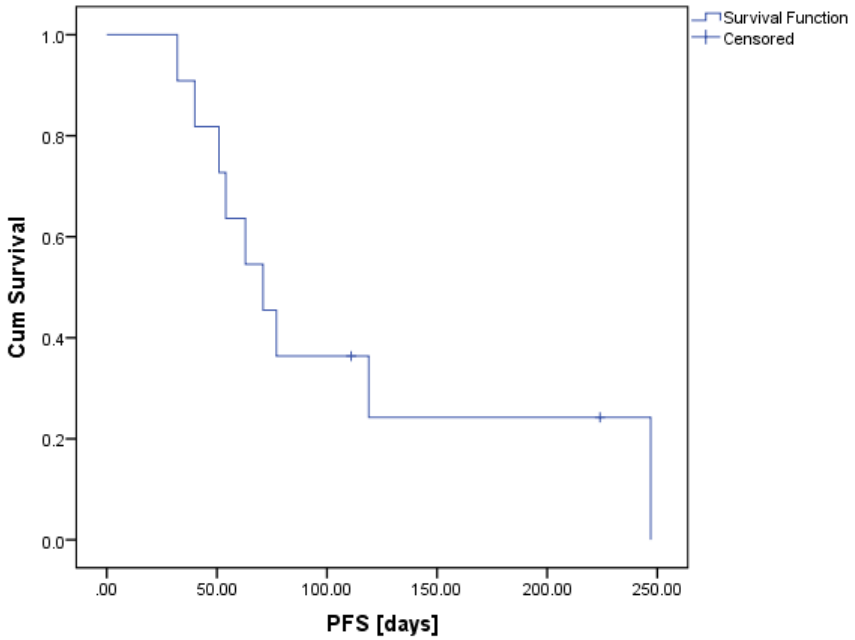


Figure 7-13. Kaplan-Meier survival plots demonstrating (a) overall survival (OS) and (b) progression-free survival (PFS) for SPARC patients treated with SBRT up until 31st August 2017.
Time was recorded from date of registration and patients were censored at data lock, or at end of trial participation if sooner.

7.4. Discussion

7.4.1. RTQA and conformity analysis

Implementation of new techniques in radiotherapy planning, such as new target volume concepts, should be subject to rigorous assessment. This is the first analysis of variability in volume delineation for margin-directed SBRT in pancreatic cancer. A method is demonstrated that has led to strong inter-user conformity for definition of the boost volume, in a region of complex anatomy, across multiple centres. No guidelines yet exist for the definition of a margin-directed radiotherapy boost in localised pancreatic cancer. However, the systematic method for definition of the boost target structure in the SPARC trial protocol has led to a high consistency in clinician target volume definition, has helped to prevent inclusion of more tissue within the target volumes than was intended by the trial design, and in doing so may have helped contribute to the low incidence of toxicity of treatment observed to date.

It is demonstrated that the investigator boost volume structures showed less inter-observer variance in volume compared with the investigator GTV structures. Investigator GTV volumes were also larger than the gold standard, while this was not the case for the boost volume. Conformity to reference, as measured by the Dice coefficient, was higher for the boost volume than for GTV, and the discordance index was higher for GTV, consistent with suspected 'over-contouring'. Radiobiological modelling suggests that radiotherapy plans based on the submitted investigator contours would have led to an increased risk of clinically important toxicity (duodenal bleed), and that the risk increased not only with size of contoured GTV, as might be expected, but particularly with degree of discordance from reference.

The usefulness of the increased conformality achieved by modern radiotherapy depends on accurate target definition by the treating clinician – "There is little point in worrying about how to deliver image-guided modulated-arc radiation plans if they are to the wrong target"

[328]. Errors in target volume delineation tend to be larger than other geometric errors in radiotherapy planning, and also cause a systematic error, not only for a specific patient but potentially for all patients treated by a given clinician or centre [329]. In theory, the GTV should be a factual entity defined by all observers in the same way but despite this, significant inter-observer variability has been recorded in contours of tumours and organs at risk [330], and here large variation is observed even among a small group of experienced clinicians. An 'expert-defined' reference has been used intentionally rather than a mathematically derived consensus contour, and has proved important in highlighting a systematic pattern of over-contouring, which would have been obscured by the use of a consensus definition.

Measures of volume alone cannot assess spatial discrepancy, and thus measures of position should be used, such as concordance indices that integrate volumetric and positional differences. The Dice coefficient indicates the overall degree of agreement between two contours. The geographical miss index reflects the amount of the reference contour not included in the investigator contour, while the discordance index indicates the amount of investigator contour that was not in the reference structure.

In these results, discordance index scores for GTV were higher than those for boost volume, geographical miss index scores were lower for GTV than for boost volume while other conformity indices were similar for the two structures. Generously contoured structures may be less likely to exclude any of the reference structures, and can achieve better geographical miss index scores [331], whereas the discordance index is useful to highlight incorrectly large target structures, ie 'too much unnecessary volume' [332]. In these data, the GTV volume correlated strongly with the discordance index ($p < 0.001$), as expected. However, GTV volume did not show a strong negative correlation with GMI, suggesting that generous contouring did not lead to improved tumour coverage. While the geographical miss index was

found to be significantly higher for the boost volume than for the GTV, the values and range (0.33, 95% CI 0.23–0.43) are similar to those reported for the GTV itself in another recent investigation of pancreatic tumour definition (median geographical miss index 0.26, inter-quartile range 0.15–0.40) [225].

Accurate GTV delineation is particularly important in pancreatic radiotherapy due to the proximity of critical structures. However, large variations can exist between pancreas treatment target contours produced by different clinicians [333, 334]. The element of this variation that is due to inadequate visualisation of the tumour on planning CT scan could potentially be addressed by additional imaging, though the optimal imaging modalities for visualising pancreatic tumours remain unknown [335]. Pancreatic tumours usually appear hypodense relative to normal pancreas on contrast-enhanced CT, but some are isodense and very difficult to define [336]. It is the junction between tumour and normal pancreatic tissue where the most variability has been seen in our results. A diagnostic quality contrast-enhanced CT in breath-hold helps visualisation of target and normal structures. Multi-modality imaging including FDG-PET and multi-parametric MRI can be used to guide the clinician but the potential effect on outcomes remains uncertain [335]. In addition, pathology correlation studies suggest that tumour size is underestimated by some imaging modalities [337, 338].

The value of direct radiologist support in radiotherapy planning is increasingly understood [339]. However, this does not obviate the requirement for the modern radiation oncologist to be skilled in multi-modality image interpretation and to have highly detailed anatomical knowledge in order to safely deliver complex treatments such as those described here.

Seven prior publications can be identified describing the use of margin-directed radiotherapy in pancreatic cancer (Table 7-6). Chuong et al. were first to publish a report of margin-directed radiotherapy in pancreatic cancer, delivering a simultaneous integrated boost to a PTV 'encompassed that portion of tumour adjacent to the vasculature resulting in the borderline designation' [340]. The authors describe that they 'tailored the high dose volume on a case per case basis...the tumor vessel interface (1 cm of vessel with 1 cm of tumor) was delineated but also modified based on proximity of critical structures' [317]. A preoperative chemoradiotherapy regimen adopted by Hirata et al. also included dose escalation, targeted at the roots of the coeliac and superior mesenteric arteries, being at 'high risk of perineural invasion but difficult to dissect completely'. The boost target volume was 'personalised according to guidance from the surgeons or reduced if necessary to meet duodenal or stomach radiotherapy dose-volume constraints' [316].

Table 7-6. Published reports of margin-directed radiotherapy in pancreatic cancer

Reference	Indication	Margin/Boost target
Chuong 2013	BRPC or LAPC	Individualised: tumour-vessel interface
Passoni 2013	LAPC	Systematic: infiltrating vessels + 1 cm within GTV
Hirata 2015	Resectable PDAC	Individualised: roots of coeliac vessels and SMA
Wang 2015	BRPC or LAPC	Systematic: tumour-vessel interface
Mellon 2015	BRPC or LAPC	Individualised: tumour vessel involvement
Shaib 2016	BRPC	Individualised: posterior margin soft tissues
SPARC	BRPC	Systematic: tumour-vessel interface

BRPC = Borderline-Resectable Pancreatic Cancer, LAPC = Locally Advanced Pancreatic Cancer, PDAC = Pancreatic ductal adenocarcinoma, SMA = Superior Mesenteric Artery

In a prospective phase-I study in patients with locally advanced pancreatic cancer, Passoni and colleagues delivered a simultaneous integrated boost to a target structure encompassing the vessels infiltrating the tumour [315]. In this case, a systematic method was used to define the target for the boost: infiltrating vessels were contoured and expanded by 1 cm, then this structure was trimmed to remain within the primary GTV. This is in contrast to our approach, in which portions of the boost volume lie outside the primary GTV. In the most recent publication in this field, the 'vessel boost' target was defined as the 5 mm of tumour around

the vessel(s) identified that rendered the tumour borderline resectable, expanded by a further 5 mm for set-up error. This methodology is similar that in use in SPARC, but in the setting of conventionally fractionated treatment, and such a technique has not yet been utilised for SBRT planning [318]. The boost volume in SPARC does not have any superior or inferior margin added prior to internal target volume and PTV definition. The rationale is to avoid irradiating parts of the vessel that are not in contact with tumour to very high dose. Part of this vessel will be used for vascular reconstruction and the long-term effect of SBRT on this tissue is unknown.

The results of the on-trial RTQA indicate a higher acceptable proportion of submitted contours for patients undergoing treatment on the trial than was the case for the pre-trial test case. This improvement is thought to have been achieved through direct feedback provided for clinicians by the RTQA team, at the contouring workshop held at the trial launch meeting, and during the ongoing RTQA process. Unfortunately, 'gold-standard' reference structures, with which to compare the submitted contours and derive conformity indices, could not be produced for each on-trial patient because not all relevant imaging was available for transfer to the RTQA team. Therefore only qualitative analysis could be undertaken.

Evidence is growing for the importance of RTQA [341] in conducting clinical trials involving radiotherapy. Consistency of treatment planning and delivery across patients and recruiting centres is required, not only for sound conclusions to be drawn regarding the treatment intervention, but also because radiotherapy that is not delivered per-protocol is associated with worse patient outcomes [342]. In a study of chemoradiotherapy for locally advanced pancreatic cancer, protocol deviations such as unnecessarily large target volumes correlated with risk of significant toxicity [343], while in a large study of adjuvant chemoradiotherapy after resection of pancreatic adenocarcinoma, failure to adhere to the radiotherapy protocol

was associated with decreased overall survival [344]. Therefore, it is recommended that radiotherapy trials are supported by a prospective and comprehensive quality assurance programme [329]. The results here add to the increasing body of evidence that pancreatic GTV delineation remains difficult, which reinforces the importance of pre-treatment central review of target structures to ensure consistency and quality across recruiting centres.

7.4.2. Preliminary trial results

This study builds on the current evidence base in SBRT for pancreatic cancer, which has so far been largely used in the locally advanced setting with promising results, and which aims to take it a step further by prospectively evaluating the safety and benefit of pre-operative margin-intense SBRT.

A five-fraction schedule aims to optimise the balance of short duration and tumouricidal biologically effective dose to the tumour with an acceptable risk of late normal tissue injury. The concept of margin-intensive therapy aims to further improve local control without increasing toxicity, as the region of integrated boost tends not to overlap with the major dose-limiting organ at risk (duodenum) helping to make safe dose escalation to this sub-volume possible.

