Adaptive Image-guided Radiotherapy Strategies for Implementation of IMRT in Gynaecological Malignancies

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Abstract

Background

Intensity-modulated radiotherapy (IMRT) for gynaecological malignancies aims to reduce toxicity and improve tumour control. However, there are several barriers to its uptake in clinical practice. Amongst these are that of pelvic organ motion, whereby due to motion of the target organs on treatment there is a risk of geographical miss with IMRT. Secondly, although new IMRT techniques may improve bowel toxicity, there is limited knowledge about dose-volume constraints for bowel, making it difficult to assess whether new techniques are likely to translate into clinical improvements. The purpose of this thesis is to address these problems.

Methods

Dose-volume constraints for late bowel toxicity are investigated initially through systematic review, followed by a dose-volume study based on toxicity data from pelvic radiotherapy patients. Pelvic organ motion is assessed in a systematic review examining organ motion patterns and potential strategies to account for this. Population-based and adaptive margin strategies are investigated in modelling studies for both definitive cervical cancer patients and post-hysterectomy patients.

Results

Initial systematic review of the literature, followed by the analysis of the toxicity and dose-volume data of 203 pelvic radiotherapy patients highlighted anal canal, bowel loops, bowel bag, sigmoid and large bowel as important organs at risk (OARs) for bowel toxicity. Dose-volume constraints were derived for these organs.

Pelvic organ motion was found to be a significant problem for gynaecological IMRT. Adaptive margin strategies, such as plan-of-the-day, were demonstrated to achieve both CTV coverage whilst reducing dose to the OARs compared to standard margins and population-based margins.

Conclusions

Dose-volume constraints derived for late bowel toxicity, if validated with independent data, may be used to reduce bowel toxicity in future patients, and as a benchmark to assess the efficacy of new IMRT techniques. Adaptive strategies for gynaecological cancers appear a promising solution for organ motion management.

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Dedication

This thesis could not have been completed without the support, encouragement and patience of my loving husband Deepak and my beautiful children Anushka and Arun. This thesis is dedicated to them.

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Presentations and Publications arising from this Thesis

See Appendix C for copies of abstracts, paper and certificates

Papers

Jadon R, Pembroke CA, Hanna CL, Palaniappan N, Evans M, Cleves AE, Staffurth, JN. A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer. Clin Oncol (R Coll Radiol). 2014 Apr; 26(4):185-96.

Oral Presentations

Jadon R, Palaniapan, N, Hanna L, Hudson E, Tanguay J, Button M, Barber J, Lester J, Evans M, Spezi E, Staffurth J**.** Prospective Study of Patient-reported Late Bowel Toxicity following Pelvic Radiotherapy.
Presented at UKRO conference, Coventry June 9th 2015

This presentation won a "highly commended" award at UKRO

Poster Presentations

Jadon R, Spezi E, Hanna L, Palaniappan N, Evans M, Hudson E, Staffurth J "Plan of the Day is the optimal approach to address organ motion for cervical cancer IMRT".
Presented at ESTRO 35, 2016 (Turin, Italy)

Jadon R, Hanna CL, Palaniappan N, Hudson E, Evans M, Mazurek A, Maloney H. "The influence of bladder and rectal filling on ITV margins for post hysterectomy endometrial and cervical cancers". Presented at ASTRO 2013 (Atlanta, USA)

Jadon R, Pembroke CA, Hanna CL, Evans M, Palaniappan N, Cleves A, Staffurth J. "A Systematic Review of Organ Motion and Image Guided Radiotherapy for Cervical Cancer".

Presented at the Bristish Gynaecological Cancer Society Meeting, Belfast June 2013

Presented at NCRI conference, Liverpool November 2013

List of Abbreviations

3D-CRT	Three dimensional conformal radiotherapy
4DCT	Four dimensional computed tomography
5-FU	5-Fluorouracil
α/β	Alpha/beta
AP	Anterior-posterior
AUC	Area Under Curve
BED	Biologically Effective Dose
BMS	Bone-marrow sparing
CBCT	Cone Beam Computed Tomography
cbCTV	Clinical target volume delineated on cone beam CT
CC	Cervical cancer
cc	cubic centimetre
CI	Confidence Interval
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
CTVempty	Clinical Target Volume on empty bladder planning scan
CTVfull	Clinical Target Volume on full bladder planning scan
CTVmid	Clinical Target Volume formed by interpolation of CTVfull & CTVempty
CTVnodes	Nodal Clinical Target Volume
CTVprimary	Primary Clinical Target Volume
Dmax	Maximum Dose
Dmean	Mean dose
Dmedian	Median dose
Dmin	Minimum Dose
DSH	Dose surface histogram

DV	Dose-volume
DVH	Dose-volume histogram
Dx%	Dose to x%
EBRT	External Beam Radiotherapy
EC	Endometrial cancer
EORTC	European Organisation for Research and Treatment of Cancer
EPID	Electronic Portal Image Device
EQD2	Equivalent dose in 2Gy/fraction
ESTRO	European Society for Radiotherapy and Oncology
F/U	Follow-up
FACT-P	Functional Assessment of Cancer Therapy
FDG-PET	Fluorodeoxyglucose positron emission tomography
FIGO	International Federation of Gynaecology and Obstetrics
GI	Gastro-intestinal
Gr2	Grade 2
Gr3	Grade 3
GTV	Gross Tumour Volume
GU	Genito-urinary
Gy	Gray
HDR	High dose rate
HPV	Human Papilloma Virus
IBD-Q	Inflammatory Bowel Disease Questionnaire
ICRU	International Commission on Radiation Units
IGRT	Image-guided radiotherapy
IM	Internal Margin
IMRT	Intensity-Modulated Radiotherapy
ITV	Internal Target Volume
KV	Kilovoltage
LACC	Locally advanced cervical cancer

LDR	Low dose rate
LENT-SOMA	Late-Effects Normal Tissue-Subjective Objective Management Analytic
LKB	Lyman Kutcher Burman
LoP	Library of Plans
LR	Left-right
MLC	Multi-Leaf Collimator
MMC	Mitomycin C
MotD	Margin of the Day
MRI	Magnetic Resonance Imaging
MV	Megavoltage
MVA	Multivariate Analysis
MVCT	Megavoltage Computed Tomography
N/A	Not applicable
NR	Not reported
NS	Not stated
NTCP	Normal Tissue Complication Probability
OAR	Organ at risk
OMP	Oncentra MasterPlan
OR	Odds Ratio
PAN	Para-aortic nodes
pCTV	Clinical Target Volume outlined on planning CT
PO	Post-operative
PotD	Plan of the Day
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PRO	Patient-reported outcome
PTV	Planning target volume
QoL	Quality of Life
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic

R	Pearsons correlation coefficient
RDcoccyx	Rectal diameter at tip of coccyx
RDmax	Maximal rectal diameter at any point
RILIT	Radiotherapy Induced Late Intestinal Toxicity
ROC	Receiver Operator Characteristic
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SBDS	Small Bowel Displacement System
SBRT	Stereotactic Body Radiotherapy
SD	Standard Deviation
SI	Superior-inferior
SIB	Simultaneous Integrated Boost
SPSS	Statistical Package for the Social Sciences
TAHBSO	Total abdominal hysterectomy and bilateral salpingo oophorectomy
TD5/5	Dose leading to a 5% complication risk at 5 years
TD50/5	Dose leading to a 50% complication risk at 5 years
ToU	Tip of Uterus
UCLA	University California Los Angeles
UVA	Univariate Analysis
VBF	Variable Bladder Filling
VMAT	Volumetric Modulated Arc Therapy
VxGy	Volume receiving x amount of dose in Gray
WCC	White cell count
WCTU	Wales Cancer Trials Unit

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1. Chapter I: Introduction

1.1. Introduction to Gynaecological Malignancies

Gynaecological malignancies account for 19% of all malignancies worldwide (1) and include cancers of the cervix, endometrium, ovary, vulva and vagina. The work of this thesis focuses on cervical and endometrial cancers.

1.1.1. Cervical Cancer

Cervical cancer is the fourth most common cancer worldwide in women with an estimated 528,000 new cases being diagnosed in 2012. Globally it accounted for 266,000 deaths in 2012, 7.5% of all female cancer deaths (2). There is significant geographic variation in the incidence seen worldwide, with a higher incidence noted in developing countries.

In the UK, cervical cancer is the 12th most common cancer, with 3064 new cases diagnosed in 2011 (3). Approximately 920 women die from cervical cancer annually in the UK, with more than 50% of these women being between 25 and 64 years old.

Cervical cancer has two age peaks of presentation, the first being age 30-34 years (20 in 100,000), and the second at 80-84 years (13 in 100,000). The key risk factor for the development of cervical cancer is exposure to human papilloma virus (HPV), found in 99.7% of cases (4). In the UK, the incidence of cervical cancer has decreased in the last 4 decades due to the introduction of the cervical cancer screening programme in 1988, and a further decrease in incidence is predicted 15-20 years from now, due to the introduction of HPV vaccination in the UK in 2008. Over 90% of cervical cancers are squamous cell carcinomas, with 7-10% being classified as adenocarcinomas, and rarer histologies being small cell, basaloid, sarcoma, adenosquamous and verrucocus carcinomas (5).

1.1.2. The role of radiotherapy in cervical cancer management

Cervical cancer is staged using the International Federation of Gynaecology and Obstetrics (FIGO) classification (table 1.1-1), and management is dependent on stage as well as the patient's performance score and co-morbidities.

Early stage disease (stage 1A or IB1 disease) is predominantly managed surgically with radical hysterectomy; however, cone biopsy may be offered to patients with stage IA disease, and radical trachlectomy to those wishing to preserve fertility. Post-operative radiotherapy after radical hysterectomy is recommended where high-risk features, such as positive surgical resection margins, lymph node involvement, lymphovascular space invasion and microscopic parametrial involvement are present. Radiotherapy alone post-

hysterectomy improves local disease control (6), and the addition of chemotherapy has been demonstrated to improve both overall and progression-free survival (7).

Table 1.1-1: FIGO staging of cervical cancer

FIGO stage	Definition	5 yr survival (%) [8]
IA1	Microscopic disease, stromal invasion≤3mm in depth and ≤7mm in horizontal spread	97.5
IA2	Microscopic disease, stromal invasion>3mm and <5mm in depth and >7mm in horizontal spread	94.8
IB1	Clinically visible lesion <4cm	89.1
IB2	Clinically visible lesion >4cm	75.7
IIA	Tumour without parametrial invasion or involvement of the lower third of vagina	73.4
IIB	Tumour with parametrial invasion	65.8
IIIA	Tumour involves lower third of vagina (no pelvic side wall invasion)	39.7
IIIB	Tumour extends to the pelvic wall and/or causes hydronephrosis or non-functionitng kidney	41.5
IVA	Tumour invades mucosa of bladder or rectum &/or extends beyond true pelvis	22.0
IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal or paraaortic lymph nodes, lung, liver or bone)	9.3

For stage IB2 to IVA disease, defined as 'locally advanced' disease, the mainstay of treatment is chemo-radiotherapy followed by intra-cavitary brachytherapy. Surgery alone is likely to leave residual disease, mandating the need for adjuvant radiotherapy. Together these modalities are considered to have an increased risk of toxicity compared to chemo-radiotherapy alone, with equivalent survival outcomes (9), hence surgery is not advocated for locally advanced disease.

The addition of concurrent chemotherapy adds a 6-10% survival advantage to radiotherapy alone and has become an international standard (10). Intra-cavitary brachytherapy after chemo-radiation has also been shown to improve survival outcomes (11) and has become an essential component of the treatment paradigm for locally advanced cervical cancer.

For those patients with stage IVB (metastatic) disease, the aim of treatment is symptom control and this may be in the form of radiotherapy, chemotherapy and/or palliative care.

Radiotherapy therefore forms a vital component of cervical cancer management, being used as a treatment modality in radical, adjuvant and palliative settings. It is indicated for 60% of cervical cancer patients (12), and advances in radiotherapy may therefore have a significant impact on outcomes for these patients.

1.1.3. Endometrial Cancer

Endometrial cancer is the sixth most common female cancer worldwide, with 320,000 new diagnoses made worldwide in 2012 (13). In the UK, it is the fourth most common cancer, with 8,500 new cases diagnosed annually and a 5-year survival of 80% (14).

Endometrial cancer occurs mainly in post-menopausal women (in 75% of cases). The main risk factors include excessive oestrogen exposure, which may arise endogenously through obesity, or exogenously with the use of hormone replacement therapy with oestrogens alone. Endometrioid carcinoma is the most common histological subtype, followed by serous and clear cell carcinomas. Endometrial cancer is also staged using FIGO staging (table 1.1-2).

Table 1.1-2: FIGO staging of endometrial cancer

FIGO stage	Definition	5 yr survival (%)[15]
IA	Tumour limited to endometrium or invades less than one-half of the myometrium	90
IB	Tumour invades one-half or more of the myometrium	78
II	Tumour invades stromal connective tissue of the cervix but does not extend beyond the uterus	74
IIIA	Tumour involves serosa and/or adnexa (direct extension or metastasis)	56
IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement	36
IIIC1	Pelvic node involvement	57
IIIC2	Para-aortic node involvement	49
IVA	Tumour invades bladder mucosa and/or bowel mucosa	22
IVB	Distant metastasis (includes metastasis to inguinal nodes, intraperitoneal disease, or lung, liver or bone.	21

1.1.4. The Role of Radiotherapy in Endometrial Cancer Management

Management of endometrial cancer is determined by both staging and other pathological findings, which categorise women into low, intermediate or high-risk groups. The majority of women present with post-menopausal vaginal bleeding and are managed surgically with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO). Adjuvant treatment may include radiotherapy, chemotherapy or a combination of both.

The management pathways are illustrated in figure 1.1-1. For low and low-intermediate risk disease no adjuvant treatment is required post-hysterectomy.

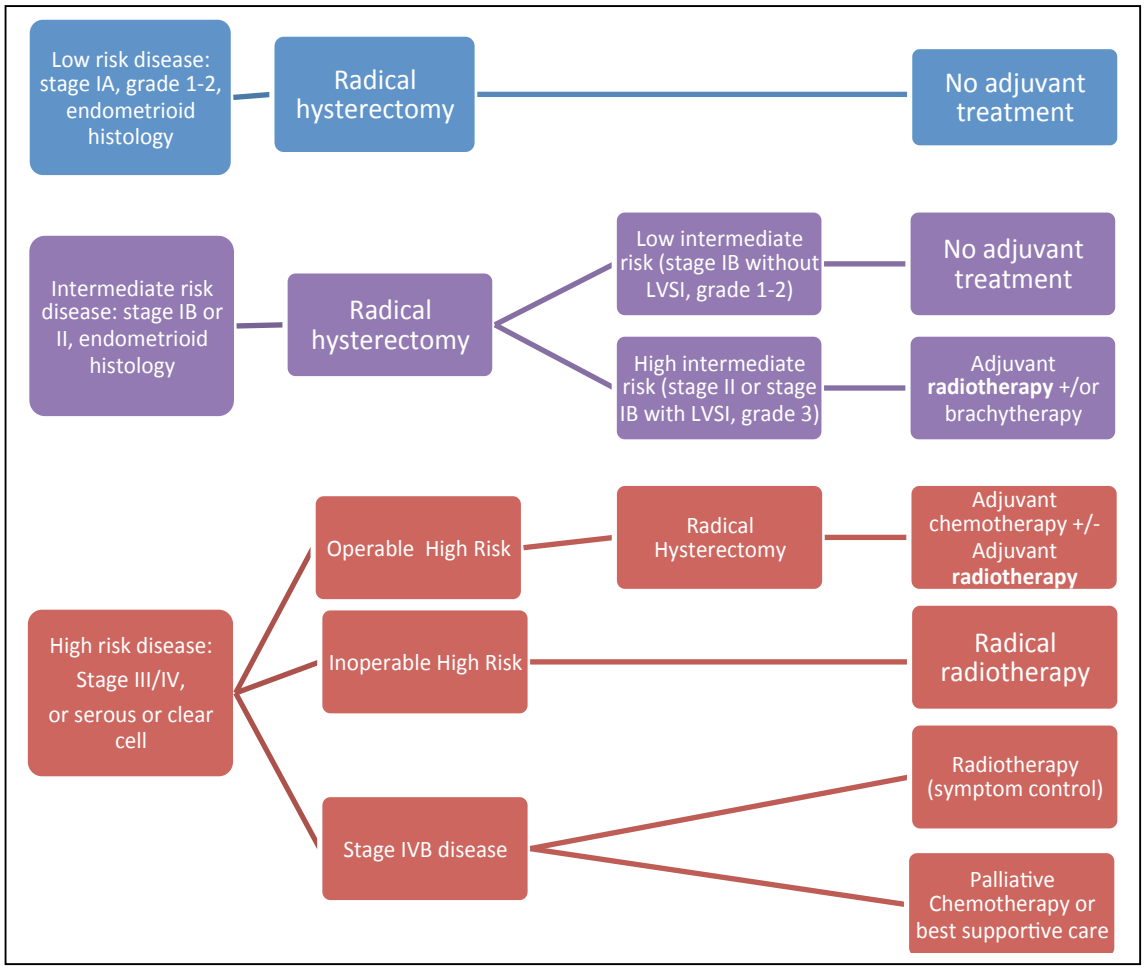


Figure 1.1-1: Overview of Endometrial Cancer Management

In patients with high-intermediate risk disease, adjuvant radiotherapy is recommended. This improves local control rates, although has no impact on overall survival (16). Intra-vaginal brachytherapy may be used alternatively with comparable outcomes (17).

There is no uniform management paradigm for Stage III/IV disease. If operable, then TAHBSO will usually be undertaken, with adjuvant chemotherapy recommended post-operatively (18). Adjuvant radiotherapy may be given, although no survival advantage has been determined.

For inoperable stage III disease, primary radical radiotherapy (with or without concurrent chemotherapy) can be considered, with survival rates of 49% at 5 years (19). The combination of external beam radiotherapy with low-dose rate (LDR) or high-dose rate (HDR) brachytherapy has also been considered (20).

For patients with stage IV disease, treatment is palliative and may be in the form of chemotherapy, radiotherapy (for symptom control) and/or palliative care.

As with cervical cancer, radiotherapy forms a key therapeutic component in managing endometrial cancers, and is indicated in up to 45% of patients (21). Advances in radiotherapy could therefore impact the outcomes of affected patients.

1.2. Limitations of current radiotherapy treatment: treatment failure

Despite the development of agreed treatment pathways and improved outcomes for patients with cervical and endometrial cancer over the last 30-40 years, improvements have been somewhat static in the last decade.

1.2.1. Survival Data

Worldwide, 5-year survival data for cervical cancer patients treated with radical radiotherapy (with or without chemotherapy) ranges from 68.3% to 19.2% (stages 1B2-IVA) (8). From national UK data, the use of chemo-radiotherapy results in overall 5-year survival of 65% for stage IB through to 44% for stage IIIB disease (22).

For endometrial cancer, early stage disease generally has a good prognosis (80-90% 5-year survival) (table 1.1-2), but for patients with stage III and IV disease, survival rates drop significantly, with estimates of 57% and 19% 5-year survival respectively (15).

1.2.2. Recurrences

Cervical and endometrial cancers recurrences occur locally (at the vaginal apex), regionally (within the pelvis), or distantly. Twenty-two per cent of patients treated with chemo-radiotherapy for cervical cancer develop local/regional recurrence and 27% develop distant metastases (22); 69-89% of recurrences occur within the first 2 years of completing treatment (23). The most common sites of distant metastases are the para-aortic lymph nodes (81%), lungs (21%) and supraclavicular nodes (7%) (24).

After radical treatment for endometrial cancer, recurrences occur in 2-15% of early stage disease (25), and in 50% of patients with advanced disease or non-endometrioid histologies (16, 26). Data from the PORTEC-1 trial found that although vaginal recurrences were low (2%) after adjuvant radiotherapy, those who did recur within the radiotherapy field had a lower overall survival rate (43% compared with 65% 5-year survival) (27).

Recurrences after radiotherapy frequently occur within the previously treated radiation field (in-field recurrence) or just beyond (marginal recurrence). In a study of 198 cervical cancer

patients who had a regional recurrence after definitive radiotherapy, 58% had a component of in-field recurrence, and 66% had a component of marginal recurrence (28). Marginal recurrences mainly occurred above the upper border of the treatment field (L4/5 vertebral body) in this study. A further study examining recurrences after chemo-radiotherapy found 55% occurred between L4/5 and the aortic bifurcation, and 45% in the para-aortic region (29).

For patients with a regional recurrence in a previously irradiated field, unless confined to the vaginal apex, the only established curative option is pelvic exenteration surgery. This is a highly radical surgery with significant physical and psychological consequences for patients. Long-term morbidity rates of 48% are reported (30), and older patients are often precluded from this procedure due to co-morbidity.

For distant recurrences, the treatment aim is palliative and chemotherapy may be an option. Recurrence within a previously irradiated site has been reported as a poor predictor of response to palliative chemotherapy, with a 5.3% response compared with 25.2% outside of the radiation field, and subsequent poorer survival (31). Those who had chemo-radiation as primary treatment show a poorer response to chemotherapy after recurrence (32).

This data highlights the importance of optimising radiotherapy for both cervical and endometrial cancers. Given the in-field and marginal recurrences demonstrated after radical radiotherapy, it is possible that dose escalation or volume extension might improve outcomes.

1.3. Limitations of current radiotherapy treatment: late toxicity

The other significant limitation of current gynaecological radiotherapy treatment is late toxicity. Toxicity occurs after pelvic radiotherapy due to radiation being delivered to the organs at risk (OARs), which surround the target organs, such as bowel, rectum, bladder, bone as well as reproductive organs.

Most patients experience acute toxicities during radiotherapy, which resolve within the first three months after treatment. A substantial number of patients also suffer late toxicity, which can be long-term or even permanent. The spectrum of late toxicity seen is common to other malignancies treated within the pelvis, including prostate, bladder, rectal and anal cancer.

1.3.1. Late bowel toxicity

The most common toxicity seen after pelvic radiation is bowel toxicity. Acute radiotherapy reactions are thought to occur due to an inflammatory reaction involving the mucosa, and then submucosa. Following this either mucosal repair can occur, whereby the patient recovers, or there is a severe inflammatory process which produces fibrosis (33). This fibrosis is further perpetuated by a cytokine cascade, which manifests as late toxicity.
A wide range of symptoms can occur under the umbrella of late toxicity, including diarrhoea, rectal bleeding, constipation, faecal incontinence, flatulence, mucus, pain, tenesmus and urgency (33). Severe (grade 3-4) toxicity can present as bowel obstruction, malabsorption, fistulae (recto-vaginal, vesicovaginal), which can require surgical intervention and may be life-threatening.

The incidence of late bowel toxicity described in the literature varies significantly depending on the source of the data. Clinical trial data report severe late bowel toxicity rates of 6-23% in gynaecological studies (34), 1.9% in bladder cancer studies (35) and 1% in prostate cancer studies involving pelvic radiotherapy (36).

Most clinical trials report late toxicity with the use of clinician-reported scores such as Radiation Therapy Oncology Group (RTOG) (37) or Common Terminology Criteria for Adverse Events (CTCAE) scores (38). The RTOG score has been used traditionally for two decades when reporting toxicity, although in the context of bowel toxicity includes only a small number of symptoms (rectal bleeding, cramp, diarrhoea and proctitis), and does not cover the entire spectrum of late toxicity symptoms. CTCAE scoring has been used more recently and is considered to be the ‘gold standard’ of reporting. It is more comprehensive than the RTOG score, however used in its entirety may be cumbersome with over 40 symptoms within the GI toxicity section. Often only grade 3 toxicity is reported, where lower grades may also be important. Currently CTCAE version 4.0 is used internationally.

It is now appreciated that although the clinician-reported scores are helpful in objectively determining serious or life-threatening toxicity, they can underestimate the extent of the problem from a patient’s perspective. Patient-reported outcome (PRO) questionnaires are therefore being used, such as the patient questionnaire from the Late-Effects Normal Tissue-Subjective Objective Management Analytic (LENT-SOMA) score (39), and other

questionnaires originally developed in gastroenterology such as the inflammatory bowel disease questionnaire (IBD-Q) (40).

In cervical cancer survivors a comparison of clinician-reported (RTOG) and patient-reported (subjective LENT-SOMA) scoring found that severe bowel toxicity (grade 3-4) was 45% with patient-reporting though only 15% with clinician-reporting in the same patients (41).

Patient-reported toxicity studies for gynaecological cancer patients have shown high rates of faecal urgency (79%), and faecal incontinence (24%) reported at 1-year post radiotherapy. At 3-years the most common symptoms experienced were urgency (33%), defecation pain (13%), diarrhoea 2-4 times a day (10%), and weekly faecal incontinence (7%) (42).

1.3.2. Late genitourinary, sexual and bone toxicity

Survivors of pelvic malignancies may also experience late genitourinary (GU) toxicity. It is hypothesised that this is due damage to vascular endothelial cells within the bladder (43).

After definitive radiotherapy for cervical cancer late GU toxicity, defined in one study as frequency, urgency and incontinence, has a reported incidence of 26% (44), with rates of 11-16% reported in the post-operative setting (16). More severe late complications such as haemorrhagic cystitis, urethral strictures and fistulae occur less commonly, in 1.3% of patients. Studies of patient-reported late urinary toxicity have found higher toxicity rates overall, with urinary urgency and incontinence reported in 27% and 45% respectively, 3 years after treatment (42).

Sexual and reproductive toxicity is also an important concern for survivors of pelvic radiotherapy. In pre-menopausal women pelvic radiation can cause ovarian failure. This not only impacts fertility, but also can increase the risk of cardiovascular disease and osteoporosis. Following pelvic radiotherapy female patients often experience vaginal stenosis (particularly after brachytherapy), vaginal dryness and dyspareunia.

In men, pelvic radiation can result in erectile dysfunction in up to 77% of cases. Both men and women report that treatment has an effect on their ability to have a sexual relationship in 23.8% (women) and 53.3% (men) (45).

Pelvic radiotherapy also has a late effect on pelvic bones: 9.7% of women who have radiotherapy for gynaecological cancers have reports of pelvic fractures within two years, the most common sites being the sacrum, pubis, iliac crest and acetabulum. Almost half of these patients present with bone pain (46).

1.3.3. Impact of late toxicity on quality of life

These late complications can have a serious impact of quality of life for survivors of pelvic malignancies. Retrospective studies reveal that 90% of patients report a permanent alteration in their bowel habit, with 50% reporting that this affects their quality of life, and 20-30% stating the effect on quality of life is moderate or severe. The most common bowel symptoms to affect quality of life are faecal incontinence (25-89%), defaecation urgency (14-79%), diarrhoea (25-67%), change in bowel habit (16-79%), pain (10-77%) and rectal bleeding (10-31%) (33).

Questionnaires examining which pelvic radiation symptoms cause most “distress” have found that “much distress” is caused by dyspareunia (24%), reduced orgasm (23%), bowel urgency (22%) and loose stool (19%) (47).

Pelvic radiation has also been shown to have an impact more globally on quality of life. For example in endometrial cancer patients, as well as higher rates of urinary incontinence, diarrhoea, and faecal leakage, radiation was associated with lower “physical functioning” and “role function” scores 13 years after radiotherapy in the PORTEC-1 trial (48).

1.4. Advances in radiotherapy treatment

The two issues described above of treatment failure and late toxicity highlight the need for improved pelvic radiotherapy treatments. Improvements that reduce the volume of normal tissues irradiated to critical levels may both improve toxicity and quality of life. Furthermore they may allow safe dose or volume escalation, hopefully improving tumour control and survival.

The last 20 years have seen the development of radiotherapy techniques with the aim of improving patient outcomes. Radiotherapy evolved from using conventional techniques, to conformal radiotherapy in the 1990s, and more recently to using intensity modulated radiotherapy (IMRT) techniques.

1.4.1. Conventional radiotherapy and 3D-Conformal radiotherapy

Conventional radiotherapy, which was used for several decades, is generally delivered with 2-dimensional beams. There was little anatomical basis for treatment planning, with a conventional simulator used to determine bony landmarks. The pelvis was often treated with large anterior and posterior beams, which although covering the tumour would also be treating large amounts of OARs.

3D-Conformal radiotherapy (3DCRT), which came into widespread use in the 1990s, aims to conform radiation delivery to tissues as accurately as possible. With the use of 3D planning CT scans target volumes are delineated by the clinician. International Commission on Radiation Units (ICRU) defined the volumes that are to be delineated as: gross tumour volume (GTV), representing gross disease; clinical target volume (CTV), to include microscopic disease; and planning target volume (PTV) to account for geometric errors (49). Radiotherapy planning of 3DCRT generally uses 'forward planning' techniques, a trial and error process, in which the planner decides initial beam parameters (such as number of beams, angle and energy), and then modifies these parameters to achieve acceptable clinical solutions. Multi-leaf collimators (MLCs) can be used to shape the beams to improve precision.

3DCRT in the pelvis traditionally uses 3 (posterior and two lateral) or 4 (anterior, posterior and two lateral) beams (illustrated in figure 1.4-1). This can deliver satisfactory coverage of the target volumes; though can still include significant volumes of the surrounding rectum, bladder and bowel.

1.4.2. Intensity modulated radiotherapy

Intensity modulated radiotherapy (IMRT) is a highly conformal type of radiotherapy which uses multiple beamlets to conform dose to the target volume or tumour. This is illustrated in figure 1.4-1. Although target volumes (GTV, CTV and PTV) are defined in the same way as 3DCRT, the planning process differs, and is known as 'inverse planning'. For inverse planning, specified dosimetric requirements for target volume coverage and OAR sparing are prioritised prior to planning. In the planning process ('optimisation') the treatment planning software performs multiple computer iterations until a mathematical solution is found which satisfies the specified requirements.

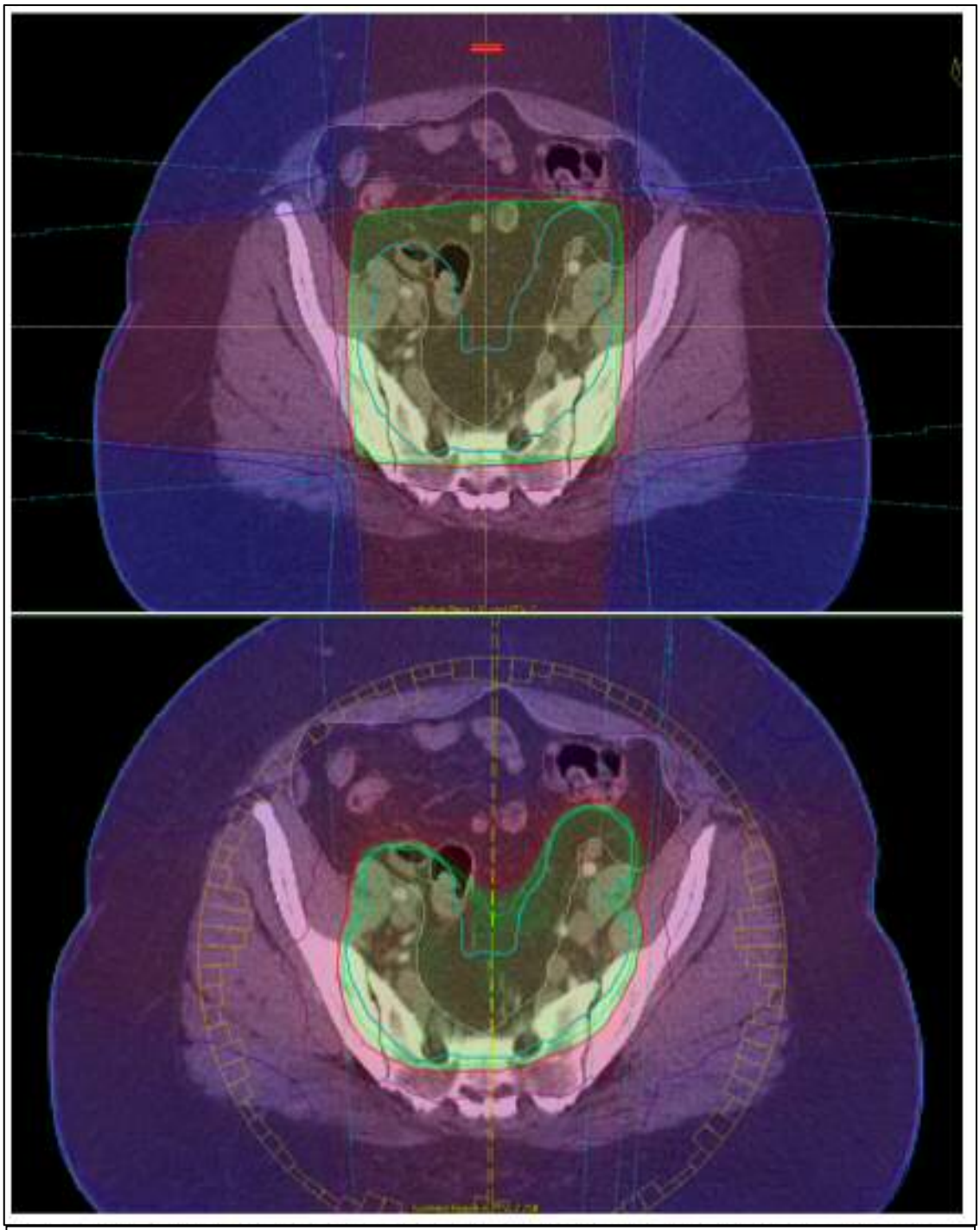


Figure 1.4-1: The first image shows a 3D-CRT pelvic plan with 4-field brick. The second image is a volumetric arc therapy (VMAT) plan. The PTV is in blue and 95% isodose in green. Increased conformality with VMAT is noted

Figure 1.4-1: 3DCRT and VMAT pelvic plans

Rather than using beams of uniform intensity as with 3DCRT, IMRT uses multiple beamlets of non-uniform intensity. When individual contributions from each beamlet are

combined, a complex ‘dose cloud’ is generated with steep dose gradients around the PTV. The result is a highly conformal treatment to the PTV, and minimisation of dose to OARs potentially resulting in reduced toxicity for patients.
IMRT may also allow dose escalation to the tumour, often with simultaneous delivery of different dose levels to different targets, known as simultaneous integrated boost (SIB) technique, with the potential of improving tumour control.

IMRT can be delivered by three main methods: step and shoot IMRT, dynamic arc therapy or tomotherapy. The step-and-shoot technique involves moving the leaves of the MLC only when the radiation beam is turned off, and they remain in their predefined positions while the required radiation is being delivered. In contrast, dynamic arc treatments (such as volumetric arc therapy (VMAT)) involve the MLCs moving continuously shaping the beam while the radiation is being delivered (figure 1.4-1). In tomotherapy, treatment is delivered with a narrow beam from a rotating gantry, which continuously revolves around the patient as the patient moves through the bore.

IMRT successes
IMRT, regardless of treatment delivery method, has been demonstrated to be successful in many clinical scenarios. In head and neck radiotherapy, IMRT can allow sparing of OARs such as the parotid gland, brainstem and spinal cord and there is randomised trial evidence demonstrating that IMRT can reduce late toxicity in patients (50, 51). IMRT is now the standard of care for head and neck cancer patients.
There has also been a widespread uptake of IMRT in prostate cancer, replacing conformal techniques. Although no randomised trials were performed, there were large comparative studies demonstrating significant reductions in acute and late GI and GU toxicity (52). As a result in 2014 78% of UK centres were treating more than 80% of their prostate cancer patients with IMRT (53). Furthermore dose escalation with the use of IMRT has been made possible.

Limitations of IMRT
IMRT does however have some limitations, dosimetrically, practically and in terms of resources or ‘cost’.
With the steep dose gradient produced by IMRT planning, there is little margin for error in terms of anatomical change. The success of IMRT is dependent on the position of the tumour (and OARs) at planning being comparable to the position for the entirety of the course of a treatment. This can be unrealistic, as inter- and intra-fractional motion of organs is likely, tumours may shrink during the course of treatment changing the anatomy,

and patients may lose weight during the course of treatment, changing their anatomy from the time of planning. These changes may lead to OAR overdosage and/or target underdosage.

IMRT generally uses an increased number of beams compared to 3DCRT, and arc therapy delivers radiation from multiple directions in a continuous beam. Although high dose is concentrated to the tumour, IMRT and arc therapy result in a 'low dose bath' whereby a much higher volume of normal tissue is treated to a low dose. Although this may not result in measurable increases in toxicity, it may theoretically lead to an increased risk of radiation-induced secondary malignancies. Predictive studies have suggested due to the increased number of monitor units the risk of secondary cancers compared with conventional radiotherapy is increased from 1% to 1.75% for patients surviving 10 years (54), although there is no clinical evidence for this as yet.

In practical terms, IMRT techniques impact on resources at all stages of treatment planning. Although the same target volumes (GTV, CTV and PTV) are outlined, more precision is required to ensure accurate delineation. This may necessitate the use of additional radiological modalities such as fluoroxydeoxyglucose positron emission tomography (FDG-PET) scans.

IMRT treatment planning, especially in the implementation stages is time consuming, with more time per patient required than a simple 3DCRT plan. In the case of squamous cell cervical cancer, a relatively fast growing tumour (category I), where timing of the radiotherapy has an important influence on outcome, it would be crucial to commence treatment in a timely fashion.

Whilst having treatment with radiotherapy, patients need to be positioned with a high degree of accuracy every day to ensure precise dose delivery, and additional on-treatment imaging may be required to verify patient and target position when IMRT is used. All these components add to the overall 'cost' of the treatment, which has limited the use of IMRT in some centres.

Cost-effectiveness is also an important consideration and there must be clear evidence of clinical benefit to patients to balance the costs. In the case of prostate cancer, this is deemed to be cost-effective. Reports from USA suggest that prostate IMRT costs $47,931 compared with 3D-CRT costing $21,865. These costs are justified on the assumptions of IMRT resulting in improved biochemical disease-free survival and reduced late toxicity (55).

1.5. The evidence for IMRT in Gynaecological cancers

With the success of IMRT demonstrated in other tumour sites, the benefits in gynaecological cancers have also been investigated.

1.5.1. Dosimetric Evidence for IMRT use

In the last decade, studies comparing IMRT with 3DRCT have demonstrated IMRT to be dosimetrically advantageous. Initial planning studies by Roeske *et al* and Heron *et al* (56-58), looking mostly at post-hysterectomy patients found that IMRT plans reduced dose to small bowel, bladder and rectum compared with 3DCRT. Roeske *et al* found that the small bowel, rectum and bladder volumes receiving 100% dose (V100%) were reduced by 50%, 23% and 23% respectively (57).

Furthermore, bone marrow of the pelvis can be relatively spared by IMRT. Much of the bone marrow reserve of the body lies in the lumbo-sacral spine and pelvic girdle. Bone-marrow sparing IMRT (BMS-IMRT), where bone marrow constraints are used, is shown to reduce the volume of bone marrow irradiated to >50% dose from 87.4% to 60%, whilst maintaining the benefits of sparing dose to bowel, rectum and bladder (59, 60).

A systematic review and meta-analysis including 13 dosimetric studies (61), pooling data from 455 gynaecological patients, concluded that IMRT significantly reduced the average percentage volumes of rectum and small bowel irradiated, although the reductions to bladder or bone marrow were not statistically significant.

Chan *et al* (62) investigated the use of IMRT for an external beam boost of 20-30Gy in the scenario of patients being unable to have intracavitary brachytherapy, either due to medical reasons or location of the tumour. Compared with 3DCRT, IMRT improved rectal and bladder dose distributions.

1.5.2. Clinical evidence for IMRT use in gynaecological cancer

Following the dosimetric studies, evidence for the clinical benefits of gynaecological IMRT have been published. The key studies are summarized in table 1.5-1, with prospective studies detailed first.

Table 1.5-1: Evidence for Gynaecological IMRT

Author	Type of study	Pt no	Clinical scenario	Techniques Compared	Dose	Acute toxicity	Late Toxicity
Gandhi, 2007 (63)	Prospective randomized study	44	LACC	IMRT vs 3DCRT	50.4Gy /28#	Gr 2 GI 31.8% IMRT; 63.6% CRT Gr 3 GI 4.5% IMRT; 27.3% CRT	Gr 2 GI 4.5% IMRT; 13.6% CRT Gr 3 GI 0% IMRT; 9.1% CRT (med F/U 21 months)
Kidd, 2010 (64)	Prospective study	452 (135 IMRT)	LACC	IMRT vs 3DCRT	50Gy	NR	Gr 3 6% IMRT; 17% CRT (med F/U 22 months)
Jhingran, 2013 (65)	Prospective Phase II multi-centre study	43	PO EC	IMRT (no comparison)	50.4Gy/ 28#	Gr 2 GI 21%; Gr3 GI 7%	NR
Mundt, 2002 (66)	Retrospective cohort	75 (40 IMRT)	Mixed CC+ EC	IMRT (vs 3DCRT retrospective cohort)	45Gy /25#	Gr 2 GI 53.4% IMRT; 96% 3DCRT	NR
Mundt, 2003 (67)	Retrospective cohort	66 (36 IMRT)	Mixed CC+ EC	IMRT (vs retrospective 3DCRT cohort)	45Gy /25#	NR	Gr 2 GI 2.8% IMRT; 16.7% CRT Gr 3 GI 0% IMRT; 3.3% CRT (med F/U 20 months)
Hasselle, 2011 (68)	Retrospective	111	Mixed CC+ EC	IMRT (no comparison)	45Gy /25#	Gr3 GI 2%	Gr3 GI 3.6%; Gr 3 GU 4.5% (med F/U 26mnths)
Beriwal, 2006 (69)	Retrospective	47	PO EC	IMRT (no comparison)	45-50.4Gy	Gr2 GI 72% Gr3 GI 0%	Gr 2 GI 0% Gr3 GI 2% (med F/U 20 months)
Shih, 2013 (70)	Retrospective	46	PO EC	IMRT (no comparison)	50.4Gy/ 28#	Gr 2 GI 11% Gr 3 GI 2%	Gr 2 GI 0% Gr3 GI 2% (med F/U 52 months)
Brixey, 2002 (71)	Retrospective cohort	124 (36 IMRT)	Mixed EC + CC	IMRT vs 3DCRT	45Gy/ 25#	Gr2+ WCC 31.2% IMRT; 60% 3DCRT	NR
Chen, 2011 (72)	Retrospective	109	LACC	IMRT (no comparison)		Gr 3 GI: 2.7% Gr 3 HM: 23.9%	Gr 3 GI 4.6%; Gr 3 GU 6.4% (med f/U 32 months)

Abbreviations: CC= cervical cancer; EC= endometrial cancer; LACC=Locally advanced cervical cancer; PO EC=Post-operative endometrial cancer; Gr2=grade 2; Gr3=grade 3; GI= gastrointestinal; GU=genitourinary; WCC=white cell count; HM=haematological.

1.5.2.1. Randomised evidence

Only one randomised study (63) comparing IMRT with 3DCRT is published which included 44 stage IIB-IIIB squamous cell cervical cancer patients. Significant improvements were seen in both acute and late GI toxicity, with late GI toxicity rates being 13.6% in the IMRT arm and 50% in the 3DCRT arm. No significant differences were seen in survival outcomes. Further clinical trials are in progress to gather randomised evidence for the use of IMRT for gynaecological malignancies, with 3 endometrial cancer phase III trials, and 1 cervical cancer phase III trial currently recruiting patients (74).

1.5.2.2. Non-randomised evidence

The majority of clinical evidence for IMRT use for endometrial and cervical cancer is based on single centre retrospective studies, with or without comparison with historical cohorts, rather than prospective or randomised evidence.

The first reports for clinical benefit of IMRT were provided by Mundt *et al* (67, 75) in a mixed groups of cervical and endometrial cancer patients. Compared with retrospective cohorts of 3DCRT-treated patients, improvements in both acute and late toxicity outcomes with IMRT were reported.

1.5.2.2.1. Post-operative cervical and endometrial studies

Particular to the post-operative setting Jhingran *et al* (65) report data from a phase II study (RTOG 0418) of post-operative endometrial cancer patients. As well as toxicity outcomes (table 1.5-1), they aimed to assess whether pelvic IMRT was feasible across multiple institutions with the use of a detailed protocol and quality assurance. They found that IMRT was feasible across 25 centres with a consensus protocol and centralised quality assurance. They reported an overall survival of 92% at 3 years, and acute GI toxicity of grade≥2 as 28%. A subset analysis of haematological toxicity (76) reported low toxicity rates overall, and high compliance with dose intensity for weekly cisplatin, despite not specifically planning to bone marrow constraints. Details of other post-operative studies are detailed in table 1.5-1 (69, 71, 77).

1.5.2.2.2. Radical chemo-radiotherapy studies

Only three studies focused purely on chemo-radiotherapy for locally advanced cervical cancer (63, 64, 72). Kidd *et al.* (64), in their relatively large prospective series of 452 patients, compared outcomes for 135 FDG-PET-guided IMRT with 317 non-IMRT patient treated for locally advanced cervical cancer. Grade 3 late toxicity was improved in the IMRT group (6% vs 17%). Unexpectedly the IMRT group showed better overall cause specific survival and overall survival compared with the 3DCRT cohort, although follow up was much shorter in the IMRT group. The authors comment that they are unsure if this

was due to difference in radiotherapy treatment alone, and may be due to the slightly higher percentages of patients in the IMRT group that had no lymph nodes involvement or received concurrent chemotherapy.

1.5.3. Extended field studies

As well as for post-operative and radical treatments, IMRT may have potential application for extended-field radiotherapy to include the para-aortic nodes (PAN). Treatment of PAN usually involves treating the pelvic nodal chain higher in the abdomen, with an upper border of T12/L1 used. Treatment is typically with a conformal anterior-posterior field arrangement. This is potentially disadvantageous as significant dose is likely to be received by kidneys and small bowel.

In cervical cancer, macroscopic involvement of PAN is associated with poor prognosis. The GOG-116 study (78) found in these patients with PAN conformal treatment of 45Gy, a 3 year overall survival rates of 39%. However grade 3 late toxicity rates of 19% were reported. A more recent study investigating optimal dose to the PAN using PET scanning to assess response suggested that a minimum total dose of 54Gy is recommended for involved PAN (79). With the use of conformal radiotherapy this is likely to further increase toxicity.

Prophylactic PAN irradiation has a potential benefit in patients without gross PAN disease with a high risk of microscopic PAN involvement. Patients with stage III disease have a 25% risk (80) and positive pelvic node patients have a 50% risk of microscopic PAN disease (81). Early studies (82) have shown that prophylactic extended field irradiation in such high-risk patients can improve survival. This however was prior to the adoption of chemoradiotherapy, so the question of whether prophylactic irradiation is necessary with modern chemoradiotherapy is unanswered. Given the rates of toxicity involved with extended field conformal radiotherapy few centres would advocate this treatment prophylactically.

IMRT techniques may be a solution in this scenario, and a few studies have examined this. A dosimetric planning study for extended field radiotherapy demonstrated that IMRT significantly reduced volume receiving 45Gy (V45) of the small bowel, rectum and bladder compared with 3DCRT (83).

Du *et al* (2010) (84) in their study of 60 patients with positive PAN, after neoadjuvant chemotherapy, randomised patients into IMRT or 3DCRT groups. With IMRT a median

dose of 63.5Gy was delivered, with 3DCRT the dose was 45-50Gy. 3-year survival was higher in the IMRT group (36.4% vs 15.6%) and acute grade 3-4 toxicity was 3.6% in the IMRT group, compared with 19% in the 3DCRT group. Other smaller studies looking at extended field IMRT have found tolerable toxicity levels with IMRT (85, 86) and low in-field recurrence rates.

1.5.4. Dose-escalation studies

Dose escalation is one of the prime aims of IMRT techniques, with the basis that most radiosensitive tumours, including cervical cancer, have a dose-response relationship. In prostate cancer, for example, dose escalation with modern radiotherapy techniques has been proven to be feasible and improve disease outcomes such as progression-free survival (87).

In gynaecological malignancies, standard external beam doses include 45Gy in 25 fractions, or 50.4Gy in 28 fractions. These doses tend not to be escalated with 3DCRT due to the risk of bowel toxicity. Rather than external beam treatment much investigation has gone into dose escalation to the primary tumour with intracavitary brachytherapy, and many centres now use higher doses of HDR brachytherapy. This reduces the risk of local recurrence, but does not benefit pelvic or para-aortic nodal relapse. Brachytherapy cannot always deliver dose to bulky tumours or parametrial extension (88), in which case an external beam boost is desirable.

Dose escalation with IMRT to both the primary tumour and to lymph node metastases could be considered, but to date only single centre series have been conducted in the form of treatment boosts. These boosts are either simultaneous (SIB) or ‘sequential’ where the boost treatment is delivered after completing the rest of treatment.

Boyle *et al* 2014 (89), examined the use of dose escalation with SIB in 39 patients with locally advanced disease (cervical, endometrial and vaginal cancers). Patients were treated with doses of up to 65Gy to areas of gross disease, such as pelvic nodes, para-aortic nodes, pelvic sidewall extension or residual primary disease. At 1 year post treatment no grade 3 or 4 toxicities were found, although 24.5% of patients had grade 1-2 late toxicities. Local control rate at 18 months was 77.2%, although longer follow-up is needed. A UK based phase I/II multicentre dose escalation trial in locally advanced cervical cancer (“DEPICT”) using SIB is currently underway.

In the post-operative setting the use of SIB with IMRT up to 60.2Gy has been investigated to the vaginal cuff in 80 high-risk cervical cancer patients (90) and in 50 high-risk endometrial cancer patients with doses of 66Gy being delivered to the vaginal cuff (91). Acceptable toxicity, disease control and survival rates were reported in both studies, though no comparison was made with non-escalated patients.

1.5.5. Uptake of IMRT for gynaecological malignancies

Given the mostly favourable growing body of evidence for IMRT in gynaecological malignancies, it has been increasingly adopted into clinical practice in the last decade. In the USA for example, it has been rapidly accepted, and rates of IMRT for endometrial cancer had risen from 3.3% in 2002 to 23.2% in 2007 (92).

A national survey addressing the uptake of IMRT in England between December 2013 and February 2014 (53) found that within the 50 radiotherapy centres in England, 33% of all radical gynaecological patients were treated with IMRT. However there was significant variation between centres. The national target for 2009 was 20% of all gynaecological patients and although 27 centres reached this target and 6 centres treated 100% of their patients with IMRT, 13 centres did not treat any of their patients with IMRT.

1.6. Reluctance towards adoption of gynaecological IMRT

Although there are many advocates of the use of IMRT in gynaecological patients, some clinicians have reservations. The first concern is the quality of evidence available. It must be noted that much of the above body of evidence is retrospectively reported data, in single centre studies, without any prospective or direct comparison to 3DCRT. Many studies report only early outcomes in terms of progression free survival and toxicity outcomes and effects on late toxicity are unknown.

International guidance has suggested that IMRT for the reduction of toxicity “may be considered” over 3DCRT, however there is insufficient data to recommend IMRT for disease related outcomes (93).

For the widespread adoption of any new treatment, it needs to be deemed cost-effective. Gynaecological IMRT has not as yet been demonstrated to be cost-effective, given the lack of definite evidence of its benefit over 3DCRT. Data from the USA examining this issue has suggested the planning cost for IMRT treatment is $2088.19 (compared with $564.69 for 4-field 3D-CRT), with treatment costs of $519.84 (compared with $262.30)

(94). This balanced against equivalent survival outcomes, likely reduced acute toxicity and unclear impact on late toxicity, resulted in IMRT not proving to be cost effective. More concrete evidence of the benefits of gynaecological IMRT is warranted, especially for late toxicity, to improve the cost-effectiveness balance.

Further to this several technical problems exist with the use of gynaecological IMRT, which must be considered before it can be used safely and efficiently. Authors of the consensus guidelines for cervical cancer IMRT outlining suggest that application of IMRT to gynaecological treatments must be done with "greater caution" (95), with other authors suggesting IMRT should not be used without consideration of the "pitfalls, hazards and cautions" (96).

National Comprehensive Cancer Network guidelines suggest that IMRT in cervical cancer should be applied with "very careful attention to detail and reproducibility, including consideration of target and normal tissue definitions, patient and internal organ motion, and rigorous dosimetric and physics quality assurance"(97). These concerns and considerations are summarised below.

1.6.1. Problems with volume definition

Given the precision of IMRT planning, accurate target volume definition is of paramount important to ensure adequate treatment. 'Consensus guidelines' for both definitive cervical cancer IMRT and post-operative endometrial/cervical cancer have been defined by the RTOG and Japanese consensus groups (95, 98-100). Despite efforts with several international gynae-oncology experts (RTOG, European Society for Radiotherapy and Oncology (ESTRO), Japanese, Canadian) there are still many uncertainties about target volume definition in relation to gynaecological tumour sites, and within the guidelines consensus was not achieved for several points regarding volume definition.

For definitive cervical cancer radiotherapy, traditionally the GTV includes gross tumour in the cervix and lymph nodes. There are two CTVs; the primary CTV, which comprises the cervix, uterus, upper vagina, and parametrium; and the nodal CTV, which comprises involved lymph nodes as well as uninvolved nodes, which are at risk of microscopic spread.

With definitive cervical IMRT in there is on going debate on whether the whole uterus should be included within the CTV. The whole uterus has traditionally been included in the primary CTV for definitive cervical treatments, given that there is no anatomical boundary between the cervix and uterus. However there is little pathological evidence to indicate the

importance of including the whole uterus. Most of the histological studies that define patterns of cervical cancer spread are from early-stage cervical cancers, post-hysterectomy, where uterine involvement is unlikely. For locally advanced cancers there is no histological data to evidence the uterus as a common site of spread as these patients are normally treated with radical radiotherapy rather than surgery. At the time the RTOG guidelines were developed, 42% of survey respondents felt it was not always necessary to include the whole uterus (95), however, as the majority of the group did so in practice, inclusion of the whole uterus was recommended.

The definition of the borders of the parametrium is also debated (95, 100), in particular the superior border. While the RTOG recommend starting to outline the parametrium at the superior border of the fallopian tube, the Japanese consensus used the upper border of the cervix, resulting in significantly different volumes depending on which definition is used. The length of uninvolved vagina to include is also disputed, with some suggesting 1.5cm below tumour, and others use bony landmarks such as the bottom of the pubic symphysis, which can be up to 4cm below tumour.

The RTOG consensus guidelines based their atlas on Magnetic Resonance Imaging (MRI)-based planning (MRI in the treatment position), with the use of structures that are visible on MRI (such as mesorectum and utero-sacral ligaments), which are not clearly visible on CT. This was despite most of their respondents (91%) using CT as the primary imaging modality. This makes application of the guidelines difficult, unless widespread uptake of MRI planning scans occurs.

The prophylactic nodal CTV in both radical cervical treatment and post-operative gynaecological treatments has also some controversy. Based on key papers by Taylor *et al*, consensus is present with regards defining the nodal CTV with a 7mm margin around the iliac vessels (101).

However where to commence the nodal volume based is not concluded. For endometrial cancer it is recommended to treat the external and internal iliac and the obturator nodes. For cervix cancer or endometrial cancers involving cervix, or where there are positive nodes involved the common iliac nodes are also included (102).

The RTOG recommend starting the nodal CTV based on bony landmark (7mm below the L4-L5 interspace), whereas others (99) recommend the use of CT anatomy, such as the

the common iliac bifurcation as the start of the nodal CTV. Bony landmarks are not truly representative of pelvic vessel anatomy and vary between patients (103).
For the lower aspect of the obturator region, which forms the inferior aspect of the nodal CTV there again is discrepancy within the available guidelines (98, 99, 102).

In summary many aspects of target volume definition in gynaecological IMRT lack clarity. With this being such a key aspect of IMRT planning this may well have impact on treatment outcome.

1.6.2. Problems with organ motion and CTV-PTV margins

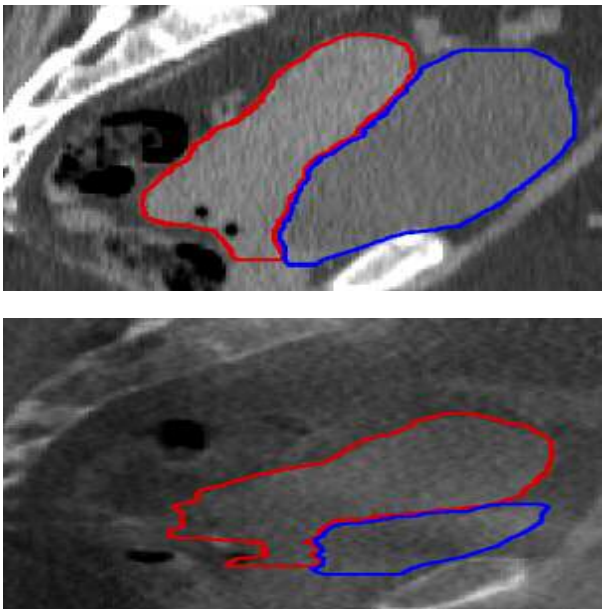
Organ motion is a known phenomenon and is a problem with pelvic radiotherapy. With highly conformal treatments such as IMRT, it is important that the target organs and OARs are in the same anatomical position on treatment as they are at the time of planning. Motion of target organs outside of the PTV may result in geographical miss and potential underdosage of the target. Motion of the OARs into to PTV may increase dose to these organs, which may result in increased toxicity. This was demonstrated in a retrospective study looking at SIB use in cervical cancer patients where 2 of 10 patients received less than 95% of the prescribed dose, and much higher doses to OARs were reported as a result of organ motion (104).

Within the pelvis many organs, including uterus/prostate, bladder, rectum, and bowel, are prone to motion during a radiotherapy treatment course. Motion in between fractions is termed inter-fractional motion, and that during a fraction is termed intra-fractional motion. Knowledge of both of these aspects is important when implementing IMRT to ensure adequate treatment margins are used, and geographical miss is minimised.

For definitive cervical treatment organ motion is a particular concern. Many studies have tried to evaluate the motion of different components of the primary CTV, though with widely variable results.
For cervical motion some studies used fiducial markers inserted into the cervix to assess motion (105, 106), and have found maximal motion of 23mm (anterior-posterior (AP)), 36mm (superior-inferior (SI)) and 23mm (left-right (LR)). Others using volumetric imaging such as Cone Beam Computed Tomography (CBCT), MRI and Megavoltage (MV) imaging (107-110) have found maximal motion of 29mm anterior, 63mm posterior, 35mm superior and 30mm inferior.

Uterine motion occurs in the anterior-posterior, superior-inferior directions with the addition of rotational motion. Margins of up to 4cm have been suggested to account for uterine motion (108).

Cervical and uterine motion may also be determined by the volume/position of neighbouring organs, such as bladder (111) or rectum (108). An example of the relationship between bladder volume and uterine position is illustrated in figure 1.6-1. There is also significant intra-patient variation in the relationship between bladder filling and uterine motion, having a major impact in some patients but hardly any in others (111).



Uterine motion with bladder filling

The initial figure shows uterine position at the time of radiotherapy planning with a bladder volume of 550ml.

The second figure shows an on-treatment CBCT of the same patient with a bladder volume of 75mls, with which the uterine position has rotated inferiorly and anteriorly.

(uterus in red; bladder in blue)

Figure 1.6-1: Uterine motion with bladder filling

With pelvic organ motion being such a potential problem, adequate CTV-PTV margins around the CTV are vital to ensure no geographical miss. The CTV-PTV margin consists of an internal margin (IM), which accounts for organ motion of the CTV, and a set-up margin. Set-up margins are determined within institutions depending on their immobilisation techniques and imaging protocols. The IM however must be determined depending on the estimated organ motion pattern of the CTV components.

For gynaecological IMRT appropriate CTV-PTV margins are unclear for both the primary CTV and the nodal CTV.

For the nodal CTV the RTOG recommend a 1.0-1.5cm CTV-PTV margin (98), and there is no mention of CTV-PTV margins by other published guidelines (99, 102). Guidelines from other pelvic tumours and from trial protocols recommend much smaller CTV-PTV margins

(5mm (112), and 7-8mm (113)). No studies are found in the literature for the basis of these margins.

For the primary CTV in definitive cervical cancer, with the large amount of motion seen especially of the uterus, large CTV-PTV margins may be required to ensure safe coverage of the CTV. Suggested CTV-PTV margins within the RTOG consensus document are 1.5cm-2cm around the CTV "if good quality daily soft tissue verification was available during treatment." They also recommend that if bone matching alone was being used "more generous margins would be necessary", although this was not quantified further (95).

The concern with the use of large margins is that although they will reduce the risk of geographical miss, they are likely to increasingly include the volume of OARs into the PTV, for example bowel and rectum. This may then negate any potential benefits of IMRT in these patients. Large margins that are population-based, may also be excessive for some patients who have very little organ motion.

In post-hysterectomy radiotherapy, the primary CTV comprises the post-hysterectomy vagina with a margin to form the 'paravaginal CTV'. Motion of this CTV has been studied in less detail than the definitive cervical cancer CTV. The vagina has been demonstrated to move 1.46cm AP, 1.2cm SI and 0.59cm LR, potentially influenced by bladder and rectal filling (114).

For this scenario the RTOG did not determine any consensus CTV-PTV margins, although suggested that a 1.0cm-1.5cm margin is "commonly advocated." They also suggested use of a vaginal ITV (internal target volume), where patients undergo planning simulation initially with a full bladder and then with an empty bladder. An ITV is constructed using the vaginal position on both scans, to account for the change that can be seen with bladder volume changes. Although this has been recommended by RTOG, no clear evidence of benefit is reported in the literature. No rectal preparation guidance is given in any of the consensus documents.