The current optimal preoperative therapy in pancreatic cancer has not been identified, and could involve chemotherapy, radiotherapy or, most likely, both [345]. The national multi-centre study ESPAC-5F has recently closed to recruitment in the UK, having the primary aim of establishing the feasibility of recruiting patients with BRPC to be randomised between two pre-operative chemotherapy regimens (GEMCAP and FOLFIRINOX), pre-operative chemoradiotherapy, and standard of care (surgery followed by adjuvant chemotherapy) [346].

These therapy options would then require definitive comparative evaluation in a subsequent larger study.

Two single-institution retrospective reviews have shown high rates of surgical resection with clear margins following SBRT in patients with BRPC [317, 347]. Rajagopalan et al. [347] describe twelve resected patients, of which seven were deemed BRPC using MDACC criteria. Most patients received gemcitabine-based systemic chemotherapy. The SBRT consisted of 24-36 Gy in three fractions, surgery took place at a median 3.3 months (range 1.5–6.6 months) and 11/12 patients had an R0 resection. Chuong et al. [317] treated 73 patients (of which 57 were deemed BRPC using NCCN criteria) with systemic gemcitabine-based chemotherapy and 5-fraction SBRT. Median dose prescribed was 35 Gy to the tumour margin, and no less than 25 Gy to the entire pancreatic tumour. Of 57 BRPC cases, 44 underwent exploratory resection and 31 of 32 resected cases had an R0 resection. No acute toxicity of Grade > 3 occurred and 5.3% (4 patients with locally advanced inoperable disease) experienced late Grade 3 toxicity (3 GI bleeding and 1 anorexia). With a median follow-up of 10.5 months (2.2-25.9 months) the median overall survival was 16.4 months in all BRPC patients, with median overall survival of 19.3 months in resected patients. As it has been seen for the patients treated in SPARC so far, radiological evidence of conventional response to treatment (ie tumour shrinkage or downstaging) is usually not seen in these patients [348]. Disappointing overall survival rates in published series (median 5–20 months) are attributed to variable provision of optimal systemic treatment.

There are several strong signals that have already emerged from the SPARC trial regarding recruitment, treatment and outcomes. However, this work represents a non-prespecified interim analysis and, therefore, any conclusions are provisional and should be interpreted with caution. Firstly, it is evident that few patients with pancreatic cancer that appear to be

borderline resectable on initial screening will ultimately prove eligible for recruitment to trials of neoadjuvant therapy. The rate of recruitment for SPARC was slower than was anticipated, and the original target for the time for accrual of 24 patients was two years. Despite this, it is demonstrated that recruiting patients to a multi-centre trial of neoadjuvant stereotactic radiotherapy is feasible in the United Kingdom. The trial remains open and hopes to complete recruitment in order to ultimately address its primary and secondary endpoints. The accrual rate that has been observed can be used to better inform estimates of recruitment to subsequent studies in the future.

The proportion of patients who entered the study relative to those screened is lower than is typical for most clinical trials. While few clinical trials report the number of patients who were screened, one study reports that, where this information has been provided, the average proportion registered from those screened is around 47%, with a very wide range from 2% to 98% [349].

This result can be explained by a specific decision that was made early in the conduct of the trial. Due to the lengthy time period that passed between the trial opening, and recruitment of the first patient, a plan was made to record the clinical information for patients whose diagnosis and local tumour staging met the eligibility criteria, even if it was known from the outset that this patient would not be able to take part in the trial for other reasons, such as a medical comorbidity. This decision was taken so that the trial management group would be able to better observe the incidence of such patients being referred for consideration of treatment in the hospitals in which the trial was open to recruitment. In practice, this plan was implemented only by the recruiting physicians in Oxford because the other centres did not have sufficient resources to report all such patients. As a result, the numbers of patients screened and the proportion of those recruited is notably different between Oxford and the

other centres, where the conventional definition of a screened patient was used. At data lock, Oxford had registered four of 51 screened patients (7.8%), Glasgow had registered five of nine screened (56%) and Leeds three from eight (38%).

The baseline characteristics for the patients recruited so far show that all met the eligibility criteria regarding patient and disease factors, and all completed radiotherapy as scheduled. The majority of patients lost weight during their time on study but the degree of weight loss was not severe.

On average, radiotherapy did not appear to cause a measurable change in primary tumour size or stage. Unfortunately, as so few patients underwent resection, there is insufficient data to comment on the microscopic or histological changes that may have taken place in the treated tumour tissue. Published data show that even where pre-operative, despite preoperative cross-sectional imaging appears to show a patient's tumour is inoperable due to persistent or increased soft-tissue after induction therapy, showing stable – or even increased – soft-tissue in the region of the primary tumour (that if it were to represent genuine tumour invasion, it would render a patient inoperable), if these patients still undergo resection then in some cases this this tissue is found not contain viable tumour cells, and may instead reflect sterilised tumour or a host reaction to the radiotherapy [350, 351]. At present it is not clear how clinicians may preoperatively differentiate between true progression and fibrotic tissue, and it may well become important for future work to determine an effective imaging modality that could achieve this.

Toxicity appears to be very limited, and in the patients treated to date there have been no dose-limiting toxicity events. This would suggest that the treatment is safe at the dose levels that have been tested thus far, but the trial management group have decided (with the

support of a trial oversight committee) that further recruitment to the current dose level is advisable. The hope is to accrue further evidence on the safety or success of surgery after SBRT because so few patients have, thus far, gone on to have a tumour resection operation. As has been discussed elsewhere in this thesis, there is some difficulty in interpreting data on toxicity outcomes when symptoms and signs of the underlying disease can overlap with those of adverse reactions to the treatment intervention. Much reliance is therefore placed on the attribution of the causality of the observed symptoms by the treating clinical team, who are assumed to know the patient best. If the attributed causality were ignored then 64% of the patients on study experienced some degree of upper GI toxicity, and 45% had toxicity symptoms of Grade 2 or higher.

It is striking that of the patients who were denied surgery due to metastatic disease becoming apparent after SBRT, **none** had received induction chemotherapy. Of those who did receive induction chemotherapy before SBRT, **none** were diagnosed with metastatic disease between SBRT and surgery. It appears that neoadjuvant radiotherapy is likely only to be appropriate as part of a multi-modality approach in which patients are initially treated with systemic chemotherapy because otherwise the risk of early progression with metastatic disease is high. There is growing evidence for increased activity of multi-agent chemotherapy regimens in the treatment of advanced pancreatic cancer, such as gemcitabine-capecitabine [352], gemcitabine-nab-paclitaxel [353], and more recently FOLFIRINOX [354]. With the apparent increase in efficacy, there has been a corresponding increasing popularity of using these agents in the neoadjuvant setting in localised pancreatic cancer [324].

Sadly, the overall disease control and survival outcomes for the patients in the study have been poor and although the patient cohort is small, the median progression-free survival (2.4 months) and overall survival (6.6 months) are lower than those seen in the published

retrospective cohorts of patients undergoing similar treatment. As an example of longer survival times, Chuong et al. [317] describe thirty patients for whom the median progression-free survival was 14.9 months and median overall survival was 20.0 months.

7.5. Conclusions

A robust systematic method for delineation of the boost volume for margin-intense pancreatic SBRT has been demonstrated, and with the use of a detailed protocol and atlas within a clinical trial setting, this has led to less inter-user variability and greater conformity with a reference contour than was observed for definition of the primary tumour GTV. We have also shown variability in GTV definition with implications for modelled toxicity risk, highlighting the difficulties in pancreatic tumour delineation and reinforcing the importance of continuing on-trial RTQA. The overall acceptance rate for on-trial target contouring was higher than was seen during pre-trial test case evaluation, which is attributed to initial and ongoing clinician education and feedback.

We have successfully opened and recruited to a trial of neoadjuvant SBRT in localised pancreatic cancer, and though recruitment rates have not met anticipated targets, the trial is expected to continue and to complete recruitment. As is the case for locally advanced pancreatic cancer, initial treatment with systemic anti-cancer therapy appears to be the optimal approach to reducing the risk of early metastatic disease progression, and if neoadjuvant radiotherapy has a role in the management of these patients then it is likely to be in addition to, rather than in place of, primary chemotherapy.

The toxicity of SBRT at the two dose-levels that have been employed thus far has been low, and it is likely that escalation to a higher dose level will be required before the maximum tolerated dose will be established. Unfortunately, very few patients have undergone

resection of their pancreatic tumour after SBRT, and thus no conclusions can be drawn at this point regarding the safety or toxicity of these therapies in combination.

Acknowledgements

Statement of personal contribution: The SPARC trial had been conceived and funding had been approved prior to my involvement. My personal contribution, prior to the study opening, was to develop the radiotherapy delivery protocol, including designing the method for definition of the radiotherapy target structures, leading the pre-trial target definition/normal tissue contouring RTQA process under the supervision of Prof Maria Hawkins, including the analysis of conformity indices and NTCP modelling as described, and to support the application for the study for approval by the local Research Ethics Committee.

On study opening, my role was (with Prof Hawkins) to support identification, screening and recruitment of suitable patients at Oxford University Hospitals, and support trial opening and assessment of patient suitability, and on-trial RTQA, for patients at other trial centres. Patient and treatment data for the trial is curated by OCTO, and was provided for me for analysis for the purpose of this thesis, but all of the analysis of data presented here is my own work, except where credited.

Prof Maria Hawkins initiated the study and is the chief investigator. Victoria Y Strauss and Lang'o Odondi, Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, developed the trial design and contributed to writing the methods and statistical analysis sections of the trial protocol, and on which some material in this chapter is based. Neel Patel, Consultant Radiologist, Oxford University Hospitals NHS Foundation Trust, contributed to definition of the reference contours for the pre-trial RTQA.

The SPARC trial is conducted in accordance with the Helsinki Declaration (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive. The trial is approved by the National Research Ethics Service Committee South Central – Oxford B (REC reference: 15/SC/0059) and is sponsored by the University of Oxford, with funding from Cancer Research UK. The Oncology Clinical Trial Office (OCTO) coordinates and manages the trial while the Centre for Statistics in Medicine, University of Oxford, will perform all statistical analysis.

8. Chapter Eight: Summary, conclusions and future directions

8.1. Summary

The principal aim of this thesis was to consider the safety and toxicity of radiotherapy as part of the radical treatment of pancreatic cancer. Firstly, I have sought to examine the relationship of dose and volume with the adverse effects of irradiation of the vital organs surrounding the pancreas, namely the stomach, duodenum and small bowel. This aim has been achieved through a number of methods including a systematic review, meta-analysis and examination of individual patient data from clinical trials of chemoradiotherapy for pancreatic cancer.

The second aim was to explore the benefits that modern radiotherapy could achieve in terms of safe escalation of biological dose, and some preliminary answers to this question have been achieved through a phase-I clinical trial of margin-intensified stereotactic hypofractionated radiotherapy. Within this study, the opportunity was also taken to examine the process of target definition of the pancreatic tumour by the treating clinical oncologist, and to examine the relationship between target definition and toxicity.

This final chapter discusses and synthesises some of the key findings of the thesis.

8.1.1. Radiotherapy toxicity in the GI tract

Systematic review and meta-analysis of published data

Numerous published findings have been compiled and analysed regarding the importance of radiotherapy dose and volume exposure for the stomach, duodenum and small bowel in predicting risk of subsequent toxicity. However, there exists heterogeneity in the derivation and reporting of dose-volume data, which has limited the ability to compare or integrate findings between studies. In this work, I have followed a hierarchical approach in which I have initially reported data in the manner it was originally published, the results of which are described in Chapter Two. Subsequently, where sufficient appropriate data were provided I have then undertaken formal model fitting (Chapter Three), or meta-analysis techniques (Chapter Four). Where this was not possible because data were not appropriate for these techniques, simple statistical comparisons have been used to generate hypotheses (Chapter Five).

In Chapter Two, I have reported how most published data has shown that the risk of upper GI toxicity depends on volumes of the stomach and duodenum receiving high radiotherapy dose, and parameters predicting increase risk include the stomach (V_{20Gy}, V_{25Gy}, $V_{50Gy,}$ and D_{2cm3},) combined gastro-duodenum structure (V_{35Gy} and V_{50Gy},) and duodenum (V_{25Gy}, V_{35Gy}, V_{40Gy}, V_{45Gy}, V_{55Gy}, D_{mean}, and D_{2cm3}). The dose-volume parameters for the small bowel that were found to be predictive of relevant toxicity varied according to the tumour site being treated: lower doses were found to be important in the treatment of rectal cancer than for gynaecological cancers, which is most likely due to the different concomitant chemotherapy regimens used between these tumours. In the treatment of rectal cancer, predictive dose-volumes included V_{5Gy}, V_{10Gy}, $V_{15Gy,}$ V_{40Gy} and V_{50Gy}, while in radiotherapy for gynaecological malignancies the predictive dose-volume metrics were V_{15Gy}, V_{30Gy}, V_{40Gy}, and V_{45Gy}. Small

bowel dose-volumes predictive of toxicity after irradiation for pancreas cancer radiotherapy included V_{40Gy} and V_{50Gy}, and for anal cancer V_{30Gy} and V_{40Gy}.

In Chapter Three, LKB model parameters were derived for the duodenum using published DVH and toxicity data. These showed a dependency on high-dose exposure, with weak volume effect, consistent with the results of previous publications. This methodology could not be used for the stomach due to the paucity of available data, and was not successful for the small bowel because the model fits were degenerate. This is postulated to be due to the fact that the LKB model refers to relative (proportional) organ volumes, while the small bowel is rarely contoured in its entirety, as would be required for accurate derivation of such values.

The results of the formal meta-analysis (Chapter Four) show an association of irradiated volume of small bowel with acute toxicity in rectal cancer chemoradiotherapy for all of the tested dose levels (V_{5Gy} to V_{40Gy}), where patients who suffered toxicity had larger irradiated small bowel volumes. Unfortunately, the number of studies that were able to contribute data to this analysis was very small (3 studies) but the effect persisted on sensitivity analysis, and again this result is consistent with the findings of past publications as reviewed in Chapter Two.

Chapter Five describes how the analysis of published small bowel DVH data from a wider set of clinical studies further shows how risk of toxicity is increased not only with increased volume of exposure (as was found in the meta-analysis in Chapter Four), but also with increasing exposed dose. It was also shown that while the effect of increased **absolute** irradiated volume was greatest for low doses, the importance of the **relative** increase in irradiated volume was greatest at high doses. This work was also able to demonstrate how the dose-volume-toxicity relationship differed in the treatment of different tumour sites, and

consistent with the published findings reviewed in Chapter Two, lower doses were seen to be more predictive in the treatment of rectal cancer (V_{35Gy}-V_{40Gy}) than in the treatment of gynaecological cancers (and V_{40Gy}-V_{50Gy}).

Finally, in this chapter it was also shown that for studies of the treatment of rectal cancer, small bowel dose-volume parameters (V_{10Gy}, V_{30Gy}, V_{35Gy}, and V_{40Gy}) were significantly predictive of population toxicity incidence using a univariate logistic regression model. The use of canonical correlation was also investigated, and this appears to be a possible means of integrating dose-volume data to derive a single parameter that correlates highly with outcome.

Analysis of toxicity data in pancreatic chemoradiotherapy

In Chapter Six, it was shown that for a cohort of patients with locally advanced pancreatic cancer treated with chemoradiotherapy in two UK clinical trials, the incidence and severity of acute toxicity was associated with the irradiated volume of stomach (most strongly for moderate to high dose, 35–45 Gy), but not small bowel or duodenum. Patients with poor baseline performance status were also at higher risk, though not significantly so. For patients in the ARCII study, risk and severity of toxicity were higher with increasing age, while for patients in SCALOP the toxicity risk and severity was greater for patients receiving concomitant gemcitabine compared with those receiving capecitabine. Similarly, risk was greater for those who had suffered more weight loss during induction chemotherapy treatment. The risk of diarrhoea, considered separately, was higher for patients with larger tumours and those with diarrhoea at baseline.

A multivariate model for the prediction of acute upper GI toxicity was derived incorporating the stomach $V_{35–45Gy,}$ chemotherapy regimen (ARCII regimen vs gemcitabine vs capecitabine)

and patient sex, and achieved an overall predictive accuracy of 71.4% and AUC of 0.745. However, on internal cross-validation the model performance was disappointing, suggesting it was likely that overfitting was taking place, and that external generalisability may be limited. Again, canonical correlation appeared a promising tool with which to incorporate information from a wider region of the DVH for organs at risk into a predictive model, but it also appeared to be at risk of overfitting.

The patients suffering acute toxicity were shown to have worse overall survival than those without. This was shown not to be due to failure to complete radiotherapy. It may in fact be due to associations with other clinical factors likely to contribute to poorer outcomes, such as age, tumour size and performance status.

8.1.2. The SPARC clinical trial

The radiotherapy quality-assurance programme for the SPARC trial has shown that the systematic method designed for delineation of the boost volume has been robust, with less inter-user variability, and greater conformity with a reference contour, than was observed for definition of the primary tumour target volume. It was also shown that this variability in target definition has implications for toxicity risk, although results of on-trial RTQA showed that following training at the launch workshop and ongoing peer-feedback, the quality of target definition improved.

The ongoing conduct of the trial has demonstrated that a multi-centre study of neoadjuvant margin-intensified stereotactic radiotherapy can be conducted in the United Kingdom, although recruitment has been slower than was hoped. The preliminary results show that toxicity of the trial intervention at the two dose-levels that have been employed thus far has been very low, and it is likely that escalation to a higher dose level will be required before the

maximum tolerated dose will be established. Unfortunately, very few patients have gone on to have surgery as intended, and as such, no conclusions can be drawn at this point regarding the possible implementation of these therapies in combination. This was usually due to progressive metastatic disease and an amendment has been made to the study protocol to permit the use of systemic therapy prior to radiotherapy within the trial, in the hope of addressing this.

8.1.3. Overall summary

Toxicity resulting from irradiation of the organs at risk of the upper GI tract in the treatment of patients with pancreatic cancer is shown to be related to dose and volume, and hence can potentially be managed if these organs are defined accurately during the planning process and exposure minimised. Evidence for the importance of the stomach in predicting toxicity comes mostly from the analysis of the individual patient clinical trial data (Chapter Six). Similarly, evidence for the importance of the duodenum and small bowel comes from the published data that has been incorporated in the model-fitting (Chapter Three) and meta-analysis work (Chapters Four and Five).

Differences in the incidence of toxicity and the dose-volume-toxicity relationship for treatments of rectal and gynaecological cancers have been emphasised (Chapters 4 and 5) and are thought to be most likely due to the different concomitant chemotherapy regimens utilised. Unfortunately, there is not sufficient data available to untangle the confounding factors of disease type, effects of concomitant chemotherapy and timing of radiotherapy in relation to surgery. Despite this, these findings strongly suggest that specific radiotherapy planning constraints should be used for each treatment indication, and that generic optimisation parameters for organs at risk – regardless of disease and concomitant chemotherapy regimen – would be inappropriate.

Further work is required to better understand normal tissue toxicity from radiotherapy, as it remains the issue that limits dose delivery and ultimately the probability of local tumour control. Radiobiological investigation is needed of the complex ongoing active response to radiation injury, with better translational corroboration with acute and delayed patient symptoms. As suggested in Chapter Four, greater harmonisation for radiotherapy dose-volume data collection and definition would facilitate improved collaboration between centres to enable this field to move forward from unvalidated single-cohort findings that have predominated.

Although objective outcome assessment tools such as CTCAE have been important in facilitating comparisons and analyses between datasets, they have been shown to possibly under-report the toxicity that radiation therapy can cause, and it may be that the use of patient-reported outcome measures would offer data with greater resolution. These could then be more accurately related to the growing amount of detailed dosimetry data that can be collated, such as the **delivered** dose calculated using on-set three-dimensional imaging.

8.2. Future work

In addition to the ongoing SPARC trial, two further projects hope to build on the foundations of work I have initiated as part of this thesis, regarding toxicity in small bowel radiotherapy, and radical radiotherapy for pancreatic cancer.

8.2.1. Analysis of small bowel toxicity in rectal cancer chemoradiotherapy

While toxicity resulting from irradiation of the small bowel is an important consideration in the treatment of pancreatic cancer, several tumours located in the pelvis – such as rectal cancer – are more common than pancreatic cancer, and small bowel toxicity resulting from treatment of these cancers affects a greater number of patients. An ongoing UK randomised

clinical trial is testing the intensification of the concomitant chemotherapy given with radiotherapy for rectal cancer by adding an additional chemotherapy drug (irinotecan) to the current standard therapeutic regimen of a fluoropyrimidine (5-FU or capecitabine). This is intended to improve rates of disease response and, therefore, possibly achieve better rates of disease control. However, it is anticipated that this will come at the potential cost of an increase in toxicity. When added to 5-FU chemotherapy in the systemic treatment of colorectal cancer, irinotecan appears to increases rates of diarrhoea: Grade 3–4 diarrhoea was seen in 31% compared with 13.2% in a large randomised trial of metastatic patients [355] and 11.9% compared with 5.6% in the adjuvant setting [356]. The addition of irinotecan to capecitabine chemoradiotherapy also leads to higher risk of GI toxicity, and diarrhoea rates of 64–89% (Grade ≥ 3 11–28%) have been seen in single arm studies [357, 358]. In a study of chemoradiotherapy using irinotecan, capecitabine and cetuximab [168], the rate of toxicity for a given volume of small bowel irradiated (18%, $V_{15Gy} \leq 125.5$ cc) was higher than in other studies using only a concomitant fluoropyrimidine (11%, $V_{15Gy} \leq 130$ cc) [162]. However, the specific interaction of irinotecan with dose-volume effects in the small bowel has not yet been studied. It may be that intensifying concomitant chemotherapy does not merely reduce the tolerated volumes, but may alter the 'threshold' dose and make lower doses (eg V_{5Gy} [168]) more important. This has implications for the use of IMRT and inherent 'low-dose bath' effect.

A sub-study within this trial has been initiated to analyse the relationship of relevant toxicity with dose-volume to the organs at risk, including the small bowel. The prospectively collected toxicity data and centrally collated quality-assured radiotherapy plan data offers a potentially unique opportunity to refine our understanding of the relationship of small bowel irradiation with acute and late toxicity. The stratified randomisation within the trial will allow clinicians to: identify the independent modulatory effect of irinotecan in addition to capecitabine on the dose-volume tolerance of the small bowel, verify that the same DVH parameters remain

important in predicting toxicity, and identify thresholds to recommend for future radiotherapy planning using this regimen. Within this study, the findings of this thesis in relation to small bowel toxicity will be tested and hopefully validated, and the canonical correlation technique will also be explored further.