1.6.3. Problems with tumour regression

A further issue is that of tumour regression during treatment. It is known that squamous cell cervical cancer is a radiosensitive tumour, and tumours have been shown to reduce during the course of a radiotherapy treatment, with mean cervical volumes reducing from 97cc to 31.9cc after a course of 45Gy (110).

This again makes IMRT challenging, as the anatomy within the pelvis is likely to change with shrinking of the GTV. With the GTV being smaller, the CTV may be considered to be smaller also. With OARs such as bladder and rectum being in close proximity, the relative positions of these OARs may also change, and they may end up receiving a higher dose than planned.
IMRT, with its precise nature, is unable to accommodate this anatomical change. Re-planning of the patient during treatment is one solution, which needs to be examined.

1.6.4. Problems with choice of IGRT technique

Following on from the above issues with organ motion, regression and lack of clear CTV-PTV margins, it becomes apparent that IMRT for gynaecological cancer cannot be delivered safely without appropriate image-guided radiotherapy (IGRT).

IGRT is a broad term which uses imaging to localise tumours initially for radiotherapy planning, and then to monitor, update and adjust treatment delivery to improve its accuracy (115). IGRT is complementary to IMRT in achieving the goals ensuring target coverage and reducing OAR doses. However the majority of the studies demonstrating evidence of the benefits of gynaecological IMRT do not even mention the IGRT techniques used for their patients.

For on-treatment imaging, the type of imaging, frequency of imaging and choice of offline versus online protocols are important considerations. Offline imaging protocols compare on-treatment imaging to a reference image offline; there is no action until the following treatment. The aim of this is to correct ‘systematic errors’ which are reproducible errors occurring in the same direction and in a similar magnitude.
Online imaging protocols compare the reference image to on-treatment imaging that is acquired and checked prior to each fraction of treatment. If a significant discrepancy is noted a correction is applied. The aim of this is to correct both ‘random errors’ and systematic errors. Random errors arise from changes in target position and shape between and during fractions of treatment and cannot be predicted.

In the case of gynaecological IMRT, UK (116) and international guidelines (95) recommend the use of soft tissue imaging to be used with IMRT techniques for both definitive and post-operative IMRT is necessary. This is due to the independence of pelvic organ motion to bony anatomy.

Many centres use imaging protocols which include day 1, 2, 3 and then weekly offline review, as standard for conformal pelvic treatments. However for gynaecological IMRT, use of online imaging is recommended (95, 116), which appears logical, given that organ filling and target volume position on one day is unlikely to be representative of the next day. This is likely to lead to random error rather than systematic error, though there is little documented in the literature to evidence this.

Even with daily online imaging, further complexity is added when using IMRT in the pelvis due to the differential motion of the nodal CTV and primary CTV. The nodal CTV is thought to have little motion compared with the primary CTV. As a result, with online imaging, if isocentre shifts are made to accommodate for the movement of the primary CTV, this may compromise coverage of nodal CTV which is unlikely to have moved in the same direction with the same magnitude.
An IGRT solution is therefore required that can accommodate the complexity of differential CTV motion.

Adaptive Radiotherapy
Adaptive radiotherapy may offer solutions to the issues of tumour regression and organ motion described above. This is defined as a "process intended to improve radiation treatment by systematically monitoring patient/treatment positional and volumetric variations and incorporating them to re-optimise the treatment plan at appropriate intervals during the course of treatment" (117).

Adaptive treatments may be used in the context of tumour regression, where the GTV has changed during treatment, as well as the position of the OARs; a re-plan part way through treatment would then be appropriate. Adaptive re-planning has been used in head and neck cancers, as with tumour shrinkage and weight loss, there is often anatomical change during treatment with the potential for OARs to be included within the PTV. Studies have shown adaptive re-planning to be beneficial in terms of sparing dose to spinal cord and parotids in selected groups of patients (118).

Adaptive radiotherapy may also be used to account for an individual's organ motion pattern, for example, with use of a 'composite strategy'. With this strategy a composite CTV is generated combining the CTV on a number of offline images for an individual patient. The composite strategy has been modelled in prostate cancer (119), where each patient's composite CTV was determined from the CTVs on imaging from the first six

fractions of treatment. A 7mm PTV margin was used around the composite, and the strategy was compared to use of a standard 10mm CTV-PTV margin. Use of the composite reduced the PTV volume by 29% and subsequently reduced dose>65Gy to the rectum by 19%.

An alternative adaptive solution is the 'plan of the day' strategy, where a library of plans is created prior to treatment and then daily online imaging is used with each fraction of treatment to select which plan best covers the CTV that day. This has been modelled in bladder cancer, with each patient having a library of plans with "small", "medium" or "large" margins used to account for inter-fraction variation in bladder filling. This has shown some promise in single centre studies for significantly reducing the volume of normal tissue irradiated whilst maintaining CTV coverage (120, 121), and is now being tested in a UK Phase II multicentre trial (122).

In gynaecological cancer IMRT, no studies have reported modelling or use of composite strategy. Plan of the day modelling for definitive cervical cancer has been initiated in the Netherlands (123) with some early clinical data to show potential feasibility (124). Its potential for organ-sparing however has not been quantified and further work is required to establish how best to form a plan library for these patients.

In post-operative gynaecological radiotherapy, no adaptive strategies have been modelled to date.

1.6.5. Problems with lack of dose constraints: "how much bowel sparing is enough?"

For pelvic radiotherapy, bowel irradiation and the subsequent bowel toxicity is a critical concern. This applies not only to gynaecological malignancies, but also for rectal, prostate and bladder cancer radiotherapy. In prostate cancer, high-risk patients have their pelvic nodes treated and may suffer toxicity resulting from high radiotherapy doses to the rectum, and moderate radiotherapy doses to the bowel. In bladder cancer, though the pelvic nodes are not routinely treated, large margins tend to be needed to accommodate organ motion of the bladder and this may result in additional irradiation of bowel.

In gynaecological malignancies, there are therefore significant parallels with other pelvic tumours. However, differences also exist - in comparison to prostate, bladder and rectal cancer radiotherapy, gynaecological radiotherapy typically involves treatment of an increased length of the pelvic nodal chain. Depending on the clinical scenario, the nodal volume may be treated up to L4/L5, the level of the aortic bifurcation, or may also include

all the para-aortic nodes (up to T12). This is significantly higher than in prostate cancer where the pelvis is treated up to L5/S1, or in rectal cancer where nodes are treated to S2/S3. This increase in PTV length significantly increases the amount of bowel that is irradiated and may increase toxicity.

The problem is compounded in the post-hysterectomy setting, when the uterus has been removed, and consequentially more bowel falls into the pelvis. Bowel is therefore more likely to be irradiated, and toxicity increased for survivors of post-hysterectomy cervical and endometrial cancer.

Much of the evidence for the use of gynaecological IMRT is based on dosimetric and small clinical studies. Dosimetric studies show IMRT can reduce bowel doses to various extents. However, there is little to suggest whether the reductions of bowel doses seen in these studies will translate into clinically meaningful reductions in bowel toxicity. As for the clinical studies, although some demonstrate reduced bowel toxicity with IMRT, again it is not clear what degree of bowel sparing with IMRT may have resulted in this toxicity reduction.

The bowel is a sizeable organ with many different components including the small bowel (duodenum, jejunum and ileum) and large bowel (caecum, colon, sigmoid and rectum and anal canal). These components, with their differing anatomy and physiology, are likely to have different radio-sensitivities, and different 'dose-volume relationships' with radiation.

The dose-volume relationship of a particular tissue quantifies the relationship between toxicity and the volume of a tissue irradiated to a specific dose level. From this, "dose-volume predictors" and "dose-volume constraints" are derived for clinical use in radiotherapy planning. Dose-volume predictors indicate which dose-volume parameters (for example, maximal dose (Dmax), or Volume receiving x Gy (VxGy)) are related to the risk of toxicity. Dose-volume constraints are the cut-offs of these dose-volume predictors; above the constraints there is higher risk of toxicity, and below the constraints there may be relative safety of avoiding toxicity.

In the early 1990s, a key paper by Emami *et al* (125), defined dose-volume limits for many tissues within the body. These were largely based on 2-dimensional planning data and "expert opinion." For bowel limits, quantification of bowel volumes was based on

“expert opinion.” For bowel limits, quantification of bowel volumes was based on orthogonal films using barium contrast, which now may be considered out of date. More recently the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) initiative updated this data with the use of 3-dimensional data and summarised their findings in a number of reviews in 2009 (126).

With relevance to late bowel toxicity, two QUANTEC summaries are found, firstly that describing rectal toxicity (127), and the second describing small bowel toxicity (128). For rectal toxicity, there is a significant amount of high quality data, mainly from prostate cancer trials, and specific dose-volume constraints are clearly recommended to reduce toxicity.

In the case of small bowel, the QUANTEC report was much less definitive. Variation in the methods of defining small bowel was identified; some papers used bowel loops with others using the concept of ‘bowel bag’. Bowel bag is the potential space for bowel within the intestinal cavity allowing for its motion during the course of radiotherapy. QUANTEC mainly reviewed acute bowel toxicity studies, and constraints were suggested for bowel loops and bowel bag to reduce acute toxicity.

For late bowel toxicity however the paucity of data was highlighted. No clear guidance on the dose-volume predictors for late bowel toxicity was provided.

With the lack of clear dose-volume constraints for late bowel toxicity, it is currently difficult to make any clear assessment on gynaecological (or other pelvic) IMRT techniques as to whether the amount of bowel spared is sufficient to reduce toxicity for patients. If sufficient bowel is not spared, it is questionable whether the implementation of new IMRT techniques, along with IGRT and potentially adaptive strategies is a worthwhile goal in this scenario.

1.7. Thesis Aims

The aims of this thesis are to investigate and offer solutions to two problems associated with the implementation of pelvic IMRT for gynaecological malignancies.

1. **Determination of dose-volume constraints for late bowel toxicity**: sparing of the bowel is identified as a key objective for pelvic IMRT, however it is not yet known what is the critical component, volume and dose level for determining the risk of late toxicity for patients. In this thesis, the dose-volume constraints that are predictive of late bowel toxicity will be determined.

2. **Assessment and management of organ motion for gynaecological IMRT:** Organ motion makes gynaecological IMRT particularly challenging. In this thesis literature on organ motion in the definitive cervical cancer setting will be systematically reviewed, and appropriate population-based and adaptive strategies to account for organ motion will be modelled.
Further, in the post-operative setting, organ motion will be quantified, and population-based strategies modelled, with an assessment of the need for adaptive strategies.

1.8. Structure of the thesis

Section A of the thesis will focus on dose-volume predictors of late bowel toxicity after pelvic radiotherapy. Chapter 2 is a systematic review of the available scientific literature to assess already known dose-volume predictors of late bowel toxicity. Chapter 3 is a study collecting patient-reported late bowel toxicity data, assessing the dosimetric predictors of this toxicity and deriving dose-volume constraints.

Section B examines the issue of organ motion specific to gynaecological malignancies and potential solutions for this. Chapter 4 and 5 investigate organ motion and potential solutions to overcome this in patients undergoing definitive radiotherapy for cervical cancer. Chapter 4 is a systematic review of organ motion and IGRT studies and Chapter 5 is a modelling study of adaptive and population-based IMRT strategies for definitive cervical cancer patients. Chapter 6 investigates organ motion in patients undergoing post-operative radiotherapy for cervical and endometrial cancer, and assesses the need for adaptive strategies in this setting. Chapter 7 is my discussion and conclusions.

Section A: Determination of Dose Volume Constraints for Bowel Toxicity

2. Chapter 2: A Systematic Review of Dose-Volume Predictors for Late Bowel Toxicity

2.1. Introduction

Late bowel toxicity is a significant problem after pelvic radiotherapy regardless of tumour site. Serious life-threatening toxicity such as bowel obstruction, fistulae and bleeding requiring transfusion occur in 4-10% of patients 5-10 years from treatment (129). Also long-term bowel symptoms, which adversely affect quality of life, can occur. 50% of pelvic radiotherapy patients report long-term bowel symptoms after radiotherapy that affect quality of life, with 2 out of 3 patients stating this effect on quality of life is “moderate” or “severe”.

A prime aim of modern radiotherapy techniques such as IMRT is to spare normal tissue to reduce both acute and late toxicity. In particular minimising late toxicity with its influence on quality of life is a key objective.

Late bowel toxicity is generally attributed to radiation both to the rectum and bowel and it is difficult to differentiate toxicity symptomatically from these two OARs. The rectum is often directly adjacent to the target organ in the pelvis, such as the prostate or cervix, and is therefore susceptible to high doses. Other parts of bowel may either be close to high dose areas, or in close proximity to prophylactic pelvic nodal volumes, which tend to be treated with more moderate doses.

New radiotherapy techniques to minimize late bowel toxicity by sparing these OARs are being introduced. In gynaecological radiotherapy there is some published evidence that IMRT techniques may reduce bowel doses. However whether these reductions in bowel doses will equate to reduced toxicity can only be predicted if the dose-volume relationship of rectum or bowel is precisely understood.

Dose-volume constraints are used in radiotherapy planning to limit the risk of toxicity. Initially retrospective studies are used to identify potential dose-volume parameters (such as maximum dose, or volume of OAR receiving x amount of dose, Vx) that are associated with a specific toxicity endpoint. From this dose-volume constraints that split patients into

high or low risk of endpoint are determined. The assumption is that prospective use of such constraints will limit future cohorts of patients developing toxicity. They can also be used as a benchmark for modelling studies of novel radiotherapeutic techniques to predict their likely benefit.

Dose-volume constraints for bowel toxicity were first examined in the 1980s. A key study by Gallagher *et al*. (130) included 150 patients with pelvic malignancies (urological, gastrointestinal and gynaecological). Orthogonal films with the use of barium contrast were used to quantify the volume of small bowel irradiated. The volumes of small bowel irradiated to specific doses were related to late toxicities. This study showed the average volume receiving radiation to be significantly higher in those manifesting chronic diarrhoea or small bowel obstruction. The incidence of these effects increased with dose received; with the incidence of late complications being 4.3% at 45Gy, 5.9% at 50Gy and 30% at 55Gy.

In 1991 this study combined with 'expert opinion' of a panel formed the basis of the 'Emami' tolerances to OARs which have been used in clinical practice for several years (125). Probabilities of 5% and 50% complication rates within five years are reported as TD5/5 and TD50/5, respectively. Emami *et al* recommended normal tissue tolerance of the bowel as a TD5/5 to 1/3 of small bowel as 50Gy and 40Gy to the whole bowel. For TD50/5 constraints suggested were for 60Gy for 1/3 small bowel irradiation and 55Gy for whole bowel. They also recommend a colon TD5/5 of 55Gy and TD50/5 of 65Gy. For rectum, no volume effect was noted, though TD5/5 of 60Gy and TD50/5 of 80Gy for whole rectum were suggested.

Following this, also with the use of 2-dimensional data, Letschert *et al* (131) studied the relationship of small bowel volumes and late diarrhoea in patients treated to 50Gy, finding that above 328cc the risk of toxicity increased to 42%, and below 77cc this reduced to <31%.

Data from these early studies have formed an important basis of the dose-volume constraints used in clinical practice, however these are based on 2-dimensional data and both imaging and radiotherapy planning techniques have significantly changed since then.

Almost twenty years later in 2010, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) initiative produced a series of reviews using 3D data to update on

the Emami recommendations. Guidance from these reviews provides dose-volume constraints for various OARs based on dose-volume data that is derived from modern radiotherapy planning techniques. QUANTEC also provided recommendations for reporting and gathering data on dose-volume dependencies on treatment outcomes (132). For bowel toxicity two QUANTEC reviews are reported, the first for rectal constraints (127) and the second for small bowel constraints (128).

2.1.1. Dose-volume predictors of the rectum

Regarding rectal toxicity QUANTEC found a number of high quality studies, mainly involving prostate cancer patients included in clinical trials. The main endpoints that were considered were rectal bleeding and grade 2 RTOG toxicity. Most studies examined the relationship between higher doses (>60Gy) and toxicity, and there was clear concordance between studies, allowing validation of the findings. Dose-volume constraints recommended were V50<50%, V60<35%, V65<25%, V70<20%, and V75<15%. Use of these constraints are predicted to limit ≥ grade 2 rectal toxicity to <15% and ≥grade 3 rectal toxicity to <10%.

Outside of QUANTEC, studies have examined constraints for lower/intermediate doses to the rectum as adhering to these may also reduce toxicity. Gulliford *et al* (133) addressed the use of intermediate dose constraints in 388 patients treated in a prostate cancer trial (RT-01), examining not only rectal bleeding, but other toxicity such as proctitis, subjective sphincter control, loose stool and urgency. They applied a number of dose constraints retrospectively to the plans of patients treated within the trial, and concluded that dose constraints of V30≤80%, V40≤65% and V50≤55% decreased the risk of moderate or severe toxicity. In agreement, Fiorini *et al* in their studies found that faecal incontinence was more predictive by V40<65-70% (134).

2.1.2. Dose-volume predictors of bowel

The QUANTEC review of small bowel data (128) identified six key papers that examined the dose-volume relationship of bowel toxicity; however these studies examined acute toxicity only. Recommended constraints from these papers were that the absolute volume of small bowel loops to receive ≥15Gy should be <120cc; if the entire volume of peritoneal space is considered the volume receiving >45 Gy should be <195 cc.

For late bowel toxicity there was no detailed dose-volume relationship analysis described. The review mentioned dose-fractionations used within certain trials and the associated late toxicity rates, though no specific dose-volume predictors can be derived from this

information. The QUANTEC reviewers suggest that the constraints identified for acute bowel toxicity may be applied for late bowel toxicity; however “this correlation is not established”.

It must be noted also that although small bowel was assessed by QUANTEC, there was no mention of the other components of bowel such as colon, and sigmoid, which may also be contributing to late bowel toxicity.

2.1.3. Lack of clear dose-volume constraints for late bowel toxicity

Despite late bowel toxicity being an important clinical problem, dose-volume constraints for bowel are not well established. QUANTEC guidance (132) highlighted issues which may hinder the development of clear and clinically useful dose-volume constraints, and have made recommendations for future studies. These issues broadly including endpoint definition, statistical standards, and standardized definition of OARs which may all be applicable in the context of late bowel toxicity.

In the last few years the paucity of dose-volume data for late bowel toxicity has been acknowledged and more studies have been reported to address this. Review of the published data is therefore important to clarify dose-volume constraints for late bowel toxicity, and be able to use these to predict the likely benefits of advanced bowel-sparing radiotherapy treatments.

2.2. Aims

The aims of the work in this chapter were to:

- Systematically review published studies investigating the dose-volume relationship of bowel with development of late bowel toxicity, and assess the quality of these studies using criteria derived from QUANTEC recommendations.
- To seek dose-volume constraints from these studies which can be applied to assess the potential ability of new gynaecological radiotherapy techniques to reduce late bowel toxicity.

2.3. Methods

2.3.1. Inclusion criteria

The inclusion criteria were as follows:

1. English language studies
2. Human studies only
3. Studies involving adults
4. Studies with patients treated with external beam radiotherapy (EBRT)
5. Studies with patients treated for tumour sites including: Any gastrointestinal (upper or lower), Urological or Gynaecological
6. Studies describing the dose-volume relationship of any component of bowel from duodenum to anal canal (excluding the rectum*)
7. Studies where toxicity after 3 months of completion of radiotherapy is reported
8. Studies aiming to correlate the dose-volume relationship of bowel/bowel components to late bowel toxicity outcome data (not simply quoting toxicity rates with a specific radiotherapy regime)

   ***dose-volume studies for the rectum were excluded given the already well established knowledge on dose-volume constraints**

2.3.2. Exclusion Criteria

1. Review articles and letters
2. Studies using brachytherapy only
3. Studies using stereotactic body radiotherapy (SBRT) – as the radiobiology is considered different with extreme hypofractionation
4. Studies searching for dose-volume constraints of the rectum, or anorectum (where anal canal was not distinguished from rectum)
5. Studies with insufficient methodological detail to be able to repeat the method on an independent sample of patients

2.3.3. Searches

A systematic search was carried out using Medline, Premedline, Embase, Pubmed and ISI Web of Science on 15th October 2013. Updated searches were performed on 10th November 2014 and 3rd September 2015 to ensure all new literature was included. Searches were performed by Mrs Bernadette Coles (Cancer Research Wales Library). The search strategy used is found in Appendix D.

Search terms around “radiotherapy, radiotherapy injuries, side effects, toxicity, intestines bowel, dose, dose fractionation, dose response relationship” were used. Duplicates of references were removed.

2.3.4. Study Selection

Two reviewers (myself and Dr Emma Higgins) independently assessed the abstracts for inclusion in the review. For those abstracts meeting the eligibility criteria, full papers were acquired and assessed further for suitability against the eligibility criteria. The reference lists of all the included papers were searched for any additional relevant references not included in the original database search.

2.3.5. Data extraction and synthesis of results

Data was extracted from each of the included papers and collected on Microsoft Excel. Bowel can be defined in several different ways and for the purpose of this work papers were divided into studies looking at the ‘whole bowel’ (including bowel loops and ‘bowel bag’), small bowel (and its components) and large bowel (and its components).

Basic information was gathered and tabulated: Number of patients, Number of patients with the toxicity endpoint studied, tumour site, OAR studied, key findings. Further analysis of the papers was performed looking at OAR and toxicity definition.

Furthermore, the recommendations from QUANTEC (132) on quality of dose-volume studies were reviewed, and those statistical and toxicity endpoint criteria that can be applied to this subject were selected (table 2.3-1). Each study was compared to these criteria as a quality assessment.

Table 2.3-1: Quality Assessment Considerations

Statistical considerations
1. Basic statistical data provided on incidence of toxicity - Both number of subjects and number of events should be reported - If an estimate of incidence is given the standard error should be supplied
2. Numerical labeling of response histogram – if into groups eg. quartiles must state number of patients in each quartile
3. When predictive models are correlated with complications parameter estimates must be stated with their standard error
4. Complication rates associated with constraints must be reported
5. “Goodness of fit” to be reported such as Chi-squared
6. Discriminator statistics reported such as receiver operating characteristic curves
7. Full organ volumes (rather than partial) should be used - If this is not possible absolute volumes should be used or a standard method of normalization - A clear statement of organ volume definition should be given
Toxicity Endpoint considerations
1. Symptom-specific information rather than a portmanteau endpoint (eg. RTOG gr 2) should be used
2. Consideration that symptoms may be attributed to pre-radiotherapy co-morbidities
3. Patient-reporting of symptoms may be important

2.4. Results

The results of the systematic search are shown in figure 2.4.1. 25 studies were included in the review (see table 2.4-1). Of these studies, 17 included patients with prostate cancer, 2 with bladder cancer, 5 with gynaecological cancers (cervical and endometrial), and 2 with pancreatic cancer.

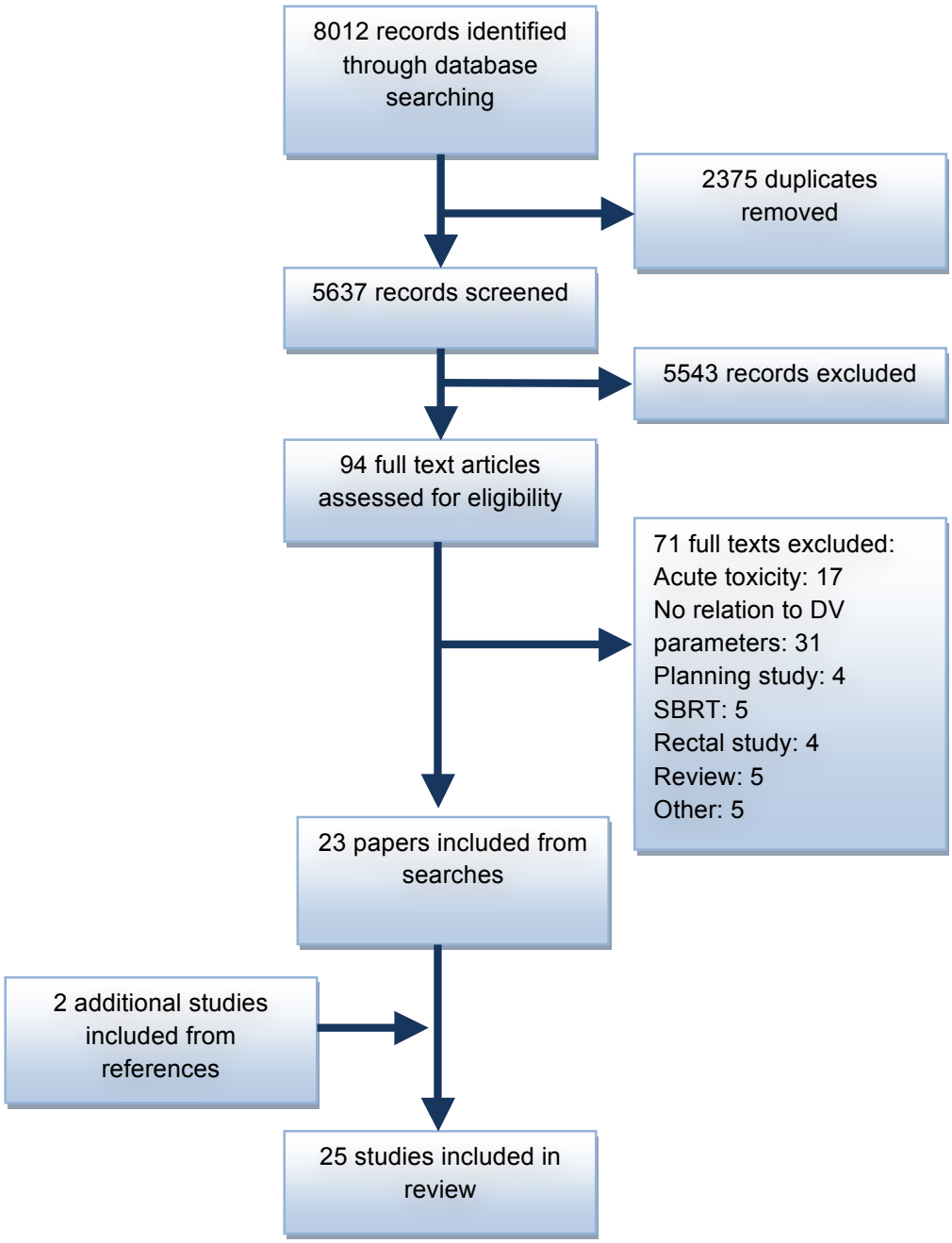


Figure 2.4-1: Systematic Search Results

The majority of studies (n=17) had less than 100 patients included, with 9 studies having less than 50 patients included. A variety of toxicity scores were used including RTOG

(n=9), CTCAE (n=6), LENT-SOMA (n=2), Radiotherapy Induced Late Intestinal Toxicity score (RILIT) (n=2), or author-defined scores (n=5). 11 studies were reported based on the use of 3DCRT, 8 studies used IMRT, and 6 used a combination of both.

The 25 studies are divided into three categories: whole bowel studies (n=7), small bowel studies (n=10) and large bowel studies (n=15) depending on the OAR studied. There was some overlap between the papers so some are featured in more than one section.

Table 2.4-1: Studies included in systematic review

Author	Year	Cancer site	No of pts	Pts with tox	OAR studied	Toxicity score used	RT Type	Primary RT Dose (Gy/#)	Pelvic RT dose (Gy/#)	Concurrent chemo use
Adkison (135)	2012	Prostate	53	20	small bowel	CTCAE v3.0	IMRT	70/28	56/28	no
al-Abany (136)	2005	Prostate	65	9	anal sphincter region	Own questionnaire	3D	70.2/39	NS	no
Alsadius (137)	2012	Prostate or prostatic bed	403	51	anal sphincter region	Own questionnaire	3D	470/35	NS	no
Buettner (138)	2012	Prostate	388	57	anal canal	Common grading scheme	3D	64/32 or 74/37	NS	no
Chopra (139)	2014	Cervix (post-op)	71	9	small bowel, large bowel	CTCAE v3.0	IG-MRT (46); 3D (25)	50/25	50/25	63/71 cisplatin
Deville(140)	2010	Prostate	30	2	intestinal cavity	RTOG	IMRT	79.2/44	45/25	no
Deville(141)	2012	Prostatic bed	36	5	intestinal cavity	RTOG	IMRT	70.2/39	45/25	no
Fokdal (142)	2005	Prostate or bladder	71	Symptom specific	small bowel	LENT-SOMA	Conformal	60/30 (bladder) 69.6/35 (prostate)	48-60Gy bladder; NS for prostate)	no
Fonteyne (143)	2007	Prostate	241	Symptom specific	small bowel, sigmoid	RTOG and “RILIT”	IMRT	74/37-80/40	NS	no
Guerrero-Urbano (112)	2010	Prostate & Pelvic nodes	79	21	bowel loops	RTOG diarrhoea & LENT SOMA diarrhoea	IMRT	70/35	50/35 or 55/35	no
Huang (144)	2011	Pancreas	46	8	duodenum	CTCAE v4.0	Conformal & IMRT	42/15	42/15; 36/15; 38/19	Gemc; 18 pts erlotinib in addition
Isohashi (145)	2013	Cervix (post-op)	97	16	peritoneal cavity, small & large bowel	RTOG/EORTC	2D or 3D	50/25	50/25	All nedaplatin
Kelly (146)	2013	Pancreas	106	20	duodenum	CTCAE v4.0	3D or IMRT	50.4/28 (78pts); 57.5-75.4 in 28-39# (28pts)	50.4/28 (78pts); 57.5-75.4 in 28-39# (28pts)	Gemc (19) 5-FU (15)/ capec (72) +/- cetuximab (21) or erlotinib (6)
Koper (147)	2004	Prostate	266	141	anal canal	RTOG (simplified) Symptom questionnaire	3D or 2D	66/33	NS	no

Author	Year	Cancer site	No of pts	Pts with tox	OAR studied	Toxicity score used	RT Type	RT Dose (Gy/#)	Pelvic RT dose (Gy/#)	Concurrent chemo use
Mavroidis (148)	2005	Prostate	65	Symptom specific	anal sphincter	Own questionnaire	3D	70.2/39	NS	no
Mcdonald (149)	2015	Bladder	47	10	bowel loops	RTOG	3D	64/32	64/32	21 received 5-FU/MMC
Mouttet-Audouard (150)	2015	Cervical	37	8	Small bowel, sigmoid	CTCAE v4.0	IMRT (tomotherapy)	60/28	50/28	Yes, cisplatin
Peeters (151)	2006	Prostate	641	146	Anal wall	RTOG/EORTC plus 5 symptoms	3D (41 pts IMRT boost)	68/34 or 78/39	NS	no
Peeters (152)	2006	Prostate	368	32	Anal wall	Incontinence (no specific questionnaire)	3D (22 pts had IMRT boost)	68/34 or 78/39	NS	no
Poorvu (153)	2013	Cervix & Endometrium (+ PA nodes)	46	3	peritoneal cavity, small bowel, duodenal segments	CTCAE v4.0	IMRT	45/25 (22pts); PAN boost 50-65 (33pts)	45/25 (22pt) plus PAN boost 50-65 (33pts)	yes, 24 pts cisplatin
Smeenk (154)	2012	Prostate	48	21	Anal sphincter muscles	Presence or absence of frequency, urgency and incontinence	3D (n=43, IMRT (n=5)	67.5/27 or 70/28	NS	no
Smeenk (155)	2012	Prostate	36	23	Anal wall	Late RILIT score: urgency, incontinence, frequency	3D	67.5/27 or 70/28	NS	no
Taussky (156)	2003	Prostate	73	unclear	anal canal	Prostate specific QoL scores: UCLA, FACT-P and EORTC QLQ-PR25	3D	66.6-72/ 37-40	NS	no
Verma (157)	2014	Cervix & Endometrium	105	9	duodenum	RTOG and endoscopic findings	IMRT	45-50 with boost 60-66Gy	45-50 with boost 60-66Gy	58 pts platinum agents
Vordermark (158)	2003	Prostate and prostatic bed	44	14% severe incontinence	anal canal	10 question continence questionnaire	3D	58-72/29-36	NS	No

Abbreviations: NS: not stated; IMRT: intensity modulated radiotherapy; RTOG: Radiation Therapy Oncology Group; CTCAE: Common Toxicity Criteria for Adverse Events; RILIT: Radiotherapy Induced Late Intestinal Toxicity; FACT-P: Functional Assessment of Cancer Therapy=Prostate; EORTC: European Organisation for Research and Treatment of Cancer; PAN: Para-aortic nodes; MMC: Mitomycin-C ; Gemc: Gembcitabine; Capec: Capecitabine

2.4.1. Whole bowel

Seven papers (including 372 patients) examined the dose-volume relationship of whole bowel either using bowel loops or intestinal/peritoneal cavity. The findings are detailed in table 2.4-2, with studies with positive findings detailed first. The last two columns indicate the quality assessments that were met (as defined in table 2.3-1). If the consideration is met the number of the consideration is noted.

2.4.1.1. Whole bowel: Peritoneal cavity/bowel bag

Of the 5 peritoneal cavity papers, 3 papers (140, 145, 153) found no dose-volume parameters of the peritoneal cavity related to late bowel toxicity. Deville *et al* (141) found an association of RTOG Grade≥1 late bowel toxicity with both volume and V20 of peritoneal cavity, though no constraints were derived. Mouttett-Audouard *et al* (150) defined their "small bowel" OAR as "the entire abdominal cavity including all possible locations to the top of iliac crests or to D12-L1 in para-aortic radiation cases," hence this is included in the whole bowel section. They found that their endpoint of "whole late digestive toxicity" was associated with small bowel dose D20%, D40%, D50%, D80% and D95%. Bowel receiving 10-30Gy was significantly associated with toxicity, though no constraints were derived.

2.4.1.2. Whole bowel: Bowel loops

Two studies (112, 149) examined the dose-volume relationship using bowel loops, defined as from the rectosigmoid junction up to 2cm above the PTV, which included sigmoid, large and small bowel. Guerrero-urbano *et al* (112) found a clear relationship between bowel volume above 450cc and increased risk of late diarrhoea (by both RTOG and LENT SOMA definitions) in patients who have prostate and pelvic nodal IMRT. Dose-volume relationships were found with RTOG scoring of diarrhoea, though not LENT SOMA. Constraints suggested were V40<124cc, V45<71cc and V60<0.5cc to reduce grade 2 toxicity in IMRT patients. No complication rates associated with these constraints are mentioned.

McDonald *et al* (149) in their study of 47 bladder cancer patients suggest threshold constraints for 25% risk of grade 1 RTOG toxicity as V30<178cc; V35<163cc; V40<151cc; V45<139cc; V50<127cc; V55<115cc; V60<98cc and V65<40cc. With these constraints the authors suggest grade 2 toxicity will be 0%.

Table 2.4-2: Whole bowel studies – significant findings and quality assessment

						Quality Assessment	
Author	**OAR studied**	**OAR defined**	**Toxicity definition**	**Pts with toxicity**	**Significant findings**	**Statistical considerat-ions met (1-7)**	**Endpoint considerat-ions met (1-3)**
Deville (141)	Intestinal cavity	Intestinal cavity below L4-5	RTOG Gr≥1	5/36 (14%)	Toxicity associated with volume & V20. No constraint specified.	1,7 (n/a: 2-6)	None
Mouttet-Audouard (150)	"Small bowel" though outlined as abdominal cavity	Entire abdominal cavity including all possible organ locations to iliac crests or D12/L1	CTCAE v4.0 Gr1-3 –diarrhoea or "whole digestive toxicity"	8/37 (21.6%) 17/37 (46%)	'Larger volumes' receiving 10-30Gy associated with diarrhoea & 'whole late digestive toxicity'	1,6,7 (n/a 2-5)	1, 2
Deville (140)	Intestinal cavity	Intestinal cavity: large & small bowel below L4-5	RTOG Gr≥2	2/30 (6%)	No dose-volume relationship found	1,7 (n/a: 2-6)	None
Isohashi (145)	Peritoneal cavity	Volume surrounding small bowel loops to edge of peritoneum	RTOG/EORTC Gr2+	16/97 (16.5%)	No dose-volume relationship found	1,4,6,7 (n/a 2,3)	2
Poorvu (153)	1. Peritoneum 2. Peritoneum + Colon	1. Possible location of small bowel exc solid organs & RP structures. 2. Peritoneum (as above) plus asc & desc colon	CTCAE v4.0 Gr3+	3/46 (6.5%)	No dose-volume relationship found	1,6,7 (n/a 2-3)	2
Guerrero-Urbano (112)	Bowel loops	Loops from recto-sigmoid junction to 2cm above PTV 2	RTOG diarrhoea; LENTSOMA consistency & frequency- worst grade	21/79 (26%) RTOG; ≥gr2 6/79 (7.6%)	Bowel volume of >450cc had both higher RTOG & LENTSOMA diarrhoea. Constraints: V40<124cc, V45 <71cc, V60 <0.5cc for RTOG<gr 2 (for IMRT)	1,7 (n/a 2-3)	1
Mcdonald (149)	Bowel loops	Loops from recto-sigmoid junction to 2cm above PTV	RTOG Gr≥1	7/47 gr1; 3/47 gr2 (6.4%)	Constraints for <25% ≥ gr2 toxicity: V30<178cc;V35<163cc;V40<151cc;V45<139c ; V50<127cc; V55<115cc; V60<98cc V65<40cc	1,4,7 (n/a 2-3)	2

Abbreviations: n/a: not applicable; Gr: Grade

2.4.2. Small Bowel and its components

Ten papers (including 836 patients) examined dose-volume relationships of the small bowel or its components. The findings are detailed in table 2.4-3. Six studied small bowel as a whole, and 4 more specifically the duodenum. No papers examining ileum or jejunum were found.

Small bowel

Of the 6 studies, 4 found no correlation with late bowel toxicity and dose-volume parameters of small bowel. Isohashi *et al* (145) found in their study of 97 cervical cancer patients that a V40 to 340cc small bowel was the best predictor of toxicity. This constraint split patients into cohorts, with 46.2% having toxicity above the constraint and 8.7% having toxicity below the constraint. Chopra *et al* (139) in a similar group of patients found on multivariate analysis that reducing V15 to below 275cc dichotomised patients into 20% toxicity above the constraint and 5% below the constraint (p=0.02). V40 was significant on univariate analysis only.

Duodenal Papers

Out of 4 papers 3 papers found a relationship between dose-volume parameters and duodenal toxicity. Huang *et al* (144) found the V25 to be the significant predictor for pancreatic cancer patients treated with concurrent gemcitabine – V25 below 45% of duodenal volume was associated with toxicity of 8%, above this toxicity was 48%. With exclusion of 18 patients who had both gemcitabine and erlotinib group V35Gy was the best predictor with a V35% of <20% splitting patients into cohorts with 41% above the constraint and 0% below the constraint.

Kelly *et al* (146) found (also in pancreatic cancer patients treated with a variety of concurrent agents) that a V55 more than 1cc was the most important predictor on multivariate analysis: higher than 1cc resulted in toxicity of 47%, compared with 9%.

Verma *et al* (157) and Poorvu *et al* (153) both examined duodenal dose-volume data in gynaecological patients. Whilst Poorvu found no dose-volume relationship, Verma also found that V55 was a significant dose-volume predictor. With a constraint of V55 of <15cc 49.6% of patients had toxicity above this constraint, and 7.4% had toxicity below this constrain

Table 2.4-3: Small bowel studies: significant findings and quality assessment

						Quality Assessment	
Author	**OAR studied**	**OAR defined**	**Toxicity definition**	**Pts with this toxicity**	**Significant findings**	**Statistical considera-tions met (1-7)**	**Endpoint considerat-ions met (1-3)**
Chopra (139)	Small bowel	2cm above target, individual small bowel loops (differentiated from large bowel – unclear how)	CTCAE v3.0 Gr3+	9/71 (12.6%)	V15<275cc, V30<190cc, V40<150cc reduces gr3 from 20% to <5%. V15 significant on multivariate analysis	1, 4, 6 (n/a 2,3)	2
Isohashi (145)	Small bowel	Bowel loops remaining after exclusion of large bowel loops	RTOG/EORTC Gr≥2	16/97 (16.5%)	V40 best predictor of late toxicity; Recommend V40<340ml to reduce toxicity from 46.2% to 8.7%	1,4,6,7 (n/a 2,3)	2
Adkison (135)	Small bowel	Not clearly defined	CTCAE v3.0 Gr1 & 2	Gr1 16/53 (30%); Gr2 4/53 (8%)	No dose-volume relationship with V30-V60 small bowel	1 (n/a 2-6)	None
Fokdal (142)	Small bowel	Opacified & unopacified small intestine loops (outer contour & contents) from 1st slice to minor pelvis	LENT-SOMA Gr1-4	Symptom specific	No dose-volume relationship found with small bowel	1,2,4,5,7 (n/a 3)	1,2,3
Fonteyne (143)	Small bowel	Not clearly defined	RTOG and "RILIT" Gr1 & Gr2	Gr1 112/241 (46%), Gr 2 32/241(13%)	No dose-volume relationship found with small bowel	1, 4, 5 (n/a 3)	1,2
Poorvu (153)	Small bowel	Opacified & Non-opacified small bowel loops	CTCAE v4.0 Gr3+	3/46 (6.5%)	No dose-volume relationship found with small bowel	1,6,7 (n/a 2-3)	2
Huang (144)	Duodenum	Duodenal bulb to ligament of Treitz	CTCAE v4.0 Gr≥3	8/46 (17.4%)	V25>45% increases toxicity from 8% to 48% Excluding patients having erlotinib the V35Gy>20% increases tox from 0% to 41%	1,4,6,7 (n/a 2,3)	2
Kelly (146)	Duodenum	Gastric pylorus until end of duodenum	CTCAE v4.0 Gr≥2	20/106 (18.9%)	V55>1cc increases toxicity risk from 9% to 47%	1,4,6,7 (n/a 2,3)	2
Poorvu (153)	Duodenal segments	D1 segment: bulblike shape & origin beyond gastric pylorus. Transitions between 2nd & 3rd was lateral border of IVC; Between 3rd & 4th was medial border of aorta	CTCAE v4.0 Gr≥3	3/46 (6.5%)	No dose-volume relationship found with duodenum	1,6,7 (n/a 2-3)	2
Verma (157)	Duodenum	From gastric outlet through transverse portion of duodenum (ascending portion excluded)	RTOG, all grades	9 / 105 (8.6%)	V55>15cc toxicity increased from 7.4% to >48.6%	1,4,6,7 (n/a 2,3)	2

2.4.3. Large Bowel and its components

Sixteen studies (including 2518 patients) were included in this section (see table 2.4-4). 11 studies examined dose to the anal canal/anorectal region. 2 papers looked at 'large bowel' and 2 at sigmoid colon.

2.4.3.1. Large bowel

"Large bowel" was examined in post-operative gynaecological patients. Chopra *et al* (139) found on multivariate analysis that V15 was associated with gr 3 CTCAE defined toxicity. Their recommendation was that reducing V15 <250cc, V30 to <100cc and V40 <90 cc could reduce grade 3 toxicity from 20% to 5%. Isohashi *et al* (145) however found no correlation with RTOG toxicity and large bowel.

2.4.3.2. Sigmoid colon

2 studies looked at the sigmoid as an OAR. Fonteyne *et al* (143) examined the dose-volume relationship of sigmoid colon and toxicity. Gr 1 RILIT was inversely related to the volume of the sigmoid colon with a smaller volume being associated with an increased toxicity risk. V40 was associated on multivariate analysis to grade 1 diarrhoea and grade 1 blood loss. Recommendations were that V40 must be<10% and V30 <16% to avoid grade 1-2 diarrhoea. Mouttet-Aldouard *et al* (150) found that "digestive toxicity" significantly correlated with sigmoid doses. They also found doses of 30-40Gy were most significant, and that D40%, D50% and D80% significantly correlated. No specific cut-offs were identified.

2.4.3.3. Anal canal

12 papers were found examining the dose-volume relationship of the anal canal and bowel toxicity. Many of the studies looked at both rectal and anal parameters, though only those related to the anal canal are discussed in this review.

2.4.3.4. Dose-volume parameters

2.4.3.4.1. Anal canal / anal sphincter region

Of the 12 papers, 11 had positive findings for relating toxicity to the anal canal/sphincter to dose-volume parameters or NTCP models. Different anatomical definitions were used though most defined the anal canal as the distal 3cm of rectum. In 5 studies (136-138, 151, 155) Dmean to the anal canal/sphincter region was considered to be most predictive, though others including Dmin (158), V65 (151) and V90% (=V>59.4Gy) (147), Dmax (142) and Dmedian were found to be important in individual studies.

Table 2.4-4: Large bowel papers: significant findings and quality assessment

						Quality Assessment	
Author	**OAR studied**	**OAR defined**	**Toxicity definition**	**Pts with toxicity**	**Significant findings**	**Statistical considerations met (1-7)**	**Endpoint considerations met (1-3)**
Chopra (139)	Large bowel	2cm above target, individual loops of large bowel	CTCAE v3.0 ≥Gr3	9/71 (12.6%)	Multivariate analysis: V15 related to gr 3 toxicity. Constraints: V15<250cc, V30<100cc, V40<90cc reduces toxicity 20% to 5%	1, 4, 6 (n/a 2,3)	2
Isohashi (145)	Large bowel	Single loop continuing from end of sigmoid to ascending colon	RTOG/EORTC, Gr≥2	16/97 (16.5%)	No constraint found for large bowel	1,4,6,7 (n/a 2,3)	2
Fonteyne (143)	Sigmoid colon	Where rectum swerves anteriorly to one slice above aortic bifurcation	RTOG and "RILIT", Gr 1 and 2	Gr 1 112/241 (46%), gr 2 32/241 (13%).	V40 associated with gr1 diarrhoea & blood loss. Constraints: V40<10%, V30<16% to avoid gr1-2 diarrhoea	1, 4, 5 (n/a 3)	1,2
Mouttet-Audouard (150)	Sigmoid colon	Anterior curvature of sigmoid colon to anterior abdominal wall	CTCAE v4.0 Gr 1-3 –"Whole digestive toxicity"	8/37 (21.6%); 17/37 (46%) (whole tox)	'Whole late digestive toxicity' associated with V10-40. No specific constraints.	1,6,7 (n/a 2-5)	1,2
al-Abany (136)	Anal sphincter region	Caudal 3cm of the rectum from anal verge (inc filling)	Own questionnaire; Faecal leakage >2X/week	9/65 (13.8%) faecal leakage	Constraints: V35<60%, V40<40% associated with no risk of faecal leakage. Increased risk with mean dose of 45-55Gy	1,4,6,7 (n/a 2,3)	1,2,3
Alsadius (137)	Anal sphincter region	Caudal part of large bowel, from end of rectal ampulla where bowel no longer had visible content or air.	Own questionnaire; Faecal leakage >once per month	51/403 (12.7%) faecal leakage	Dmean<40Gy reduces risk from 17% to 4%.	1,2,4,5,7 (n/a 3)	1,2,3
Fokdal (142)	Anal canal	Outer contour of the structure extending from anal verge 2 cm cranially	LENT SOMA score	Urge: 27/71 (38%); Incontinence: 21/71 (30%)	Urgency related to Dmed>33.8: increases toxicity 31% to 47% Incontinence related to Dmax> 53.8 increases 14% to 44%	1,2,4,5,7 (n/a 3)	1,2,3
Vorderm ark (158)	Anal canal	Anal verge to the section below visible rectal lumen, corresponding to the upper border of the levator ani muscle	"Solid soiling" (Severe incontinence) Own continence questionnaire	6/44 (14%)	Severe incontinence - ass with Dmin (23.1Gy) - related to portals extending 2 mm below ischial tuberosities (compared with 5mm above)	1, 7 (n/a 2-3)	1,2,3

Koper (147)	Anal canal	Caudal 3cm of the intestine	RTOG gr1 +2; Plus symptom questionnaire.	141/248 (57%)	D90% (=54.9Gy) to associated with ≥ Gr1 rectal toxicity	1,6,7 (n/a 2-3)	2,3
Taussky (156)	Anal canal	Most distal 2-3cm of rectum	10 questions from UCLA-PCI, FACT-P & EORTC QLQ -PR25	Unclear	no relation with anal canal DVH found	7 (N/a: 2-3)	3
Buettner (138)	Anal canal	Caudal 3cm of rectum	Common grading scheme; subjective sphincter control at highest grade	57/388 (14.7%)	DSH data: Toxicity correlated with dose to anal surface: lateral extent 53Gy>56%. DVH data: Dmean 47Gy to anal sphincter volume correlated with sphincter toxicity. Constraints: Dmean of >30Gy. NTCP modeling to LKB model (parameters defined)	1,3,6,7 (n/a 2)	1,2,3
Peeters (151)	Anal wall	Wall of caudal 3cm of anorectum (method described)	RTOG/EORTC ≥ Gr 2 and ≥Gr 3 Plus incontinence pad use>2x/wk	Gr≥ 2 165/641 (25.7%) Gr≥ 3 27/641 (4.2%)	Dmean increase from 19Gy to 52Gy increased Gr2 toxicity: 16% to 31%. V65 & Dmean most sig for incontinence. Dmean increase by 33Gy increased incontinence by 12%	1,2,4,6,7 (n/a 3)	1,2
Mavroidis (148)	Anal sphincter region	Musculaure layer around the rectal aperture, 3cm caudal from anal verge	Own questionnaire	faecal leakage 19/65 (29%); blood/mucus 22/65 (34%)	Relative seriality NTCP model of anal sphincter for incontinence, blood/mucus. Parameters defined (see text)	1, 3, 5, 6, 7 (n/a 2)	1,3
Peeters (152)	Anal canal wall	Wall of caudal 3cm of anorectum (method described)	Incontinence requiring pad use>2x/wk;	32 (7%)	NTCP LKB model of incontinence with anal wall dose parameters (see text)	1,3,4,5,6,7 (n/a: 2)	1,3
Smeenk (154)	Anal sphincter muscles	Individual muscles defined (Internal anal sphincter (IAS), external anal sphincter (EAS), puborectalis and levator ani)	Frequency, Urgency, Incontinence	21/48 (44%)	For complication <5% Dmean<30Gy to IAS; <10Gy to EAS, <50Gy to puborectalis, <40Gy to levator ani	1, 4,5 (n/a 2)	1.2.3
Smeenk (155)	Anal wall	Continuation of rectal wall from anal verge to slice below lowest slice with a rectal balloon	Frequency, urgency, incontinence	39% frequency, 31% urgency, 31% incontinence	For urgency: Anal wall Dmean<38Gy risk <15%, >38Gy risk is 62%	1,4,7 (n/a 2,3,5,6)	1,3

Dmean

5 studies (see table 2.4-5) found Dmean anal canal/sphincter region to be predictive of toxicity, 4 of faecal incontinence and 1 of faecal urgency. The Dmean was converted to an equivalent dose in 2Gy fractions. As it can be seen there is relative consistency in the recommended Dmean constraints between 40-47Gy, despite the OARs being defined slightly differently. Though Buettner *et al* found a Dmean of 47Gy to be most statistically significant, they recommend an optimal constraint of <30Gy. Peeters *et al*, despite their large study did not suggest a specific constraint though noted an increase Dmean above 52Gy results in toxicity of 31%.

Table 2.4-5: Anal canal Dmean findings

Study	No of pts	OAR	Endpoint	Dmean (in EQD2) constraint	Risk of endpoint below this constraint	Risk of endpoint above this constraint
Al-albany	65	Anal sphincter region	Incontinence >2X/week	43.2	8%	52%
Alsadius	403	Anal canal	Incontinence >1x/month	40	5.2%	21%
Buettner	388	Anal sphincter region	Incontinence : moderate/severe (gr2)	47, though <30Gy ideal	5% (approx; read from graph)	
Smeenk	36	Anal canal wall	Urgency present	41.8	15%	62%
Peeters	641	Anal canal wall	Incontinence requiring pad >2x/week	No constraint specified	16% at 19Gy	31% at 52Gy

Other DVH parameters

Koper *et al* (147) found that a V>90% dose (in their study 59.4Gy) to the anal canal was significantly associated with toxicity. Vordemark *et al* (158) found the parameter Dmin to be significantly different in patients with complete continence (Dmin 15.1Gy) and severe incontinence (Dmin 23.1Gy) (p=0.04). A threshold of Dmin<20 was suggested, however 1 patient with severe incontinence (of 6) had a Dmin much lower than this. They also compared the 2 groups in terms of the lower border of the treatment fields – those with severe incontinence ended 2mm below ischial tuberosities versus 5mm above ischial tuberosities.

Fokdal *et al* found a relationship between urgency and Dmedian, and incontinence and Dmax (159). Their cut-offs suggest above a Dmedian of 33.8Gy risk of urgency is 47% below is 31%. Incontinence was related to maximal anal canal dose: above a Dmax of

53.8Gy risk is 44%, below is 14%. V65 anal canal wall was also strongly associated with incontinence (151).

Anal sphincter muscles

Smeenk *et al* (154) also approached the anal canal region by relating dose to individual sphincter muscles for the presence or absence of three symptoms: urgency, frequency and incontinence. Their suggestion to keep urgency and incontinence below 5% was for Dmean to be <30Gy to the internal anal sphincter, <10Gy to the external sphincter, <50Gy to puborectalis, <40 to the levator ani muscles.

Dose surface parameters

Buettner *et al* (138) examined incontinence in prostate patients. As well as DVH data, dose surface maps (DSM) for the anal canal were used. These give more spatial information compared with a traditional DVH. They found that to the lateral extent a dose of 53Gy of 56% was most correlated with subjective sphincter toxicity. They recommend 45Gy (ideally 27Gy) for surface-based mean-dose to the anal canal to reduce toxicity.

NTCP modeling

Three studies used NTCP models to relate late toxicity data with dosimetric parameters. Buettner *et al* (138) fitted mean-dose anal canal data to a Lyman-Kutcher-Burman (LKB) model, identified parameters related to grade 2 RTOG toxicity: TD50 of 120, m of 0.42. Peeters *et al* also fitted data to an LKB model (152) – with the parameters of anal wall dose to incontinence requiring pads >x2/week of n=7.48; TD50=105; m=0.46. They further modified their model to incorporate a previous history of abdominal surgery and found this improved the model fit, suggesting a decreased radiation tolerance for patients with this risk factor.

Mavroidis *et al* (148) modelled dose to the anal sphincter region for ‘faecal leakage’ and ‘blood or phlegm’ in stools using the relative seriality NTCP model. They found parameters of $D50$ = 70.2 Gy, γ = 1.22, s = 0.35 for incontinence and $D50$ = 74.0 Gy, γ = 0.75, $s \approx 0$ for blood or mucus with a recommendation that reducing the biologically effective uniform dose (EUD) to anal sphincter < 40–45 Gy may significantly reduce toxicity.

2.4.4. Quality Assessment

Quality assessment considerations for each paper are detailed in tables 2.4-2, 2.4-3 and 2.4-4. If, for example considerations 1 and 3 (from table 2.3-1) was met a ‘1,3’ was noted in the column.

Statistical criteria

The majority of papers provided adequate information on basic statistical data (24/25), and clear definition of OARs (22/25). Constraints were derived in 15 papers, with associate complication rates stated in 13 papers. Of the 15 papers goodness of fit was reported in 7 papers, with discriminator statistics reported in 14 papers. For the 3 papers with NTCP models all provided parameter estimates with standard error.

Endpoint criteria

Overall toxicity grades rather than individual symptoms were assessed in 12 of 25 studies, with patient-reporting found in 10 studies (9 of which were studies of the anal canal). 16 of the studies looked at co-morbidity to assess its contribution to late toxicity and this was taken into account in multivariate analyses if thought to be associated.

2.5. Discussion

Late bowel toxicity is a common occurrence, and reduction of bowel toxicity is a key goal of modern radiotherapy techniques. Dose-volume predictors and constraints for late bowel toxicity after pelvic radiotherapy are not well established and it is difficult to determine the likely efficacy of new radiotherapy techniques without this knowledge.

This systematic review aimed to examine the currently published literature for dose-volume predictors and constraints to reduce the risk of late bowel toxicity. 25 studies including 3718 patients were found after systematic searching and matching of studies to specified inclusion criteria. Key findings were relatively consistent dose-volume constraints for anal canal as an OAR in five of the studies. Constraints were also suggested in individual studies for bowel loops, small bowel, duodenum and large bowel though these findings were not corroborated with other studies.

Although the focus of this thesis is gynaecological malignancies, within this review all pelvic malignancy diagnoses were included, with the rationale that the dose-volume response to bowel should be the same regardless of primary tumour. This approach has been used both in historic papers (125, 130) and more recently QUANTEC guidelines. Though it is known that other patient- and treatment-related factors associated with specific diagnoses, such as previous surgery, concurrent treatments and co-morbidities, may influence late toxicity, these factors should be accounted for in the statistical analysis of the individual studies and were not reason for exclusion from this review.

2.5.1. Whole bowel studies

Delineation of bowel traditionally is defined with individual loops visible on the planning CT. This however does not take into account inter- and intra-fractional variation of the bowel over the course of treatment. It has been suggested that only 19.2% of the bowel occupies the same space over time (160). To account for this motion the 'potential space' where bowel may lie is outlined, and denoted as 'bowel bag', 'intestinal cavity' or 'peritoneal cavity'.

For acute toxicity QUANTEC recommend the peritoneal cavity constraint of V45<195cc based on a study by Roeske *et al* (56) in 50 patients with cervical cancer. They suggest that such a limit may also be applied in late toxicity, though this "correlation is not yet established." Dose-volume parameters of bowel bag have been found to be more predictive than those of bowel loops (161) for acute bowel toxicity.

In this systematic review, 2 of 5 studies found a correlation with dose-volume parameters of the peritoneal cavity and late toxicity. There was some concordance between the two studies with one study finding V20 peritoneal cavity to be important (141), and the other suggesting V10-V30 (150). However no volume cut-offs or constraints were defined by either study.

There was no concordance demonstrated in the studies with the V45 constraint recommended by QUANTEC for acute toxicity. Poorvu *et al* (153) found no toxicity constraints using two definitions of peritoneum. In addition they applied the QUANTEC dose constraints to bowel bag (V45<195cc) and found this to have limited sensitivity 0 of 3 cases (0%) though a specificity in 32 of 39 cases (82%). For peritoneal cavity, therefore, no specific constraints for late toxicity can be concluded from this review.

Guerrero-Urbano *et al* (112) and McDonald *et al* (149) both suggest dose-volume constraints for RTOG defined toxicity, with Guerrero-Urbano finding constraints specifically for diarrhoea. Both studies defined bowel loops with the same method, though despite this their suggested constraints are significantly different, for example V60 (equivalent dose of 58.5Gy) of <98cc compared with a V60 (equivalent dose of 56.6Gy) of <0.5cc. McDonald *et al* defined their model for grade≥2 toxicity, with only 3 patients in their study having grade ≥2 toxicity. With this lack of concordance in the findings it is again difficult to recommend any specific bowel loop constraints.

2.5.2. Small bowel studies

For small bowel QUANTEC recommend constraints of V15<120cc for acute toxicity. This is based on initial modelling studies in rectal cancer by Baglan *et al* (162), which has subsequently been validated by Robertson *et al* (163). The studies were found to have concordant results with three other studies (164-166) including rectal and cervix cancer patients.

In this chapter only 2 of 6 small bowel papers found a dose-volume relationship of the small bowel with late toxicity. Both Isohashi *et al* (145) and Chopra *et al* (139) studied in similar groups of patients, treated with similar dose-fractionations. Isohashi *et al* found V40 was most significant parameter, though in contrast Chopra *et al* found V15 to be significant on multivariate analysis. V40 was significant on univariate analysis by Chopra *et al* too, however when comparing the findings, one suggests a V40<150cc and the other V40<340cc. Reasons for the lack of concordant results between papers could be due to different toxicity scoring systems and Isohashi *et al* only considering grade 3 toxicity.
Although V15 was found to be significant by Chopra et al, their suggestion of V15<275cc was dissimilar to that recommended by QUANTEC.

Five of the six small bowel studies used an overall grade score (either CTCAE or RTOG) rather than individual symptom analysis, which may account for the lack of consistent constraints found. Patient numbers in all these studies were relatively small, many with <100 patients (and small numbers of patients with defined toxicity endpoint).

For the duodenum two studies (146, 157) found the V55 to be a predictive parameter of toxicity, though one with a constraint of 1cc and another with 15cc. Again this could be due to different clinical scenarios and different scoring system used (RTOG versus CTCAE). In all four duodenal papers different dose-fractionations were used, and the full detail of the dose-fractionation data was not available making it is impossible to directly compare their findings with conversion of dose using BED calculations.

As for whole bowel, it is difficult to choose constraints for small bowel and duodenum from the results of single studies. Each of the above studies did consider some of the statistical and endpoint considerations as recommended by QUANTEC, and their findings could be important, however further validation is needed with additional data.

2.5.3. Large bowel studies

For “large bowel” Chopra *et al* defined constraints (V15<250cc, V30<100cc, V40<90cc) to reduce toxicity from 20% to 5%. However there was no concordance with the second study (145) where no correlation was found.