8.2.2. Functional imaging in pancreatic cancer chemoradiotherapy

The SCALOP-2 clinical trial (ISRCTN50083238) aims to assess the benefit of chemoradiotherapy over chemotherapy alone for patients with locally advanced pancreatic cancer, and of dose-escalated radiotherapy achieved using IMRT. Half the patients treated with radiotherapy will receive the standard dose of 50.4 Gy in 28 fractions, while half will receive an escalated dose of 60 Gy delivered in thirty fractions. Unfortunately, there is not yet an established means of predicting which patients are likely to benefit from loco-regional treatment, nor detecting during treatment which are demonstrating response or resistance. A functional imaging sub-study has been designed to take place within this clinical trial with the aim of evaluating functional imaging modalities that are available which can assess important tumour parameters such as hypoxia and proliferation, and could potentially achieve these aims. Furthermore, these functional imaging modalities could also be used to define sub-volumes of tumours to be targeted for dose escalation according to similar biological characteristics.

Pancreatic cancers show high levels of hypoxia [359]. Hypoxia levels in resected pancreatic cancers predict prognosis [360] and tumour hypoxia is known to cause resistance to radiotherapy [361], thus making it worthwhile to examine as a method of stratification for treatment modification such as dose escalation. FMISO-PET can be used to visualise hypoxic regions of tissue [362] and predicts response before or during radiotherapy in head and neck cancer [363, 364]. Similar results have been shown using other PET hypoxia tracers such as

FAZA and HX4 in head and neck cancer, and in non-small cell lung cancer [365, 366]. Radiotherapy planning to target hypoxic sub-volumes on FMISO imaging has also been demonstrated in head and neck cancer [367-369], while hypoxia-PET tracers have also shown utility for dose painting in non-small cell lung cancer [370].

Work by the Oxford Cancer Imaging Centre has demonstrated FMISO uptake in pancreatic tumours and regions of peak FMISO uptake proved spatially consistent supporting the potential use of FMISO-PET to define hypoxic biological target volumes for radiotherapy dose escalation [371]. Potential disadvantages of FMISO-PET imaging are that it is expensive and technically challenging to implement and it seems that a more widely available alternative would be required for routine clinical application. Multi-parametric MRI is a promising alternative imaging modality that can provide information on a number of important tumour characteristics including hypoxia, perfusion and proliferation.

Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) is used to assess tumour perfusion and vascular permeability. In cervical cancer, changes in perfusion – seen on DCE MRI after 2 weeks of radiotherapy – predicted outcome [372]. Diffusion-weighted MRI detects changes in the molecular diffusion of water molecules within tissues, a surrogate for cell density and tumour grade. In head and neck cancer, diffusion-weighted MRI shows potential as an early predictor of treatment response [363, 373].

In pancreatic tumours multi-parametric MRI can measure tumour fibrosis, vascularity and discriminate tumour from normal tissue [374-378], but it has not yet been evaluated as a tool for assessment of pancreatic cancer response to chemoradiotherapy. A proposed study would use paired imaging within patients at key time-points in relation to treatment within the SCALOP-2 trial: at baseline and after induction chemotherapy, before and after

commencement of nelfinavir, and before and after commencement of chemoradiotherapy. The aim would be to explore the potential of these imaging modalities in prediction of or assessment of response to these treatment interventions.

8.3. Outlook for pancreatic cancer radiotherapy

With the results of the LAP-07 study indicating that the addition of radiotherapy to chemotherapy may not offer an overall survival advantage [12], the limited effectiveness of conventional radiotherapy for radical treatment of pancreatic cancer has become clear. Conventional chemoradiotherapy delivers inadequate dose to achieve satisfactory chances of controlling the targeted disease while poorly conforming this dose away from the surrounding organs at risk. Image-guided intensity-modulated radiotherapy aims to achieve safe, tolerable dose escalation, and the potential benefits of this in the management of locally advanced pancreatic cancer will be investigated as part of the SCALOP-2 trial. Stereotactic radiotherapy has the potential to achieve further biological dose escalation and accuracy. Recent publications such as a large retrospective database analysis [379],and a systematic review of the published evidence [380], have lent further support to the proponents of the role of SBRT in treating pancreatic cancer [381, 382]. However, conclusive data from prospective controlled clinical trials is still required. In the United States, the role of SBRT over and above FOLFIRINOX chemotherapy alone in locally advanced pancreatic cancer will be assessed in a phase-III randomised trial which is currently recruiting (NCT01926197), and investigators are in the process of opening a similar study for patients with BRPC (Alliance A021501) [383].

Unfortunately the SPARC trial has now closed to recruitment of new patients. A similar dose escalation phase-I trial, that has reported since the SPARC study opened, has found that the highest dose level they tested was safe (36 Gy in three fractions) [312]. This result supports ongoing attempts to identify a maximal safe dose, in order to identify an appropriate dose to

take forward for further evaluation. It is hoped that it will be possible to include SBRT in a randomised trial to find definitive evidence of its effectiveness, and confirmation of how it best fits with other available treatments. While the recent ESPAC-5F trial (ISRCTN89500674) has recently finished recruitment and will compare neoadjuvant chemoradiotherapy with chemotherapy regimens (or surgery alone), a sequential multi-modality approach to radical treatment of these patients is already being adopted by some clinical teams, with promising results in retrospective data [345]. Further evidence is required from prospective trials, and the PRECISION-PANC platform offers a structure for rigorous evaluation of interventions such as SBRT and molecularly-targeted therapies, set to take place in the PRIMUS-002 study (ISRCTN34129115).

Accurate disease staging is crucial to inform treatment decisions, and the full results are eagerly awaited for the PET-PANC study, in which initial results showed the results of FDG-PET-CT scans influenced treatment management, compared with that based on standard of care investigations in 45% of patients [384]. Better patient selection is likely to lead to the impression of improved outcomes for interventions directed towards localised disease, because with more sensitive detection of metastatic disease spread, fewer patients may remain appropriate to treat with surgery or radiotherapy.

Proponents of the use of particle therapy such as that with protons have also demonstrated the potential advantages of these technologies in terms of the dose-distribution that can be achieved [385], although a definitive clinical benefit over the use of photon therapy has not been proven. In the meantime, novel emerging radiotherapy equipment technology promises to enhance the delivery of photon radiotherapy to pancreatic tumours, through the improved tumour and soft-tissue visualisation that can be achieved using MR-guided radiotherapy [386]. Adaptive treatment planning is used to derive a new dose distribution for the anatomy as

visualised prior to each treatment. This can facilitate safe individualised target dose-escalation, with the possibility to further improve the therapeutic ratio beyond what has been achieved using CBCT-based image-guided radiotherapy. Promising outcomes data have already begun to emerge indicating the excellent results that could be achieved with such technology [387]. Patients have been treated with prescription doses up to 100 Gy $BED_{10,}$ and retrospective comparisons have shown that those receiving higher doses (>70 Gy) shown to enjoy better overall survival [388].

In summary, following recent clinical trials results, it had appeared to some that the days of radical radiotherapy for pancreatic cancer may be numbered. However, a thriving community of scientists and oncologists are still striving to improve outcomes for patients with this disease using radiotherapy, and their response has been clear: “the report of our demise was an exaggeration”.

9. Appendix

Appendix A – Search strings and supplementary data table for Chapter Two

1) Search string used in SCOPUS database

((((TITLE ("pancrea* neoplasm*") OR ABS ("pancrea* neoplasm*"))) OR ((TITLE ("pancrea* cancer*") OR ABS ("pancrea* cancer*"))) OR ((TITLE (stomach) OR ABS (stomach))) OR ((TITLE (gastric) OR ABS (gastric)))) OR (((TITLE ("small bowel") OR ABS ("small bowel"))) OR ((TITLE (duodenum) OR ABS (duodenum))) OR ((TITLE (ileum) OR ABS (ileum))) OR ((TITLE (jejunum) OR ABS (jejunum))))) AND ((TITLE (toxicit*) OR ABS (toxicit*))) AND ((TITLE (patients OR trial* OR "case series") OR ABS (patients OR trial* OR "case series"))) AND ((TITLE ((dos* OR fraction*) AND (radiation* OR radiotherap*)) OR ABS ((dos* OR fraction*) AND (radiation* OR radiotherap*)))) AND (EXCLUDE (PUBYEAR , 2001) OR EXCLUDE (PUBYEAR , 2000) OR EXCLUDE (PUBYEAR , 1999) OR EXCLUDE (PUBYEAR , 1998) OR EXCLUDE (PUBYEAR , 1997) OR EXCLUDE (PUBYEAR , 1996) OR EXCLUDE (PUBYEAR , 1995) OR EXCLUDE (PUBYEAR , 1994) OR EXCLUDE (PUBYEAR , 1993) OR EXCLUDE (PUBYEAR , 1992) OR EXCLUDE (PUBYEAR , 1991) OR EXCLUDE (PUBYEAR , 1990) OR EXCLUDE (PUBYEAR , 1989) OR EXCLUDE (PUBYEAR , 1988) OR EXCLUDE (PUBYEAR , 1987) OR EXCLUDE (PUBYEAR , 1986) OR EXCLUDE (PUBYEAR , 1985) OR EXCLUDE (PUBYEAR , 1983) OR EXCLUDE (PUBYEAR , 1982) OR EXCLUDE (PUBYEAR , 1981) OR EXCLUDE (PUBYEAR , 1980)) AND (LIMIT-TO (LANGUAGE , "English"))

Results – 498

2) Search string used in Medline database

	Search terms	Related terms?	Results
1	Exp pancreatic neoplasms/		59002
2	"pancrea* neoplasm*".ti,ab.	Y	1227
3	"pancrea* cancer*".ti,ab.	Y	25103
4	Exp stomach/	y	111445
5	duodenum.ti,ab.		28515
6	"small bowel".ti,ab.	y	27562
7	ileum.ti,ab.	Y	27956
8	jejunum.ti,ab.	Y	17881
9	Exp small intestine/	Y	12035
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9		345015
11	toxicit*.ti,ab.	Y	283690
12	patients.ti,ab.	Y	4254781
13	trial*.ti,ab.	Y	692462
14	“case series”.ti,ab.	Y	40802
15	Exp clinical trial/		827153
16	12 or 13 or 14 or 15		4846929
17	Exp chemoradiotherapy/		4570
18	chemoradiotherapy.ti,ab.	Y	9337
19	Radiation dose.ti,ab.	Y	17331
20	((dosimetr* or fractionat*) and (radiation* or radiotherap*)).ti,ab.	Y	20576
21	17 or 18 or 19 or 20		46980
22	10 and 11 and 16 and 21		355
23	Limited to English with abstracts and 2002-present		299

3) Search terms and sequence used in EMBASE database search

	Search terms	Results
1	Exp pancreatic neoplasms/	95213
2	"pancrea* neoplasm*".ti,ab.	1583
3	"pancrea* cancer*".ti,ab.	33662
4	Exp stomach/	153290
5	duodenum.ti,ab.	34049
6	"small bowel".ti,ab.	36038
7	ileum.ti,ab.	33325
8	jejunum.ti,ab.	20698
9	Exp small intestine/	169538
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	437235
11	toxicit*.ti,ab.	362527
12	patients.ti,ab.	5533624
13	trial*.ti,ab.	857975
14	“case series”. ti,ab.	3386
15	Exp clinical trial/	999280
16	12 or 13 or 14 or 15	6235208
17	Exp chemoradiotherapy/	16171
18	chemoradiotherapy.ti,ab.	13656
19	Radiation dose.ti,ab.	23429
20	((dosimetr* or fractionat*) and (radiation* or radiotherap*)).ti,ab.	29421
21	17 or 18 or 19 or 20	72167
22	10 and 11 and 16 and 21	693
23	Limited to English with abstracts and 2002-present	632

Table 9-1. Findings of published analyses of the dose-volume relationship for the small bowel

Reference	Cancer site	Data	N =	Concurrent chemo	RT dose [Gy]	RT planning	Toxicity outcome	Small bowel dose-volume parameter predictive of toxicity (with threshold if reported)
Baglan 2002 [159]	Rectum	R	40	5-FU	50.4 Gy in 28 # (45 Gy to pelvis)	3D-CRT	Acute small bowel Grade ≥ 3	V_{15Gy} 150 cm^3
Tho 2006 [160]	Rectum	P	41	5-FU	45 Gy in 25 #	3D-CRT	Acute diarrhoea Grade ≥ 2	V_{5Gy} to $V_{42.75Gy}$
Gunnlaugsson 2007 [161]	Rectum	R	28	Oxaliplatin & 5-FU	50.4 Gy in 28 # or 50 Gy in 25 #	3D-CRT	Acute diarrhoea Grade ≥ 2	V_{15Gy} to V_{45Gy}
Robertson 2008 [192]	Rectum	P	96	5-FU	45 Gy in 25 #	3D-CRT	Acute diarrhoea Grade ≥ 3	V_{5Gy} 500 cm^3, V_{10Gy} 300 cm^3, V_{15Gy} 150 cm^3, V_{20Gy} 145 cm^3, V_{25Gy} 140 cm^3, V_{30Gy} 135 cm^3, V_{35Gy} 130 cm^3, V_{40Gy} 125 cm^3
Robertson 2010 [162]	Rectum	Mix	152	5-FU	45 Gy in 25 #	3D-CRT	Acute diarrhoea Grade ≥ 3	V_{15Gy} 130 cm^3
Arbea 2012 [166]	Rectum	R	100	Capecitabine-oxaliplatin	47.5 Gy in 20 #	IMRT	Acute diarrhoea Grade ≥ 3	V_{10Gy} 92.6 cm^3, V_{15Gy} 78.8 cm^3, V_{50Gy} 4.44 cm^3
Chen 2012 [165]	Rectum	P	66	5-FU/ capecitabine	50.4 Gy in 28 #	3D-CRT	Patient-reported GI	V_{15Gy}
Banerjee 2013 [167]	Rectum	R	67	5-FU	50.4 Gy in 28 #	3D-CRT	Acute small bowel Grade ≥3	V_{15Gy}–V_{45Gy}; V_{25Gy} 190 cm^3 (650 cm^3 for peritoneal cavity) V_{15Gy} 275 cm^3 (830 cm^3 for peritoneal cavity)
Reis 2015 [168]	Rectum	P	45	Cetuximab, cape, irinotecan	50.4 Gy in 28 #	3D-CRT	Acute diarrhoea	V_{5Gy} > 291.94 cm^3 V_{15Gy} > 125.5 cm^3
Roeske 2003 [163]	Gynae	P	50	Cisplatin (52%)	45 Gy in 25 #	IMRT	Acute GI	V_{45Gy} 195 cm^3 (for single small bowel structure)
Huang 2007 [164]	Gynae	P	80	Cisplatin-5-FU (63%)	45–50.4 Gy in 25–28 #	3D-CRT	Acute diarrhoea Grade 2–3	$V_{40\%}$ (15.8 Gy) if no prior surgery $V_{100\%}$ (39.6 Gy) if prior surgery
Chi 2012 [169]	Endometrial	P	32	Carbo/cisplatin (12.5%)	48 Gy ± 3 Gy	IMRT	Acute lower GI Grade ≥ 2	V_{45Gy} (for intestinal cavity)
Ray 2013 [250]	Gynae	R	60	None	50.4 Gy in 28 #	3D-CRT (26) /IMRT (34)	Acute diarrhoea Grade ≥ 2	V_{35Gy}, V_{40Gy}
Chopra 2014 [171]	Cervix	P	71	Cisplatin	50 Gy in 25 #	IMRT	Acute & late GI Grade ≥ 3	V_{15Gy} 275 cm^3, V_{30Gy} < 190 cm^3, V_{40Gy} < 150 cm^3
Rath 2014 [170]	Cervix	P	44	Cisplatin	50.4 Gy in 28 #	3D-CRT (22) /IMRT (22)	Acute GI	$V_{90\%}$, $V_{100\%}$, V_{45Gy} > 180 cm^3 (for peritoneal cavity)
DeFoe 2010 [172]	Anus	P	58	MMC/5-FU	45–67.6 Gy	IMRT	Acute GI Grade ≥ 3	V_{30Gy} > 310 cm^3, V_{40Gy} > 70 cm^3
Nakamura 2012 [144]	Pancreas	R	40	Gemcitabine	54 Gy in 30 #	3D-CRT + IMRT boost	Acute GI Grade ≥ 3	GI toxicity: D_{2cm^3} 53.7 Gy, V_{40Gy} 17 cm^3, V_{50Gy} 10 cm^3 (Also upper GI bleed: D_{mean} 24.6 Gy)
Fiorino 2009 [173]	Prostate nodes	Mix	191	None	50.4 Gy in 28 #	3D-CRT (91) /IMRT (84)	Acute GI Grade ≥ 2	V_{20Gy}–V_{50Gy} (for intestinal cavity)

(R = retrospective, P = prospective NS = not specified; IMRT= intensity modulated radiotherapy; GI = gastrointestinal, 5-FU = 5-fluorouracil, cape = capecitabine, MMC = mitomycin C)

Appendix B – Supplementary tables and plots for Chapter Five

Study	Patients	N =	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}
Baglan	**All**	*40*	*529*	*316*	*175*	*153*	*141*	*132*	*124*	*113*		
	Grade 0–2	30	439	246	127	108	99	92	86	78		
	Grade ≥ 3	10	798	524	319	286	267	251	237	216		
Banerjee	**All**	*67*	*289*	*242*	*210*	*187*	*138*	*90*	*78*	*68*	*30*	
	Grade 0–2	56	229	184	155	132	90	56	47	39	23	
	Grade ≥ 3	11	595	540	493	470	383	261	238	217	67	
Chen 07	**All**	*68*					*243*		*157*		*110*	*83*
	IMRT	33					221		99		34	11
	'Box-RT'	35					263		212		181	150
Robertson	**All**	*96*	*482*	*242*	*127*	*105*	*94*	*81*	*75*	*67*		
	Grade 0–2	76	447	213	102	83	74	66	61	54		
	Grade ≥ 3	20	614	352	223	190	170	140	128	116		
Tho	**All**	*41*	*79*	*66*	*46*	*21*	*15*	*14*	*12*	*5*		
	Grade 0–1	32	24	16	4	0	0	0	0	0		
	Grade ≥ 2	9	276	244	194	94	70	64	54	23		
Van der Voort	**All**	*189*	*225*	*199*	*159*	*125*						
	DSS	54	194	176	124	78						
	No DSS	135	238	208	173	144						
Huang 07	**All**	*80*	*425*	*383*	*352*	*326*	*254*	*197*	*164*	*146*	*131*	*111*
	Group I	49	455	412	379	353	272	216	183	163	145	123
	Group II	31	379	338	309	283	226	167	135	120	108	93
Gunnlaugsson	**All**	*28*	*285*	*268*	*228*	*161*	*143*	*128*	*121*	*114*	*103*	*68*
	Grade 0–1	17	225	203	152	78	65	59	57	52	48	33
	Grade ≥ 2	11	379	368	347	289	264	234	221	209	188	121
	All	*63*	*239*	*207*	*184*	*156*	*113*	*66*	*41*	*26*		
Xu	**Grade 0–1**	27	268	230	203	174	127	75	47	30		
	Grade ≥ 2	36	217	189	169	143	103	60	37	23		
Ito	**All**	*39*	*178*	*157*	*145*	*65*	*54*	*50*	*44*	*40*	*34*	
	Grade 0–2	13	169	150	140	64	53	49	43	38	32	
	Grade ≥ 3	26	182	161	148	66	55	50	45	41	35	

Table 9-2. Studies in which small bowel DVH data was reported for cohorts or sub-groups only. The data representing the whole study (indicated by italic typeface) was calculated as a weighted mean from the two groups. All DVH values are in cm^3

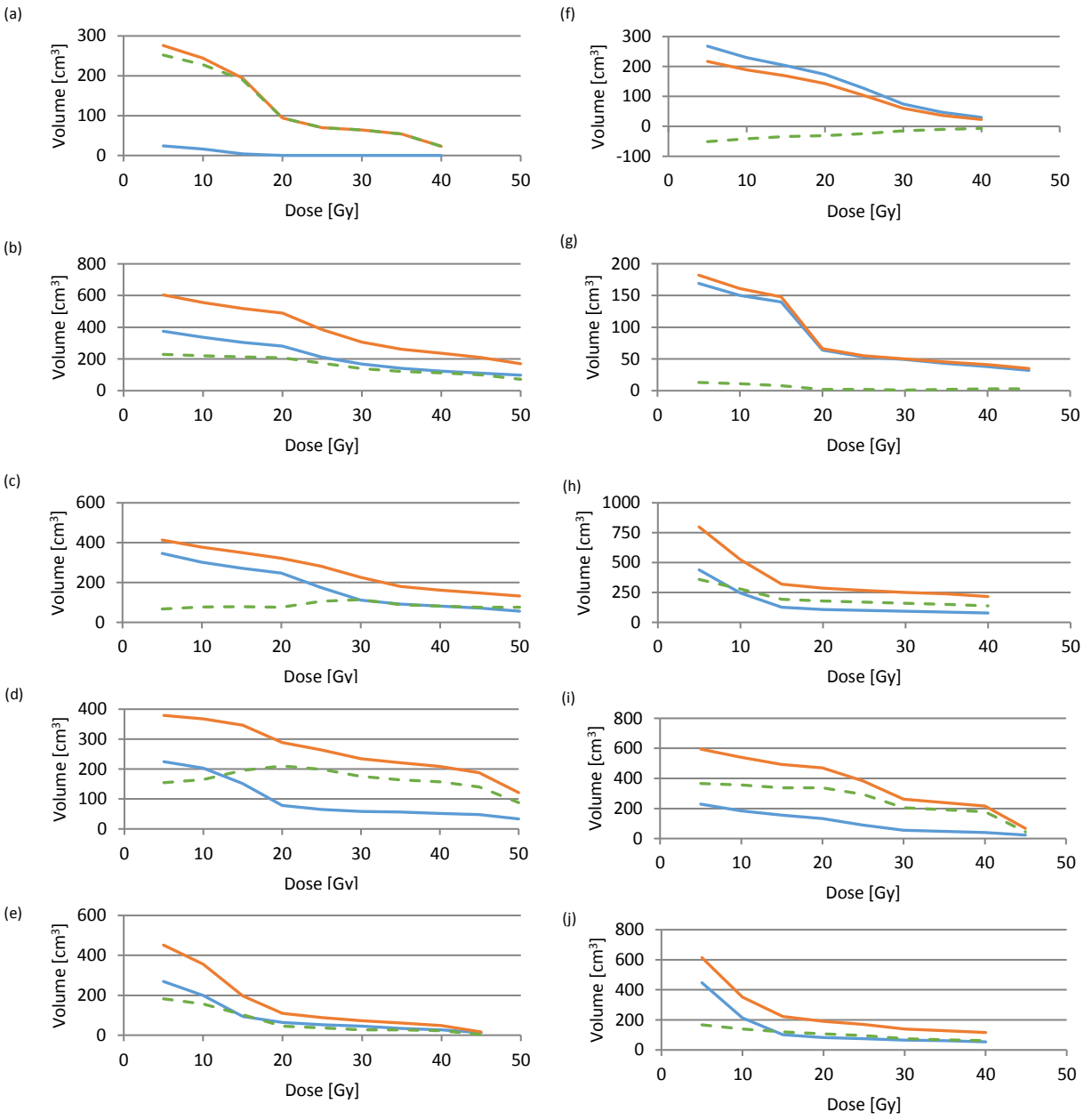


Figure 9-1. Absolute cumulative volume of irradiated small bowel for cohorts of patients with Grade 0–1 (blue) and Grade ≥ 2 (orange) toxicity, and absolute difference (dashed green)
(a) Tho et al. (b) Huang et al. group I – no prior abdominal surgery (c) Huang et al. group II – prior abdominal surgery (d) Gunnlaugsson et al. (e) Reis et al. (f) Xu et al. (g) Ito et al. (h) Baglan et al. (i) Banerjee et al. (j) Robertson et al.