Fonteyne *et al* (143) examined the sigmoid colon and made recommendations (V40<10%, V30<16%) to avoid grade 1-2 diarrhoea. There was some correlation with a second paper (150) which also found V30 and V40 to be of importance, though this was not quantified. This may well be useful clinically though again further validation is needed.

2.5.4. Anal canal studies

Of all the components of bowel studied, most data was available in studies regarding the anal canal/anal sphincter region. This was due to large studies of prostate patients, often from clinical trials, where both high quality late toxicity data and dosimetric data are found. 10 of the studies used individual symptoms reported by patients rather than an overall toxicity score, an important consideration recommended by QUANTEC. The main symptom studied was faecal incontinence (‘faecal loss’ or ‘faecal leakage’), though urgency and frequency were also addressed. Statistical and endpoint measures were met much more frequently in these studies suggesting a higher quality. Some were still limited by the lack of baseline data and information on co-morbidities.

From the available data it is clear that there is a definite relationship between dose-volume parameters to the anal canal and incontinence. Dmean was found to be the most significant parameter in 5 different studies (see table 2.4-5), most with relatively large populations of patients, allowing for its conclusive use. There were different definitions in the endpoint and OAR definitions, however, relatively consistent constraints for Dmean of 40-47Gy were found.

From the available data it may be concluded, that the constraint Dmean of <40Gy (in 2Gy fractions) to the anal canal is likely to improve patient toxicity.

2.5.5. Quality assessment measures

QUANTEC provided guidance on quality assessment of papers when considering different dose-volume studies together for clinical use or meta-analysis. Statistical criteria were considered with varying degrees between studies, generally with the larger studies looking at anal canal focusing more on these statistics, and the smaller studies looking at small bowel for example not addressing these concepts. Clear definition of the OAR was found

in all but three studies. However in between studies definitions varied significantly, making pooling of results/conclusions difficult.

Normal tissue complication probability (NTCP) modelling is considered a more robust method to test the relationship of a dose-volume parameter with a toxicity endpoint compared with simple correlation alone. The main NTCP models within the literature are Lyman-Kutcher-Burman, and Relative Seriality models, and these were investigated within this review with regards the anal canal in three studies.

In terms of toxicity endpoint QUANTEC recommended that individual symptoms are used in place of "portmanteau" endpoints such as "RTOG grade 2", which could mean a variety of different toxicities. Only 13 studies used individual symptoms rather than an overall score, and with ten of these studies producing more conclusive results. QUANTEC also suggest that patient-reporting of toxicity may be of benefit, and this was noted to be used in the majority of papers reporting dose-volume constraints to the anal canal, where conclusive results were found.

2.5.6. Strengths and Limitations

This review has many strengths, including that the literature search was performed systematically with potential studies being assessed by two separate investigators. A heterogeneous group of studies were compared and contrasted with different primary tumour sites, based on the assumption that the dose-volume response to bowel should be similar for all pelvic radiotherapy treatments.

The importance of the anal canal as an OAR was highlighted in this review, which has not been such a prominent OAR in the literature and is rarely considered in clinical or trial protocols.

Limitations of this chapter include the exclusions made at the onset which may have prevented additional information from being gathered. A "cut-off" definition of late toxicity, as "after 3 months of radiotherapy" to distinguish between acute and late toxicity was used. There is some evidence to suggest that acute and late toxicity should not be entirely distinguished as late toxicity may be a continuum of acute toxicity (a "consequential late effect") (167). The time-point when acute becomes late may not be 3 months for all patients developing bowel toxicity and there is a potential that studies where toxicity developed earlier may have contributed to the information gathered.

By excluding studies that focussed on the rectum, studies examining the 'anorectum' may have been excluded. Similarly some studies looking at the 'gastro-duodenum' were not

included as they included dose-volume parameters for the stomach which is beyond the scope of this review.
Studies using SBRT were also excluded as with the large fraction sizes used in these studies whether the results would be directly comparable radiobiologically to standard fractionation is not known, and a simple BED conversion may not be enough, as the validity of the linear quadratic model is questioned with extreme hypofractionation (168).

Although all pelvic tumour sites were included assuming that bowel would have the same dose-volume response, other contributing factors may influence late toxicity such as concurrent chemotherapy or brachytherapy, or specific patient-related factors. Though it is expected that individual authors may account for these factors statistically this may not always be possible and may result in the inconsistent results found.

Furthermore many of the studies found no correlation with OAR dose parameters and late bowel toxicity, and this is assumed to be because of methodological reasons. The alternative reason could be that in fact the particular OARs may genuinely not have any influence on late toxicity, and rather than dose-volume predictors, other considerations such as inherent radiosensitivity of individual patients, may be the main predictors of toxicity.

2.6. Conclusions

This systematic review aimed to seek dose-volume constraints for late bowel toxicity from the published literature which can be applied to assess the usefulness of advanced radiotherapy techniques in gynaecological malignancies.
To reduce late bowel toxicity such as incontinence and urgency, reduction of the anal canal mean dose to <40Gy is an important constraint.
For other components of bowel, though some dose-volume constraints are found, individual studies do not correlate with each other, and reliable constraints cannot be found in the published data.

2.7. Future Work

Future studies should aim to derive bowel dose-volume constraints for late toxicity with quality considerations as recommended by QUANTEC. Validation of constraints found

within this systematic review with additional data in future studies may be a good starting point, potentially enabling the constraints to be used clinically.

2.8. Acknowledgements

All systematic searches for this review were performed by Ms Bernadette Coles, Cancer Research Wales Library, Velindre Cancer Centre, Cardiff.

Review of initial references was performed independently by myself and Dr Emma Higgins, Specialist Registrar in Clinical Oncology, Velindre Cancer Centre, Cardiff.

All other components of this work was performed by myself.

3. Chapter III: Definition of dose-volume constraints for patient-reported late bowel toxicity

3.1. Introduction

Late bowel toxicity is a significant problem for survivors of pelvic malignancies. During radiotherapy planning dose-volume constraints are used to limit the development of toxicity. Reliable dose-volume constraints for bowel toxicity may be useful to assess the toxicity-reducing ability of IMRT techniques in gynaecological malignancies.

The previous chapter of this thesis systematically reviewed the available literature on dose-volume constraints for late bowel toxicity. The anal canal was found to be an important OAR with dose-volume constraints available from the literature, which aim to reduce faecal incontinence.

Other components of bowel, including bowel loops, small bowel, duodenum and sigmoid were identified as potential OARs for late bowel toxicity. Dose-volume relationships for these OARs were described, and some constraints suggested, however there was little corroborative evidence in other studies to validate these findings.

The systematic review also highlighted the need for further studies to carefully consider toxicity endpoints, the OAR being studied and the statistical methods used to assess the data. This chapter aims to further knowledge and corroborate data from published studies on dose-volume constraints for patient-reported late bowel toxicity whilst taking these considerations into account.

3.1.1. Toxicity considerations

Late bowel toxicity includes a multitude of symptoms, which can be graded by different scoring systems and at different time-points, and these factors must be clearly defined in dose-volume studies.

Symptoms

Prioritising which individual symptoms within the umbrella of bowel toxicity to study is an important question. One possible avenue is to examine symptoms perceived by patients as influencing their quality of life. Andreyev *et al* (33) reported in their review of patient reported studies after pelvic radiotherapy that symptoms affecting quality of life include

faecal incontinence (25-89%), change in bowel habit (18-79%), faecal urgency (10-79%), and rectal bleeding (11-31%). Another study found that diarrhoea, bleeding, urgency and pain caused most distress (169). After review of the literature the following four symptoms were selected for this work: faecal urgency, faecal incontinence, diarrhoea and rectal bleeding.

Scoring system

Radiation toxicity has traditionally been graded with the Radiation Therapy Oncology Group (RTOG) score. The RTOG bowel toxicity score comprises only a small number of symptoms, including bleeding, proctitis and diarrhoea (37). Other bowel symptoms that may impact quality of life, such as faecal incontinence and urgency, are not included. Scores from individual symptoms tend to be grouped together to form an overall RTOG score from 0-4, with grade 3-4 considered clinically most important.

The Common Terminology Criteria for Adverse Events (CTCAE) grading has been used preferentially in recent years, especially in clinical trials, as it is more comprehensive in terms of symptom inclusion (38).

The LENT-SOMA (Late Effects of Normal Tissues-Subjective, Objective, Management and Analytic Measure) score was developed in the 1990s (39). It comprises a subjective ('S') component, which was converted into a patient-reported questionnaire in 2003, and has been validated in the literature (170, 171). It also includes three other components: objective, management and analysis, and there is flexibility whether one or all components are used.

RTOG and CTCAE are clinician-reported scores, which potentially underestimate toxicity compared with patient-reported scores. A comparison of RTOG and subjective LENT-SOMA scoring in survivors of cervical cancer found that severe bowel toxicity (grade 3-4) was 45% with patient-reporting though only 15% with clinician-reporting (41). The importance of patient-reporting is being acknowledged and a patient-reported CTCAE (PRO-CTCAE) is being developed to be used alongside the CTCAE score (172).

The UCLA prostate cancer index is a subjective quality of life (QoL) score used in prostate cancer, where patients report "bowel bother" symptoms on a linear scale from 0-100. Though this is demonstrated to be useful, it was also found to be limited in terms of symptoms compared to the LENT SOMA score (173). Further the Inflammatory Bowel Disease Questionnaire (IBDQ) questionnaire has been also been applied in the radiotherapy setting and found to be reliable for assessing toxicity symptoms (40). Other

scores, such as the EORTC-CLC-30, are used to assess patient-reported toxicity though with the focus being on Qol (174).

When considering a toxicity score for dose-volume studies QUANTEC recommend the outcomes to be “clinically relevant” scores of individual symptoms (rather than a collective overall score) and suggest the use of patient-reported outcomes (PROs) (132).
After a review of the literature on available toxicity scoring LENT-SOMA was chosen because it has a comprehensive coverage of bowel symptoms, is validated and can be used in a variety of ways (including clinician and patient reporting) hence best fitting the QUANTEC recommended criteria.

With respect to toxicity grade many of the studies in the systematic review considered endpoints of grade 3 and above as important, and grade 2 or below as being “low grade” or mild. However, when the definitions of individual bowel symptoms are examined it is clear that lower grades of toxicity may be impactful on daily life. Grade 2 diarrhoea, for example by RTOG is defined as “bowel movement more than 5 times a day” (37), by CTCAE v4.0 as an “increase of 4-6 stools per day over baseline” (38), and by LENT SOMA as “bowel movement 5-8 times a day” (39). To qualify these grades of toxicity as low grade may underrate the impact of these symptoms on an individual, especially if these symptoms are life-long. In view of this, all grades of toxicity were considered as important to include in this work.

Choice of toxicity time-point
Late bowel toxicity can occur at any time, some studies suggest that most patients develop toxicity within the first two years after treatment (175); others report a median onset at 9 months after radiotherapy (176). Prostate cancer studies have reported a maximal toxicity at around 18 months post-radiotherapy (177). From this, collection of toxicity data after 9 months though within the first 2 years of radiotherapy completion was deemed appropriate for capture of late bowel toxicity. The two time-points selected for this work were 12 months and 24 months after radiotherapy completion.

3.1.2. Choice of OAR

Bowel toxicity symptoms may be caused by radiation to all or any part of the bowel from duodenum to anal canal. Diarrhoea, for example, may be caused by small bowel injury (resulting from bacterial overgrowth, bile sale malabsorption, or changes in small bowel transit) (33); large bowel injury may result in strictures which can diarrhoea and rectal injury may also present with diarrhoea. As discussed in chapter II, bowel itself can be

defined and divided in a number of ways: bowel loops, bowel bag, small bowel, large bowel, sigmoid colon and anal canal all have been studied as OARs for late toxicity with varying degrees of positive findings. All of these have potential to be important OARs without clear evidence of the importance of one over the other. Therefore an inclusive, exploratory approach of all potential OARs was chosen in this work.

Statistical Considerations

QUANTEC have made recommendations on the statistical requirements for studies addressing dose-volume dependence (132). These include clear statistical data on patients included and patients with toxicity, and for complication rates to be stated with any constraints. Any suggested models should have an assessment of their "goodness of fit" of the model to the data and discriminator statistics should be considered. Cross validation with independent data are likely to add to the quality of data. All of these recommendations were therefore considered in this work as far as possible.

3.2. Aims

The aims of this section of this thesis were to:

- Correlate late bowel toxicity data with dose-volume parameters of the different components of bowel.
- To seek dose-volume constraints from this analysis
- To corroborate dose-volume constraints found within the literature (in chapter II) with the toxicity data collected in this section.

3.3. Methods

3.3.1. Patient selection

Patients treated with pelvic radiotherapy from September 2012 to January 2014 were identified using a hospital database ("CANISC") at Velindre Cancer Centre, Cardiff. The following inclusion and exclusion criteria were used:

Inclusion criteria:

1. Patients treated for gynaecological (cervical and endometrial) and urological (prostate and bladder) malignancies
   Amongst the prostate cancer patients only patients who had their pelvic nodes treated in addition to the prostate were included.
2. Patients treated with radical or adjuvant intent

3. Patients treated with any type of radical radiotherapy – conformal, IMRT or VMAT
4. Patients who remained alive and recurrence-free at 12 months after completion of radiotherapy

Exclusion criteria:

1. Patients treated for lower gastro-intestinal malignancies (as it was considered that bowel surgery may be a significant confounding factor)
2. Patients treated with palliative radiotherapy
3. Patients treated with brachytherapy only
4. Patients unwell or with dementia who may be unable to return questionnaires

3.3.2. Toxicity Questionnaires

Patients were sent toxicity questionnaires via post 12 months post-radiotherapy and 24 months post-radiotherapy; completed questionnaires were returned via freepost.

The patient-reported LENT-SOMA questionnaire sent included questions on ten bowel symptoms; sexual and genito-urinary questions were not included in view of the fact that this focus of the study was late GI toxicity. A copy of the questionnaire used is included in Appendix B.

An additional question was added: “are any of the symptoms you report longstanding, i.e. started prior to radiotherapy?” with a free text space. This was added in the absence of baseline scores acknowledging that bowel symptoms may be pre-existing or due to other co-morbidities.

3.3.3. Exclusion of returned questionnaires

Returned questionnaires were excluded from analysis if:

1. Patients were incorrectly identified as having their prostate and pelvis treated when only the prostate was treated.
2. Patients who reported that all their symptoms were due to another known bowel condition, or other causes such as chemotherapy for another malignancy.
   For those who mentioned single symptoms as being longstanding, but other symptoms as starting after radiotherapy, the longstanding symptoms were excluded though the remainder of the questionnaire was included.
3. Questionnaires were returned completely blank. Those with some questions unanswered remained included.

3.3.4. Toxicity data collection

From the questionnaires reported grades of faecal urgency, faecal incontinence, diarrhoea and bleeding were recorded. In addition an "overall" LENT SOMA score was recorded. This was defined as the highest grade of any symptom (from the ten symptoms on the questionnaire).

Potential confounding factors

Patient and treatment-related factors that may be related to toxicity were retrospectively collected from the patient's electronic records as in table 3.3-1.

Table 3.3-1: Patient, disease and treatment-related factors

Patient and Disease-Related Factors	Treatment-Related Factors
- Age at commencing radiotherapy - Gender - Disease Site - Stage of disease	- Total dose/Fractionation - Pelvic/Nodal dose/fractionation - Fraction size - Radiotherapy technique (conformal versus IMRT/VMAT) - Intent (definitive or adjuvant) - Concurrent chemotherapy use - Brachytherapy use - Hormone use

3.3.5. Organs at risk (OARs) definitions

Each patient's planning CT was restored onto OncentraMasterplan version 4.3 (OMP). The following OARs were contoured: bowel loops, bowel bag, small bowel, large bowel, colon, sigmoid, rectum and anal canal.

OARs were defined with guidance from Dr George Joseph (GJ), consultant radiologist, in conjunction with the use of the RTOG consensus document for "Pelvic Normal Tissue Contouring Guidelines" (178). All outlining was performed by myself, with the first eight cases being checked by GJ.

The definitions are detailed in table 3.3-2:

Table 3.3-2: Definitions of OARs

Structure	Definition	Comments
Bowel loops	Bowel loops (including contents) from the recto-sigmoid junction inferiorly to 4.2cm above the PTV superiorly.	4.2cm chosen as it was noted on VMAT plans that low dose is still found 3cm above the PTV. An additional 1cm was added to ensure all dose would be included to make 4cm. 4.2cm had to be used as 3mm slices.
Bowel bag	The entire abdominal/pelvic contents were initially outlined. The inferior slice was the most inferior small or large bowel loop (regardless of relation to rectum). The superior slice was 4.2cm above the PTV. Then all non-GI structures (muscle, bone, kidney, bladder, prostate, and uterus) were excluded.	As per RTOG guidelines
Anal Canal	Anal verge identified and 3cm of anal canal/distal rectum were outlined caudally, inclusive of contents	
Rectum	Defined inferiorly from the ischial tuberosities to the recto-sigmoid junction	
Sigmoid	Commenced inferiorly at the recto-sigmoid junction, followed to the most anterior-lateral point where it becomes descending colon	
Colon	Included caecum, ascending colon, transverse colon and descending colon found in the slices up to 4.2cm above the PTV. Descending colon: commenced proximal to sigmoid. Ascending colon: continued inferiorly from caecum. Transverse colon: distinguished from small bowel by following the continuation of ascending and descending colon on the coronal sections.	
Large Bowel	Sigmoid and colon were combined	Performed using Union function on OMP
Small Bowel	All other bowel loops identified within 4.2cm above the PTV which were not large bowel.	No bowel contrast used

3.3.6. Dose-volume data collection

Dose-volume data was collected using in-house software “DVHImport”, coded by Phillip Parsons (PP), physicist at Velindre Cancer Centre, which allows data to be converted from OMP to Microsoft Excel. Data was collected in the format of VxGy, the Volume receiving xGy in 0.1Gy dose bins from 0.1Gy to 75Gy.

Patients in this study had been treated with a variety of different fraction sizes from 1.8Gy–3Gy. To enable comparability between patients, all dose-volume data was converted to 2Gy/# equivalent doses, using the EQD_2 equation (Equation 1), derived from the linear

quadratic equation. An α/β ratio of 3 was used, which is commonly used for late reactions of the rectum (179). No other specific α/β ratios were found for bowel within the literature.

Equation 1: EQD2 formula

$$EQD_2 = n*d*(d+\alpha/\beta) / (2+\alpha/\beta)$$

(n=no of fractions, d=dose per fraction, α/β = alpha beta ratio)

From the EQD2-converted data Vx dose parameters were recorded: V5, V10, V15 up to V75 at 5Gy intervals. For each OAR absolute volume data (in cc) was collected, though for sigmoid, rectum and anal canal % volume data was also collected as the entire organs were outlined. Median dose (Dmedian), Minimum dose (Dmin), Maximum dose (D0.1cc), and total volume of each OAR were also recorded.

Brachytherapy doses

Some of the gynaecological patients within the study had brachytherapy in addition to external beam radiotherapy. Methods to combine DVHs of the external beam and brachytherapy data were sought, however a robust solution was not found despite seeking advice from Professor Roger Dale, Professor of Radiobiology, Imperial College London.

The main reason is that the CT planning was performed for these treatments at different times in different treatment positions. The anatomical position of all structures including bowel would be different in the two scans, and this would not be reflected in the DVH data, where an area of high dose on one scan may not be representative on the second scan.

In view of this a pragmatic decision was made to assess the addition of brachytherapy statistically as one of the treatment related co-factors, and if found to be associated with increased toxicity to take this into account on multivariate analysis.

3.3.7. Data analysis

Statistical analyses were all performed on SPSS 20 in a number of stages as illustrated in the diagram below (figure 3.3-1). All analyses were performed on the 12 month toxicity data, with the 24 month data only being used for re-exploration of the constraints derived. Lajos Katona (LK) and Catharine Porter (CP) at Wales Cancer Trials Unit (WCTU) provided statistical advice for the regression analysis and derivation of constraints.

Figure 3.3-1: Schematic diagram of data analysis

Toxicity data analysis

For the 5 toxicity endpoints (faecal urgency, faecal incontinence, diarrhoea, bleeding and overall score) the proportions of each patient with the specific toxicity was assessed.

Each endpoint was recorded as:

1) Absent or present (grade 0 vs grade 1-4)

2) Low grade or high grade (grade 0-2 vs grade 3-4)

Association between the recorded patient- and treatment-related factors and each toxicity endpoint was assessed with Chi-squared analysis ($p<0.05$ was considered statistically significant).

Univariate and Multivariate analysis

Binary logistic regression was used to determine the predictive value of the dose-volume parameters for the toxicity endpoints.

Initially a simple 'enter' univariate (UVA) logistic regression was used between each dose-volume parameter and each toxicity endpoint. A p-value of <0.2 was considered as significant at this stage in order not to exclude clinically significant parameters based on overly stringent statistical testing.

For those parameters that were positive on UVA, a multivariate analysis (MVA) was performed. Patient and treatment-related co-variates that were statistically associated on Chi-squared analysis or considered to be clinically related to late toxicity were included in the multivariate model.

For MVA, a backward-stepwise regression analysis was used (180-182). This automated method eliminates variables from the model to include only those that are significant. This approach also takes into account multiple hypothesis testing (avoiding the need for approaches such as Bonferroni corrections). Significance level for MVA was $p<0.05$. The odds ratio (OR) and confidence interval (CI) for each positive parameter was noted.

Dose constraint derivation and goodness-of- fit analysis

Constraints were derived from each dose-volume parameter that was positive on MVA. For each dose-volume parameter the predictive probability from the logistic regression was obtained from SPSS. This was plotted against the volume of the OAR in question.

An example is illustrated in figure 3.2, where the OAR volume is on the x-axis and predicted probability on the y-axis. At different values of predicted probability constraints were determined from the x-axis. For example for a predicted probability of 0.2, the suggested constraint is 46cc, and for 0.5 the constraint is 200cc.

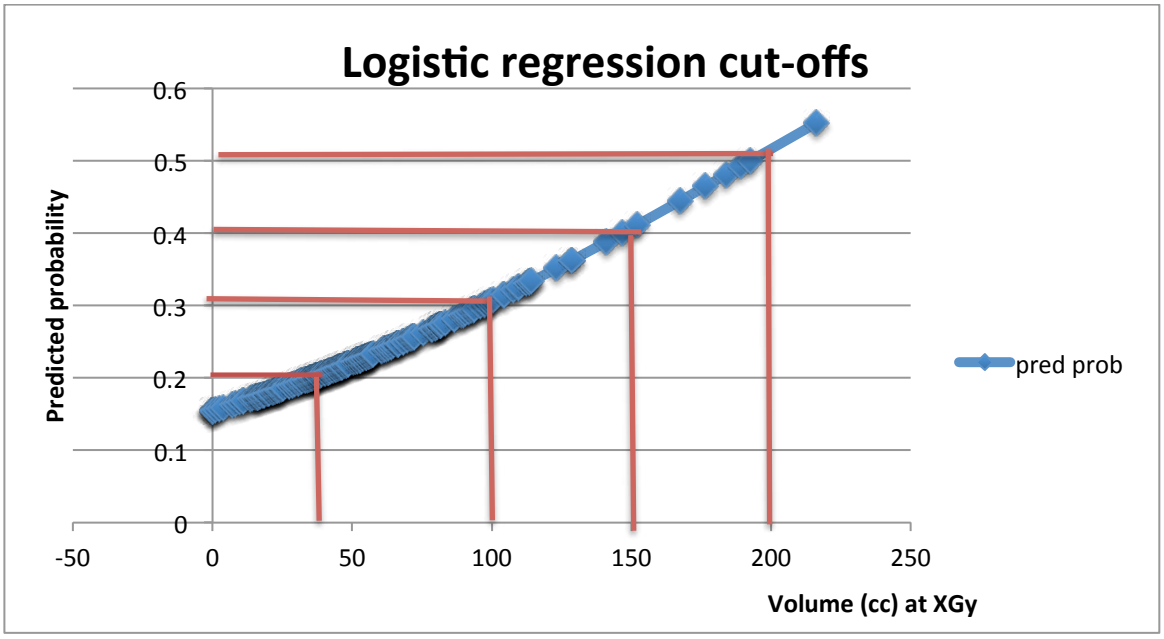


Figure 3.3-2: Logistic Regression cut-offs

Toxicity rates above and below each constraint were assessed. If the toxicity rates above and below the constraint were significantly different (as determined by Pearson's chi-squared testing, $p<0.05$) these were classed as having a "good fit" to the data and were included (183) for further assessment.

Assessment of each constraint: clinical value, accuracy, discriminator testing, and re-exploration with 24 month data

Clinical value

For each constraint the rate of toxicity above and below the constraint was assessed. If the toxicity rate below the constraint was >25% the constraint was disregarded.

Accuracy testing: sensitivity and specificity

For the remaining constraints sensitivity and specificity was calculated. Sensitivity is defined as the proportion of individuals with the toxicity endpoint who are correctly identified as having dose-volume parameters above the constraint. Specificity is defined as the proportion of individuals without the toxicity endpoint who are correctly identified as having dose-volume parameters below the constraint.

Discriminator testing: Receiver Operative Characteristic (ROC) analysis

ROC analysis was performed to determine how well each constraint discriminates those with and without toxicity. The 'Area under curve' (AUC) statistic from ROC analysis tests discriminatory ability, with a value of 1 suggesting perfect discrimination and 0.5 suggesting discrimination no better than chance.

Re-exploration with 24 month results

Constraints derived using 12 month toxicity data were "re-explored" on the toxicity data collected at 24 months with the same "goodness of fit" method as in 3.3.7.3.

3.3.8. Corroboration of constraints from within the literature

Toxicity data from the 12 month time point was used to evaluate dose-volume constraints for late bowel toxicity from the literature. This included the acute bowel toxicity constraints from QUANTEC, and other constraints from the literature found in the systematic review (chapter II of this thesis). These are detailed in table 3.3-3.

Each dose-volume constraint was converted using the EQD2 formula, and the dose level nearest to the EQD2 was used. Toxicity rates in patients above and below each constraints were assessed, and differences assessed for statistical significance using Pearson's chi squared testing, $p<0.05$.

Table 3.3-3: Dose-volume constraints from the literature

Study/Guideline	OAR	Constraints
QUANTEC (Roeske et al(56)) (acute toxicity)	Peritoneal Cavity	V45<195cc
Guerrero-urbano et al (112)	Bowel loops	V40<124cc; V45<71cc; V60<0.5cc
McDonald et al (149)	Bowel loops	V30<178cc; V35<163cc; V40<151cc; V45<139cc
		V50<127cc; V55<115cc; V60<98cc V65<40cc
QUANTEC (Baglan et al (162)) (acute toxicity)	Small bowel	V15<120cc
Chopra et al (139)	Small bowel	V15<275cc; V30<190cc; V40<150cc
Isohashi et al (145)	Small bowel	V40<340cc
Fonteyne et al (143)	Sigmoid	V40<10%; V30<16%
Chopra et al (139)	Large bowel	V15<250cc; V30<100cc; V40<90cc
Multiple studies (136-138, 155, 184)	Anal canal	Dmean<40Gy

3.4. Results

3.4.1. Questionnaires sent and returned

Initially 364 patients were identified, including 48 cervical, 67 endometrial, 195 prostate and 54 bladder cancer patients. After exclusions (see table 3.4-1) questionnaires were sent to 306 patients. The response rates were 74% at 12 months, and 69.5% at 24 months.

Table 3.4-1: Patient inclusions and exclusions

		All Patients	Cervical	Endometrial	Prostate	Bladder
Patients identified		364	48	67	195	54
Patients Excluded at 12 months	Died	39 (11%)	6 (12.5%)	9 (13%)	4 (2%)	20 (37%)
	Local recurrence	8 (2%)	1 (2%)	4 (6%)	1 (0.5%)	2 (4%)
	Distant recurrence	7 (2%)	0	1 (1.5%)	2 (1%)	4 (7.4%)
	Other	4 (1%)	1 (2%)	2 (3%)	0	1 (2%)
Questionnaires Sent		306 (84%)	40 (83%)	51 (76%)	188 (96%)	27 (50%)
Questionnaires Returned		226 (74%)	18 (45%)	39 (77%)	149 (79%)	20 (74%)
Questionnaires excluded from analysis	Prostate only (no pelvis)	19	0	0	19	0
	Symptoms predate RT	1	0	1	0	0
	Other	3	0	0	2	1
Total no. Included in 12 month analysis (%)		**203**	**18 (8.9%)**	**38 (18.7%)**	**128 (63%)**	**19 (9.4%)**
Excluded at 24 months	Died	2 (1%)	0	0	1	1
	Local recurrence	3 (1.5%)	0	1	2	0
	Distant recurrence	6 (3%)	0	0	4	2
	Unwell (non-cancer related)	3 (1.5%)	0	0	2	1
	2yr point after collection ended	38 (18.7%)	3	9	21	5
Questionnaires sent		151	15	28	98	10
No of questionnaires included in 24 month analysis (%)		**105**	**7 (6.7%)**	**18 (17.1%)**	**73 (69.5%)**	**7 (6.7%)**

3.4.2. Patient, disease and treatment characteristics

Patient, disease and treatment characteristics from the 12 month time-point are summarised in table 3.4-2. A median age of 70 years (range 35-92) was found, with a male predominance (70%). Disease stage was difficult to compare overall as urological

cancers were staged with Tumour, Node, Metastases (TNM) staging, and gynaecological cancers with FIGO staging.

Conformal radiotherapy was used for most (73%), with IMRT/VMAT treatments being used 27% of the time, reflective of the phasing-in of IMRT within our department.

Table 3.4-2: Patient, Treatment and Disease Characteristics

		All patients	Cervical	Endometrial	Prostate	Bladder
	Number	203	18	38	128	19
Patient characterstics						
Age	**Median**	70	66.5	68.5	71	76
	Range	35-92	35-92	43-82	54-87	60-87
Gender	**Male**	143 (70%)	n/a	n/a	128(100%)	15 (79%)
	Female	60 (30%)	18 (100%)	38 (100%)	n/a	4 (21%)
Stage						
T-Category	**T1**				2 (1.5%)	0
	T2				26 (20%)	7 (37%)
	T3				92 (72%)	11 (58%)
	T4				6 (5%)	0
	Recurrence				1 (0.8%)	0
	Unknown				1 (0.8%)	0
	Small cell				0	1 (5%)
N-Category	**N0**				82 (63%)	15 (79%)
	N1				46 (35%)	1 (5%)
	N2				n/a	2 (10.5%)
FIGO stage	**I**		3 (17%)	17 (45%)		
	II		9 (50%)	7 (18.4%)		
	III		3 (17%)	14 (37%)		
	IV		2 (11%)	0		
	Recurrence		1 (5.5%)	0		
Treatment characteristics						
Treatment intent	**Radical**	156 (77%)	15 (83%)	0	122 (94%)	19 (100%)
	Adjuvant	47 (23%)	3 (17%)	38 (100%)	6 (5%)	0
Treatment type	**3D-Conformal**	149 (73%)	15 (83%)	30 (79%)		
	IMRT/VMAT	56 (27%)	3 (17%)	8 (21.5%)		
Concurrent chemotherapy	**Used**	23 (11.3%)	13 (72%)	3 (8%)	0	12 (63%)
	Agents		Cisplatin (n=11),Carboplatin (n=2)	Cisplatin (n=3)	n/a	MMC/5FU (n=6) Cisplatin (n=1)
Brachytherapy	**Used**	49 (24.1%)	17 (9%)	32 (84%)	0	n/a
	Doses		21.3Gy/3# (n=15); 15Gy/5# (n=2)	15Gy/5#	n/a	n/a
Hormones	**Neoadjuvant**	127 (63%)	n/a	n/a	127 (98%)	n/a
	Adjuvant	116 (57%)	n/a	n/a	116 (89%)	n/a
Fraction Size (Gy)	**1.8**	29 (14%)	18 (100%)	11 (29%)	0	0
	2	83 (41%)	0	27 (71%)	56 (44%)	0
	2.75	30 (15%)	0	0	11 (8.6%)	19 (100%)
	3	61 (30%)	0	0	61 (48%)	0

Radiotherapy doses

15 dose fractionations schedules were used (figure 3.4-1), the most common being 60Gy/20# and 74Gy/37# (prostate cancer); 45Gy/25# (cervical and high-risk endometrial cancer), and 40Gy/20# (endometrial cancer).

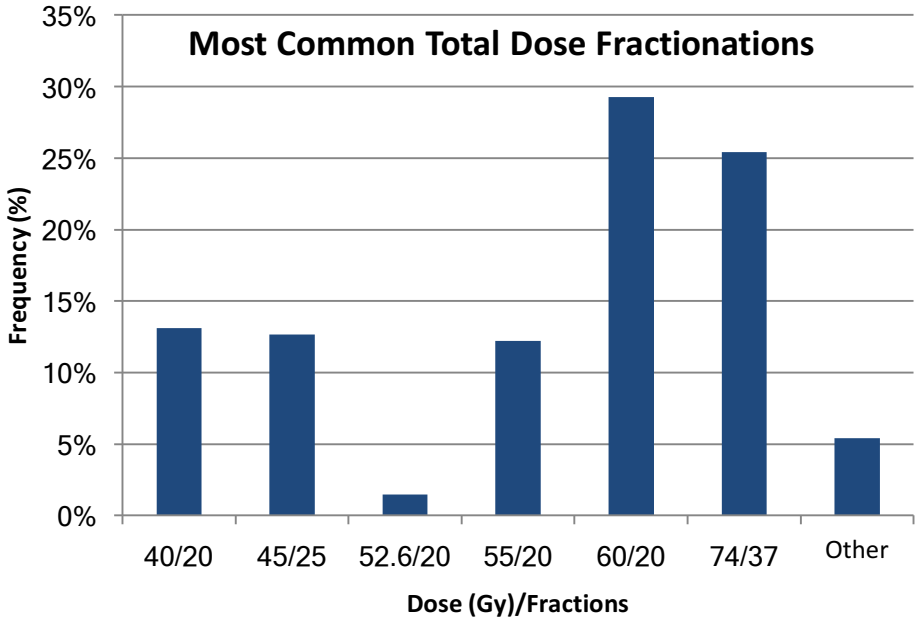


Figure 3.4-1: Common dose fractionations

The dose to the pelvis/nodes varied between 31Gy and 63Gy (in 2Gy fractions), with the most common dose ranges being between 40-44Gy (65% of patients), and 45-50Gy (19% of patients). 13 patients had a boost to positive nodes ranging from 53.2Gy to 60.3Gy.

3.4.3. Data analysis

12 month toxicity data

Toxicity data for the five endpoints are shown in table 3.4-3. 79.5% of patients reported some degree of toxicity at 12 months. There was a high proportion of high-grade toxicity (43.4%), and this appeared to reflect the rate of high-grade faecal urgency, which was present in 41.3% of patients.

Table 3.4-3: 12 month toxicity data

	Diarrhoea	Faecal Urgency	Faecal Incontinence	Bleeding	Overall toxicity
Question answered	196(97%)	197(97%)	177(87%)	201(99%)	n/a
Toxicity Present	37(18.7%)	100(52.3%)	42(23.5%)	28(13.9%)	163(79.5%)
High grade (3-4)	3(1.5%)	82(41.3%)	6(3.3%)	1(0.5%)	89(43.4%)

Details of specific grades for each endpoint are illustrated below in figure 3.4-2:

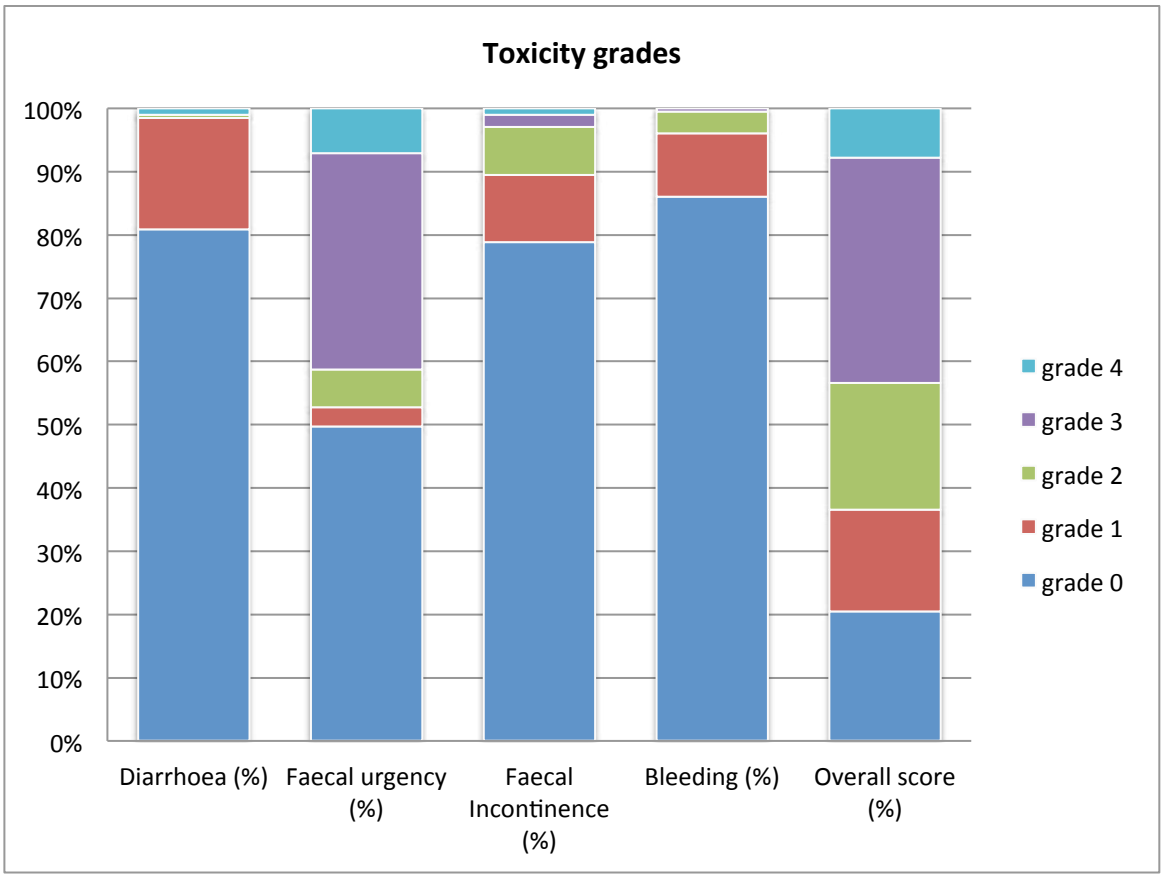


Figure 3.4-2: Toxicity Grades

Similar patterns of overall toxicity grade were seen regardless of diagnosis (figure 3.4-3):

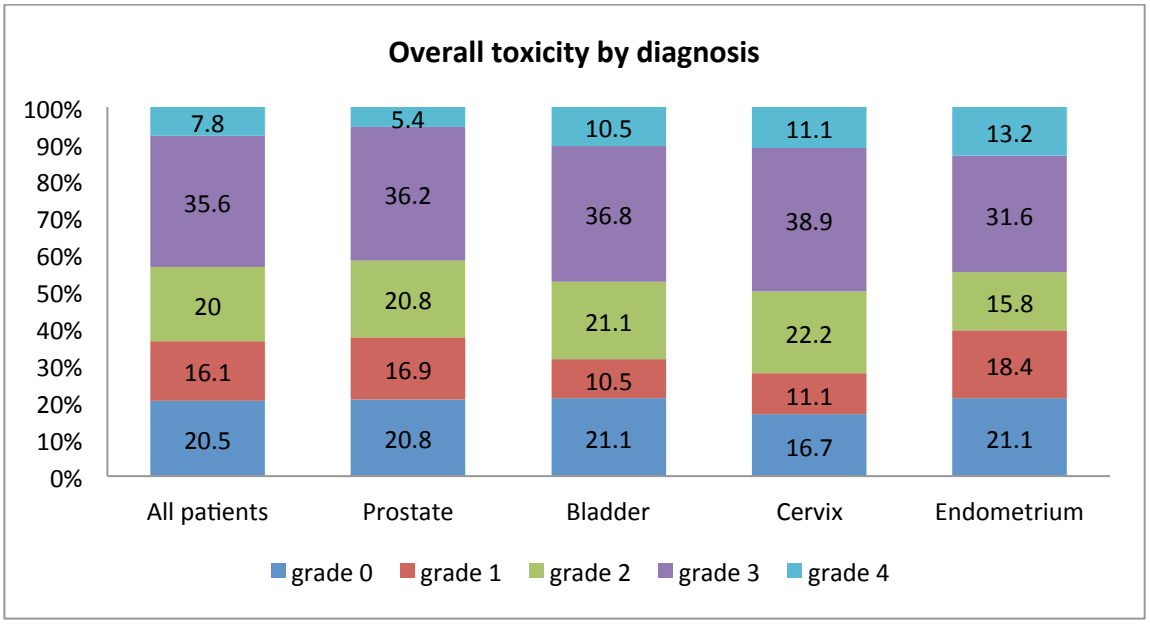


Figure 3.4-3: Overall toxicity grades by diagnosis

24 month data

At 24 months 79% reported late toxicity, similar to at 12 months, with the proportion of high grade toxicity being 37%. All 4 symptoms showed a trend towards decreasing from 12 months to 24 months (see figure 3.4-4), though this difference was not statistically significant.

Compared with at 12 months 51% reported the same overall score, 22% a higher score and 28% lower score than at 12 months.

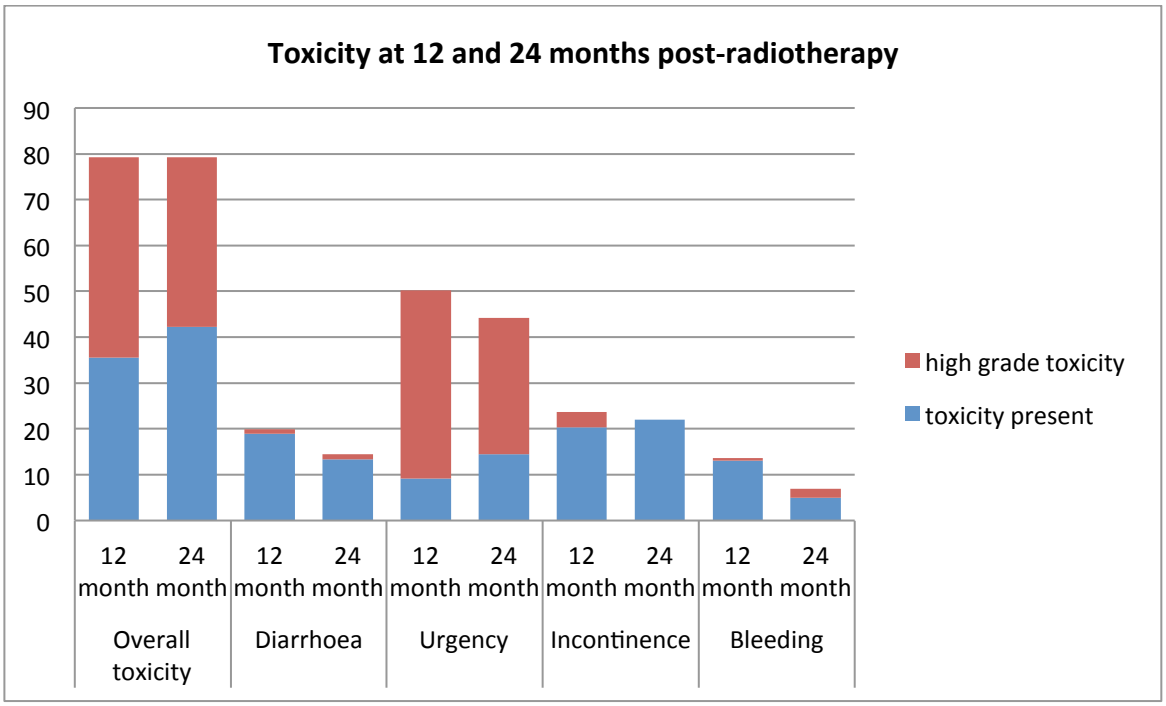


Figure 3.4-4: Toxicity at 12 and 24 months post-radiotherapy

3.4.4. Associations with patient- and treatment-related factors

On chi-squared analysis of patient- and treatment-related factors no associations were found for urgency, bleeding and overall score. For diarrhoea and incontinence the statistically significant results (in bold) are shown in table 3.4-4.

Table 3.4-4: Chi-squared associations with diarrhoea and incontinence

Presence of	Diarrhoea	Incontinence	Comments
Age (<70 vs >70)	**15.0 (p=0.00)**	**8.025 (p=0.005)**	30.1% of younger patients reported diarrhoea compared with 8.6% of older patients. 33.3% of younger patients reported incontinence compared with 15.3% of older patients
Gender (F vs M)	**3.93 (p=0.047)**	1.19 (p=0.28)	27.1% of female patients reported diarrhea compared with 15.1% of male patients.
RT Type (conformal vs IMRT)	0.13 (p=0.91)	**4.29 (p=0.04)**	34% of patients treated with IMRT or VMAT reported incontinence compared with 19% of patients treated with conformal radiotherapy

3.4.5. Univariate and multivariate analysis

On UVA 116 dose-volume parameters were related to toxicity ($p<0.2$). MVA was performed on these with co-variates of age, gender, RT type, fraction size and diagnosis.

On MVA bowel bag, bowel loops, sigmoid, large bowel and rectum had dose-volume parameters that were predictive of toxicity ($p<0.05$). These are shown in Table 3.4-5.

Table 3.4-5: Multivariate Analysis

BOWEL BAG			**Univariate analysis**			**Multivariate analysis**		
Parameter	Predictive of		p value	OR	CI	p value	OR	CI
V5	Diarrhoea	present	0.083	1	1-1.001	**0.027**	**1.001**	**1-1.002**
BOWEL LOOPS								
V45	Urgency	present	0.043	1.008	1-1.015	**0.027**	**1.009**	**1.001-1.02**
Total Volume			0.055	1.001	1-1.001	**0.014**	**1.002**	**1.00-1.003**
V50	Diarrhoea	present	0.089	1.011	0.99-1.03	**0.004**	**1.067**	**1.021-1.12**
V45	Overall Score	high grade	0.124	1.004	0.99-1.01	**0.047**	**1.006**	**1-1.013**
SIGMOID (cc)								
Dmedian	Urgency	present	0.111	1.02	0.996-1.04	**0.02**	**1.031**	**1.005-1.058**
V35	Incontin-ence	present	0.048	1.009	1-1.018	**0.049**	**1.011**	**1-1.021**
SIGMOID (%)								
V10	Urgency	high grade	0.06	1.015	0.999-1.03	**0.016**	**1.022**	**1.004-1.04**
V15	Urgency	high grade	0.048	1.015	1-1.03	**0.012**	**1.022**	**1.005-1.04**
V20	Urgency	high grade	0.074	1.012	0.999-1.03	**0.019**	**1.019**	**1.003-1.035**
V25	Urgency	high grade	0.082	1.011	0.999-1.02	**0.02**	**1.017**	**1.003-1.031**
V15	Overall score	high grade	0.095	1.012	0.998-1.03	**0.018**	**1.019**	**1.003-1.035**
LARGE BOWEL								
Dmedian	Urgency	high grade	0.016	1.027	1.005-1.05	**0.002**	**1.019**	**1.016-1.07**
V15	Diarrhoea	present	0.118	1.003	0.99-1.006	**0.049**	**1.004**	**1.00-1.008**
Dmedian	Overall score	high grade	0.097	1.018	0.997-1.04	**0.01**	**1.033**	**1.008-1.059**
RECTUM								
V70	Overall score	present	0.078	1.202	0.98-1.48	**0.026**	**1.301**	**1.032-1.64**

Small bowel, colon and anal canal had no positive predictors. For bowel loops V45 and total volume were predictive of faecal urgency, and V50 was of diarrhoea.

Figure 3.4-5 illustrates three of the dose-volume relationships found, comparing the mean DVH for all patients with toxicity (red line) and the mean DVH for all patients without toxicity (blue line). The top figure shows the dose-volume relationship for bowel loops with the presence of faecal urgency. At all dose levels those with urgency had a larger volume of bowel loops irradiated, though this was only significant on MVA at the V45 level.

The sigmoid had the most number of positive parameters. On MVA V10-V25 were predictors for high grade faecal urgency (illustrated in figure 3.7 middle figure), Dmedian for the presence of urgency, and V35 for faecal incontinence.

For large bowel Dmedian large bowel was predictive for both high grade faecal urgency, and overall high grade toxicity. V15 large bowel was also positive for the presence of diarrhoea. The relationship of large bowel with diarrhoea is illustrated below (figure 3.7 bottom figure), with V15 being the only level statistically significant on MVA.

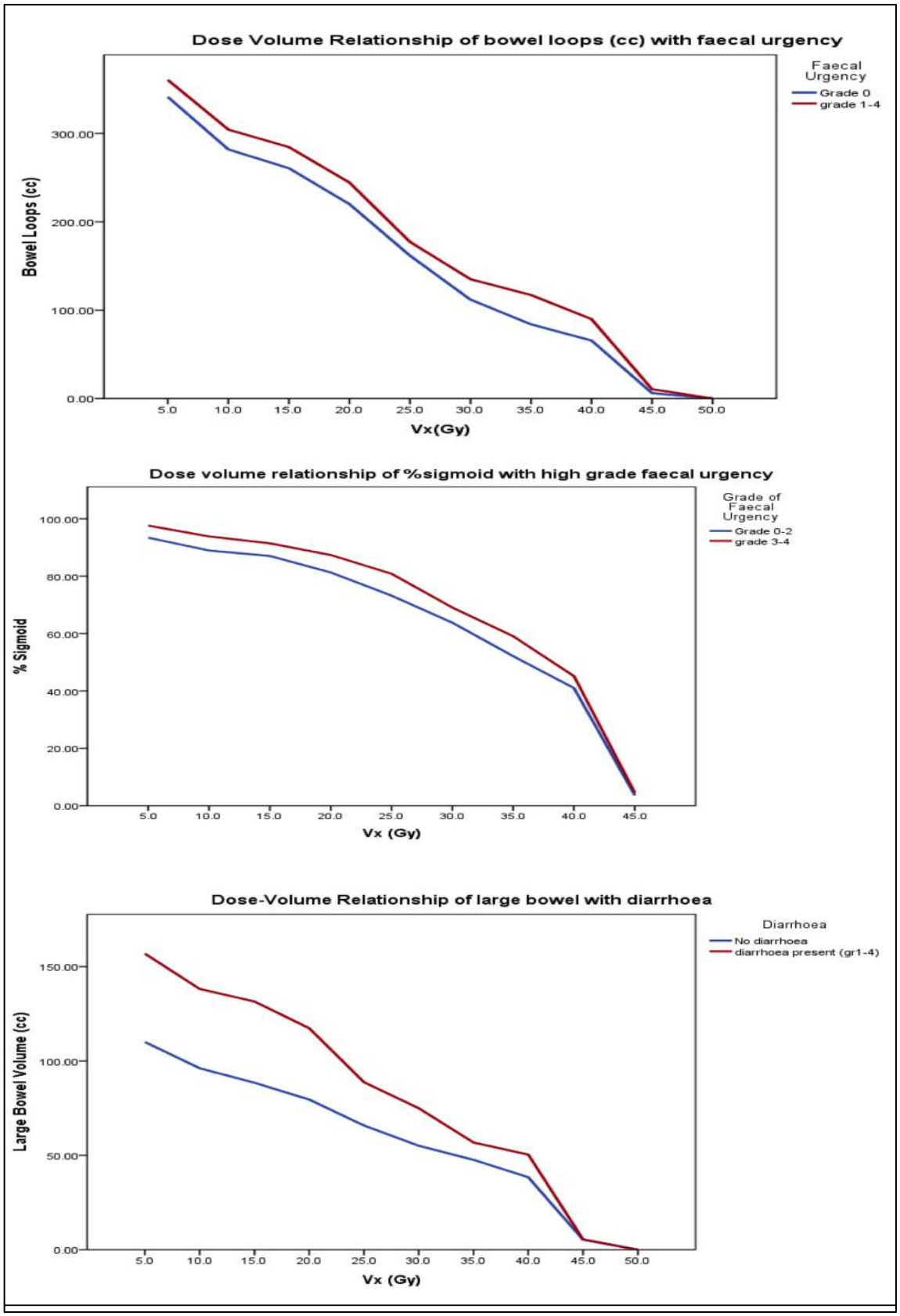


Figure 3.4-5 Dose-volume Relationships

3.4.6. Dose-volume constraints

Twenty seven dose-volume constraints for the dose-volume parameters positive on MVA were derived, with the toxicity rates above and below the chosen cut-offs and the associated goodness of fit chi-squared results shown in table 3.4-6.

Table 3.4-6: Dose-volume Constraints

OAR	Para-meter	Toxicity endpoint		Cut-off	Value	Toxicity above value	Toxicity below value	Chi-squared	p-value
Bowel bag	V5	Diarrhoea	Present	0.2	1689cc	27.9%	14.8%	4.67	0.03
Bowel Loops	V45	Urgency	Present	0.6	85.1cc	87%	47%	8.61	0.003
				0.65	122.5cc	90%	48%	6.66	0.01
				0.7	148 cc	100%	48.4%	7.19	0.007
	Total volume	Urgency	Present	0.5	665 cc	60%	43.5%	5.07	0.024
				0.6	1229cc	87%	47%	8.611	0.003
	V50	Diarrhoea	Present	0.35	80.97cc	50%	17.9%	3.92	0.048
	V45	Overall score	High grade	0.55	127.3cc	85.7%	41.5%	5.38	0.02
				0.65	224.1cc	100%	42.2%	4.03	0.045
Large bowel	V15	Diarrhoea	Present	0.2	154.1cc	30.8%	14.6%	6.536	0.011
				0.3	60.8cc	44.4%	17.6%	4.026	0.045
	Dmedian	Urgency	High grade	0.4	15.9Gy	48%	33.7%	4.46	0.035
				0.39	13.4Gy	50%	30.8%	7.48	0.006
				0.38	12.1Gy	49.1%	31.0%	6.54	0.011
				0.35	7.86Gy	46.2%	31.3%	4.006	0.045
	Dmedian	Overall score	High grade	0.42	13.4Gy	50	35.8%	4.16	0.041
Sigmoid (cc)	Dmedian	Urgency	Present	0.4	10.8Gy	52.8%	26.3%	4.82	0.028
				0.41	13.8Gy	53.7%	22.7%	7.506	0.006
				0.43	17.7Gy	53.8%	25%	6.97	0.008
	V35	Incontinence	Present	0.25	69.7Gy	34%	19.4%	4.378	0.036
Sigmoid (%)	V10	Urgency	High grade	0.3	52.6%	43.8%	19.0%	4.73	0.03
	V15	Urgency	High grade	0.3	47.5%	44%	18.2%	5.38	0.02
	V20	Urgency	High grade	0.35	55.7%	44.4%	25.7%	4.17	0.041
	V25	Urgency	High grade	0.33	36.2%	43.9%	23.1%	4.026	0.045
	V15	Overall score	High grade	0.35	51.9%	46.1%	24%	4.35	0.037
Rectum (cc)	V70	Overall score	Present	0.8	1.5cc	86.3%	75.4%	3.395	0.065
				0.86	3.56cc	93.9%	76.5%	5.14	0.023

3.4.7. Assessment of constraints

Clinical Value

Though being statistically significant many of the constraints would not be valuable in clinical practice, as the rate of toxicity below the constraint were too high. All constraints below which toxicity was higher than 25% were removed from further analysis (n=18).

Accuracy, Discrimination and Re-exploration at 24 months

The remaining nine constraints were assessed further as in table 3.4-7

Table 3.4-7: Sensitivity, specificity, ROC-data and Re-exploration with 24 month data

Parameter		Toxicity endpoint	Cut-off	Sensi-tivity	Specificity	ROC data		Re-exploration with 24 month data			
						AUC	p-value	Tox above	Tox below	Chi-sq	p-value
Bowel bag	V5	Diarrhoea	1689cc	46%	72%	0.6	0.06	**25.8%**	**9.1%**	**4.8**	**0.029**
Bowel Loops	V50	Diarrhoea	81cc	8%	**98%**	0.5	0.996	0%	14.6%	0.17	0.68
Large bowel	V15	Diarrhoea	154.1cc	43%	77%	**0.602**	**0.05**	24%	11%	2.5	0.114
			60.8cc	11%	**97%**			17.7%	6.9%	1.9	0.168
Sigm-oid (cc)	Dmedian	Urgency	13.8Gy	**95%**	17%	0.56	0.215	46.3%	22.2%	1.94	0.164
			17.7Gy	**94%**	18%			46.8%	20%	2.63	0.105
	V35	Incontinence	69.7cc	43%	74%	**0.61**	**0.035**	28%	19.7%	0.73	0.393
Sigm-oid (%)	V10	High grade urgency	52.6%	**95%**	15%	0.57	0.099	30.9%	14.3%	0.86	0.353
	V15	High grade urgency	47.5%	**95%**	16%	0.57	0.1	31.3%	12.5%	1.24	0.265
	V25	High grade urgency	36.2%	**93%**	17%	0.57	0.112	31.6%	11.1%	1.65	0.199
	V15	High grade Overall score	51.9%	**93%**	17%	0.56	0.161	39.2%	12.5%	2.25	0.133

At 24 months 8 out of the 9 constraints dichotomised patients such that a higher toxicity rate was found above the constraint and a lower toxicity rate was found below the constraint. Of all the constraints, that for bowel bag V5 constraint statistically significantly dichotomised patients at 24 months.

The sigmoid constraints largely had high sensitivities, whereas the V15 large bowel and V50 bowel loops had a high specificity. ROC-analysis did not reveal any of the parameters to have high discriminatory value, though out of them all large bowel V15 and sigmoid V35 showed relative promise.

3.4.8. Corroboration of constraints from within the literature

Table 3.4-8 shows the corroboration of constraints from the literature to data from the current study. Constraints from 2 of the studies (highlighted in bold) were corroborated by the data from patients in this study, both in relation to bowel loops, and significantly dichotomised patients with and without toxicity. Applying the other constraints to the current study data did not show any corroboration, for example with the QUANTEC constraint V45<195cc the rates of toxicity above and below the constraint were 50.6% above and 50% below for urgency; 24.5% above and 22.7% below for incontinence; 14.8% above and 21.7% below for diarrhoea and 13.6% above and 13.6% below for bleeding.

Table 3.4-8: Corroboration of constraints from literature

Study/Guideline	OAR	Constraint	EQD2 equiv	Corroboration to current study data	p-value
QUANTEC acute (Roeske (56))	Peritoneal Cavity	V45<195cc	V43.2	None found	
Guerrero-urbano (112)	**Bowel loops**	**V40<124**	**V33.1**	**Faecal Incontinence: 34.2% to 15.2%**	**0.003**
		V45<71	**V38.6**	**Faecal urgency: 59.4 to 41.9%** **Faecal incontinence: 32.6% to 14.6%** **Diarrhoea: 24.5% to 13.2%**	**0.015** **0.006** **0.046**
		V60<0.5	V56.6	None found	
McDonald (149)	**Bowel loops**	V30<178cc	V23.6	None found	
		V35<163cc	V28.6	None found	
		V40<151cc	V34	None found	
		V45<139cc	V39.66	None found	
		V50<127cc	**V45.6**	**Faecal urgency: 100% to 48.4%** **Overall toxicity: 85.7% to 41.5%**	**0.014** **0.04**
		V55<115cc	V51.9	None found	
		V60<98cc	V58.5	None found	
		V65<40cc	V65.4	None found	
QUANTEC acute (Baglan (162))	Small bowel	V15<120cc	V10.8	None found	
Chopra (139)	Small bowel	V15<275cc	V10.8	None found	
		V30<190cc	V25.2	None found	
		V40<150cc	V36.8	None found	
Isohashi (145)	Small bowel	V40<340cc	V36.8	None found	
				None found	
Fonteyne(143)	Sigmoid	V40<10%	V32.7	None found	
		V30<16%	V22.9	None found	
Chopra (139)	Large bowel	V15<250cc	V10.8	None found	
		V30<100cc	V25.2	None found	
		V40<90cc	V36.8	None found	
Multiple studies (136-138, 155, 184)	Anal canal	Dmean<40Gy		All patients under this constraint, so could not be applied	

3.5. Discussion

This section of this thesis assessed patient-reported late bowel toxicity in 203 patients 12 months after pelvic radiotherapy. 79.5% of patients reported late bowel toxicity, with 43.4% reporting high-grade toxicity. Late bowel toxicity was predicted by dose-volume parameters to bowel bag, bowel loops, sigmoid and large bowel. Statistically significant dose-volume constraints were derived for these four OARs.

3.5.1. Toxicity Data

The most frequently reported symptom was faecal urgency, with 41% of patients reporting either this as grade 3 ("daily") or grade 4 ("constantly"). This finding was in concordance with published literature, with faecal urgency rates of 45.1% reported in men and 58.7% in women after pelvic radiotherapy (45). In this study faecal incontinence was also seen commonly, reported by 23%. Again this had similarity to published patient-reported studies where rates of 15-24% (42, 45) are seen.

Age was found to be an important confounding factor in this chapter, with a lower age being associated with higher rates of diarrhoea and incontinence. On regression analysis for example being below or above 63 years of age was associated with diarrhoea rates of 41% compared with 19% above. One explanation for this may be that clinicians may treat younger patients with comparatively larger treatment volumes and/or increased doses relative to older patients, though further analysis would be needed to confirm this hypothesis.