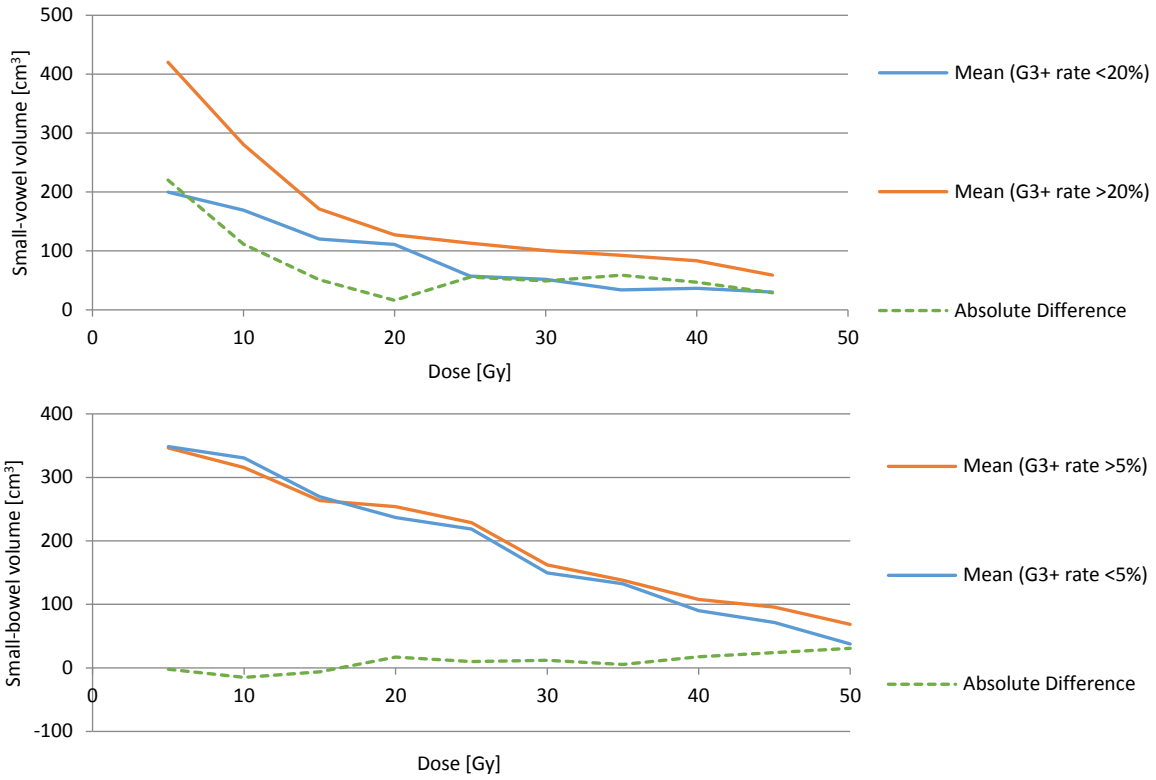


Figure 9-2. Mean irradiated small bowel cumulative volume for studies with high (orange) or low (blue) rates of toxicity, and absolute difference between means (dashed green). Top: rectal cancer, bottom: gynaecological cancers.

Publication	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}
Abelson	**309**	**267**	**229**	**195**	**164**	134	**105**	**74**	40	**3**
Baglan	529	316	175	153	141	132	124	113	**70**	**6**
Banerjee	289	242	211	188	138	90	78	68	30	**2**
Chen 12	206	**128**	66	**32**	19	**14**	12	**9**	**5**	**0**
Chi	349	325	303	271	240	209	181	142	80	20
Chopra	**256**	**238**	218	**198**	**180**	166	**154**	127	**72**	**49**
Gunnlaugsson	285	268	228	161	143	128	121	114	103	68
Huang	425	383	352	326	254	197	165	146	80	20
Macchia (ARC)	**380**	282	164	126	100	80	62	44	14	1
Macchia (3D-CRT)	**421**	385	341	313	270	161	108	85	48	6
Martin	265	233	215	199	186	135	82	68	61	33
Milano	**236**	**191**	**149**	**111**	**79**	54	**37**	24	**12**	**9**
Reis	385	297	155	91	76	63	51	41	15	**1**
Robertson	482	242	127	105	94	81	75	67	**40**	**0**
Tho	79	66	46	21	15	14	12	5	**0**	**0**
Van der Voort	225	199	159	125	**100**	**81**	**64**	**48**	**28**	**2**

Table 9-3. Source data values and imputed values (indicated in bold) derived by fitting cubic splines to published points for small bowel cumulative DVH.

Parameter	Correlation	95% CI		*P* value
V_{5Gy}	0.260	-0.270	0.670	0.330
V_{10Gy}	0.048	-0.459	0.531	0.860
V_{15Gy}	-0.182	-0.621	0.345	0.500
V_{20Gy}	-0.241	-0.658	0.289	0.369
V_{25Gy}	-0.222	-0.647	0.307	0.408
V_{30Gy}	-0.123	-0.583	0.397	0.650
V_{35Gy}	0.014	-0.485	0.506	0.959
V_{40Gy}	0.139	-0.383	0.594	0.609
V_{45Gy}	0.247	-0.283	0.662	0.356
V_{50Gy}	0.222	-0.308	0.646	0.410

Table 9-4. Correlations of cumulative DVH parameters with toxicity outcome, with 95% confidence intervals and p-value.

Parameter	Correlation	95% CI		*P* value
$V_{5–10Gy}$	0.382	-0.141	0.738	0.148
$V_{10–15Gy}$	0.443	-0.068	0.769	0.086
$V_{15–20Gy}$	0.397	-0.124	0.746	0.129
$V_{20–25Gy}$	-0.246	-0.661	0.285	0.359
$V_{25–30Gy}$	-0.365	-0.729	0.160	0.165
$V_{30–35Gy}$	-0.502	-0.799	-0.008	**0.048**
$V_{35–40Gy}$	-0.548	-0.821	-0.072	**0.028**
$V_{40–45Gy}$	-0.079	-0.553	0.433	0.770
$V_{45–50Gy}$	0.167	-0.359	0.612	0.537
$V_{\geq 50Gy}$	0.218	-0.311	0.644	0.417

Table 9-5. Correlations of differential DVH parameters with toxicity outcome, with 95% confidence intervals and p-value. P values < 0.05 highlighted in bold.

Publication	N	P	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}	VFactor
Abelson 12	47	0.04	309.4	266.6	229.0	195.3	164.2	134.4	104.6	73.5	39.8	3.0	0.411
Baglan 02	40	0.25	528.8	315.5	175.0	152.5	141.0	131.8	123.8	112.5	70.1	5.5	-0.384
Banerjee 13	67	0.16	289.1	242.4	210.5	187.5	138.1	89.7	78.4	68.2	30.2	1.9	0.025
Chen 12	66	0.13	206.0	127.7	66.0	32.4	19.0	14.1	12.0	9.1	5.0	0.4	-0.079
Chi 12	32	0	348.5	325.0	303.3	271.4	239.9	208.7	180.5	141.5	79.9	20.1	0.184
Chopra 14	71	0.13	255.8	237.8	218.0	198.2	180.2	166.0	153.7	127.0	72.1	48.6	0.113
Gunnlaugsson 07	28	0.29	285.4	267.9	228.2	160.9	143.1	127.6	121.2	113.6	102.7	67.9	-0.479
Huang 07	80	0.15	425.2	383.4	351.7	326.0	253.8	197.3	164.5	146.3	79.9	20.1	-0.105
Macchia 14 (ARC)	30	0	380.2	281.7	163.5	125.7	100.3	79.7	62.1	43.8	13.5	0.9	0.234
Macchia 14 (3D-CRT)	30	0.03	421.1	384.7	341.3	313.2	269.9	161.2	107.6	85.2	48.4	6.3	0.246
Martin 05	32	0.07	265.2	232.7	214.9	199.4	186.4	134.9	81.8	67.6	60.7	33.0	0.198
Milano 04	17	0	236.4	191.2	148.9	111.0	78.9	54.1	37.0	24.3	12.2	9.0	0.265
Reis 15	45	0.29	385.2	296.8	155.1	90.9	75.5	63.1	51.4	40.9	15.4	0.8	-0.352
Robertson 08	96	0.21	481.8	242.0	127.2	105.3	94.0	81.4	75.0	66.9	39.9	0.0	-0.175
Tho 06	41	0.09	79.3	66.0	45.7	20.6	15.4	14.0	11.9	5.0	0.0	0.0	-0.012
Van der Voort 12	189	0.16	225.2	198.8	159.1	125.3	100.3	80.9	64.3	47.6	27.9	2.4	0.116
Coefficient			0.0002	0.0020	-0.0138	0.0223	-0.0093	-0.0050	0.041	-0.0515	0.0086	0.0076	

Table 9-6. Cumulative absolute DVH volumes for small bowel from published studies. N = number of patients in cohort/publication, P = proportional incidence of toxicity (Grade ≥ 3 diarrhoea), V_{5Gy} = Absolute volume of small bowel receiving ≥ 5 Gy [cm³], VFactor = derived DVH parameter for each cohort/publication, Coefficient = Derived canonical correlation coefficient for each DVH parameter.