Assessment of treatment-related factors found that the use of IMRT techniques was associated with increased faecal incontinence, not only on initial Chi-squared testing, but also on univariate and multivariate analysis. This pattern was seen both in prostate and gynaecological cancer patients. No clear dosimetric reason was found for this, and further ongoing assessment of late toxicity in IMRT treated patients is warranted.

It has been suggested in the literature that concurrent chemotherapy may contribute to late bowel toxicity(33); however no increased late bowel toxicity was found in patients with the use of concurrent chemotherapy compared with those without.

3.5.2. Dose-volume constraints

In this section of the thesis, 9 statistically significant and potentially clinically useful dose-volume constraints were derived for 4 OARS: bowel loops, bowel bag, sigmoid and large bowel.

The importance of bowel loops as an OAR for late toxicity was confirmed with data from this work, corroborating findings from two published studies. In their study of prostate and

pelvic node patients Guerrero-Urbano *et al* (112) suggested constraints of V40<124cc and V45<71cc. Use of their V45 constraint on toxicity data from this study successfully dichotomised patients with and without toxicity for three symptoms. Toxicity rates above and below this constraint were 32.6% and 14.6% (p=0.006), 24.5% and 13.2% (p=0.046), and 59.4% and 41.9% (p=0.015) for incontinence, diarrhoea and urgency respectively.
Their V40 constraint was applicable for incontinence seen in our study, toxicity above their constraint being 34.2% and below being 15.2 % (p=0.03). A further similarity was that we also found the total volume of bowel loops to be predictive of urgency, though the constraints derived in our study were not clinically applicable, as below the constraint the rate of toxicity was 43.5%.
McDonald *et al* (149) suggested bowel loops constraints in bladder cancer patients. Although most of their constraints could not be corroborated by data in this study, their V50<127cc (EQD2=45Gy) was applicable to our data and significantly dichotomised patients with faecal urgency and overall toxicity. Again however the "split" of toxicity still would mean that patients below the constraint 48.4% would still have faecal urgency, and 41.5% high grade overall toxicity which would not be considered clinically acceptable.

For bowel loops, the constraint derived within this study with some potential for clinical use was V50<80.9cc, which dichotomises patients with diarrhoea from 50% to 17.9%. Though having a high specificity of 99%, caution must be applied given its extremely low specificity, and AUC value of 0.5 (no discriminatory ability). The constraint could not be verified with the 24 month data. On balance therefore, this constraint is not recommended to be of value.

For bowel bag parameters, although a correlation is reported with late toxicity there are no published constraints in the literature. Mouttett-Aldouard *et al* (150) in their study of cervical cancer patients found correlation with late "whole digestive toxicity" and V10-V30 of the bowel bag.
In this chapter though V5-V35 bowel bag were correlated with toxicity on UVA, on MVA only very low dose, V5 was associated with diarrhoea. A constraint of V5<1689cc dichotomised patients between 28.9% and 14.8% (p=0.03). This parameter was weakly correlated on ROC analysis (AUC 0.6). At 24 months toxicity above and below this constraint was 25.8% and 9% (p=0.029) adding to its strength. This would therefore be a recommended constraint from this study, and is a novel finding.

Though doses as small as 5Gy may be deemed insignificant, this finding may hold importance with the increased use of IMRT techniques where a highly conformal dose distribution to the target is balanced by large areas of low dose bath.
For acute bowel toxicity QUANTEC recommend a bowel bag constraint of V45<195cc. In the sample of patients in this study the constraint was not corroborated.

Small bowel dose-volume parameters had no predictive value for late toxicity, and constraints could not be derived, which concurred with results of four other published studies (135, 142, 143, 153). Neither of the small bowel constraints from two studies (V15<275cc, V40<340cc) (139, 145) were substantiated in the patients in this study. The QUANTEC acute toxicity parameter of V15<120cc could not be corroborated with late toxicity in our study.

The sigmoid colon was identified as a key OAR for late bowel toxicity. Seven parameters remained positive on MVA for sigmoid, predictive for faecal urgency, faecal incontinence and overall toxicity, and statistically significant constraints could be derived from these.
High-grade faecal urgency, seen in 41.3% of patients in this study was predicted by V10-V25 of sigmoid. For example the V10<52.6% sigmoid constraint dichotomised patients with faecal urgency from 43.8% to 19%, which would be an important clinical benefit. The V10-V25 constraints had high sensitivities (89-95%), and validation was seen with 24 month data, where toxicity was dichotomised from 30.9-31.9% to 11.4-15.4%, which despite not being statistically significant differences would be clinically desirable.
Sigmoid Dmedian was also predictive of faecal urgency, with a constraint of Dmedian<13.8Gy dichotomising patients from 53.7% above the constraint to 22.7% below, with a high sensitivity of 95% and some concordance seen with 24 month data also.
The sigmoid as a late toxicity OAR has been mentioned by Mouttet-Aldouard *et al* in cervical cancer patients and Fonteyne *et al* in prostate cancer patients (185). Fonteyne *et al* suggest sigmoid constraints of V40<10% and V30<16%, though these constraints could not be corroborated with our data. Mouttet-Aldouard *et al* (150) also suggest that V10-V40 of sigmoid were important for overall toxicity, showing some concordance with our findings, though no constraints were specified in their study.

Large bowel V15 was predictive of diarrhoea on MVA, with ROC analysis showing a weak but statistically significant discriminatory ability. With a cut-off of 60.9cc rates of diarrhoea were dichotomised from 44.4% to 17.6% at 12 months, and 17.7% to 6.9% at 24 months. Specificity was 97% for this cut-off, and this may be a useful constraint clinically. Large

bowel V15 was also found to be significant in a study by Chopra et al (139), though their constraints were not substatiated in our study data, and this may be as their toxicity endpoint was grade 3 toxicity.

For the rectum no additional constraints were derived in this study, and the majority of patients met the constraints recommended by QUANTEC (127) and Gulliford et al.(133) . For the anal canal, 100% of patients met the suggested constraint from chapter II of this thesis, Dmean<40Gy. No additional constraints were derived.

Therefore, from this work suggested constraints are:

1. Bowel loops V38.6Gy<71cc for diarrhoea (any grade)
2. Bowel bag V5Gy<1689cc for urgency, incontinence and diarrhoea (any grade)
3. Sigmoid V10Gy<52.6% for faecal urgency (high grade)
4. Sigmoid V25Gy<36.2% for faecal urgency (high grade)
5. Sigmoid Dmedian<13.7Gy for faecal urgency (any grade)
6. Large bowel V15Gy<60.8cc for diarrhoea (any grade)

3.5.3. Strengths of Study

This study had many strengths. The toxicity data was collected from an unselected group of non-trial patients, with the aim of assessing “real world” toxicity, and to examine dose parameters and constraints that can be widely applicable. The main analysis was performed on 203 patients, a sample size that was larger than most of the studies (19 of 25) in the systematic review in chapter II.

Patient-reported data, as opposed to clinician-reported data was used from a validated questionnaire with a good response rate (74%).(186)

A symptom-based approach was largely adopted, as recommended by QUANTEC, focussing on those symptoms which are thought to affect quality of life, and important to improve for patients. Overall toxicity scores were also studied, though in this sample of patients the overall toxicity score was largely influenced by the score for faecal urgency, and added little to the study.

Statistically, as many of the recommendations as possible of QUANTEC were followed, including stating the toxicity levels, goodness of fit statistics, discrimination and validation.

Some findings from this study corroborated data from published literature suggesting the methods used were robust.

Relatively novel findings were found highlighting the importance of less established OARs such as sigmoid, large bowel and bowel bag. Sigmoid dose parameters were particularly

associated with faecal urgency, a symptom recently highlighted as being important in the literature, with a case made for its inclusion in CTCAE (187).

3.5.4. Limitations

There were also limitations to this work. Time limitations on the study did not allow patient's toxicity data to be collected at baseline, and the findings of this study are based on the presumption that the symptoms reported are toxicity, rather than being "normal" for an individual patient or due to other co-morbidity. An additional question to assess if patient's symptoms are pre-existing was added to compensate for this, however this would be prone to recall bias and cannot completely be relied on.

Previous bowel surgery (188) and the presence of inflammatory bowel disease (189) are important co-morbidities when considering late bowel toxicity. This data could not be collected retrospectively from the hospital records as it was not reliably recorded, and in hindsight should have been collected when the questionnaires were sent.

The overall aim of this work in the context of this thesis is to derive constraints for use in gynaecological IMRT. The majority of patients included in this study were prostate cancer patients (given its higher incidence) and treated with conformal treatments rather than IMRT (given the time when the data was collected). On one hand this may not matter, as bowel constraints should be the same regardless of tumour diagnosis and type of radiotherapy planning. The influences of tumour diagnosis, brachytherapy, hormones and concurrent chemotherapy on toxicity were assessed statistically and had no apparent impact. On the other hand, gynaecological radiotherapy is different to prostate pelvic node radiotherapy in that treatment volumes can be as high as the bifurcation of the aorta, and therefore bowel volume is likely to be much higher. The inclusion of more gynaecological patients within the study may have given more conclusive results for dose-volume parameters of small bowel for example.

For the OARs and dose-volume parameters studied there may be significant overlap, which may hinder the clarity of the results. For example sigmoid forms part of large bowel which forms part of bowel loops. Similarly with the use of cumulative dose-volume data, parameters V5, V10 etc will all have overlap.

None of the constraints recommended had perfect attributes of high sensitivity, high specificity, and discriminatory value. Though some were highly specific others were highly sensitive and balance was not always achieved; although on review of the literature this is

not uncommon, and many authors do not report these statistics. Though an attempt to re-explore and validate the constraints with 24 month data was made, these toxicity scores were not totally independent with 50% of patients having the same toxicity score at 24 months that was found at 12 months. An independent data set to properly externally validate these findings would be important.

Given the exploratory nature of the work done, a large number of dose-volume parameters from many OARs were tested for predicting toxicity. This would increase the risk of chance findings, and appropriate statistical testing was attempted to minimise this risk.

The analyses performed in this thesis were regression analyses attempting to link dose parameters from the DVH to toxicity endpoints. DVH data does not take into account spatial information and thus this kind of analysis may have limitations. A superior method to analyse this data would be to use NTCP modelling, though this was beyond the scope of this current work due to time constraints.

Finally, dose-volume data was taken from the “snapshot” planning CT scan. Pelvic organ motion is a known phenomenon not only for tumour sites but for OARs also. It is known that organs such as the rectum can move significantly during treatment and the dose to the rectum at the time of planning can be different to the accumulated dose on treatment (190). It is likely that other components of bowel also move significantly during the course of treatment, and toxicity may be better associated to the accumulated dose rather than the planning dose. This may be an important consideration for future work.

3.6. Conclusions

Patient-reported late bowel toxicity is a common occurrence, with faecal urgency being reported most frequently. Late bowel toxicity can be predicted by dose-volume parameters to bowel loops, bowel bag, sigmoid and large bowel. Constraints for these OARs to prophylactically reduce the toxicities studied are suggested in this study, for bowel loops confirming those within published literature, as well as novel constraints for bowel bag, sigmoid and large bowel.

3.7. Future work

The dose-volume constraints derived in this study will first need to be assessed to see if they are achievable practically when treatment planning for gynaecological patients, for example for many patients where the PTV encompasses the uterus for example lowering the dose to the sigmoid colon may be difficult to achieve without PTV compromise, or

increased dose to other OARs. If they can be achieved, external validation of these constraints with toxicity data from an independent sample of patients would be the next step. If validated these constraints can be used to model novel radiotherapeutic techniques to assess their likely benefit in limiting toxicity, and the true benefits of the constraints may be assessed in prospective study.

3.8. Acknowledgements

Dr George Joseph (Consultant Radiologist, Velindre Cancer Centre) inputted with definition of OARs, and assessed correct delineation of the OARs for the first eight patients.

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Section B: Assessment and Management of Organ Motion for Gynaecological IMRT

4. Chapter IV: A Systematic Review of Organ Motion and Image-guided Strategies in External Beam Radiotherapy for Cervical Cancer

4.1. Introduction

For cervical cancer survivors, toxicity from pelvic radiotherapy is a major problem, and IMRT is therefore desirable to reduce the risk of toxicity. The last 15 years have seen the emergence of IMRT techniques for cervical cancer and the evidence to support its use in definitive cervical cancer is summarized in chapter I. Planning studies comparing IMRT with conformal radiotherapy demonstrate reduced doses to bowel, rectum, bladder and bone marrow with IMRT (56, 83, 191). Arc therapies, such as volumetric arc therapy (VMAT) and RapidArc, improve OAR sparing further, with the added benefit of a shorter treatment delivery time (192). Clinical data suggest these dosimetric observations may translate to improved toxicity for patients, though clinical data are limited in terms of the quality of studies. Two prospective studies, one of which is randomised, suggest that IMRT can improve late GI toxicity (63, 64) over conformal radiotherapy.

Despite this there has not been widespread uptake of IMRT for cervical cancer. One reason is the lack of clear dose-volume constraints to prevent late bowel toxicity, as discussed in the last two chapters of this thesis. Another major issue is the problem of organ motion and unclear guidance on its management. This issue is addressed in the work in this section of the thesis, with Chapters IV and V focusing on definitive cervical cancer and Chapter VI focusing on adjuvant radiotherapy for post-hysterectomy cervical and endometrial cancer.

4.1.1. The problem of pelvic organ motion

Pelvic organs are naturally prone to positional and volumetric changes over time. As a result the pelvic anatomy at the time of radiotherapy planning may differ from the pelvic anatomy during treatment. These individual organ changes may result in variations in CTV position and shape.

When conventional ‘box’ radiotherapy techniques are used, the irradiated volume encompasses the whole pelvis from the sacral promontary to the obturator foramen.

Internal organ motion is thus less important because the CTV is more likely to remain within the irradiated volume.

However with IMRT complex dose distributions are achieved with steep dose gradients around the target, meaning that organ motion needs to be considered to avoid geographical miss. The successful implementation of IMRT relies on accurate CTV delineation and selection of an appropriate margin around the CTV to form the PTV. The CTV-PTV margin has two components: the internal margin, which encompasses the internal target volume (ITV) and accounts for organ motion, and the set-up margin which accounts for patient set-up and delivery errors (193).

In the case of definitive cervical cancer treatment, the CTV consists of cervix, uterus, upper vagina, parametrium, ovaries and pelvic lymph nodes. Each of these components may have their own organ motion pattern, and comprehension of these patterns is important. In close proximity to the CTV lies rectum, bladder and bowel which with their own positional and volumetric variation may influence the position of the CTV components. Knowledge also of the influences of adjacent organ filling is required to determine an appropriate ITV.

Though consensus guidelines exist for delineation of CTV in definitive cervical cancer IMRT (95), there is a paucity of information on appropriate margins to be used. RTOG recommend a 1.5-2cm CTV-PTV margin, however no clear rationale for this is given. Margins should be evidenced based, ideally utilising data from individual treating institutions. They should be large enough to minimize geographical miss. However, if these margins are too large, they are likely to incorporate OARs within the PTV, and the clinical advantages of IMRT will be reduced (194).

4.1.2. Image-guided radiotherapy

Image-guided radiotherapy (IGRT) is the use of imaging initially to plan radiotherapy, and then to monitor, update and adjust the treatment process to improve its accuracy (115). IGRT is complementary to IMRT in achieving its goals to ensure target coverage and reduce OAR doses. It has many aspects, including patient set-up, patient preparation, margin use and on-treatment imaging. Patient set-up includes the patient's position on treatment and the use of immobilisation devices to maintain patients in a consistent position for each treatment.

Patient preparation involves the use of protocols to reduce internal organ motion, for example breathing techniques for lung cancer treatments, and the use of rectal enemas for

prostate cancer patients. There are no widely used preparation protocols in cervical cancer.

On-treatment imaging or verification aims to ensure that the area treated is that as planned, reducing the risk of geographical miss. The type of imaging, frequency of imaging and choice of offline versus online protocols are important components of this. “Offline imaging” uses imaging before or after treatment to match to a reference image offline (ie without the patient on the couch). The aim of this is to correct ‘systematic errors’ which are reproducible errors occurring in the same direction and in a similar magnitude with each fraction of radiotherapy. “Online imaging” is acquired, checked and corrected prior to treatment with the aim of correcting both random and systematic errors. Random errors arise from changes in target position and shape between and during fractions of treatment. The type of matching is an additional consideration with bone-bone matching or soft tissue matching being potential options.

A further concept is that of adaptive radiotherapy, whereby an individual’s organ motion, as determined by on-treatment imaging, is used to modify the treatment during its course. This has been studied in other pelvic tumour sites such as bladder cancer, and prostate cancer, though its use in cervical cancer is to be established.

At a time when IMRT for cervical cancer is being adopted, the most reproducible and clinically practical IGRT methods must be determined.

4.2. Aims

To systematically review published studies to determine:

- The patterns and extent of pelvic inter-fraction and intra-fraction organ motion in cervical cancer EBRT.
- The correlation of these organ motion patterns with bladder and rectal filling
- Appropriate image-guided solutions to manage pelvic organ motion in cervical radiotherapy

4.3. Methods

4.3.1. Inclusion criteria

The inclusion criteria were as follows:

1. English language studies
2. Human studies only
3. Studies involving adults
4. Studies with patients treated with external beam radiotherapy for cervical cancer
5. Studies examining interfractional and intrafractional organ motion in cervical cancer radiotherapy
6. Studies examining IGRT techniques in cervical cancer radiotherapy

4.3.2. Exclusion criteria

1. Review articles and letters
2. Studies using brachytherapy only
3. Studies with post-operative cervical and endometrial cancer rather than radical treatments

4.3.3. Quality criteria

With many of the studies around this subject being observational, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (195) could not be followed, as these guidelines are applicable to mainly interventional and randomized trials. In view of this three quality criteria were defined for inclusion of studies into this review:

a. Was the spectrum of patients included representative of those in clinical practice?

b. Were the methods described in sufficient detail to permit replication of the study at a different institution?

c. Were the outcomes measured appropriate to the aims of the study?

Studies not meeting all three criteria were excluded from the review.

4.3.4. Information sources and search strategy

Searches were performed using Medline, preMedline, Embase, Cochrane Library, Web of Science and CINAHL, no date or language restrictions were applied. Update searches were performed in February 2013, and November 2015 and included an additional Pubmed search for e-publications ahead of print. The search strategy is in Appendix D.

All searches were performed by Ms Anne Cleves, Assistant manager, Cancer Research Wales Library, Cardiff. Peer-reviewed papers and conference abstracts were sought. Database appropriate strategies were developed around terms for Uterine Neoplasms, Image guided Radiotherapy, Organ motion and target volume using controlled vocabulary and text word terms.

4.3.5. Study Selection

Two reviewers (myself and Dr Catharine Pembroke, specialist registrar) independently screened the abstracts for inclusion in the review. For abstracts meeting the eligibility, full papers were acquired and assessed further for suitability against the eligibility criteria. Consensus between the two reviewers was gained for studies to be included.

The reference lists of all included papers were hand-searched for any additional relevant references.

4.3.6. Data Extraction and synthesis of results

Data was extracted from each of the included papers and collected on Microsoft Excel. Included studies were subdivided by subject into the following categories: interfraction motion (cervix, uterus, lymph nodes, CTV motion); intrafraction motion; correlation with bladder and rectal filling; patient positioning and preparation; margins for organ motion; on-treatment imaging modality and marker use; online and offline strategy; adaptive strategies.

4.4. Results

Outcomes of the systematic search are illustrated in Figure 4.4-1.

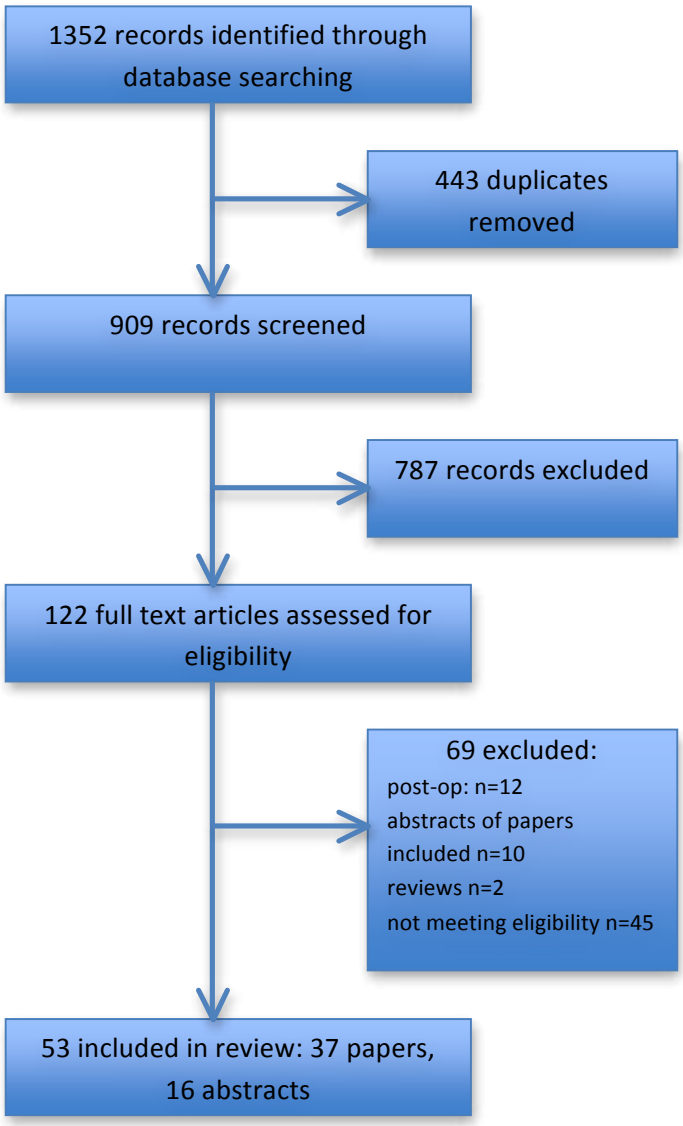

Figure 4.4-1: Results of systematic Search

Overall, 53 relevant studies were used for analysis including 16 conference abstracts. 22 studies were prospective studies, though the majority was retrospective analyses of previously acquired imaging. Aspects covered by the studies overlapped, as detailed in Table 4.4-1.

Table 4.4-1: Summary of included studies

Author	Year	Paper (P) Abstract (A)	Pt no	Prospective (P) /Retrospective (R)	Organ Motion								Study summary
					Inter-fraction	Intra-fraction	Bladder	Rectum	Position/ Prep	Margins	Imaging/ Marker	Adaptive	
Adli (196)	2003	P	16	P					X				Assessment of prone positioning on small bowel dosimetry
Ahmad(197)	2008	P	24	R			X						Studies bladder volumes variation using bladder ultrasound
Ahmad (111)	2011	P	13	R	X		X						Relation of bladder filling to cervix/uterine motion
Ahmad (198)	2013	P	14	R								X	Margin-of-the day modeling study
Beadle (110)	2009	P	16	R	X		X						Cervical motion, and in relation to bladder filling
Bhaumik (199)	2014	A	20	P					X				Comparing small bowel coverage in prone and supine position
Bhuva (200)	2015	A	11	R					X				Use of ITV formed by CTVs on full bladder & empty bladder scans
Bloemers (201)	2010	A	16	R	X		X			X			Coverage of uterine CTV in relation to bladder filling
Bondar (202)	2011	P	13	R			X						Predictive models for cervix-uterine motion based on bladder filling
Bondar(123)	2012	P	14	R								X	Adaptive strategies for cervical cancer
Bondar(203)	2014	P	13	R	X		X						Motion of iliac vessels (nodal volume)
Buchali (204)	1999	P	29	R	X		X	X					Uterine movement in relation to bladder & rectal filling
Chan (108)	2008	P	20	R	X	X	X	X		X			Inter- and intra-fraction motion using MRI
Collen (109)	2009	P	10	R	X	X	X			X			Inter- and intrafraction motion study with CT
De Pree (205)	2007	A	9	P	X		X				X		Cervical motion measured using marker
Georg (206)	2006	P	20	R			X						Association of bladder volume with small and large bowel sparing
Gordon (207)	2011	P	10	R						X			Use of tapered margins with larger uterine and smaller cervix margin
Haripotepornkul (105)	2011	P	10	R	X	X							Inter- and intra-fraction cervical motion using KV imaging
Heijkoop(124)	2014	P	64	P								X	Clinical implementation of Plan of the Day
Heijkoop (208)	2015	A	16	R		X	X	X		X			Intrafractional motion of cervix-uterus measured on CBCT

Author	Year	Paper (P) Abstract (A)	Pt no	Prospective(P) /Retrospective (R)	Organ Motion				IGRT				Study Summary
					Inter-fraction	Intra-fraction	Bladder	Rectum	Position/	Margins	Imaging/ Marker	Adaptive	
Hoogeman (209)	2012	A	21	P								X	Implementation of plan of the day strategy
Huh (210)	2004	P	66	R	X								Interfraction motion study of the uterus highlighting rotational motion
Huh (211)	2004	P	10	P					X				Assessment of small bowel displacement system (SBDS)
Kaatee (212)	2002	P	10	R	X						X		Interfraction motion of the cervix with KV imaging and markers
Kager (213)	2014	A	6	P								X	Clinical implementation of plan-of-the-day
Kerkhof (214)	2008	P	11	R								X	Modelling of adaptive replanning with 4mm margin compared with standard 15mm margin
Kerkhof (215)	2009	P	22	R		X	X						Intrafraction motion measured with MRI over 16 minutes and correlation with bladder filling
Khan (216)	2012	P	50	R								X	Optimised individualized PTV margin modeling study
Langerak (217)	2015	P	50	P	X					X	X		Interfraction cervical motion using polymeric markers
Latifi (218)	2013	A	14	P	X					X	X		Cervical margin determined with gold fiducial markers and MVCT
Lee (106)	2004	P	17	R	X					X			Uterine sleeve used to determine cervical motion and margins
Lee (219)	2007	P	13	R					X				Study of uterine position on treatment with SBDS
Lim (220)	2009	P	20	R						X			Modelling of different margins considering interfraction motion using MRI
Lim (221)	2014	P	30	P								X	Comparison of automated replanning due to anatomy change with replanning only when dosimetric reductions occur
Mahantshetty (222)	2014	A	40	R	X					X			Inter-fraction motion of the CTV nodes and uterus-cervix complex using daily CBCT
Malyapa (223)	2001	A	16	P						X			Uterine margins to account for motion
Mayr (224)	2006	A	12	P		X							Intrafractional motion measured by dynamic MRI
Mens (225)	2011	A	12	P	X						X		Submucosal placement of polymeric markers used to measure cervical motion
Oh (226)	2013	P	15	P							X	X	Compared the use of bony matching and soft tissue matching using on-treatment MRI
Park (227)	2005	P	10	P					X				Study of SBDS displacement small bowel

Author	Year	Paper (P) Abstract (A)	Pt no	Prospective(P) /Retrospective (R)	Organ Motion				IGRT				Study Summary
					Inter-fraction	Intra-fraction	Bladder	Rectum	Position/ Prep	Margins	Imaging/ Marker	Adaptive	
Pinkawa (228)	2003	P	20	P					X				Compares supine and prone positioning in terms of rectum and bowel sparing
Raj (229)	2005	A	10	P		X	X			X			Intrafractional motion of the cervix and its relation to bladder filling
Schippers (230)	2014	P	17	R	X					X			Motion study of lymph nodes on MRI
Stewart (231)	2010	P	33	P								X	Replanning of IMRT plans with 3mm margins based on weekly MRI imaging
Stromberger (232)	2010	P	10	P					X				Impact of prone position on small bowel dosimetry
Taylor (233)	2008	P	33	P	X		X	X		X			Interfractional study of cervical, uterine and vaginal motion using MRI. Influence of bladder and rectal filling.
Tyagi (234)	2011	P	10	R	X		X	X		X			CTV motion measured with daily CBCT
Van de Bunt (235)	2006	P	14	R	X		X	X		X			Use of weekly MRI to derive CTV-PTV margins
Van den Bosch (236)	2014	A	10	R								X	Development of criteria to determine which patients may benefit from plan of the day
Van den Bosch (237)	2015	A	5	R						X			Assessment of structure-specific margins for cervix, uterus and vagina
Van der Heide (238)	2007	A	20	R	X		X	X		X			Strategies to manage interfraction motion
Yamamato (239)	2004	P	10	P		X					X		Intra-fractional cervical organ motion using gold markers
Wang (240)	2012	A		P	X	X				X			Inter- and Intrafractional motion measured with 4D-CT

Abbreviations: SBDS: small bowel displacement system; MVCT: megavoltage computed tomography; 4D-CT: 4-dimensional computed tomography

4.5. Interfractional Motion

4.5.1. Cervix Motion

Twelve studies, including a total of 209 patients, examined interfractional cervix motion. Details of these studies are shown in table 4.5-1.

A variety of imaging modalities were used to assess motion. 5 studies used portal imaging with fiducial markers, either using seeds (105, 205, 212, 225) or a ring (106) as a marker. 7 studies used volumetric imaging, including 5 using CT-based studies (CT/megavoltageCT (MVCT)/4-dimensional CT (4DCT) and cone beam CT (CBCT) (109, 110, 218, 237, 240) and 2 MRI-based studies (108, 233). Motion was measured either at the cervix itself (centre of mass, cervical os, cervical boundaries) or by using fiducial markers as a surrogate for cervix position.

Overall the predominant cervical motion was in the anteroposterior (AP) and superiorinferior (SI) directions, with relatively less seen laterally. Inter-fraction average cervical movements ranged from 0.4mm to 16mm in the AP, 0.5mm to 8mm in the SI and 0.2 to 10mm in the lateral directions depending on the method used to measure it. Studies using fiducial markers reported smaller magnitude of motion than other methods compared with those measuring motion of the cervical boundary or perimeter.

Table 4.5-1: Interfraction Cervical Motion

Ref	Pt no	Modality	Imaging Frequency	Measurement Method	Average Movement (mm)				Maximal movement (mm)		
					Statistic Used	AP	SI	LR	AP	SI	LR
Kaatee (212)	10	EPID & seeds	Daily	Seed motion	Mean of means Systematic motion Random motion	1.7 3.5 3.9	3.0 4.1 3.7	-1.3 3.7 2.2	NR	NR	NR
Haripotepornkul (105)	10	KV portal & seeds	Daily	Seed motion	Mean (SD)	4.2 (3.5)	4.1 (3.2)	1.9 (1.9)	18	18	14
DePree (205)	9	KV portal & seeds	Daily	Seed motion	Mean Systematic motion Random motion	-1.2 10.0 6.8	2.6 5.1 4.9	-1.5 4.1 2.8			
Latifi (218)	14	MVCT & seeds	Daily	Seed motion	Mean (SD)	4.4 (2.1)	4.7 (2.5)	2.2 (1.9)	Up to 34mm		
Mens (225)	12	KV portal, CBCT & seeds	Daily portal & biweekly CBCT	Seed motion	Systemic motion Random motion	7.9 6.2	6.9 4.9	6.6 2.2			
Langerak (237)	50	CBCT & seeds	Daily	Marker centroid position	Mean Systematic motion Random motion	1.0 5.5 4.5	-3.9 5.1 3.6	0.4 3.4 2.2			
Lee (106)	17	Portal films	Weekly	Ring motion	Median	16	8	10	23	36	23
Chan (108)	20	MRI	Weekly	Cervical os	Grand mean Mean range	2.4 11.2	1.5 11.3	NR	NR	NR	NR
Taylor (233)	33	MRI	2 days	Post-inf cervix	Median Mean (SD)	3 4.1(4.4)	3 2.7 (2.8)	0 0.3(0.8)	19	12	3
Wang (240)	8	4DCT	Week 1, 3, 5	Post-inf cervix	Mean (SD)	7.9 (6.8)	3.8 (4.0)	3.9 (3.8)			
Beadle (110)	16	CT	Weekly	Centre of mass	Mean max	21	16	8	25	33	14
				Perimeter	Mean max	A: 17 P: 18	S: 23 I: 13	L: 9 R: 8	A: 29 P:63	S:35 I: 30	L:18 R:18
Collen (109)	10	MVCT	Daily	Boundary shifts	Mean (SD)	A:0.4 (10.1) P: -3.0 (6.9)	S:2.2(8.0) I: 0.5 (5.0)	L: -3.5 (6.9) R: 0.2 (4.5)	NR	NR	NR

Abbreviations NR: not reported; AP: anterior-posterior; SI: superior-inferior; LR: left-right

4.5.2. Uterine motion

Five studies, including 84 patients, report interfraction uterine motion. Results of these are shown in table 4.5-2.

Overall the uterus moves more than and independently of the cervix. Chan *et al* assessed the motion of the cervical os, uterine canal and uterine fundus in 23 patients using weekly cinematic-MRI and described. The uterine fundus was more mobile than the uterine canal, with the cervical os moving the least (108).

Taylor *et al* (233) assessed uterine motion with MRI imaging on two consecutive days. As well as translational movements, rotational aspects were noted, with the uterus being able to rotate from anteversion to retroversion. Of note, one patient had a rotation in uterine angle of 91 degrees, with the fundus moving up to 48mm in the AP direction. Variation in uterine angle was also described by Huh *et al* (210) using MRI scans, finding that 18% of patients showed positional changes of 30 degrees or more. 11% of patients who had an anteverted uterus at planning became retroverted during treatment.

4.5.3. Lymph node motion

Interfraction nodal motion is assessed in 3 studies including 70 patients (see table 4.5-2). Schippers *et al* (230) examined the motion of 39 visible lymph nodes in 17 patients with weekly MRI. Inhomogenous margins of 5-9mm, as a surrogate measurement of movement (Table 4.5-4) appropriately covered 95% of the nodal volumes.

Bondar *et al* (203) made an assessment of nodal motion by investigating motion of the iliac vessels, as a surrogate, as well as any visible enlarged nodes in 13 cervical cancer patients. They found the motion to be patient-specific, and after correction for set-up error with bony anatomy matching (translational and rotational) they found there was a large range of motion of the nodal vessels of 7.6-23.8mm. Mahanshetty *et al* (222) in their abstract found that in 40 patients with daily CBCT scans (767 scans) evaluated, that the pelvic nodal CTV had significant motion in all 6 directions (table 4.5-2).

4.5.4. Overall CTV motion

CTV motion (comprising pelvic nodes, cervix, uterus, parametrium and upper vagina) was assessed in one study, by Tyagi *et al* with the use of daily CBCT (234), measuring poisitional changes in CTV centre of mass (see table 4.5-2). They found an overall mean motion of 3mm (AP), -4.6mm (SI) and -0.28mm (LR).

Table 4.5-2: Interfraction motion of uterus, lymph node volumes and overall CTV

Target measured	Ref	Pt no	Modality	Imaging Frequency	Measurement Method	Average Movement (mm)				Maximal movement (mm)		
						Statistic	AP	SI	LR	AP	SI	LR
Uterine Motion	Taylor (233)	33	MRI	2 days	Sup-ant fundus	Median Mean (SD)	5 7(9)	5 7.1 (6.8)	0 0.8 (1.3)	48	32	5
	Wang (240)	8	4DCT	Wk 1, 3, 5	Sup fundus	Mean (SD)	14.2(10.5)	9.5 (6.6)	6.5 (4.8)	NR	NR	NR
	Chan (108)	20	MRI	Weekly	Uterine fundus	Grand mean Mean range	-4.6 14.5	7.8 24.4	NR	NR	NR	NR
					Uterine canal	Mean Mean range	-4.8 13.1	5.7 15.7	NR	NR	NR	NR
	Collen (109)	10	MVCT	Daily	Boundary shifts	Mean (SD)	A: 3.3 (11.9) P: 0.3 (11.7)	S: 6.1 (11.6) I: 5 (11.2)	L: 0.7 (8.1) R: -0.6 (7.5)			
	Lee2007 (219)	13	CT (using SBDS)	Weekly	Distance from isocentre	Mean	A: -1.1 P: -.4.3	S: -6.1 I: NR	R: -2.6 L: -1.2	A:20 P:28	S:45 I: NR	L: 28 R:21
Nodal Motion	Schippers (230)	17	MRI	Weekly	Margin from enlarged node	Mean	A: 7 P: 8	S: 7 I: 9	R:5 L:8	NR	NR	NR
	Bondar (203)	13	CT	Baseline and 40Gy	Iliac vessel moton	Mean	A: 9.4 P11.5	S: 7.8 I:10.1	L: 8.5 R: 9.1	23.8mm (direction not specified)		
	Mahantshetty (222)	40	CBCT	Daily	Pelvic node shift after bony match	Mean	A: 10.7 P: 12.9	S: 10.4 I: 12	L: 8.8 R: 8.7	A: 48 P: 25	S: 38 I: 31	L: 43 R: 22
CTV motion	Tyagi (234)	10	CBCT	Daily	CTV centroid position	Mean (SD)	3 (5)	-4.6 (3.9)	-0.28 (1.3)	18.9	-15.3	3.5

NR: Not reported; SD: standard deviation

4.5.5. Organ motion: Intrafraction

Eight studies examine intrafraction organ motion incorporating 108 patients (table 4.5-3), using cinematic-MRI, CT and portal imaging pre- and post- each fraction.

Intrafraction motion of the uterus and cervix was small, with a mean range of 0.1mm-4.2mm. Displacements greater than 5mm occurred less than 3% of the time (224), with displacements of >10mm 0.3% and 0.2% of the time with uterus and cervix respectively.

As with interfraction motion, Chan *et al* noted the uterine fundus moved more than uterine canal and cervical os (108). There was no predominant direction of intrafraction movement identified. Kerkhof *et al* (215) measure intrafraction motion with 4 MRI scans over 16 minutes, they noted the range of motion increased with time, 0.1mm in 4 minutes and 0.6mm in 16 minutes.

Table 4.5-3: Intrafraction Motion

Ref	Pt no	Imaging modality	Measured Point of interest	Average Movement (mm)				Maximal movement		
				Statistic Used	AP	SI	LR	AP	SI	LR
Chan (108)	20	Cinematic MRI over 30 mins	Uterine fundus	Grand mean Mean range	-1.1 12	-3.1 18.8		NR		
			Uterine canal	Grand mean Mean range	0.3 11.3	-1.8 12.8		NR		
			Cervical os	Grand mean Mean range	-0.1 10.6	-0.5 11.2		NR		
Haripotepornkunal (105)	10	KV portal images pre and post RT	Seed motion	Mean (SD)	2.9(2.7)	2.6 (2.4)	1.6(2.0)	15	15	13
Wang (240)	8	4DCT	Cervix	Mean (SD)	1.7(1.2)	1.6 (1.4)	1.4(1.1)			
			Uterine body	Mean (SD)	2.0(1.5)	2.0 (1.7)	1.8(1.4)			
Kerkhof (215)	22	MRI scans: 4 scans in 16 min	CTV motion	Median	0.1 (in 4 minutes); 0.2 (in 9 minutes); 0.6 (in 16 minutes)					
Mayr (224)	12	MRI every 3 secs over 2 mins	'Tumour region'	Mean (SD)	0.9 (6.3)			6.2 (3.6)		
			Uterus	Mean (SD)	1.2 (0.5)			9.0 (4.1)		
Raj (229)	10	MRI every 6 secs for 20 minutes	Cervix	Mean max	A:1.4 P: 5.1	S: 3.9 I: 2.9	NR			
Yamamato (239)	10	Orthogonal X-rays & markers	Cervix	95% CI in motion	1.4-3.4	2.4-4.2	1.9-2.5			
Heijkoop (208)	16	CBCT pre and post fraction	Cervix-uterus	Mean (SD)	3.4 (2.1)	4.7 (2.8)	3.0 (1.4)			

4.5.6. Impact of bladder filling on organ motion

The correlation of bladder filling with interfraction cervix-uterine motion is examined by 12 studies (108-111, 201, 203-205, 233-235, 238) including 230 patients.

Overall bladder volumes altered the position of the tip of uterus (ToU) in both AP and SI directions (111, 204, 233) and the effect was patient-specific. With variable bladder filling ranges of ToU motion of 5mm-40mm in the SI and 0mm-65mm in AP direction were observed among patients (111). Those with a more consistent bladder volume (variability < 50mls) on consecutive days had an average superior ToU motion of 4.2mm compared with those with greater variability (> 50ml), who had superior motion of 11.2mm (233).
Buchali *et al* (204) found the uterus to move 7mm superior and 4mm posterior from empty bladder (using a catheter) to full bladder (filling via catheter to a maximally tolerated volume) with less motion noted in cervical position. These results are difficult to fully interpret as both bladder and rectum were filled and emptied at once, and also the maximal bladder filling was only 175ml, which is considerably less than a typically full bladder volume.

Bladder filling had less impact on cervix motion than uterine motion (233, 235) with a 5.5mm inferior and 3.9mm anterior shift in cervical position demonstrated from empty to full bladder (110). Bladder volume also had a moderate correlation with nodal motion (203), though the clear pattern of this is not stated.

One study examined the relationship of bladder filling on small bowel position. The small bowel sparing effect of IMRT correlated with bladder size (Pearson's R=0.7). Larger bladder volumes appeared to displace the small bowel reducing the volume receiving >50Gy by 83cm^3 (range 0-292cm^3) (206).

Over the course of radiotherapy treatment a systematic reduction in mean bladder volume was found in 3 studies (108, 109, 197). A decrease in mean bladder volumes from 156cc to 88cc between the first and last weeks of treatment is reported. Chan *et al* found that for every 10cc decrease in bladder volume the uterine fundus moved 18mm inferiorly, the uterine canal moving 8mm inferiorly and the cervical os 3mm anteriorly (108). Tyagi *et al* demonstrated a similar pattern, though with a smaller magnitude, such that a 10cc increase in bladder volume corresponds to superior shift in CTV centroid of 0.1mm (234).

Retrospective analysis suggests pre-treatment bladder volumes may influence CTV-ITV margins (235). Larger (>115mls) baseline bladder volumes required a greater (12mm) inferior CTV-ITV margin than the 7mm required for those with smaller volumes (<115ml).

Three studies assessed the effect of bladder filling on intrafraction movement. Both Kerkhoff *et al* (215) and Heijkoop *et al* (208) demonstrated statistically significant correlations (R=0.46; R=0.6 respectively) between intra-fraction bladder filling and average intrafractional CTV motion. Chan *et al* found no significant influence of bladder volumes on intra-scan motion (108).

4.5.7. Impact of rectal filling on organ motion

Five studies including 103 patients report the impact of rectal filling on cervix-uterine motion, particularly AP and SI movements (108, 204, 233, 235, 238). A greater influence on cervical and upper vaginal motion compared to the uterus was noted (233). Significant correlations between rectal volume and AP shifts of the GTV, CTV and upper vagina were noted with correlation coefficients of 0.71, 0.79 and 0.66 respectively (238). In one individual, a 19mm AP shift of cervix position resulted from rectal diameter change from 71 to 34mm (233). A $6cm^3$ decrease in rectosigmoid filling corresponded to inferior motion of uterine canal (3.6mm) and cervical os (2.6mm)(108).

Retrospective analysis showed those with pre-treatment rectal volumes >70cc required greater posterior and inferior internal margins (20mm and 12mm respectively), than those with a smaller baseline rectal volume (<70cc) (10mm and 6mm)(235). Though daily variations in rectal volumes are reported (ranges between 21-150cc), no systematic change during the course of treatment was identified (233, 238). No correlation was noted with iliac vessel motion (representing CTVnodes) and rectal filling (203).

4.5.8. IGRT solutions

Many studies relevant to IGRT solutions were identified and were categorized as below:

4.5.9. Patient positioning

Prone positioning with use of belly board device (allowing superior and anterior displacement of the small bowel) is compared with supine position in 4 studies including 66 patients. Prone positioning using a 'limited' arc planning technique in 16 patients (9 having definitive radiotherapy) reduced small bowel volumes receiving >45Gy (V45) from 19% to 12.5% but increased large bowel volumes receiving >50Gy from 6.9% to 14.8% (196). Similarly using a 7-field IMRT technique small bowel V45 reduced from 20.3% to 13.7%, though V40 rectum increased from 69.5% to 79.4% (232). Prone positioning did

not significantly reduce small bowel doses with conformal planning (228) in one study, however was found to reduce small bowel volumes significantly in another study (199).

The use of the “small bowel displacement system” (SBDS), a Styrofoam compression device placed under the abdomen in the prone position in addition to a bellyboard was reported in three studies including 33 patients (219, 227, 241). With IMRT treatment SBDS use reduced the mean small bowel volume within the PTV from 67.9% to 16.8%.

Patient Preparation

With the noted patterns of bladder filling and uterine motion, early investigation into potential solutions has been described by Bhuva *et al* (200). The use of an ITV is investigated where the CTV is outlined on a “bladder full” planning scan and a “bladder empty” planning scan; these volumes are fused and a ITV-PTV margin is applied. In the 11 patients studied they found that a 10mm ITV-PTV margin allowed CTV coverage in 37/40 CBCTs studied and a 12mm margin allowed coverage in 39/40 CBCTs, compared with a standard isotropic 15mm margin which allowed coverage in only 16/40 scans.

There were no studies that evaluated rectal preparation protocols as a means of reducing cervix-uterine motion or doses to OARs.

Margins for organ motion

Fifteen studies including 271 patients proposed internal margins to allow for cervix-uterine motion (Table 4.5-4) based on organ motion studies.

Table 4.5-4: Suggested Margins for Organ Motion

Ref	Pt No	Imaging modality	Imaging frequency	Margin around:	Margins suggested (mm)		
					AP	SI	LR
Chan (108)	20	MRI	Weekly	Cervical Os	10-15 (all directions)		
Latifi (218)	14	MVCT with gold seeds	Daily	Fiducial marker COM	12	11	8
Collen (109)	10	MVCT	Daily	Cervix	A:17 P:12	S:15 I: 9	L:9 R:8
Wang (240)	8	4DCT	Week 1, 3 and 5	Cervix	19	10	9
Van de Bunt (235)	20	MRI	Weekly	GTV	A:12 P:14	S:4 I:8	L:11 R:12
Van den Bosch (237)	5	CBCT	Weekly	Cervix	Mean 7mm (max 10mm)		
Langerak (237)	50	CBCT with polymeric markers	Daily	Cervix	15.2	16.6	8.7
Malyapa (223)	16	CT	wk 2 & 4	Uterus	21.0 (10.1) (range 10.1-30.8)		
Chan (108)	20	MRI	Weekly	Uterine fundus	10-40 (all directions)		
				Uterine Canal	10-12.5 (all directions)		
Collen (109)	10	MVCT	Daily	Uterus	A:19 P:19	S:20 I:19	L:13 R:13
Wang (240)	8	4DCT	Week 1, 3 and 5	Uterus	32	20	14
Van den Bosch	5	CBCT	Weekly	Uterus	Mean 10mm (max 18mm)		
Schippers (230)	17	MRI	weekly	Enlarged lymph nodes	A: 7 P: 8	S: 7 I: 9	R:5 L:8
Mahantshetty(222)	40	CBCT	Daily	Pelvic nodal CTV	10-15mm (all directions)		
Tyagi (234)	10	CBCT	Daily	CTV	15.3 (grand mean) 35 to encompass all volumes all fractions		
Kaatee (212)	10	EPID with seeds	Daily	CTV	12	12.1	10.2
Taylor (233)	33	MRI	2 days	CTV	15	15	7
Lee (106)	17	Portal films & metallic ring	Weekly	CTV	22.9	15.4	17.5
Van de Bunt (235)	20	MRI	Weekly	CTV	A:24 P:17	S:11 I:8	L:16 R:12

Suggested isotropic internal margins ranging from 10-21mm were suggested, though most studies suggested anisotropic margins. These ranged from 12-32 (AP); 8-20 (SI) and 7-17.5 (LR).

Structure-specific isotropic margins are proposed in two studies with different margins for different components of CTV. Chan *et al* suggested margins of up to 4cm around the uterine fundus and 1.25cm around the cervix (108), and Van den Bosch *et al* suggested maximal margins of 10mm and 18mm for cervix and uterus respectively based on weekly CBCT analysis.

A further study modelled 1cm, 2.4cm and 'tapered margins' (2.4cm around the fundus narrowing to 1cm around cervix) combined with different 'motion' models by Khan *et al*. A 1cm margin led to insufficient fundal coverage of approximately 5Gy as an effect of motion (10% of the prescribed dose). Use of the tapered margin restored this loss of dose coverage, with slight increases in bowel and rectal doses (V50.5 from 17.8 to 19.0, and 46.2 to 48.3 respectively)(216).

Additionally three studies used pre-set margins to assess on-treatment CTV coverage. Tyagi *et al* (234) found the use of 15mm isotropic margin failed to encompass the entire CTV in 32% of fractions, studied however the mean volume "missed" was 4cc. Bloemers *et al* investigated the use of an anisotropic (20mm SI and AP margins, 10mm LR) and demonstrated insufficient CTV coverage in 13% of fractions (201). Conversely, dosimetric analysis in a study by Lim *et al* using 5mm and 20mm PTV margins with IMRT suggested a 5mm margin allowed for pelvic organ motion with adequate dose delivered to 98% of the CTV in 95% of patients, using weekly MRI scans. Of note, one of the twenty patients studied had significant underdosing due to unpredictable target motion (220).

Regarding nodal internal margins, 9mm margins for visible nodes are suggested by one study (230), and 10-15mm margins suggested by another study (222) for the whole nodal CTV although maximal movements of up to 43mm of the CTV are noted. Consensus guidelines suggest a 7mm CTV-PTV margin for nodal volumes. (12).

On-treatment imaging modality, matching and marker use

Imaging modalities were not directly compared in any study, though 3 studies report inter-observer variability as a measure of reproducibility. Using MRI inter-observer mean differences of -0.66 to 0.25mm were reported when determining uterine position (108). MVCT use was found to have inter-observer variability of -0.4 to 1.0mm at cervix and 0.2

to 0.9mm at uterus (109). Using CBCT mean inter-observer variability led to differences in margins required of 4.1mm (234).

'Fiducial' markers (tantalum, gold and polymeric) were used in 6 studies. Good marker visualisation was reported with planar KV imaging (90% visualised) and CBCT (100%) (225). Initially high marker loss rates of 14%-50% were found (205, 212), though in the more recent study by Langerak *et al* (217) with the use of polymeric markers marker loss was only 6%. The authors used an alternative means of marker implantation by which the markers were implanted 5mm into the submucosal tissue of the vagina in four directions around the cervix. They also report significant less streaking artefact with the use of polymeric markers compared with gold markers.
Lee *et al* used a metallic ring as a fiducial marker which was sutured in with the use of a uterine sleeve prior to treatment (106). Fixation was good with this approach though may be a practical challenge for routine clinical use.

One study (Oh *et al* (226)) compared the use of soft tissue matching and bony matching for treatment verification in 15 patients. For soft-tissue matching on-treatment MRI was used, and found this to be increasingly enhancing of target coverage, as well as being cost-effective, as they postulated that increased replans would be required based on bony matching.

3.8.1.2. Offline versus online IGRT solutions

No studies directly compared offline versus online imaging strategies for management of organ motion. Most of the images acquired in the sections above were as part of an offline protocol with weekly imaging.

4.5.10. Individualised and adaptive strategies

Eight studies discuss the use of individualised strategies, proposed around the concept of patient-specific uterine motion with variable bladder filling (123, 124, 198, 202, 207, 209, 213, 236).

Non-adaptive and adaptive strategies are compared in an important study by Bondar *et al* (123). Each strategy was tested against CT scans that had been acquired with variable bladder filling (VBF), with 9-10 scans acquired pre-treatment and after 40Gy of treatment.
Initially a non-adaptive ITV approach (as described above) was modelled. The ITV required a PTV margin of 7-10mm to cover the CTVs on the VBF scans. With a

population-based approach, where no ITV was used, a PTV margin of 38mm was required.

Compared with a population-based approach the ITV reduced average PTV volume by 48%, reducing bladder and rectal volumes within the PTV by 5-45% and 26-74% respectively.

The study went on to examine an adaptive strategy, 'plan of the day' (PotD). This concept uses formation of a library of plans per patient, and each day an appropriate plan based is chosen based on imaging that day. In this study plan libraries were generated using scans with VBF, either a 2-plan, 3-plan or daily plan library was generated. The PotD was chosen based on bladder volume on ultrasound. The authors concluded the adaptive approach increased OAR sparing compared to non-adaptive methods but the precise amounts were not quantified. No added benefits were seen with the use of a 3-plan library, or daily plan library over a 2-plan library.

Heijkoop *et al* (124), took these concepts further with clinical implementation initially in 24 patients where either an ITV-based IMRT plan was chosen, or a backup 3D conformal plan was chosen depending on the patients anatomy on daily CBCT. The IMRT plan could be used in 17 of 24 patients for all treatments, though the benefits in terms of OAR sparing are not quantified.

In their second phase of 40 patients, a backup 3D conformal plan, and either one or 2 IMRT plans were produced. 2 IMRT plans were used for patients who were noted to have a cervix-uterus motion of >2.5cm at the time of planning (n=11). These were empty-to-half full, and half-full to full ITVs depending on bladder filling. For patients with <2.5cm motion a single IMRT plan was produced as in the first phase (n=29). IMRT could be used in 81% of treatment fractions. A potential bowel sparing effect was noted for 11 patients with 2 IMRT plans however this approach was not quantitatively compared with the other strategy or the use of a conformal plan throughout.

Other authors have also suggested that plan of the day may be required only for certain patients (236), such as those where the uterus on empty bladder planning scan was outside a 1cm margin around the uterus on the full bladder scan. These concepts need further analysis before firm conclusions can be made.

A further adaptive study, 'Margin of the day' (MotD), was modelled by the same research group (198). Again modelling took place on VBF scans acquired pre-treatment and after 40Gy, 9-10 scans per patient. Incremental isotropic PTV margins of 5mm-45mm in steps

of 5mm around the CTV at planning were modelled for 14 patients. The number of plans per patient was determined based on the range of motion seen in the scans, with patients needing 3-8 plans in their library (median of 5). The maximum range in one patient was from 10mm to 45mm. MotD was compared with a population-based margin of 15mm. They found that a population-based margin of 15mm around the cervix uterus resulted in underdosage in six patients out of the 14 studied. In these six patients, MotD improved CTV coverage but did not result in an increase in the average bowel V99, bladder and recum V90 parameters studied. For the 8 patients where the population-based margin was sufficient, MotD reduced the irradiated volume by 11%.

Another individualised strategy proposed is the 'optimised PTV margin' where 758 landmarks are placed over the planning CTV, and vectors from these landmarks to the on-treatment CBCT CTVs are measured, forming an optimised PTV margin with high target coverage with reduced OAR volumes in the PTV, so far this has only been modelled retrospectively (216).

4.5.11. Adaptive Replanning Studies

Replanning was modelled with MRI by Kerkhof *et al* (214) in their study of 11 patients. With weekly MRI scans they created 4 IMRT plans per patient with a PTV margin of 4mm to model an "online IMRT" approach. They compared volumetric and dosimetric parameters with a fixed 15mm "pre-IMRT" approach. A significant reduction in doses to OAR that overlaps within the primary PTV- bladder (53% to 11%), rectum (57% to 13%), bowel (12% to 1%), sigmoid (63% to 13%) were noted with the 'online' plan. The practicalities of how this could be implemented prospectively with daily adaptation were not considered, suggestions were either a library of plans or a new treatment plans based on daily anatomy.

Work from Princess Margaret Cancer Centre, Toronto, has also addressed the issue of replanning (221, 226, 231). Initially Stewart *et al* (231) modelled the use of replanning to accommodate for organ motion with weekly MRI scans in 33 patients. They compared the use of a "no replan" strategy, where a plan based on the planning MRI was compared with a "replan" strategy. This involved an automated replan performed on the updated weekly MRI. Both strategies were modelled with a 3mm PTV margin. With no-replan 27% of patients failed to meet the 95% prescription dose and this was improved in the "replan" strategy, though doses to rectum and bowel increased in 52%.

Lim *et al* (221) modelled 2 adaptive strategies on the same patients, also using 3mm margins. Either an automated adaptive IMRT (A-IMRT) approach where a replan was

treatment based on anatomical change, or a dosimetric-triggered adaptive replan (D-IMRT) which was performed only if anatomical change led to underdosing of the CTV or PTV. The D-IMRT approach reduced replanning frequency by 23%, and improved coverage from 90% of patients to 100% of patients compared with A-IMRT.

Although this concept is promising it is important to note the CTV definition in these studies was limited superiorly to 2cm above GTV and did not encompass the whole uterus. Compared to the rest of the studies within this systematic review this CTV is likely to have significant less motion with the uterus being most prone to organ motion.

4.6. Discussion

This systematic review summarizes the results of 53 studies examining inter- and intra-fraction organ motion during radiotherapy for cervical cancer and the potential IGRT solutions to account for this motion. The results could help inform future IMRT planning and verification protocols for definitive cervical cancer radiotherapy.

4.6.1. Interfraction and intrafraction motion

Multiple studies exist within the literature examining predominantly cervical and uterine motion. These studies highlight that cervical motion and uterine motion is an important consideration, and must be addressed when determining an IMRT protocol. The uterus was more mobile than the cervix; Taylor *et al* examined both uterine and cervical motion and demonstrated greater ToU motion in the AP (maximal 48mm) and SI (maximal 32mm) directions compared to cervical motion in the AP (maximal 19mm) and SI (maximal 12mm) directions (233). Cervical motion is translational, though the uterus is prone to both translational and rotational change, adding to its complexity. Direct comparison between studies of uterine-cervix movement is difficult as each study uses different methods to measure motion and report different statistics.

Many studies report the impact of bladder filling on uterine motion. With bladder filling the tip of uterus can move in the anterior direction of 65mm (111), however this pattern is patient specific and cannot be predicted. Rectal filling was associated with anterior-posterior motion of the cervix.

Intra-fraction motion also exists, though is relatively much less pronounced than interfraction motion and both are likely be accounted for within internal margins. Studies looked at intrafraction motion over for example a timespan of 16 minutes (224), however

with the use of arc therapies such as VMAT, this issue may become much less important as delivery times shorten to 2-3 minutes.

4.6.2. IGRT considerations

3.8.1.3. Patient positioning and patient preparation

Studies addressing patient positioning were not conclusive. Though prone positioning has been shown to reduce small bowel within the treatment field, it can be associated with considerable set-up errors (up to 15mm) caused by AP sacral rotations (-14º-11.5º) (242). Increasing PTV margins to account for these errors possibly negates the benefits of small bowel sparing.

In terms of patient preparation, bladder filling is an important factor to manage uterine motion. The use of "strict" bladder filling protocols is likely to be insufficient. Studies in other pelvic tumour sites, such as post-hysterectomy endometrial, bladder and prostate cancer (114, 243, 244) show that despite strict drinking protocols a constant bladder volume is difficult to maintain. Bladder volume has been shown to systematically reduce during treatment, probably due to reduced bladder capacity and radiation cystitis (108, 109, 111) adding to the problem of maintaining a consistent bladder volume. The concept of an ITV may be an important solution in this setting (123, 200) though needs more investigation to confirm its benefits and ITV-PTV margins that are appropriate.

With regards to rectal filling, no guidance is derived from this literature review. Extrapolation from prostate cancer, where bowel preparation is commonly used to maintain an empty rectum, may suggest its potential use in cervical cancer. This hypothesis would need to be tested clinically to assess its value in gynaecological malignancies.

3.8.1.4. Margins to account for motion

RTOG consensus documents aim to aid delineation of target volume for cervical cancer IMRT, though there is minimal information with regards the CTV-PTV margins. They report that 15-20mm margins are commonly advocated (95).

From the studies within this review a wide range of isotropic internal margins (from 10mm up to 21mm) and anisotropic margins (up to 32mm AP, 20mm SI and 17.5mm laterally) were suggested. This implies that commonly used CTV-PTV margins of 1.5-2cm may be insufficient. However a wide variety of methods were used to derive these proposed margins so it is unclear what the optimal margins should be.

Structure-specific margins, with a larger uterine margin (4cm) and a smaller cervical margin (1.25cm) potentially would allow for the differences in the movement observed (108). The concern with large margins such as 4cm around the uterus is that this will lead to significant inclusion of OARs within the PTV and negate the benefits of IMRT. Further there is ongoing debate as to whether the uterine fundus should be included within the CTV for all patients, as there is limited data suggesting the fundus to be a common site for microscopic spread in cervical cancer. This important issue needs addressing given that the fundus is the most mobile CTV component and therefore the margins required to account for its motion are so much greater.

Lymph node motion is also an important consideration in cervical cancer where lymph nodes are a common site of disease recurrence, and geographical miss must be avoided. Schippers *et al* (230) provide some data regarding lymph nodes visible on MRI, suggesting a 9mm margin around these should be used. However for elective nodal CTV, Bondar *et al* (203) suggest that such a margin would be insufficient. Mahanshetty studied a large number of data (776 daily CBCTs in 40 patients) and suggest margins of 10-15mm margins. However the authors do not clearly state how their CTV was defined or how the margins were calculated, as they had patients with motion of up to 48mm anteriorly for example.

As well as internal margins, consideration of set-up margins to create a PTV is also necessary when developing an IMRT/IGRT protocol, though is beyond the scope of this review. Studies using daily CBCT suggest set-up margins of up to 11.6mm (SI), 9.6mm (LR) and 8.2mm (AP), which would be a significant addition to internal margins (245). Set-up margins should be centre-specific as they are dependent on patient positioning, immobilisation and imaging protocols.