Publication	N	P	$V_{5–10Gy}$	$V_{10–15Gy}$	$V_{15–20Gy}$	$V_{20–25Gy}$	$V_{25–30Gy}$	$V_{30–35Gy}$	$V_{35–40Gy}$	$V_{40–45Gy}$	$V_{45–50Gy}$	$V_{≥50Gy}$	VFactor
Abelson 12	47	0.04	42.8	37.6	33.7	31.1	29.8	29.8	31.1	33.7	36.8	3.0	0.411
Baglan 02	40	0.25	213.3	140.5	22.5	11.5	9.2	8.0	11.3	42.4	64.6	5.5	-0.384
Banerjee 13	67	0.16	46.7	31.9	23.0	49.4	48.4	11.3	10.2	38.0	28.3	1.9	0.025
Chen 12	66	0.13	78.3	61.7	33.6	13.4	4.9	2.1	2.9	4.1	4.6	0.4	-0.079
Chi 12	32	0	23.5	21.7	31.9	31.5	31.2	28.2	39.0	61.6	59.8	20.1	0.184
Chopra 14	71	0.13	18.0	19.8	19.8	18.0	14.2	12.3	26.7	54.9	23.5	48.6	0.113
Gunnlaugsson 07	28	0.29	17.5	39.7	67.3	17.8	15.5	6.4	7.6	10.9	34.8	67.9	-0.479
Huang 07	80	0.15	41.8	31.7	25.7	72.2	56.5	32.8	18.2	66.4	59.8	20.1	-0.105
Macchia 14 (ARC)	30	0	98.5	118.2	37.8	25.4	20.6	17.6	18.3	30.3	12.6	0.9	0.234
Macchia 14 (3D-CRT)	30	0.03	36.4	43.4	28.1	43.3	108.7	53.6	22.4	36.8	42.1	6.3	0.246
Martin 05	32	0.07	32.5	17.8	15.5	13.1	51.5	53.1	14.2	6.9	27.7	33.0	0.198
Milano 04	17	0	45.2	42.3	37.9	32.1	24.8	17.1	12.7	12.1	3.2	9.0	0.265
Reis 15	45	0.29	88.4	141.7	64.2	15.4	12.4	11.7	10.5	25.5	14.6	0.8	-0.352
Robertson 08	96	0.21	239.8	114.8	21.9	11.3	12.6	6.4	8.1	27.0	39.9	0.0	-0.175
Tho 06	41	0.09	13.3	20.3	25.1	5.2	1.4	2.1	6.9	5.0	0.0	0.0	-0.012
Van der Voort 12	189	0.16	26.4	39.7	33.8	25.0	19.4	16.6	16.7	19.7	25.5	2.4	0.116
Coefficient			0.0002	0.0021	-0.0116	0.0107	0.0014	-0.0036	0.0370	-0.0145	-0.0059	0.0016	

Table 9-7. Differential absolute DVH volumes for small bowel from published studies. N = number of patients in cohort/publication, P = proportional incidence of toxicity (Grade ≥ 3 diarrhoea), $V_{5–10Gy}$ = Absolute volume of small bowel receiving between 5 and 10 Gy [cm^3], VFactor = derived DVH parameter for each cohort/publication, Coefficient = Derived canonical correlation coefficient for each DVH parameter).

Publication	N	P	V_{5Gy}	V_{10Gy}	V_{15Gy}	V_{20Gy}	V_{25Gy}	V_{30Gy}	V_{35Gy}	V_{40Gy}	V_{45Gy}	V_{50Gy}	VFactor
Baglan 02	40	0.25	213.3	140.5	22.5	11.5	9.2	8.0	11.3	42.4	64.6	5.5	1.1886899
Banerjee 13	67	0.16	46.7	31.9	23.0	49.4	48.4	11.3	10.2	38.0	28.3	1.9	0.7326647
Chen 12	66	0.13	78.3	61.7	33.6	13.4	4.9	2.1	2.9	4.1	4.6	0.4	0.5806564
Gunnlaugsson 07	28	0.29	17.5	39.7	67.3	17.8	15.5	6.4	7.6	10.9	34.8	67.9	1.3913677
Reis 15	45	0.29	88.4	141.7	64.2	15.4	12.4	11.7	10.5	25.5	14.6	0.8	1.3913677
Robertson 08	96	0.21	239.8	114.8	21.9	11.3	12.6	6.4	8.1	27.0	39.9	0.0	0.9860120
Tho 06	41	0.09	13.3	20.3	25.1	5.2	1.4	2.1	6.9	5.0	0.0	0.0	0.3779785
Van der Voort 12	189	0.16	26.4	39.7	33.8	25.0	19.4	16.6	16.7	19.7	25.5	2.4	0.7326647
Coefficient			0.00039	0.00238	0.00967	-0.02286	0.02235	-0.01280	0.00452				

Table 9-8. Cumulative absolute DVH volumes for small bowel from published studies of treatment of rectal cancer. N = number of patients in cohort/publication, P = proportional incidence of toxicity (Grade ≥ 3 diarrhoea), V_{5Gy} = Absolute volume of small bowel receiving ≥ 5 Gy [cm3], VFactor = derived canonical variate for each cohort/publication, Coefficient = Derived canonical correlation coefficient for each DVH parameter.

Adverse Event	Grade	Grade Description
Anorexia	1	Loss of appetite without alteration in eating habits
	2	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated
	3	Associated with significant weight loss or malnutrition (eg inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Diarrhoea	1	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline
	2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
	3	Increase of ≥ 7 stools per day over baseline; incontinence; hospital indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Intra-abdominal haemorrhage	2	Medical intervention or minor cauterization indicated
	3	Transfusion, radiologic, endoscopic, or elective operative intervention indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Nausea	1	Loss of appetite without alteration in eating habits
	2	Oral intake decreased without significant weight loss, dehydration or malnutrition
	3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Gastrointestinal – Other, specify	5	Death
Small intestinal perforation	2	Symptomatic; medical intervention indicated
	3	Severe symptoms; elective operative intervention indicated
	4	Life-threatening consequences; urgent operative intervention indicated
	5	Death
Small intestinal stenosis	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Symptomatic; altered GI function
	3	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated
	4	Life-threatening consequences; urgent operative intervention indicated
	5	Death
Small intestine ulcer	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
	2	Symptomatic; altered GI function; limiting instrumental ADL
	3	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disabling
	4	Life-threatening consequences; urgent operative intervention indicated
	5	Death
Vomiting	1	**1–2 episodes (separated by 5 minutes) in 24 hrs**
	2	**3–5 episodes (separated by 5 minutes) in 24 hrs**
	3	≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death

Table 9-9. CTCAE v4 gastrointestinal adverse events and grades [37]

Grade	Scoring Criteria
	Upper GI
1	Anorexia with ≤ 5% weight loss from pre-treatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics
2	Anorexia with ≤ 15% weight loss from pre-treatment baseline/nausea and/ or vomiting requiring antiemetics/ abdominal pain requiring analgesics
3	Anorexia with > 15% weight loss from pre-treatment baseline or requiring N-G tube or parenteral support. Nausea and/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/ hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops
4	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
5	Death
	Lower GI
1	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics
2	Diarrhoea requiring parasympatholytic drugs (eg Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics
3	Diarrhoea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)
4	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
5	Death

Table 9-10. RTOG acute radiation morbidity grading scale and criteria for upper GI and lower GI toxicity [38]

Grade	Criteria
	Diarrhoea
1	Increase of 2–3 stools over pre-RT
2	Increase of 4–6 stools/day, or nocturnal stools, or moderate cramping
3	Increase of 7–9 stools/day or incontinence or severe cramping
4	Increase of ≥ 10 stools/day or grossly bloody diarrhoea, or need for parenteral support
5	Death
	Nausea
1	Able to eat/reasonable intake
2	Intake significantly decreased but can eat
3	No significant intake
	Vomiting
1	1 episode in 24 hrs
2	2–5 episodes in 24 hrs
3	6–10 episodes in 24 hrs
4	> 10 or requiring parenteral support
5	Death

Table 9-11. RTOG cooperative group grading scale and criteria for symptoms relevant to upper and lower GI toxicity [255]

Appendix C – Supplementary tables and data for Chapter Six

ECOG		**Karnofsky**	
Grade		Grade	
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints; no evidence of disease
		90	Able to carry on normal activities; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg office work	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do active work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Requires occasional assistance, but able to care for most of his needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalisation is indicated though death not imminent
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick; hospitalisation and active supportive care necessary
		10	Moribund
5	Dead	0	Dead

Table 9-12. Table for conversion of performance status scale adapted from Oken et al. [270]

	Combined cohort	*p*	ARCII	*P*	SCALOP	*p*
Stomach						
V_{0Gy}	1.000 (0.999-1.002)	0.721	0.999 (0.993-1.006)	0.829	1.001 (0.999-1.003)	0.463
V_{5Gy}	1.002 (0.999-1.005)	0.268	1.005 (0.996-1.014)	0.287	1.001 (0.998-1.005)	0.460
V_{10Gy}	1.002 (0.998-1.005)	0.281	1.009 (0.997-1.020)	0.146	1.001 (0.997-1.005)	0.610
V_{15Gy}	1.002 (0.998-1.006)	0.293	1.012 (0.998-1.026)	0.091	1.001 (0.997-1.005)	0.717
V_{20Gy}	1.002 (0.998-1.006)	0.349	1.015 (0.999-1.031)	0.069	1.000 (0.996-1.005)	0.858
V_{25Gy}	1.002 (0.998-1.007)	0.325	1.017 (0.999-1.036)	0.061	1.001 (0.996-1.006)	0.811
V_{30Gy}	1.006 (0.999-1.013)	0.090	1.023 (0.999-1.047)	0.056	1.002 (0.995-1.010)	0.508
V_{35Gy}	1.012 (1.002-1.023)	0.014	1.033 (1.000-1.066)	0.051	1.007 (0.996-1.019)	0.225
V_{40Gy}	1.013 (1.002-1.025)	0.024	1.036 (1.000-1.073)	0.048	1.007 (0.994-1.020)	0.284
V_{45Gy}	1.014 (1.001-1.028)	0.039	1.036 (0.999-1.073)	0.055	1.008 (0.993-1.024)	0.288
V_{50Gy}	1.021 (1.001-1.041)	0.039	1.037 (0.993-1.084)	0.103	1.013 (0.989-1.038)	0.285
V_{55Gy}	-		1.046 (0.981-1.115)	0.166	-	
Duodenum						
V_{0Gy}	1.006 (0.994-1.019)	0.332	1.013 (0.968-1.061)	0.570	1.009 (0.995-1.023)	0.209
V_{5Gy}	1.010 (0.996-1.023)	0.173	1.012 (0.966-1.059)	0.623	1.011 (0.996-1.026)	0.141
V_{10Gy}	1.008 (0.994-1.021)	0.258	1.010 (0.966-1.057)	0.658	1.008 (0.994-1.022)	0.253
V_{15Gy}	1.008 (0.994-1.021)	0.265	1.010 (0.965-1.056)	0.679	1.008 (0.994-1.022)	0.272
V_{20Gy}	1.007 (0.993-1.020)	0.347	1.010 (0.966-1.057)	0.655	1.006 (0.992-1.021)	0.384
V_{25Gy}	1.007 (0.993-1.021)	0.304	1.011 (0.966-1.058)	0.643	1.007 (0.992-1.022)	0.362
V_{30Gy}	1.007 (0.993-1.021)	0.338	1.002 (0.958-1.049)	0.915	1.007 (0.992-1.022)	0.359
V_{35Gy}	1.008 (0.993-1.023)	0.296	0.995 (0.955-1.037)	0.800	1.009 (0.993-1.026)	0.275
V_{40Gy}	1.008 (0.993-1.024)	0.292	0.993 (0.952-1.036)	0.744	1.009 (0.993-1.026)	0.274
V_{45Gy}	1.006 (0.990-1.021)	0.467	0.984 (0.947-1.023)	0.424	1.009 (0.992-1.026)	0.322
V_{50Gy}	1.010 (0.991-1.030)	0.303	0.992 (0.948-1.039)	0.745	1.012 (0.988-1.037)	0.336
V_{55Gy}	-		1.008 (0.957-1.061)	0.772	-	
Small bowel						
V_{0Gy}	1.000 (0.998-1.002)	0.941	1.000 (0.997-1.003)	0.865	1.000 (0.997-1.003)	0.922
V_{5Gy}	1.000 (0.998-1.003)	0.883	1.000 (0.996-1.004)	0.911	1.001 (0.997-1.005)	0.642
V_{10Gy}	1.001 (0.998-1.003)	0.733	1.000 (0.995-1.005)	0.905	1.002 (0.997-1.006)	0.453
V_{15Gy}	1.001 (0.997-1.004)	0.715	0.999 (0.993-1.005)	0.775	1.002 (0.997-1.007)	0.384
V_{20Gy}	1.000 (0.996-1.004)	0.966	0.997 (0.989-1.005)	0.460	1.002 (0.997-1.007)	0.531
V_{25Gy}	0.999 (0.994-1.004)	0.746	0.996 (0.985-1.007)	0.440	1.001 (0.995-1.007)	0.829
V_{30Gy}	0.999 (0.992-1.007)	0.849	0.997 (0.982-1.011)	0.653	1.001 (0.992-1.009)	0.911
V_{35Gy}	0.997 (0.983-1.010)	0.626	0.998 (0.979-1.018)	0.851	0.995 (0.976-1.015)	0.652
V_{40Gy}	0.997 (0.978-1.016)	0.721	0.998 (0.974-1.023)	0.883	0.995 (0.963-1.027)	0.754
V_{45Gy}	0.994 (0.967-1.021)	0.662	0.999 (0.965-1.034)	0.949	0.988 (0.946-1.032)	0.595
V_{50Gy}	0.990 (0.948-1.034)	0.656	1.006 (0.957-1.059)	0.807	0.972 (0.897-1.053)	0.489
V_{55Gy}	-		1.007 (0.929-1.091)	0.865	-	

Table 9-13. Table of results of univariate logistic regression analysis of 'conventional' (ie cumulative absolute) DVH parameters against risk of clinically significant toxicity in the ARCII, SCALOP and combined cohorts.

For the stomach and duodenum, the dependent variable was the cumulative incidence of Grade 2-5 upper GI toxicity. For the small bowel, the dependent variable was the cumulative incidence of Grade 2-5 diarrhoea.

Reference	Cancer site	N	Concurrent Chemotherapy	RT Dose-Schedule	RT technique	Toxicity Outcome	Predictive dose-volume parameter and threshold values (with risk comparison) where reported
Murphy 2007 [87]	LAPC	74	Gemcitabine	36 Gy in 15 #	3D	Duodenal	Duodenum gEUD
Huang 2012 [88]	LAPC	46	Gemcitabine ± erlotinib	36 Gy in 15 #	3D (40)/ IMRT (6)	Grade ≥ 3 GI	All patients: Duodenum V_{25Gy} 45% (8% vs 48%) Non-erlotinib: Duodenum V_{35Gy} 20% (0% vs 41%)
Nakamura 2012 [83]	LAPC	40	Gemcitabine	54 Gy in 30 #	3D + IMRT boost	Acute GI & Upper GI Bleed	Stomach V_{50Gy} 16 cm^3 (9% vs 61%) Stomach D_{2cm^3} 53.6 Gy (0% vs 57%) StoDuo V_{50Gy} 33 cm^3 (0% vs 44%)
Kelly 2013 [89]	LAPC	106	Gemcitabine ± 5-FU/cape ± EGFRi	50.4 Gy in 28 #	3D (75)/ IMRT (31)	Grade ≥ 2 Duodenal	Duodenum V_{55Gy} 1 cm^3
Cattaneo 2013 [90]	LAPC	61	Capecitabine or 5-FU	44 ± 15 Gy boost, in 15 #	IMRT	Grade ≥ 2 GI	Stomach V_{20Gy} 31% Duodenum V_{40Gy} 16% Duodenum V_{45Gy} 2.6%
Kim 2009 [149]	HCC	73	None	36 Gy in 12 #	3D	Grade ≥ 3 gastroduodenal	Gastroduodenum V_{35Gy} 5% (4% vs 48%)
Yoon 2013 [153]	HCC	90	None	33 Gy in 11 #	3D	Grade ≥ 2 gastroduodenal	Stomach V_{25Gy} 6.3% (2.9% vs 57.1%) Duodenum V_{35Gy} 5.4% (9.4% vs 45.9%)
Pan 2003 [148]	Hepatic tumours	92	Hepatic arterial chemotherapy	1.5 Gy per # BD with chemo or 1.8 – 3 Gy per # QDS without	3D	Upper GI bleed	Stomach TD_{50} 62 Gy Duodenum TD_{50} 180 Gy
Feng 2012 [145]	Hepatic tumours	116	IV 5-FU or Hepatic FUDR	54 Gy in 28 # or 1.5 Gy per # BD regimen with FUDR	3D	Gastric bleeding	Stomach D_{max}
Juloori 2013 [147]	Oesophagus	286	NS	45–50.4 Gy in 25–28 #	3D / IMRT	Grade ≥ 2 acute anorexia	Stomach /fundus D_{mean}

Table 9-14. Findings of published analyses of the dose-volume relationships of GI organs at risk in pancreatic cancer radiotherapy, or of treatment of other conditions in which relationships with stomach DVH are identified. Risk comparison, where reported, indicates proportional incidence of specified toxicity for patients whose radiotherapy plans achieved or did not achieve the specified threshold value

(N = number of patients analysed; RT = radiotherapy; # = fractions; LAPC = locally advanced pancreatic cancer; Gy = Gray; 3D = 3-dimensional conformal radiotherapy; gEUD = generalised Equivalent Uniform Dose; IMRT= intensity modulated radiotherapy; 5-FU = 5-fluorouracil; cape = capecitabine; EGFRi = epithelial growth factor receptor inhibitor; HCC = hepato-cellular carcinoma; GI = gastrointestinal; StoDuo = combined stomach and duodenum volume; IV = Intravenous; Hepatic FUDR = intrahepatic infusion of 5-fluorodeoxyuridine; NS = not specified; D_{max} = maximum dose; D_{mean} = mean dose)

Appendix D – Supplementary tables and data for Chapter Seven

Inclusion criteria	Exclusion criteria
1. Borderline resectable localised tumour of the pancreatic head/uncinate process/body as per NCCN Guidelines (tumours of the tail of pancreas are not eligible for inclusion) or operable tumour in contact with vessels increasing the risk of positive margin as defined by CT ± MRI ± PET criteria within 28 ± 7 days prior to trial entry, de novo or following systemic treatment. 2. Histologically proven pancreatic ductal adenocarcinoma or cytological proven pancreatic malignancy 3. Able to undergo biliary drainage using a stent 4. Deemed fit and suitable for surgical resection. 5. No overt metastases or uncertain status with investigations suspicious of possible metastatic disease (eg small equivocal pulmonary nodule(s)). 6. Male or female, Age ≥16 years 7. Life expectancy of at least 6 months 8. ECOG performance status 0–1 9. The patient is willing and able to comply with the protocol for the duration of the study, and scheduled follow-up visits and examinations 10. Written (signed and dated) informed consent and be capable of co-operating with protocol 11. Haematological and biochemical indices within specified ranges.	1. Definitive metastatic disease or local disease that cannot be encompassed in the SBRT field. 2. History of previous or concurrent malignancy diagnoses for which the expected prognosis is likely to be worse than that of the current diagnosis of pancreatic cancer (excludes for example: eg localised prostate cancer, early colorectal cancer, early breast cancer, curatively-treated basal cell carcinoma of skin, carcinoma in situ of cervix; curatively treated cancer of other sites who are recurrence free for > 3 years). 3. Serious medical or psychological condition precluding trial intervention. 4. Previous upper abdominal or right chest wall radiotherapy where 30% of the liver has received > 15Gy. 5. Pregnancy: Pregnant or breast-feeding women are ineligible. Women of childbearing potential must use effective methods of contraception. 6. Any other psychological, social, or medical condition, physical examination finding or laboratory abnormality that the Investigator considers makes the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of the trial results.

Table 9-15. SPARC patient revised inclusion and exclusion criteria

Description		Optimal	Mandatory
PTV[@]	$D_{95\%}$[†]	≥ 95%	≥ 90%[‡]
PTV_M	$D_{95\%}$	≥ 95%	≥ 90%
	D_{max} (0.1 cc)	≤ 120%	≤ 130%
Combined Kidneys	Mean dose	< 10 Gy	-
If solitary kidney, or if one kidney mean > 10Gy	V_{10Gy}[#]	< 10%	< 45%
Liver	V_{10Gy}	< 70%	-
	Mean dose	< 15 Gy	< 15.5 Gy
Stomach	D_{max} (0.5 cc)	< 33 Gy	< 35 Gy
	D_{5cc}	< 25 Gy	-
	D_{10cc}	-	< 25 Gy
	D_{50cc}	< 12 Gy	-
Small bowel	D_{max} (0.5 cc)	< 30 Gy	< 35 Gy
	D_{5cc}	< 25 Gy	-
	D_{10cc}	-	< 25 Gy
Duodenum	D_{max} (0.5 cc)	-	< 35 Gy
	D_{1cc}	< 33 Gy	-
	D_{5cc}	< 25 Gy	-
	D_{9cc}	< 15 Gy	-
	D_{10cc}	-	< 25 Gy
Spinal Cord PRV	D_{max} (0.5 cc)	-	< 25 Gy
Large Bowel	D_{max} (0.5 cc)	< 32 Gy	-
Common Bile Duct	D_{max} (0.5 cc)	< 50 Gy	-

Table 9-16. Radiotherapy planning dose-volume constraints

Dose Limiting Toxicity (DLT)	1. Grade ≥ 3 upper GI bleeding 2. Grade ≥ 4 nausea/vomiting uncontrolled after 48 hours of standard treatment 3. Grade ≥ 4 pancreatitis not stent related 4. Interruption of SBRT > 1 week due to SBRT-related AEs 5. Grade ≥ 4 vascular events: SMV thrombosis, bowel ischaemia due to SMA arteritis/stenosis, friable vessels at surgery 6. Other AEs that the TMG agrees to be dose limiting and possibly related to SBRT such as Grade ≥ 3 GI fistula > 30 days after surgery
Adverse Event (AE)	Any unfavourable event or outcome that arises during or after a treatment intervention in a clinical trial.
Suspected Adverse Reaction (SAR)	An adverse event for which there is a reasonable probability that it was caused by the treatment being investigated.
Unexpected Adverse Reaction	An adverse reaction that is not thought to be part of the known toxicity events or risks associated with a treatment intervention.
Serious Adverse Event (SAE) or Reaction (SAR)	Adverse event or adverse reaction that is considered life-threatening, or results in death, admission to hospital or extension of a stay in hospital, or causes lasting or considerable disability or incapacity, or is a congenital anomaly or birth defect.

Table 9-17. Adverse events constituting a DLT, if observed during the DLT assessment period, graded according to CTCAE v4.03

Patient	SP-C1-102	SP-C1-104	SP-C2-106	SP-C2-108
Baseline CA19-9 [U/ml]	62214	54	119	457
Final CA19-9 [U/ml]	18749	10	40	82
Final time point [days]	38	198	192	175

Table 9-18. CA19-9 values for patients whose value fell at final recording relative to baseline.

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