4.6.3. On-treatment verification

Daily online imaging may reduce both internal and set-up margins, yet to date no studies directly compare online versus offline modalities in this setting. Many centres use imaging protocols such as day 1, 2, 3 and then weekly offline guidance as standard for conformal pelvic treatments. However both UK National Guidance (193), and international guidance (95) recommend an offline strategy is likely to be insufficient for cervical cancer IMRT, given the unpredictable nature of uterine movement, and this is confirmed by the significant random error noted in this review (108, 212, 225). The use of soft tissue

imaging to be used with IMRT techniques for both radical and post-operative IMRT is also recommended. This is due to the independence of pelvic organ motion to bony anatomy.

However even with daily online volumetric imaging, simple translational shifts are likely to be insufficient to compensate for the complexity motion of this target volume. A translational shift to accommodate change in uterine position may lead to poor coverage of the more static pelvic node volumes. An IGRT solution is therefore required that can accomodate the complexity of differential CTV motion whilst taking into account the intra-patient variation of organ motion.

4.6.4. Adaptive and Individualised Strategies

Individualised adaptive approaches are likely to be important avenues of research in cervical cancer given the complex, patient-specific nature of CTV organ movement. Adaptive planning has been studied in other tumour sites. In bladder cancer for example the plan of the day has been modelled, with each patient having a library of plans with “small”, “medium” or “large” margins used. This has shown some promise in single centre studies for significantly reducing the volume of normal tissue irradiated whilst maintaining CTV coverage (120, 121), and is now being tested in a UK Phase II multicentre trial (122).

Within this review two concepts around plan of the day have been modelled. Plan of the day (PotD), has been modelled by Bondar *et al* with some clinical implementation by Heijkoop *et al*. This group compared PoTD against two other strategies, including the use of a non-adaptive ITV, taking into account organ motion on two scans only at the time of planning, and a population-based margin of 38mm. With the individualised strategies smaller PTVs are possible with sparing of OARs, however the sparing of OARs was not quantified which would be essential to know when deciding whether to implement a technique that is likely to be time- and labour-intensive.

The other concept was margin of the day, but with patients needing up to 8 plans prior to commencing radiotherapy the labour-intensitivity of this strategy must be considered, unless a more automated planning process can be used.

With regards to replanning strategies the studies described use very small margins (3-4mm), and weekly imaging only. CTV definition is variable, with some studies not taking into the account the whole uterus which is included in RTOG defined cervical cancer guidelines. The true benefits of these methods need therefore to be investigated before they can be adopted.

4.6.5. Strengths and limitations

The work in this chapter had strengths; the search strategy was comprehensive and a detailed assessment of all relevant aspect to this subject could be performed. Limitations were that some aspects, such as organ motion in brachytherapy were not covered, although external beam radiotherapy is the focus of this thesis and thus thought not as relevant. Some of the exclusion criteria such as studies limited to English may have excluded potential useful data.

4.7. Conclusions and Future Work

Interfractional organ motion for cervical cancer is a significant concern. Uterine motion is more predominant than cervical motion. Uterine motion is influenced by bladder filling and cervical motion more by rectal filling. Despite a number of studies on this subject findings are difficult to compare given the variety of methodologies used to derive them. This makes direct application of these results on prospective patients difficult.

There are still many unexplored research avenues with regards to IGRT for cervical cancer, including protocols for bladder and rectal filling to limit organ motion. As for margins, a range of population-based margins are suggested in the literature, and optimal margins cannot be concluded from this work. Given that organ motion patterns are patient-specific, adaptive individualized approaches may be of benefit to avoid unnecessary irradiation of OARs in patients where organ motion is minimal.

Future work would aim to extend knowledge of adaptive strategies and to quantify their likely benefits of such strategies in terms of CTV coverage and OAR sparing.

4.8. Acknowledgements

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All other work was performed by myself.

5. Chapter V: Comparison of margin strategies for definitive cervix IMRT

5.1. Introduction

Although IMRT for cervical cancer is desirable, pelvic organ motion is an important barrier towards its widespread adoption. Published literature of cervical cancer organ motion and its possible solutions are reviewed in chapter IV of this thesis.

A promising avenue of solutions highlighted in the systematic review is the use of different margin strategies. Although these have been proposed and assessed in the literature, the benefits and drawbacks of each solution are not quantified such that an overall best solution can be chosen. In this section of the thesis these margin strategies will be compared and analysed in detail.

Margin strategies can be categorised into population-based margins, individualised non-adaptive margins and individualised adaptive margins.

5.1.1. Population-based margins

Isotropic margins

Traditionally standard radiotherapy treatments use isotropic PTV margins around a CTV which are large enough to account for organ motion and set-up error. However in cervical cancer IMRT the most appropriate isotropic margin to use is unclear.

RTOG published guidelines (95) for IMRT outlining in cervical cancer and suggested isotropic CTV-PTV margins of 1.5 to 2cm may be suitable if “good quality daily soft tissue imaging” is available, however if bone matching is being used “larger” margins should be used. Trial protocols (113) suggest 2-3cm, and many centres use 2cm isotropic margins as a standard. Suggested isotropic margins from organ motion studies range widely from 1-3.5cm (234, 237). There is little validation of these margins in independent samples of patients, and their success in clinical practice is unknown.

Anisotropic Margins

Anisotropic margin use is another solution with the knowledge that both the uterus and cervix move more in A-P direction compared with other directions. Tailoring margins in specific directions may be of value to spare neighbouring OARs whilst maintaining coverage. Population-based anisotropic margins from individual studies are suggested in

studies as summarised in the previous chapter. Again the variation between studies is significant, for example for anterior margins there is a range of margins from 7-32 mm (237, 240), and superior margins from 11mm to 20mm (109, 235). Comparisons of these margins with isotropic margins and validation of their use in clinical practice is not found.

Structure-specific margins

A key finding from the previous chapter was that different components of the primary CTV in cervical cancer have different motion patterns. A further solution therefore is that of structure-specific margins. Just as different margins are applied to pelvic nodal CTV and the primary CTV, further subdivision of the primary CTV into uterus, cervix, vagina etc. may avoid excessively large margins for components of the CTV where there is less motion. This concept was suggested in a key paper by Chan *et al*. (108), with 4cm and 1.25cm margins for uterus and cervix proposed respectively. A further study suggested 1.8cm around the uterus and 1cm around the cervix (237). The benefits of these margins over simple isotropic or anisotropic margins have not been quantified as yet.

Benefits of all population-based margin solutions are their simplicity, whereby a margin is applied prior to treatment and little extra is required. Drawbacks are that for patients with limited organ motion population-based margins may well be excessive, with unnecessary inclusion of OARs within the PTV.

5.1.2. Individualised non-adaptive margins: Internal target volume

The internal target volume (ITV) solution in gynaecological cancers attempts to take into account CTV motion in relationship to bladder filling. This is ascertained by a patient having two planning scans, one with a full bladder and one with an empty bladder. The primary CTV on the full bladder scan is combined with the primary CTV on the empty bladder scan forming an ITV. Around this ITV a further margin is added to create a PTV, and those who have recommended this method in the literature have used margins of 7-12mm (123, 200).

RTOG guidance has recommended this method for post-operative gynaecological patients (98), though do not mention its use for radical cervical cancer patients. In radical cervical cancer there is a suggestion that this method is likely to improve coverage compared with 15mm isotropic margins (200). Reported clinical outcomes with this method in 22 patients has found acceptable toxicity and locoregional control, though there is no comparison made with standard isotropic margins (246).

Although the ITV methods allows for individual patient organ motion based on bladder filling, it takes little account of rectal filling. It also requires the additional exposure from a second empty bladder planning CT scan.

5.1.3. Individualised adaptive margins

Further to the ITV concept is the use of adaptive margins where treatment is modified to adapt to the patient's anatomy whilst on treatment using information from on-treatment imaging.

5.1.3.1. Composite volumes

One adaptive approach is the use of 'composite volume'. For each patient this uses multiple images acquired at the start of treatment, for example from the first 3 or 5 days. The CTV is outlined on each image and a union of the CTVs forms a 'composite'. To this a small margin is added for set-up error to form a PTV.

This approach has been studied in bladder cancer and in prostate cancer (119, 247) though to date has not been addressed in cervical cancer. In prostate cancer, a composite from the first six fractions of treatment was generated with a 7mm PTV margin. Compared to a standard 10mm margin this reduced the irradiated volume and rectal doses. In bladder cancer, a composite using the first five fractions of treatment, reduced treatment volumes by 40% compared with a standard isotropic margin.

This approach would require the patient to have a 'standard' margin for the first few fractions of treatment and then for the treatment to be replanned after the first few fractions once the composite has been created, which may add to the departmental workload.

5.1.3.2. Plan of the Day

An alternative approach is 'Plan of the Day' (PotD) where a patient has a library of plans (LoP) generated based on their pre-treatment imaging. The patient commences treatment with daily online imaging. Each day the most appropriate plan is chosen based on the patient's anatomy that day.

This has been used in bladder cancer, with each patient having a library with "small", "medium" or "large" margins used. This has shown some promise in single centre studies (120, 121), and is now being tested in a UK Phase II multicentre trial (122).

In cervical cancer rather than having different margins sizes applied the LoP is generated based on plans with different degrees of bladder filling, as this is likely to impact uterine position, and would take into account the rotational motion of the uterus.

In cervical cancer radiotherapy Bondar *et al* (123) modelled PotD. In their study they modelled the range of CTV position from full to empty bladder, and chose two or three mid-range CTVs, to which 7-10mm PTV margins were added. The library was then tested against 6-7 CT scans per patient, with plans chosen based on bladder volumes on bladder US scans. They found their method reduced bladder within the PTV by up to 10%, and rectum by up to 9% compared to an ITV, though this was not quantified dosimetrically.

Heijkoop *et al* (124) clinically implemented some of these concepts from this study, with a two-plan library or three-plan library chosen depending on the range of uterine motion for that patient. Plans were chosen daily based on CTV position as seen on daily online CBCT. If the plan library did not offer an appropriate plan a 3D-conformal plan was used as a "back-up", and this was needed in 17.5% of all fractions. Overall the authors found PotD to be clinically feasible, and plan selection was possible in a timely manner with a well-trained team. OAR sparing however was not fully detailed compared to a standard margin, making it difficult to quantify the achievable benefits.

Although these initial PotD studies are promising, many questions remain unanswered about PotD methodology; for example – the appropriate number of plans; the requirement for a backup plan; the optimal bladder protocol to yield the largest variation between full and empty bladder scans; appropriate PTV margins for each plan.
PotD techniques will increase departmental workload, potentially requiring additional planning scans, technology and manpower to "interpolate" volumes, generation of multiple plans and training of radiotherapy staff to choose the appropriate plan for the day. Therefore comparison of PotD techniques against other margin strategies is of vital importance to quantify its benefits in terms of CTV coverage, OAR sparing and subsequent clinical benefit and determine its cost-effectiveness.

5.2. Aims

The aims of this work were:

- To compare the relative utility of different margin strategies for addressing the issue of internal organ motion in cervical cancer radiotherapy, in terms of CTV coverage and OAR sparing.
- To determine the most promising strategy from the strategies modelled based on volumetric assessment

- To dosimetrically model the most promising strategy in comparison to standard treatment
- To model dose escalation for the most promising strategy when sufficient bowel sparing is achieved

5.3. General Methods

Planning and treatment verification imaging from patients treated definitively for cervical cancer from April 2013 to September 2015 were analysed retrospectively.

All patients meeting the inclusion criteria below were included consecutively:

5.3.1. Inclusion:

1. Patients treated for cervical cancer with definitive intent
2. Patients who had two planning scans (full bladder and empty bladder)
3. Patients who had at least 6 CBCT scans during treatment to allow sufficient analysis of organ motion.

5.3.2. Exclusion:

1. Post-hysterectomy patients
2. Patients with hip replacements, which cause artefact on their CBCT
3. Patients with long treatment volumes (sup-inf) where the CBCT scans did not include the lower pelvis, e.g. where para-aortic nodes were being treated

5.3.3. Patient treatment

All patients received treatment as part of routine care in our institution, and this is detailed in the following sections:

Patients were treated with external beam radiotherapy (EBRT) with a prescribed dose of 45Gy in 25 fractions. Concurrent chemotherapy (usually weekly cisplatin 40mg/m2) was administered unless clinically inappropriate. External beam radiation therapy was followed by intracavitary high-dose rate brachytherapy, delivering 21.3Gy in 3 fractions prescribed to point A in once weekly fractions.

Simulation

Patients were simulated in the supine position and immobilised with the OncologySystems Limited Combifix. Intravenous contrast was used to highlight vasculature where patients had sufficient renal function. Patients were scanned using Siemens Somatom Sensation CT scanners.

Two planning scans, a “full bladder” and “empty bladder” scan were acquired for each patient, as was departmental policy in our institution since April 2013. For the full bladder

scan patients were scanned from T10 to below the perineum. Patients were asked to empty their bladder then drink 200-300mls of fluid 30 minutes prior to full bladder simulation. After acquisition of the full bladder scan patients were asked to void their bladder, and the empty bladder scan was acquired, from L4/5 to the perineum.
No rectal preparation protocol was used for either scan.

Target volume delineation
Target volumes were outlined on the full bladder planning scan on Oncentra Masterplan (OMP) version 4.3. The full bladder and empty bladder scans were co-registered with the mutual information algorithm.
The CTVnodes was delineated from a 7mm margin around pelvic vessels from the bifurcation of the aorta (for node positive patients) and from the L4/5 junction (for node negative patients). Further expansion of the CTV nodes included the presacral region from the sacral promontory to the pirifomis muscle, and to include the obturator nodes until the superior aspect of the obturator foramen. An 8mm margin was added to CTVnodes to form PTVnodes.
The CTVprimary consisted of the GTV (determined by MRI and FDG-PET scans) plus a 1cm margin. The CTV was further extended to include the rest of the cervix, uterus, parametrium and 2cm vagina below the GTV. Parametrial borders included the broad ligament superiorly, and pelvic diaphragm inferiorly. Laterally this was extended to the pelvic nodal CTV, anteriorly to posterior bladder and posteriorly to mid-rectum.
A 1-2cm CTV-PTV margin was applied around the primary CTV (depending on clinician preference). The PTV was then checked against the empty bladder planning scan to check that all CTV components on the empty bladder scan were within the PTV outlined on the full bladder scan.

Treatment planning and delivery
Patients were treated using 3D-conformal planning with four-field technique to a prescription of 45Gy in 25 fractions on Elekta Synergy Precise units. On treatment patients followed the same drinking protocol as in planning.
Each patient had an offline CBCT scan, acquired with use of the XVI software version 4.5.1, on day 1,2,3 and then weekly scans over the remaining 4 weeks. An offline protocol was used to assess these scans. Online CBCTs were acquired when there were concerns about target volume coverage and the reasons for additional scans documented.

5.4. Modelling study methods

5.4.1. Stages of Investigation

This study was performed in 4 stages as illustrated in figure 5.4-1:

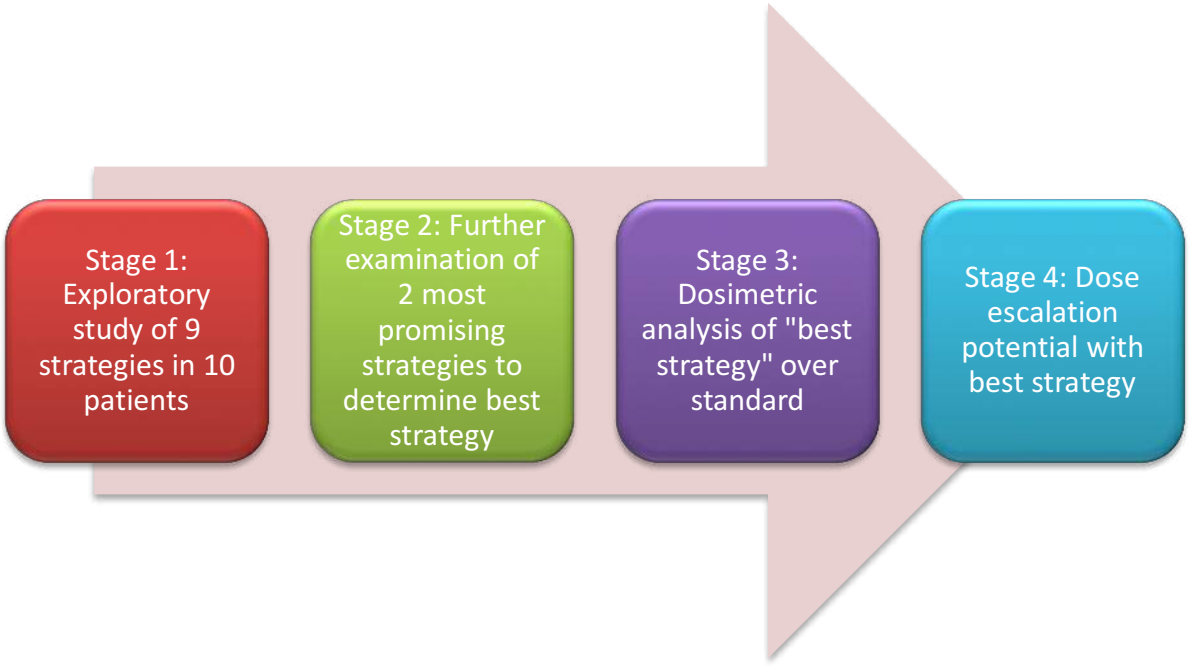


Figure 5.4-1: Stages of investigation

5.4.2. Fusion and target volume modification for modelling study

Prior to the above stages each patient's images were prepared with fusion, target volume modification and OAR outlining.

Full bladder planning scans were co-registered with the empty bladder planning scans, and then to each CBCT for that patient using the mutual information algorithm on OMP. Fusion was checked for adequacy at three bony landmarks – femoral heads (on axial view), tip of sacrum (on sagittal view), and pubic symphysis (both on axial and sagittal views). If the fusion was not visually satisfactory then manual adjustments were made to correct it.

CTVnodes was used as delineated for the patients original treatment on the full bladder scan, though was checked to ensure that protocol was adhered to. CTVnodes was not delineated on CBCT scans as nodal motion was not being measured in this study.

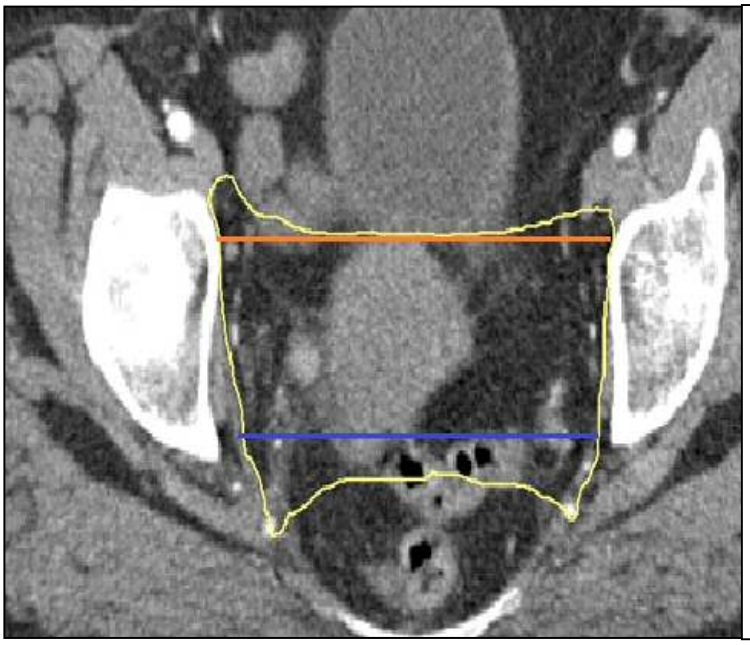
CTVprimary was delineated on the full bladder scan (CTVfull), the empty bladder scan (CTVempty), and every CBCT scan (cbCTV1, cbCTV2, etc.).

CTVprimary had to be modified compared to the departmental standard protocol (as in 5.3.3) for the purpose of this study. The reason for this was that the CTV needed to be consistently delineated on both planning CT and all CBCTs, and several structures were not clearly visible on CBCT.

These modifications were as follows in table 5.4-1:

Table 5.4-1: Modifications to CTVprimary for modelling study

Issue	Modification in this study
GTV not visible on CBCT	No GTV outlined, instead a CTV of whole cervix, uterus, upper vagina and parametrium used. Upper vagina usually is 2cm below visible GTV, instead the lower border of pubic symphysis was used as a landmark
Anterior parametrial border: external iliac vessels not clear on CBCT	Anterior border taken as the anterior most extent of the uterus/cervix and a straight horizontal line was extended from this point to reach the CTVnodes on either side (figure 5.4-2)
Posterior parametrial border: mesorectum and internal iliac vessels not clear on CBCT	Posterior border taken as a straight line across the posterior most aspect of the uterus/cervix to reach the CTVnodes (figure 5.4-2)



In figure 5.4-2 the yellow lines demonstrate the standard borders used with curving from the posterior bladder to the external iliac vessels anteriorly. This was modified to the orange line shown, the anterior aspect of the cervix/uterus.

Posteriorly instead of curving around mesorectum to the internal iliac vessels, as these structures are not seen consistently on CBCT, instead the blue line was used as posterior border, posterior aspect of the cervix/uterus. Laterally the CTV nodes are reached though not shown in this image

Figure 5.4-2: Anterior and posterior parametrial borders used in modelling study

5.4.3. Organs at risk (OARs)

OARs were outlined on the full bladder planning scan only. Four key OARs were used in this study, bowel loops, bowel bag, rectum and bladder for stages 1 and 2. For stages 3 the small bowel, anal canal, sigmoid, and large bowel were also delineated given the dose-volume constraints discussed in Chapter II and III of this thesis. Definitions are detailed in table 5.4-2, justifications of these definitions can be found in chapter III section 3.3.5.

Table 5.4-2: Definitions of OARs

Structure	Definition
Bowel loops	Bowel loops (including contents) from the recto-sigmoid junction inferiorly to 4.2cm above the PTV superiorly.
Bowel bag	The entire abdominal/pelvic contents were initially outlined. The inferior slice was the most inferior small or large bowel loop (regardless of relation to rectum). The superior slice was 4.2cm above the PTV. Then all non-GI structures (muscle, bone, kidney, bladder, prostate, and uterus) were excluded.
Rectum	Defined inferiorly from the ischial tuberosities to the recto-sigmoid junction
Bladder	Whole bladder from apex to base
Anal Canal	Anal verge identified and 3cm of anal canal/distal rectum were outlined caudally, inclusive of contents
Sigmoid	Commenced inferiorly at the recto-sigmoid junction, followed to the most anterior-lateral point where it becomes descending colon
Large Bowel	Sigmoid and colon were combined
Small Bowel	All other bowel loops identified within 4.2cm above the PTV which were not large bowel.

5.5. Stage 1 methods: volumetric strategy modelling

Nine different margin strategies were modelled on the first 10 patients in the study. Each strategy was compared against a "standard margin", which in this study was an isotropic 2cm margin around the primary CTV.

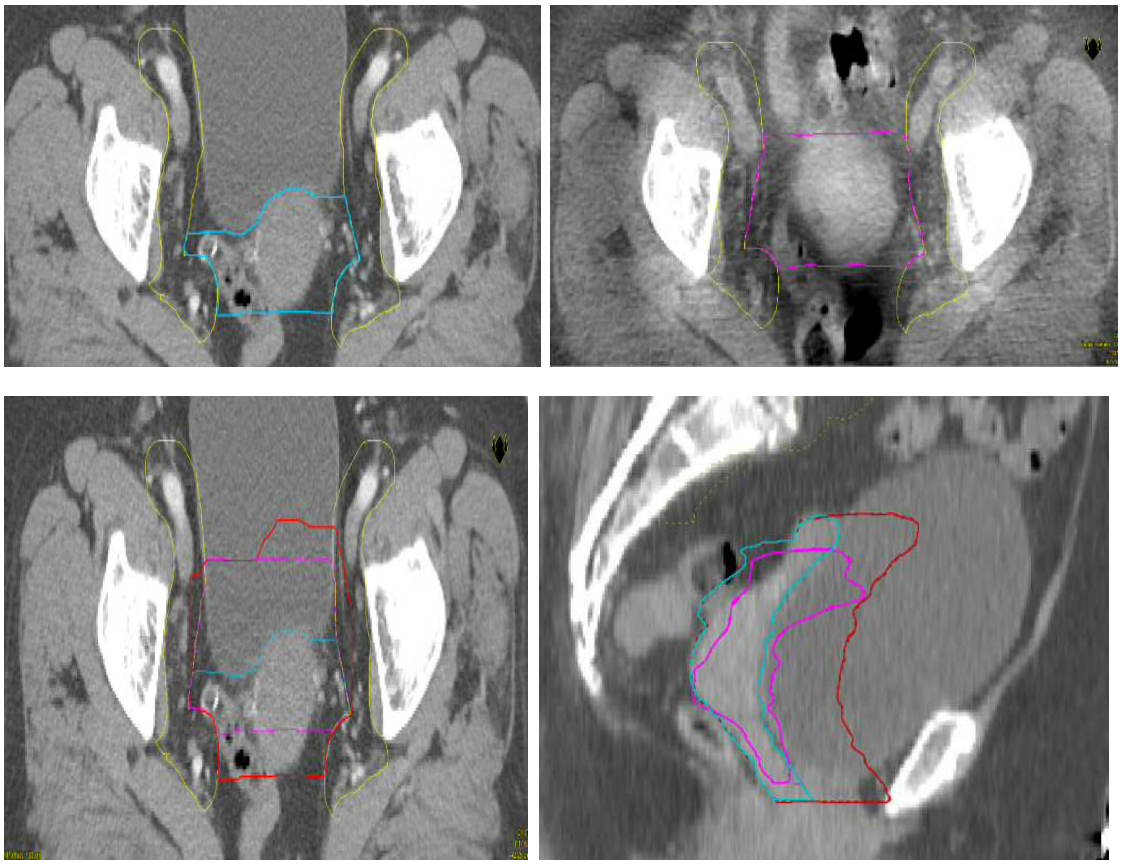
The strategies modelled are summarized in table 5.5-1, with further description of some below:

Table 5.5-1: Summary of strategies used

	Strategy name	Structures used/formed	Margin Applied	Reference
Std	Standard	CTVfull	2cm isotropic margin to PTV	RTOG (95)
1	Iso_1.5	CTVfull	1.5cm isotropic margin to PTV	RTOG (95)
2	Anisotropic	CTVfull	Population-based anisotropic margin (results in section 5.11.1)	
3	Structure-specific	Uterus, cervix, vagina and parametrium from CTVfull	4cm margin around uterus (1cm inferiorly); 1.3cm margin around cervix, vagina & parametrium	Chan *et al*.(108)
4	ITV	ITV = CTVfull + CTVempty	1cm margin to PTV	Bhuva *et al* (200)
5	Composite1	Composite = ITV + cbCTV1 + cbCTV2 + cbCTV3	5mm margin to PTV	
6	Composite 2	Composite = ITV + cbCTV1 + cbCTV2 + cbCTV3	10mm margin to PTV	
7	PotD1	CTVfull, CTVmid or CTV empty	Library of 4 plans: - PTVfull= CTVfull + 7mm - PTVmid= CTVmid + 7mm - PTVempty=CTVempty +7mm - Backup plan =CTVfull+2cm	
8	PotD2	CTVfull, CTVmid or CTV empty	Library of 4 plans: - PTVfull= CTVfull + 10mm - PTVmid= CTVmid + 10mm - PTVempty=CTVempty +10mm - Backup plan =CTVfull+2cm	
9	PotD3	CTVfull, CTVmid or CTV empty	Library of 3 plans: - PTVfull= CTVfull + 10mm - PTVmid= CTVmid + 10mm - PTVempty=CTVempty +10mm	

Anisotropic margins: An anisotropic population-based margin was added around CTVfull derived from the CBCTs of the first 10 patients. For each CTVempty and cbCTV the margin around CTVfull required to fully cover the CTV in superior, anterior, posterior, left and right directions was determined. This was done by separately growing margins in

each direction at 2mm intervals from 0-70mm around CTVfull and choosing the tightest margin in each direction that will fully cover each CBCT being assessed. An example is shown in figure 5.5-1.

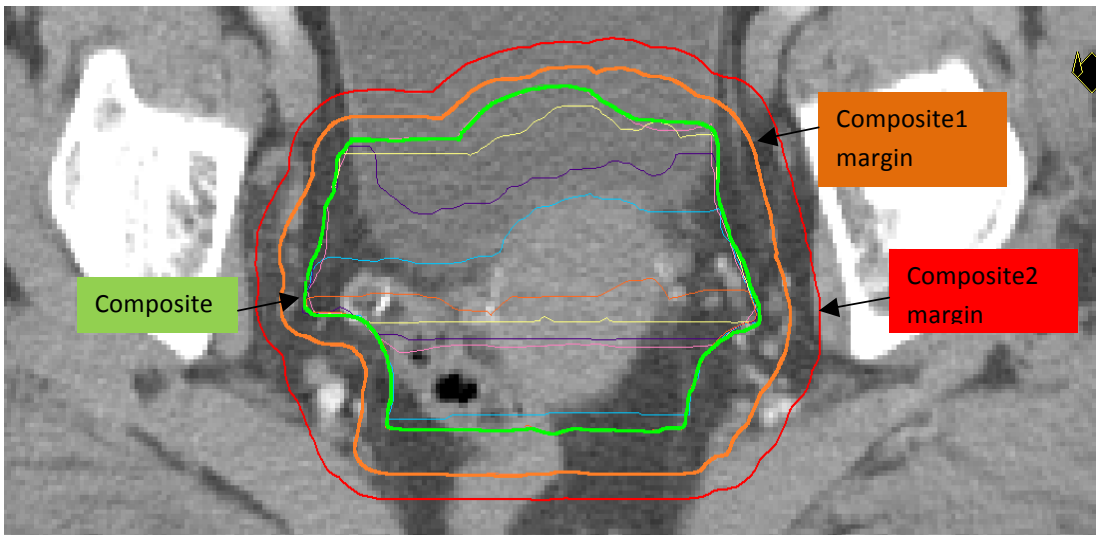


The figure gives an example of anisotropic margin derivation. The first image shows CTVfull (in blue) on the full bladder planning scan. The second image shows cbCTV1 (in pink) on the CBCT from day 1 of treatment, which shows the CTV has moved anteriorly. An anterior margin of 32mm (in red) around CTVfull was required to encompass cbCTV1. This was checked on the sagittal section where the need for the 32mm margin is demonstrated to cover cbCTV1 (in pink).

Figure 5.5-1: Anisotropic Margin Derivation

In each direction for all 10 patients the margin required to cover 95% of all cbCTVs studied was determined. As no inferior margin can be derived in this study as a bony landmark was used for inferior border of the CTV, a 1.5cm margin was applied inferiorly for the anisotropic margin. This was chosen to account for vaginal motion in a previous study performed at our institution.

Composite strategies



The composite of CTVfull, CTV empty, cbCTV1, cbCTV2 and cbCTV3 is shown in green. A 5mm CTV-PTV margin around this forms Composite1 (orange) and a 10mm CTV-PTV margin forms Composite2 (red).

Figure 5.5-2: Composite Margin Derivation

CTVfull, CTVempty, cbCTV1, cbCTV2 and cbCTV3 were combined together to form a composite using the union function. A PTV margin of 5mm was added in composite 1 strategy, and 10mm in composite 2 strategy. These are illustrated in figure 5.5-2.

For the composite strategy to be used practically patients need to be treated for the first 5 days with a standard 2cm margin. Three days are needed to acquired cbCTV1, cbCTV2 and cbCTV3 and two days are to replan the patients treatment plan based on the composite. In view of this the composite strategies were proportionately modelled with 5#s of standard margin treatment, and 20#s of composite use.

Plan of the Day (PotD)

Library of Plans (LoP) creation

From the CTVfull and CTVempty a third CTV was created interpolating these two volumes to form 'CTV mid'. This was performed by Professor Emiliano Spezi using structure-guided deformable image registration on the Velocity software (version 3.1, Varian Medical Systems) which maps the CTVempty onto CTVfull in relation to bladder filling.

Custom software developed in the Matlab environment by Professor Spezi was then used with a scaling factor of 0.7 in order to give a CTVmid, with a bladder volume which is 70% between that on the full bladder scan and empty bladder scan. This scaling factor was

chosen rather than 0.5 as with a bladder volume 50% that between full and empty bladder scans very little variation in CTV was noted.

An example of a CTVmid volume is illustrated in figure 5.5-3.

To each CTV (CTVfull, CTVmid, and CTVempty) a CTV-PTV margin was added, 7mm in PotD1 strategy and 10mm in PotD2 and PotD3 strategies. These PTVs were termed as 'plans', forming a library of plans: full, mid and empty.

For each CBCT the plan from the library was chosen based on which PTV covered >99% of the cbCTV. In addition, if two PTVs had equivalent levels of cbCTV coverage then the plan which maximally avoided critical OAR was selected (prioritised as bowel>bowel bag>rectum>bladder).

In addition in PotD1 and PotD2 strategies, a standard PTV ("standard plan") was used (defined as CTVfull with a 2cm isotropic margin) when >99% of the CTV was not being covered by any of the 3 plans. PotD3 had no backup plan use.

Extrapolation of PotD data over the whole course of radiotherapy

For each patient the number of each plan chosen (full, mid, empty or backup) was noted and the proportion of each determined in relation to the number of CBCTs for that patient. This was then proportionately increased to determine how many fractions (out of a total 25) would use each plan.

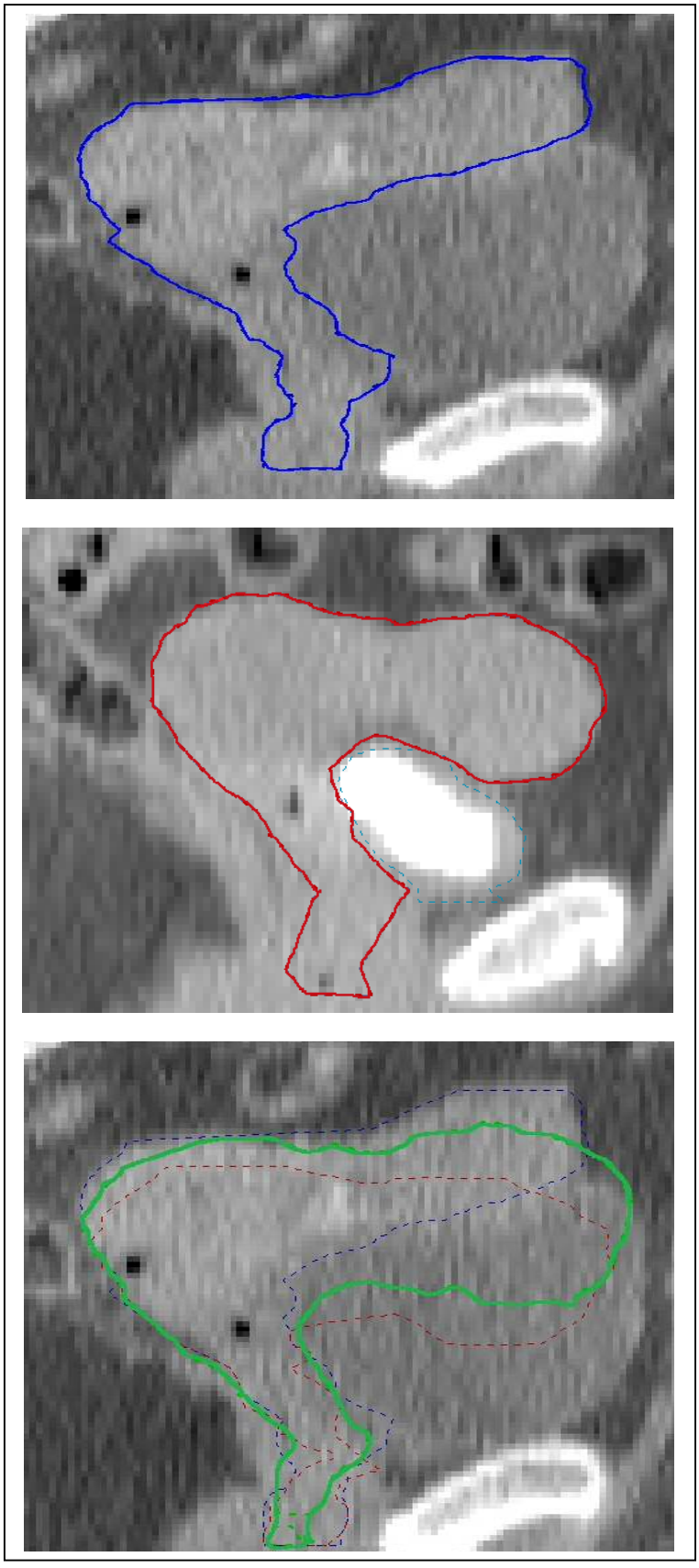


Figure 5.5-3: Plan of the day library of plans: CTVfull, CTVempty and CTVmid

5.5.1. Assessment of each strategy

Each of the 9 margin strategies were assessed on each cbCTV for:

1. **PTV volume**
2. **CTV coverage**
    a. "Encompassed" or "missed": if cbCTV is >99% covered this is "encompassed", if <99% of the cbCTV is covered this is "missed".
    b. % coverage: the % of the cbCTV included within the PTV
    c. Size of miss
    d. Direction of miss
    e. Site of miss: for each CTV miss the component(s) where the miss occurs is noted: tip of uterus (ToU), anterior uterus, posterior uterus, cervix, vagina or parametrium; see figure 5.5-4.

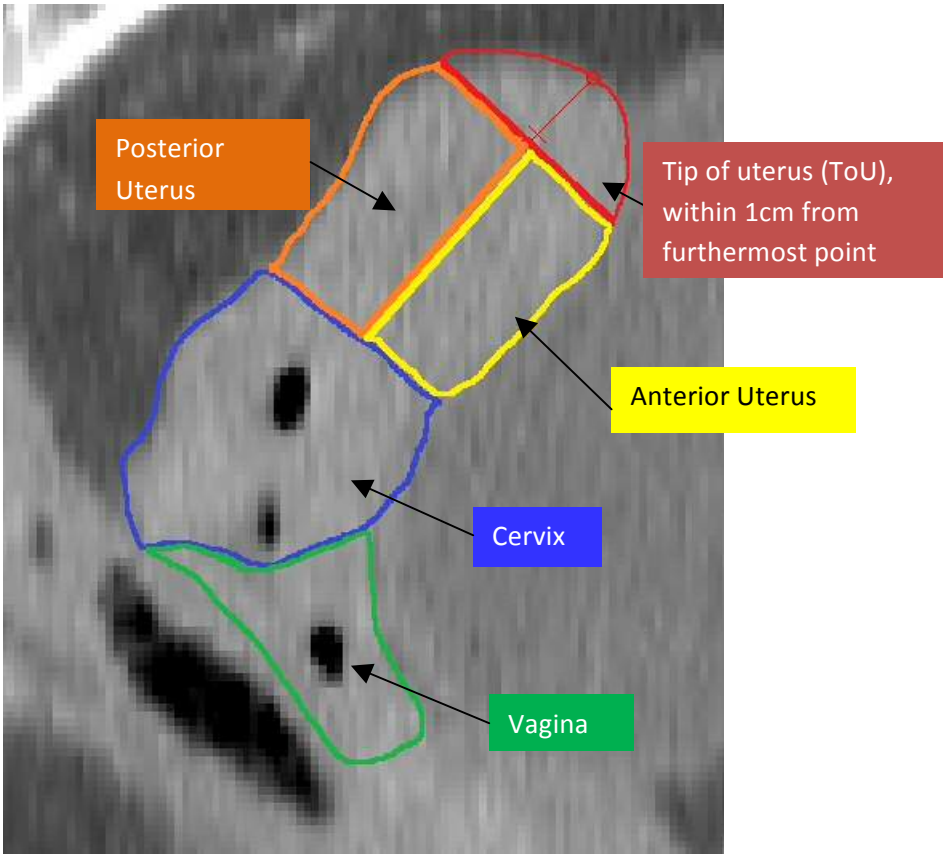


Figure 5.5-4: Sites of CTV miss

3. **OAR within PTV**

For bladder and rectum the % volume of OAR within the PTV was noted. For bowel and bowel bag the volume of OAR in cc within the PTV was noted.

5.5.2. Statistical Analysis

The mean values of each of the above assessments for each strategy were compared with the mean values when using a standard margin. Differences in these means were tested using Mann-Whitney U testing, given that the data was non-normally distributed (significance level of $p<0.05$ was used). All statistics were performed on SPSS version 20.

Determination of "best" strategies

The two "best" potential strategies were determined by assessing those with the overall ability to: improve CTV coverage, improve OAR sparing and reduce PTV volume. OAR sparing was prioritised in order of bowel, bowel bag, rectum and then bladder.

5.6. Stage 2 Methods

The two strategies that best performed with these criteria were further analysed in Stage 2 with all additional patients meeting inclusion criteria. Methods were as described above (stage 1) and statistical analysis made with all patients including those in stage 1. Based on the same criteria as in 5.5.2 the single "best strategy" was determined from the results of Stage 2.

5.7. Stage 3 Methods

The best strategy from stage 2 was used to define volumes for VMAT planning. The resulting plan was compared dosimetrically to two other plans, a 3D-conformal plan with a standard margin, and a VMAT plan with a standard margin.

3D-conformal planning was used as it is the current standard of planning of for cervical cancer radiotherapy within our institution. VMAT planning with a standard margin was performed for direct comparison of the margin strategy rather than differences being confounded by plan type.

Each PTVprimary was combined with a PTVnodes to form a PTVfinal. Treatment plans were generated by experienced treatment planners/physicists (Kathryn Morgan, Christian McCracken, Aileen Lyons, Rhydian Maggs), using OncentraMasterplan (OMP) V4.3 software. VMAT plans were created with the use of a class solution that had previously been developed for post-operative gynaecological patients.

Dummy volumes were automatically generated using a pre-determined “script” on Prosoma version 3.3, which relied on structure addition/subtraction/intersection and application of margins to produce patient-specific dummy volumes. These were then exported to OMP where the plan was produced using the inverse optimisation module. A dual arc technique was used with the use of 6MV photons.

The primary aim was to obtain at least 95% of the prescribed dose to 99% of the PTV. The secondary aim was to reduce OAR doses as much as possible, without compromise to target coverage.

Forward planned 3D-conformal plans were composed of 4 fields of 10MV photons, at orthogonal angles, with wedging as appropriate to improve coverage and uniformity. Where required additional ‘filler’ segments were added to shield regions of high dose and/or boost regions of low dose.

5.7.1. Coverage assessment

The prescription for each plan was 45Gy in 25#, 1.8Gy per fraction. Each plan was assessed according to the following with dosimetric criteria:

1. 99% of the PTVfinal to receive at least 95% (42.7Gy) of the prescribed dose
2. Dmedian of 99-101%
3. An ICRU maximum of 107% (48.15Gy) to 1.8cc

5.7.2. OAR assessment

DVH data for each patient was imported into Microsoft Excel by DVHImport software programmed by Phil Parsons (Physicist, Velindre Cancer Centre)

For each OAR, the mean dose-volume histograms for all patients planned were compared to assess benefits of the strategy. Following this a range of dose-volume constraints as in table 5.7-1 were used (from published literature, chapter III of this thesis, and some departmental constraints) to compare strategies and determine whether the “best strategy” improved the chances of the constraints being met compared with the standard plans.

No bladder constraints are found in the published literature for toxicity reduction at the doses used for cervical cancer patients (45Gy). In view of this planning-based constraints developed in Velindre Cancer Centre were used as a metric to test the strategies, acknowledging that they may not have any impact on bladder toxicity.

DVH data was converted using the EQD2 formula so constraints defined for 2Gy fractions could be applied (α/β of 3).

Table 5.7-1: Constraints used for dosimetric analysis

OAR	Type of constraint	Source of constraint	Constraint	EQD2
Bowel	Toxicity based	Guerrero-Urbano *et al* (112) (validated in Chapter III thesis)	V40<71cc	V38.6<71cc
Bowel bag	Toxicity based	QUANTEC (128) Chapter III thesis	V45<195cc V5<1689cc	V43.2<195cc V5<1689cc
Rectum	Toxicity based	Gulliford *et al* (133)	V30<80% V40<65%	V30<80% V40<65%
Bladder	Planning based	Departmental	V35<70% V45<10% V45<20%	V30.8<70% V43.2<10% (optimal) V43.2<20% (mandatory)
Small bowel	Toxicity based	QUANTEC (128)	V15<120cc	V10.8<120cc
Anal canal	Toxicity based	Systematic review (ch II)	Dmean<40Gy	Dmean<40Gy
Sigmoid	Toxicity based	Chapter III thesis	V10<52.6% V25<36.2% Dmedian<13.7Gy	V10<52.6% V25<36.2% Dmedian<13.7Gy
Large Bowel	Toxicity based	Chapter III thesis	V15<60.8cc	V15<60.8cc

5.8. Stage 4 methods: Dose escalation

In cases where bowel sparing was shown to be feasible in stage 3 of the study (determined by the bowel dose constraint V38.6<71cc being met), dose escalation was modelled.

Increasing the dose to PTVnodes and PTVprimary fraction by fraction (by 1.8Gy at a time) was modelled until the bowel dose constraint V38.6<71cc, rectal constraints of 30Gy<80% and 40Gy<65%, and anal canal constraints of Dmean<40Gy were met. Once these constraints were being breached then the dose escalation modelling was stopped.

An additional high dose constraint for bowel was added to ensure that bowel doses were not being pushed too high (bowel V56.6Gy>0.5cc, taken from Guerrero-Urbano *et al* (112))

5.9. Results

5.9.1. Patient characteristics

Ten patients were included in stage 1 and a total of 111 scans were assessed (including 10 full bladder, 10 empty bladder and 91 CBCT scans). For stage 2 10 additional patients were studied. For the total 20 patients 212 scans (including 20 full bladder, 20 empty bladder scans and 172 CBCT scans were assessed).

Patient characteristics are outlined in table 5.9-1. The mean age was 60.4 years, and 13/20 patients had concurrent chemotherapy.

Each patient had between 7 and 13 CBCTs with a mean of 8.6 scans. 14 patients had additional scans to those specified in the departmental protocol and the reasons are noted were all due to changes in bladder, bowel or rectal position or filling compared with that at planning.

Table 5.9-1: Patient characteristics

Pt no	Age (yrs)	Stage	Radiotherapy Regime (Gy/#)	Concurrent Chemotherapy	No of CBCTs
1	71	IIB	45/25	cisplatin weekly	9
2	49	IIIB	45/25	cisplatin weekly	7
3	51	IIA	45/25	No	13
4	35	IIIB	45/25	cisplatin weekly	7
5	54	IIB	45/25	cisplatin weekly	8
6	74	IIB	45/25	No	12
7	41	II	45/25	cisplatin weekly	7
8	53	III	45/25 to pelvis, 18/10 inguinal nodes	cisplatin weekly	10
9	55	IIB	45/25	cisplatin weekly	8
10	29	IIB	45/25	cisplatin (2 cycles) then carboplatin	10
11	65	IIB	45/25	Cisplatin	7
12	65	IIB	45/25	cisplatin weekly	9
13	83	II	45/25	no chemo	7
14	62	IIIB	45/25	no chemo	9
15	68	IIB	45/25	cisplatin weekly	7
16	82	IB2	45/25	no chemo	9
17	29	IB2	45/25	Cisplatin weekly	8
18	84	IVA	45/25	no chemo	8
19	62	IB2	45/25	cisplatin weekly	6
20	93	IIB	45/25	no chemo	11

5.9.2. CTV volumes over time

CTV volumes ranged from 69.8cc to 443cc, with a mean volume of 175.4cc. 16 of the 20 patients had a smaller CTV volume at the end of treatment compared with at planning which may reflect tumour regression. Mean CTV volumes over time are shown in Figure 5.9-1.

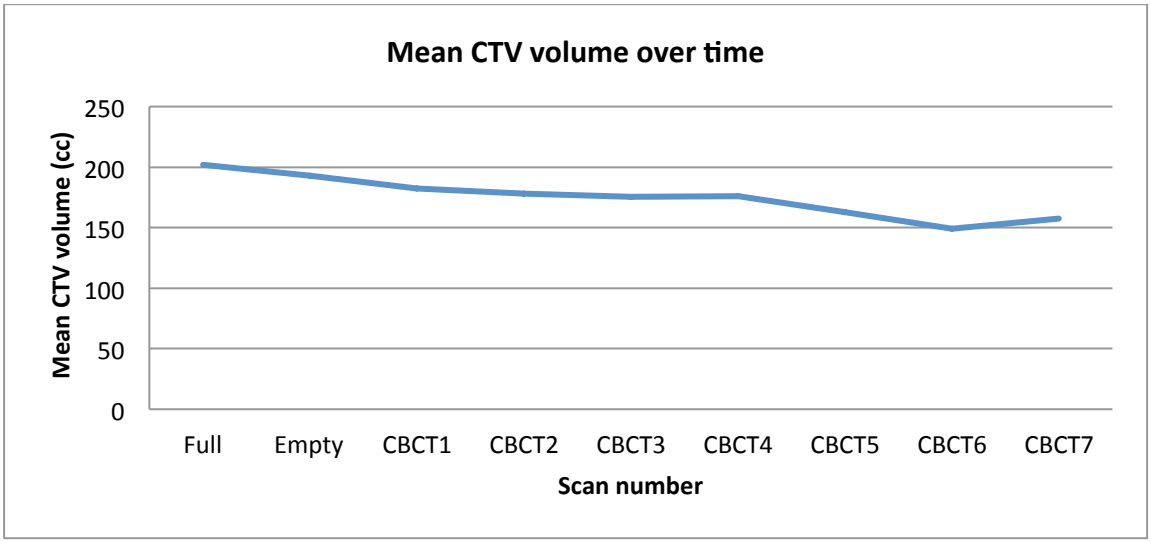


Figure 5.9-1: CTV volumes over time

5.10. Stage 1 results

5.10.1. Population-based anisotropic margins

These were derived from the directional margins for the 101 CTVs from 10 patients. Statistics for these are shown in table 5.10-1. Margins encompassing the CTV in 95% of CBCTs assessed were taken as the population-based margins. These were significantly larger anteriorly compared with other directions.

Table 5.10-1: Anisotropic margins derived from 10 patients

	Anterior (mm)	Posterior (mm)	Superior (mm)	Left (mm)	Right (mm)
Min	0	0	0	0	0
25% quartile	10	4	0	8	8
Median	22	10	0	22	20
75% quartile	40	22	3	34	32
90%	56	30	12	38	46
95%	**60**	**36**	**18**	**40**	**48**
Max	70	54	21	50	56

5.10.2. Plan-of-the day strategies (PotD1, PotD2 and PotD3)

The overall use of the library plans for each strategy is shown in figure 5.10-1, With PotD1 (7mm margins) the backup plan was required 70% of the time; and with PotD2 (10mm margins) a back-up plan was required 50% of the time.

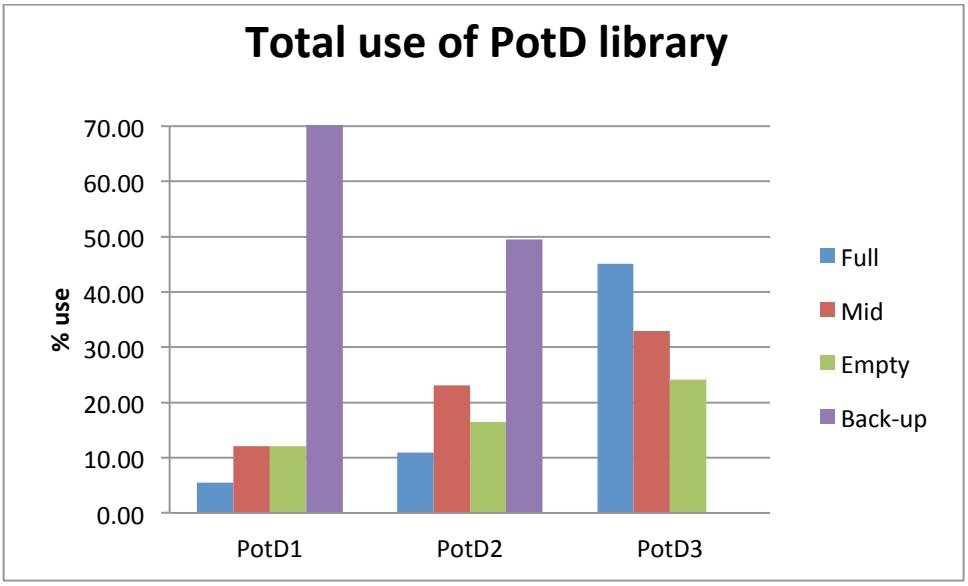


Figure 5.10-1: Plan library use

Individual patient variation of plan use is noted in table 5.10-2. For some patients e.g. patient 3 and 6 the plan library was not suitable and a back-up plan was required most of the time. For others, such as patient 2, a single plan from the library was used throughout.

Table 5.10-2: Plan-of-the-day modelling use

	PotD 1 (7mm margins with Back-up)				PotD2 (10mm margin with Back-up)				PotD3 (10mm margin with no Back-up)		
	Full	**Mid**	**Empty**	**Back-up**	**Full**	**Mid**	**Empty**	**Back-up**	**Full**	**Mid**	**Empty**
Pt1	3	2	0	4	2	5	1	1	3	5	1
Pt2	0	0	7	0	0	0	7	0	0	0	7
Pt3	0	0	0	13	0	2	0	11	6	7	0
Pt4	0	0	1	6	0	0	1	6	6	0	1
Pt5	0	0	0	8	0	0	0	8	6	2	0
Pt6	0	1	2	9	0	2	3	7	2	2	10
Pt7	0	2	0	5	0	3	0	4	3	4	0
Pt8	0	6	0	4	2	7	1	0	2	7	1
Pt9	1	0	0	7	2	1	0	5	7	1	0
Pt10	1	0	1	8	4	1	2	3	6	2	2
Total (%)	5 (5.5%)	11 (12%)	11 (12%)	64 (70%)	10 (11%)	21 (23%)	15 (15%)	45 (50%)	41 (45%)	30 (33%)	22 (24%)

5.11. Comparison of strategies

5.11.1. PTV volume

PTV volumes are shown in figure 5.11-1. The PTV volumes when a standard margin is used is represented by the purple bar, with the line across the bar representing median volume. Srategies which increase median PTV volume compared with standard are in red, and those which reduce PTV volume are in green.

Anisotropic margins doubled the PTV size and a structure-specific margin increased it by 34% on average. All other strategies reduced PTV volume. These changes were all statistically significant ($p<0.05$) apart from the reduction from PotD1.

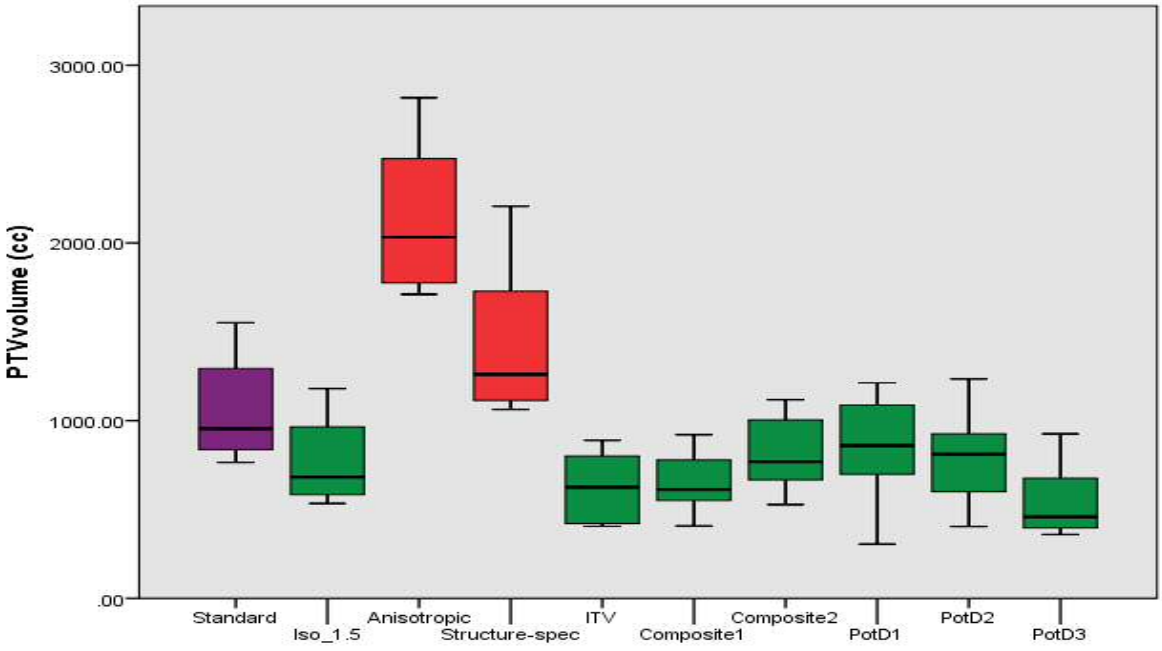


Figure 5.11-1: PTV Volumes with different strategies

5.11.2. CTV coverage and misses

CTV coverage and misses CTV coverage is shown in table 5.11-1. The mean % coverage for the standard margin was 99.6% for all CBCTs studied. For all strategies studied the mean coverage was good ranging from 97.24% to 99.98%.

Table 5.11-1: CTV coverage compared with standard margin

	Iso_1.5	Aniso-tropic	Structure-specific	ITV	Composite 1	Composite 2	PotD1	PotD2	PotD3
Change from standard	Reduced 1.3%	Increased 0.42%	Reduced 0.23%	Reduced 1.35%	Reduced 0.36%	Reduced 0.19%	Increased 0.05%	Reduced 0.01%	Reduced 2.3%
p-value	**0.043**	**0.011**	0.912	**0.015**	0.436	0.684	0.796	0.529	**0.019**

Looking at those with CTV "encompassed" and CTV "missed", the standard 2cm margin resulted in misses in 13 scans studied, with a mean miss of 3% in those 13 scans.

Five of the strategies increased the number of CTV misses (see figure 5.11-2). An isotropic 1.5cm margin increased misses to 34%, and an ITV to 45% Structure-specific, composite 1 and PotD3 stratgies all increased misses, with PotD3, where no back-up plan was used, increasing the rate of miss to 49%. This would therefore not be a clinically useful strategy.

Four strategies reduced the rate of CTV misses. Anisotropic margins, as expected reduced the number of misses, down to 1%. With the adaptive strategies, the Composite2 strategy best improved coverage by 6% (p=0.026). PotD1 and PotD2 also both improved CTV misses, though to a smaller degree.

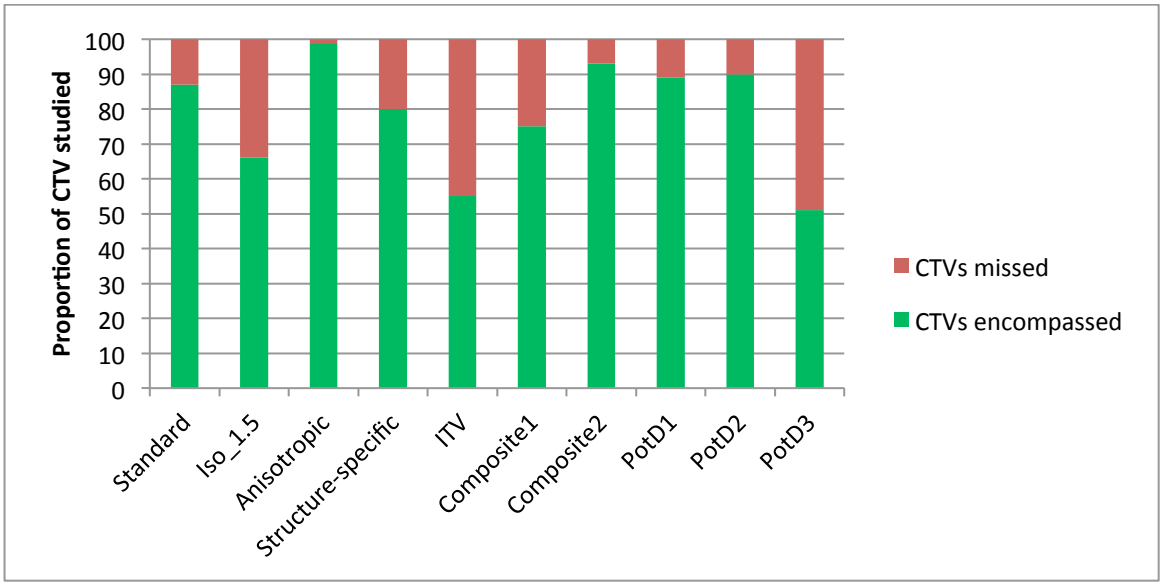


Figure 5.11-2: CTVs encompassed and missed by strategy

5.11.3. Details of CTV 'Misses'

Size of misses

Of those misses that occurred with a standard margin, these were on average 3% of the CTV. The mean size of misses for other strategies (see table 5.11-2) ranged from 1.7% (with anisotropic) to 5.6% with PotD3. The largest miss for any patient was with ITV where 19% of the CTV was missed.

Table 5.11-2 Size of CTV Misses

	Standard	Iso_1.5	Aniso-tropic	Structure-specific	ITV	Composite 1	Composite 2	PotD1	PotD2	PotD3
Mean miss (cc)	3.0	1.74	4.9	4.9	8.3	5.3	3.5	5.9	4.3	2.8
Mean miss (%)	3%	5%	1.7%	3.2%	4.5%	4%	2.3%	3%	2.5%	5.6%
Maximum misses (%)	6.6%	14.3%	1.72%	7.7%	19%	11%	4.5%	5.2%	5.2%	8.7%

Direction of misses

The most common directions of miss were anterior and posterior as in figure 5.11-3.

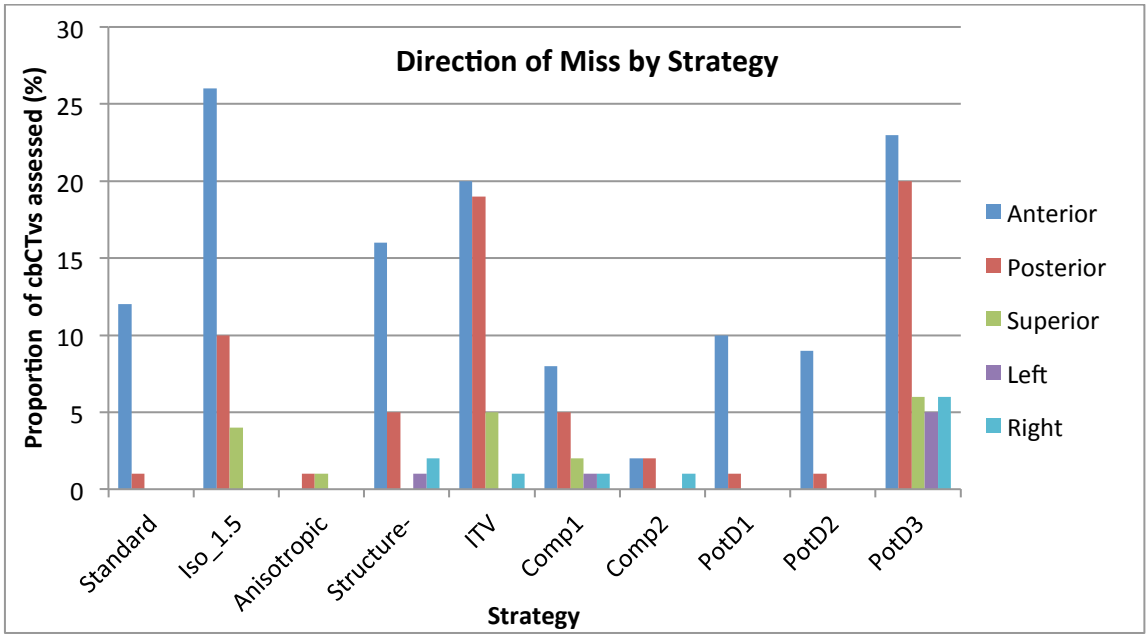


Figure 5.11-3: Direction of misses

Sites of Misses

Figure 5.11-4 shows the most common sites of miss were ToU followed by parametrium. The cervix, the most important site to not be missed, had misses with PoTD3, isotropic 1.5cm and ITV margins.

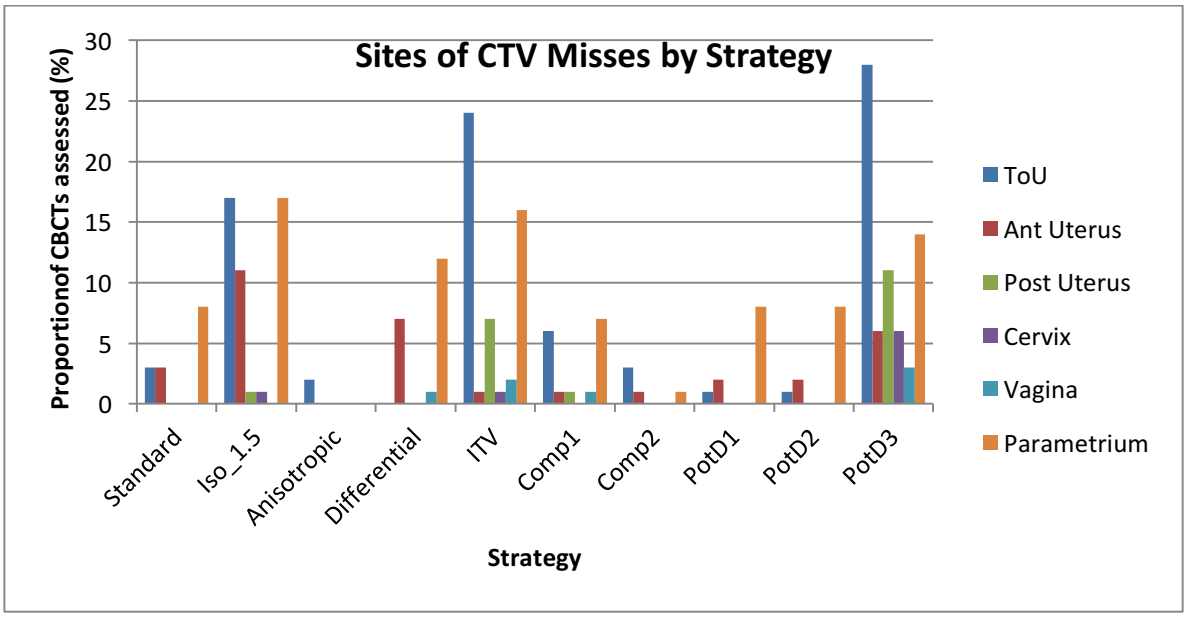


Figure 5.11-4: Sites of CTV miss

5.11.4. OARs within the PTV

Figure 5.11-5 shows the OARs within the PTV for each strategy, with standard margin in purple, those with a median reduction in green, and increase in red. The use of anisotropic margin increased all four OARs within the PTV. Structure-specific margins increased bowel and bowel bag within the PTV. All other strategies reduced OARs within the PTV, in particular PotD3.

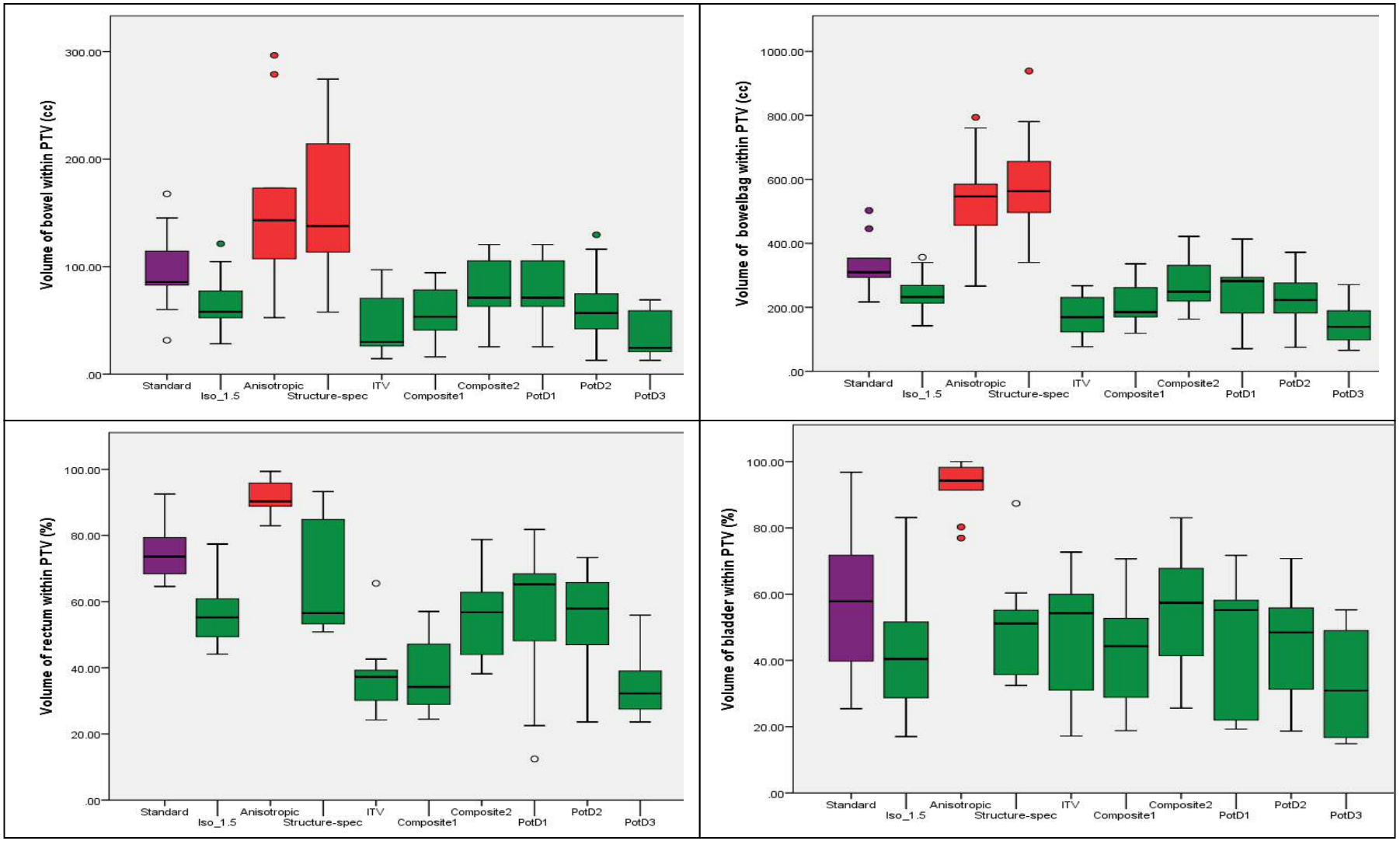


Figure 5.11-5: OARs within PTV by strategy

5.11.5. Stage 1 Overall results

Table 5.11-3: Summary of strategies

Strategy	PTV volume	CTVs encompassed	Bowel in PTV	Bowel bag in PTV	Rectum in PTV	Bladder in PTV
Iso_1.5	**Reduced**	**Reduced**	Reduced	Reduced	**Reduced**	Reduced
Anisotropic	**Increased**	**Increased**	**Increased**	**Increased**	**Increased**	**Increased**
Structure-specific	**Increased**	Reduced	**Increased**	**Increased**	Reduced	Increased
ITV	**Reduced**	**Reduced**	**Reduced**	**Reduced**	**Reduced**	Reduced
Composite1	**Reduced**	Reduced	**Reduced**	**Reduced**	**Reduced**	**Reduced**
Composite2	**Reduced**	Increased	Reduced	Reduced	**Reduced**	Reduced
PotD1	**Reduced**	Increased	Reduced	Reduced	**Reduced**	Reduced
PotD2	**Reduced**	Increased	Reduced	Reduced	**Reduced**	Reduced
PotD3	**Reduced**	Reduced	Reduced	**Reduced**	**Reduced**	**Reduced**

A summary of the nine strategies is shown in table 5.11-3. Improvements are in green and worsening in red. Statistically significant changes ($p<0.05$) from standard are highlighted in bold.

Strategies that reduced the CTVs encompassed compared to standard margin were not assessed any further (Iso_1.5, structure-specific, ITV, composite1 and PotD3).

The anisotropic margin although improved coverage resulted in a mean doubling of PTV volume, with resultant increases in all four OARs within the PTV. This was therefore not considered further.

The remaining strategies, Composite2, PotD1 and PotD2, all improved coverage and reduced OAR sparing. Comparing the use of PotD1 and PotD2 in PotD1 a backup plan had to be used in 70% of scans assessed, compared with 50% with PotD2.

In view of this Composite2 and PotD2 were taken into stage 2 for further analysis.

5.12. Stage 2 results

In stage 2 a standard margin was compared with composite2 and PotD2 strategy for an additional 10 patients. Details of the use of PotD2 strategy are detailed below for all 20 patients (including the first 10 from stage 1) in figure 5.12-1. Overall the plan library could be used in 62% of fractions studied, with the backup plan being used in 38% of fractions.

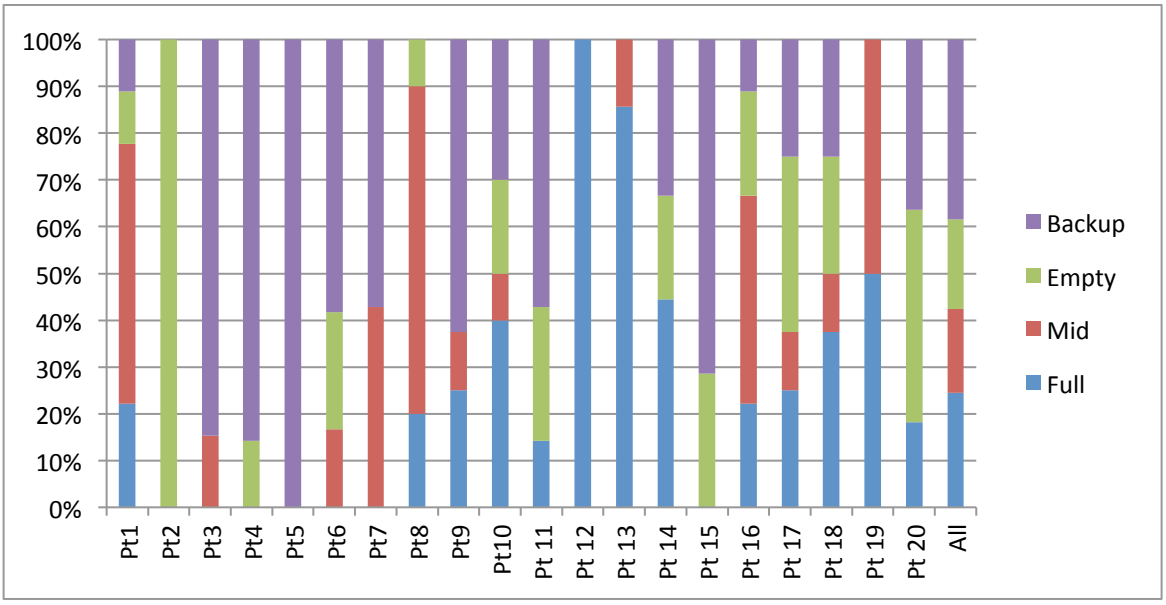


Figure 5.12-1: Plan library use with 20 patients using PotD2 strategy

The results for all 20 patients in terms of PTV volume, CTV coverage and OARs within the PTV are shown in table 5.12-1. PTV volume was significantly reduced with both strategies, though CTV coverage was similar. CTV misses were slightly improved (non-significant) with both adaptive strategies over a standard margin.

PotD2 strategy reduced bowel, bowel bag, rectum and bladder within the PTV more than composite2 strategy (non-significant difference between the two strategies). Compared to a standard margin the reductions in all four OARs seen with PotD2 were statistically significant. In one patient for example, PotD strategy demonstrated the ability to reduce bowel in the PTV by 78.7%.

Table 5.12-1: Comparison of Composite2 and PotD2 against standard

	Standard	Composite2	PotD2
Mean PTV vol (cc)	1053.1	779.8	733.4
Mean change from standard (p-value)		**Reduced 26% (p=0.001)**	**Reduced 30.8% (p=0.000)**
Mean % CTV coverage	99.51	99.79	99.64
Change from standard (p-value)		Increased 0.29 % (p=0.596)	Increased 0.14% (p=0.113)
No of CTVs encompassed (%)	176 (91.7%)	104 (92.9%)	160 (93.2%)
Change from standard		Increased 1.2%	Increased 1.5%
No of CTVs missed (%)	16 (8.3%)	7 (6%)	12 (7%)
Mean bowel in PTV (cc)	119.57	86.84	73.87
Reduction from standard		27.7% (p=0.094)	**39.4% (p=0.015)**
Mean bowel bag in PTV (cc)	356.79	277.78	221.76
Reduction from standard		**18.0% (p=0.004)**	**34.4% (p=0.000)**
Mean rectum in PTV (%)	73.53	62.16	50.29
Reduction from standard		**15.1% (p=0.000)**	**31.8% (p=0.000)**
Mean bladder in PTV (%)	55.32	48.93	38.62
Reduction from standard		10.27% (p=0.33)	**30.39% (p=0.009)**

The OARs within the PTV are shown in figure 5.12-2 and 5.12-3 below

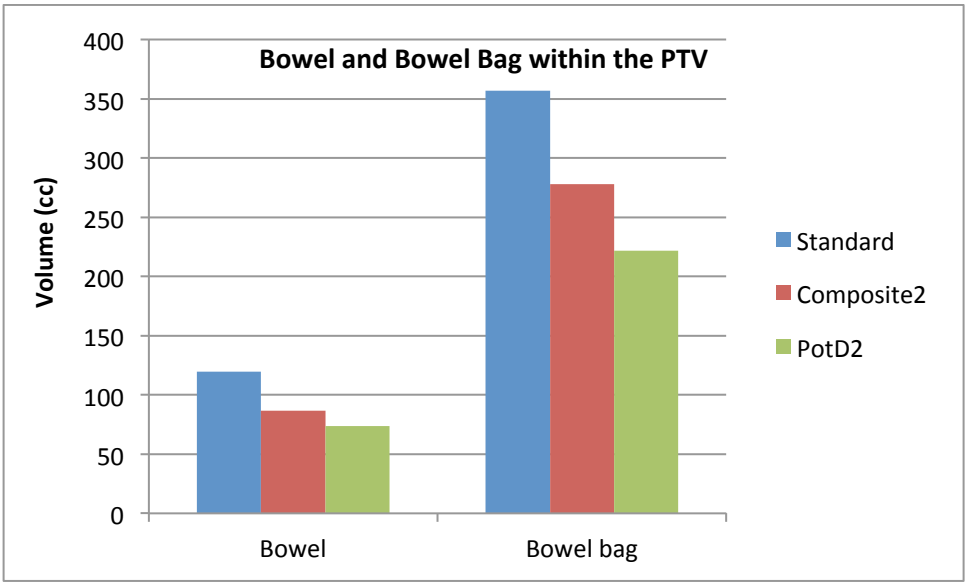


Figure 5.12-2: Bowel and Bowel bag in PTV

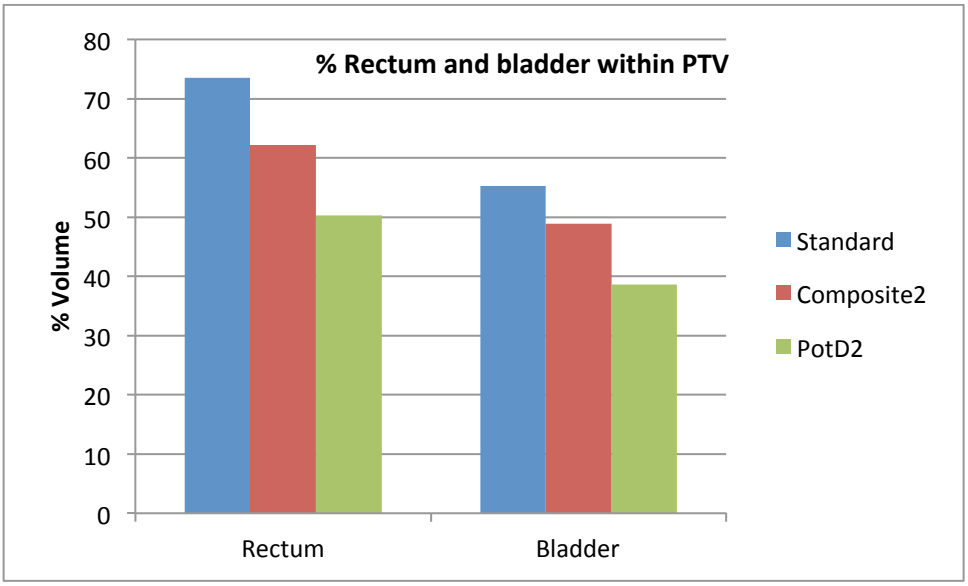


Figure 5.12-3: % rectum and bladder within PTV

In view of the above trends PotD2 was considered the "best strategy", and was taken forward for dosimetric modelling.

5.13. Stage 3 Results

Dosimetric modelling was performed for the first 10 patients in this study. For each patient three planning techniques were compared; a 3D conformal plan with 2cm standard margin around PTVprimary ("conformal"), a VMAT plan with a 2cm standard margin ("VMAT_standard"), and a VMAT plan with PotD2 ("VMAT_PotD2").

5.13.1. PTV coverage

All plans met the criteria of D99>95% though for most patients conformal plans had higher % coverage than VMAT plans. A Dmedian of 99-101% was met by the majority of plans, though 6 of the VMAT plans had Dmedian between 101.1 and 102.9. One of the plans had a ICRU maximum of 108.3% and on review was clinically acceptable.

5.14. OAR analysis

5.14.1. DVH analysis

Bowel loops, bowel bag, large and small bowel

The mean DVHs for each planning technique for bowel loops and bowel bag are illustrated in figure 5.14-1. A similar pattern was seen for small and large bowel. In doses higher than V15 an advantage is seen with VMAT planning over conformal planning. However comparing VMAT_standard and VMAT_PotD2 there is little difference in the mean DVHs.

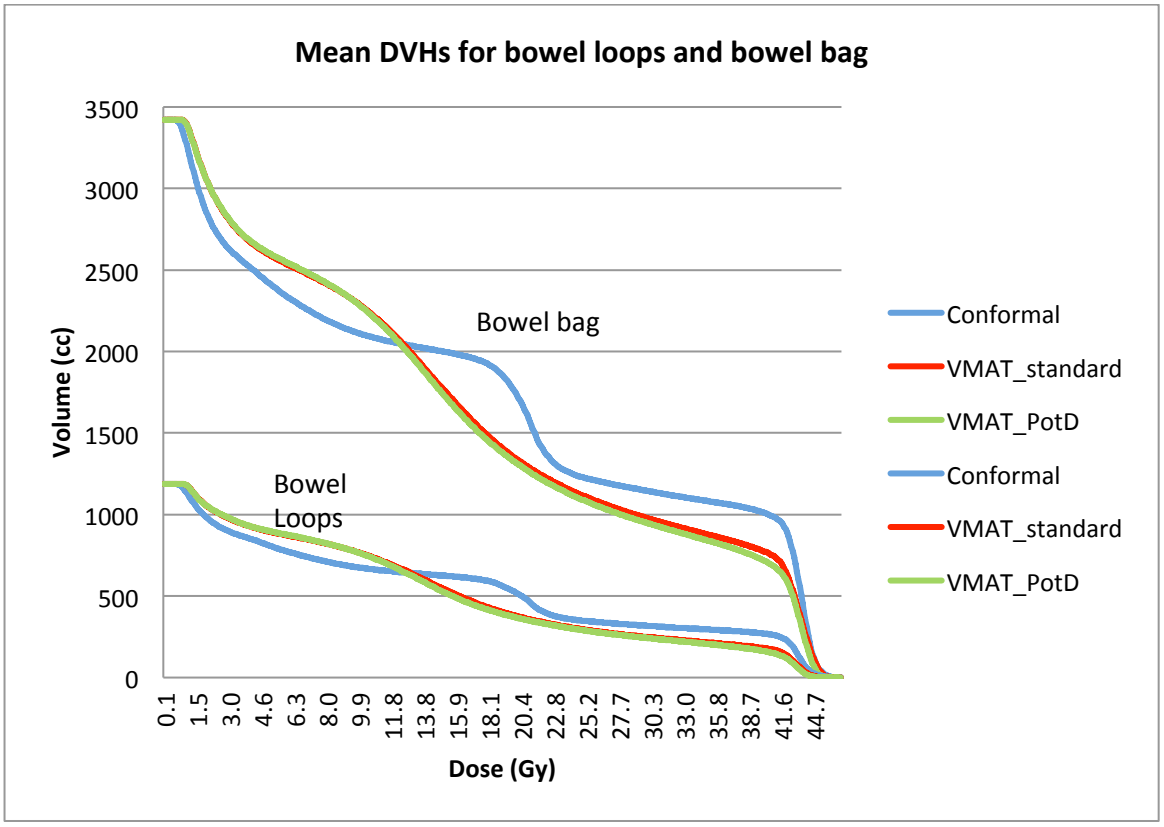


Figure 5.14-1: Mean bowel and bowel bag DVHs

Rectum

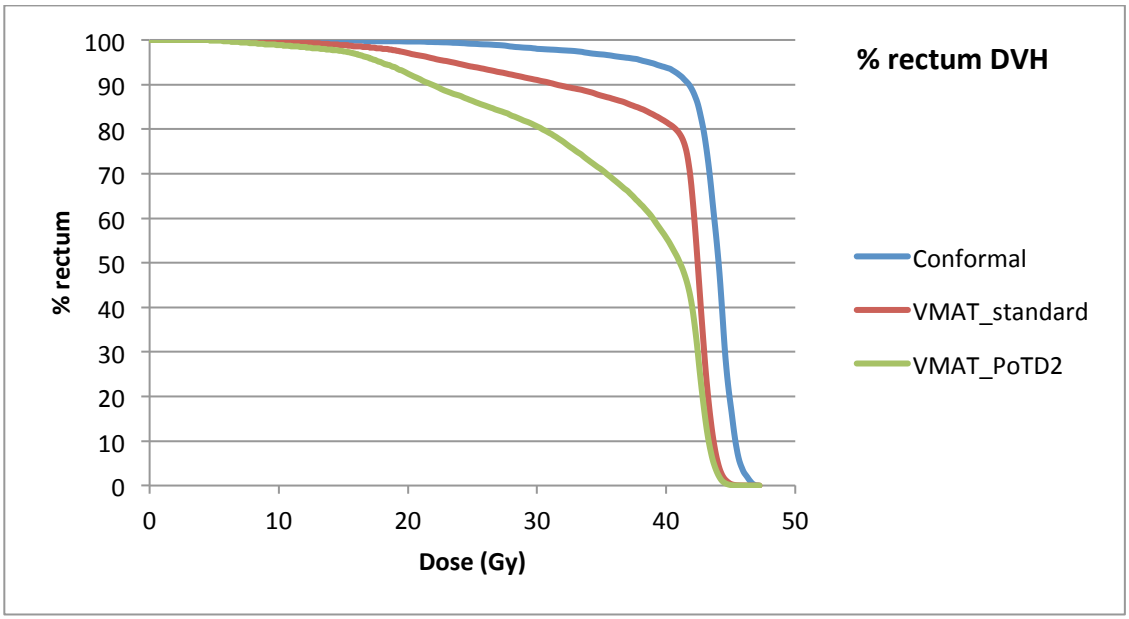


Figure 5.14-2: Mean rectal DVH

A different pattern is seen with the rectum. The mean rectal DVH for each strategy is shown in figure 5.14-2. As expected, overall VMAT planning improved the DVH compared with conformal planning. However in addition there is a clear separation of the curves with

the use of VMAT_PotD2 over VMAT_standard from dose levels 20-45Gy, which is statistically significant at multiple levels between V25 and V45.

5.14.1.3. Anal Canal

For the anal canal the DVH comparison is shown in figure 5.14-3. VMAT_standard improved dosimetry at all dose levels compared with conformal although these were not significant. VMAT_PotD2 however significantly improved dosimetry at V20, V30 and V40 (p=0.015, p=0.043, and p=0.09) compared with conformal planning. Comparing VMAT_PotD2 with VMAT_standard there was improved dosimetry overall, with significance at the V40 level (p=0.035).

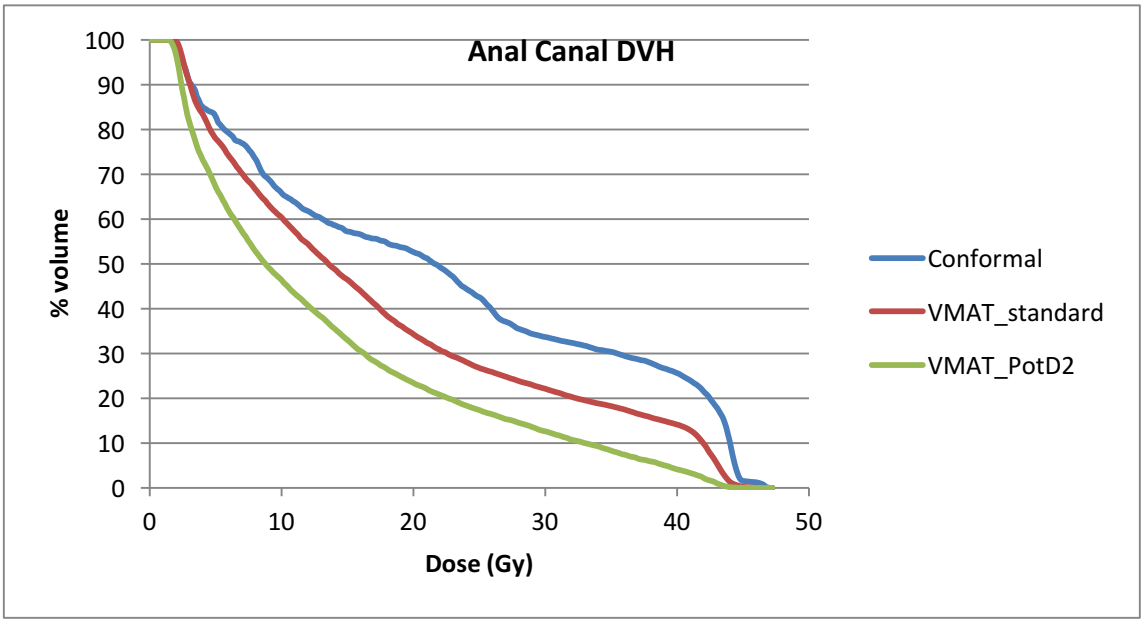


Figure 5.14-3: Mean Anal Canal DVH

5.14.1.4. Bladder

The mean DVH for bladder is shown in figure 5.14-4 again demonstrating improved dosimetry of VMAT_PotD2 over VMAT_standard and conformal plans, albeit non-statistically significant.

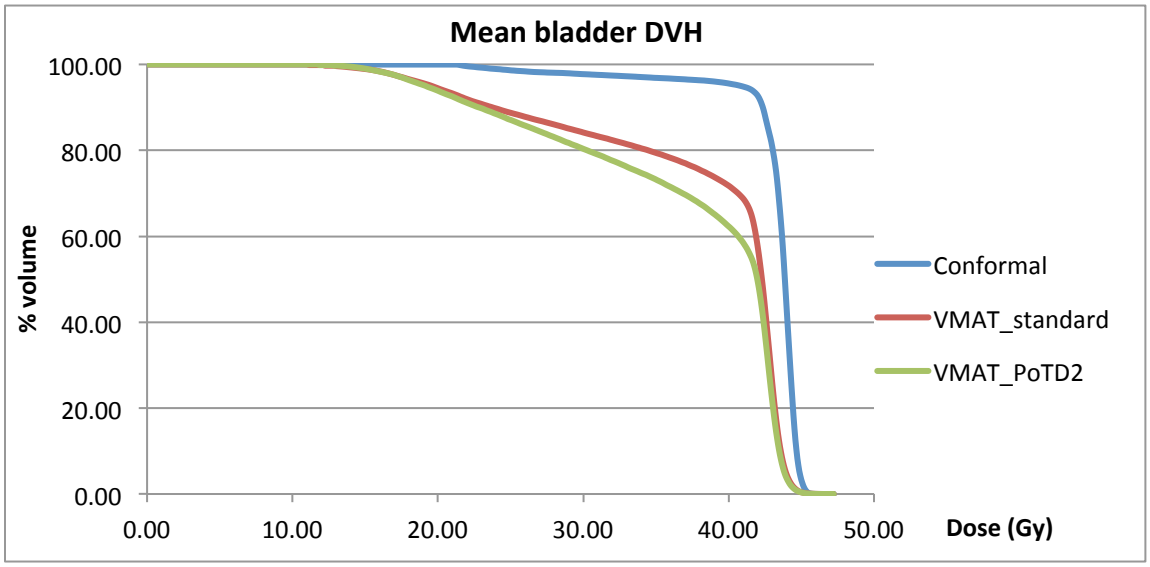


Figure 5.14-4: Mean Bladder DVH

Sigmoid

Figure 5.14-5 shows the mean sigmoid DVH. Marginal benefit was seen at V40 comparing VMAT_PotD2 with VMAT_standard, although this was not statistically significant.

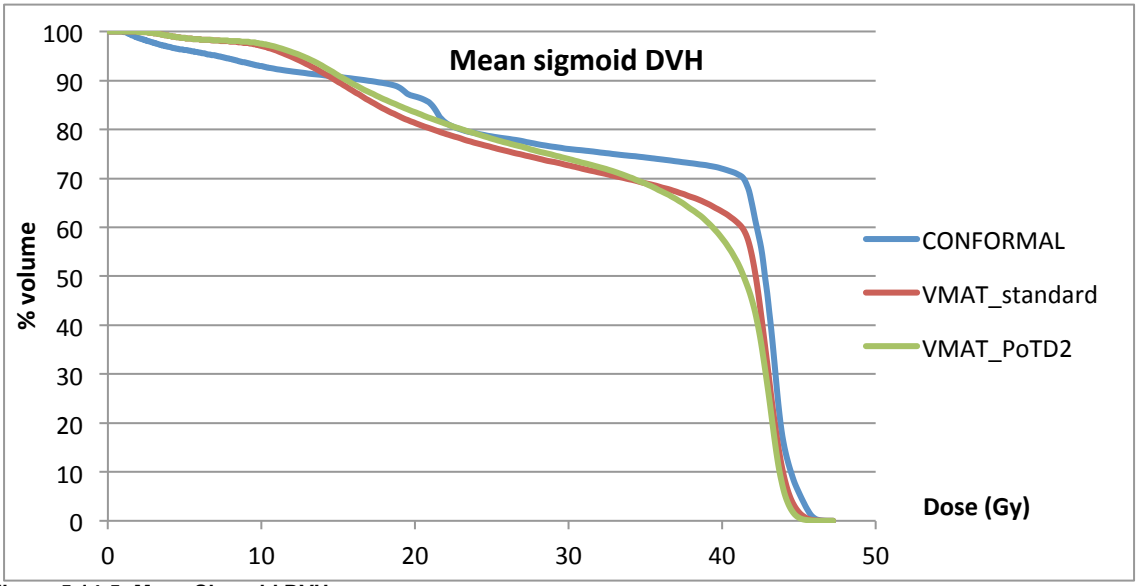


Figure 5.14-5: Mean Sigmoid DVH

5.14.2. Constraint Analysis

The three planning techniques were assessed against dose-volume constraints as in table 5.14-1.

Table 5.14-1: Comparison of Conformal, VMAT_standard and VMAT_PotD2 with dose-volume constraints

		No of patients meeting constraint (out of 10)		
OAR	EQD2 of constraint	Conformal	VMAT_Standard	VMAT_PotD2
Bowel loops	V38.6<71cc	0	1	1
Bowel bag	V43.2<195cc	1	0	1
	V5<1689cc	2	2	2
Rectum	V30<80%	0	0	3
	V40<65%	0	0	7
Bladder	V30.8<70%	0	2	2
	V43.2<10% (opt)	0	0	1
	V43.2<20% (mand)	0	7	8
Small bowel	V10.8<120cc	0	0	0
Anal canal	Dmean<40Gy	8	10	10
Sigmoid	V15<47.5%	0	1	1
	V25<36.2%	1	1	1
	Dmedian <13.7Gy	0	0	0
Large Bowel	V15<60.8cc	0	1	1

Dosimetric benefits were seen for rectum, anal canal and bladder. For the rectum in particular, dose-volume constraints for V30 and V40 that were not met with either conformal or VMAT_standard planning in any patients were met with VMAT_PotD2 in 3 and 7 patients respectively. Figure 5.14-6 illustrates the V40 rectum across all 10 patients with clear benefits seen with VMAT_PotD2.

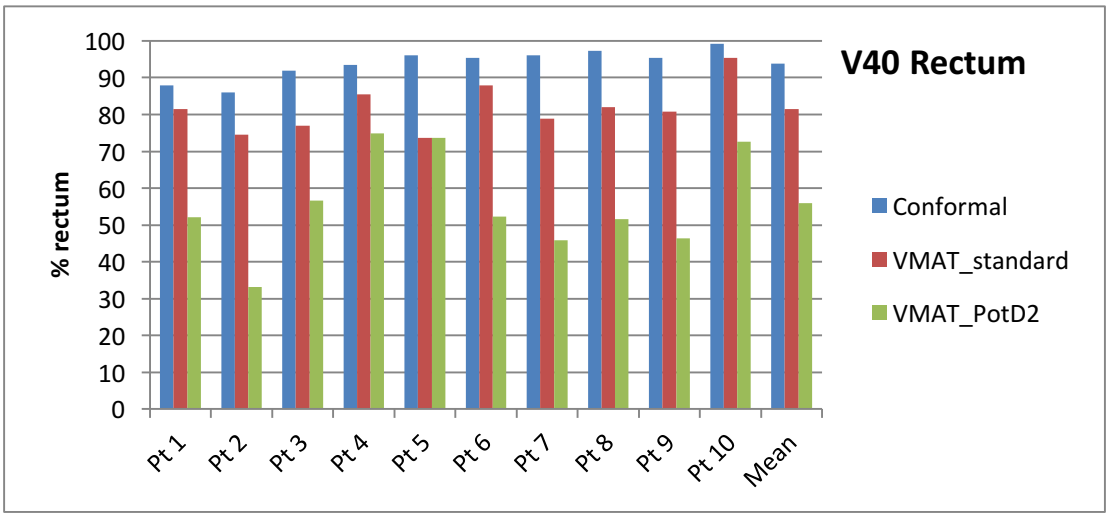


Figure 5.14-6: V40 Rectum

At both dose levels studied there was a statistically significant improvement with the use of VMAT_PotD2 over VMAT_standard (table 5.14-2).

Table 5.14-2: Comparison of V30 and V40 rectum between techniques

Dose level	Conformal (mean)	VMAT_standard (mean)	VMAT_PotD2 (mean)	Significance between VMAT_standard and VMAT_PotD2
V30	98.02%	90.9%	80.6%	p=0.023
V40	93.75%	81.5%	55.9%	p=<0.001

The constraint for anal canal (Dmean<40Gy) was met by all plans in all patients, however as seen in figure 5.14-7 the use of VMAT_PotD2 reduced Dmean anal canal in all patients more than VMAT_standard.

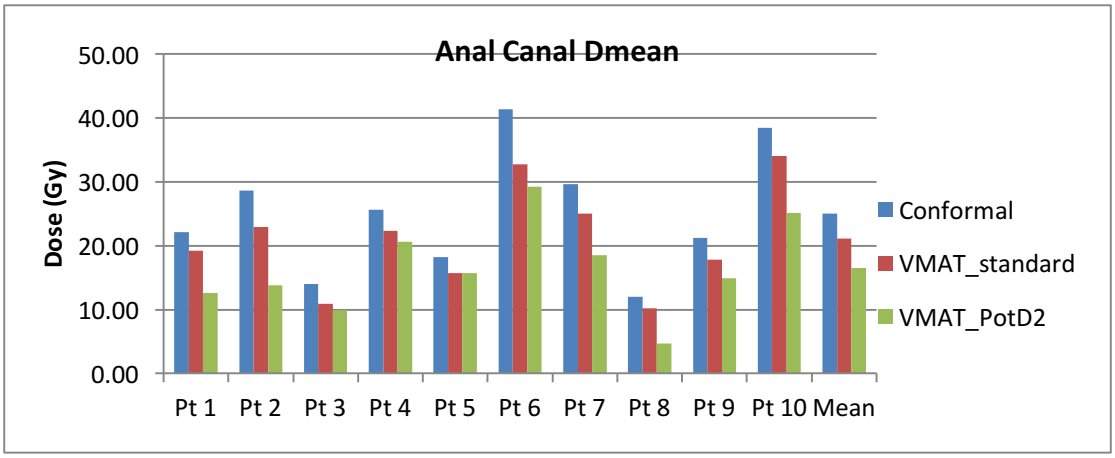


Figure 5.14-7: Dmean Anal Canal

With the lack of toxicity-based constraints for bladder, only two departmental constraints were assessed. Figure 5.14-8 shows the V43.2 for each patient. A major improvement is

seen with the use of VMAT over conformal planning (statistically significant,p=<0.001), with mean doses at V43.2 being 76.75% with conformal radiotherapy, 23.6% with VMAT_standard and 18.7% with VMAT_PotD2. Although improvements were seen for 7 out of 10 patients with VMAT_PotD2 compared with VMAT_standard, the differences did not reach statistical significance.

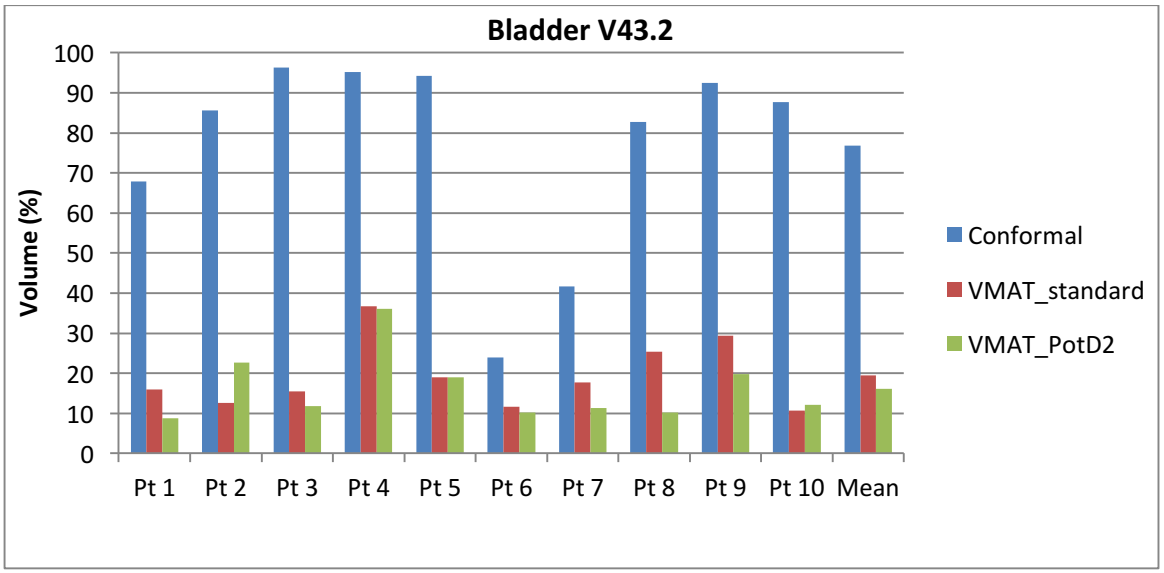


Figure 5.14-8: V43.2Gy Bladder

The bowel loops constraint of V38.6<71cc, was only met by one patient (patient 1) with both types of VMAT planning (see figure 5.14-9). Although a lower V38.6 was seen in 9/10 patients with VMAT_PotD2 compared with VMAT_standard, again statistical significance was not reached.

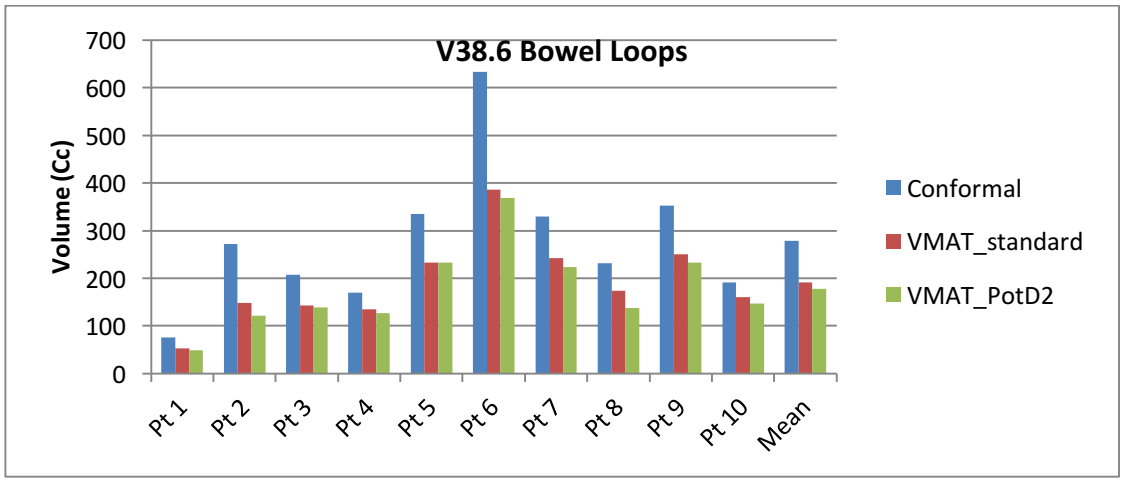


Figure 5.14-9: V38.6 Bowel Loops

For small bowel, large bowel, sigmoid and bowel bag the use of VMAT_PotD2 did not increase the likelihood of the constraints studied being met compared with VMAT_standard.

5.15. Stage 4: Dose escalation

From the results of stage 3 only one patient (patient 1) met the dose-volume constraint for bowel, V38.6<71cc. Dose escalation was modelled for this patient, where the plan library had been used for 88% of fractions. For this patient at 45Gy/25#s the bowel loops V38.6 was 48.9cc with VMAT_PotD2, compared with 53.4cc for VMAT_standard and 75.8cc for conformal plans

Dose was escalated by a fraction at a time (steps of 1.8Gy). The constraints for bowel, rectum and anal canal were examined with each step of escalation. An additional high dose constraint for bowel was added to ensure that bowel doses were not being pushed too high (bowel V56.6Gy>0.5cc, taken from Guerrero-Urbano *et al* (112))

The table below (table 5.15-1) shows the details of dose escalation for patient 1:

Table 5.15-1: Dose escalation for patient 1

	OAR volume (cc) or % of OAR volume receiving dose of given constraint or higher			
Constraint	45Gy/25#s	48.6Gy/27#s	54Gy/30#s	57.6Gy/32#s
Bowel 38.6Gy<71cc	48.93	56.14	64.96	71.04
Bowel 56.6Gy<0.5cc	0	0	0	0.77
Rectum 30Gy<80%	70%	72.7%	76.9%	79.11%
Rectum 40Gy<65%	52.2%	60.8%	65.7%	68.16%
Anal canal Dmean <40Gy	12.58	13.53	14.98	15.8

The number of fractions was increased to 27#s, 30#s and 32#s. This shows that for this patient with the use of VMAT_PotD2 strategy that dose escalation is feasible up to 54Gy/30# with toxicity-based constraints being met for bowel, rectum and anal canal, an increase of total dose of 9Gy. Even at this dose level the V38.6 did not reach that of the conformal plan.

A further increase to 57.6Gy/32#s started to breach constraints as shown in pink in the table.

5.16. Discussion

Cervical cancer IMRT has the potential to improve late toxicity and disease outcomes. However due to the internal organ motion seen within the CTV, there are concerns regarding geographical miss and underdosage of the target.

In this section of the thesis different margin strategies were compared to address organ motion in cervical cancer, contrasting their ability to maintain or improve target volume coverage, whilst reducing dose to OARs.

Adaptive strategies were found to be most promising compared to population-based strategies balancing CTV coverage with OAR sparing. Both composite and PotD strategies showed potential, though PotD reduced the volume of OARs within the PTV the most. Dosimetric analysis confirmed benefits of PotD over conformal planning and VMAT_standard in terms of dose sparing to the rectum, anal canal and bladder, and to a minimal extent bowel and bowel bag.

5.16.1. Stages 1 and 2: Volumetric comparison of margin strategies

Stage 1 of this study compared 9 different margin strategies to a standard 2cm isotropic margin. As a standard, the 2cm isotropic margin was not faultless, as it led to CTV misses in 13 of 101 scans assessed. Misses ranged from 1.1-6.6% of CTV volumes, though in view of its common use in clinical practice and clinical trials, and as suggested by RTOG guidance this was thought to be representative of what many centres would use.

The use of a smaller isotropic margin of 1.5cm, as a potential margin suggested by RTOG increased the CTV misses considerably and would not be acceptable.

Anisotropic margins of 6cm anterior, 3.6cm posterior, 1.8cm superior, 4cm left and 4.5cm right were derived to account for motion in 95% of CBCTs. The pattern of these margins had some agreement with published studies, where larger AP margins are suggested. The size of the anterior margins however was much larger than in published studies. From the systematic review in chapter IV the largest comparable margins were 4cm around the uterus (Chan *et al* al (108)) and 3.2cm AP margins (Wang *et al* (240)).

In this study with margins derived from data from only 10 patients, it is questionable whether these margins are influenced by outliers. Contrary to this idea however is that anterior margins above 3.2cm for example (as per Wang *et al* (240)) were needed in 6 of 10 patients studied, and larger than 40mm were needed in 5 of 10 patients, suggesting

that large anterior margins were genuinely required in a significant proportion of patients within this study, not just one or two outliers.

A potential reason for the large margins were because the margins were grown 2-dimensionally rather than 3- dimensionally which is artificial in reality, as the effects of growing the margins separately in different planes may over-compensate what is required. For example part of an anterior margin may in fact be contributed to by superior margins from the slice above.

The superior margins derived (18mm), were comparable to other studies where 20mm margins are suggested (109, 240). Posterior margins of 36mm were comparable to the 32mm AP margins suggested. Lateral margins were large in our study, and this was mainly due to lateral positions of the parametrium, though in reality lateral motion of the CTVprimary would be absorbed by the PTVnodal volumes.

Use of these large anisotropic margins improved CTV coverage, however this was at the cost of doubling the PTV size, and significantly increasing all the OARs studied within the PTV that would receive the treatment dose. In view of this the anisotropic margins were also discounted as the strategy of choice.

Structure-specific margins, as described in the literature (108, 237), were studied with larger margins for the uterus and smaller margins for the cervix/vagina. In our patients this was not more successful than a standard margin, in fact there was a worsening of both CTVmisses and OAR volumes in the PTV. This may be improved by further refinements of the margins used for uterus and cervix, as the uterine margin especially superiorly was higher than required for most of our patients.

The use of the ITV strategy was disappointing despite its early use in the literature being promising (200). The rate of CTVs missed was significantly increased compared with a standard margin. A reason for this may be that the bladder filling protocol used within our institution was inadequate, such that bladder volumes on the “full bladder” scan and “empty bladder” scans were not significantly different. Of the twenty patients studied 3 patients actually had a larger bladder volume on the empty scan than on the full scan. The mean difference for all patients was only 150mls, which may not be a large enough difference between full and empty bladders. Improvement on the bladder filling protocol could be addressed in a prospective study.

The two margin concepts that yielded most promising results were the composite strategy and the Plan of the Day (PotD) strategies and these two strategies were modelled in all 20 patients in stage 2.

Composite strategy has not previously been studied in cervical cancer. Compared with a standard isotropic margin, the 'composite2' strategy with a 10mm margin to PTV was beneficial for all measures studied – CTV coverage was improved, whilst significantly reducing PTV volume (p=0.001), rectum (p=0.004) and bowel bag (p=0.00). Bowel loops and bladder were also reduced (non-significantly). This margin strategy showed much potential and would be a novel area to investigate.

The PotD strategies were also promising. From stage 1 results, 2 methodological conclusions could be made from the first ten patients studied. Firstly that a back-up plan is required for a plan library, as PotD3, which did not use a back-up plan had CTV misses in 49%. Secondly, as with PotD1 the use of 7mm CTV-PTV margins are likely to be too small, as with the use of 7mm margins the back-up plan had to be used 70% of the time.

Of the PotD strategies, PotD2, which used 10mm CTV-PTV margins and a standard plan as a back-up, was most effective. Comparing Composite2 and PotD2 strategies volumetrically revealed virtually equivalent CTV covering potential in 20 patients. Despite the need for back-up plan use in 38% of fractions, use of PotD2 resulted in statistically significant reductions of all 4 OARs within the PTV, compared with only rectum and bowel bag with the use of Composite2.
The use of Velocity for derivation of a "mid-volume" was useful, with the PTVmid being used in 18% of CBCTs studied. The software, once initial problems were resolved, was quick and efficient to use, and could be used in clinical practice by treatment planners.

5.16.2. Stage 3 and Stage 4: Dosimetric analysis and escalation

As can be expected the use of a VMAT_standard plan over a 3D-conformal plan resulted in considerably improved dosimetry for the OARs studied. Compared with VMAT_standard, VMAT_PotD2 was beneficial in terms of dose sparing to some of the OARs studied.
Benefits to higher dose levels of bowel and bowel bag were seen with VMAT_PotD2 compared with VMAT_standard, although these benefits were minimal and statistically non-significant. This contrasted the volumetric analysis, where highly significant results

were seen. This discrepancy in findings is because the volumetric analysis of stage 1 and 2 was assessing OARs in relation to the PTVprimary only.

In gynaecological cancers both PTVnodes and PTVprimary are treated. The volume of bowel and bowel bag within or close to the PTVnodes volume can be significant, especially when nodal volumes extend up to include the para-aortic nodes. In view of this the effect of the bowel/bowel bag sparing that is seen lower in the pelvis with the use of VMAT_PotD2 is minimised when compared with the large proportion of bowel/bowel bag that is seen with PTVnodes.

In this work CTV-PTV margins of 8mm were used for PTVnodes, however as discussed in 2 studies in the previous chapter (203, 230) these margins may actually be insufficient. Increasing the PTVnodal margins further is likely to include more bowel/bowel bag into the PTV.

Even the most effective strategy to address pelvic organ motion of the CTVprimary will not be able to improve the dosimetric consequences of having large amounts of bowel within PTVnodes.

On the other hand, rectum, anal canal and bladder, were clearly improved with VMAT_PotD2 over VMAT_standard, with statistically significant differences seen for rectum and anal canal between the two techniques.

For the rectum the constraints used to compare techniques were V30<80% and V40<65%. Use of this constraint may prophylactically reduce toxicities such as bleeding, proctitis, sphincter control and urgency (133). VMAT_PotD2 significantly reduces rectum volumes treated at these levels, which may contribute to improved toxicity for patients.

With the use of VMAT_PotD2 these constraints are met in 30% of patients for the V30 constraint, and in 70% of patients for the V40 constraint, compared with 0% of the time with VMAT_standard planning.

For the anal canal Dmean is the dosimetric parameter associated with faecal incontinence. Dmean was already low for all patients included, though VMAT_PotD2 further improved this. For bladder no reliable toxicity-related dose constraints are published at doses lower than 45Gy. With the use of departmental planning constraints PotD2 improves the likelihood of meeting these constraints. It cannot be predicted whether this level of dosimetric improvement will improve toxicity outcomes for patients.

The other OARs studied were sigmoid and large bowel, with constraints derived in chapter III of this thesis, and small bowel with use of QUANTEC recommended constraints (128). These constraints were met in very few plans of the 10 patients studied, the large bowel constraint V15<60.8cc for example was only met by one patient in both VMAT plans.
It may be that these constraints are not always feasible in the use of cervical cancer radiotherapy, as the QUANTEC constraints were derived in rectal cancer patients, and the constraints derived in this thesis were a mixture of urological and gynaecological patients, with definitive cervical cancer patients being a small proportion of 17 of 203 patients studied.

In terms of dose escalation, only 1 patient met the bowel loops constraint of V38.6<71cc with VMAT planning and consequently dose escalation was only modelled in that one patient. In this patient with the use of VMAT_PotD2 the patient would have been able to have an additional 5 fractions, increasing the dose used from 45Gy to 54Gy. For 9 of the 10 patients, though not meeting the constraint some benefit was noted at the V38.6 dose level with the use of VMAT_PotD2 over VMAT_standard. If not for focus solely on this constraint, dose escalation could be modelled for other patients also.

An alternative approach may have been to escalate the doses of VMAT_PotD2 to the level of the bowel doses achieved by conformal planning with 45Gy/25#s, given that these patients have already been treated with conformal radiotherapy with presumed acceptable toxicity. However for this approach the whole DVH would need to be considered, as given the shape of the DVH it is likely that at higher dose levels the limits of the conformal radiotherapy would be reached by small amounts of dose escalation.

5.16.3. Limitations and Strengths

This study was originally planned to be a prospective study with assessment of each strategy with daily CBCT. Due to resource constraints within the department, this was not possible and a retrospective study was performed on days 1,2,3 and then weekly scans. The use of daily CBCTs would give much more information regarding the success or failures of different techniques, rather than weekly scans that may not represent the whole treatment course.
Performing a prospective study may have allowed for improved patient preparation, such as improved bladder filling protocol. As mentioned above the full and empty bladder scans were not always significantly varied. In the study by Heijkoop *et al* for example, with

different drinking protocols they aimed for a full bladder of 700mls and empty bladder of <50mls, which was achieved in our study of 0/20 of our full bladder scans and 3/20 of empty bladder scans. The authors do not comment on the success of their bladder protocol, however this protocol has allowed use of their plan library in 82.5%, compared with 61.6% in our study.

The patient number was limited to 20 due to the exclusion criteria, and the main reason that many patients were excluded due to long PTV volumes. Many patients had involved pelvic nodal disease and were treated up to the aortic bifurcation if not higher. The longer PTV volumes exceeded the maximal length of the CBCT scan, the CBCT was centred higher up and did not fully encompass the lower pelvis, which was key to this study hence the need for exclusion. In view of this the results of this study may be biased towards node-negative patients or patients where for example smaller PTV volumes were used, possibly due to age or co-morbidity. The impact of these factors on organ motion is unknown.

The use of on-treatment CBCT as a modality for analysis did have some drawbacks as not all structures, including GTV could be seen. As a result modifications had to be made to the studied CTV and for example inferior motion could not be studied as a bony landmark was as the inferior most border of the CTV. The use of on-treatment MRI for example may have been a better solution, albeit less readily available in the clinical setting. With MRI tumour regression and its impact on organ motion may also have been studied.

Much of the focus of stage 1 was around “CTV misses”, with CTV misses commonly involving the tip of uterus (ToU). The importance of ToU misses is questionable. Though RTOG consensus guidelines (95) suggest that the whole uterus should be included in the CTV, this was a debated topic when the consensus guidelines were drawn up, with 42% of panel members not believing the whole uterus needs to be included.

There is little published literature to highlight the importance of the uterus as a common site of recurrence, though part of the reason for this may be that the whole uterus is always included in conformal treatments, and not treating the whole uterus is somewhat against convention. Some of the strategies were rejected as a consequence of ToU misses, and in fact may have been promising.

Many of the CTV misses were small, and resulted again in strategies appearing less favourable even though they may not have had any impact on dosimetry and when planned may have been inside the 95% isodose.

In stage 3 dosimetric analysis of PotD was only performed in the first ten patients, though the next ten patients are in progress and may add further to the results.

Despite the limitations, many strengths were also noted. Included patients were selected consecutively over time regardless of the number of on-treatment images. A large proportion (14 of 20) had more on-treatment imaging than the protocol reflecting the fact that pelvic organ motion is an issue in these patients even with conformal planning, and making the results more applicable to “real world” patients.

A wide variety of strategies were compared, ranging from simple isotropic margins to more complex adaptive strategies and an in-depth analysis was performed. All CTV outlining was performed by a single operator (myself) reducing inconsistency. All strategies were compared volumetrically and dosimetrically on the same patients allowing for direct comparison which is lacking in many of the published studies so far making conclusions on which strategy is best very difficult.

As far as possible an attempt was made to quantify any benefits seen in terms of toxicity-based dose-volume constraints, with the aim of predicting if any noted dosimetric benefits may improve patient outcomes.

The use of simple strategies such as 15mm isotropic margin, as suggested by RTOG (95), were discounted, which is a useful finding, unpublished in the literature. Composite strategy has not been assessed previously in this setting, and its potential was a novel finding.

5.17. Conclusions

Organ motion is a barrier to implementation of definitive cervical cancer IMRT. Margin strategies offer a solution though the use of adaptive individualised strategies holds more promise than population-based margins. In particular, plan of the day best balances CTV coverage with OAR sparing. Significant dosimetric improvements with this technique were found to the rectum and anal canal, and with the rectum this may translate into clinical benefits.

5.18. Future work

Although PotD was promising in this study, further work is required in the form of a prospective study to refine the methods used. Bladder filling forms the basis of the plan library for plan of the day and methods to maximise the difference between empty and full bladder on planning CT would be crucial. If this is achieved then PotD techniques should be validated in a larger number of patients.

5.19. Acknowledgements

Professor Emiliano Spezi contributed to this work by creation of 'CTVmid' volumes by deformable registration on Velocity and coding of Matlab software.

Kathryn Morgan, Christian McCracken, Aileen Lyons and Rhydian Maggs performed treatment planning for stage 3 of this study.

Philip Parsons programmed in-house software (DVHimport) to allow dose-volume data to be transferred to Microsoft Excel for analysis.

All other work was performed by myself.

6. Chapter VI: Organ motion and margins required for post-hysterectomy gynaecological IMRT

6.1. Introduction

Post-hysterectomy pelvic radiotherapy is recommended for endometrial and cervical cancer patients with high-risk pathological features following hysterectomy. For those with cervical cancer this can improve survival (248, 249), and for those with endometrial cancer improve local control (48). However, as with definitive cervical cancer radiotherapy, these benefits can come at a cost of significant late toxicity from radiation to rectum, bladder and bowel. Furthermore in the absence of a uterus an increased amount of bowel can be displaced into the pelvis, with irradiation of this bowel further increasing the risk of toxicity.

IMRT is therefore highly desirable in the post-hysterectomy radiotherapy setting, aiming primarily to reduce toxicity. In this scenario, the CTV comprises the paravagina and the pelvic nodes. The paravaginal CTV is formed of the vagina that remains post-hysterectomy and paravaginal tissue. The vagina is the most common site of disease recurrence post-hysterectomy and its coverage therefore of paramount importance. Anatomically it lies between the bladder and the rectum, which are both prone to volume and positional changes, potentially impacting on the position of the vagina.

As previously described, an important concern with gynaecological IMRT is pelvic organ motion, and the risk of geographic miss and underdosage of the target given the high level of conformity in IMRT planning. This has been described in the definitive cervical cancer radiotherapy setting in the last two chapters of this thesis. In the post-hysterectomy setting, it is paravaginal CTV motion that is of concern, and quantifying this motion is key to developing safe, evidence-based internal margins.

However, compared with definitive cervical cancer treatment there have been far fewer studies to quantify organ motion in the post-hysterectomy setting, despite the fact that many more women are treated with post-hysterectomy RT than with definitive radiotherapy. Six studies (114, 250-254), 5 using vaginal fiducial markers, have been

published with some assessment of vaginal motion in this setting. The results are summarised in table 6.1-1.

Table 6.1-1: Summary of post-hysterectomy organ motion studies

	Pt no	Modality	Mean motion (mm)			Maximum motion (mm)			Suggested margins
			AP	SI	LR	AP	SI	LR	
Harris *et al* (250)	22	MVCT + fiducials	4.0 (2.8)	4.0 (3.7)	1.2 (1.0)	19.3	15	8.1	16mm isotropic
Ma *et al* (251)	11	MVCT+ Fiducials	12.9 (6.7)	10.3 (7.6)	-	30.7	27	-	-
Rash *et al* (252)	5	MVCT+ Fiducials	7	2.9	3	28	12	7	-
Chopra *et al* (253)	16	MVCT+ Fiducials	2.8 (3.3)	4.0 (3.5)	1.2 (1.3)				10.6mm AP, 10.3mm SI, 4.1mm LR
Jhingran *et al* (114)	16	CT+fiducials	7.3 (3.6)	7.0 (3.8)	2.5 (1.4)	27.9	21	9	-
Jurgenliemk-schulz *et al* (254)	15	MRI	-	-	-	-	-	-	23mm AP, 15mm SI and 18mm LR

Motion in the anterior-posterior (AP) direction was predominant, with the average magnitude of this varying between studies from 2.8mm to 12.9mm making conclusions difficult.

Problems with vaginal marker use include loss of markers on treatment (114), and the fact that they are only a point representation of an organ that can deform in shape on treatment. Ma *et al* (251) used vaginal fiducial markers and daily MVCT however their findings are difficult to interpret as at simulation they used a 2.5cm vaginal dilator which was not used on treatment.

Jurgenliemk-Schulz *et al* (254) adopted a different approach to measure motion, which was to look at margins required to encompass the boundaries of the vagina as it moves on treatment. In their study of 15 patients with weekly MRI scans, they also found that AP motion predominated. They suggested margins of 23mm anterior-posterior (AP), 15mm superior-inferior (SI) and 18mm lateral margins would cover vaginal motion in 95% of cases. Their findings have not been validated in other studies.

Unlike in definitive cervical cancer treatment where the influence of bladder and rectal filling on CTV motion is well researched, there is limited and conflicting information on their influence in the post-hysterectomy setting. Jhingran *et al* (114) found a relationship with bladder filling and vaginal motion in 6 of 16 patients in AP and SI directions, whereas Jurgenliemk-Schulz *et al* found no correlation. Jhingran *et al* also found a correlation with

AP motion and rectal filling in 6/16 patients, though Jurgenliemk-Schulz found a weak correlation only.

Suggested CTV-PTV margins included isotropic 16mm margins (250), or anisotropic margins: 10.6mm AP, 10.3mm SI, and 4.1mm LR (253) and 23mm AP, 15mm SI and 18mm LR (254). The RTOG consensus guidelines (98) do not give any definitive guidance on CTV-PTV margins, though suggest that an isoptropic 1.0-1.5cm margin is "commonly advocated." For bladder filling, RTOG suggest that an ITV formed by combining the CTV on a full bladder scan, with the CTV on an empty bladder scan may be useful. One study that used this as part of their protocol (114) has suggested "this approach must be used with caution", as bladder volumes at planning were not representative of those on treatment. Chopra *et al* (253) compared this approach with their population-based margin, and reported on the impact on PTV size and dose coverage, however did not specifically address the geographical miss with either approach.

It has been suggested that organ motion in this scenario is patient-specific (114), as it is known to be for definitive radiotherapy for cervical cancer, and thus adaptive and/or individualised strategies may be of value. Conceptually as in other pelvic tumours, strategies such as composite strategy, plan of the day, or margin of the day may be useful However there is no modelling of any of these strategies in the post-hysterectomy pelvis in the published literature.

In summary, although attempts to measure vaginal motion have been made in the literature, findings of these studies are varied and cannot be used to make definitive conclusions. Unlike in definitive cervical cancer radiotherapy, the influence of bladder and rectal filling on vaginal motion is unclear. Furthermore, management of organ motion in this scenario, either through the use of margins, patient preparation protocols or adaptive strategies are under-examined avenues of research, despite the increasing use of IMRT.

6.2. Aims

The aims of this work were to:

- Examine organ motion patterns of the paravaginal CTV in the post-hysterectomy setting
- Correlate paravaginal CTV motion with rectal and bladder filling
- Assess the use of potential margin solutions for paravaginal CTV motion, including 10mm and 15mm isotropic margins (as suggested by RTOG), suitable anisotropic margins and adaptive solutions.

6.3. Methods

A retrospective analysis was carried out on on-treatment CBCT imaging data from 20 patients treated with adjuvant pelvic radiotherapy between January 2011 and August 2013 in Velindre Cancer Centre. The following criteria inclusion and exclusion criteria were used:

6.3.1. Inclusion:

1. Patients with cervical or endometrial cancer who had undergone hysterectomy and required adjuvant radiotherapy.
2. Patients who had at least 5 CBCT scans during treatment to allow sufficient analysis of organ motion

6.3.2. Exclusion:

1. Patients with hip replacements, which cause artefact on CT scanning
2. Patients with long treatment volumes (superior-inferior) where the CBCT scans did not include the lower pelvis, e.g. where para-aortic nodes were being treated

6.3.3. Patient treatment overview

Patients were treated as standard in our institution, and details of this standard treatment are described in the following few sections:

All cervical cancer patients were treated adjuvantly with 45Gy in 25 fractions with concurrent chemotherapy, unless clinically inappropriate. All endometrial cancer patients were treated adjuvantly with 40Gy in 20 fractions as standard, with higher-risk patients (defined on pathological findings) being treated with 45Gy in 25 fractions and concurrent chemotherapy. Following EBRT certain patients had intra-vaginal brachytherapy at a dose of 15Gy in 5 fractions over one week.

Simulation

For simulation and treatment, patients were positioned supine and immobilised using the Oncology Systems Limited Combifix. Using a standard Siemens Somatom Sensation CT scanner, patients were scanned from L3 to below the perineum. Patients were asked to empty their bladders and then drink 200-300mls of water 30 minutes prior to their planning CT as standard protocol in our institution. No specific rectal emptying instructions were given.

Target volume delineation

Target volumes were outlined on Oncentra Masterplan (OMP) version 4.3. For the CTV nodal volume the pelvic vessels were outlined from the bifurcation of the aorta (for node positive patients) and from the L4/5 junction (for node negative patients), a 7mm margin

was added to form CTVnodes (102). The CTVnodes was further expanded to include the presacral region from the sacral promontory to the pirifomis muscle, and to include the obturator nodes to the superior aspect of the obturator foramen. An 8mm margin was added to CTVnodes to form PTVnodes.

For the paravaginal CTV, the vagina was outlined superiorly from where it becomes visible (including 'dog ears') to 1cm above the inferior aspect of the obturator foramen. Paravaginal CTV was formed according to RTOG guidance (98) by adding a 5mm margin anteriorly and posteriorly to the vagina, and then manually extending the volume laterally to the reach the pelvic nodal volume. Rectum and bladder were excluded from the CTV, whilst maintaining of a minimum CTV dimension of 15mm anterior-posteriorly in the midline of the vagina. At times this meant the CTV was only marginally wider than the vagina. Inferiorly where there was no pelvic node volume laterally, the volume was extended laterally to the medial aspect of the pelvic floor muscles.

CTV-PTV margins used for the paravaginal CTV within the patient group varied with clinician preference and type of radiotherapy planning used.

Treatment planning and delivery

This study was performed at a time of transition in the way gynaecological oncology radiotherapy was planned at Velindre Cancer Centre. As a result, 10 patients were treated with conformal radiotherapy and 10 patients using volumetric modulated arc therapy (VMAT).

Conformal radiotherapy was delivered using a 'four field brick' technique. VMAT was delivered using a fully optimized, single iteration VMAT plan created using a class solution planning approach developed in-house. All patients were treated using Elekta Synergy linear accelerators, and CBCT scans acquired during treatment on "XVI release 4.5.1".

Each patient had a CBCT scans on days 1, 2, 3 of their treatment followed by weekly imaging. Images were assessed using an offline strategy.

6.3.4. Fusion and outlining for modeling study

For the purpose of this study all CBCT scans were co-registered with their respective planning scans on OMP using a mutual information algorithm, excluding set-up error. Fusion was checked for adequacy at three bony landmarks – femoral heads (on axial view), tip of sacrum (on sagittal view), and pubic symphysis (both on axial and sagittal

views). If the fusion was not visually satisfactory then manual adjustments were made to correct it.

The paravaginal CTV was already present on the planning scan and this was checked for adequacy, modifying it if necessary, and labelled as pCTV. On each CBCT scan the vagina and paravaginal CTV were retrospectively outlined as specified in 6.3.3, and labelled as cbCTV1, cbCTV2 etc. The length of vagina included on each CBCT was equal to the length of the vagina used on the planning scan for that patient to give a realistic estimate of inferior CTV motion, rather than to follow a bony landmark. pCTV volumes were noted and assessed for changes over time, which would be unlikely given that this is adjuvant treatment.

To study the relationship of rectal and bladder filling with paravaginal motion, the rectum and bladder were retrospectively outlined on each planning scan and every CBCT scan in the study. The rectum was outlined from the sigmoid flexure to ischial tuberosities to determine its volume. Furthermore rectal diameter was measured at two predefined points: the maximal diameter at any point ('RDmax') and the tip of the coccyx ('RDcoccyx'). These levels were chosen, as they are easily identifiable and therefore likely to be reproducible. The entire bladder was outlined to determine its volume.
Each of these measures/diameters was also recorded to assess changes over time. It has been suggested in the literature that bladder volumes decrease over the course of radiotherapy treatment (108, 109).
Rectal and bladder "variability" were determined for all measurements, defined as the difference between the volume/diameter on each CBCT scan compared with the planning scan.

6.3.5. Analysis strategy

Analysis was carried out in three stages:
Step 1. Organ motion of the paravaginal CTV was quantified
Step 2. Paravaginal CTV motion was correlated to rectal and bladder filling
Step 3. Margin strategies to account for organ motion were compared

Step 1: Organ motion
Motion of the paravaginal CTV was quantified by defining a range of margins separately in anterior, posterior, left, right, superior and inferior directions in 1mm increments (from 1mm to 49mm) around pCTV for each patient. Each cbCTV was analysed to determine the

smallest margin to fully encompass the cbCTV in each of the six directions. This margin was taken as a surrogate for motion the cbCTV on each image studied. An example of this process is shown in figure 6.3-1.

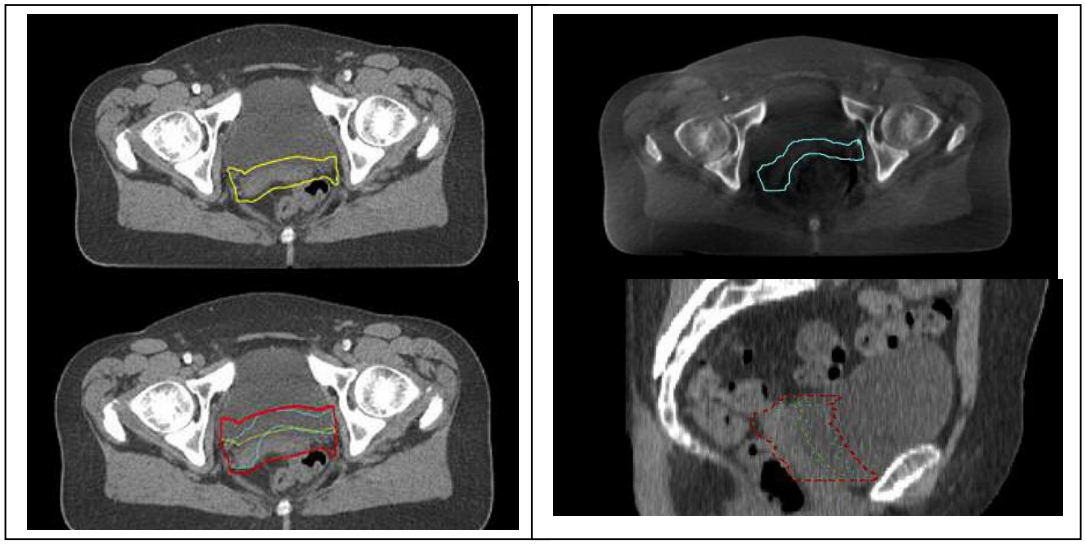


Figure 6.3-1: Determination of CTV motion: pCTV in yellow on the planning scan (top left), and the cbCTV in blue on the CBCT scan (top right). The red volume shows pCTV with an 18mm anterior margin, fully encompassing the cbCTV anteriorly, on an axial (bottom left) and sagittal view (bottom right).

Figure 6.3-1: Determination of CTV motion

This methodology has been used both in definitive cervical cancer and post-hysterectomy gynaecological studies (235, 254). This method was chosen over the use of fiducial markers given the potential limitations of markers in terms of marker loss, and concern over the use of a point measurement for a structure such as the vagina which may deform on treatment.

The margins required in each direction to cover 95% of all cbCTVs for all patients studied was then determined. These margins were taken forward as the anisotropic margins for the next analysis.

Step 2: Correlation of organ motion with rectal and bladder filling

Patterns of rectal filling and bladder filling measures over time were sought. Correlations between rectal and bladder variability and CTV motion was determined using Pearson's Correlation Coefficient ('R'). All statistical analyses performed on SPSS version 20. Correlations were considered statistically significant with a p-value of <0.05.

Step 3: Comparison of margin strategies

The following margin strategies were compared:

1) 10mm isotropic margins

2) 15mm isotropic margins

3) Population-based anisotropic margins as determined in stage 1

4) Margin of the day strategy

Margin of the day (MotD) strategy was chosen to assess whether an adaptive strategy would demonstrate any additional value to either isotropic or anisotropic margins.

Plan of the day, as modelled in definitive cervical cancer patients in Chapter V, would be difficult in these patients given the less clear correlation with bladder filling and vaginal motion, and the lack of full and empty bladder planning scans available in this retrospective study.

The use of composite strategy was also promising in chapter V, however in the current study would be difficult, as some patients had only 5 CBCTs, and with a composite of 3 or 5 scans, this would leave only 0-2 CBCTs to assess the adequacy of the strategy, which would be insufficient.

MotD concept has been described in the definitive cervical cancer setting by Ahmad *et al* (255) and involves a "margin library" whereby multiple plans are made per patient with different isotropic margins around the planning CTV. In this case margins from 10mm up to 35mm margins at 5mm intervals were used. For each CBCT the smallest margin to encompass the CTV that day from the library of 6 margins was chosen.

For each strategy the following were compared:

1. PTV volume
2. CTV coverage
    a. "Encompassed" or "missed", with the cbCTV considered encompassed if >99% was covered
    b. % coverage
    c. Mean and overall range of misses
3. OAR within PTV: The % bladder volume, % rectal volume and bowel volume (in cc) within the PTV

Differences between the mean of the above measures for each strategy were compared using Mann-Whitney testing (as non-parametric data). A p-value of <0.05 was considered statistically significant.

6.4. Results

6.4.1. Patient and scan details

Twenty post-hysterectomy patients were included in the study, including 14 patients with endometrial cancer and 6 with cervical cancer. Details of their characteristics are shown in table 6.4-1. The median age was 65 (range 33-81). Patient 1 had high-risk endometrial cancer so was treated with 45Gy in 25 fractions with concurrent weekly cisplatin chemotherapy. Patient 7 was treated for a recurrence of her disease after hysterectomy, however as this was sub-centimeter disease, she was still included as it was thought her organ motion should be similar to the other patients within the study.

Each patient studied had 5-7 offline CBCTs. In total, 20 planning scans and 116 CBCT scans were examined. 1 of the CBCT scans was unusable (patient 14 CT5) as no structures were visible, therefore 115 scans were analysed in total.

Table 6.4-1: Patient and Treatment characteristics

Pt no	Age (yrs)	Diagnosis	Stage	Radiotherapy Regime (Gy/#)	Radiotherapy Planning	Concurrent Chemotherapy	No of CBCTs available
1	45	Endometrial	III	45/25	Conformal	Cisplatin	6
2	67	Endometrial	IB	40/20	Conformal	None	5
3	81	Endometrial	II	40/20	Conformal	None	6
4	73	Endometrial	IB	40/20	Conformal	None	6
5	52	Endometrial	III	40/20	Conformal	None	6
6	73	Endometrial	II	40/20	Conformal	None	5
7	63	Cervical	Recurrence	45/25	Conformal	Cisplatin (1 cycle), then carboplatin	6
8	42	Cervical	IB1	45/25	Conformal	Cisplatin	6
9	68	Endometrial	IB	40/20	Conformal	No	5
10	79	Cervical	IIB	45/25	Conformal	No	6
11	78	Endometrial	IIIA	40/20	VMAT	No	5
12	73	Endometrial	IB	40/20	VMAT	No	6
13	46	Endometrial	IIIC	40/20	VMAT	No	6
14	63	Endometrial	II	40/20	VMAT	No	6
15	57	Cervical	IIIB	45/25	VMAT	Cisplatin	7
16	33	Cervical	IB1	45/25	VMAT	Cisplatin	6
17	69	Endometrial	II	40/20	VMAT	No	5
18	81	Endometrial	IB	40/20	VMAT	No	6
19	35	Cervical	III	45/25	VMAT	Cisplatin	6
20	63	Endometrial	IB	40/20	VMAT	No	5

6.4.2. CTV, rectal and bladder volumes and measures

The minimum, maximum, and mean statistics are tabulated for CTV, rectum and bladder for all scans of all patients (table 6.4-2).

Table: 6.4-2: Descriptive statistics for CTV, rectum and bladder

	CTV volume (cc)	Bladder volume (cc)	Rectal volume (cc)	RDMax (cm)	RDCoccyx (cm)
Min	44.1	32.2	32.8	2.5	1.6
Max	127.6	980.5	242.7	7.1	6.4
Mean	86.4	308.4	96.00	4.7	3.4
Std dev	17.4	182.8	38.7	0.9	0.8

6.4.3. Trends over Time

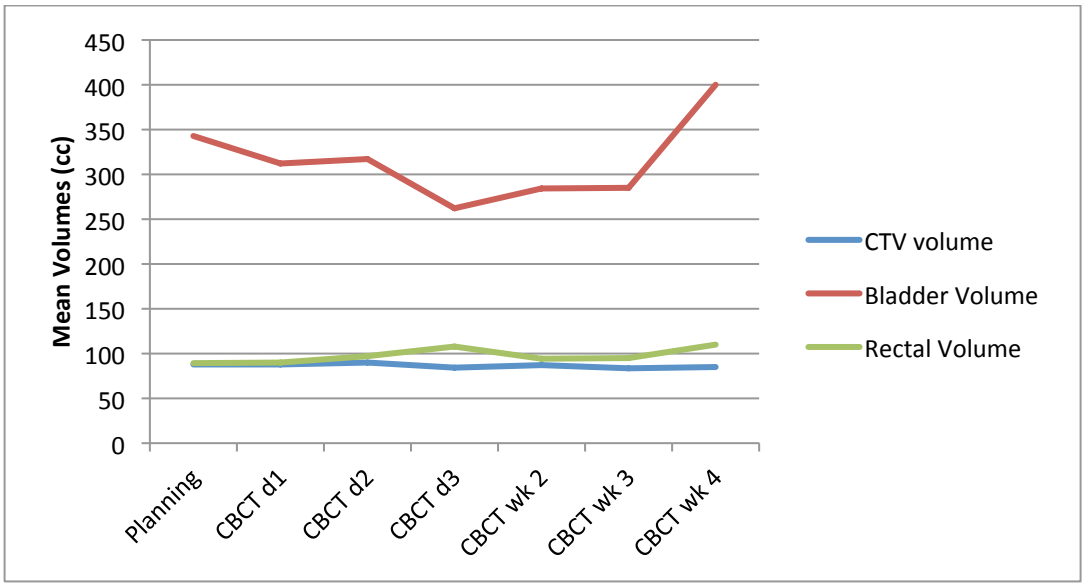


Figure 6.4-1: CTV, rectal and bladder volumes over time

Figure 6.4-1 shows the mean volumes of CTV paravagina, bladder and rectum over the time studied. No definitive trends were noted over the course of radiotherapy.

6.4.4. Rectal and Bladder variability

Rectal variability differed greatly between patients, with the largest increase from baseline being 156.6cc and the largest decrease being 121.5cc. The mean variability of the CBCTs studied was 29.8cc in rectal volume and 1.04cm in RDMax.

Figure 6.4-2 shows examples of rectal variability in three patients, with the 0cc on the vertical axis representing the rectal volume on the planning CT. Patient 4 had a relatively minimal rectal variability with a maximal change of 38cc, in contrast to patient 3 where the largest variability was seen. Patient 7 had a large rectal volume at planning, though throughout treatment rectal volume was much smaller.

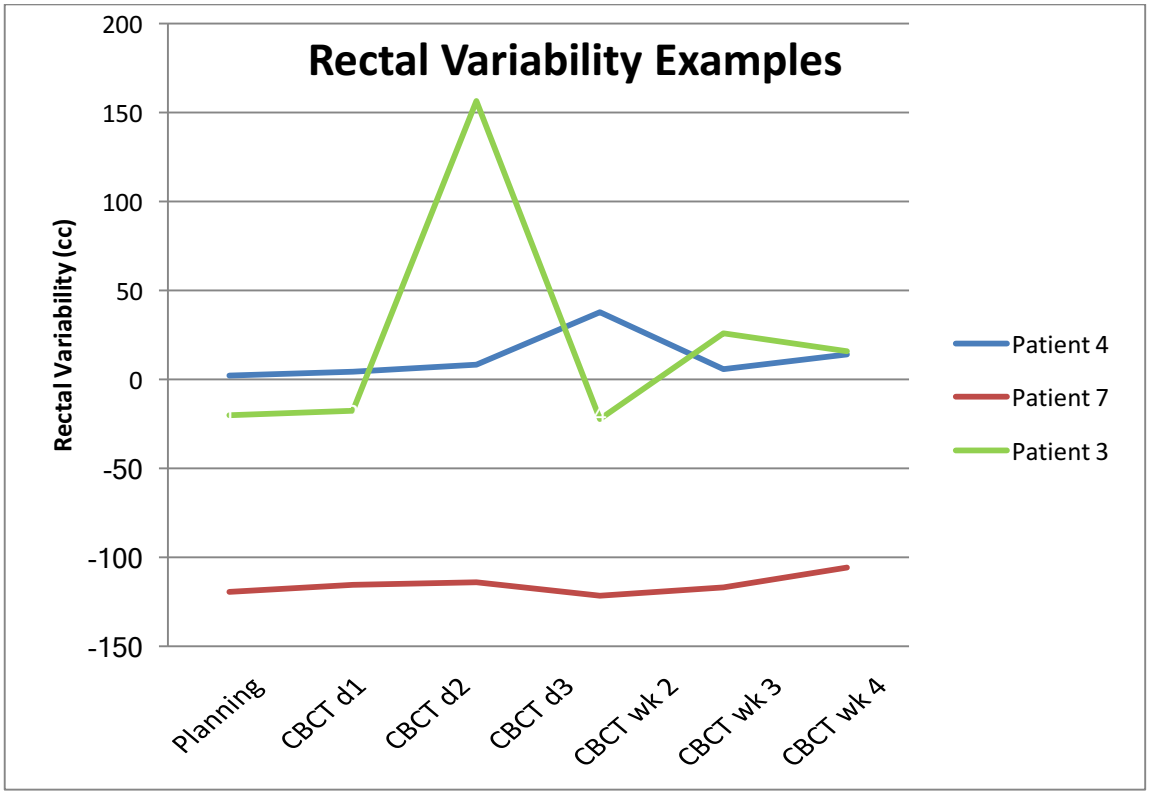


Figure 6.4-2: Rectal Variability Examples

Mean bladder variability for all CBCT was 146.6cc, with a maximal bladder variability of 606.8cc noted in one patient.

Seven CBCT scans were taken on the day of concurrent cisplatin chemotherapy, but there was no evidence of increased bladder volume on these days which may be expected with the intravenous fluids given with cisplatin.

6.4.5. Stage 1 results: Paravaginal CTV motion

Table 6.4-3 shows the maximal paravaginal CTV motion for each patient in each direction, and then summarises the data for all 115 CBCTs analysed. This suggests the predominant direction of margins is in the AP directions, with anterior movement occurring more prominently. To completely cover 95% of cbCTVs (n=109) the margins required were 25mm anterior, 29mm posterior, 6mm superior, 12mm inferior, 14mm left and 10mm right.

To completely cover 100% of cbCTVs margins of 31mm anterior, 49mm posterior, 21mm superior, 24mm inferior, 16mm left and 14mm right would be needed.

Table 6.4-3: Maximal Paravaginal CTV motion per patient (mm)

		Ant	Post	Sup	Inf	Left	Right
	Pt 1	16	18	9	6	4	4
	Pt 2	18	10	3	9	6	6
	Pt 3	16	18	0	15	12	8
	Pt 4	25	6	6	3	6	8
	Pt 5	24	10	21	12	6	4
	Pt 6	24	8	6	9	6	4
	Pt 7	0	49	3	6	6	2
	Pt 8	14	12	0	6	6	2
	Pt 9	12	13	0	6	6	4
	Pt 10	19	29	9	9	14	14
	Pt 11	12	17	6	0	16	14
	Pt 12	31	1	15	9	6	10
	Pt 13	25	12	6	6	11	10
	Pt 14	17	8	0	12	10	6
	Pt 15	15	10	0	6	8	8
	Pt 16	13	15	6	21	10	8
	Pt 17	22	7	3	12	11	6
	Pt 18	8	21	0	3	8	8
	Pt 19	19	20	0	24	15	12
	Pt 20	21	16	0	6	15	7
	Min	0	1	0	0	4	2
	Max	31	49	21	24	16	14
	Median	17.5	12.5	3	7.5	8	8
Minimum margin required to cover	90% of CBCTs	22	18	6	9	11	10
	95% of CBCTs	**25**	**29**	**6**	**12**	**14**	**10**

6.4.6. Stage 2: The influence of rectal and bladder variability on motion

Rectal volumes/diameters at planning had no correlation with the margins required on treatment. However rectal variability had a significant influence on anterior and posterior margins needed.

In particular the size of posterior margins was correlated with variability in RDcoccyx (R=-0.75), RDmax (R=-0.73) and rectal volume (-0.7) (all $p<0.0001$). Patients with a large rectum at planning and then smaller rectum on treatment needed larger posterior margins. Anterior margins were also correlated with changes in rectal variability, RDcoccyx (R=0.6), RDmax (0.53), and for rectal volume (R=0.44) (all $p<0.05$). No correlation was noted in other directions. RDcoccyx data is illustrated in figure 6.4-3.

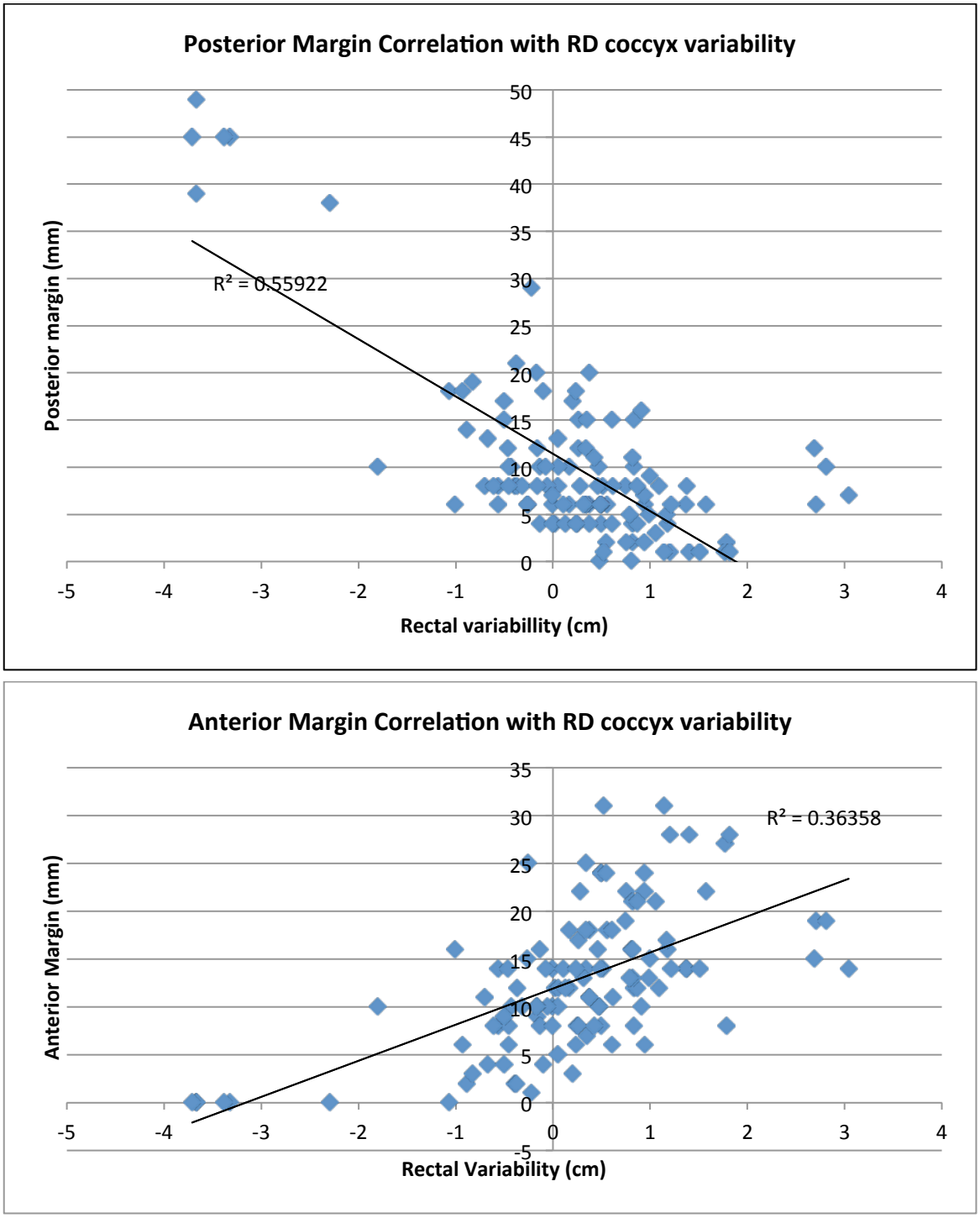


Figure 6.4-3: Correlations of RDcoccyx with anterior and posterior margins

Specific bladder volumes at the time of planning had no correlation with the margins required. However bladder variability was correlated with anterior margins (R=0.44, p<0.0001). Weaker yet significant correlations with posterior and superior margins, (R=0.37, R=0.33, p<0.05) were also found. A weak correlation between initial bladder

volume change, large bladder volume changes and the need for larger margins was noted (R=0.59, p<0.01).

Two patients (patient 7 and 12) in particular had a significantly large AP motion, one (patient 7) with a maximum posterior motion of 49mm. Patients 7's planning and on-treatment CBCTs are illustrated in figure 6.4-4. This patient's organ motion was associated with rectal filling, as she had a maximum rectal diameter of 7.09 cm at planning (top image) which reduced by 3.14cm to 3.95cm on treatment (lower image).

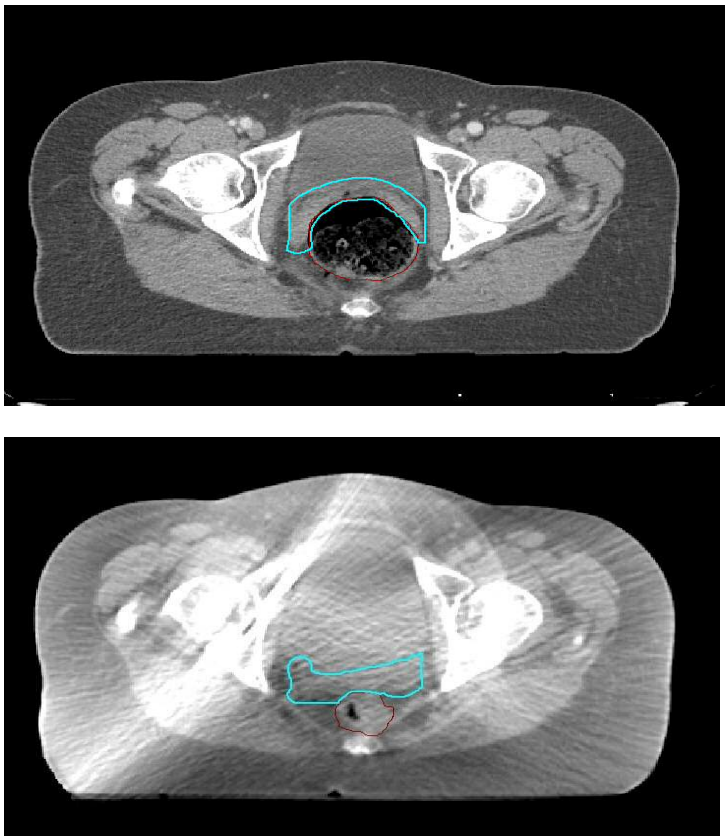


Figure 6.4-4: Patient 7 organ motion

This patient was treated now 4 years ago, and since then there is increased awareness of organ motion, this patient is likely to have been rescanned at planning after evacuation of her rectum in attempt to reduce rectal distension. As her posterior margins fell into the highest 5% of CBCTs, posterior margin data from her scans was not included when determining anisotropic margins.

Patient 12 had significant anterior motion (31mm) on treatment, which may have been in relation to variable bladder filling, with her bladder volume at planning being 531cc, reducing to 125cc during treatment. However, this was not consistent with all patients, as

even those with bladder filling changes of 600mls did not have as much anterior motion. The strength of the influences of bladder and rectal filling appear to be patient-specific.

6.4.7. Stage 3: Margin strategy assessments

Margin of the day usage

The frequency of the margins chosen within the margin library is shown in table 6.4-4. The 35mm margin did not need to be used for any patient. 15 of 20 patients used only 10mm and 15mm margins.

Table 6.4-4: Margin of the day use

	10mm	15mm	20mm	25mm	30mm	35mm
Pt 1	5	1	0	0	0	0
Pt 2	5	0	0	0	0	0
Pt 3	5	1	0	0	0	0
Pt 4	3	3	0	0	0	0
Pt 5	3	3	0	0	0	0
Pt 6	4	1	0	0	0	0
Pt 7	0	0	1	4	1	0
Pt 8	6	0	0	0	0	0
Pt 9	5	0	0	0	0	0
Pt 10	3	2	1	0	0	0
Pt 11	4	1	0	0	0	0
Pt 12	0	0	3	3	0	0
Pt 13	0	6	0	0	0	0
Pt 14	6	0	0	0	0	0
Pt 15	7	0	0	0	0	0
Pt 16	0	2	3	1	0	0
Pt 17	2	3	0	0	0	0
Pt 18	1	4	0	0	0	0
Pt 19	4	0	0	2	0	0
Pt 20	5	1	0	0	0	0
total	68	28	8	10	1	0
% of total	59.13	24.35	6.96	8.70	0.87	0

6.4.8. Comparison of CTV coverage, PTV volume and OARs included

The PTV volume, CTV coverage and OARs within the PTV is shown in table 6.4-5 for the four different margin strategies, and individual patient data for each strategy in figure 6.4-5. CTV coverage was insufficient (only 62.5% of cbCTVs studied) with an isotropic 10mm margin. Coverage was significantly improved by use of a 15mm margin (p=0.004), anisotropic margin (p=0.013) and margin of the day (p=0.00), which encompassed 100% of cbCTVs.

In the patients with more organ motion (patients 7 and 12), isotropic 10mm and 15mm margins were not sufficient for any of the CBCTs assessed. The anisotropic margin was sufficient for one of these patients but the MotD was for both.

Table 6.4-5: Comparison of margin strategies

	Isotropic 10mm	Isotropic 15mm	Anisotropic	MotD
Mean PTV vol (cc)	314.56	478.57	531.01	430.90
Mean % CTV coverage	96.14	98.51	99.34	99.88
No of CTVs encompassed (%)	75 (65.2%)	99 (86.1%)	105 (91.3%)	115 (100%)
Mean proportion of CTV missed (%) (range)	11.3% (1.03-40.8%)	10.9% (3.3-26.6%)	6.6% (1.8-17.3%)	0
Mean % bladder in PTV	21.64	33.63	43.83	26.61
Mean % rectum in PTV	30.88	44.40	63.65	39.15
Mean bowel volume in PTV (cc)	9.99	21.63	11.54	18.09

Individual patient data for CTVs encompassed is illustrated in figure 6.4-5.

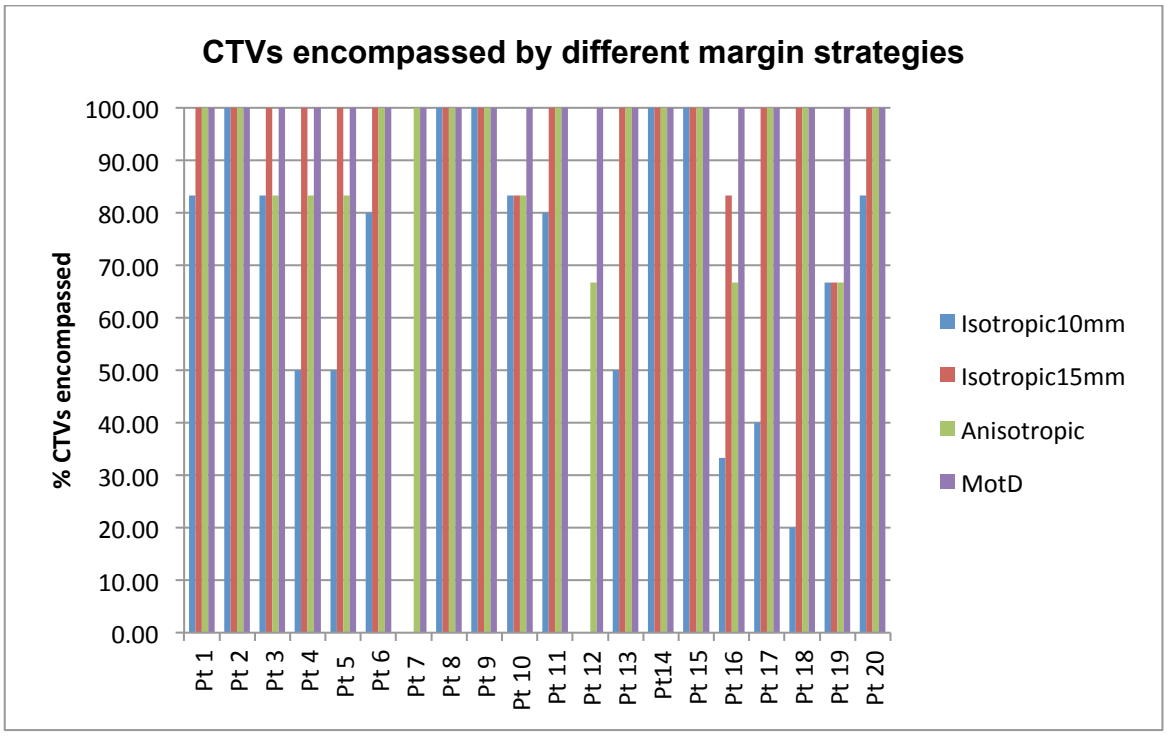


Figure 6.4-5: Comparison of margins for CTVs encompassed

As expected PTV volume was smallest with an isotropic 10mm margin, yet this was at the expense of CTV coverage. The mean data regarding OAR sparing according to strategy is illustrated in figures 6.4-6 and 6.4-7.

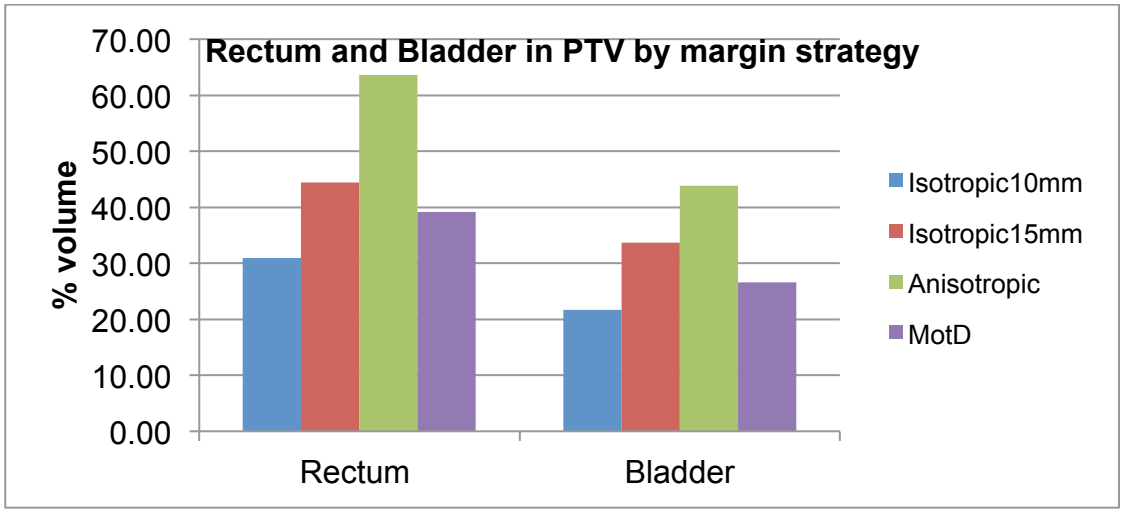


Figure 6.4-6: Rectum and bladder within PTV

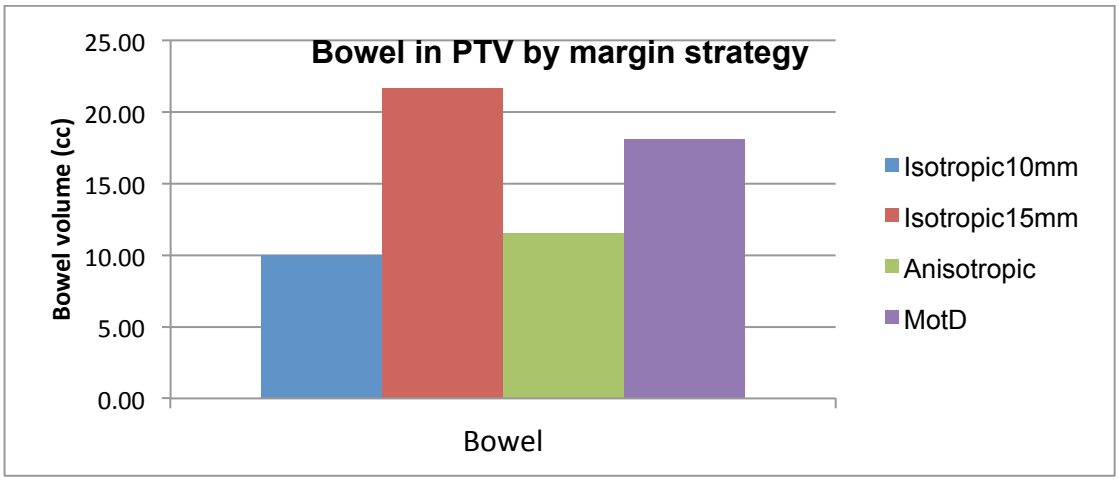


Figure 6.4-7: Bowel within the PTV

As 10mm margins inadequately encompassed cbCTVs studied, with 34.8% of CTVs missed, this was not considered further. The remaining three strategies were examined further. Considering rectum within the PTV, use of anisotropic margin (with its large posterior component, 29mm) lead to an increased mean volume of rectum from 44.4% with a 15mm margin to 63.65% with an anisotropic margin (p=0.02)). Comparing MotD and 15mm margins, MotD had a reduced amount of rectum within the PTV, though this was non-significant (p=0.27).

Again with bladder, MotD had the least amount of bladder in the PTV, though the difference between this strategy and use of a 15mm margin was non-significant (p=0.19).

For bowel, it was the use of anisotropic margin that led to the lowest volume of bowel being irradiated, presumably due to the smaller superior margin (6mm).

6.5. Discussion

Safe delivery of IMRT in the post-hysterectomy gynaecological patients requires knowledge of paravaginal CTV motion and determination of margins to account for this motion. In this section of the thesis key findings were that paravaginal CTV motion is a significant issue, with AP motion being most predominant. AP CTV motion is correlated with rectal variability between planning and on-treatment, with some impact of bladder variability also. In these patients 10mm isotropic margins are inadequate. Coverage can be improved with anisotropic margins, 15mm isotropic margins and margin of the day strategy. Overall MotD best improved CTV coverage with relative sparing of rectum and bladder within the PTV, and is therefore the preferred margin strategy.

As in the limited published literature regarding organ motion in this setting, CTV motion in this study was found to be an important consideration. In this study population-based anisotropic margins of 25mm anterior, 29mm posterior, 6mm superior, 12mm inferior, 14mm left and 10mm right were found to account for the motion in 95% of CBCTs studied. These findings, in part, agree with Jurgenliemk-Schulz *et al* (254) who used similar methodology, and suggested margins of 23mm AP, 15mm SI, and 18mm LR. Compared with the other published studies (114, 250-253), the motion detected in our study was much greater in magnitude. These differences are likely to be due to methodological differences, as in the other studies vaginal motion was determined using a point representation (fiducial marker within the vagina). The vagina is a deformable and non-uniform organ, and motion of a fiducial marker may not represent its entire motion, therefore I believed this to be a more realistic method of assessing motion.

Rectal variability was significantly correlated with the magnitude of posterior margins ($R=0.74$, $p<0.001$) and, to a lesser extent, with anterior margins. These findings have some agreement with other studies, where Jhingran *et al* (114) found rectal filling was associated with vaginal motion in the AP direction in 6 of 16 patients. Rash *et al* (252) in their small study of 5 patients also found a correlation with AP motion and rectal diameter ($R=0.53$). One can conclude that rectal filling does influence paravaginal CTV motion; however this pattern is not seen to the same degree in all patients.

Despite the significant influence of rectal variability on CTV motion, no guidance is available for rectal management in gynaecological radiotherapy. In the case of prostate cancer a distended rectum at planning has been associated with poorer CTV coverage and consequentially poorer clinical outcomes (256, 257). Many institutions follow a

protocol to ensure a rectum of <4cm in diameter at the time of planning and whilst on treatment for prostate patients. In post-hysterectomy patients, as noted in this work, this would not be a useful measure in the population of patients studied, as a rectal diameter of >4cm was found in 77% of scans examined. Rather than the absolute value of rectal diameter, it would be maintenance of the same rectal diameter on treatment as that at planning that would be of importance.

Bladder variability had a moderate correlation with paravaginal CTV motion in the anterior direction, R=0.44 ($p<0.001$). Jhingran *et al* (114) found an influence of bladder filling in 6 of 16 of their patients, though Jurgenliemk-Schulz *et al* (254) found no correlation at all. Again all that can be concluded is that bladder variability may influence motion, though this pattern is not as robust as rectal variability.

Within the RTOG consensus guidelines (98) the influence of bladder filling is considered important and the use of an ITV is advocated, based on CTV position on a 'full' bladder planning scan combined with CTV position on an empty bladder planning scan. To date this approach has not been proven to be successful. One study using this method found (114) that on treatment patients often had a "fuller" or "emptier" bladder than their 'full' and "empty" bladder volumes at the time of planning. Others (253) demonstrated that the use of an ITV generated by the full and empty bladder approach had decreased target coverage compared to a population-based ITV. Findings in this chapter suggest the ITV approach may be of benefit in some patients where bladder filling is influential on CTV position, although a more pressing issue would be rectal filling management.

An important finding of this work was that isotropic 10mm margins were insufficient to cover 95% of the CTV in 38% of cbCTVs studied, and this finding concurred with that of one other study. The potential advocated margin by RTOG of 10mm is therefore inappropriate.

15mm margins improved coverage, though were still insufficient in 14% of cbCTVs studied. Anisotropic margins improved coverage to 91% of CBCTs, but at the expense of significant increases in dose to rectum and bladder. In comparison MotD to anisotropic margins improved CTV coverage to 100% and reduced PTV volume, resulting in reduced doses to rectum and bladder, although not to bowel.

Overall MotD may offer a balanced solution to account for organ motion in the post-hysterectomy setting. The drawback of MotD would be that for each patient 5 IMRT plans would need to be produced, and daily online IGRT would be required. This would have

practical and workforce implications, and it would need to be assessed in more detail in a dosimetric study, and potentially a prospective study to assess its clinical feasibility and cost effectiveness.

An intermediate solution may be to have a margin library of 10mm and 15mm (which was sufficient for 75% of all CBCT in this work), and then a large margin plan as a back-up, such as 30mm, for the remaining treatment days. A further concept that may be worth addressing is a margin of the day with anisotropic margins, larger in AP directions, this method is already in use in the ongoing bladder cancer trial, Hybrid (122).

6.5.1. Strengths and Limitations

This is the first study to use kV CBCT as a means for evaluating CTV margins in the post-hysterectomy setting, which may be more accurate than previous studies using MV imaging of fiducial markers and more clinically applicable than studies using on-treatment MRI. CBCT is available in most clinical departments, and in this study the vagina, bladder and rectum were all visible in all CBCT scans used, especially when using axial imaging in conjunction with coronal and sagittal views.

This work also is novel as adaptive strategy for post-hysterectomy patients has not previously been examined in published literature, and margin-of-the-day is demonstrated to have significant promise. Adaptive strategy may be an important area of research in future, enabling more effective IMRT in this setting.

The study does have some limitations; firstly all assessments are based on retrospective assessment of weekly CBCT scans, whereas daily CBCT scans may be a more realistic representation of daily anatomical variations. With the nature of a retrospective study bladder and rectal protocols could not be adapted. Secondly, this study did not assess the other significant component of PTV – PTVnodes. Measuring of pelvic node motion on CBCT is difficult, and appropriate CTV-PTV margins remain unclear within the literature (203, 230). Although anisotropic margins were derived, as was the case in chapter 5, these were derived 2-dimensionally, and it may be that the addition of separate margins in all 6 directions result in an overly large margin, as for example a component of the anterior margin could be contributed from superior margins.

6.6. Conclusions

This work has demonstrated that paravaginal CTV motion is a significant consideration for post-hysterectomy IMRT. Rectal filling variation contributes significantly to this motion in AP directions in some patients. 10mm isotropic margins are inadequate for IMRT in these patients and although 15mm margins are better, the use of population-based anisotropic margins can further improve CTV coverage. A margin of the day adaptive strategy, appeared more effective than anisotropic margins and even though this strategy may have workload implications, it is most suitable to IMRT use in terms of balancing CTV coverage and OAR sparing.

6.7. Future Work

Although a volumetric assessment of MotD and other strategies was performed, a dosimetric analysis of MotD is required to further model its benefits. If found to be advantageous dosimetrically compared with non-adaptive approaches MotD could be further investigated in prospective study.

Aside from margin based solutions, the use of rectal measures in the post-hysterectomy setting is an important avenue of investigation. The use of measures such as dietary modification, oral laxatives and enemas should be investigated in prospective study to potentially reduce rectal variability and consequently margin size.

6.7.1. Acknowledgements

Guidance on fusion of CBCT scans was provided by Dr Nachi Palaniappan (Consultant Clinical oncologist, Velindre Cancer Centre) and Mr Arek Mazurek (Physicist, Velindre Cancer Centre). All work for this study was conducted by myself.

7. Thesis summary and conclusions

7.1. Introduction

Implementation of pelvic IMRT for gynaecological cancers is a desirable goal to reduce toxicity for patients. Though theoretically beneficial, there are several practical barriers to its widespread adoption. Concerns include the lack of consensus on target volume definition, lack of appropriate dose-volume constraints for quantifying toxicity reduction, and lack of optimal management strategies for organ motion and tumour regression.

This thesis focused on two of these concerns; Section A (chapters II and III) investigated dose-volume predictors and constraints for late bowel toxicity; Section B (chapters IV, V and VI) examined organ motion in both the definitive and post-hysterectomy settings, with an assessment of strategies to manage this motion. Key findings, conclusions and proposed future work for these sections are summarised below.

7.2. Section A: Dose-volume constraints for late bowel toxicity

Bowel toxicity is the key concern with pelvic radiotherapy, and unfortunately occurs commonly with an impact on quality of life for pelvic cancer survivors. When implementing new radiotherapy techniques that may reduce toxicity it is important to know the appropriate dose-volume constraints to assess the likely genuine benefits of the new technique.

A systematic review was performed in chapter II to examine and appraise the published literature on dose-volume constraints for late bowel toxicity. Within the 25 studies included, seven papers addressed the whole bowel (either as peritoneal cavity or bowel loops), ten papers looked at small bowel and duodenum, and fifteen studies at components of large bowel.

This review highlighted the anal canal as an important OAR, and its dose-volume parameters, particularly Dmean was associated with late toxicities such as faecal urgency and faecal incontinence. Given that a number of studies were found with similar findings it was concluded that a Dmean of <40Gy is associated with reduced toxicity from the anal canal.

Regarding other definitions or components of bowel, dose-volume parameters of small bowel, bowel loops, large bowel and sigmoid colon were all suggested to have an association with late bowel toxicity, and constraints were derived for some of these organs.

However, none of these individual findings or constraints were corroborated in other studies, and firm conclusions on these components of bowel could not be made based on the published literature.

Chapter III aimed to further the information gathered from chapter II. In this chapter a dose-volume toxicity study, based on late bowel toxicity data collected prospectively at Velindre Cancer Centre was performed. High rates of patient-reported late bowel toxicity were found in the 203 patients who returned questionnaires 12 months after completion of their pelvic radiotherapy. Symptoms of late toxicity were reported by 79% of patients, with the most common symptom being faecal urgency, which was severe (grade 3-4) in 41.3% of patients (defined as “daily” or “continuously”).

Dose-volume parameters of different bowel OARs were studied to assess their predictive value for faecal urgency, faecal incontinence, diarrhoea, and rectal bleeding. Constraints for these parameters were derived which dichotomised patients into groups with higher and lower rates of toxicity, and their “goodness-of-fit” was determined.

From this work the four OARs that were found to be relevant were bowel loops, bowel bag, sigmoid and large bowel and statistically significant constraints were derived for each of these. The sigmoid was highlighted as a particularly important OAR for the development of faecal urgency, which is a novel finding.

Furthermore the toxicity data collected in chapter III was used to corroborate constraints from the systematic review in chapter II. In particular, the constraint for bowel loops described by Guerrero-Urbano *et al* (112) (V38.6<71cc) successfully dichotomised patients with faecal urgency, faecal incontinence, and diarrhoea (all $p<0.05$), validating their findings in our study patients.

7.2.1. Recommendations from this section

Based on combined analysis of chapters II and III, the following dose constraints for late bowel toxicity are recommended:

- Bowel loops V38.6<71cc for faecal urgency, diarrhea and incontinence (any grade)
- Bowel bag V5<1689cc for diarrhoea (any grade)
- Sigmoid V10<52.6% for faecal urgency (high grade)
- Sigmoid V25<36.2% for faecal urgency (high grade)
- Sigmoid Dmedian<13.7Gy for faecal urgency (any grade)
- Large bowel V15<60.8cc for diarrhoea (any grade)
- Anal Canal Dmean<40Gy for incontinence

7.3. Section B: Assessment and management of pelvic organ motion

The second issue addressed within this thesis was pelvic organ motion, which was investigated for both definitive cervical cancer and post-hysterectomy cervical and endometrial cancer.

7.3.1. Definitive cervical cancer

For definitive cervical cancer radiotherapy patterns of organ motion and solutions to account for this motion were initially sought in a systematic review and secondly in a retrospective modeling study.

The systematic review included 53 papers, and detailed studies looking at the motion of the cervix, uterus, whole CTV, and lymph nodes. Key findings were that organ motion was significant and cannot be ignored when considering IMRT. Uterine motion had a greater magnitude than cervical motion, with the added complexity of translational and rotational movement. Uterine motion was related to bladder filling, whereas rectal filling was more associated with cervix motion. These patterns were patient-specific, and not applicable in all patients to the same degree.

With this in mind the concept of individualized and adaptive strategies in this group of patients emerged. Preliminary planning studies and early clinical studies have been performed assessing strategies such as plan of the day (PotD) and margin of the day (MotD). From the published literature however the benefits of these methods compared with standard techniques in terms of coverage and OAR sparing have not been quantified.

The exploratory study performed in Chapter V built on the findings of the systematic review. Using retrospective data from patients treated with definitive radiotherapy for cervical cancer at our centre, a comparison of nine different margin strategies was made.

Key findings were that adaptive margin strategies were better than population-based margins in terms of balancing CTV coverage and sparing of OARs. Isotropic margins of 15mm, as proposed by RTOG were insufficient. Anisotropic margins (6cm anterior, 3.6cm posterior, 1.8cm superior, 4.0cm left and 4.8cm right) improved CTV coverage but significantly increased, at times doubling, the volumes of OARs within the PTV.

The most promising strategies volumetrically were composite strategies and PotD, both in terms of CTV coverage whilst sparing OARs.

Dosimetrically PotD significantly reduced dose to the rectum, bladder and anal canal compared with a standard VMAT plan. The dose-volume constraints for rectum were statistically significantly improved, which could correlate with a reduction in toxicity (133).

However when considering bowel loops, bowel bag, sigmoid and large bowel (the OARs determined as important in chapter III), there was no statistically significant dosimetric improvement when comparing PotD with a standard VMAT plan.

With an important theme of this thesis being bowel sparing and late bowel toxicity reduction, this study identified that even with the best technique for pelvic organ motion management, although sparing of the rectum and anal canal is possible, bowel dosimetry is unlikely to majorly improve over that of a standard VMAT plan.

Of note, the bowel loops constraints could not be met by either standard VMAT plans or PotD VMAT plans in 9 out of 10 patients. The reason for this is likely to be the large volumes of bowel that are irradiated higher up in the abdomen, rather than lower in the pelvis. With adaptive strategies, although the volume of bowel within the primary PTV being significantly reduced, this cannot compensate for the large amount of bowel within the nodal PTV which remains high regardless of whether an adaptive technique is used or not.

For the one patient where bowel dose-volume constraints were met with PotD, dose escalation modeling was carried out. An additional 9Gy in 5 fractions could be added before the bowel dose constraints were met. With the use of PotD and a dose of 54Gy, the doses to bowel were still lower than use of a conformal plan with a dose of 45Gy. Although in only one patient, this does highlight the potential that for individual patients who do have favourable bowel dosimetry that dose escalation may be possible, and an individualized approach to dose escalation may therefore be worth investigating.

7.3.2. Post-hysterectomy cervical and endometrial cancer

In the post-hysterectomy setting, given the limited published data on paravaginal motion, in chapter VI a retrospective study was performed to assess organ motion of the paravaginal CTV, and its relation to bladder and rectal filling. The paravaginal CTV moved significantly on treatment, predominantly in the anterior-posterior direction, although the magnitude of motion varied from patient to patient. Posterior motion was correlated ($R=0.7$, $p<0.0001$) with change in rectal filling between planning and treatment, and bladder filling had a weaker correlation with anterior motion, which did concur with some of the previous published findings (114, 254).

Margin strategies to allow for this motion were volumetrically assessed in twenty patients. 10mm isotropic margins (as suggested by RTOG) were found to be insufficient resulting in geographic miss in 34.8% of CBCTs studied. The use of either 15mm isotropic margins or population-based anisotropic margins (25mm anterior, 29mm posterior, 6mm superior, 12mm inferior, 10mm left and 14mm right) improved CTV coverage. However anisotropic

margins doubled the % volume of rectum and % volume of bladder found within the PTV compared with a 10mm margin, making it a less appealing strategy.

An adaptive strategy, margin of the day (MotD), was modelled. This strategy demonstrated most promise in terms of CTV coverage allowing 100% of coverage. It also allowed increased sparing of rectum and bladder compared with 15mm isotropic margins (by 7% and 5.3% respectively), with a more substantial sparing compared with anisotropic margins (by 24.5%, p=<0.001 and 17.2%, p=0.004).

7.3.3. Recommendations from this section

From this section of work the key recommendations are:

-If IMRT is to be delivered safely and effectively for gynaecological malignancies appropriate strategies to monitor and manage organ motion is required. Given the magnitude of organ motion in certain patients daily on-treatment imaging is required to ensure target coverage if IMRT is to be used.

- Given the relation of rectal and bladder filling to organ motion in both of the radiotherapy scenarios studied maintenance of consistent rectal and bladder filling from the time of planning and whilst on treatment is important

- For both definitive and post-operative radiotherapy adaptive strategies such as plan of the day or margin of the day would optimise CTV coverage whilst reducing dose to some OARs when compared to population-based margins.

7.4. Future Work

The work in Section A led to derivation of dose-volume constraints for four OARs. Future work would aim to validate these constraints and to determine their value in the different pelvic tumour sites. In chapter III dose-volume constraints were derived from a mixed case selection of prostate, cervical, endometrial and bladder patients with the aim of being inclusive, however the majority of patients (63%) studied ended up being prostate cancer patients, given its high incidence. Although theoretically these dose constraints should be applicable to all pelvic radiotherapy patients, it is unclear whether in practice this will be the case, and certainly in the ten patients with cervical cancer that were planned in chapter V these constraints were largely unachievable with either conformal or VMAT planning that was used.

With the focus of this work being gynaecological malignancies I would first want to assess the dose constraints derived in an independent group of patients with cervical and

endometrial cancer. The collection of late toxicity data is ongoing within Velindre Cancer Centre for gynaecological patients. I would choose a sample of these patients for which late toxicity data is available and determine whether the dose-volume constraints from chapter III successfully dichotomise patients with and without toxicity.
If the constraints are validated in an independent group of gynaecological patients this would confirm their potential value for future patients. These constraints could be tested in a prospective study to assess their ability to reduce the risk of toxicity.
Similar work could be performed to validate the dose-volume constraints for patients treated with prostate and pelvic node radiotherapy, bladder cancer and rectal cancer, with either the use of toxicity data collected for clinical practice, or from clinical trials.

If the constraints are found to be valid in independent groups of patients, but are difficult to achieve with current planning techniques, especially for gynaecological patients where there are large volumes of bowel close to PTV, then alternative planning techniques could be sought. Proton techniques are being developed and their potential in cervical cancer radiotherapy has been studied in planning studies (258, 259), and have been found to be beneficial compared with IMRT and VMAT techniques in terms of bowel sparing. Future studies would then compare the use of IMRT/VMAT with proton therapy to enable these bowel dose constraints to be met.

The toxicity data and dosimetric data collected in this thesis could also be used for normal tissue complication probability (NTCP) modelling, which is considered a superior method to predict toxicity rather than dose-volume metrics alone. In chapter III dose-volume relationships were sought from DVH parameters, which are not ideal as they disregard spatial information (126). NTCP modeling uses both dosimetric and anatomical information and may allow for improved modeling of toxicity. These models could potentially be used in combination with other factors, such as clinical factors, in nomograms, such that an individual patient's risk of toxicity can be calculated prior to commencing treatment based on both dosimetric and clinical factors (260).
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The work from Section B highlighted the importance of adaptive strategies in gynaecological malignancies to manage organ motion whilst reducing dose to pelvic organs such as rectum, bladder and anal canal. In particular in definitive cervical cancer PotD appeared most promising and I would aim to take this concept further in future.

I would plan to first perform a prospective single-centre feasibility study of PotD in a small number of patients, for example 20 patients. Patients would be treated with PotD as modelled in chapter V, with a library of three plans (full, mid and empty bladder) and a back-up plan. They would have daily online CBCT prior to treatment and each day the most appropriate plan would be chosen based on the patients anatomy that day.
The prime aims of this work would be to assess the feasibility of this technique in clinical practice given the increased workload for all teams involved. For physics teams this would require streamlining of the process for plan library generation, as this would involve 4 plans rather than a single plan. For the radiographer team this would involve training staff to be able to choose between plans in the plan library based on information from the online CBCT that day.
One of the main concerns highlighted in chapter V was that the back-up plan had to be used in a large proportion of patients, as the full and empty bladder planning scans were not sufficiently different from each other and the extent of the range of CTV motion between these scans did not represent that on treatment. Use and assessment of a refined bladder protocol to allow greater variation between a full bladder planning CT and an empty bladder planning CT and an improved plan library would be a further aim of this study.
Dosimetric benefits of the method would again be assessed by comparing the use of PotD against a conformal plan with a standard margin for these patients.

If this study confirmed the dosimetric benefits and feasibility of PotD in cervical cancer then the next step would be a randomised study comparing PotD with standard treatment, with clinical outcomes of acute toxicity, local control and late toxicity being the endpoints measured.

For post-hysterectomy gynaecological malignancies one of the key findings from the work in chapter VI was that rectal variation was related to CTV motion and subsequently larger margins. The use of rectal measures such as rectal enemas are used commonly in prostate cancer and I would propose to use these in a prospective study in post-hysterectomy gynaecological patients to determine if their use can reduce variation in rectal filling and CTV motion. Patients would be asked to use enemas at planning and prior to each treatment, and their organ motion would be assessed on daily CBCT. Their organ motion would be compared against a group of patients treated with standard practice (without rectal measures).

Margin of the day for post-hysterectomy patients have been demonstrated to be beneficial on volumetric analysis in chapter VI. I would plan to assess this benefit dosimetrically with a planning study of these patients. If this was found to be significantly beneficial then clinical implementation of these methods could be considered.

7.5. Final conclusions

This thesis aimed to address practical issues which hamper the implementation of gynaecological IMRT. The work presented in this thesis has furthered knowledge of dose-volume constraints for late bowel toxicity symptoms. If validated in future groups of patients these may be helpful in preventing late bowel toxicity, improving outcomes for survivors of pelvic radiotherapy.

For management of pelvic organ motion both in the definitive cervical cancer radiotherapy and post-hysterectomy settings, adaptive margin strategies rather than population-based margins are most beneficial in terms of balancing improved CTV coverage and reduced OARs within the PTV. The knowledge acquired from these studies would hopefully form a basis for further research addressing clinical feasibility of these methods. This may in turn lead to a change of clinical practice and allow for safer and more efficient IMRT techniques for gynaecological patients.

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Appendix A: Letter from Research and Development Department

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Email: Sarah.Townsend@wales.nhs.uk
Tel: 029 20 615888 ext: 4670

Dear Rashmi

I can confirm that from the summaries you have provided I consider these studies to be service evaluation.
As such neither ethical approval or R&D permission will be required.

Best wishes,

Sarah Townsend
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Appendix B: Bowel toxicity questionnaire (chapter III)

Velindre Cancer Centre
Canolfan Ganser Felindre

Patient Name:

Patient Number:

Dear patient,

This questionnaire is to assess the symptoms that you may be experiencing since your radiotherapy treatment approximately 12 months ago. Please circle the most appropriate answer as to how you have been **feeling in the last two weeks**.

If any of your symptoms are longstanding (i.e. started prior to radiotherapy) please give details of this in the comments section at the end. Please return this questionnaire in the pre-paid envelope within the next two weeks. Many thanks.

	0	1	2	3	4
Have you had any diarrhoea recently? If so, how many times?	Never	2-4 times/ day	5-8 times/ day	>8 times/ day	Uncontrolled
Are you taking medication for diarrhoea? If so what and how often?	No	Yes	Name of medication and how often?		
How would you describe the consistency of your stool?	Normal	Bulky	Loose	Mucous/ Watery	
Do you get any pain when you open your bowels?	Never	Occasionally	Intermittent	Persistent	Unremitting
If yes, how severe is the pain?		Minimal	Tolerable	Intense	Excruciating
Do you take painkillers for this? If so which painkillers and how often?	No	Yes	Name of painkiller and how often?		
When you feel a desire to open your bowels do you need to go straight away?	No	Monthly	Weekly	Daily	Constantly
Have you suffered any constipation?	No	Yes			
If yes, how often do you open your bowels?	> than 4times per week	3-4 times per week	2 per week	Once per week	Less than this
Have you passed any black motions recently? If so, how often?	Never	Monthly	Weekly	Daily	Constantly
What is your current weight in Kg					
How often have you felt the desire to open your bowels urgently and were unable to?	Never	Monthly	Weekly	Daily	Constantly
Have you passed any sticky or slimy motions?	No	Rarely	Sometimes	Often	Always

How often have you had any difficulty controlling you bowels? (eg. any accidents)	Never	Monthly	Weekly	Daily	Constantly
If so, have you had to use pads?	No	Occasionally	Intermittently	Persistently	Needed operation

Have you had any bleeding when you have opened you bowels recently?	No	Rarely	Occasionally >2/week	Persistent/ Daily	Regular heavy bleeding
If you had bleeding, was any of the following required?		Laxative, iron tablets	Occasional transfusion	Frequent transfusion	Needed operation
Have you had any tests or investigations to do with bowel symptoms?	No	Yes	If so do you know what and when?		
Have you had any operations to help with bowel symptoms or problems?	No	Yes	If so do you know what and when?		

Comments:
Are any of the above symptoms you describe longstanding? (ie. started before radiotherapy). If so please mention these here with any details you feel relevant.

Any other comments:

Thank you for completing this questionnaire.

Appendix C: Presentations and Publications from this thesis

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Overview

A Systematic Review of Organ Motion and Image-guided Strategies in External Beam Radiotherapy for Cervical Cancer

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Abstract

Advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), may significantly benefit cervical cancer patients, in terms of reducing late toxicity and potentiating dose escalation. Given the steep dose gradients around the planning target volume (PTV) with IMRT planning, internal movement of organs during treatment may cause geographical miss of the target and unnecessary organs at risk (OAR) inclusion into high dose regions. It is therefore important to consider the extent and patterns of organ motion and to investigate potential image-guided radiotherapy (IGRT) solutions before implementing IMRT for cervical cancer. A systematic literature search was carried out using Medline, Embase, Cochrane Library, Web of Science, Cinahl and Pubmed. Database-appropriate search strategies were developed based upon terms for uterine neoplasms, IGRT, organ motion and target volume. In total, 448 studies were identified and screened to find 39 relevant studies, 12 of which were abstracts. These studies show that within the target volume for cervical cancer radiotherapy, uterine motion is greater than cervical. Uterine motion is predominantly influenced by bladder filling, cervical motion by rectal filling. Organ motion patterns are patient specific, with some having very little (5 mm) and others having much larger shifts (40 mm) of the target volume. Population-based clinical target volume (CTV)–PTV margins would be large (up to 4 cm around the uterus), resulting in unnecessary OAR inclusion within the PTV, reducing the benefits of IMRT. Potential solutions include anisotropic margins with increased margins in the anteroposterior and superoinferior directions, or greater PTV margins around the uterine fundus than the cervix. As pelvic organ motion seems to be patient specific, individualised PTV margins and adaptive IGRT strategies have also been recommended to ensure target volume coverage while increasing OAR sparing. Although these strategies are promising, they need significant validation before they can be adopted into clinical practice.

Key words: Cervical cancer; external beam radiotherapy; IGRT; image guidance; IMRT; organ motion

Statement of Search Strategies Used and Sources of Information

Searches were carried out using Medline, premedline, Embase, Cochrane Library, Web of Science and CINAHL; no date or language restrictions were applied. Update searches were carried out in February 2013 and included an additional Pubmed search for e-publications ahead of print. Hand searches of reference lists were also undertaken. Peer-reviewed papers and conference abstracts were sought. Database-appropriate strategies were developed around the terms for uterine neoplasms, image-guided radiotherapy, organ motion and target volume using controlled vocabulary and text word terms.

Introduction

Cervical cancer is the third most common female cancer worldwide, with 60% of patients being diagnosed under the age of 50 years. Most patients have locally advanced disease where the standard treatment is chemoradiation followed by brachytherapy, with expected cure rates of 30–90% depending on stage [1]. Pelvic chemoradiation is associated

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with severe (grade 3–4) gastrointestinal and genitourinary late toxicity rates of 6–23% [2], often leaving young patients with distressing lifelong symptoms, including malabsorption, incontinence and fistulae.

Intensity-modulated Radiotherapy for Cervical Cancer

Recent years have seen the emergence of intensity-modulated radiotherapy (IMRT) for cervical cancer, which enables highly conformal dose delivery to target volumes (cervix, uterus, parametrium and pelvic lymph nodes) with a reduced dose to organs at risk (OAR) (bowel, rectum, bladder) [3–6].

Dosimetric reports show significantly reduced doses to bowel, rectum, bladder and bone marrow with IMRT for cervical cancer compared with traditional planning approaches [7–9]. Arc therapies, such as volumetric arc therapy and RapidArc, improve OAR sparing further, with the added benefit of a shorter treatment delivery time [10,11].

Early clinical data suggest that these dosimetric observations translate to less toxicity for patients [3,6,12]. A retrospective study showed reduced late gastrointestinal toxicity from 50% to 11% (all grades) [4]. Furthermore, IMRT may potentially allow dose escalation, as well as incorporation of 'boosts' to high risk areas to improve tumour control and survival.

The Problem of Organ Motion

Pelvic organs are naturally prone to positional and volumetric changes over time. As a result, the pelvic anatomy at the time of radiotherapy planning may differ from the pelvic anatomy during treatment. These individual organ changes may result in variations in the clinical target volume (CTV) position and shape.

When conventional 'box' radiotherapy techniques are used, the irradiated volume encompasses the whole pelvis from the sacral promontory to the obturator foramen. Internal organ motion is thus less important because the CTV is more likely to remain within the irradiated volume. The complex dose distributions achieved with IMRT, with concavities and relatively steep dose gradients, mean that the potential impact of internal organ motion needs to be revisited to avoid geographical miss.

The successful implementation of IMRT relies on accurate delineation of the CTV and selection of an appropriate margin around the CTV to form the planning target volume (PTV). Consensus outlining guidelines for cervical cancer IMRT recommend that the CTV should comprise the gross tumour volume (GTV), cervix, uterus, upper vagina, parametrium and pelvic nodes (obturator, common, internal and external iliac) [13]. The CTV–PTV margin has two components: the internal margin, which accounts for organ motion, and the set-up margin, which accounts for patient set-up and delivery errors [14].

Knowledge of organ motion within the CTV and the influences of adjacent organ filling (bladder, rectum, bowel) is required to determine an appropriate internal target volume (ITV). Margins should be evidenced based, ideally, utilising data from the treating institution. They should be large enough to minimise/prevent geographical miss, yet not too large or the clinical advantages of IMRT will be minimised [15].

Image-guided radiotherapy (IGRT), with its many aspects, including patient set-up, preparation, margin use and on-treatment imaging, aims to reduce geometric uncertainty. At a time when IMRT for cervical cancer is being adopted, the most reproducible and clinically practical IGRT methods must be determined.

Aims

The aims of this review are to evaluate external beam radiotherapy and the patterns and extent of pelvic interfraction and intrafraction organ motion reported for cervical cancer. Correlations of motion with bladder and rectal filling and IGRT solutions are reviewed.

Materials and Methods

Information Sources and Search Strategy

Searches were carried out using Medline, premedline, Embase, Cochrane Library, Web of Science and CINAHL; no date or language restrictions were applied. Update searches were carried out in February 2013 and included an additional Pubmed search for e-publications ahead of print. Hand searches of reference lists were also undertaken. Peer-reviewed papers and conference abstracts were sought. Database-appropriate strategies were developed around the terms for uterine neoplasms, image-guided radiotherapy, organ motion and target volume using controlled vocabulary and text word terms.

Eligibility Criteria

English and French language studies examining interfractional and intrafractional organ motion and IGRT techniques during external beam radiotherapy for definitive cervical cancer treatment were included. With the focus being on IMRT, brachytherapy studies were excluded. Postoperative cervical and endometrial cancer studies were excluded due to differing anatomies.

The quality and eligibility of the studies were assessed using three criteria: (i) Was the spectrum of patients included representative of those in clinical practice? (ii) Were the methods described in sufficient detail to permit replication of the study? (iii) Were the outcomes measured appropriate to the aims of the study?

Initial abstracts were screened for relevance by two authors (RJ, CAP), followed by assessment for eligibility of full-length articles.

Results

Outcomes of the systematic search are illustrated in Figure 1. Overall, 39 relevant studies (12 of which were

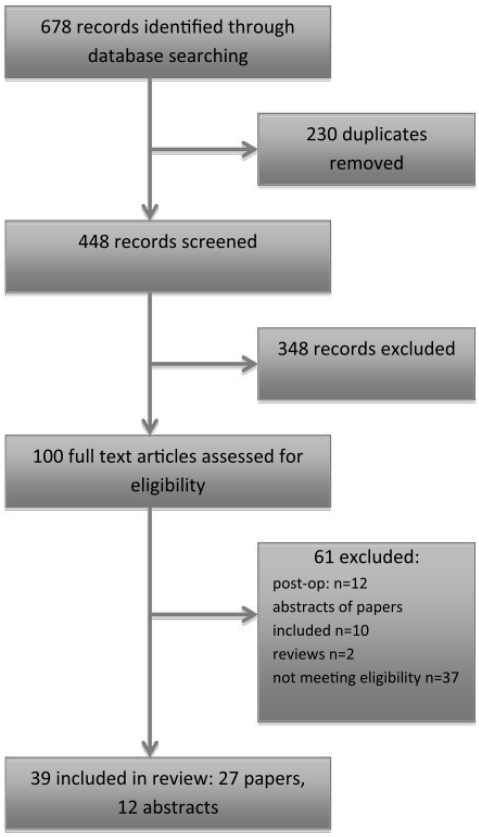

Fig 1. Systematic search outcomes.

conference abstracts) were included. Fourteen studies were prospective studies, although most were retrospective analyses of previously acquired imaging. Aspects covered by the studies overlapped, as detailed in Table 1.

Organ Motion: Interfraction

Cervix Motion

Eleven studies, including a total of 160 patients, examined interfraction cervix motion, with four using computed tomography-based imaging (computed tomography/megavoltage computed tomography/four-dimensional computed tomography) [19,20,23,24], two using magnetic resonance imaging (MRI) [21,22] and five using portal imaging with fiducial markers [16–18,25,26]. Motion was measured either at the cervix itself (centre of mass, cervical os, cervical boundaries) or by using fiducial markers as a cervical surrogate. The results are presented in Table 2.

Most studies showed greater cervical motion in the anteroposterior and superior–inferior directions, with less seen laterally. The heterogeneous nature of the data collection makes direct comparisons difficult. Those studies using fiducial markers reported smaller movements than other methods. Interfraction mean cervical movements ranged from 2.3 to 16 mm in the anterior–posterior, 2.7 to 8 mm in the superior–inferior and 0.3 to 10 mm in the lateral directions.

Table 1
Summary of studies

	No. of studies	References
Interfractional motion:		
- Cervix	11	[16] [17] [18] [19] [20] [21] **[22]** **[23]*** [24] * **[25]*** **[26]***
- Uterus	6	[20] [21] **[22]** **[23]*** [27] [28]
- Lymph Nodes	2	[29] * [30] *
- Clinical target volume motion	1	[31]
Intrafractional motion	7	[18] [21] **[23]*** [32] **[33]*** **[34]** **[35]***
Correlation with bladder filling	12	[19] [20] [21] **[22]** [31] [32] [36] [37] [38] [39] [40] * [41]
Correlation with rectum filling	5	[21] **[22]** [31] [39] [40] *
Patient positioning	6	[27] **[42]** **[43]** **[44]** **[45]** **[46]**
Patient preparation	0	
Margins for organ motion	14	[16] [17] [20] [21] **[22]** **[23]*** [24] * [29] * [30] * [31] **[47]*** [48] * [49] [50]
Imaging modality and marker use	8	[16] [17] [20] [21] [24] * **[25]** * **[26]** * [31]
Online and offline strategy	0	
Adaptive and individualised strategies	4	[51] [52] **[53]*** [54]

References in bold refer to prospective studies.
* Abstract form.

Uterine Motion

Five studies including 84 patients reported interfraction uterine motion [20–23,27,28] (Table 2). Overall, the uterus moved more than and independently of the cervix. The uterine fundus had more motion than the uterine canal [21].

A further study reported uterine angle rotations of 30° or more in 18% of patients [28]. The degree of rotation was higher in patients under the age of 60 years. Eleven per cent of patients who had an anteverted uterus at planning became retroverted during treatment [28]. An individual uterine rotation of 91° was reported, with the fundus moving up to a maximum of 48 mm in the anterior–posterior direction [22].

Lymph Node Motion

Interfraction nodal motion was assessed in two abstracts [29,30]. Assessment of the elective nodal CTV (obturator

Table 2
Interfraction organ motion

Target measured	Reference	Patient no.	Modality	Imaging frequency	Measurement method	Average movement (mm)				Maximal movement (mm)		
						Statistic used	Anterior–posterior	Superior–inferior	Left–right	Anterior–posterior	Superior–inferior	Left – right
Cervix motion	[16]	10	EPID & seeds	Daily	Seed motion	Mean of means	1.7	3.0	−1.3	NR	NR	NR
						Systematic motion	3.5	4.1	3.7			
						Random motion	3.9	3.7	2.2			
	[18]	10	kV portal & seeds	Daily	Seed motion	Mean (SD)	4.2 (3.5)	4.1 (3.2)	1.9 (1.9)	18	18	14
	[26]	9	kV portal & seeds	Daily	Seed motion	Mean	−1.2	2.6	−1.5			
						Systematic motion	10.0	5.1	4.1			
						Random motion	6.8	4.9	2.8			
	[24]	15	MVCT and seeds	Daily	Seed motion	Mean (SD)	7.6 (3.4) (all directions)			0.7–25 mm		
	[25]	12	kV portal, CBCT and seeds	Daily portal and biweekly CBCT	Seed motion	Systematic motion	7.9	6.9	6.6			
						Random motion	6.2	4.9	2.2			
	[17]	17	Portal films	Weekly	Ring motion	Median	16	8	10	23	36	23
	[21]	20	MRI	Weekly	Cervical os	Grand mean	2.4	1.5	NR	NR	NR	NR
						Mean range	11.2	11.3				
	[22]	33	MRI	2 days	Post-inferior cervix	Median	3	3	0	19	12	3
						Mean (SD)	4.1 (4.4)	2.7 (2.8)	0.3 (0.8)			
	[23]	8	4DCT	Weeks 1, 3, 5	Post-inferior cervix	Mean (SD)	7.9 (6.8)	3.8 (4.0)	3.9 (3.8)			
	[19]	16	CT	Weekly	Centre of mass	Mean max	21	16	8	25	33	14
					Perimeter	Mean max	Anterior: 17	Superior: 23	Left: 9	Anterior: 29	Superior: 35	Left: 18
							Posterior: 18	Inferior: 13	Right: 8	Posterior: 63	Inferior: 30	Right: 18
	[20]	10	MVCT	Daily	Boundary shifts	Mean (SD)	Anterior: 0.4 (10.1)	Superior: 2.2 (8.0)	Left: −3.5 (6.9)	NR	NR	NR
							Posterior: −3.0 (6.9)	Inferior: 0.5 (5.0)	Right: 0.2 (4.5)			
Uterine motion	**[22]**	33	MRI	2 days	Superior–anterior fundus	Median	5	5	0	48	32	5
						Mean (SD)	7 (9)	7.1 (6.8)	0.8 (1.3)			
	[23]	8	4DCT				14.2 (10.5)	9.5 (6.6)	6.5 (4.8)	NR	NR	NR

				Weeks 1, 3, 5	Superior fundus	Mean (SD)						
	[21]	20	MRI	Weekly	Uterine fundus	Grand mean	−4.6	7.8	NR	NR	NR	NR
						Mean range	14.5	24.4				
					Uterine canal	Mean	−4.8	5.7	NR	NR	NR	NR
						Mean range	13.1	15.7				
	[20]	10	MVCT	Daily	Boundary shifts	Mean (SD)	Anterior: 3.3 (11.9)	Superior: 6.1 (11.6)	Right: −0.6 (7.5)			
							Posterior: 0.3 (11.7)	Inferior: 5 (11.2)	Left: 0.7 (8.1)			
	[27]	13	CT (using SBDS)	Weekly	Distance from isocentre	Mean	Anterior: −1.1	Superior: −6.1	Right: −2.6	Anterior: 20	Superior: 45	Left: 28
							Posterior: −4.3	Inferior: NR	Left: −1.2	Posterior: 28	Inferior: NR	Right: 21
Lymph node motion	[29]	17	MRI	Weekly	Margin from enlarged node	Mean	Anterior: 7 Posterior: 8	Superior: 7 Inferior: 9	Right: 5 Left: 8	NR	NR	NR
	[30]	13	CT	At 40 Gy	Nodal CTV translational	Median	13–15 (direction not specified)			30 (direction not specified)		
CTV motion	[31]	10	CBCT	Daily	CTV centroid position	Mean (SD)	3 (5)	−4.6 (3.9)	−0.28 (1.3)	18.9	−15.3	3.5

References in bold refer to prospective studies.
EPID, electronic portal imaging device; kV, kilovoltage; MVCT, megavoltage computed tomography; CBCT, cone beam computed tomography; MRI, magnetic resonance imaging; 4DCT, four-dimensional computed tomography; SBDS, small bowel displacement system; CT, computed tomography: AP, anterior–posterior: SI, superior–inferior; LR, left–right; NR, not reported; SD, standard deviation.

Larger (>115 ml) baseline bladder volumes required a greater (12 mm) inferior CTV–ITV margin than the 7 mm required for those with smaller volumes (<115 ml).

Impact of Rectal Filling on Organ Motion

Five studies including 103 patients reported the impact of rectal filling on cervix–uterine motion, particularly anterior–posterior and superior–inferior movements [21,22,31,39,40]. A greater influence on cervical and upper vaginal motion compared with the uterus was noted [22]. Significant correlations between rectal volume and anterior–posterior shifts in the GTV, CTV and upper vagina were noted, with correlation coefficients of 0.71, 0.79 and 0.66, respectively [22,40]. In one individual, a 19 mm anterior–posterior shift in cervix position resulted from a rectal diameter change from 71 to 34 mm [22]. A 6 cm^3 decrease in rectosigmoid filling corresponded to inferior motion of the uterine canal (3.6 mm) and cervical os (2.6 mm) [21].

A retrospective analysis showed those with pretreatment rectal volumes >70 cm^3 required greater posterior and inferior internal margins (20 and 12 mm, respectively), than those with a smaller baseline rectal volume (<70 cm^3) (10 and 6 mm) [39]. Although daily variations in rectal volumes were reported (ranges between 21 and 150 cm^3), no systematic change during the course of treatment was identified [21,40].

Image-guided Radiotherapy Solutions

Many studies relevant to IGRT solutions were identified and were categorised as follows.

Patient Positioning and Preparation

Prone positioning with use of a belly board device (allowing superior and anterior displacement of the small bowel) was compared with the supine position in three studies including 46 patients. Prone positioning using a 'limited' arc technique in 16 patients (nine having definitive radiotherapy) reduced small bowel volumes receiving >45 Gy (V45) from 19 to 12.5%, but increased large bowel volumes receiving >50 Gy from 6.9 to 14.8% [42]. Similarly, using a seven-field IMRT technique, small bowel V45 was reduced from 20.3 to 13.7%, although V40 rectum increased from 69.5 to 79.4% [43]. Prone positioning did not significantly reduce small bowel doses with conformal planning [45].

The use of the small bowel displacement system, a Styrofoam compression device placed under the abdomen in the prone position in addition to a bellyboard, was reported in three studies including 33 patients [27,44,46]. With IMRT treatment, small bowel displacement system use reduced the mean small bowel volume within the PTV from 67.9 to 16.8% [46].

There were no studies that evaluated bladder and rectal preparation protocols as a means of reducing cervix–uterine motion or doses to OARs.

Margins for Organ Motion

Nine studies including 176 patients proposed internal margins to allow for cervix–uterine motion (Table 4). Isotropic internal margins ranging from 15.3 to 21 mm around the CTV were suggested, although most studies suggested anisotropic margins ranging from 12 to 32 (anterior–posterior); 8 to 20 (superior–inferior) and 7 to 17.5 mm (left–right).

Three further studies used pre-set margins to assess on-treatment CTV coverage. The use of a 15 mm isotropic margin failed to encompass the entire CTV in 32% of fractions. However, the mean volume 'missed' was 4 cm^3 [31]. The use of an anisotropic (20 mm superior–inferior and anterior–posterior margins, 10 mm left–right) showed insufficient CTV coverage in 13% of fractions [48]. Conversely, dosimetric analysis using 5 and 20 mm PTV margins with IMRT suggested that a 5 mm margin allowed for pelvic organ motion with adequate dose delivered to 98% of the CTV in 95% of patients, using weekly MRI scans. Of note, one patient had significant underdosing due to unpredictable target motion [49].

Site-specific non-uniform margins were proposed, with up to 4 cm around the uterine fundus and 1.25 cm around the cervix [21]. A further study modelled 1, 2.4 cm and 'tapered margins' (2.4 cm around the fundus narrowing to 1 cm around the cervix) combined with different 'motion' models. A 1 cm margin led to insufficient fundal coverage of about 5 Gy as an effect of motion (10% of the prescribed dose). Use of the tapered margin restored coverage, with slight increases in bowel and rectal doses (V50.5 from 17.8 to 19.0, and 46.2 to 48.3, respectively) [50].

Regarding nodal internal margins, the evidence is limited. The above mentioned abstracts [29,30] gave contradictory advice, with a 1 cm margin deemed as sufficient in one study and insufficient in another. Consensus guidelines suggest a 7 mm CTV–PTV margin for nodal volumes [13].

Imaging Modality and Marker Use

Imaging modalities were not directly compared in any study, although three studies reported inter-observer variability as a measure of reproducibility. Using MRI inter-observer mean differences of −0.66 to 0.25 mm were reported when determining uterine position [21]. Mega-voltage computed tomography use was found to have inter-observer variability of −0.4 to 1.0 mm at the cervix and 0.2 to 0.9 mm at the uterus [20]. Using CBCT, the mean inter-observer variability led to differences in margins required of 4.1 mm [31].

'Fiducial' markers (tantalum, gold and polymeric) were used in five studies. Good marker visualisation was reported with planar kilovoltage imaging (90% visualised) and CBCT (100%) [25]. However, marker loss rates of 14–42% were found [16,26].

Offline versus Online Image-guided Radiotherapy Solutions

No studies directly compared offline versus online imaging strategies for the management of organ motion.

Individualised and Adaptive Strategies

Four studies discussed the use of individualised strategies, proposed around the concept of patient-specific

Table 4
Suggested margins for organ motion

Reference	Patient no.	Imaging modality	Imaging frequency	Margin around	Margins suggested (mm)		
					Anterior–posterior	Superior–inferior	Left–right
[20]	10	MVCT	Daily	Cervix	Anterior: 17 Posterior: 12	Superior: 15 Inferior: 9	Left: 9 Right: 8
[23]	8	4DCT	Weeks 1, 3 and 5	Cervix	19	10	9
[21]	20	MRI	Weekly	Cervical Os	10–15 (all directions)		
[24]	15	MVCT with gold seeds	Daily	Fiducial marker COM	17 (all directions)		
[20]	10	MVCT	Daily	Uterus	Anterior: 19 Posterior: 19	Superior: 20 Inferior: 19	Left: 13 Right: 13
[23]	8	4DCT	Weeks 1, 3 and 5	Uterus	32	20	14
[46]	16	CT	Weeks 2 and 4	Uterus	21.0 (10.1) (range of 10.1–30.8)		
[21]	20	MRI	Weekly	Uterine fundus	10–40 (all directions)		
[21]	20	MRI	Weekly	Uterine Canal	10–12.5 (all directions)		
[29]	17	MRI	Weekly	Enlarged lymph nodes	Anterior: 7 Posterior: 8	Superior: 7 Inferior: 9	Right: 5 Left: 8
[39]	20	MRI	Weekly	GTV	Anterior: 12 Posterior: 14	Superior: 4 Inferior: 8	Left: 11 Right: 12
[16]	10	EPID with seeds	Daily	CTV	12	12.1	10.2
[31]	10	CBCT	Daily	CTV	15.3 (grand mean) 35 to encompass all volumes all fractions		
[22]	33	MRI	2 days	CTV	15	15	7
[17]	17	Portal films and metallic ring	Weekly	CTV	22.9	15.4	17.5
[39]	20	MRI	Weekly	CTV	A: 24 P: 17	S: 11 I: 8	L: 16 R: 12

References in bold refer to prospective studies.
MRI, magnetic resonance imaging; RT, radiotherapy; kV, kilovoltage; 4DCT, four-dimensional computed tomography; SD, standard deviation; NR, not reported; CI, confidence interval; CTV, clinical target volume.

uterine motion with variable bladder filling [51–54]. Non-adaptive and adaptive strategies were compared in one study [52], initially using a 'non-adaptive' approach of a 'model-based ITV' formed by the CTV delineated on pre-treatment computed tomography scans with a full and empty bladder. This allowed PTV margins of 7–10 mm to account for organ motion as opposed to the 38 mm PTV margins required for a population-based approach. As a result, the average PTV volume reduced by 48%, subsequently reducing bladder and rectal volumes within the PTV by 5–45% and 26–74%, respectively.

The study went on to examine adaptive strategies using plan of the day. This concept uses the formation of a library of plans per patient. Each day an appropriate plan is chosen based on imaging that day. In the case of this study, plan libraries were generated using scans with variable bladder filling (and hence different uterine positions) and the plan of the day chosen was based on bladder volume on ultrasound. They showed that the adaptive approach increased OAR sparing compared with non-adaptive methods, but the precise amounts were not quantified. The plan of the day strategy has been shown to be clinically reproducible in 21 patients [53].

Another individualised strategy proposed is the 'optimised PTV margin' where 758 landmarks are placed over the planning CTV and vectors from these landmarks to the on-treatment CBCT CTVs are measured, forming an optimised PTV margin with high target coverage with reduced OAR volumes in the PTV. So far this has only been modelled retrospectively [54].

Discussion

This systematic review summarises the results of 39 studies that highlight the issue of interfraction and intrafraction cervix–uterine motion and the influence of bladder and rectal filling during radiotherapy for cervical cancer. Aspects of IGRT that may be used to account for this motion are examined. The results could help inform future IMRT planning and verification protocols for cervical cancer.

Interfraction cervical and uterine motion is significant. The uterus is more mobile than the cervix and prone to both rotational and translational shifts. Studies that have examined both uterine and cervical motion showed greater ToU motion in the anterior–posterior (maximal 48 mm) and superior–inferior (maximal 32 mm) directions compared with cervical motion in the anterior–posterior (maximal 19 mm) and superior–inferior (maximal 12 mm) directions [22]. Bladder filling has more impact on uterine motion and

rectal filling more impact on cervical and vaginal motion (see Figures 2 and 3).

Intrafraction motion is less pronounced than interfraction motion and both will be accounted for within internal margins. The issue of intrafraction motion may become less important as delivery times shorten with the use of arc therapies.

A direct comparison between studies of uterine–cervix movement is difficult, as each study used different methods to measure motion, reported different statistics and used different instructions to compute their margins. Isotropic internal margins of 15.3–21 mm and anisotropic margins of up to 32 mm anterior–posterior, 20 mm superior–inferior and 17.5 mm laterally were suggested, implying that commonly used CTV–PTV margins of 1–1.5 cm may be insufficient [3,6,16].

Non-uniform margins, with a larger uterine margin and a smaller cervical margin, would potentially allow for the differences in the movement observed. However, there is ongoing debate as to whether the uterine fundus should be included within the CTV, as there are few data to suggest it is a common site for microscopic spread in cervical cancer. This important issue needs addressing, given that the fundus is the most mobile CTV component and therefore the margins required to account for its motion are so much greater.

Despite showing that bladder filling can influence uterine motion, no studies have investigated interventions to standardise rectal or bladder volumes in cervical cancer. Studies in other pelvic tumour sites, such as post-hysterectomy endometrial, bladder and prostate cancer [55–57] show that despite strict drinking protocols, a constant bladder volume is difficult to maintain. Bladder volume has been shown to systematically reduce during treatment, probably due to reduced bladder capacity and radiation cystitis [20,21,37], adding to the problem of maintaining a standardised bladder volume. Many centres adopt a 'comfortably full bladder' approach, in order to spare small bowel within the treatment field.

As well as internal margins, consideration of set-up margins to create a PTV is also necessary when developing an IMRT/IGRT protocol, although that is beyond the scope of this review. Two studies using daily CBCT suggested set-up margins of up to 11.6 mm (superior–inferior), 9.6 mm (left–right) and 8.2 mm (anterior–posterior) [58] and 8.3 mm (superior–inferior), 9.1 mm (left–right) and 5.5 mm (anterior–posterior), which would be significant additions to internal margins [59]. We would recommend that centre-specific set-up margins are determined, as they

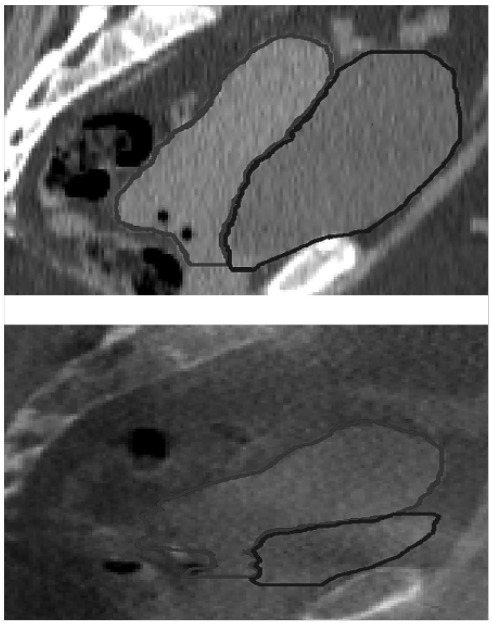

Fig 2. Uterine position with bladder filling (uterus in red; bladder in blue). The initial figure shows the uterine position at planning with a bladder volume of 550 ml. The second figure shows on-treatment cone beam computed tomography of the same patient with a bladder volume of 75 ml, with which the uterine position has moved both inferiorly and anteriorly.

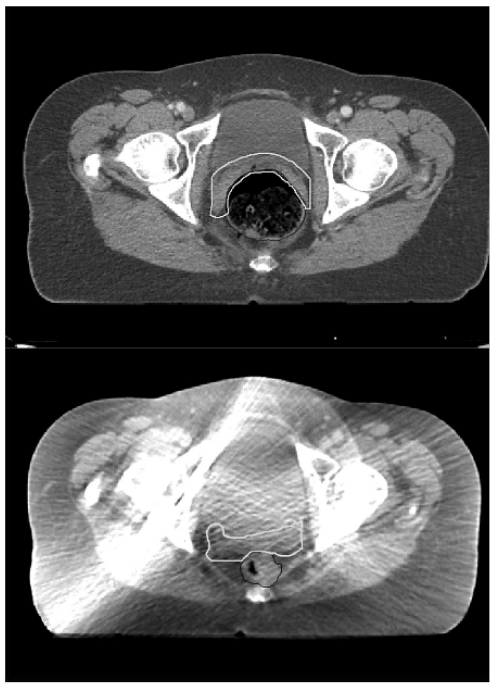

Fig 3. Vaginal position with rectal filling (rectum in brown; vaginal clinical target volume in turquoise). The initial figure shows the vaginal position at planning with a distended rectum. The second figure shows on-treatment cone beam computed tomography of the same patient with a much smaller rectum, with which the vaginal position has moved posteriorly.

are dependent on patient positioning, immobilisation and imaging protocols.

Although prone positioning has been shown to reduce small bowel within the treatment field, it is also associated with considerable set-up errors (up to 15 mm) caused by anterior–posterior sacral rotations (−14° to 11.5°) [60]. Increasing PTV margins to account for this possibly negates the benefits of small bowel sparing.

Daily online imaging may reduce both internal and set-up margins, yet to date no studies have directly compared online versus offline modalities in this setting. According to UK National Guidance [61], an offline strategy is probably insufficient for cervical cancer IMRT, given the unpredictable nature of uterine movement; this was confirmed by the significant random error noted in this review [16,21,25].

However, even with daily online imaging, simple translational shifts are probably insufficient to compensate for the complexity motion of this target volume, which not only comprises pelvic organs that move independently of each other and are influenced by adjacent organs, but also relatively static pelvic nodal volumes.

Individualised adaptive approaches are probably important avenues of research in cervical cancer given the complex, patient-specific nature of CTV organ movement, and are being successfully implemented in other tumour sites, such as bladder cancer [62,63] Accounting for uterine rotations within the volume creates a particular challenge and adaptive approaches may offer solutions. Further promising individualised strategies are being assessed but have been excluded from this review as they remain in their conceptual stages and further validation is required.

A separate but important issue beyond the scope of this review is that of tumour regression. Significant reductions in GTV during treatment is reported [19,64,65], with one study showing a mean reduction of 62.3% after 45 Gy [19]. Given these findings, the question of adaptive replanning during treatment arises. To date there is limited evidence to promote this.

Although our systematic search was comprehensive, there are limitations. Studies were limited to English and French. Studies relating to brachytherapy in cervical cancer were excluded, which may be important when considering late toxicity. Postoperative studies were excluded, as it was felt the pelvic anatomy would be significantly different.

The areas for future research identified include the use of bladder and rectal filling protocols to promote consistency of target volume position, the use of 'tapered' margins and the benefits of individualised adaptive strategies.

Conclusions

Pelvic organ motion is patient specific and population-based PTV margins may be larger than required for most patients and may result in unnecessary OAR irradiation. Individualised margins offer potential solutions to maximise CTV coverage while minimising OAR dose. Further validation of these adaptive strategies with clinical outcomes is necessary before they can be adopted into clinical use.

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Oral Presentation at UKRO – prize certificate

UKRO

We confirm that

Dr Rashmi Jadon

has been awarded a highly commended prize in the UKRO 2015 proffered paper competition

'A prospective study of patient-reported late bowel toxicity following pelvic radiotherapy'

At Ricoh Arena, Coventry

8 – 10 June 2015

Professor Andy Beavis
President of UKRO

Poster Viewing Abstract 2557; Table Dose percentage related to the prescribed dose (5 Gy)

A)								
		D0.1 cc	**D1 cc**	**D2 cc**	**D5 cc**	**D10 cc**	**V5 Gy**	**AUC**
Bladder	**Basal**	100.9 ± 27	79.4 ± 18.6	70.7 ± 18.1	52 ± 26.6	38.4 ± 26.7	0.4 ± 0.5	56 ± 35.5
	Post	116.6 ± 48.3	88.6 ± 23.6	79.5 ± 19.9	65.6 ± 17.9	48.5 ± 25.2	1.1 ±2.4	84.3 ± 81
	P	.3003	.0413	.0186	.0157	.0235	.1707	.0157
Rectum	**Basal**	141.1 ± 23.4	112.7 ± 15	101.2 ± 14.5	82.1 ± 13.6	65.7 ± 12.2	2.51 ± 2.1	93.8 ± 49.5
	Post	125.2 ± 11.9	101.4 ± 12.6	90.3 ± 12.1	72.2 ± 10.6	56.2 ± 10.1	1.32 ± 0.8	63.1 ±23.4
	P	.011	.0052	.0035	.0023	.0019	.0035	.0029
B)								
		D2 cm^2	**D5 cm^2**	**D10 cm^2**	**D15 cm^2**	**D20 cm^2**	**A5 Gy**	**AUC**
R. surface	**Basal**	133.5 ± 14.3	115 ± 16.3	91 ± 18.9	70.9 ± 15.1	57.2 ± 12	8.2 ± 3.4	124 ± 29
	Post	120 ± 15.5	103.4 ± 16.3	78.8 ± 13.1	62.9 ±11.8	50.1 ± 16.5	5.7 ± 2.5	102 ± 26.6
	P	.0052	.0063	.0029	.0035	.0063	.0035	.0029

Materials/Methods: Fourteen pairs of brachytherapy planning CT scans derived from 11 patients were re-segmented and re-planned using the same parameters. All patients underwent brachytherapy with vaginal cylinders. Gas pocket removal was carried out with a rectal tube. A CT-set before and after gas removal, with a rectal tube, were acquired without any other modification. A CT-based plan was computed for each image set. Metrics derived from bladder and rectum dose-volume histograms (DVH) and dose-surface histograms (DSH) were extracted. The area under the curve (AUC) was calculated to describe the integral absorbed dose. Non-parametric paired non-parametrical tests were performed (Kruskal-Wallis and Wilcoxon signed-rank test).

Results: Rectum volume decreased significantly from 77.8 ± 45 cc to 55.43 ± 17.6 cc ($p = 0.0052$) after gas removal. Such volume diminution represented a significant reduction on all rectal DVH parameters analyzed but $D_{25\%}$ and $D_{50\%}$. Rectum DSH parameters results were similar to DVH. A significant increase on DVH metrics was observed despite a non-significant increase of the bladder volume.

Conclusions: Gas pocket removal is a simple and inexpensive maneuver that decreases the rectal dose thus it could improve the therapeutic ratio. Changes on bladder are deemed to be linked with the increase on urine volume due to the interval between scans.

Author Disclosure: S. Sabater: None. I. Andres: None. M. Sevillano: None. R. Berenguer: None. S. Machin-Hamalainen: None. M. Arenas: None.

2558

The Impact of Rectal and Bladder Filling on Internal Target Volume Margins in Postoperative Endometrial and Cervical Cancer Patients

R. Jadon,[1] C.L. Hanna,[1] N. Palaniappan,[1] E. Hudson,[1] M. Evans,[1] H. Maloney,[1] A. Mazurek,[2] and J. Staffurth[3]; *[1]Department of Clinical Oncology, Velindre Cancer Centre, Cardiff, United Kingdom, [2]Department of Medical Physics, Velindre Cancer Centre, Cardiff, United Kingdom, [3]School of Medicine, Cardiff University, Cardiff, United Kingdom*

Purpose/Objective(s): Vaginal vault motion poses an important challenge during IMRT for post-operative endometrial and cervical cancer (post-op) patients. Large PTV margins, of which internal target volume (ITV) margins are the major component, are required to allow for this motion, especially in the anterior-posterior (AP) direction. This study assesses patterns of rectal and bladder filling in this setting to determine their correlation with required ITV margins and identify future interventional strategies.

Materials/Methods: Image sets, comprising a pre-treatment CT (pre-CT) and 5-6 CBCT scans, for 10 post-op patients were retrospectively analyzed. No specific bladder or rectal filling protocols had been used. Each CBCT was co-registered with the respective pre-CT using a mutual information algorithm. On each scan the vaginal CTV, rectum and bladder were outlined. For each CBCT an anisotropic margin was generated around the pre-CT CTV such that the CBCT CTV was fully encompassed in 6 directions (ant, post, sup, inf, left and right). Rectal filling was assessed by 4 measures: rectal volume (RV); AP rectal diameter (RD) at S4/S5 border; RD at the tip of coccyx and maximum RD at any point. Rectal distension was defined as RD $\geq$ 4 cm at any point. Patterns of bladder and rectal filling were observed and correlated with the generated ITV margins.

Results: Large interfractional bladder variations were observed (median 247 cc [range, 197-528 cc]), though did not correlate with margin size. Rectal distension was noted at least once in all patients, and in 5/10 pre-CTs and 45/57 CBCTs. No trend was found towards decreasing RD over time and 6 patients had a larger RD in week 4 than in week 1. Variations in rectal filling between pre-CT and CBCT scans strongly correlated with margin size. There were statistically significant correlations (all $p < 0.001$) between posterior margins and variations in RV ($R = -0.80$), maximal RD ($R = -0.74$), and RD at the coccyx ($R = -0.86$). Anterior margin correlated with RD changes at coccyx ($R = 0.65$).

Conclusions: AP margins required to allow for vaginal motion are sizeable and limit the benefits of IMRT in this setting. Required margins are associated with inconsistent rectal filling between pre- and on-treatment imaging. Maintenance of consistent rectal filling using dietary advice, laxatives or enemas should be investigated to reduce these margins.

Author Disclosure: R. Jadon: None. C.L. Hanna: None. N. Palaniappan: None. E. Hudson: None. M. Evans: None. H. Maloney: None. A. Mazurek: None. J. Staffurth: None.

Poster Viewing Abstract 2558; Table Margins required

	Margin Size (mm)						
	Day 1 Median (min-max)	Day 2 Median (min-max)	Day 3 Median (min-max)	Week 2 Median (min-max)	Week 3 Median (min-max)	Week 4 Median (min-max)	Overall margin to cover 95% of CBCT CTVs
Ant	8 (1-22)	10 (1-20)	13.5 (4-19)	10 (1-18)	11 (1-19)	10 (1-15)	19 mm
Post	7.5 (4-28)	8 (4-29)	8 (2-23)	10 (4-29)	8 (4-31)	9 (6-29)	29 mm
Sup	1.5 (1-8)	4 (1-24)	1.5 (1-8)	2 (1-8)	1.5 (1-4)	4 (1-10)	10 mm
Inf	5 (1-10)	4 (1-10)	6 (1-12)	2 (1-15)	7 (1-17)	2 (1-15)	15 mm
Left	2 (1-4)	2 (1-8)	2 (2-6)	2 (1-4)	2 (2-6)	2 (2-6)	6 mm
Right	2 (1-4)	2 (1-6)	2 (2-8)	2 (2-6)	2 (2-8)	2 (2-2)	6 mm

2559

Outcomes of Patients With Carcinosarcoma Treated With Combined External Beam Radiation, Brachytherapy, and Chemotherapy

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Purpose/Objective(s): Carcinosarcoma represents a rare, aggressive subtype of endometrial cancer and the optimal adjuvant treatment is unclear. We sought to characterize outcomes of patients treated for this

illustrates a small disparity from the reference whereas the fourth category show strong differences. Our hypothesis is that these categories can be used to identify patients in need of treatment adaptation. The Figure 1 shows the V95(%) parameter extracted from either the planning CT or the daily CBCT plan, as function of the average γ value for all beams. This average γ value is evaluated on the whole EPID image (Figure 1a) or the projected PTV1 image (Figure 1b). The horizontal dash line represent the dose tolerance for PTV1 (99%). There is a correlation between the average γ and the PTV1 V95(%) but the projected PTV1 on the EPID image does provide additional information regarding the degree of error. However, the V95(%) variation from the original and deformed contours is related to the degree of error as indicated in Table 1.

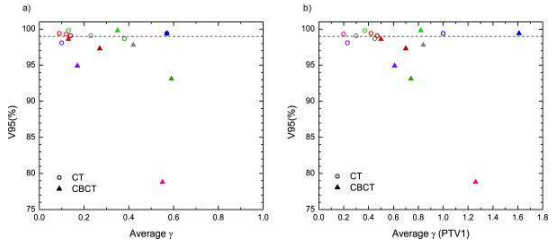

Table 1

Category	Nb of cases	$\left(\frac{V95(\%)_{CT} - V95(\%)_{CBCT}}{V95(\%)_{CT}}\right)$
1	4	1.47
2	2	3.49
3+	2	10.32

Conclusion: In summary, we demonstrated that PTV1 projection on the EPID plan does not provide new information on the plan deterioration. However, this method was more sensitive to anatomical changes and could be used as an indicator instead of the mean γ on the whole EPID image. In the following steps, the organs at risk projections will be evaluated to verify if they do provide new information. This approach is valuable for the treatment quality, but does not increase the dose to the patient or the time required for treating a fraction. Image acquisition and analysis can be easily automatized to further minimize the impact on the clinical workload.

EP-1819

Plan of the Day is the optimal approach to address organ motion for cervical cancer IMRT

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Purpose or Objective: Intensity modulated radiotherapy (IMRT) for cervical cancer is challenging due to organ motion within the CTV, comprising cervix, uterus, vagina, parametrium and pelvic nodes. Large CTV-PTV margins to compensate for this motion result in large volumes of organs at risk (OARs) within the PTV, negating the benefits of IMRT. Furthemore, there is significant intra-patient variation in organ motion therefore individualised adaptive strategies may be appropriate.

One option is Composite Strategy (CS) where a composite is formed from CTVs using planning scans and initial on-treatment cone beam CT (CBCT) scans. A second is Plan of the Day (PotD), where a plan library is created and the most appropriate plan chosen each day based on CTV position.

Material and Methods: Retrospective analysis of planning scans (full bladder (FB) and empty bladder (EB)) and on-treatment CBCTs for patients treated with radical radiotherapy for cervical cancer was performed.

CBCT scans were rigidly co-registered with FB scans on Oncentra Masterplan. On each scan the primary CTV (pCTV) comprising cervix, uterus, vagina, parametrium was outlined. On the FB scan bowel bag, bowel loops, rectum and bladder were outlined as OARs.

We modelled:

1) Standard margin: a 2cm isotropic CTV-PTV margin around the pCTV

2) CS: a composite was formed from pCTVs from FB, EB, and day 1-3 CBCTs, with a 1cm margin to PTV

3) PotD: a 3-plan library was created using pCTVs from FB and EB scans. A third mid-volume CTV was generated using deformable image registration on Velocity (v3.1, Varian Medical Systems) and custom software developed in Matlab. A 1cm margin was added to each CTV to generate PTVfull, PTVmid and PTVempty. If none of the 3 plans covered the CTV then a 'back-up' standard 2cm margin was chosen.

The remaining CBCT scans for each patient were used to compare PTV volumes, CTV coverage, and OARs within PTV. Statistical differences were tested using Mann Whitney-U.

Results: 141 scans were assessed for 14 patients (FB, EB and 7-13 CBCTs each). The table below shows mean measures of the 3 strategies. The 3-library PotD could only be used in 58% of scans assessed, and the back-up plan was used for the remainder. Despite this PotD significantly reduced mean bowel, bowel bag, rectum and bladder in the PTV, whilst maintaining CTV coverage.

		Mean PTV Volume (cc)	Mean CTV coverage (%)	Mean Bowel in PTV (cc)	Mean Bowel bag in PTV (cc)	Mean Rectum in PTV (%)	Mean Bladder in PTV (%)
Standard margin		1061.65	99.6	111.8	366.5	71.9	59.3
Composite Strategy		798.36	99.9	84.8	295.4	62.8	55.45
	Change from standard margin	Reduced 24.8%	Improved 0.19%	Reduced 24.1%	Reduced 19.4%	Reduced 12.7%	Reduced 6.5%
	p-value (compared with standard margin)	**0.007**	0.137	0.265	0.15	0.137	0.7
Plan of the Day Strategy		765.2	99.6	68.3	226.2	49.9	43.44
	Change from standard margin	Reduced 27.9%	No change	Reduced 38.9%	Reduced 37.7%	Reduced 30.5%	Reduced 26.7%
	p-value (compared with standard margin)	**0.012**		**0.05**	**0.006**	**0.000**	**0.027**

Conclusion: Adaptive strategies show promise. PotD, even when the plan library was only used in 58% of scans, increased OAR sparing compared with CS. Dosimetric analysis of these strategies with IMRT planning is ongoing.

EP-1820

On the use of deformable image registration to evaluate the need to perform ART in head and neck cancer

P. Delgado-Tapia[1], M. Lizondo[1], A. Latorre-Musoll[1], N. Jornet[1], T. Eudaldo[1], P. Carrasco[1], A. Ruiz-Martinez[1], C. Cases[1], M. Ribas[1]

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Purpose or Objective: ART is a time-consuming process and the question "do we need to replan?" is not always easy to answer. In this work, we investigate: (i) if Deformable Image Registration (DIR) software can provide reliable criteria to decide if we need to replan; (ii) if we can use DIR to replan the treatment without performing a new planning CT.

Appendix D: Search Strategies for systematic reviews

Systematic Review Searching Record

Question title:
Bowel toxicity following radiotherapy

Literature search details

Date Restriction & Why: none

Language Restriction & Why :none

Database name	Dates covered	No. of References	Date of search
Medline	1946-2013	2107	15.10.13
Premedline	15.10.13	69	15.10.13
Embase	1974- 2013	2597	16.10.13
Pubmed		188	
ISI Web of Science ***(Includes Science Citation Index & ISI Index to Conference proceedings)***	1900- 2013	1753	18.10.13
Total refs			

Total References retrieved (after de-duplication):

MEDLINE[OVID]

1	exp radiotherapy/	137329	Advanced
2	exp radiation injuries/	57035	Advanced
3	(radiotherap* or radiat* or irradiat*).tw.	431482	Advanced

4	radiation effects/	27553	Advanced
5	or/1-4	498983	Advanced
6	(ae or to or po or co).fs.	3161332	Advanced
7	(safe or safety).ti,ab.	420402	Advanced
8	side effect$.ti,ab.	171180	Advanced
9	((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.	291512	Advanced
10	(toxicity or complication$ or noxious or tolerability).ti,ab.	836950	Advanced
11	or/6-10	3940352	Advanced
12	5 and 11	134114	Advanced
13	exp Intestines/re [Radiation Effects]	4036	Advanced
14	((bowel* or intestin* or gastrointestin* or colon* or colorectal or rectal or rectum or gut*) adj3 (toxic* or morbidit* or injur* or dysfunction*)).tw.	16662	Advanced
15	13 or 14	20037	Advanced
16	12 and 15	3204	Advanced
17	exp Radiotherapy Dosage/	49002	Advanced
18	exp Dose Fractionation/	6190	Advanced
19	dose-response relationship, radiation/	34319	Advanced
20	(dose or dosage or dosimetric or fraction* or gray*).tw.	1294070	Advanced
21	or/17-20	1329367	Advanced
22	16 and 21	2107	Advanced

Embase [OVID]

1	exp radiotherapy/	374826	Advanced
2	exp radiation injury/	58645	Advanced

#3	Search **(#1 or #2)**	694710
#2	Search **(((radiotherapy[MeSH Major Topic]) OR radiation injuries[MeSH Major Topic])) OR ((radiotherap* or radiat* or irradiat*))**	694710
#1	Search **(radiotherapy[MeSH Major Topic]) OR radiation injuries[MeSH Major Topic]**	

Web of Knowledge
Science Citation Index

#9 #8 AND #5
DocType=All document types; Language=All languages;

#8 #7 OR #6
DocType=All document types; Language=All languages;

#7 TS=(dosimetric or fraction* or gray*)
DocType=All document types; Language=All languages;

#6 TS=(dose response)
DocType=All document types; Language=All languages;

#5 #4 AND #3
DocType=All document types; Language=All languages;

#4 TS=(bowel* or intestin* or gastrointestin* or colon* or colorectal or rectal or rectum or gut*)
DocType=All document types; Language=All languages;

#3 #2 AND #1
DocType=All document types; Language=All languages;

#2 TS=(adverse or toxic* or harm*)
DocType=All document types; Language=All languages;

#1 TS=(radiotherapy)

#3	Search **(#1 or #2)**	694710
#2	Search **(((radiotherapy[MeSH Major Topic]) OR radiation injuries[MeSH Major Topic])) OR ((radiotherap* or radiat* or irradiat*))**	694710
#1	Search **(radiotherapy[MeSH Major Topic]) OR radiation injuries[MeSH Major Topic]**	

Web of Knowledge
Science Citation Index

#9 #8 AND #5
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#8 #7 OR #6
DocType=All document types; Language=All languages;

#7 TS=(dosimetric or fraction* or gray*)
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#6 TS=(dose response)
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#5 #4 AND #3
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#4 TS=(bowel* or intestin* or gastrointestin* or colon* or colorectal or rectal or rectum or gut*)
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#3 #2 AND #1
DocType=All document types; Language=All languages;

#2 TS=(adverse or toxic* or harm*)
DocType=All document types; Language=All languages;

#1 TS=(radiotherapy)

CANCER RESEARCH WALES LIBRARY

Systematic Review Searching Record

Question title: Organ Motion in Cervical/Endometrial Cancer

1. Literature search details

Date Restriction: None

Language Restriction: All

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1946 - present	166	166	08/10/2012
Premedline	present	2	2	16/10/2012
Embase	1947 - present	294	294	10/10/2012
Cochrane Library	Issue 10	6	6	18/10/2012
Web of Science	1899 - present	109	109	18/10/2012
CINAHL	1981 - present	28	28	16/10/2012

Total References retrieved (after de-duplication): 408

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Uterine Neoplasms/

2. (cervi adj3 (cancer* or neoplas* or carcinom* or tumo?r* or malignan*)).tw.*

3. (endometr adj3 (cancer* or neoplas* or carcinom* or tumo?r* or malignan*)).tw.*

4. (uter adj3 (cancer* or neoplas* or carcinom* or tumo?r* or malignan*)).tw.*

5. or/1-4

6. exp Radiotherapy/

7. ((radiat or radio*) adj3 (therap* or treat*)).tw.*

8. ((image guid or intensity modulated) adj3 (radiat* or radio*)).tw.*

9. (igrt or imrt).tw.

10. exp Tomography, X-Ray Computed/

11. (CT or CAT).tw.

12. (comput adj3 tomograph*).tw.*

13. exp Magnetic Resonance Imaging/

14. ((magnetic resonance or MR or NMR or diffusion weighted) adj2 imag).tw.*

15. (MRI or DWI).tw.

16. or/6-15

17. exp Organ Size/

18. exp Organs at Risk/

19. exp Movement/

20. exp motion/

21. ((vagin or uter* or organ*) adj3 (mov* or motion* or mobil* or displace*)).tw.*

22. (interfract adj3 (motion* or mov* or displace*)).tw.*

23. (internal adj3 (margin or boundar*)).tw.*

24. ((target or shape or volume or margin or boundar*) adj2 (var* or change*)).tw.*

25. or/17-24

26. 5 and 16 and 25

2. Any further comments:

<u>Sifting Criteria</u>: