Standardisation and optimisation of radical radiotherapy for cervix cancer.

A thesis submitted to University College London (UCL)

for the degree of MD (Res)

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Declaration

I, Gemma Katherine Eminowicz, confirm that the work presented in this thesis is my own. Where information has been derived from other sources I confirm that this has been indicated in the thesis.

Signed _____   Date _____

Abstract

Cervical cancer is a significant worldwide health burden despite primary and secondary prevention measures in developed countries. Survival rates for locally advanced cervical cancers treated with radical chemoradiation (FIGO stage IB2 to IVA) ranges from 10 to 85% at 5 years. A significant proportion of patients relapse within the pelvis and therefore the quality and accuracy of radiotherapy delivery is paramount. This thesis aims to review the extent of potential uncertainties within cervical cancer radiotherapy with the aim of developing and assessing methods to optimise and standardise those uncertainties.

To date, the INTERLACE trial radiotherapy quality assurance (RTQA) programme has been completed by over half of United Kingdom (UK) centres treating cervical cancer. Using these RTQA test cases, I analysed one of largest known uncertainties in radiotherapy planning; target volume delineation. Having quantified the variation in comparison to a gold standard I investigated the dosimetric impact of the observed variation. I also produced a step-by-step pictorial delineation atlas, having reviewed all available published guidance, and assessed its impact on delineation variation.

Daily variation in pelvic organ position is the second uncertainty investigated within this thesis. By retrospectively reviewing computed tomography (CT) imaging during chemoradiation for cervical cancer I analysed the variation of bladder and bowel filling and its relationship with target volume position and coverage. The movements that I measured allowed me to calculate margins necessary to maintain acceptable coverage. However, by understanding the variation observed I propose methods of standardisation that can be applied in UK clinical practice without the need to increase margin size. I also estimated the dosimetric impact of this variation and the subsequent potential dosimetric gain of the standardisation methods.

Table of contents

Variability of clinical target volume delineation for definitive radiotherapy in cervix cancer. Radiother Oncol **117**: 542-547.

The dosimetric impact of target volume delineation variation for cervical cancer radiotherapy. Radiother Oncol [Epub ahead of print]

Improving target volume delineation in intact cervical carcinoma: literature review and step-by-step pictorial atlas to aid contouring." Prac Radiat Oncol [Epub ahead of print]

Pelvic organ motion during radiotherapy for cervical cancer: understanding patterns and recommended patient preparation. Clin Oncol [Epub ahead of print]

List of Figures

List of Tables

List of Abbreviations

2D-RT	Two dimensional radiotherapy
3D-CRT	Three dimensional conformal radiotherapy
ACS	American Cancer Society
AJCC	American joint committee on cancer
AP	Anterior-posterior
ASTRO	American Society for Radiation Oncology
BT	Brachytherapy
CBCT	Cone beam computed tomography
CERR	Computational environment for radiotherapy research software
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CNS	Central nervous system
COM	Centre of mass
CR	Complete response
CRT	Chemoradiotherapy
CRUK	Cancer Research United Kingdom
CT	Computed tomography
CTV	Clinical target volume
DFS	Disease free survival
DICOM	Digital imaging and communications in medicine
DRR	Digitally reconstructed radiograph
DVH	Doze volume histogram
DW-MRI	Diffusion weighted-Magnetic resonance imaging
EBRT	External beam radiotherapy
EMBRACE	An international study on MRI-guided brachytherapy in locally advanced cervical cancer
EPID	Electronic portal imaging device
EQD2	Equivalent dose in 2 Gray fractions
ESTRO	European society for radiotherapy and oncology
EUA	Examination under anaesthetic

FDG-PET/CT	Fluorodeoxyglucose-Positron emission tomography/computed tomography
FIGO	International federation of gynaecology and obstetrics
GEC	The groupe europeen de curietherapie
GOG	Gynecologic oncology group
GSCTV	Gold standard clinical target volume
GSPTV	Gold standard planning target volume
GSPTVCM	Gold standard planning target volume with most commonly applied margins
GTV	Gross tumour volume
Gy	Gray (radiation unit)
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR-CTV	High risk clinical target volume
IGBT	Image guided brachytherapy
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
INTERLACE	A phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patient with locally advanced cervical cancer
IPEM	Institute of physics and engineering in medicine
IR-CTV	Intermediate risk clinical target volume
ITV	Internal target volume
IVC	Inferior vena cava
JCI	Jaccard conformity index
JCOG	Japan clinical oncology group
LACC	Locally advanced cervical cancer
LDR	Low dose rate
LEEP	Loop electrosurgical excisional procedure
LN	Lymph node
LVSI	Lymphovascular space invasion
MDR	Medium dose rate
MESH	Medical subject headings
MLC	Multi-leaf collimator

MRI	Magnetic resonance imaging
MVR	Maximum volume ratio
NCI	National Cancer Institute
NCIC	National cancer institute of Canada
NHS	National Health Service
OAR	Organs at risk
OBI	On-board imaging
OS	Overall survival
PGI	Postgraduate institute of medical education and research (Chandighar, India)
PI	Principle investigator
PTV	Planning target volume
RCR	Royal college of radiologists (UK)
RT	Radiotherapy
RTOG	Radiation therapy oncology group
RTQA	Radiotherapy quality assurance
SBRT	Stereotactic body radiotherapy
SCoR	Society and college of radiographers
SD	Standard deviation
SHERRI	Surrey heuristic engine for radiotherapy radiobiology and imaging
STAPLE	Simultaneous truth and performance level estimation
TMG	Trial management group
TPS	Treatment planning system
UCLH	University College London Hospital
UK	United Kingdom
VMAT	Volumetric modulated arc therapy

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Finally, the sincerest thanks are extended to my husband, William, without whom I would not be where I am now. He is always the person to encourage me to push that little further and follow paths which create exciting new avenues, such as this research degree.

Chapter 1:

Introduction: Radical chemo-radiation for cervical cancer

1.1. Epidemiology

Worldwide, cervical carcinoma is the fourth most common cancer in women and seventh most common overall (GLOBOCAN 2012). In 2012, 528000 women across the world were diagnosed with cervical cancer, predominantly in the developing world. In Eastern and Mid Africa cervical cancer remains the most common cancer in women and in England it remains the most common cancer in women aged 15-34 (ONS 2013). The worldwide age standardised incidence varies from 42.7 per 100000 population in Eastern Africa to 4.4 per 100,000 in Western Asia (GLOBOCAN 2012). In England the age standardised incidence was 8.7 per 100,000 women in 2011 (ONS 2013).

1.2. Aetiology

Human papilloma virus (HPV) infection causes cervical cancer and is prevalent in almost 100% of cases (Walboomers et al. 1999; Smith et al. 2007). HPV16 and HPV18 are the most common carcinogenic types, associated with 55% and 15% of cervical cancer cases respectively (Smith et al. 2007; De Sanjose et al. 2010; Saslow et al. 2012). HPV18 is associated with poorly differentiated histology, adeno-squamous and adenocarcinomas, whilst other types are associated with squamous cell cancers (Smith et al. 2007).

Carcinogenic forms of HPV are found in up to 18-22% of women, peaking at ages 20-25. Higher risk groups are women of black ethnicity, smokers, with low educational level, multiple sexual partners, early age at first intercourse or pregnancy and concomitant infections (e.g. bacterial vaginosis, chlamydia trachomatis) (McCormish 2011; Oakeshott et al. 2012; Tay et al. 2014).

70% of HPV infection clears within one year and 90% within two (Franco et al. 1999; Oakeshott et al. 2012). Persistent infection is key to cervical intra-epithelial neoplasia (CIN) development, the precursor to cervical cancer (Saslow et al. 2012). 20% of women with persistent HPV infection at one year develop CIN or cancer within 5 years (Oakeshott et al. 2012).

Risk factors for HPV persistence include immunocompromised state (human immunodeficiency virus (HIV), post organ transplantation) (McCormish 2011), potential genetic host susceptibility (Oakeshott et al. 2012) and smoking (Roura et al. 2014).

Interestingly, the two fold increased CIN3 and cervical cancer risk with smoking is potentially independent of HPV status (McCormish 2011). Passive smoking data is conflicting but a meta-analysis demonstrated a 73% increased risk in passive smokers (Louie et al. 2011; Zeng et al. 2012).

Other factors increasing cervical cancer risk include the oral contraceptive pill (McCormish 2011), hormone replacement therapy (adenocarcinomas) (Jaakkola et al. 2012) and prenatal diethylstilboestrol exposure (clear cell adenocarcinomas) (McCormish 2011).

1.3. Presentation

Clinical presentation of cervical cancer depends upon disease extent at time of presentation.

1.3.1. Microscopic disease

Microscopic disease does not commonly cause symptoms. Patients therefore usually present following a positive screening test, as discussed in section 1.4.

1.3.2. Locally advanced disease

The majority of cases are locally advanced at diagnosis and most commonly present with abnormal bleeding, usually intermenstrual, post-coital or post-menopausal. Women may also complain of vaginal discharge or dyspareunia. If disease is locally infiltrative, pelvic pain, sciatic nerve symptoms or, rarely, bladder and bowel symptoms can occur (Benedet et al. 2000). Renal impairment secondary to ureteric obstruction is indicative of pelvic sidewall disease but enlarged para-aortic nodes must be ruled out as a potential obstructive site.

1.3.3. Metastatic disease

Only a small number of patients present with metastatic disease. Pattern of spread is locally within the pelvis and via lymph nodes. First sites of metastases are therefore aortic and mediastinal lymph nodes (Benedet et al. 2000). Blood borne spread to liver, lungs and bone is also seen but less commonly.

1.4. Prevention and early detection

1.4.1. Screening

National screening programmes, i.e. secondary prevention interventions, have successfully been implemented in the United Kingdom (UK) and other western countries. Screening introduced in the UK in 1988 uses cytological smear tests for women aged 25 to 64 years old every 3 to 5 years. It has reduced the number of invasive cancers diagnosed from 4082 in 1988 to 2511 in 2011 and is estimated to prevent approximately 5000 deaths per year (Peto et al. 2004).

The American Cancer Society (ACS) recommends a 'risk adapted approach' using either 3 yearly cytology or 5 yearly cytology and HPV co-testing at ages 30-65 following a systematic evidence review (Saslow et al. 2012). Four large European randomised trials showed that HPV based approaches can protect 60-70% better against cervical cancer than cytology alone (Ronco et al. 2014).

Unfortunately not all women are compliant with screening attendance and half of reported cervical cancer cases are in these un-screened women (Saslow et al. 2012).

1.4.2. Primary prevention

HPV16 and 18 can be vaccinated against, with over 99% effectiveness in preventing HPV related cervical changes providing no active infection is present (Lu et al. 2011). Therefore, the UK national immunisation programme for school girls aged 12-13 was introduced in 2008, capturing females before the peak HPV prevalence. The true benefit will hopefully be seen in time.

1.5. Diagnosis and staging

1.5.1. Clinical examination

Clinical examination is the primary staging tool for cervical cancer. Vaginal and rectal examination can show the local disease extent including parametrial or pelvic sidewall extension. Full external examination may detect distant disease, for example supraclavicular fossa lymphadenopathy. Pelvic examination is tolerated better under anaesthetic (examination under anaesthetic; EUA) allowing biopsy, cystoscopy or sigmoidoscopy if necessary. Suspected bladder and/or rectal involvement must be confirmed on biopsy. Bullous oedema does not determine local organ invasion (Benedet et al. 2000). Clinical

drawings (Fig.1.1) are useful to facilitate staging and, if treated with chemoradiation, can guide targeted treatment delivery. Additional investigations do not alter the International federation of Obstetricians and Gynaecologist (FIGO) staging but are useful to guide treatment planning (Benedet et al. 2000).
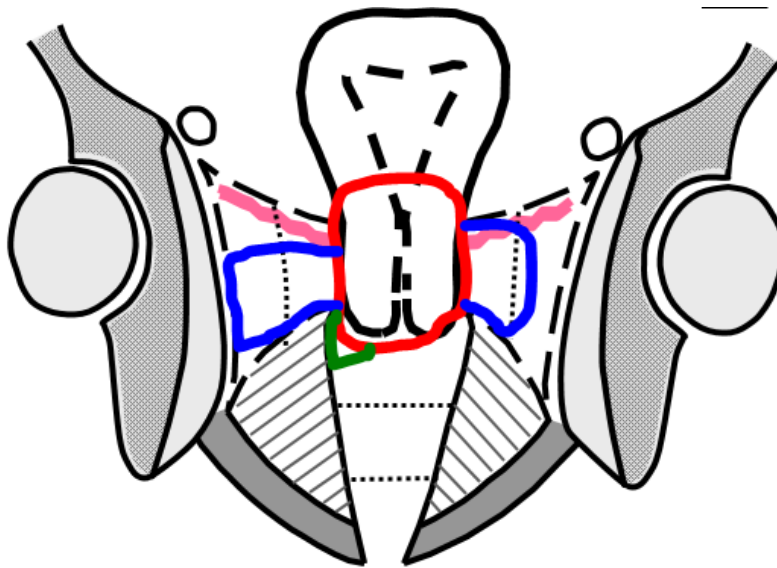
Figure 1.1: Example clinical drawing of cervical cancer extending to right sidewall (FIGO IIIB) using the EMBRACE study template: red=cervical tumour, blue=parametrial invasion, green=vaginal invasion

1.5.2. Histological confirmation

Diagnosis must be confirmed histologically, usually by biopsy at colposcopy or EUA. Approximately 80-90% are squamous cell carcinomas (Benedet et al. 2000; Saslow et al. 2012). Other pathologies include adenocarcinoma (10-15%), adeno-squamous carcinoma (3-5%), clear cell carcinoma (rare), and neuroendocrine carcinomas (rare) (Benedet et al. 2000).

CIN is the pre-invasive stage of squamous cell cancer with a 15 year lag. CIN1 (mild dyskaryosis) resolves spontaneously in 50% and CIN 2/3 (moderate/severe dyskaryosis) resolves spontaneously in one third. 30% of untreated CIN3 will result in cancer over a 30 year period (Saslow et al. 2012).

In general, squamous cell carcinoma represents a chemotherapy and radiotherapy (RT) sensitive group whereas adenocarcinomas are less chemotherapy and RT sensitive.

1.5.3. Imaging modalities

In the western world, Computed Tomography (CT) chest and abdomen is routine to rule out distant disease before proceeding with curative treatment. Magnetic Resonance Imaging (MRI) is superior to CT for pelvic tissues due to the high spatial and contrast resolution (Fig.1.2). MRI has high local staging accuracy of 92% and is up to 100% sensitive with a 98% negative predictive value for parametrial and 93% accuracy for vaginal extension (Camisão et al. 2007). The European Society of Urogenital Radiology advocates T2 weighted MRI to characterise local disease and T1 weighted axial images to assess lymph node status (Balleyguier et al. 2011).

Figure 1.2: Anonymised diagnostic T2 weighted sagittal MRI confirming cervical cancer (arrowed).

Additional imaging modalities can provide functional data, including 18fluorodeoxyglucose-positron emission tomography (FDG-PET) and diffusion weighted-(DW-)MRI (Downey et al. 2011). For staging purposes PET-CT is sensitive (80-90%) and specific (90-100%) (Nogami et al. 2014) and is useful in unclear or ambiguous cases. It can also distinguish between post-RT change and residual or recurrent disease in follow-up. Additional functional data may have prognostic and predictive benefits and is an area of ongoing research (Downey et al. 2011).

1.5.4. Nodal staging

The risk of nodal spread increases with increasing stage. For stage IB2, approximately 15-20% will have pelvic lymph node involvement, 30% in IIB, 50% IIIB and 80% FIGO stage IVA. For para-aortic nodal involvement the percentages are 5-10%, 15%, 30% and 50% for IB2, IIB, IIIB, and IVA respectively (Taylor et al. 2006). Lymph node status is not included in the FIGO staging detailed in 1.5.5. However, accurate nodal staging is essential for chemoradiation to guide the superior radiation field border.

Nodal staging with CT alone does not detect microscopic disease and therefore para-aortic nodal sampling may be used. This has risks including lymphocyst development but provides more accurate staging information (Tsunoda et al. 2015). Patients unsuitable for nodal sampling may undergo FDG-PET/CT (Fig.1.3.) as an alternative due to sensitivity of 72-100% and specificity of 95-99% for para-aortic nodal metastases (Nogami et al. 2014).
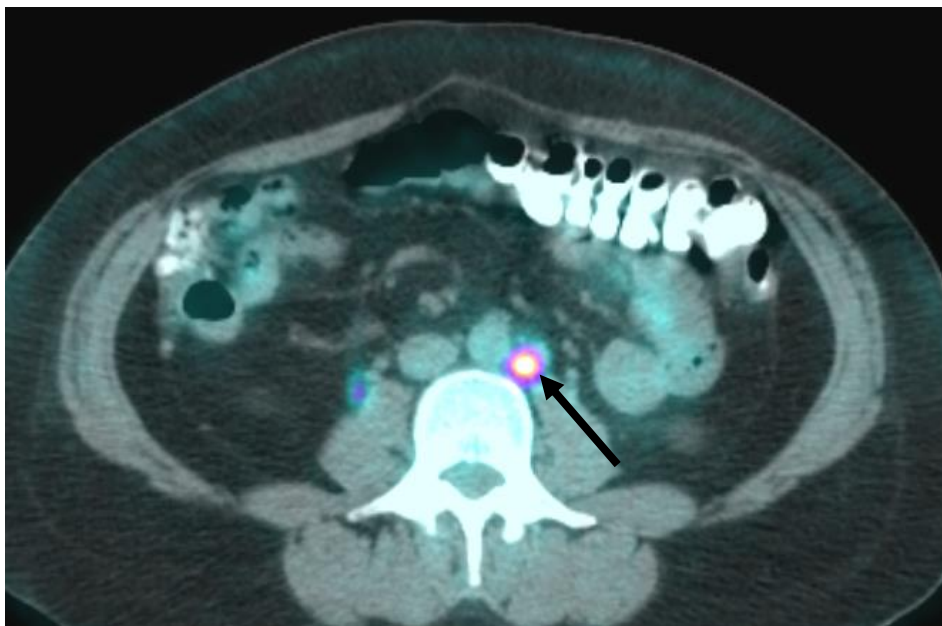
Figure 1.3: Example anonymised transverse FDG-PET/CT image highlighting a positive para-aortic node (arrowed).

1.5.5. Staging definition and associated survival rates

Staging is documented as per the FIGO staging (Camisão et al. 2007; Mutch 2009) (Table 1.1, Fig.1.4). As FIGO stage increases 5 year survival decreases, see Table 1.1. The American Joint Committee on Cancer (AJCC) 'TNM' staging system also exists which

individually scores tumour (T), nodes (N) and metastases (M). This is more commonly used when describing the pathological staging if treated with surgery (Benedet et al. 2000).

Table 1.1: FIGO 2008 staging and survival rates (Mutch 2009)

Stage			Clinical findings	TNM	5 yr surv
I			Limited to cervix	T1M0	
	IA		Micro-invasion limited to cervix		>95%
		IA1	≤3mm depth invasion, largest extension ≤7mm	T1a1M0	
		IA2	3-5mm depth invasion, extension ≤7mm	T1a2M0	
	IB		Clinically visible, larger than IA, limited to cervix		
		IB1	≤4cm in greatest dimension	T1b1M0	~90%
		IB2	>4cm in greatest dimension	T1b2M0	80-85%
II			Invades beyond uterus but not to pelvic sidewall or lower third of vagina		75-78%
	IIA		No parametrial invasion	T2aM0	
		IIA1	≤4cm in greatest dimension		
		IIA2	>4cm in greatest dimension		
	IIB		Parametrial invasion	T2bM0	
III	IIIA		Invades lower third of vagina	T3aM0	35-50%
	IIIB		Extends to pelvic sidewall and/or hydronephrosis/non-functioning kidney	T3bM0	
IV			Extends beyond true pelvis or biopsy proven bladder/rectal invasion		
	IVA		Invading bladder/rectum	T4M0	15-30%
	IVB		Distant metastases	Any M1	<10%

Figure 1.4: Pictorial images demonstrating FIGO staging for cervical cancer (Camisão et al. 2007).
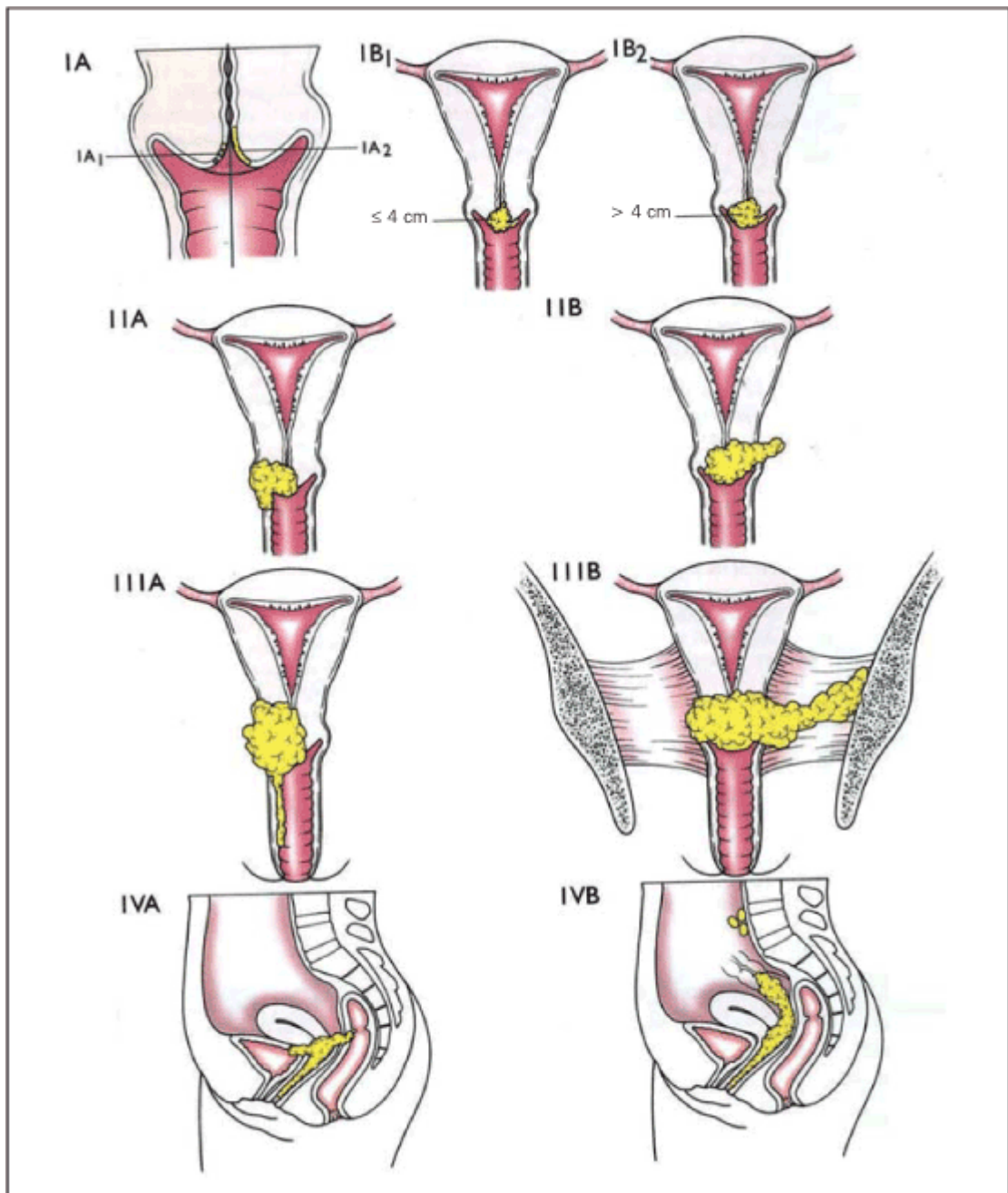
1.6. Management overview

Treatment depends upon disease stage and analysis of prognostic factors such as tumour volume, presence of lymphovascular space invasion (LVSI) and to a lesser extent the histological subtype and grade (Benedet et al. 2000). See Table 1.2 for an overview. Here, I briefly discuss management of all stages, and, beyond this section, will focus on locally advanced cervical cancer only as this is where chemoradiation is used.

1.6.1. Abnormal screening results

Non-invasive disease is most commonly detected via screening (Screening and Immunisations team Health and Social Care Information Centre 2013). Referral for colposcopy is triggered if the cytology results show inadequate or borderline x3, mild dyskaryosis x2, moderate or severe dyskaryosis x1 or possible invasion x1 (urgent referral). If mild dyskaryosis is reported once, a repeat is performed at 6 months, and if changes are persistent then colposcopy should be performed.

At colposcopy visualisation with 15x magnification is performed and biopsy, conisation, loop electrosurgical excisional procedure (LEEP) or laser or cryotherapy ablation can be performed. If tumour is visible at colposcopy then biopsy and appropriate staging is performed.

1.6.2. Localised early stage disease

Disease localised to the cervix (FIGO stage I) is generally treated surgically with total abdominal hysterectomy or radical hysterectomy and consideration of lymph node dissection. In bulky cases i.e. FIGO IB2, management is as for locally advanced disease. RT alone can achieve equal disease control and survival. A randomised trial allocated stage Ib-IIa patients between surgery and RT finding equal survival outcomes but less severe morbidity in RT patients (Landoni et al. 1997).

Post-operative RT is advised if there are positive or close margins, more than two positive lymph nodes or parametrial extension (Benedet et al. 2000). The definition of 'close margins' is not well defined and usually ranges from 2 to 5mm, in general extrapolated from evidence in other tumour sites. If an incidental malignancy is diagnosed at hysterectomy for suspected benign pathology, full surgical management is necessary or post-operative RT.

Trachelectomy is a surgical approach in patients wishing to preserve fertility and should only be performed by experienced clinicians in small tumours.

If a patient with stage I disease is unfit for surgery they may be suitable for radical RT alone, delivered as detailed in section 1.7.

1.6.3. Locally advanced disease

Locally advanced disease includes a wide range of stages including FIGO IIA to IVA. These are treated with a combination of RT, brachytherapy and chemotherapy. Section 1.7 describes this in detail. This is the patient cohort that this work focuses on.

1.6.4. Metastatic disease

Treatment of metastatic disease depends upon symptoms, disease location and patient fitness. Patients with para-aortic nodes, even though metastatic, can still be treated radically with chemoradiation. Otherwise patients with recurrent or metastatic disease beyond the para-aortic nodes, if fit enough, are managed with combination chemotherapy. First line is usually a doublet combination of carboplatin or cisplatin, paclitaxel, topotecan, or gemcitabine, most commonly carboplatin and paclitaxel. Bevacizumab increases median overall survival (OS) by almost 4 months in addition to chemotherapy (Tewari et al. 2014). Second line treatment is not effective with a wide range of options due to limited evidence. Trials are therefore encouraged in patients with a good performance status. Otherwise, localised treatment such as RT or surgery can palliate symptoms such as bleeding or pain.

Table 1.2: Overview of management according to FIGO stage

FIGO stage	Recommended Treatment
Pre-invasive	Ablative e.g. cryotherapy, laser vaporisation, electrocautery Excisional e.g. cold conization, LEEP (Loop electrosurgical excisional procedure), laser Simple hysterectomy (if fertility preservation not necessary)
IA	Cone biopsy and careful follow-up, if invasion<3mm from basement membrane and clear margins Total abdominal hysterectomy (preferred if IA2) Brachytherapy alone
IB1	Radical hysterectomy with pelvic node dissection Definitive radiotherapy: whole pelvis and brachytherapy Trachelectomy with pelvic node dissection (fertility preserving)
IB2-IVA	Nodal staging with para-aortic sampling or FDG-PET/CT Concurrent chemoradiation: cisplatin with whole pelvis radiotherapy and brachytherapy
Node positive	Consider para-aortic nodal radiotherapy if common iliac or para-aortic nodes involved
IVB	Combination chemotherapy

1.7. Current practice in cervical RT

1.7.1. RT planning and delivery

RT for locally advanced cervical cancer can be delivered using two-dimensional radiotherapy (2D-RT), three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT) (Taylor et al. 2006; Barrett et al. 2009). Most western world centres treat with 3D-CRT or IMRT. In less developed countries, 2D-RT is still used. IMRT is detailed in section 1.8.1 including a review of evidence supporting this technique.

Irrespective of delivery method, all patients undergo a planning appointment. For 2D-RT plain X-Rays are acquired whereas for 3D-CRT and IMRT a planning CT scan is acquired. These are performed in the treatment position, most commonly supine, arms on chest with a knee rest and ankle stocks. Patients may be treated lying supine on a belly board. The belly board aims to push small bowel out of the radiation field but set-up is more difficult and less reproducible.

In general, a 'comfortably full bladder' and empty rectum is aimed for at planning and during treatment. The 'comfortably full bladder' is another method of displacing small bowel out of the radiation field. Bladder and rectal filling is discussed in more detail in section 1.9.2 and Chapter 5 and 6.

Ideally, a patient's position should be identical daily to ensure treatment accuracy. This 'set-up' can be verified by imaging with an electronic portal imaging device (EPID) usually on day 1-3 or 1-5 then once weekly. This creates digitally reconstructed radiographs (DRRs) which are compared with the planning imaging. If necessary, position shifts can be applied to match the planning set-up. Daily imaging may be necessary in patients with a difficult set-up e.g. obese patients.

The dose prescription varies across the UK and Europe. Most UK centres prescribe 50.4Gray (Gy) in 28 daily fractions over 5.5 weeks to the pelvis but in Europe 45Gy in 25 daily fractions over 5 weeks is more common. Para-aortic nodes, if treated, are prescribed to 45Gy in 25 daily fractions. This is followed by brachytherapy, described in section 1.7.4, to an ideal equivalent dose in 2Gy fractions (EQD2) of minimum 80-85Gy. Use of 45Gy to the pelvis,

instead of 50.4, increases the likelihood of achieving higher brachytherapy doses and is therefore favoured within many centres.

1.7.2. Two-dimensional radiotherapy (2D-RT)

2D-RT uses X-Rays to conventionally simulate treatment if cross-sectional imaging is not available. The patient is clinically examined in the treatment position. The lower border of vaginal disease or the level of introitus is marked with a radio-opaque marker. X-Ray images are then taken anterior-posterior and laterally. The field borders are defined on these X-Rays according to anatomy as per Table 1.3 and Fig.1.5. Diagnostic imaging can aid adaptation of borders to ensure adequate target coverage. Shielding can be added over the posterior sacrum on lateral X-Ray and small bowel superior-laterally on the anterior-posterior X-Ray. These fields are then used to create a four-field brick arrangement.

If available, 3D-CRT is preferred as 2D-RT has a high risk of unnecessary normal tissue irradiation.
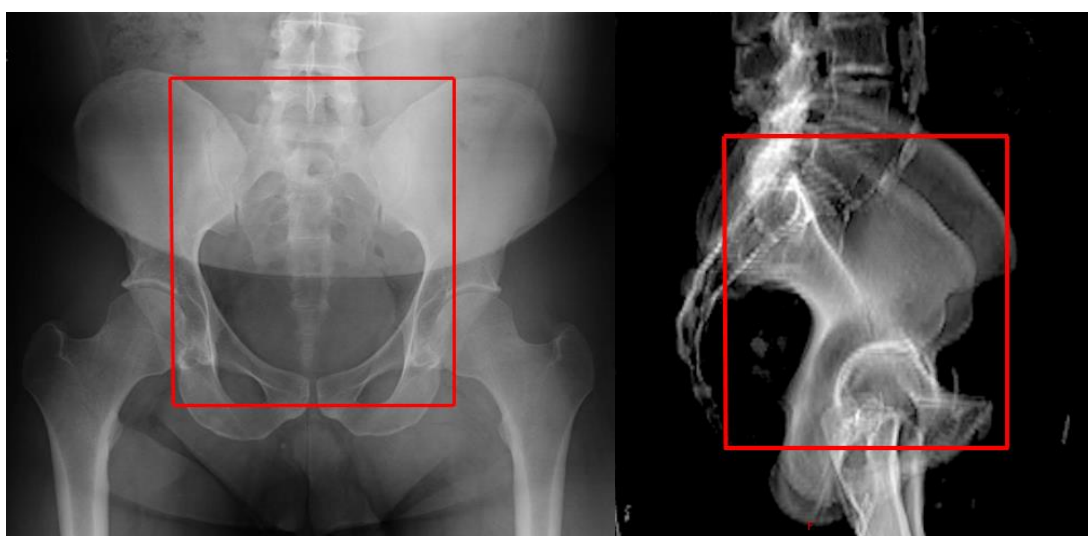
Figure 1.5: Cervical pelvic RT treatment fields on anterior-posterior and lateral X-Rays.

Border	Anatomical position (4 field)
Superior	L4/5
Inferior	3cm below vaginal disease (inferior obturator foramen)
Lateral	1-2cm lateral to pelvic brim
Anterior	1cm anterior to pubic symphysis
Posterior	S2/3 (Entire sacrum if uterosacral ligament involved)

Table 1.3: Anatomical borders of pelvis only RT field edges when using 2D-RT.

1.7.3. Three-dimensional conformal radiotherapy (3D-CRT)

For 3D-CRT a planning CT is acquired to allow clinical target volume (CTV) localisation and creation of the planning target volume (PTV). This uses the patient's individual anatomy and knowledge of disease spread to increase RT accuracy. CTV comprises two distinct volumes; primary CTV and nodal CTV (Taylor et al. 2006; Barrett et al. 2009). The primary CTV includes the cervical tumour and areas of potential local invasion. The nodal CTV includes the 'at risk' nodal groups. See Table 1.4.

Volume	Anatomical areas included
Primary CTV	Gross tumour volume (GTV), cervix, entire uterus, upper vagina, bilateral parametria
Nodal CTV (node negative)	Common iliac, internal and external iliac, presacral and obturator nodes. Created by adding a 7mm margin to the corresponding blood vessels, editing for bone and muscle and adding a presacral strip. Superiorly CTV extends up to aortic bifurcation Include inguinal nodes if FIGO IIIA
Nodal CTV (node positive)	As node negative with at least 2cm margin from involved nodes. Include para-aortic region up to T11/12 or T12/L1 if common iliac node positive

Table 1.4: Definition of clinical target volume (CTV) for cervical cancer

CTV definition can be optimised by fusing diagnostic imaging. Intravenous contrast can be administered to highlight blood vessels which facilitates nodal CTV delineation. Guidelines exist regarding delineation of CTV (Taylor et al. 2005; Small et al. 2008; Lim et al. 2011) and organs at risk (OARs) (Gay et al. 2012), discussed further in Chapters 2 and 4.

Margins are added to CTVs to account for uncertainties in set-up including daily organ motion, discussed further in section 1.9.2 and Chapter 6. In general, margins up to 20 mm are applied to the primary CTV and up to 10mm to the nodal CTV. Once the total PTV is defined, a four-field brick arrangement is applied as for 2D-RT. This is then tailored using small strips of shielding (multi-leaf collimators, MLCs) to cover PTV with 95% dose. See Fig. 1.6. Dose volume histograms (DVHs) show how much dose is delivered to what volume of targets and OARs (Fig. 1.7).

When treating the para-aortic nodal region a PTV is created but the approach to planning varies. Some centres treat with an anterior and posterior field but most centres use 3 or 4 fields. The main limitation is kidney dose and often shielding is necessary to reduce this.
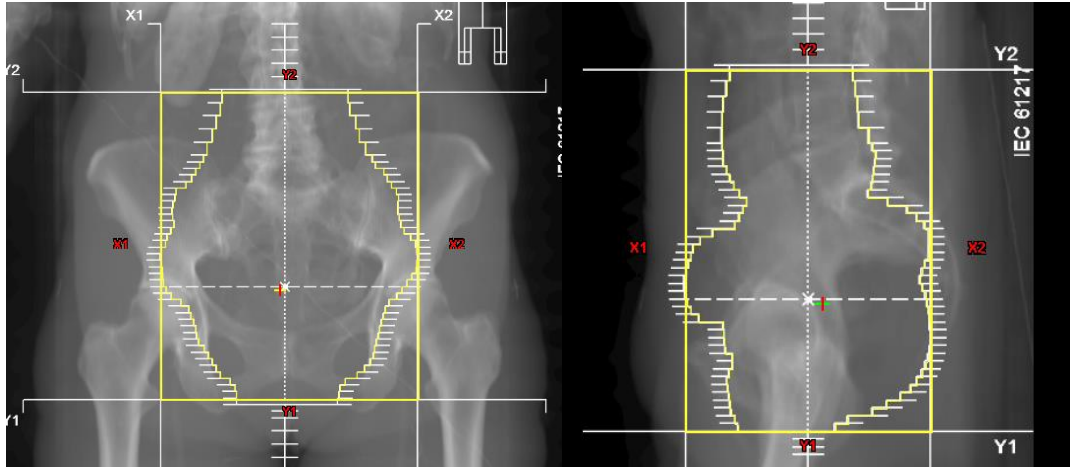
Figure 1.6: 3D-CRT fields on anterior-posterior and lateral DRRs showing shaping of beam with MLCs; X and Y jaws in thick yellow, MLCs thin yellow (and white lines)
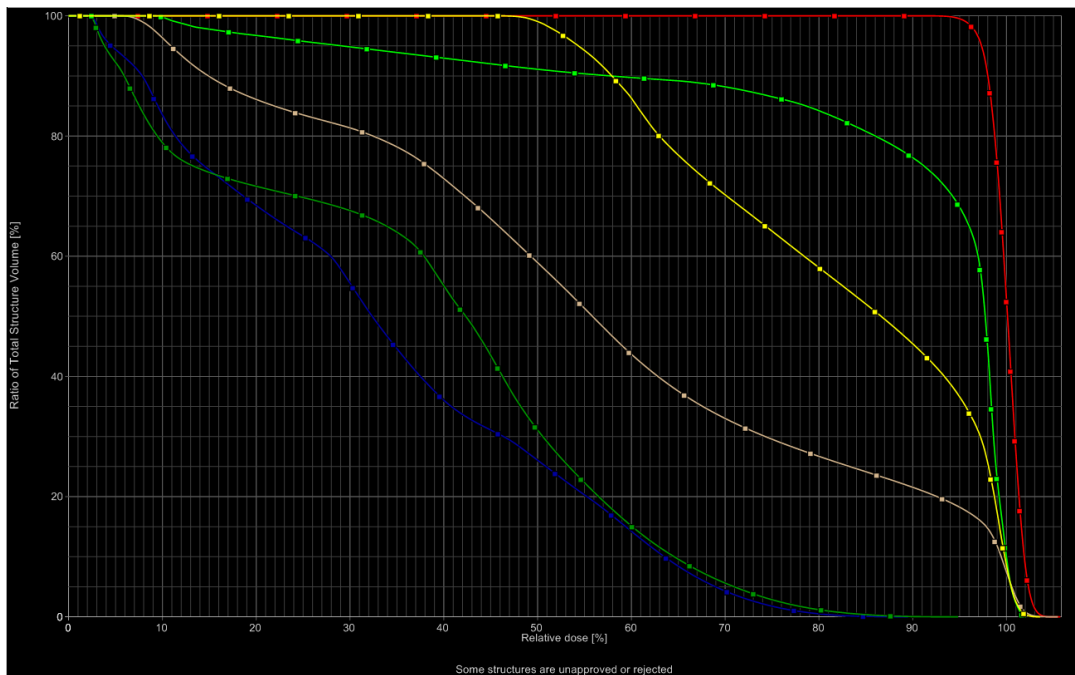
Figure 1.7: Dose volume histogram showing percentage of prescription dose (x axis) and percentage volume of structure receiving dose (y axis); PTV=red, Rectum=yellow, Bladder=light green, Bowel sac=white, Femurs (individual)=blue and dark green.

1.7.4. Brachytherapy

Brachytherapy (BT) delivers short distance radiation near to or inside tumour. It is given after EBRT to boost primary tumour dose and involves surgical insertion of an intra-uterine tube and ovoids or ring at the vaginal fornixes (Fig.1.8.). A radiation source e.g. Iridium 192 (for

high dose rate (HDR)) is inserted into these tubes to deliver radiation internally with a steep dose drop off allowing high tumour dose and low OAR dose. This traditionally delivers a pear shaped radiation distribution prescribed to Point A which is 2cm superior to the lateral fornix and 2cm lateral to the central uterine canal (Fig.1.9.). Many different regimens and delivery methods are used, including low dose rate (LDR), medium dose rate (MDR), HDR, and pulsed BT. For HDR BT, most commonly used due to short treatment delivery time, 21Gy-28Gy in 3-4 fractions is an established prescription.
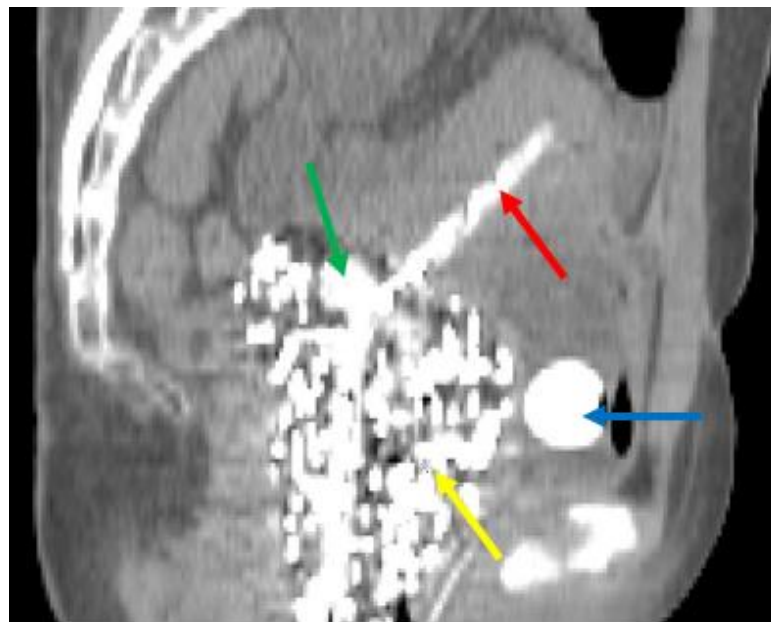
Figure 1.8: Sagittal CT of intrauterine tube (red arrow) and ring (green arrow) positioned for brachytherapy with packing in vagina (yellow arrow) and urinary catheter balloon (blue arrow)
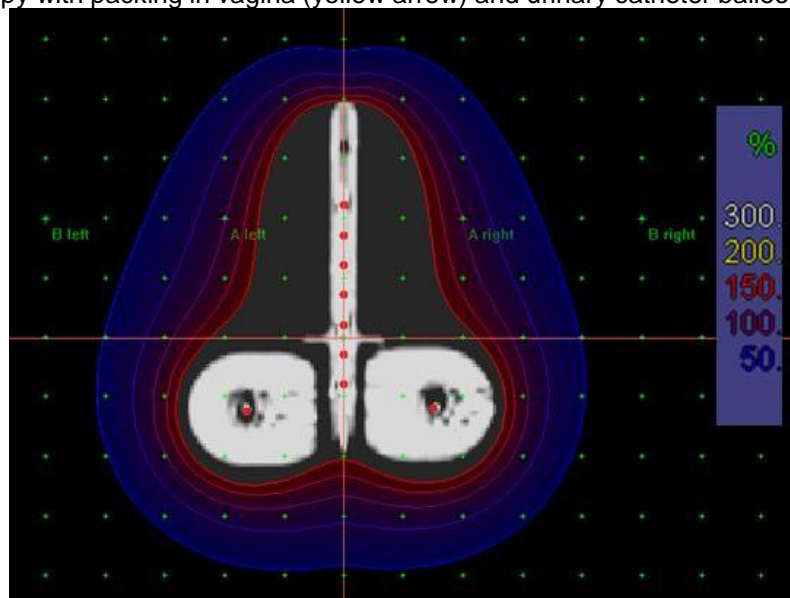
Figure 1.9: Standard brachytherapy 'pear-shaped' dose distribution prescribed to Point A. Green dots represent 1cm distance (intra-uterine tube is 4cm long), Red dots are dwell positions of radiation source. Point A and B are labelled, left and right. Coloured isodoses represent percentage of prescribed dose ranging from 50% to 300%.

If a patient is unsuitable for BT, for technical or medical reasons, IMRT can be used as an alternative but will not deliver as high EQD2 doses (Schefter et al. 2002; Chan et al. 2006). Due to this dose detriment patients who receive an IMRT boost instead of BT have an inferior survival, hazard ratio 1.86 (Gill et al. 2014).

1.7.5. Concurrent chemotherapy

In 1999 the radiation therapy oncology group (RTOG) 90-01 study, Gynecologic Oncology Group (GOG) 120 study, and GOG 123 study all demonstrated a significant survival advantage with the addition of concurrent platinum based chemotherapy to RT (Keys et al. 1999; Morris et al. 1999; Rose et al. 1999). These trials led to the National Cancer Institute (NCI) issuing an alert recommending the use of concurrent cisplatin-based chemotherapy with RT in women undergoing curative treatment (NCI 1999). This practice was widely adopted in the UK (McCormack et al. 2001).

More recently, a meta-analysis based on 18 trials from 11 countries confirmed a 6% improvement in 5-year OS from 60 to 66%, HR 0.81, and an 8% improvement in DFS from 50 to 58% with chemotherapy (CCCMAC 2008). Whilst the benefits were seen across all stages regardless of age, histology and grade they appeared to be lower in patients with more advanced disease. For stage Ib-IIa a 10% 5 year survival benefit was seen but for stage IIB the benefit was 7% and for III-IVa 3%. The most common regimen is single agent weekly cisplatin 40mg/m^2 for five to six cycles.

1.8. Recent advances in cervical RT

1.8.1. Intensity modulated radiotherapy (IMRT)

Using concurrent chemoradiation as described above leads to significant morbidity. 18%, 45% and 53% of patients experience low grade genitourinary, gastrointestinal and haematological toxicity with 1.5%, 8% and 28% experiencing grade 3 or 4 genitourinary, gastrointestinal and haematological toxicity. Late complications are less well documented and range from 5-25% of patients (Loiselle et al. 2010).

IMRT increases conformality to target volumes compared to 3D-CRT thereby increasing normal tissue sparing. It uses numerous beam segments and modulated beam intensity (or fluence) to deliver steep dose gradients and shapes, such as concave, that would otherwise be unachievable. See Fig. 1.10 comparing dose coverage using 3D-CRT and IMRT.

IMRT use is established for many tumour sites such as head and neck and urology where avoidance of OARs, e.g. spinal cord and rectum respectively, is significantly optimised (Wagner et al. 2013).

IMRT for gynaecological cancer reduces high doses to bladder, rectum, bone marrow and small bowel over 3D-CRT. The largest benefit is observed for small bowel with as little as 33cc instead of 318cc receiving 45Gy (Igdem et al. 2009). Treating pelvis and para-aortic region using four-field, seven-field and nine-field IMRT techniques has been compared with two and four-field 3D-CRT. All OARs received less prescription dose (45Gy) with IMRT; small bowel volume more than halved (34% to 13%); rectal volume decreased by a factor of 7 (~45% to 6%); bladder volume halved (~60% to 30%) (Portelance et al. 2001). Another study concluded similar findings of halved small bowel volume irradiated at 45Gy with IMRT (17% versus 34%) and 23% reduction in volume of bladder and rectum receiving 45Gy. Small bowel receiving more than 30Gy was also significantly reduced (Roeske et al. 2000). Many further studies to date have confirmed this favourable dosimetry of IMRT over 3D-CRT for gynaecological cancer (Heron et al. 2003; Lv et al. 2014).
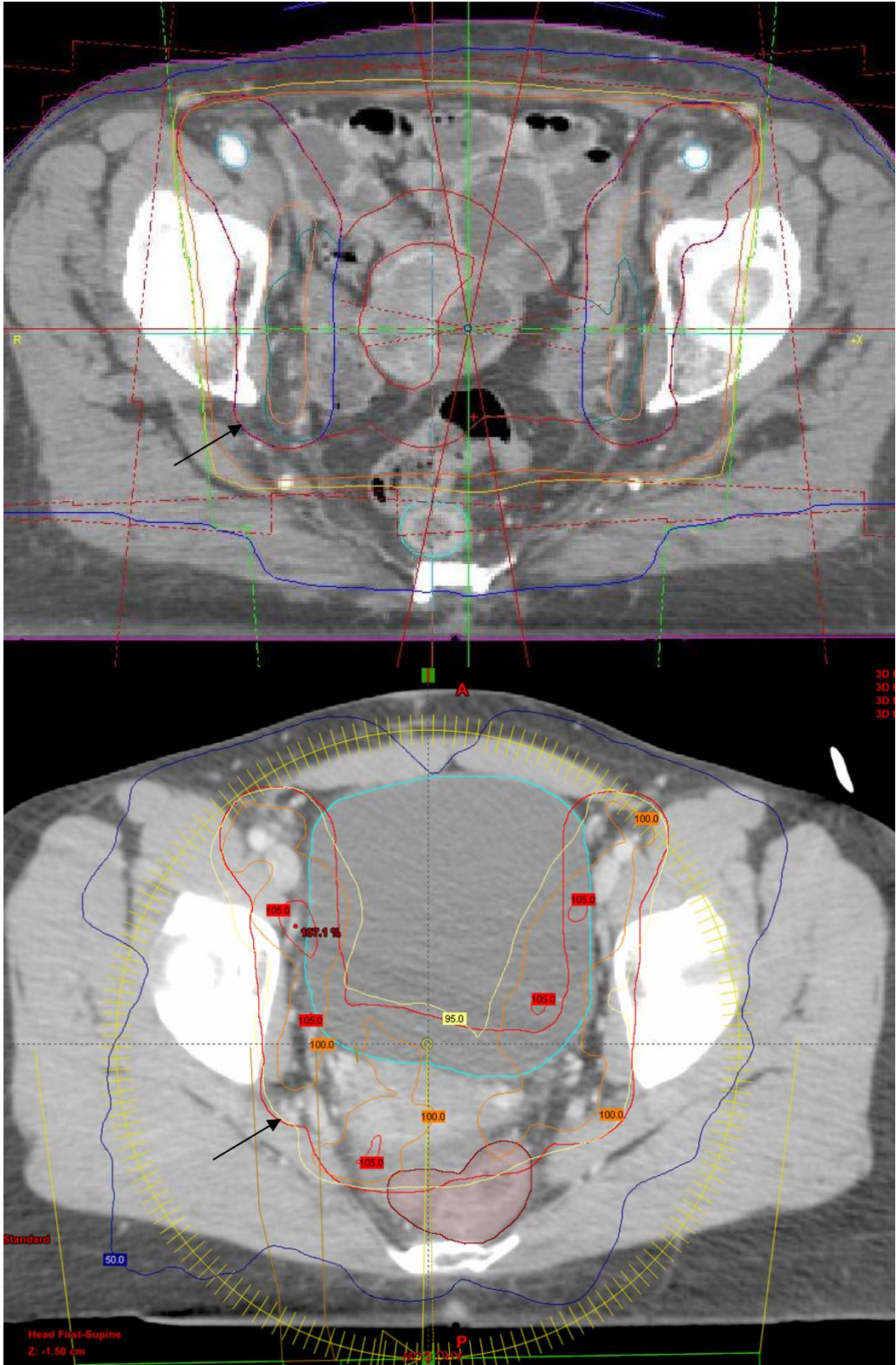
Figure 1.10: Transverse CT images showing the dose distribution of 3D-CRT (top) versus IMRT (bottom) for cervical RT. Yellow line=95% prescribed dose, orange=100%, red=105%, blue=50%. Red structure arrowed(u shaped)=PTV. The IMRT plan (bottom) conforms better with concavity anteriorly compared to the 3D-CRT (top) box shape.

Most of these studies include small patient numbers, post-operative patients and applied CTV to PTV margins of 5-10mm. This dosimetric benefit may therefore overestimate the true benefit for intact cervical cancer as post-operative CTVs are smaller and larger margins are likely to be necessary (see section 1.9.2). Increasing margin size decreases OAR dose sparing with IMRT, as expected in view of increased volume overlap (Ahamad et al. 2005). Retrospective re-planning of 50 cases used margins more representative of clinical practice at 15mm anterior-posterior and superior-inferior and up to 30mm if uterine involvement was confirmed. This comparison concluded reductions in V30, V40, V45 and V50 for all OARs with IMRT even with these larger margins (Forrest et al. 2012).

Most studies do not detail their delineation or bladder and bowel preparation methods. This is important, especially when considering bowel due to variable clinical practice, i.e. bowel loops versus part of versus whole abdominal cavity, discussed further in Chapter 4. This could alter results, especially if absolute volume benefits are reported. Bladder filling also influences bowel sparing. A decrease in IMRT small bowel sparing is seen with an increasingly full bladder specifically for patients with intact cervical cancer. Conversely, the same study reported that large bowel sparing decreases with increasing bladder size (Georg et al. 2006).

Even with these factors taken into account, IMRT clearly has a proven dosimetric benefit. The question is therefore what clinical benefit this translates to. The most evidence to date is regarding reduced bowel toxicity. Statistically significant reductions in grade 3 diarrhoea were reported in a randomised cohort of 72 patients; 5.6% versus 30.6% (Yu et al. 2015). Mundt et al analysed acute and chronic toxicity with IMRT compared to unmatched control groups receiving 3D-CRT showing a reduction in acute gastrointestinal toxicity from 95% to 53% and chronic toxicity from 50% to 11% (Mundt et al. 2001; Mundt et al. 2002; Mundt et al. 2003). Proportionately more 3D-CRT patients received concomitant chemotherapy and were higher stage with subsequently larger CTVs which may confound these findings. Reported reductions in acute genitourinary toxicity have not been statistically significant but are arguably clinically significant (7% versus 16%) with little data on chronic toxicity (Mundt et al. 2001; Mundt et al. 2002). Further studies have quoted similar acute and chronic toxicity improvements with IMRT (Chen et al. 2007; Hasselle et al. 2011; Du et al. 2012; Gandhi et al. 2013; Ray et al. 2013; Chen et al. 2015). Of note, no difference in survival was found in any of these studies.

IMRT is more expensive to deliver than 3D-CRT. This initial reduced cost-effectiveness becomes increasingly cost-effective over time due to reduced toxicity in gynaecological post-operative patients (Chen et al. 2015). Interestingly, a similar cost-effectiveness ratio calculation concluded that the IMRT initial cost is too expensive except for in extended field RT (Lesnock et al. 2013).

Haematological toxicity in this patient cohort is important due to chemotherapy administration. Anaemia, leukopenia, neutropenia and thrombocytopenia rates with IMRT have therefore been investigated. No statistical difference in acute but a trend of higher chronic toxicity with IMRT despite reduced bone marrow V30Gy and V40Gy was reported (Erpolat et al. 2014). This is possibly because of larger low dose radiation delivery. Other studies found no difference in acute haematological toxicity with 3D-CRT and IMRT but on further analyses the IMRT group received significantly more chemotherapy. Comparison of concurrent chemotherapy patients alone revealed higher grade 2 white cell toxicity with 3D-CRT (60% versus 31%) (Brixey et al. 2002) suggesting IMRT increases the likelihood of more chemotherapy administration. Further studies have confirmed reduced haematological toxicity with IMRT (Albuquerque et al. 2011; Hui et al. 2014). Key parameters predicting acute toxicity are V40Gy and median dose (Klopp et al. 2013). Overall, this evidence favours IMRT to minimise haematological toxicity thereby increasing the likelihood of administering all chemotherapy cycles.

Pelvic bone irradiation causes direct bone effects in addition to the discussed haematological toxicity. Sacral insufficiency fractures, osteonecrosis and osteomyelitis can severely impair quality of life. Comparison of 141 3D-CRT with 81 IMRT patients who received gynaecological post-operative RT showed no significant fracture rate difference with an approximate 5% risk at 5 years. The IMRT cohort received significantly more chemotherapy and no pelvic bone dose constraint was documented (Shih et al. 2013). However, using a 45Gy maximum pelvic bone dose constraint, 83 cervical IMRT patients were compared with a matched 3D-CRT group. A significant reduction in bone complications was reported with IMRT; 4% versus 17% and symptomatic complications were reduced at 4% versus 13% (Ioffe et al. 2014). More data is needed but it appears IMRT may clinically significantly reduce bone complications.

Treating para-aortic nodes with extended field RT increases toxicity. Only small cohort studies using IMRT have been published, consistently reporting lower toxicity rates than with 3D-CRT. Conventional RT results in grade 3 or greater acute toxicity in up to 49% of cases. In comparison, only 2 (15%) out of 13 patients developed grade 3 or greater acute toxicity using IMRT (Salama et al. 2006). Out of 36 IMRT patients 28% (10/36) had myelotoxicity, only 3% (1/36 for each) experienced acute genitourinary or gastrointestinal toxicity rates and two year toxicity was 10% (Beriwal et al. 2007). No grade 3 or greater genitourinary or gastrointestinal acute toxicity was reported for a further cohort of 22 patients and, again myelosuppression was the treatment limiting toxicity (Gerszten et al. 2006). Further studies have investigated feasibility of dose escalating involved para-aortic nodes using IMRT. This has confirmed improved dosimetric distributions, reduced acute and late toxicity and improved survival. IMRT for para-aortic RT is beneficial as part of a pelvic and para-aortic IMRT plan or in addition to a conventional pelvic RT plan (Ahmed et al. 2004; Du et al. 2010; Verma et al. 2014).

Other investigated applications of IMRT include treatment of isolated para-aortic nodal metastases (Aoki et al. 2003) and boosting primary tumour if technical or medical reasons prohibit brachytherapy delivery (Schefter et al. 2002; Chan et al. 2006; Gill et al. 2014). The doses achieved with IMRT are lower than with brachytherapy and subsequent outcomes are suboptimal. This should therefore only be used if an absolute contraindication to brachytherapy exists.

Disadvantages of IMRT include the extra initial cost as already discussed and increasing technology and expertise needed. IMRT also conforms so tightly to PTV that concern exists regarding recurrences at field edge or worse survival outcomes. However, outcomes so far are reassuring with good OS and DFS rates. Reported three year OS is 69-78% with chemoradiation using IMRT and three year pelvic failure rate is only 14% with favourable toxicity as detailed above (Chen et al. 2011; Hasselle et al. 2011). Accurate target volume delineation remains essential to ensure satisfactory outcomes (Wagner et al. 2013), as discussed in section 1.9.1. Unknown effects include the consequences of peripheral dose increase and the effects of IMRT on late second cancer risk. Peripheral dose does increase with IMRT but this increase is very small at 0.12% of prescribed dose (Salz et al. 2012). This effect was less with 6MV versus 15MV and the actual clinical consequence is unclear. The

absolute risk of second cancers is increased with IMRT to 1.75% at 10 years compared with 1% for 3D-CRT. This is a combination of increased low dose volume and monitor units (absorbed dose measurement), accounting for 0.5% and 0.25% increase respectively (Hall et al. 2003). These figures were calculated for 6MV IMRT and will be higher if higher energy is used, e.g. 18MV or Tomotherapy. These treatment energy effects are striking with a 6% relative increase using 6MV versus a 26% increase using 18MV. Overall, this is still less than a 1% absolute increase in risk (Zwahlen et al. 2009).

IMRT can be delivered using different approaches. The dynamic (sliding window) approach moves MLCs across the field whilst the beam is on to alter the intensity. Step-and-shoot uses multiple static beams of varying shapes. Volumetric modulated arc therapy (VMAT) delivers radiation as the machine is moving around the patient in an arc. VMAT delivers lower peripheral tissue doses, lower monitor units and shorter treatment time with similar target dose coverage compared to seven-field step-and-shoot IMRT (Jia et al. 2014). Similar findings with RapidArc (VMAT delivery method, Varian Medical Systems, Palo Alto, CA) compared with five-field IMRT lead to a reduction in normal tissue complication probability with comparable target coverage (Cozzi et al. 2008). Twelve and twenty-field IMRT plans showed superior OAR sparing and similar PTV coverage but take more than five times longer than single arc VMAT (Sharfo et al. 2015). Treatment time is important for service implications and positional consistency and therefore volumetric approaches may be favoured in clinical practice.

The evidence presented here supports IMRT use especially in patients receiving concurrent chemotherapy and extended field RT. The practical application however does highlight some challenges which are discussed further in section 1.9 and are the focus of this work.

1.8.2. MRI guided brachytherapy

Using a pre-defined BT plan, as discussed in section 1.7.4, is not in keeping with targeted RT delivery. Therefore, in 2005, the Groupe Europeen de Curietherapie- European Society for Radiotherapy and Oncology (GEC-ESTRO) published 3D image-guided brachytherapy (IGBT) delivery recommendations (Haie-Meder et al. 2005). Subsequent Royal College of Radiologist guidance (RCR 2008) and the EMBRACE study group have established MRI-guided BT as standard of care across Europe. MRI is used to delineate the high risk CTV (HR-

CTV) and intermediate risk CTV (IR-CTV) (Table 1.5, Fig. 1.11). Optimisation of the standard 'pear-shaped' plan is then performed to deliver dose to HR-CTV rather than Point A. Dose is prescribed to D90 i.e. at least 90% of HR-CTV is receiving prescribed dose.

Target	Description
HR-CTV	Macroscopic tumour extension at time of brachytherapy + whole cervix + presumed extra cervical tumour extension
IR-CTV	HR-CTV + macroscopic tumour extension at diagnosis providing a minimal margin of 10 mm to residual disease at time of brachytherapy in direction of potential spread. A reduced margin should be used towards an intact anatomical barrier

Table 1.5: CTV definition according to GEC-ESTRO and EMBRACE guidance
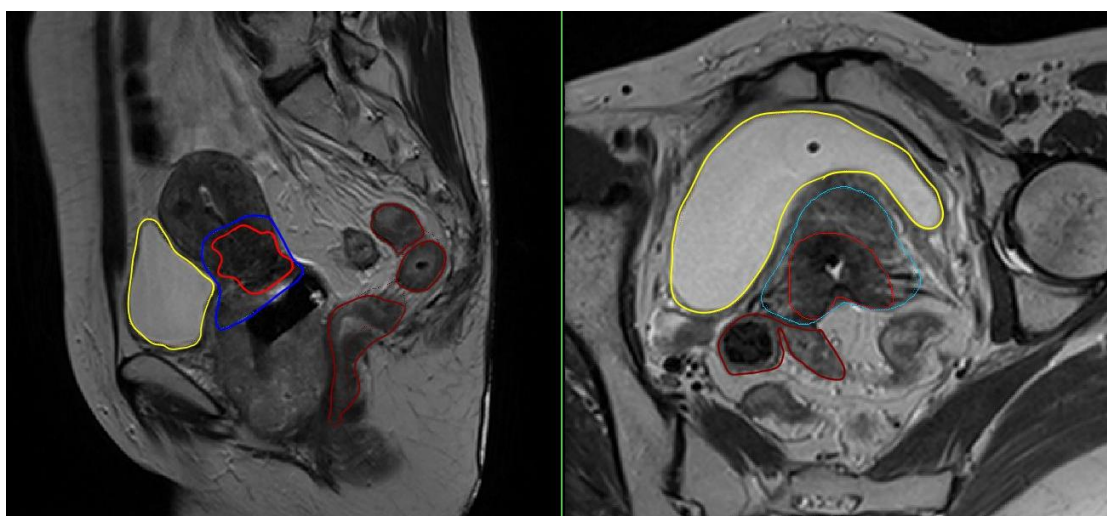
Figure 1.11: Sagittal and para-uterine MRI images with intrauterine tube and ring in-situ for cervical brachytherapy. HR-CTV (red), IR-CTV (blue), bladder (yellow) and rectum (maroon) outlined.

Interstitial needles may be necessary to ensure tumour coverage, especially in cases with parametrial and pelvic sidewall extension. The EMBRACE2 study will investigate dose optimisation and continues to develop IGBT.

BT is not the focus of this work and will therefore not be discussed in any further detail.

1.8.3. Stereotactic Body Radiotherapy

Stereotactic Body Radiotherapy (SBRT) uses multiple co-planar beams which intersect at the target to deliver highly conformal dose distributions. The dose within target is heterogenous mimicking, but not as heterogenous as, dose distributions of BT, i.e. a proportion of target receives significantly higher than the prescribed dose. Small case series and retrospective studies have been published utilising SBRT in place of BT for cervical cancer or comparing the two techniques (Cengiz et al. 2012; Haas et al. 2012; Hsieh et al. 2013). These have

shown that SBRT is a feasible alternative with good early outcomes. However, SBRT still needs margins to be applied, requires image guidance e.g. real time tracking with fiducial markers, and is unlikely to achieve the maximum doses of >300% prescribed achieved with BT (Al Feghali et al. 2016). Most evidence is also in the recurrent setting or in patients unable to undergo BT. SBRT is therefore not recommended as an alternative to BT unless an absolute contraindication exists for BT. SBRT use in the recurrent setting is increasing and is under investigation.

1.9. Challenges in RT delivery

As IMRT conforms more tightly to target volumes many technical challenges are highlighted. This section introduces what I consider to be two of the key challenges in current cervical cancer RT, especially in the IMRT era. These are areas where data specific to cervical cancer either does not exist or are conflicting. This is therefore the focus of my work presented here.

Increased conformality with IMRT increases the importance of delineation accuracy. This is concerning as target volume delineation is well documented to be one of the largest uncertainties in RT planning in many tumour sites. However, there is little evidence investigating delineation variation specific to cervical cancer EBRT as discussed in section 1.9.1. Chapter 2 to 4 therefore investigate this.

Organ motion is the second important challenge which is emphasised by increased IMRT conformality. Bladder and bowel are known to vary in size and shape daily. There are published data regarding this but the data on its impact on cervical cancer EBRT are limited and lacks consistency, as discussed in section 1.9.2. Also, despite studies investigating this, no guidance exists regarding measures to reduce organ motion and little data is published regarding the actual dose effect of daily organ position variation. Chapter 5 and 6 address these issues.

1.9.1. Target delineation

Inter-observer variability has been confirmed across many tumour sites, including oesophageal, prostate, head and neck, bladder, breast and lung (Cazzaniga et al. 1998; Valley et al. 1998; Meijer et al. 2003; Li et al. 2009; Vorwerk et al. 2009; Gwynne et al. 2011). Since the introduction of IGBT, variation has also been documented in cervical brachytherapy

(Petric et al. 2008; Dimopoulos et al. 2009; Hellebust et al. 2013; Petric et al. 2013). Comparison of HR-CTV delineated on CT versus MRI concluded that small delineation differences can lead to altered target dosing when optimising a brachytherapy plan to a volume (Eskander et al. 2010; Krishnatry et al. 2012). Dosimetric variations large enough to alter treatment optimisation were found when five clinicians delineated OARs for brachytherapy (Duane et al. 2014).

To my knowledge, only three studies have assessed inter-observer variation of EBRT GTV and CTV delineation for cervical cancer (Weiss et al. 2003; Wu et al. 2005; Lim et al. 2015). A single centre study of 3 cervical cancer cases independently outlined (CTV) by seven clinicians was published. Through analysis of anatomical areas included within the outline, ratio of largest to smallest volume, ratio of common to encompassing volumes and differences in maximum diameters they concluded that large variations were observed despite wide agreement between physicians regarding anatomical areas contoured. Up to 19cm variation was seen in the craniocaudal direction, and the ratio of largest to smallest CTV volume ranged from 3.6 to 4.9 (Weiss et al. 2003). A further study analysed 6 observers contouring cervical GTV alone on MRI for 20 cases (Wu et al. 2005). Statistically significant differences in GTV volume on MRI were found. Median difference in maximum to minimum delineated volume was more than 40cm^3. Percentage volume differences were not published. Challenges reported by observers included technical factors, e.g. susceptibility artefacts and partial voluming, patient factors including other pathologies such as atypical myxoma and tumour factors including parametrial extension and post radiation changes including heterogeneity and necrosis. These findings are interesting but the clinical impact is unclear as CTV delineation on CT imaging is more representative of current practice. The third study is therefore more clinically relevant as it compared primary and nodal CTVs delineated by 12 experts for 3 complex cases using Simultaneous truth and performance level estimation (STAPLE) sensitivity and specificity assessment (Lim et al. 2015). They concluded moderate to substantial agreement with heterogeneity greatest for the cervix and vagina. In Chapter 2, using the UK INTERLACE radiotherapy quality assurance (RTQA) test cases I quantify the variation witnessed between 21 observers for primary and nodal CTV in two independent cases. This is a larger cohort that previously reported on.

To estimate the clinical impact, in Chapter 3 I assess the dosimetric impact of the delineation variation observed in these RTQA cases. To my knowledge, no previous studies have quantified this.

Delineation guidance has been shown to reduce variation in some tumour sites, discussed further in Chapter 4, but not cervical EBRT. I therefore review the available delineation guidance for cervical EBRT, create a pictorial delineation atlas and monitor its impact on the observed variation in Chapter 4.

1.9.2. Target position daily variation

Pelvic organ position variation is seen during chemoradiation, primarily due to bladder and rectal filling variations (Wagner et al. 2013; Jadon et al. 2014). Increased conformality with IMRT raises concern of target under-coverage if organs move from planning position. Jadon et al systematically reviewed the literature investigating organ motion to date (2014), reviewing 39 studies, 12 of which were conference abstracts. These studies were heterogeneous and in general of small case numbers. The patterns observed appear to be patient specific and vary largely, from 5mm to 40mm shifts (Jadon et al. 2014). Bladder volume decreases through treatment as does uterine volume (Lee et al. 2007; Ahmad et al. 2008). Maximum uterine movements are seen superiorly then anterior-posteriorly with small vaginal and cervical movements and minimal movement laterally (Chan et al. 2008; Taylor et al. 2008). Some studies confirmed a correlation between bladder filling and uterine movement, primarily superior-inferiorly, and rectal filling with cervical and vaginal movement, primarily anterior-posteriorly (Buchali et al. 1999; Taylor et al. 2008), whilst others were unable to explain inter-scan motion by bladder and rectal filling changes (Chan et al. 2008; van de Bunt et al. 2008). Bladder filling alone has reportedly moved the cervix 15mm (Beadle et al. 2009; Haripotepornkul et al. 2011). The largest uterine movements reported were up to 65mm with a 'comfortably full bladder'. This was therefore considered an unacceptable set-up error and alternative bladder filling was recommended such as variably full bladders (Ahmad et al. 2011).

This heterogeneous data from small studies illustrate that pelvic organ motion is at times very large and in part predictable. Overall, uterine motion is larger than cervical with bladder filling affecting both uterine and cervical motion and rectal filling affecting cervical. Other factors also

influence target position which are not fully understood. Use of bladder and bowel preparation regimens could minimise this but, to my knowledge, no published recommendations exist.

Tumour regression may confound some of the above findings. Cervical tumour volume reductions are reportedly 31-70% through treatment and can occur rapidly, with time to 50% reduction reported at only 21 days (Lee et al. 2004; Beadle et al. 2009; Herrera et al. 2013). As tumour regresses cervical motion may increase leading to target under-coverage as, in theory, locally invasive tumour fixes cervical position. There is no evidence supporting this. In fact, after delivery of 30Gy, target coverage remained adequate despite a 46% mean GTV reduction (range 6.1-100%) (van de Bunt et al. 2006). Perhaps the original CTV is large enough to cover any additional movement. Of interest, in this situation, replanning reduced bowel dose and this approach could therefore optimise OAR dose (van de Bunt et al. 2006). Using CBCT imaging taken during the course of cervical chemoradiation for ten patients I investigate organ motion to understand organ filling effects on CTV coverage and how to minimise variation. I specifically analyse the imaging to create a clinically applicable bladder and bowel preparation protocol. Chapter 5 presents this analysis and my proposed protocol. As previously stated, no published recommendations exist.

CTV to PTV margins are applied to account for organ motion and position changes through treatment. However, cervical cancer margins applied in the literature are as little as 3mm (Stewart et al. 2010) yet target moves up to 65mm. Due to the motion data already discussed, variation of margins around uterus and cervix appears a logical approach. Isotropic margins of 4cm at the fundus and 1.5cm at the os have been proposed but the importance of soft tissue imaging was emphasised as even 4cm did not guarantee coverage (Chan et al. 2008). Delineating the cervix and uterus separately on CT is impractical and a large 4cm margin will negate IMRT benefit. An alternative is anisotropic margins such as 15mm anterior-posteriorly, and superior-inferiorly with 7mm laterally (Taylor et al. 2008). These recommendations are based on consecutive day scans and may underestimate movements over a course of RT. Other studies propose CTV margins of 8-24mm with some suggesting specified margins for each direction (Buchali et al. 1999; van de Bunt et al. 2008). Being so prescriptive is unnecessary and clinically questionable. Within the two current UK cervical RT studies (DEPICT, INTERLACE (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=11775))

CTV margins of 15-20mm anterior-posteriorly and superior-inferiorly with 7-10mm laterally are applied. The European EMBRACE2 study (www.embracestudy.dk) also uses 15mm margins with discretionary adaption if less or more movement may be expected. They also suggest the internal target volume (ITV) approach, discussed in Chapter 7. Assessing the data presented already, 15mm margins are likely to account for cervical variation but not all uterine movements. However, the necessary dose for uninvolved uterus is unclear as no recurrences are documented there.

Van herk et al published a mathematical approach to calculating margins using random and systematic errors from patient cohorts (van Herk et al. 2000). Using this method in Chapter 5 I calculate the margin necessary to account for the set up and organ motion errors in my ten cases and compare this with the published data.

The dosimetric impact of organ motion has been investigated in only a few small (~10 cases) studies with variable results. Through summing DVHs, a trend of decreasing coverage with time was seen without statistically significant dose reductions using a 15mm margin (Han et al. 2006) whereas a 1cm margin reduced delivered dose by approximately 5Gy, from 48.75Gy, and use of a tapered margin (2.4cm at fundus to 1cm at cervix) improved uterine coverage but increased normal tissue doses (Gordon et al. 2011). Conversely, uterine D98% (dose delivered to 98% volume) was maintained above 90% of prescribed dose for each fraction treated with a 5mm margin IMRT plan (Jensen et al. 2015). Cervix dose was not detailed. These findings highlight the importance of margin size but do not inform on overall dose delivered to specific points within CTV. This point dose information is difficult to calculate, especially when the organ changes shape and dimensions as well as position. This is however important to ensure the same area is not consistently under-dosed. Deformable dose algorithm software, such as MORFEUS, converts outlines into representative three-dimensional surface measures and is able to overlay each mesh and estimate dose to each point within the structure. This was used to compare a four-field box, large margin IMRT plan (20mm margin except inferior 10mm) and small (5mm) margin IMRT plan for 20 cervical patients (Lim et al. 2009). No significant difference in planned and delivered dose was found but small decreases were seen in GTV and CTV dose with the small margin IMRT plan. The accumulated D98% remained ≥95% in all cases for GTV and 19/20 cases for CTV, and

therefore the 5mm margin plan was deemed adequate. This is in agreement with Jensen et al but not Gordon et al. In a larger cohort (33 women), using 3mm margins, MORFEUS showed that, without replanning, acceptable dose, defined as D98≥95% dose, was achieved in only 73% of cases (Stewart et al. 2010). By weekly replanning, this coverage was achieved in all. Interestingly, only Gordon et al detail where dose is compromised. They describe dose detriment at the uterine fundus, an area of lower relapse risk and therefore less clinically relevant. 5Gy compromise may therefore be accepted. This would be unacceptable in the cervical region.

Together, these studies demonstrate potential dose detriment, the magnitude of which remains unclear. Results using dose deformation software are more representative but also involve assumptions e.g. weekly imaging represents daily position, and detail is lacking regarding where dose is compromised. Absolute minimum dose required is also unclear as dose prescriptions between studies varies, ranging from 45 to 50Gy in 25 to 30 fractions, as does practice across countries. Despite these uncertainties, processes are clearly needed during IMRT to minimise and account for organ motion. Options include patient specific margins with anisotropic margins, strict bladder and bowel preparation and adaptive RT (Jadon et al. 2014). Adaptive RT, detailed further in Chapter 7, applies approaches to compensate for daily changes. An example is creation of an 'internal target volume' (ITV) based of variable bladder filling scans and selection of a bladder empty-to half-full and half-full-to-full dependent on daily bladder filling (Bondar et al. 2012). Whilst these methods undergo validation ongoing monitoring is essential.

In Chapter 6 I investigate the dose effect of the observed organ motion in my patient cohort, if treatment was delivered using IMRT, using a novel vector-based technique to assess central point doses. These results contribute further to the proposed preparation protocol discussed in Chapter 5.

1.10. Thesis statement

In the current era of evidence based medicine and with the introduction of advanced RT techniques focus must remain on safe treatment delivery. Technological advances are increasing the complexity and accuracy of RT for locally advanced cervical cancer. Understanding the variabilities within our RT planning process is vital to ensuring treatment accuracy. This work therefore studies potential variables within the RT process to understand their importance and establish methods of reducing variation, thereby improving the quality and hence the therapeutic ratio in this patient group. To achieve this I focus on two key challenges; target volume delineation and daily pelvic organ position variation. I quantify the variation in cervical cancer target volume delineation (Chapter 2) and assess its dosimetric impact if treatment was delivered with IMRT (Chapter 3). I then review the available cervical cancer delineation guidance, using this to create a pictorial delineation atlas and after implementing this atlas assess for changes in the observed variation (Chapter 4). Using imaging taken during chemoradiation for ten patients I analyse bladder and rectal filling and its impact on CTV coverage (Chapter 5). I also use this cohort to calculate CTV to PTV margins and propose a bladder and bowel preparation protocol (Chapter 5). The dosimetric impact of this variation if treatment was delivered with IMRT is evaluated by using a novel vector based technique (Chapter 6).

Overall, the aim of this work is to demonstrate that a better understanding of delineation and organ position variation during chemoradiation will improve standardisation of RT and facilitate safe introduction of advanced techniques, ultimately improving outcomes and lessening toxicity.

Chapter 2

Variation of clinical target volume (CTV) delineation in cervical cancer radiotherapy

across the UK.

2.1. Introduction

Many centres within Europe and the UK use IMRT for the curative treatment of cervical cancer. IMRT reduces the dose delivered to OARs compared with 3D-CRT (Portelance et al. 2001; Forrest et al. 2012) thereby leading to reduced toxicity rates (Mundt et al. 2001; Salama et al. 2004). It does this by conforming the RT dose much closer to the target volumes. Therefore, to ensure precise and safe treatment delivery when using IMRT it is vital to delineate the GTV, CTV and OARs accurately. However, it is well documented that one of the largest uncertainties within RT planning is target volume delineation. Significant inter-observer variability has been published across many tumour sites, and in cervical brachytherapy since the introduction of MRI-guided techniques as described in Chapter 1, section 1.9.1. There are only a few studies which assess inter-observer variation of EBRT GTV and CTV delineation for cervical cancer, as detailed in 1.9.1 (Weiss et al. 2003; Wu et al. 2005; Lim et al. 2015). Weiss et al, in 2003, studied 3 cervical cancer cases which were independently outlined (CTV) by seven clinicians finding significant variations, up to 19cm. In 2005, Wu et al published (Wu et al. 2005) on the variation seen between 6 observers contouring 20 cases' cervical GTV on MRI. Statistically significant volume differences were found. In contrast, moderate to substantial agreement was found by Lim et al having compared 12 experts' primary and nodal CTV outlines for 3 complex cases (Lim et al. 2015).

As part of the INTERLACE RTQA participating centres outline and plan two test locally advanced cervical cancer cases following trial protocol. This chapter firstly reviews the methods applied in the literature to quantify delineation variation. Then, using the most appropriate of these parameters to analyse the outlining variation, I analyse the variation between the first RTQA test cases submitted by 21 of the UK INTERLACE centres. My analysis of variation witnessed within the INTERLACE RTQA was published in Radiotherapy and Oncology (Eminowicz et al. 2015).

2.2. Assessment methods for delineation variation quantification

2.2.1. Methods of literature review and quantification method comparison.

To understand which quantification methods are most frequently used to analyse delineation variability, a literature review was performed. The pubmed/medline central database was

searched with the MESH term 'radiotherapy' in combinations with the terms 'target volume outlining', 'target volume delineation', 'volume delineation', 'volume outlining', 'variability', and 'quantification'. All articles presenting delineation comparison between observers and/or cases were selected and reviewed for details of publication, primary theme of article, tumour sites included, number of observers, number of cases, and number and details of quantification parameters selected to represent delineation variation. This provided an overview of how delineation variation is quantified and presented in published data. The quantification methods published were then examined and the articles that presented methods of quantifying delineation variation were reviewed separately to aid understanding of these methods. By explaining the theory behind these methods, a combination of parameters is selected as an optimum approach to analyse delineation variation in cervical EBRT. This selection is based on published parameter combinations in addition to the theoretical understanding of these methods.

2.2.2. Quantification methods literature review results

The literature review was completed on 3rd April 2014. 113 articles were identified through the search methods. 14 of these articles were not included in the full analysis because either they did not present any outlining comparison (6) or they focussed on specific techniques of assessing delineation variation and were therefore reviewed when discussing the theory behind methods used. Therefore, 99 (for summary Table see Appendix 1) articles in total were reviewed. These all present results of comparisons in delineation between observers, cases or process of delineation. These were published between 1991 and 2014. 54 were published between 2007 and 2012. No correlation was found between year of publication and number of methods used to quantify delineation variation. The main theme of the articles include the existence of inter-observer variation (29 articles), factors influencing inter-observer variation including use of guidelines or specific imaging techniques (53), accuracy of automated segmentation (4), RTQA (2), and the presence and impact of inter-observer variation on dosimetry (11). These 99 articles were published in 21 different journals, the majority (70%) in one of two journals; the 'International Journal of Radiation Oncology Biology and Physics' and 'Radiotherapy and Oncology'. The vast majority (97) focus on a single tumour site. The most common tumour sites are prostate (29 articles), lung (15), head and neck (11), breast

(11) and CNS (9). The number of observers performing delineation ranges from 1 to 48, median 6. Only 2 articles use 1 observer. 52 articles use between 3 and 7 observers. The number of cases delineated ranges from 1 to 42, median 9. 41 articles use 5 or less cases. Overall, the number of cases and observers is negatively correlated (pearson correlation -0.4, p<0.001 two tailed sig test) with articles that use a low number of cases being more likely to use a high number of observers and vice versa.

The majority of articles (82) use more than one parameter to quantify delineation variation. There appears to be no correlation between whether the articles focus solely on delineation variation and the number of methods applied. The following description includes the most commonly used methods and is therefore not exhaustive.

2.2.3. Explanation of quantification methods and parameters

For the purposes of description the assessment methods are divided into four groups: Volumetric, Dimensional, Positional and Statistical measures of agreement.

Volumetric parameters: volume, volume overlap methods

Volume

In line with previous reviews (Jameson et al. 2010; Fotina et al. 2012), the most commonly used parameter was volume. 87 out of the 99 articles analysed volume in their results. This included absolute volume measurements, including changes, and conventional statistics (mean, standard deviation (SD)). This is easily computed and easily understood by clinicians and gives clinical information as it represents the irradiated tissue volume.

Maximum to minimum ratio, also termed the maximum volume ratio (MVR) (Logue et al. 1998), gives a simple useful assessment of inter-observer variation. It is easily computed and understood but is significantly affected by outliers and by volume size.

Coefficient of variance was used to represent volume variation in 18 of the articles;

$$Coefficient\ of\ variance = \frac{standard\ deviation\ of\ the\ volume}{mean\ volume}$$

This calculation eliminates bias due to volume size and conventional statistics can still be applied.

The calculations discussed so far do not give any information on position or shape of the structures: as seen in Fig. 2.1 similar volumes can have very different shapes and locations.
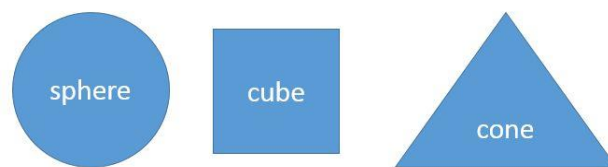
Figure 2.1: Three differing outlines with the same volume.

Volume overlap measures

Volume overlap measures were the second most common method applied, in 54 articles. There are many differing calculations which fall into this category but the underlying concept is the same. Terminology lacks consistency. Some calculations are identical but have differing names. The terms used include conformity index, conformality index, concordance index, concordance volume, ratio of common to encompassing volume, and percentage overlap. The most commonly used is the index that Paul Jaccard created in 1901 for botanic comparisons and originally called it the 'coefficient de communaute' (Jaccard 1901). This has subsequently been adopted for delineation comparisons and forms the Jaccard conformity index (JCI).

$$Jaccard\ CI = \frac{volume\ of\ intersection\ AnB\ (i.e.common\ volume)}{volume\ of\ union\ AuB\ (i.e.encompassing\ volume)}$$

Fig. 2.2 illustrates this calculation. Perfectly overlapping outlines have a JCI of 1.0, and a JCI of 0.5 equates to a 66% overlap, JCI 0.6 75% overlap, 0.7 approximately 82% overlap and 0.82 90% overlap.
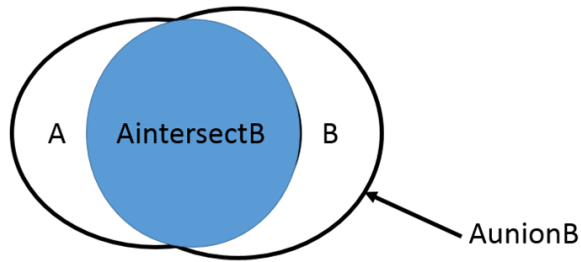
$$Jaccard\ CI = \frac{volume\ of\ intersection\ AnB\ (i.e.\ common\ volume)}{volume\ of\ union\ AuB\ (i.e.\ encompassing\ volume)}$$

Figure 2.2: Diagram illustrating Jaccard Conformity Index (JCI)

The JCI compares two outlines only, can be calculated easily and takes into account volume and position. Ideally a reference volume is needed and the results are affected by volume size. The JCI gives no information on the shape or location of the structures. It is also not clear what is an 'acceptable' result, despite knowing 1 is perfect agreement and 0 is no agreement. Other terms such as percent volume overlap (Rao et al. 2005; Li et al. 2009) use the same calculation.

The Kouwenhoven is a generalised conformity index that can compute multiple volumes in one equation by using confidence levels, i.e. the proportionate number of outlines including each point (Kouwenhoven et al. 2009). This is not as simple to calculate but does not need a reference volume and facilitates analysis of multiple volumes in one calculation.

Dimensional parameters: encompassing and surface

Dimensional parameters were used in 46 articles. They can be categorised into two distinct groups; encompassing dimensions, e.g. diameter, and surface dimensions.

Encompassing dimensions

Distance measurements are termed encompassing dimensional parameters. They provide information on the overall size of the structure. This includes length, width, and boundary distances i.e. distance from centre of volume in certain axis, maximum X, Y, Z limit in all 6 directions (anterior, posterior, inferior, superior, left and right lateral).

These are useful in the clinical situation where you are expecting the volume to be regular or spherical e.g. prostate (Cazzaniga et al. 1998; Debois et al. 1999) or where it is clinically relevant e.g. length in oesophageal cancer (Schreurs et al. 2010). These measurements are also easily understood and processed.

Surface dimensions

Other dimensional parameters assess small differences in the surface location of two outlines. These include the average surface distance (Li et al. 2009; Shaikh et al. 2010), median surface distance (Deurloo et al. 2005), surface congruence analysis (Wijesooriya et al. 2008), maximum surface separation (Hausdorff) (Rao et al. 2005), and radial line measurement variation (Seddon et al. 2000). These calculations are variations of assessing distances along different angles or points of the outline, usually from the centre of the volume. The average surface distance was the most commonly used of these parameters, applied in 11 articles. It involves calculating the average of the minimum distance from a point on one outline to the other for all pixels (Li et al. 2009; Shaikh et al. 2010). The Hausdorff maximum surface separation is similar, calculating the average distance between 2562 points on 2 outlines. These are complex calculations which cannot be performed using a treatment planning system (TPS). However, interpretation is relatively simple. Clinicians can understand an average distance difference and the results are clinically relevant. A specific cut off figure cannot be used for these parameters as the result is biased by volume size and the clinical implications of the same distance may be very different for a small versus large volume.

Positional

COM and Shift in COM

Centre of mass (COM) or shift in COM were applied in 23 out of the 99 articles. COM is a simple calculation which can be performed on all TPSs. It is not useful as a single parameter as it does not inform on anything other than the central position of a structure. As can be seen in Fig. 2.3 two outlines can be very different with an identical COM**.**
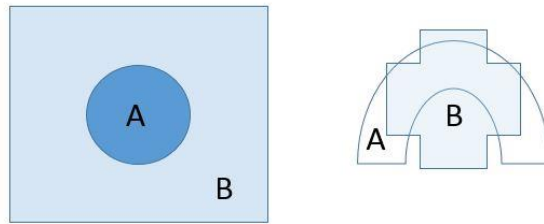
Figure 2.3: Illustrations of outlines with the same COM.

Shift in COM is more clinically useful and is another understandable concept for clinicians as it is clinically relevant. These parameters are most useful if the outline is a spherical or uniform structure e.g. prostate (Villeirs et al. 2005; Song et al. 2006).

Statistical measure of agreement

Intraclass correlation coefficient

Intraclass correlation coefficient is a statistical measure of proportion of variance which creates a result that can be interpreted in the same way as the pearson correlation coefficient. This was originally described as a method of quantifying the variation of assessing dental caries in a trial setting (Fleiss et al. 1979). Multiple outlines can be compared simultaneously. It is complex, makes assumptions of uniform error variance, and many options apply e.g. one way versus two way, consistency versus agreement etc. This cannot be calculated using a TPS and is more difficult to interpret than the previously discussed parameters. This is the likely reason that it was only used in 6 of the papers reviewed. This is also referred to as the concordance correlation coefficient (Buis et al. 2007).

Suggestions for reporting

None of the parameters detailed here are sufficient alone to describe the detail necessary for outline variation. Conformity index is the most useful single parameter because it informs on volume and position together. Application of more than three parameters is unnecessary and becomes complicated and confusing. My recommendation is therefore that 2 or 3 parameters are used which includes at least 1 volumetric parameter. The combination should depend upon what type of outline is being compared. For example, prostate outlines can be compared

by COM, JCI and encompassing dimensions whereas a pelvic nodal outline should be compared by total volume, JCI, and encompassing dimensions. Alongside any quantitative review a qualitative assessment is always necessary. For some outlines qualitative assessment can be quantified e.g. in a pelvic nodal outline the proportion of outlines including certain anatomical regions can be calculated.

The following analyses of the cervical primary and nodal CTV will therefore include total volume, JCI, and maximum X, Y, Z limit in all 6 directions (anterior, posterior, inferior, superior, left and right lateral). Within the qualitative assessment the proportion of centres including specified anatomical areas will also be reported.

2.3. Methods of delineation variation analysis

2.3.1.   Delineation process

To complete the INTERLACE RTQA each investigator delineated two test cases (as detailed in the INTERLACE RTQA pack v1.4; see Appendix 2). Case 1 was a 64 year old with a bulky barrel shaped FIGO stage 3B squamous carcinoma with bilateral parametrial extension, right pelvic sidewall extension and ureteric obstruction. Case 2 was a 64 year old with a smaller FIGO stage 2B squamous carcinoma with bilateral parametrial extension and involvement of the lower uterus extending 2cm proximal to internal os. All investigators had access to the RTQA pack (v1.4 seen in Appendix 2). This includes the anonymised patient history, EUA findings and imaging reports. The investigators did not have the diagnostic MRI images, which would standardly be used for reference when outlining on designated planning CT. The planning CT, acquired with 0.25cm slice thickness, was available in 'digital imaging and communications in medicine' (DICOM) format and could be imported into any TPS. This allowed the investigator to outline the cases on the TPS which they are familiar with and use in their normal daily practice. The first 10 centres completed delineation using the INTERLACE protocol version 1 (V1) and the subsequent 11 centres used an updated version (V1.4). V1 and V1.4 differ regarding inclusion of upper vagina and bilateral parametria in CTV2 for V1 and CTV1 for V1.4. There is no other difference in the outlining guidance or resources supplied between V1 and V1.4. Therefore, both protocols recommend inclusion of the same anatomical areas within the combined CTV1 and CTV2. This includes tumour, entire cervix, bilateral

parametria, ovaries if seen, upper vagina, entire uterus, and high risk pelvic nodal areas as discussed later. Delineation review by the INTERLACE RTQA team was performed. This involved assessment of protocol compliance and compilation of a report detailing areas of variation from protocol. All cases that were deemed not protocol compliant were returned to the relevant centre with the report and had to be edited according to the report and resubmitted. The resubmissions were only approved once fully protocol compliant.

2.3.2. Gold standard delineation

To facilitate the assessment of protocol compliance gold standard outlines for case 1 and case 2 were required. To create these gold standard outlines 5 members of the trial management group (TMG) who were experienced RT clinicians working in 5 different UK centres independently completed the two RTQA test cases. The TMG is a consortium of 15 professionals, including 4 consultant clinical oncologists, 2 clinical oncology research fellows (including myself), 1 RTQA physicist and 3 medical oncologists. The 5 RT clinicians downloaded the two test cases onto their TPS and delineated them following protocol as each participating centre would do. These independent outlines were then imported in DICOM format onto one planning CT and were simultaneously and anonymously visually and qualitatively reviewed by the TMG. A consensus outline for each OAR and CTV was then manually created and this is the 'TMG gold standard'.

Due to the lack of a mathematical or computational approach to the creation of this TMG gold standard I decided to quantitatively validate this outline. Therefore, a separate STAPLE outline, as described by Warfield et al was created for both test cases (Warfield et al. 2004). This STAPLE algorithm applies an expectation-maximisation algorithm to multiple outlines of one case to compute a probabilistic estimate of the true (gold standard) outline. By using all of the submitted outlines together STAPLE estimates the optimal outline combination by weighting each outline depending upon the estimated performance level. It also incorporates spatial distribution and spatial homogeneity constraints models (Warfield et al. 2004). To create the STAPLE, a confidence level in outline agreement must be selected. For our algorithm we applied a 95% confidence level. Using this 95% confidence level I imported all 21 centres' outlines into CERR (a computational environment for radiotherapy research

software) (Deasy et al. 2003) and created the STAPLE outline. I then imported the TMG gold standard outline into CERR to allow direct comparison and validation. Areas of variation between the TMG and STAPLE outline were reviewed and alterations were made to the TMG gold standard if clinically relevant differences were observed. This led to the creation of an 'optimised gold standard' outline (GSCTV1+2) which is the reference volume I used.

2.3.3. Delineation comparison

The combined 'CTV1+2' was analysed to allow comparison of all cases together as individual analysis of CTV1 and CTV2 would highlight inconsistencies due to variation in upper vagina and parametrial inclusion between protocols as explained earlier (section 2.3.1). The anatomical areas included in the combined CTV1+2 was identical for V1 and V1.4; tumour, entire cervix, bilateral parametria, ovaries if seen, upper vagina, entire uterus, and high risk pelvic nodal areas. Each CTV1+2 outline was imported into CERR and SHERRI (surrey heuristic engine for radiotherapy radiobiology and imaging). The maximum distance from the DICOM centre (i.e. CT reference point), total volume (CTV1+2), JCI and anatomical regions included were analysed on CERR. Volume and JCI were also calculated using SHERRI to validate the CERR results.

CTV1+2 total volume was calculated on CERR and SHERRI separately. The average of these two calculations was recorded as the result.

The maximum distance from the DICOM centre in all 6 directions was calculated by recording the most extreme X, Y or Z coordinate in all 6 directions (anterior, posterior, inferior, superior, left and right lateral) on which CTV1+2 is seen. The X, Y and Z coordinates represent the distance in centimetres from the DICOM centre. The most extreme point in one direction for two independent outlines are not necessarily at the same point along the axis. This means they may be in different anatomical regions.

The JCI, as explained above, was calculated for each outline against the optimised gold standard outline (GSCTV1+2). This calculation is programmed into SHERRI. Manual calculations on CERR were performed to validate the SHERRI result. The optimal JCI result is unclear from the literature even though clearly closer to 1 is better. A poor correlation of outlines has previously been documented as JCI<0.5 (Peterson et al. 2007; Jena et al. 2010)

and Gwynne et al suggested JCI ≥ 0.7 is acceptable (Gwynne et al. 2013). This level of JCI≥ 0.7 is what I applied for my analysis and equates to approximately 82% overlap.

A visual review of each outline was performed on CERR to record the proportion of outlines which included the following anatomical areas:

- Common iliac nodal region

- Internal iliac nodal region

- External iliac nodal region

- Obturator nodal region

- Pudendal nodal region

- Inguinofemoral nodal region

- Presacral nodal region

- Sacral foramina

According to the protocols the common iliac, internal iliac, external iliac, obturator and presacral nodal regions should be outlined. The pudendal and inguinofemoral regions should not be included. There was no guidance regarding inclusion of sacral foramina, and one can conclude that this therefore may represent each centres' local practice.

The following were also reviewed

- The most superior CTV1+2 extent, representing the level of the aortic bifurcation

- The most inferior CTV1+2 extent, representing the length of vagina included

- Overlap with muscle and/or bone

- Spaces laterally between CTV and muscle and/or bone

Neither of the two test cases had any vaginal tumour extension. This therefore means that the protocol advises the upper half of the vagina should be outlined. Muscle and bone should be edited out of CTV and there should be no gaps laterally between muscle and/or bone of the pelvic sidewall and CTV.

2.3.4. Statistical analysis

Mean, standard deviations (SDs) and 95% confidence intervals (Cis) were calculated following review of the Q-Q plots confirming normality using IBM SPSS Statistics 22. One sample t-tests were calculated for all parameters versus the optimised gold standard to assess for variation between centres. The percentage of centres including the specified anatomical regions was calculated and 95% CIs were derived using the Exact Confidence Limits for p tables.

2.4. Results of analysis of UK cervical cancer delineation comparison

2.4.1. Gold standard validation

The STAPLE algorithm created a larger CTV than the TMG for both cases. Case 1 STAPLE volume was 647cc compared to 598cc (TMG). Case 2 STAPLE volume was 773cc compared to 735cc (TMG). The mean volume of all centres' CTVs was lower than the TMG and STAPLE volumes at 518cc for case 1 (95%CI 483cc-553cc) and 629cc for case 2 (95%CI 592cc-666cc). The TMG and STAPLE volumes are therefore not within these 95% CIs; the TMG outline was 45cc larger than the upper limit of the 95%CI for case 1 and 69cc larger for case 2.

The superior border of the TMG and STAPLE outlines for both cases were within 0.25cm of each other. The extreme points along each axis were within 0.3cm of each other for case 1, 0.5cm for case 2. These results suggest similarity between the two outlines and the differences will have minimal clinical implications.

The JCI was 0.76 for case 1 and 0.79 for case 2, corresponding to approximately 86% and 89% overlap. Both of these values are above the 'acceptable' cut-off of 0.7. The only discrepancies between areas included in CTV were the sacral foramina and pudendal nodal region; the TMG outline included the sacral foramina whereas the STAPLE did not; the TMG did not include the pudendal nodal region and the STAPLE did. The most evident clinically important variation between the TMG and STAPLE outline was the length of vagina included. The TMG outline included a longer proportion of vagina; 0.75cm longer in case 1 and 1cm longer in case 2. The mean vaginal length of all centres' was 1.5cm shorter than the TMG for case 1 and 1cm shorter for case 2. We therefore applied the mean length from all outlines to the gold standard. We edited the TMG gold standard inferior border to create an 'optimised

gold standard' and this is our reference outline (GSCTV1+2). This GSCTV1+2 has an improved JCI of 0.77 for case 1 and 0.81 for case 2 compared with the STAPLE CTV.

2.4.2. Variation between centres

Variation between centres: Volume. (Table 2.1, and Figure 2.4)

Case 1

Mean volume was 518cc (SD 82cc, 95%CI 483-553), ranging from 340cc to 676cc, representing a maximum 1.99 fold difference.

Case 2

Mean volume was 615cc (SD 89cc, 95%CI 592-666), ranging from 458cc to 806cc, representing a maximum 1.76 fold difference.
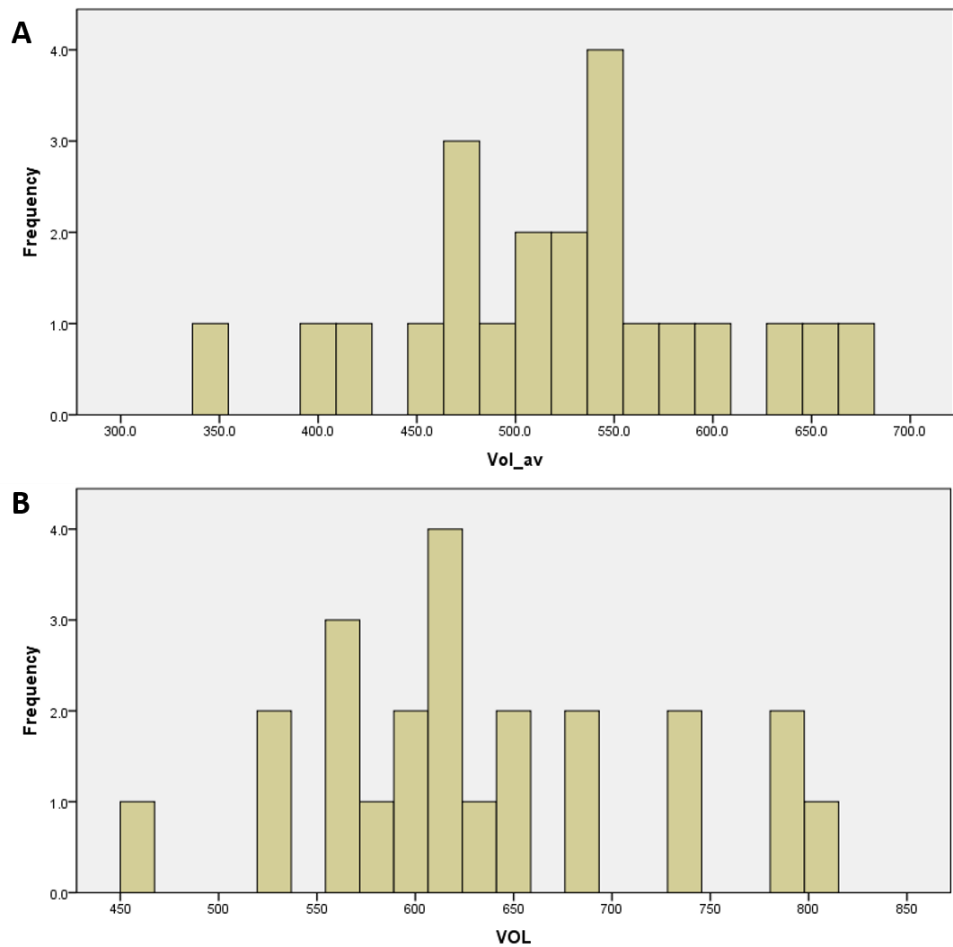
Figure 2.4: Histogram of volume distribution for case 1 (A) and 2(B)

Variation between centres: Maximum distance from CT reference point (Table 2.1, Fig. 2.5)

Case 1

Differences of up to 2 to 3cm are seen in the most extreme points along the anterior posterior and lateral axis. Anteriorly the range was 2.1cm, posteriorly 3.2cm, right lateral 2cm and left lateral 2.9cm with SD 0.6 to 0.8. Fig. 2.5 illustrates these results, showing a 2cm range posteriorly if 2 outliers are excluded and 1.25cm left laterally if 4 outliers are excluded. The extreme points in these directions are of very small volume and therefore minimal importance.

	CASE 1				CASE 2			
	Mean	Min;Max	SD	95% CI	Mean	Min;Max	SD	95% CI
Volume (cc)	518	340;676	82	483;553	629	458;806	89	592;666
Sup (aortic bifurcation) (Z cm)	-13.1	-14.75;-10.75	0.85	-13.26;-12.94	-13.5	-14.0;-13.0	0.37	-13.65;-13.35
Inf (vagina) (Z cm)	4.2	3.25;5.75	0.71	3.9;4.5	3.9	2.5;6.0	0.84	3.55;4.25
Ant (Y cm)	5.0	3.71;5.86	0.60	4.74;5.26	6.6	5.08;7.32	0.57	6.36;6.84
Post (Y cm)	-7.8	-9.86;-6.64	0.78	-8.13;-7.47	-6.4	-8.11;-5.86	0.48	-6.6;-6.2
Right lat (X cm)	-8.8	-8.96;-6.93	0.72	-9.11;-8.49	-8.6	-9.67;-7.52	0.54	-8.83;-8.37
Left lateral (X cm)	7.6	5.96;8.89	0.68	7.31;7.89	7.5	6.54;8.50	0.48	7.3;7.7
JCI	0.64	0.51;0.81	0.07	0.61;0.67	0.67	0.57;0.79	0.06	0.65;0.69

Table 2.1: Variation in CTV1+2 outline between centres for Case 1 and Case 2

The largest variation was in the superior and inferior borders. These correspond to anatomical locations which clinicians specifically define and are of larger volume than the lateral and anterior-posterior directions. Case 1 displayed a range of 4cm for the aortic bifurcation (most superior transverse slice) and 2.5cm for inferior vagina (most inferior transverse slice). Superiorly (see Fig. 2.5) 15 out of 21 centres were within 1.25cm agreement and 6 centres were outliers to this. Inferiorly it is less clear which results are outliers.

Case 2

Case 2 results are similar to case 1 (Table 2.1, Fig. 2.5). A 2-2.2 cm range in the anterior, posterior and lateral directions is seen with SD of maximum 0.6cm. These are all small volume points. The aortic bifurcation was defined more consistently than case 1, with a range of 1cm, SD 0.4cm. The inferior vagina was less consistently defined with a range of 3.5cm, SD 0.8cm. Fig. 2.5 illustrates the range is 1.25cm if 6 outliers are excluded, but in this situation 27% of centres are 'outliers'.
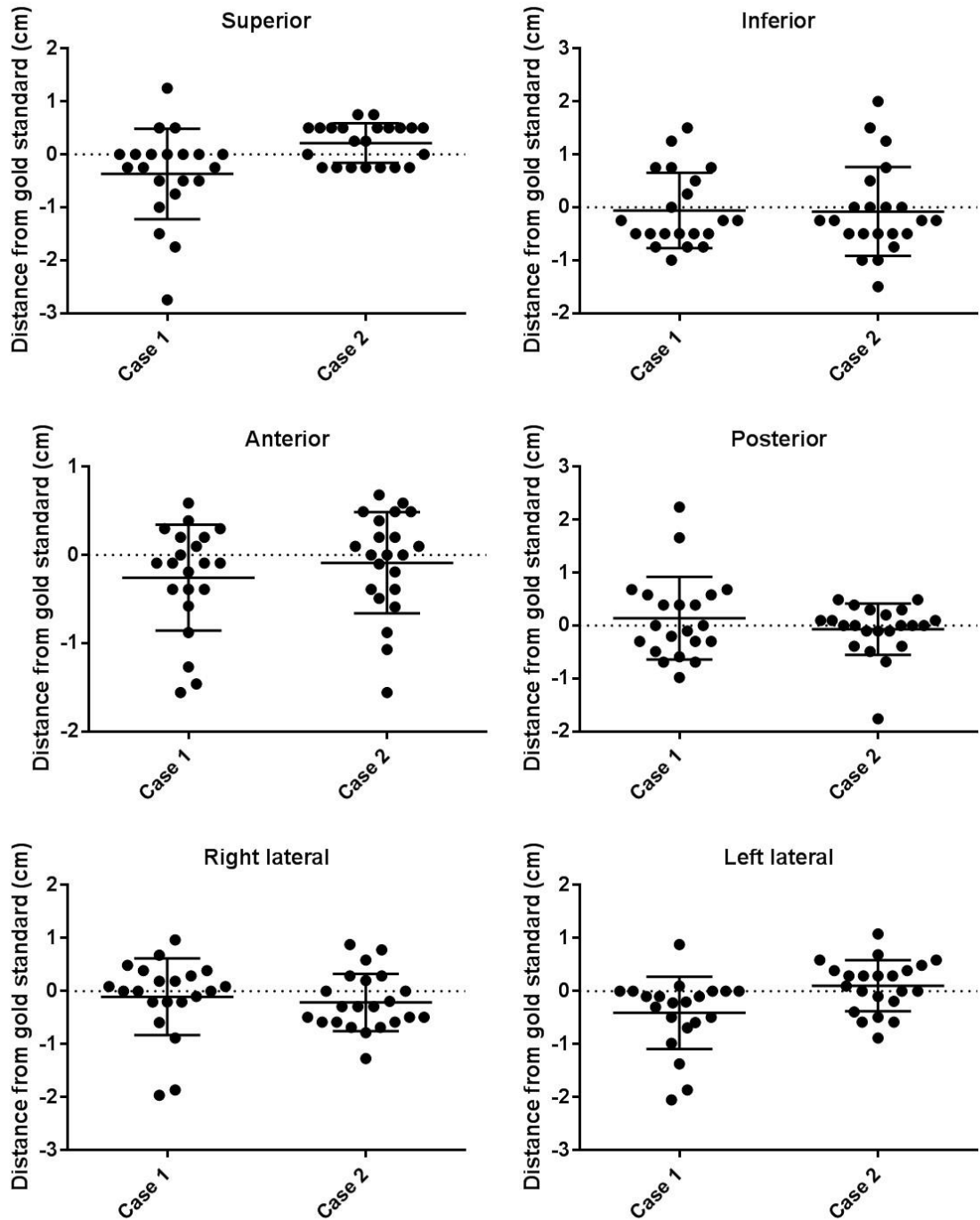
Figure 2.5: Graph illustrating furthest point along each axis in which CTV1+2 is visible, plotted as distance (cm) from GSCTV1+2.

2.4.3. Variation from GSCTV1+2 and protocol

Variation from GSCTV1+2: JCI. (Table 2.1, Fig. 2.6 and 2.7).

Case 1

The mean JCI was 0.64, corresponding to an approximate 78% overlap, SD 0.07, 95%CI 0.61-0.67. The range was 0.51 to 0.81. No cases demonstrated poor concordance (JCI<0.5). 3 out of 21 (14%) achieved acceptable concordance (JCI≥0.7).
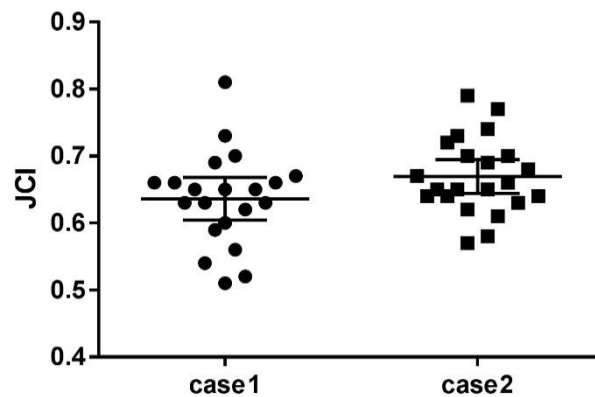
Figure 2.6: JCI for all centres including mean and standard deviation.

Case2

The mean JCI for case 2 was higher at 0.67, SD 0.06, 95%CI 0.65-0.69. The results ranged from 0.57 to 0.81 suggesting more agreement compared to case 1. No cases demonstrated poor concordance (JCI<0.5). 7 out of 22 outlines (32%) achieved good concordance (JCI≥0.7).

Fig. 2.7 shows transverse CT slices with all centres' outlines (white) and the gold standard (black) for case 1 (Fig. 2.7a&b) and 2 (Fig. 2.7c&d).

Anatomical regions included and nodal outlining (Table 2.2)

The anatomical regions to be included within CTV1+2 according to the INTERLACE protocol are discussed within the methods. Table 2.2 shows the anatomical regions (column one), the percentage of centres' outlines including those regions (case 1 column two, case 2 column three) and the protocol recommendations (column four).

The largest discrepancy between the centres and protocol recommendation was in coverage of obturator, pudendal and presacral nodal regions. The obturator and presacral regions should be included. 52% of case 1 outlines and 50% of case 2 outlines included the obturator and 67% of case 1 and 59% of case 2 included the presacral region. The pudendal region should not be included but was included in 43% of case 1 and 73% of case 2 outlines.

Anatomical region	Case 1 (%,95% CI)	Case 2 (%,95% CI)	Protocol
Common iliac nodal region	95% (76.2-99.9)	100% (84.6-100)	Yes
Internal iliac nodal region	100% (83.9-100)	100% (84.2-100)	Yes
External iliac nodal region	86% (63.7-97.0)	95% (77.2-99.9)	Yes
Obturator nodal region	52% (29.8-74.3)	50% (28.2-71.8)	Yes
Pudendal nodal region	43% (21.8-66.0)	73% (49.8-89.3)	No
Inguinofemoral nodal region	33% (14.6-57.0)	18% (5.2-40.3))	No
Presacral nodal region	67% (43.0-85.4))	59% (36.3-79.3)	Yes
Sacral foramina	29% (11.3-52.2)	41% (20.7-63.6)	No guide
Aortic bifurcation GS+/- 0.5cm	71% (47.8-88.7)	91% (70.8-98.9)	
Vaginal length mean +/-0.5cm	67% (43.0-85.4)	64% (40.7-82.8)	
Overlap with muscle/bone	10% (1.2-30.4)	23% (7.8-45.4)	No
Lateral Gaps	24% (8.2-47.2)	23% (7.8-45.4)	No

Table 2.2: Percentage of CTV outlines that complied with protocol for anatomical region
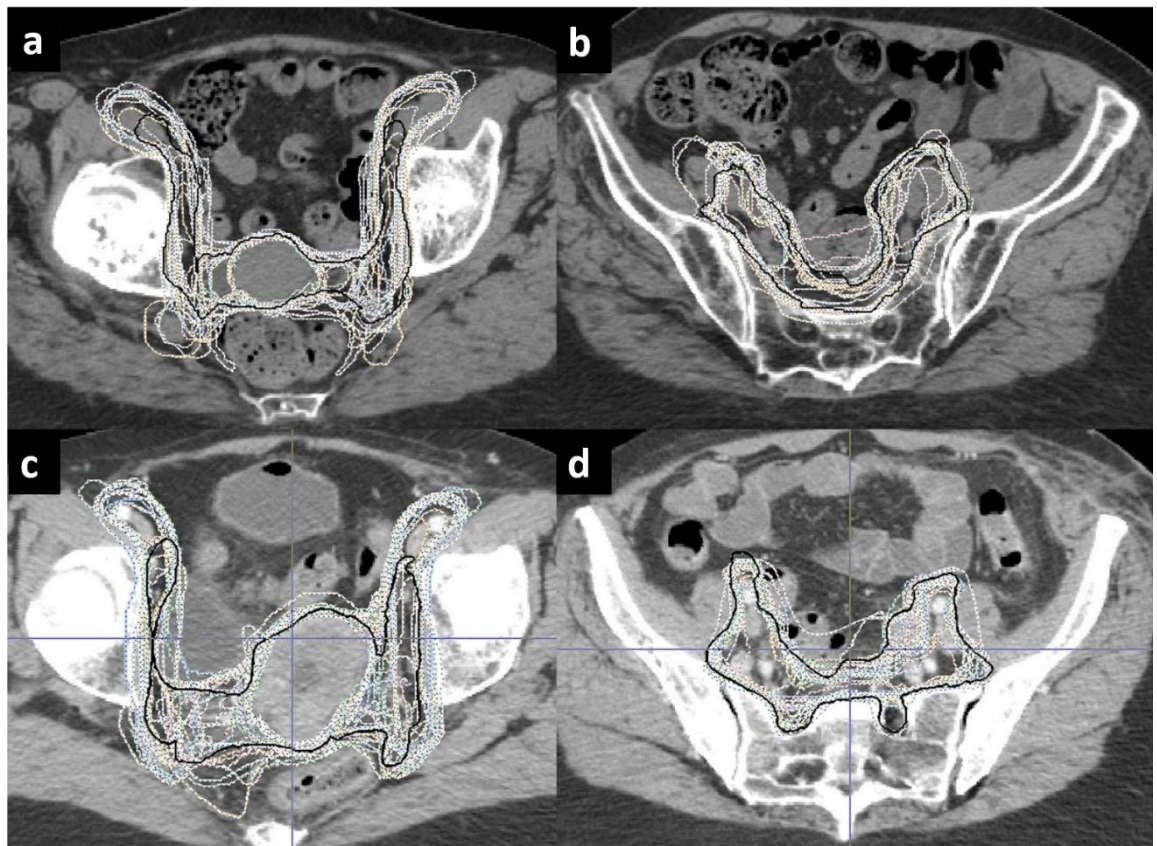
Figure.2.7: Transverse CT images of CTVs (white) and GSCTV1+2(black) for case 1 (a&b) and 2 (c&d) at sacro-iliac level (a&c) and superior to femoral heads (b&d).

2.5. Discussion

This data confirms that cervical cancer delineation varies between UK centres. This is, to my knowledge, the first time such detailed quantification has been performed for cervical primary and nodal CTV between so many UK centres. These results are not unexpected given previous publications in other tumours sites as well as smaller cervical cancer studies (Cazzaniga et al. 1998; Valley et al. 1998; Meijer et al. 2003; Weiss et al. 2003; Wu et al. 2005; Li et al. 2009; Vorwerk et al. 2009; Gwynne et al. 2011). However, they are still of significant interest and concern.

A large range in CTV1+2 volume between all UK centres' outlines is demonstrated with a maximum two-fold difference in case 1 and 1.8 fold difference in case 2. This has clinical implications regarding the irradiated tissue volume and hence normal tissue toxicity in the short and long term. Multiple areas of variation contribute to these volume differences. Lateral and anterior posterior variations are small points and therefore unlikely to contribute greatly to volume discrepancies. Larger variations are seen superiorly and inferiorly which will impact on volume variation. What is of concern is that the inferior and superior margins are specified anatomical landmarks that the clinicians decide upon. There was a clinically relevant maximum 4cm variation in defining the aortic bifurcation. This is a well defined anatomical landmark which can be seen clearly on CT. Similarly a maximum 3.5cm variation was observed in defining the mid-vagina. Difficulty visualising the superior and inferior extent of vagina on CT will account for some of this variation as it is well known that CT is suboptimal for this. As MRI is being used more frequently for planning this will hopefully improve. Techniques such as use of introitus marker, vaginal dobbie or surgical clips at the top of vagina can also potentially help reduce this variation. Other factors contributing to volume variation are differences in obturator, pudendal, inguinofemoral and presacral nodal coverage. For both test cases mean nodal CTV volume was more than double mean primary CTV volume. Therefore nodal variations will contribute more to overall volume variation. A high proportion of centres did not include the presacral and obturator nodal regions (33%/41% and 48%/50% respectively for case 1/2). The pudendal and inguinofemoral nodes were included in 43%/73% and 33%/18% respectively for case 1/2. These variations are highly likely to contribute to the

volume variation and were observed despite the use of a protocol. Some of this variation may reflect changes to usual practice in an attempt to comply with a new protocol or represent what is each centre's usual practice. However, the difference in percentage including presacral, pudendal and inguinofemoral nodes between case 1 and 2 suggests inconsistency which could be more readily explained by a lack of anatomical knowledge.

On visual qualitative review, another area of variation is the lateral parametria. Some centres did not extend laterally to cover the whole parametria, some extended to the muscle and bone of the pelvic sidewall and others were in-between. In clinical practice it is well known that the lateral parametria are difficult to define, especially on CT. I review this in more detail in Chapter 4. This variation however has not affected my results here as the lateral border is nodal (CTV2) not from CTV1. This is also unlikely to currently have any clinical impact as the prescription dose is the same for PTV1 and PTV2 and the nodal border should ensure adequate parametria coverage. This is still an important area to clarify as dose delivery is becoming more complex and delineation of GTV/high risk CTV etc. is necessary.

Overall 86% of case 1 outlines and 68% of case 2 outlines demonstrated a JCI of 0.5-0.7 compared to GSCTV1+2, corresponding to 66%-82% overlap. This confirms the inter-observer variation in cervical CTV delineation reported by Weiss et al (Weiss et al. 2003). However, their qualitative conclusion that wide agreement existed between physicians regarding anatomical areas contoured differs from my findings. This may be because my study reviews UK practice rather than single centre practice as one would expect more consistency within one centre. Their other results (maximum variation was 19cm craniocaudally; ratio of largest to smallest CTV volume was 3.6 to 4.9) are in keeping but of a greater magnitude than observed within my study. In 2005, Wu et al published (Wu et al. 2005) on the variation seen between 6 observers contouring cervical GTV on MRI for 20 cases. This study is of interest, especially as it attempts to illicit the reasons behind variation, but the largest differences seen in my cases relate to nodal anatomy and superior/inferior aspects rather than GTV. It is therefore difficult to compare results. It is important to note that Wu et al studied many more cases than I did. One may speculate therefore that a limitation of my study is only comparing two cases. However, I believe a huge strength of my study is analysing 21 different outlines which is a large observer number and is not easily replicated. In 2012 50 trusts were delivering

RT treatment within the UK and not all of those treat cervical cancer. These 21 centres therefore represent approximately 45-50% of the entire UK. Also, referring back to the literature review of inter-observer variation studies it is common that studies with a lot of observers have a small number of cases. On review of the statistical results, the 95% CIs overlap for both cases JCI and deviation of X, Y, Z furthest points compared with GSCTV1+2. This demonstrates no statistical difference between the two cases overall suggesting that both are giving similar results compared with GSCTV1+2 and are therefore representative.

Having analysed these outlines I can speculate that reasons for protocol deviation are multifactorial. Key reasons include differences in usual clinical practice between centres, insufficient protocol detail and lack of sufficient anatomy training. What my data does confirm is that protocol use alone is not sufficient in eliminating inter-observer variation.

I suspect that differences in clinical practice as well as published guidelines contribute to the variation identified. This is illustrated by considering the inferior nodal CTV extent. There are multiple guidelines for pelvic nodal anatomy in gynaecological cancer, detailed in Chapter 4. Taylor et al depict inferior nodal CTV as mid-femoral heads (Taylor et al. 2007), whilst the Japan clinical oncology group (JCOG) recommend the superior aspect of obturator foramen (Toita et al. 2010) and RTOG recommend superior femoral heads (Small et al. 2008). This therefore leads to differences in clinical practice between centres even in the 'evidence based medicine' era. I noted this to be an area of considerable variation when visual qualitative review was completed. Obturator coverage was 52% for case 1 and 50% for case 2. Sacral foramina inclusion was neither addressed by the protocols nor published guidelines (Taylor et al. 2005; Small et al. 2008) and 29% of centres included the sacral foramina in case 1 and 41% in case 2. Some of this variation may be due to a lack of consensus and differing practice between centres. I suspect this explains the variation in obturator coverage. However, if differing practice between centres was the sole explanation for sacral foramina inclusion, one would expect consistency in the proportion included between case 1 and 2 which there is not.

Lack of protocol clarity will certainly account for some variation. The use of detailed protocols has been documented to minimise inter-observer variation for other trials in prostate bed RT and head and neck RT (Valley et al. 1998; Mitchell et al. 2009). Attempting to improve this, I

have reviewed the available guidance and created a pictorial atlas focusing on anatomical areas of greatest observed variation (see Chapter 4). Central review of cases with regular feedback in a trial setting and review of cases with a radiologist are other methods of reducing variation (Valley et al. 1998). Within INTERLACE real time delineation review for all INTERLACE patients is offered, providing a detailed step-by-step report with snapshots to aid explanation. Interestingly, the vast majority of centres still request real time review even though this is no longer compulsory. I believe this illustrates an increase in willingness to improve our standards of delineation and planning.

Within the UK clinical oncologists do not receive specific anatomy or radiology training. Most clinicians are self-taught. This lack of formal education needs to be addressed as more conformal RT techniques become routine practice. Published guidelines e.g. nodal mapping guidance (Taylor et al. 2005; Small et al. 2008) and primary CTV consensus guidelines (Lim et al. 2011) exist and their use is strongly encouraged. However, time and resource constraints may lead to UK clinicians not accessing these whilst outlining. These guidelines are referenced at online and face-to-face ESTRO and RCR courses on which practice cases are outlined and compared anonymously. This use of consensus guidelines, training and collaboration between clinicians is vital to ensure that all clinically relevant areas are treated whilst minimising normal tissue radiation exposure especially in the era of advanced RT techniques. It may also be appropriate to incorporate formal radiology teaching into the UK clinical oncology training programme or even radiology placements within the training rotations.

The data I have presented here has clearly demonstrated delineation variations for cervical cancer. Methods to reduce the systematic reasons for this variation are necessary, especially with emerging IMRT use. This includes implementation of clear guidelines, ongoing education and collaboration between clinicians. However, this variation highlights the question of what the clinical consequences are. This is of major interest. Parameters such as volume variation give an impression of the magnitude of difference in irradiated volume which could have clinical implications particularly for normal tissue toxicity. However, the direct dosimetric impact of these variations is the real question. Using these RTQA cases I can investigate the direct dosimetric impact of this variation if IMRT was to be adopted. The next chapter therefore

aims to answer this question: how different is what we plan to deliver to what the gold standard

receives.

Chapter 3

The dosimetric impact of the observed delineation variation for clinical target volume

(CTV) in cervical cancer radiotherapy.

3.1. Introduction

My analysis of INTERLACE RTQA has demonstrated variation in UK cervical EBRT CTV delineation, as discussed in Chapter 2 (Eminowicz et al. 2015). Wide variation was shown with an almost two fold difference in CTV1+2 volume and a minimum JCI of 0.51 versus gold standard. This is of alarming magnitude. However, the potential clinical impact of such variation remains unclear. This can be estimated by calculating the dosimetric impact.

Following the adoption of MRI guided cervical brachytherapy, HR-CTV delineation variation has been reported. Subsequent dosimetric studies have shown potential dose uncertainties up to 5Gy (Hellebust et al. 2013) but the dosimetric impact of variation in EBRT cervical target volume delineation has not been quantified.

In other tumour sites EBRT inter-observer delineation variation has led to lower tumour control probability and differing OAR doses (Loo et al. 2012; Lobefalo et al. 2013; Jameson et al. 2014). In lung cancer, Jameson et al demonstrated that variations in outline volume, dimension and conformity indices led to lower tumour control probability due to poorer plan coverage (Jameson et al. 2014). In head and neck RT, when 7 clinicians outlined parotids for 10 cases, Loo et al found that almost half of outlines varied enough from the initial to necessitate re-planning (Loo et al. 2012). In a rectal cancer study, Lobefalo et al evaluated 4 clinicians outlining 10 cases. Plans were created for each PTV and the dose to the other clinicians' (non-target) PTVs was calculated. Mean V95% to non-target PTV was 93.7% with 3D conformal EBRT and 86.5% with IMRT. However, the mean V95% improved from 86.5% to 94.5% following the introduction of guidelines (Lobefalo et al. 2013).

As modern RT techniques such as IMRT are increasingly used for cervical cancer the accuracy of delineation becomes more important, as emphasised by Lobefalo et al's results. The aim of this chapter is to quantify the dosimetric impact of the reported delineation variation from Chapter 2, if treatment was delivered with IMRT. This work has been accepted for publication in Radiotherapy and Oncology (Eminowicz et al. 2016).

3.2. Methods

3.2.1. Delineation process and creation of GSPTV

The delineation process, outlining comparison methods and CTV results are presented in Chapter 2 and have been published (Eminowicz et al. 2015). As detailed in section 2.3.2. the INTERLACE GSCTV1+2 was created from an expert consensus outline and was then validated using the STAPLE algorithm (Warfield et al. 2004; Eminowicz et al. 2015). The INTERLACE protocol recommended a range of CTV to PTV margins; 15-20mm anteriorly, posteriorly, superiorly and inferiorly and 7-10mm laterally for primary CTV (CTV1) and circumferential 7-8mm for nodal CTV (CTV2). To create each centre's gold standard PTV (GSPTV) the GSCTV was grown by margins identical to the individual centre's margins applied. Each centre therefore had its own PTV1+2 (delineated and created by the centre) and GSPTV (individual centre's margins applied to GSCTV). The PTV1+2 is the volume planned to and the GSPTV is the gold standard volume that should receive the radiation prescription. The application of each centre's margins reduces potential confounding of results due to CTV-PTV margin differences.

In addition, to assess what impact the margin differences do have, the most commonly applied margins were added to the GSCTV to create GSPTVCM. These were 15mm anteriorly, posteriorly, superiorly and inferiorly and 7mm laterally for CTV1 and 8mm for CTV2.

3.2.2. Planning method

Each centre's DICOM structure set and corresponding CT data was imported into Eclipse v11 [Varian Medical Systems, Palo Alto] TPS. A dual arc RapidArc treatment plan was created for each centre's PTV1+2 outline following the INTERLACE protocol. Prescribed dose was 50.4Gy in 28 daily fractions delivering 1.8Gy per fraction. Dose delivered to 98%(D98%), 95%(D95%) and 2%(D2%) of PTV were required to be ≥95%, ≥97% and ≤107% of prescribed dose respectively. Lobefalo et al described acceptable plan coverage as V95%>95% prescribed dose (Lobefalo et al. 2013). The 'Body' outline was created automatically by the TPS. Plans were inversely optimised, prioritising PTV coverage. OARs were optimised outside of PTV1+2 only. To this end, a 'RectumOPT' structure was created by extracting the Rectum volume from PTV1+2 with an additional 1-2mm margin. A 'Steering' volume was also created by outlining the entire abdominal cavity and extracting this from PTV1+2 with an additional 8mm margin. See Figure 3.1.

I calculated the plans using Anisotropic Analytical Algorithm. My optimised plans were then evaluated and checked by an experienced Physicist. The DICOM imaging, structure and dose data were then exported into CERR (Deasy et al. 2003) for DVH analysis and visual qualitative review.
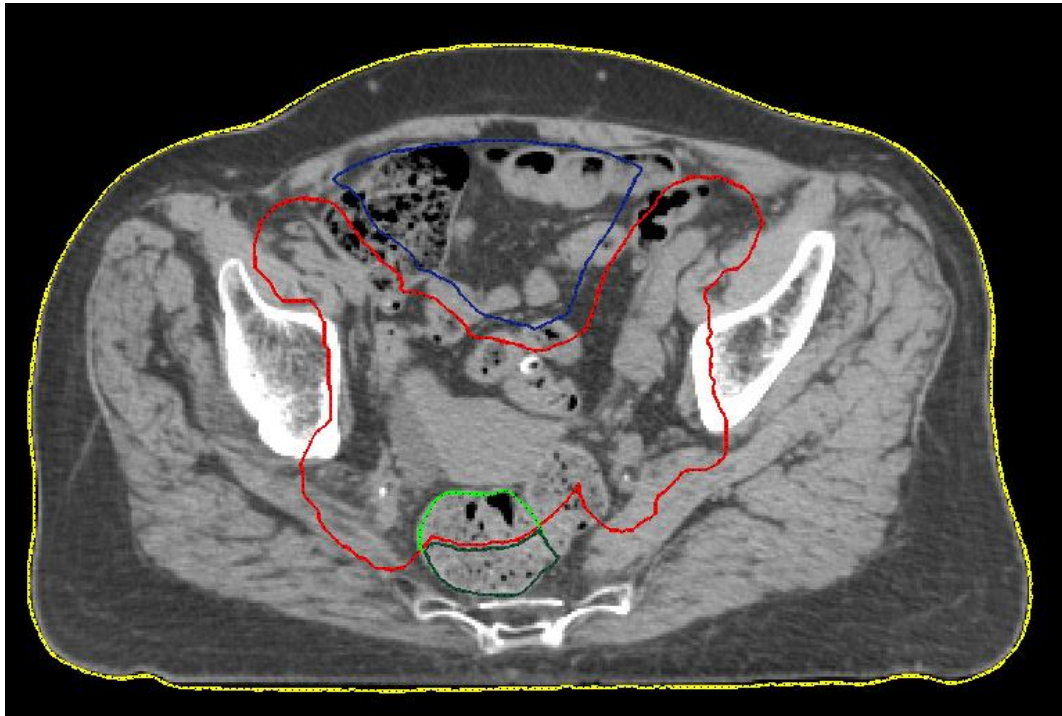
Figure 3.1: Transverse CT images with PTV (red), Rectum (light green), Body (yellow), Steering (blue) and RectumOPT (dark green) structures.

3.2.3. Dosimetric comparison

Each GSPTV outline was imported into each corresponding individual plan on CERR and DVHs were analysed. The D99%, D98%, D95%, D2%, D1% and mean dose delivered (Dmean) for each centre's PTV1+2 and GSPTV were extracted using CERR. In addition, for each PTV1+2 and GSPTV, the percentage volume receiving at least 95% dose (V95%) was calculated. This process was also performed for the GSPTVCM. This selection of parameters gives an overview of dose delivered and are often those reported in the clinical setting.

Visual qualitative review of GSCTV and GSPTV coverage by 95% dose was also performed using CERR. The 95% isodose was exported as a structure and visually compared simultaneously with GSCTV and GSPTV. This highlighted clear areas of under-dosage where

the 95% isodose did not cover GSCTV or GSPTV. This visual review was also performed using the GSPTVCM.

3.2.4.   Statistical analysis

Mean, SD, and 95% CIs were calculated following QQ plots review confirming normality using IBM SPSS Statistics 22. P values were derived from one sample t-tests (compared against set value) and paired t-tests (comparing PTV1+2 and GSPTV DVH parameters and GSPTV with GSPTVCM).

3.3. Results

3.3.1. DVH parameters for PTV1+2 and GSPTV

Dose delivered to 99%(D99%), 98%(D98%), 95%(D95%), 2%(D2%) and 1%(D1%) of PTV

D98%≥95%, D95%≥97% and D1%≤105% were achieved for all PTV1+2 structures as this was the structure planned to. For GSPTV, D1% was achieved for all plans. However, GSPTV D98% and D95% were achieved for no plans. Using Lobefalo et al's definition of acceptable plan coverage (V95%>95%) only 1 plan in total achieved acceptable coverage. GSPTV D95% was greater than or equal to 95% for 1 plan for case 1 and no plans for case 2. Table 3.1 shows mean (in Gy and percentage of prescribed dose (50.4Gy)) and standard deviations for all parameters for both cases. A paired t-test showed significant differences (Table 3.2) for all parameters except D2% and D1% (maximum doses). Figure 3.2 illustrates the cumulative DVHs for all of the GSPTVs for case 1 (Fig.3.2a) and case 2 (Fig.3.2b). Figure 3.3 shows direct DVH comparisons for representative cases of PTV1+2 (planned) and GSPTV (ideal treated volume) coverage.

Fig 3.2a:Cumulative DVH showing dose delivered to GSPTV for all centre's plans for case 1.
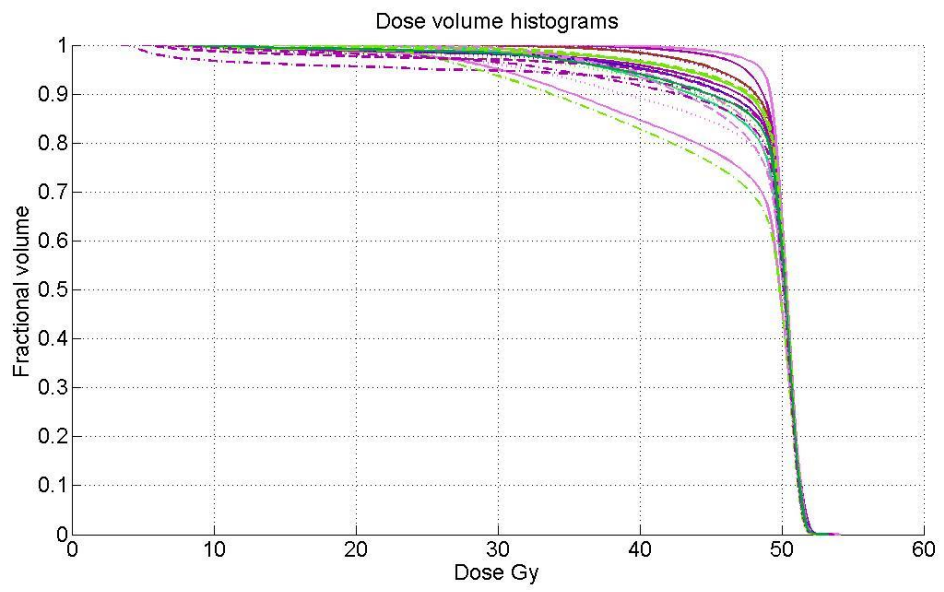
Fig 3.2b:Cumulative DVH showing dose delivered to GSPTV for all centre's plans for case 2.
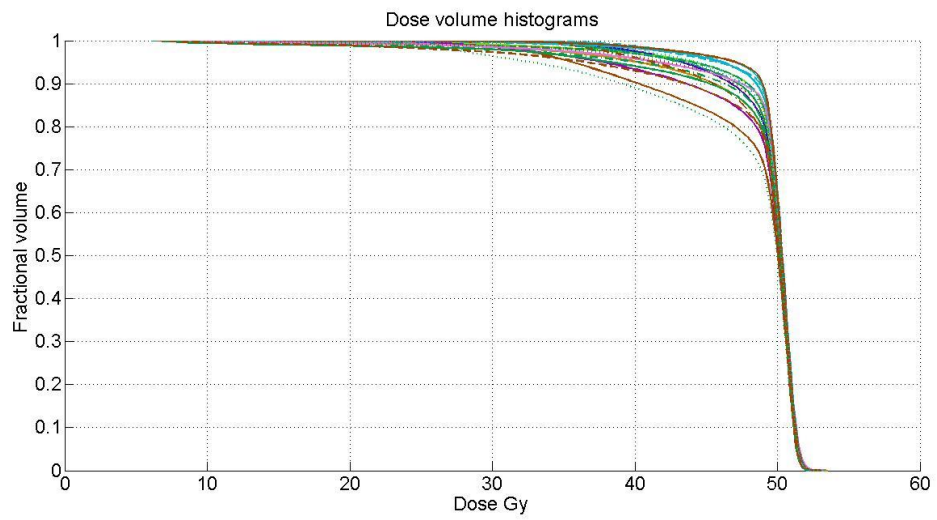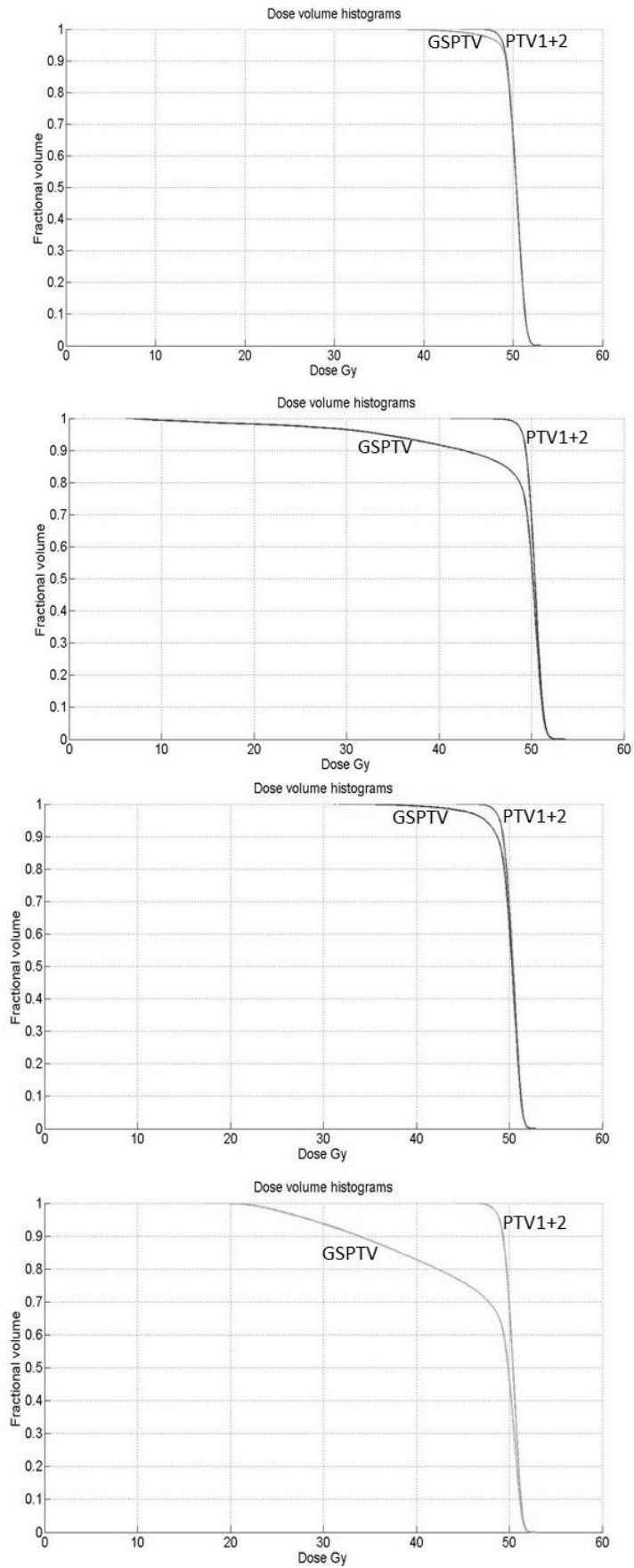
Figure 3.3: Cumulative DVHs directly comparing dose to centre's PTV1+2 (planned volume) and GSPTV (ideal treated volume) for four representative cases.

Mean dose (Dmean) delivered to PTV

Dmean was statistically significantly lower for GSPTV compared with planned PTV1+2 for both cases. The magnitude of difference was 2-3% of prescribed dose; 3.3% for case 1 and 2.3% for case2. Dmean was less than 98% prescribed dose in 15 (71%, case 1) and 10 (45%, case 2) plans and less than 95% in 4 (19%, case 1) and 1 (5%, case 2) plans.

Parameter	Case1				Case 2			
	Centres' PTV1+2		GSPTV		Centres' PTV1+2		GSPTV	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
D99% (Gy) [% of 50.4]	48.06 [95.3]	0.17	23.92 [47.5]	11.8	48.03 [95.3]	0.15	30.39 [60.3]	7.0
D98% (Gy) [% of 50.4]	48.48 [96.2]	0.14	30.83 [61.2]	9.8	48.47 [96.2]	0.12	35.70 [70.8]	5.0
D95% (Gy) [% of 50.4]	49.04 [97.3]	0.10	39.13 [77.6]	6.2	49.04 [97.3]	0.08	42.12 [83.6]	4.0
D2% (Gy) [%of 50.4]	51.7 [102.6]	0.14	51.71 [102.6]	0.11	51.7 [102.6]	0.08	51.68 [102.5]	0.09
D1% (Gy) [% of 50.4]	51.9 [103.0]	0.11	51.9 [103.0]	0.11	51.9 [103.0]	0.11	51.9 [103.0]	0.09
V95% (%)	99.9	0.07	85.88	6.2	99.8	0.07	87.9	5.0
Dmean (Gy) [% of 50.4]	50.4 [100]		48.76 [96.7]	1.01	50.4 [100]		49.25 [97.7]	0.64

Table 3.1: Mean and SD of DVH parameters including V95 for each centre's PTV1+2 (planned volume) and the GSPTV (ideal treated volume) for Case 1 and 2.

Percentage PTV volume receiving at least 95% prescribed dose (V95%)

No plans achieved GSPTV V95% of 95% or higher. V95% of 90% or higher was not achieved in 15 (case 1) and 14 (case 2) plans, 71% and 64% overall. 2 (case 1) and 2 (case 2) plans did not achieve V95% of 80% or higher. The absolute GSPTV volume outside the 95% isodose ranged from 83cc to 458cc (case 1) and 94cc to 425cc (case 2). Overall, case 1 GSPTV V95% ranged from 70% to 95%, mean 85.9% (SD 6%). For case 2, mean was 87.9% (SD 5%) with results ranging from 76% to 95%. For case 1, PTV1+2 V95% was minimum 99.8%, mean 99.9%, and case 2 was minimum 99.7%, mean 99.8%. This is a statistically significant (p<10⁻

[8]) mean difference of 14% for case 1 (95%CI 11.2%-16.9%), and 12% for case 2 (95%CI 9.7%-14.1%).

Parameter	Case 1			Case 2		
	Difference	95%CI	P value	Difference	95%CI	P value
D99% (Gy) [%of 50.4]	24.1 [47.9]	18.7-29.6	1×10^{-8}	17.6 [34.9]	14.5-20.7	1×10^{-10}
D98% (Gy) [%of 50.4]	17.6 [34.9]	13.2-22.1	7×10^{-8}	12.8 [25.4]	10.5-15.0	8×10^{-11}
D95% (Gy) [%of 50.4]	9.9 [19.6]	7.0-12.8	5×10^{-7}	6.9 [13.4]	5.1-8.7	7×10^{-8}
D2% (Gy) [%of 50.4]	0.02 [0]	-0.06-0.03	0.68	0.00 [0]	-0.03-0.04	0.77
D1% (Gy) [%of50.4]	0.00 [0]	-0.02-0.03	0.77	0.00 [0]	-0.01-0.02	0.58
V95% (%)	14.0	11.2-16.9	2×10^{-9}	11.9	9.7-14.1	3×10^{-10}
Dmean (Gy) [%of 50.4]	1.6 [3.2]	1.2-2.1	3×10^{-7}	1.1 [2.2]	0.9-1.4	4×10^{-8}

Table 3.2: DVH parameter differences between PTV1+2 dose (planned volume) and GSPTV dose (ideal treated volume)

3.3.2. Comparison of GSPTV with GSPTVCM

The results for GSPTVCM are very similar to those for each centre's GSPTV. Table 3.3 depicts the mean results for each PTV. In general the dose coverage of the GSPTVCM was slightly better. This is not surprising as 6 centres had applied the most commonly applied margins in their practice, 5 had applied the same margins except for 3 mm less laterally on CTV1, and 5 had applied an additional 5mm anteriorly, posteriorly, superiorly and inferiorly and were therefore bigger overall. This difference was statistically significant for the D98%, D95%, V95% and mean dose for case 2 only when analysing the two cases separately using paired t-tests. If both cases are analysed together the difference was statistically significant for all parameters except D2% (p=1, therefore no difference) and V95% (p=0.051 therefore borderline). If the cases which applied the most commonly used margins for their GSPTV were excluded, the difference observed was bigger but the statistical significance remained almost identical. Despite statistical significance I would argue that these differences were not clinically significant. Table 3.4 shows the differences for all cases excluding those with the most

commonly applied margins applied for their GSPTV. This represents the plans with the largest difference between GSPTV and GSPTVCM. The D99% was the largest observed difference; 1.5% dose 95%CI 0.64-2.9%. In clinical practice difference is very small compared to the drop in coverage overall. This is therefore of minimal clinical significance. Due to the similar results I did not perform any further analyses using GSPTVCM.

Parameter	Case1		Case 2	
	GSPTV	GSPTVCM	GSPTV	GSPTVCM
D99% (Gy)	23.92	24.93	30.39	31.45
[% of 50.4]	[47.5]	[49.5]	[60.3]	[62.4]
D98% (Gy)	30.83	31.31	35.70	36.63
[% of 50.4]	[61.2]	[62.1]	[70.8]	[72.7]
D95% (Gy)	39.13	39.30	42.12	42.86
[% of 50.4]	[77.6]	[78.0]	[83.6]	[85.0]
D2% (Gy)	51.7	51.7	51.7	51.7
[%of 50.4]	[102.6]	[102.6]	[102.5]	[102.5]
D1% (Gy)	51.9	51.9	51.9	51.9
[% of 50.4]	[103.0]	[103.0]	[103.0]	[103.0]
V95% (%)	85.9	85.8	87.9	89.1
Dmean (Gy)	48.8	48.8	49.3	49.4
[% of 50.4]	[96.7]	[96.8]	[97.7]	[98.0]

Table 3.3: Comparison of mean results for each DVH parameter (column 1) using GSPTV according to each centre's applied CTV to PTV margins and the GSPTVCM using the most commonly applied margin for case 1 (column 2 and 3) and case 2 (column 4 and 5).

Parameter	Difference	95% CI	P value
D99%	1.49	0.64-2.9	0.041
D98%	1.01	0.14-1.88	0.024
D95%	0.68	0.104-1.26	0.022
D2%	0		1.00
V95	0.79	-0.003-1.59	0.051
Dmean	0.14	0.3-0.25	0.014

Table 3.4: Differences between DVH parameters for GSPTV and GSPTVCM with cases excluded where GSCTV had most common margins applied.

3.3.3. Qualitative review of extreme cases

On visual review, the area of CTV1 least likely to be covered by 95% dose was the lower aspect i.e. vagina and paravaginal tissue. This area was not covered by 95% dose in 5 plans (24%) for case 1 and 8 (36%) for case 2. Cervix and GTV was covered with a minimum margin of 9mm in all plans for both cases. Areas of CTV2 least likely to be covered by 95% dose

include the lower obturator nodes, anterior external iliac nodes and lateral recesses between

the psoas muscle and vertebrae/bones. Only 4 plans (19%) for case 1 and 9 (41%) for case

2 delivered 95% dose to the entire obturator nodal outline with as much as 4cm (case 1) and

5.2cm (case 2) of CTV2 extending anteriorly to the 95% isodose (arrowed in Fig.3.4a, 3.5a).

Cranial to the femoral heads 6 (29%) plans of case 1 and 5 (23%) of case 2 do not cover the

entire external iliac nodal region with 95% dose. CTV2 extends up to 4cm (case 1) and 6cm

(case 2) anterior to the 95% isodose in this region (arrowed in Fig.3.4b, 3.5b).
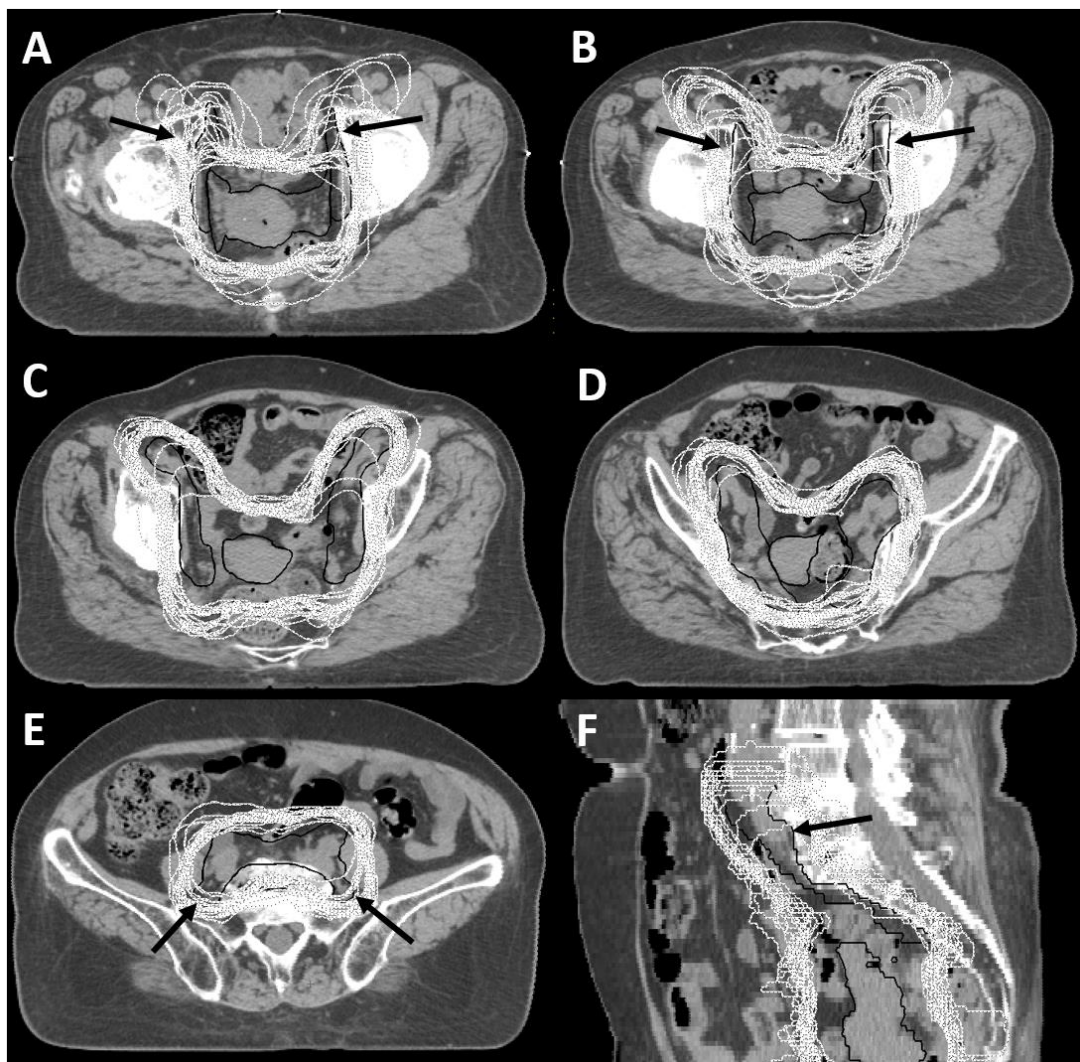
Figure 3.4: Transverse (a-e) and sagittal (f) CT images illustrating all 95% isodoses (white lines) and GSCTV (black line) for case 1. The regions least frequently covered by 95% isodose were the obturator nodes (arrowed in a), external iliac nodes (arrowed in b) and lateral recesses between psoas and bones (arrowed in e).The superior common iliac nodes were not covered by the 95% isodose in 5 cases (arrowed in f).

In 13 plans (62%) for case 1 and 16 (73%) for case 2 95% dose does not cover CTV2 in the

lateral recesses between the psoas and bones by maximum 1.4cm (arrowed in Fig.3.4e,

3.5e,f). For case 1 the superior CTV2 aspect was also not covered in 5 (24%) plans with a maximum length of 2.5cm outside the 95% isodose (arrowed in Fig.3.4f). In the majority of plans there was minimal margin between the GSCTV anteriorly and the 95% isodose (seen in Fig.3.4d,e, 3.5d,e,f). The 95% isodose did not cover CTV2 anteriorly in the common iliac region in 11 plans (52%) of case 1 and 17 (77%) of case 2. Half of the 95% isodose lines were 3mm or closer to anterior CTV2 in the iliac region for both cases.
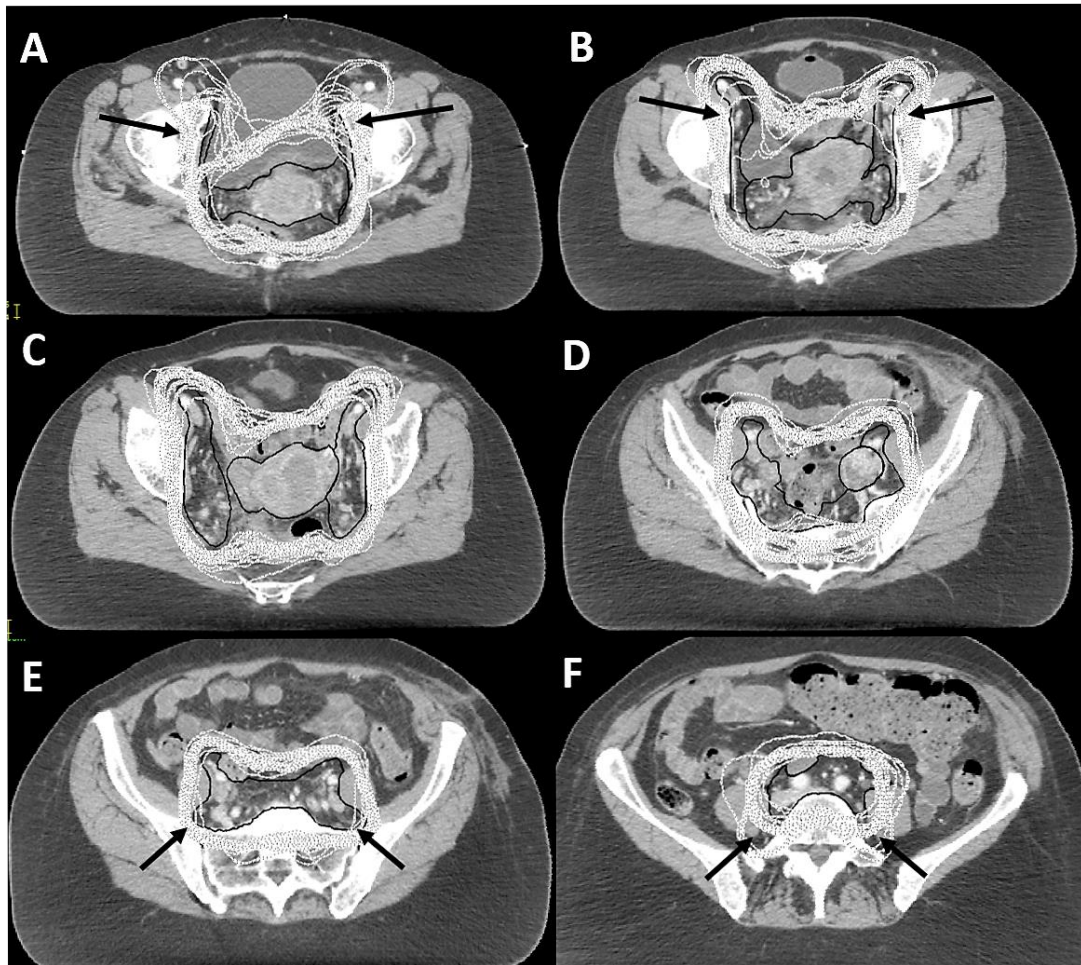
Figure 3.5: Transverse CT images illustrating all 95% isodoses (white lines) and GSCTV (black line) for case 2. The regions less likely to be covered by 95% isodose were the obturator nodes (arrowed in a), external iliac nodes (arrowed in b) and lateral recesses between psoas and bones (arrowed in e,f).

3.4. Discussion

My results suggest that CTV delineation variation leads to significant decreases in dose delivered to the ideal treated volume (GSPTV) if treatment is delivered with IMRT. Comparing plan coverage of GSPTV with planned PTV1+2, V95% is on average 10-15% lower and D95% is on average 10-20% lower. When an IMRT plan was created for each centre's PTV1+2, GSPTV coverage was not acceptable when reviewing all parameters or V95 as a single parameter. In clinical practice re-planning would be advised. D95% of at least 95% is argued to be an acceptable constraint, whilst using D95% of at least 97% as an objective. Even with this lower constraint GSPTV coverage was only achieved for 1 plan in total.

My findings are in line with conclusions from other tumour sites where detrimental plan coverage and need for re-planning are reported. This is especially true regarding the rectal cancer study published by Lobefalo et al. My mean V95% to target PTV of 85.9% and 87.9% was in line with their results of 86.5% with IMRT. Interestingly, they reported that 3D conformal EBRT maintained V95% at 93.7% confirming that this reduction in dose is predominantly due to increased conformality with IMRT. The target volume for rectal cancer has many similarities to the cervical cancer target volume due to pelvic nodal coverage. On my visual review there were large nodal areas not covered by 95% dose and this may account for similarities in results between these studies. There are also clear differences in anatomy and the other area of poor coverage seen in my study was the vagina which is not included in the rectal CTV.

To my knowledge, this work is the first to quantify the dosimetric effects of EBRT delineation variation in cervical cancer. Following the introduction of IGBT the dosimetric effect of HRCTV delineation variation has been investigated resulting in multiple publications. Hellebust et al reported that, in 10 cases outlined by 6 clinicians, inter-observer variation led to a +/-5Gy uncertainty in HRCTV dose (Hellebust et al. 2013). The dose effect for OARs (rectum and bladder) was reported to be less, but still significant with +/-2-3Gy uncertainty. On the contrary, Petric et al analysed 13 cases outlined by 2 clinicians in 2 different planes (transverse and para-transverse) and reported no significant contour variation or differences in DVH parameters when a standard plan was applied (Petric et al. 2008). This concordance was attributed to adherence to guidelines which may be true in view of Lobefalo et al's findings.

However, these results may also be due to only 2 observers performing the delineation. Our results are not directly comparable to these studies but they do highlight the importance of quantifying the impact of EBRT delineation variation on dose as the potential dose detriment will be additive.

To understand the clinical importance of the dose detriment found in my results, I undertook a visual qualitative review. This review, discussed in relation to published recurrence patterns, gives my results some clinical context. In general, the GTV was well covered with a margin because of its central location within PTV. However, the lower vaginal outline, external iliac, obturator and superior common iliac nodes/aortic bifurcation were frequently not covered by 95% dose. The superior nodal area is of particular clinical concern as superior marginal nodal recurrences are well documented (Beadle et al. 2010; Rai et al. 2014). This is also an area where, as discussed in Chapter 2, variation exists despite a clear consensus regarding the definition being the aortic bifurcation which should be relatively easy to define. Pelvic nodal recurrences reportedly occur in only a small proportion of patients, approximately 1.5-3% (Beadle et al. 2010; Forrest et al. 2010; Rai et al. 2014). Within preliminary EMBRACE analysis 62 patients were found to have post treatment nodal failures out of 816 patients analysed. The vast majority (69%) were para-aortic supporting the importance of accurate superior border selection. They also reported 45% had iliac recurrences and 11% obturator recurrences (Nomden et al, EMBRACE work in progress). These figures indicate these nodal areas are important but in practice affect a very small proportion of patients. Post RT lower vaginal recurrences are even less frequently reported. Both the pelvic nodal regions and the vagina receive dose from brachytherapy which may contribute to the reduced recurrence rate. With the standard brachytherapy distribution vaginal doses are high. However, with evolving IGBT techniques and increasing awareness of the importance of vaginal toxicity, reductions in vaginal dose are seen. EBRT will then become a proportionately bigger contributor to vaginal dose. I am therefore concerned that as we adopt more conformal RT techniques this may lead to higher recurrence rates if coverage is compromised. A further step to understand the clinical context of the dose effect seen would be to investigate correlation between the variation observed and a tumour control probability model as described by Jameson et al for lung cancer (Jameson et al. 2014) but this is beyond the scope of this work. From my qualitative

review in the context of published recurrence patterns, the superior border of the nodal volume appears the most important to correctly define.

The analysis comparing each centre's GSPTV and the GSPTV with the most commonly applied margins; 15mm anteriorly, posteriorly, superiorly, inferiorly and 10mm laterally for CTV1 with 8mm circumferentially for CTV2 (GSPTVCM), presented here was of additional interest. Differences were seen that were statistically significant but not of a clinically significant magnitude. This suggests the dose variation observed is not strongly affected by the variation in CTV to PTV margin size. One method of compensation for the variation in CTV delineation would be application of larger CTV to PTV margins to account for this additional uncertainty. However, due to such small differences seen with varying margin size the magnitude of increase in margin size would be so large that it would negate the benefit of more conformal techniques such as IMRT. This is therefore less desirable.

When drawing conclusions factors that have not been controlled for must be considered that could influence or bias my results.

No single optimal gold standard outline creation method exists leading to uncertainties regarding the validity of using a gold standard outline. My previously described strong methodology of combining an expert consensus outline and a STAPLE algorithm uses two well-established methods (Warfield et al. 2004). The GSPTV was agreed by multiple UK clinicians from different centres and subsequently validated by the mathematically derived STAPLE outline using all 21 centre's submitted outlines. It is therefore a robust gold standard.

These results are based on RTQA exercises rather than real life cases which may lead to biased results. The clinicians performing the delineation did not have access to the diagnostic imaging other than the written reports which is not representative of clinical practice. Potential lack of time and sense of unimportance when outlining test cases rather than clinical cases could in theory lead to more extreme variation than in clinical practice. However, most clinicians refer to protocol when outlining trial cases, whether test or not, which may actually reduce variation delineation (Mitchell et al. 2009).

For each centre's plan we used all outlines delineated and submitted by the centre including OARs. This resultant OAR outline variation could in theory lead to dosimetric variations that

may affect results. However, rectum was the only OAR optimised against (predominantly D2cc) and minimal variation was observed in this outline other than the superior and inferior aspects which would not be likely to impact on optimisation. On DVH review, the gold standard rectum D2cc was within 0.1Gy of the planned rectum D2cc for all cases. This therefore supports the assumption that rectum delineation variation is unlikely to affect my results.

It is important to note that at the time of RTQA submission (September 2012 to September 2014) no centres were routinely using IMRT. All centres were using 3D-CRT and were therefore familiar with delineating CTVs and OARs but the dosimetric effect reported here would not be seen with 3D-CRT. All centres received detailed descriptive feedback on their outlines in comparison with protocol. All centres edited their outlines according to protocol before being approved for trial recruitment. Subsequent monitoring of real time cases has shown a decrease in the amount of editing required, as discussed further in Chapter 4.

It is clear from these results that minimising outlining variation is important, especially at a time of increasing IMRT use. Centralised review, as occurs within INTERLACE and other RT trials, as well as the use of detailed pictorial guidelines or radiology input (Petric et al. 2008; Dimopoulos et al. 2009; Mitchell et al. 2009; Lobefalo et al. 2013) are helpful in achieving this goal. Published guidelines for nodal CTV (Taylor et al. 2005; Small et al. 2008; Toita et al. 2010; Bansal et al. 2013) and primary CTV (Lim et al. 2011; Toita et al. 2011; Bansal et al. 2013) in cervical cancer are available and should be utilised. The evidence from Lobefalo et al is striking regarding the positive impact that guideline use can have. I address this in the next chapter focussing on cervical EBRT. Finally, educational groups such as ESTRO and RCR have acknowledged the need for delineation training and now provide online as well as face to face delineation workshops and courses which should be utilised.

Chapter 4

Clinical target volume (CTV) and organs at risk (OAR) delineation atlas for cervical cancer radiotherapy: justification, creation and impact.

4.1. Introduction

Inter-observer delineation variation has been shown to exist across multiple tumour sites (Cazzaniga et al. 1998; Valley et al. 1998; Meijer et al. 2003; Li et al. 2009; Vorwerk et al. 2009; Gwynne et al. 2011) including cervical cancer (Petric et al. 2008; Dimopoulos et al. 2009). Chapter 2 reports on my analysis of the two INTERLACE RTQA EBRT delineation cases for 21 UK centres (Eminowicz et al. 2015). Significant variation was demonstrated in line with other publications (Weiss et al. 2003; Wu et al. 2005). In Chapter 3 I showed that this inter-observer variation leads to statistically and potentially clinically important decreases in dosimetric coverage with on average a 10-20% lower D95% and a 10-15% lower V95% than planned. Efforts are therefore imperative to reduce this inter-observer variation. Options include the introduction of detailed delineation guidelines which has been effective in other tumour sites. Six specialists outlined the prostate bed of three cases without guidelines and repeated the process three weeks later using the RADICALS trial protocol and outlining guidelines. The mean CTV volume increased with the use of the protocol and inter-observer variation decreased. This was represented by a 1.3 to 1.8 fold decrease in the maximum volume ratio and 1.4 to 2.1 fold decrease in the coefficient of variation (Mitchell et al. 2009). For cervical brachytherapy the introduction of the GEC-ESTRO guidelines and systematic training facilitated improved inter-observer agreement with no differences in mean volumes and good conformity indices (Petric et al. 2008; Dimopoulos et al. 2009). Dosimetric differences have also been reduced with the use of guidelines when analysing 4 clinicians outlining 10 rectal carcinoma cases without then with guidelines (Lobefalo et al. 2013). The V95% to true target PTV was increased from 86.5% to 94.5% with the use of guidelines as described in Chapter 3.

The aim of this chapter is to review current UK clinician education and confidence, review the guidance available for cervical cancer EBRT delineation, highlight areas of inconsistency within published guidelines and clinical practice observed within INTERLACE RTQA, create a delineation atlas and assess the impact of this atlas within the INTERLACE RTQA. The delineation atlas presented here is applicable to all patients being treated with EBRT independent of their simulation process and RT delivery method. The atlas is not applicable for brachytherapy delineation as this differs in some respects and clear guidance already

exists (Haie-Meder et al. 2005). This literature review and delineation atlas has been accepted for publication in Practical Radiation Oncology (Eminowicz et al. 2016).

4.2. Methods

4.2.1 Review of clinicians' experience and confidence

To assess experience and confidence of clinicians across the UK I recorded their self-reported levels of training and confidence in outlining specific anatomical areas. This data was collected anonymously using a questionnaire (see Appendix 3) that was sent out by the clinical trials unit to all principal investigators (PIs) registered within the INTERLACE trial at recruiting and non-recruiting centres. This questionnaire was sent to all PIs at two separate timepoints; before implementation of the atlas and then 18 months later. The questionnaire included questions on clinical practice, previous training and level of confidence in anatomy knowledge. For level of confidence I asked clinicians to score confidence from 1 to 4 for defining ten specified anatomical structures, with 1 equating to 'unable to identify', 2 'can occasionally identify', 3 'confident with most cases' and 4 'confident in all cases with rare exceptions'. The maximum score any one clinician could score was 40 and this would equate to complete confidence in all areas. The lowest would be 10 meaning unable to identify any areas. The statistical analysis was performed using means, SD, 95%CI and independent sample t-tests.

4.2.2 Literature search of guidelines for cervical cancer RT delineation

I performed a literature search using the Pubmed/Medline central database with the MESH terms 'uterine cervical neoplasm', 'radiotherapy' and 'guidelines as topic' in combination with the Pubmed search terms 'contouring', 'outlining', 'atlas' and 'target volume definition'. The articles that included delineation guidelines for cervical cancer published in the last 10 years were selected and reviewed. The references within these articles were also reviewed to ensure no key articles were missed. The articles referred to delineation of:

- the primary CTV, to include GTV, uterus, bilateral ovaries if seen, bilateral parametria, uterosacral ligaments, and vagina (referred to as CTV1)

- the pelvic nodal CTV, to include the common iliac, internal and external iliac, upper pre-sacral and obturator nodal regions (referred to as CTV2)

- the para-aortic nodal CTV (referred to as CTV3)

- OARs;

  o anorectum,

  o bladder,

  o femur (right and left),

  o bowel,

  o kidney (right and left),

  o spinal cord

4.2.3 Positive para-aortic nodal case review

To assist with CTV3 outlining recommendations I reviewed all cases with involved para-aortic nodes treated with chemoradiation between 2010 and 2014 at my institution (UCLH). For each case I examined the diagnostic MRI and CT and noted the location of enlarged para-aortic nodes in relation to the vascular anatomy.

4.2.4 Review of variations in guidance and INTERLACE RTQA

I reviewed the INTERLACE RTQA cases' outlining from the 21 participating centres using CERR and SHERRI as discussed in Chapter 2. In addition to calculating the proportion of centres outlining specified anatomical areas, I visualised all 21 centres' CTV outlines simultaneously on CERR to identify other areas of variation.

I highlighted the inconsistencies within and between the published guidelines, routine UK practice and the INTERLACE RTQA experience as variations in practice. These identified variations were reviewed within the INTERLACE TMG who discussed each identified variation in detail and individual expert opinion was collated.

4.2.5 Creation of delineation atlas

Following these detailed discussions, delineation recommendations were agreed between TMG members. Following this consensus agreement I anonymised two cases which had been

treated at UCLH and used them to demonstrate the agreed step by step instructions and produce the complete pictorial atlas. Once I had completed this, an expert gynaecological radiologist reviewed this atlas to ensure anatomical accuracy. Oncologists (consultants and specialist registrars) at UCLH then applied the atlas in clinical practice to ensure comprehension. These guidelines have been incorporated into the INTERLACE RTQA pack and are therefore available for use by all clinicians participating in INTERLACE.

4.2.6 Assessment of impact of delineation atlas implementation

To assess the impact of this atlas I monitored the INTERLACE RTQA test cases and real time review cases. For each RTQA test case and real time review case, a report is generated by the RTQA team which recommends outlining changes if necessary. Using these reports I recorded the number of structures that did not require any changes for each case out of Bladder, Rectum, CTV1 and CTV2. If a case was outlined very well, no changes were recommended and the score is 4. If all structures required changes the score is 0. I then compared the scores of all cases before and after inclusion of the delineation atlas in the RTQA pack by using an independent samples t-test.

In addition, I compared the clinicians' confidence questionnaire results before and after atlas implementation by using independent samples t-test.

4.3. Results

4.3.1 Clinicians' experience and confidence

27 questionnaires were sent out anonymously at both time points. 18 (67%) clinicians returned them before atlas implementation and 13 (48%) returned them afterwards. Before atlas implementation 14 had completed the RTQA process, 5 were routinely using IMRT and 13 were reportedly self-taught. 4 had completed online courses, 3 completed local courses, 5 national courses and 10 attended international courses. The areas of least confidence were uterosacral ligaments (mean 2.7 SD 0.8), superior border of parametrium (mean 2.6, SD 0.8), posterior border of parametrium (mean 2.7 SD 0.8), and inferior border of parametrium (mean 2.6, SD 1.8). Overall total ranged from 24 to 40, mean 32 and SD 5. The results for after atlas implementation are discussed in section 4.3.6.

4.3.2 Literature review results

Seven key articles on gynaecology RT guidelines were identified and reviewed (Table 4.1). Five of these articles were written by collaborative groups; RTOG, JCOG, ESTRO and National Cancer Institute of Canada (NCIC). The remaining two articles were from a single institution. The guideline topics were the delineation of OARs (Gay et al. 2012), primary CTV (CTV1) (Lim et al. 2011; Toita et al. 2011), pelvic nodal CTV (CTV2) (Taylor et al. 2005; Small et al. 2008; Toita et al. 2010), and both CTV1 and CTV2 (Bansal et al. 2013). All contained pictorial images to aid explanation and improve understanding. There were no published guidelines for para-aortic nodal (CTV3) delineation but articles were identified describing cervical cancer para-aortic node distribution with delineation suggestions (Fontanilla et al. 2013; Kabolizadeh et al. 2013; Takiar et al. 2013). Additional pelvic nodal outlining articles were identified and reviewed (Chao et al. 2002; Shih et al. 2005; Dinniwell et al. 2009). These were not classified as key articles as they were not for cervical cancer cases alone.

RTOG published a consensus panel atlas in 2012 for normal pelvic tissues (Gay et al. 2012) as variability had been observed within gynaecological, urological and gastrointestinal trials. These are the only guidelines published on OAR delineation.

In 2011 an international Gynaecology IMRT consortium published guidelines for primary CTV (CTV1) delineation in the definitive treatment of cervical cancer in preparation for an RTOG proposed prospective phase 2 trial investigating IMRT in cervical cancer (Lim et al. 2011). This consortium included representatives from RTOG, NCIC, JCOG and ESTRO. A survey was initially completed on the use of IMRT, imaging modalities used for RT planning and CTV definition. A meeting, at which current data was reviewed, was held resulting in a draft consensus document. This draft document was then tested by all of the consortium members. Using the STAPLE algorithm outline (described in Chapter 2) areas of discordance were highlighted then discussed and resolved. In the same year the Radiation Therapy Study Group of JCOG published their guidelines as a result of increased IMRT use in Japan. They undertook a comprehensive literature review and examined multiple test cases via email communication and at three face-to-face meetings prior to reaching a consensus (Toita et al. 2011). In 2013, Bansal et al from the Postgraduate Institute of Medical Education and

Research (PGI) in Chandighar, India published a literature review and, following review of cases treated at their institution, their guidelines for both primary and nodal CTV in cervical cancer (Bansal et al. 2013).

Taylor et al (2005) investigated the distribution of pelvic lymph nodes by intravenous administration of iron oxide particles before MRI. They demonstrated that a 7 mm margin around blood vessels with minor modifications achieves 99% coverage of pelvic nodes. This led to their 7 mm margin recommendation for pelvic nodal delineation (Taylor et al. 2005). These margins are smaller than the previously recommended 1-2cm margins published by Chao et al following lymphangiography of 6 cervical cancer patients (Chao et al. 2002). However, Chao et al also recommended further editing due to concern regarding OAR doses including truncation of the outline 5mm into bladder and bowel. Dinniwell et al (2009) applied a similar investigation method as Taylor et al to a cohort of patients which only included 5 cervical cancer patients. They recommend a 9-12 mm expansion depending upon the anatomic region that you are expanding (Dinniwell et al. 2009). Shih et al recommend a 20mm margin after using a similar technique for prostate cancer cases (Shih et al. 2005). This study did not consider normal tissue coverage implications which Taylor and Dinniwell did. RTOG collaboration, JCOG and PGI have since published guidelines adopting the 7 mm margin (Small et al. 2008; Toita et al. 2010; Bansal et al. 2013).

No published guidelines were found regarding delineation of the para-aortic nodal region. Two articles were reviewed which reported on the location of para-aortic nodes in gynaecological cancers and made recommendations for para-aortic nodal outlining. Kabolizadeh et al retrospectively reviewed the location of 133 malignant lymph nodes from 46 patients with pelvic cancers. They found 59% of nodes were in the left para-aortic region, 35% aorto-caval and only 6% right para-caval (Kabolizadeh et al. 2013). Takiar et al used FDG-PET/CT to identify 72 involved para-aortic nodes in cervical cancer patients. They reported similar findings with 51% of nodes in the left para-aortic region, 44% in the aorto-caval and 4% in the right para-caval region (Takiar et al. 2013).

4.3.3 Positive para-aortic nodal case review

Eleven patients were identified with enlarged para-aortic nodes on imaging at presentation from all cases treated with chemoradiation between 2010 and 2014 in UCLH.

Review of the imaging for these cases showed

- 3 cases with enlarged left para-aortic nodes only

- 2 cases with enlarged aortocaval and left paraaortic nodes

- 6 cases with enlarged aortocaval nodes only

- 0 cases with enlarged right paracaval nodes

These findings suggest that nodal risk is highest around the aorta and aortocaval space. This is in line with published data on the distribution of para-aortic nodal spread described earlier (Kabolizadeh et al. 2013; Takiar et al. 2013).

4.3.4 Areas of variation and best practice recommendations (Table 4.2)

Ten areas of variation in practice were identified; three of these were regarding OARs, three regarding CTV1 and four regarding CTV2. There was no complete guidance found for para-aortic nodal CTV delineation which is the eleventh area I discuss in detail here.

OAR definition

Discrepancies between RTOG published recommendations (Gay et al. 2012) and clinical practice observed in INTERLACE relate to the femur and the bowel outlines (Table 4.2). Pragmatically, our atlas includes anus and rectum as one structure. As knowledge increases regarding dose toxicity effects, different dose limits may be applicable and therefore anus and rectum may be delineated separately. Dose delivered to bone marrow should also be considered when using IMRT chemoradiation to minimise haematological toxicity. However, no published recommendations exist for bone marrow delineation and many centres use automated pelvic bone delineation as a surrogate. We have therefore not included this OAR in our atlas.

Table 4.1: Published delineation guidelines for cervical cancer RT.

Authors	Year	Title	Contents
Bansal et al PGI	2013	Literature review with PGI guidelines for delineation of clinical target volume for intact carcinoma cervix	Definition of nodal and primary CTV; CTV nodal to include common, external and internal iliac, pre-sacral and obturator, CTV primary includes GTV, uterine cervix, uterine corpus, parametrium, upper vagina and uterosacral ligaments
Gay et al RTOG Panel	2012	Pelvic Normal Tissue Contouring Guidelines for Radiation Therapy: A Radiation Therapy Oncology Group Consensus	Definition of male and female pelvic normal tissue contouring atlas: for gynae details AnoRectum, Sigmoid, BowelBag, Bladder, Uterocervix, Adnexa and Femur
Lim et al RTOG Gyn IMRT consortium	2011	Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer	CTV to include GTV, cervix, uterus, parametria (borders defined), ovaries and vaginal tissues
Small et al RTOG with GOG, ESTRO, NCIC, ACRIN	2008	Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer	Definition of CTVs for postoperative cervical/endometrial cancer: Nodal CTV to include the common, external and internal iliac, and presacral nodal regions, Upper vagina and paravaginal soft tissue lateral to vagina also to be included.
Taylor et al	2005	Mapping Pelvic Lymph nodes: guidelines for delineation in intensity-modulated radiotherapy	Recommended nodal CTV guidelines based on blood vessels with a modified 7mm margin; common, internal and external iliac, obturator and presacral regions
Toita et al JCOG	2010	A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer	Definition of pelvic nodal CTV; common, external and internal iliac, obturator and presacral regions
Toita et al JCOG	2011	A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer	Definition of primary CTV for cervical cancer; GTV, uterine cervix, uterine corpus, parametrium (borders defined), vagina and ovaries

Table 4.2: Areas of variation regarding OAR and CTV definition for cervical cancer RT

	Area of variation	Published guidance/clinical practice	Discussion	Our recommendation
OAR (Gay et al. 2012)	Femoral head vs proximal femur	RTOG: proximal femur Observed practice variable	Beams likely to travel through proximal femur and osteoradionecrosis aetiology unclear	Proximal femur
	Bowel bag vs loops	RTOG: bowel bag Observed practice variable	Bowel moves daily in abdominal cavity therefore bag more representative	Bowel bag
	Subtract CTV from bowel	RTOG: subtraction of 'any overlapping non-GI structures'	CTV1 should definitely be subtracted CTV2 should also be subtracted as bowel unlikely to overlap daily	Subtract CTV1 and CTV2 from bowel
CTV1 Primary (Lim et al. 2011; Toita et al. 2011; Bansal et al. 2013)	Vaginal length to include	RTOG, JCOG and PGI: upper 1/2 if no vaginal disease, 2/3 if upper disease, 3/3 if extensive disease INTERLACE: upper ½/2cm below disease	Volumes likely to be similar; 2cm below disease may be smaller. 2cm margin on known disease (EUA and MRI) adequate and clearer to define/reproducible	Upper ½ or 2cm below known disease
	Lateral parametrial border	RTOG, JCOG and PGI: pelvic sidewall defined as muscle/ischial ramus Medial sidewall is peritoneal reflection	Even though the medial sidewall is the peritoneal reflection RTOG/JCOG definition is more reproducible and practical	Medial edge of internal obturator muscle/ischial ramus
	Posterior parametrial border	RTOG, PGI: entire mesorectum if FIGO 3b JCOG: include perirectal tissue if significant parametrial involvement	Improved imaging techniques allow detection of involvement of uterosacral ligaments and mesorectum	Include mesorectum only if radiologically or clinically involved
CTV2 Nodal (Taylor et al. 2005; Small et al. 2008; Toita et al. 2010; Bansal et al. 2013)	Inferior border of obturator nodes	PGI, JCOG: superior obturator foramen RTOG: superior femoral head Taylor et al: mid femoral head	Obturator nodes are at risk and anatomically do not leave the pelvis until just above the obturator foramen	1cm superior to obturator foramen or mid-femoral head
	Subtraction of bladder/bowel	JCOG: bowel not routinely excluded RTOG: bowel and bladder excluded	Bowel and bladder position varies according to daily variation, bladder filling etc.	Only subtract bone and muscle for CTV2
	Inclusion of sacral foramina	RTOG, JCOG, PGI: exclude sacral foramina	No evidence inclusion necessary and increases bone toxicity	Exclude sacral foramina
	Superior border of CTV2	RTOG: bony anatomy Taylor et al, JCOG, PGI: aortic bifurcation	Should not relate to bony anatomy, should relate to nodal anatomy	Aortic bifurcation
	Margin around large nodes	PGI: 10mm around enlarged node	Nodes well defined on CT but margin needed	3 to 5mm margin
CTV3 PAnodes	Para-aortic volume definition	No guidance. Distribution suggests low risk lateral to IVC	From experience nodal disease seen around aorta/aortocaval area	Aorta and medial half IVC with 7mm margin

Femur definition

In the INTERLACE study, differences were observed between centres in defining the femoral outline. The INTERLACE protocol version 1 recommended delineation of the femoral head alone, consistent with many centres' observed practice. However, it is important to consider late radiation effects as this impacts quality of life. Osteoradionecrosis of the hip is a rare but significant late complication (Mehmood et al. 2014). The mechanism of osteoradionecrosis and bone effects of RT are not fully understood (Higham et al. 2015). Osteoradionecrosis risk may be related to femoral neck radiation dose. It was therefore agreed to follow the RTOG recommendation to include the whole proximal femur to the inferior margin of the lesser trochanter (Gay et al. 2012) as seen in Fig. 1.6a and 1.6b of the delineation atlas. This ensures full documentation and minimisation of dose to femoral head and neck. We have amended the trial protocol accordingly.

Bowel definition

Experience from the INTERLACE RTQA has been that standard practice across the UK varies from centre to centre regarding delineation of the bowel. Some centres outline the abdominal cavity (bowel bag) whilst others outline individual bowel loops. A well-documented relationship exists between dose volume parameters and acute toxicity for bowel loops and bowel bag (Roeske et al. 2003; Simpson et al. 2012; Banerjee et al. 2013). Small bowel volume receiving 45 Gray significantly correlated with acute toxicity in 50 patients receiving pelvic RT for gynaecological cancer (Roeske et al. 2003) and in 50 patients receiving RT for cervical cancer (Simpson et al. 2012). In a cohort of 67 rectal cancer patients Banerjee et al found that a relationship existed for both bowel loops and the peritoneal space with greatest sensitivity associated with the volume receiving between 15 and 25 Gray (Banerjee et al. 2013). Approximately 80% of bowel loops moved location during a course of treatment for prostate cancer patients. The consequence of this was underestimation of bowel volume receiving 45Gy by approximately 10% if bowel loops are outlined. Sanguinetti et al therefore recommend using a bowel structure which takes into account this internal organ motion to ensure the maximum protection of bowel from toxicity (Sanguineti et al. 2008). It was therefore agreed best practice is delineation of the RTOG 'bowel bag' to ensure safer practice (Gay et

al. 2012). This concept of 'bowel bag' is novel for some UK centres. Clarity of the steps required to create this structure is essential for consistency. The first step is to outline the abdominal cavity and this is relatively easily defined. RTOG then recommend clinicians 'subtract any overlapping non-GI normal structures' from the abdominal cavity outline. The bladder and uterus (CTV1) should therefore be subtracted. There is no clear guidance regarding whether CTV2 (the pelvic nodal CTV) should also be subtracted. CTV2, discussed below in detail, represents the location of nodes at risk of microscopic disease. Bowel loops can overlap with this area but this is unlikely to happen on a daily basis. Overlapping competing structures are problematic for some IMRT TPSs so it was agreed that best practice would be to subtract CTV2 from the bowel bag (see Fig. 1.5a-d of delineation atlas).

CTV1 definition

The Gyn IMRT consortium, JCOG and PGI guidelines for tissue coverage in CTV1 are consistent and include the uterus, ovaries if visible, GTV to include whole cervix and entire extent of local disease, vagina and bilateral parametria (see Fig. 2.1, 2.2. and 2.3 of delineation atlas). There are differences in practice observed in INTERLACE and these guidelines with respect to the extent and definition of vagina and parametria (see Table 4.2).

Vagina

The Gyn IMRT consortium, JCOG and PGI guidelines recommend treatment of the upper half if there is no vaginal involvement, upper two thirds if the upper vagina is involved and the whole vagina if there is extensive involvement. The INTERLACE protocol recommends treatment of the upper half of the vagina or 2cm below known disease, whichever is longer. In practice, the difference in CTV between these two definitions is small. Sometimes, including 2cm below known disease creates shorter outlines. It was concluded that best practice is to include a 2cm margin below known disease. This is an easier, more consistent method and avoids the ambiguity of differentiating 'upper' from 'extensive' involvement.

Experience from the INTERLACE RTQA programme also highlighted the difficulty in outlining the vagina, in particular defining the superior and inferior (introitus) aspects on CT. Agreement was to recommend using the clitoral crura as a marker for the introitus as demonstrated in Fig. 2.6 in the delineation atlas (O'Connell et al. 2005).

Alternative methods to clinical examination and MRI of localising the vagina and distal tumour extent include fiducial markers and vaginal dobbie at simulation. Within the UK and internationally some centres insert a vaginal dobbie at RT simulation (Ma et al. 2012). This can distort anatomy, and be uncomfortable for patients. Fiducial markers can also highlight the inferior vaginal extent of tumour. These are inserted surgically, reproducibility is uncertain and there is a risk of markers falling out or moving (Jhingran et al. 2012). Neither method is routine UK practice. Neither method is an ideal solution for this ambiguity. As the planning process becomes more complex MRI may be more commonly used to delineate the GTV and CTV which will significantly aid visualising the inferior and superior vaginal extent.

Parametria

The lateral border of the parametrial volume in the Gyn IMRT consortium, JCOG and PGI guidelines is quoted as the pelvic sidewall, which they define as the 'medial edge of the internal obturator muscle and ischial ramus'. However observed practice in INTERLACE and anatomical definition of the lateral parametria is the peritoneal reflection. Surgically, resection of the parametrium will not extend beyond the vessels (Nakamura et al. 2014). Despite these discrepancies we agreed to use the medial edge of the muscle or bone as the lateral border as this is a more readily reproducible anatomical boundary. The true parametria probably lies approximately 1cm medial to this border and some experienced clinicians use this as a rough guide. However, when producing guidance for wider use, a slightly over-generous but reproducible border is the safest approach. If MRI is adopted for delineation the parametrial borders are more visible and this guidance may change. Use of this definition leads to overlap between the CTV1 and CTV2 outline which does not need to be edited.

The definition of the posterior border of the parametria varies between guidelines and recommended coverage varies according to FIGO stage. RTOG and PGI recommend inclusion of the whole mesorectum in patients with FIGO IIIb disease. JCOG guidance suggests inclusion of the perirectal tissue only when there is bulky central tumour or extensive parametrial involvement. These approaches ensure inclusion of mesorectal pre-sacral nodes. With advances in modern imaging, involvement of the mesorectum or mesorectal nodes is more easily identified. Including the mesorectum within the CTV increases the irradiated

volume. On balance, it was decided to only include the mesorectum or perirectal tissue where there is clinical or radiological involvement by tumour. Within the delineation atlas, Table 1 and Fig. 2.4 define the parametrial borders.

CTV2 definition

RTOG, Taylor et al and PGI guidelines are in agreement regarding which nodal groups should be included in CTV2. However, variation exists regarding the superior and inferior nodal extent, the inclusion or otherwise of the sacral foramina, the subtraction of OARs and the margin around enlarged nodes.

Superior border of CTV2

RTOG define the superior transverse slice of CTV2 by bony anatomy; 7 mm inferior to the L4/5 junction (Small et al. 2008). This approach was previously adopted for conventional RT when two-dimensional imaging was used. Taylor et al, JCOG and PGI recommend that CTV2 should extend to the aortic bifurcation (Taylor et al. 2005; Toita et al. 2010; Bansal et al. 2013). At ASTRO 2014 the RTOG consensus group updated their guidelines with recommendations based on vascular anatomy (Small et al. 2014). We agree the risk of nodal micro-metastases is not limited by bony anatomy. We therefore recommend that best practice is to extend contouring up to the aortic bifurcation.

Inferior border of CTV2

RTQA experience highlights clinical CTV2 inferior border definition varies widely. This relates to obturator nodal coverage which is still debated. Taylor et al illustrated coverage of nodes inferiorly to the level of the mid-femoral heads (Taylor et al. 2007). RTOG define the inferior extent at the superior border of the femoral heads (when the external iliac vessels finish). JCOG extend coverage inferiorly to the level of the superior aspect of the obturator foramen (Toita et al. 2010). Anatomically the obturator nodes extend inferiorly to obturator foramen which is lower than the superior border of the femoral heads. We therefore agree with Taylor et al and recommend including the nodes up to approximately 1cm above the obturator foramen. Depending upon pelvic tilt, this often corresponds to the level of the mid femoral head.

Steps to create CTV2

RTOG guidance recommends subtraction of bladder and bowel from CTV2. This has been observed practice in INTERLACE. However, concern exists because bowel is not a fixed structure and bladder filling is variable. For this reason, we recommend not to edit CTV2 for bladder and bowel in view of the possible consequence of inadequate nodal coverage.

Inferiorly, Taylor et al recommend using an 18mm wide strip to cover the obturator nodal region. Previously, editing for bladder would narrow this outline. Therefore it was agreed to recommend a narrower strip of 10-18mm to cover the obturator nodes. This is only applicable below the level of the superior margin of the femoral head, i.e. below the external iliac volume (see Fig. 3.7 in the delineation atlas).

Sacral foramina

Within the INTERLACE study, variation was observed regarding inclusion of the sacral foramina in CTV2 as described in Chapter 2. Published guidelines give no recommendation regarding coverage of the foramina. Inclusion of the sacral foramina leads to an increased risk of insufficiency fractures and impaired quality of life (Ikushima et al. 2006). In view of this, it was decided to exclude the sacral foramina but include the presacral space as seen in the delineation altas Fig. 3.3.

Margin around enlarged nodes

PGI guidelines suggest a 10 mm margin from enlarged nodes to CTV. RTOG and JCOG guidance do not make any recommendation. Enlarged nodes are usually well defined on CT and MRI. It was therefore agreed that the CTV2 around an enlarged node would be achieved by adding the 7 mm margin around blood vessels plus an additional 5 mm margin to allow for extracapsular nodal extension.

CTV3 definition

No published guidelines were found addressing delineation of the para-aortic nodal volume. Articles describing the anatomical distribution of para-aortic nodes in cervical cancer using FDG-PET (Fontanilla et al. 2013; Kabolizadeh et al. 2013; Takiar et al. 2013) were therefore reviewed, as discussed in the literature review results. Extrapolating from pelvic nodal

contouring the para-aortic nodal outline is often created by adding a 7 mm margin around blood vessels and editing for bone and muscle. In practice this is often subsequently edited to minimise kidney dose especially on the side of the IVC. Some centres only outline the aorta whereas other centres outline aorta and IVC. This is neither consistent nor easily reproducible. Following the review of cases at our institution described above, it is proposed that a 7 mm margin around the entire IVC is unnecessary. Inclusion of the aortocaval space is essential. Our findings and this recommendation is consistent with the published data on para-aortic nodal distribution. As discussed earlier, only 4-6% of nodes are reported to be in the right para-caval region (Kabolizadeh et al. 2013; Takiar et al. 2013). There are guidelines for para-aortic nodal delineation for other cancers, e.g. pancreatic cancer which recommend a margin around the aorta only. This is unlikely to ensure adequate coverage in cervical cancer (Kabolizadeh et al. 2013). To ensure adequate coverage it is proposed that a 7 mm margin is used around the aorta and the medial half of the IVC as illustrated in Fig. 4.1 in the delineation atlas. This should only then be edited to minimise renal dose as a last resort.

4.3.5 Complete step-by-step delineation atlas

I created the following pictorial atlas using example cases to illustrate the entire delineation process for CTV1, CTV2, CTV3 and all OARs; the complete atlas is shown here. For CTV2 outlining, the step-by-step approach can be laborious. Therefore, clinicians with extensive experience may freehand delineate CTV2 using a tool such as pearl to ensure a 7mm margin around blood vessels.

Atlas to facilitate CT outlining of structures for cervical cancer radiotherapy.

Key:

OAR = Organs at risk; normal tissue structures which are at risk of receiving radiation dose

CTV = Clinical Target Volume; the area of known disease and area at risk of sub-clinical disease

PTV = Planning Target Volume; the area to which radiation is prescribed, usually CTV plus a margin to account for set-up error and organ motion.

Section 1: Organ At Risk (OAR) guidelines (Gay et al. 2012):

1.1: Bladder (Fig. 1.1).

Outline the outer wall of the entire bladder (arrowed in Fig. 1.1a and 1.1b).
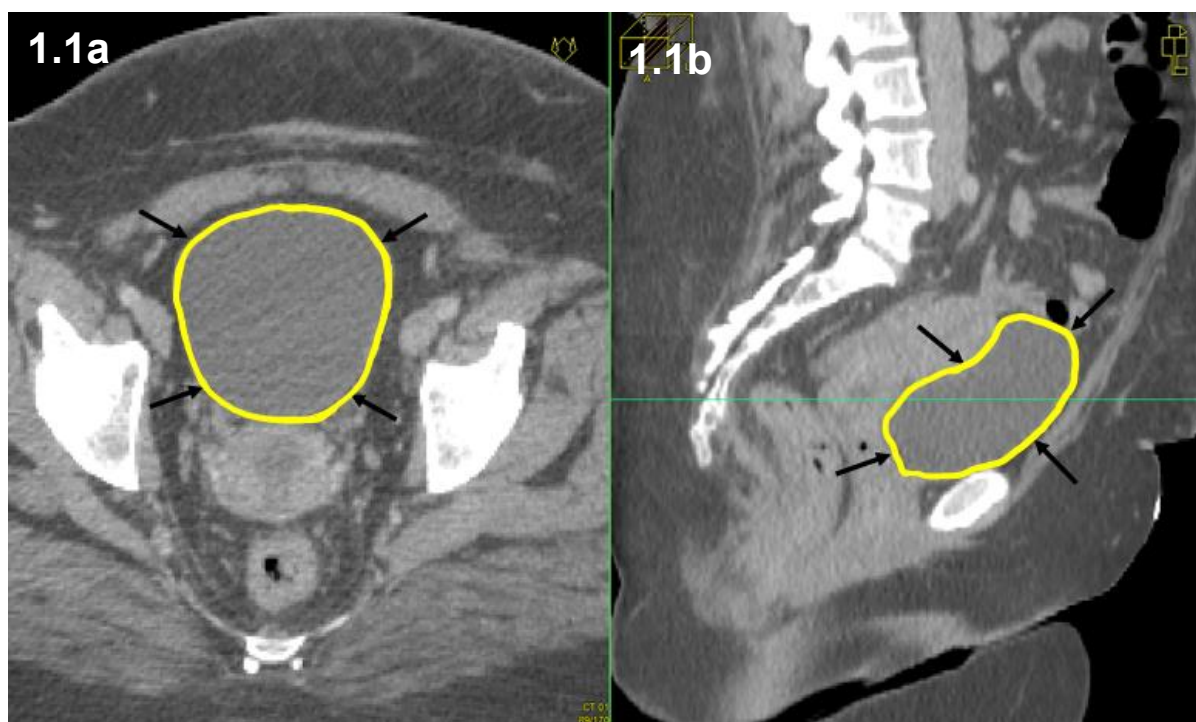
Fig. 1.1: Transverse (a) and Sagittal (b) CT with bladder outlined as arrowed.

1.2: Rectum (Fig. 1.2).

Outline the outer wall of the rectum (arrowed in Fig. 1.2a and 1.2b) and anus (arrowed in Fig. 1.2c and 1.2d) from the anal sphincter to the transition anteriorly into the sigmoid colon (arrowed in Fig. 1.2e and 1.2f).
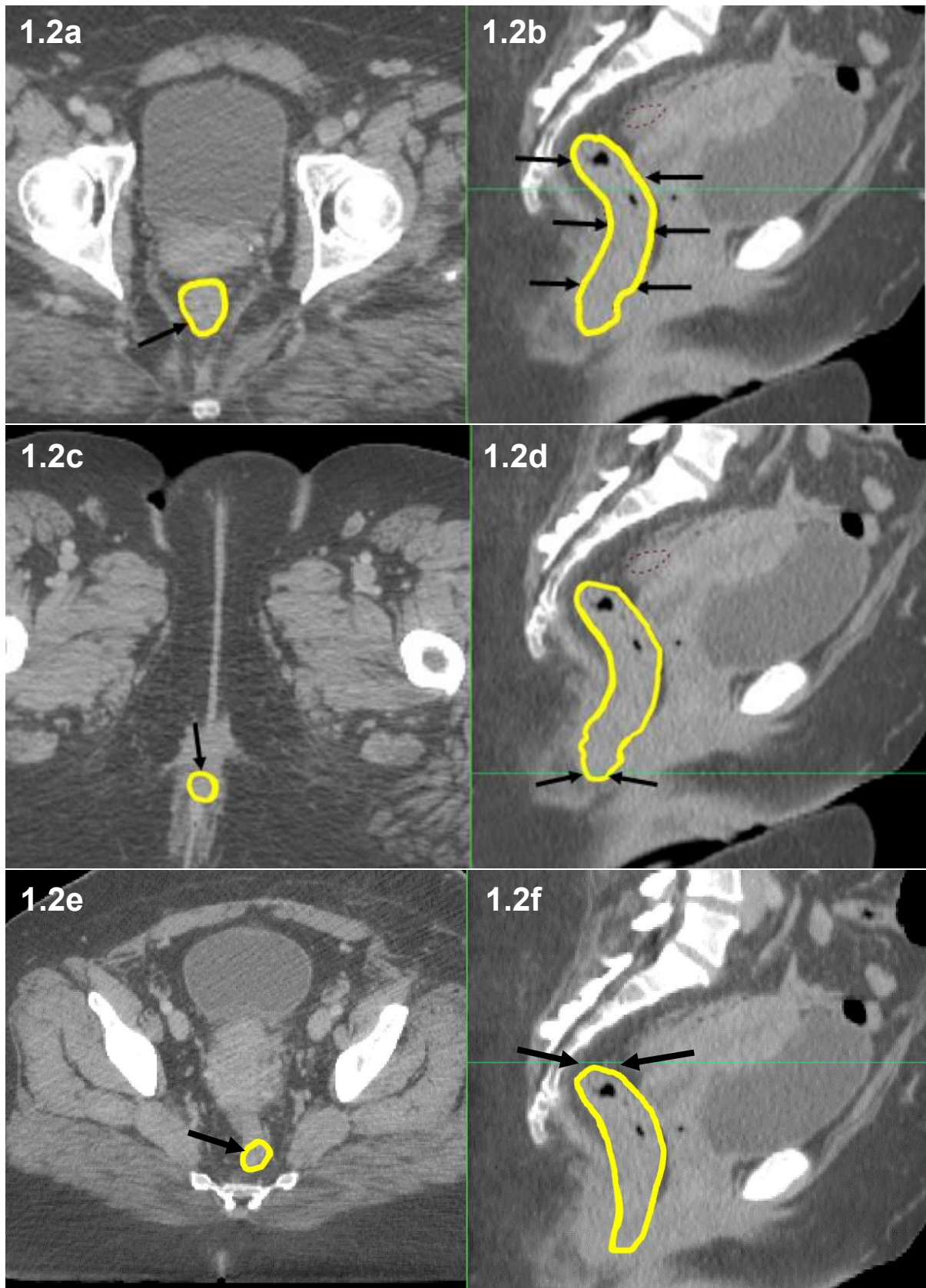
Fig. 1.2: Transverse (a) and Sagittal (b) CT at level of mid-femoral heads with rectum outlined (arrowed in a and b); Transverse (c) and sagittal (d) CT at level of anus (arrowed in c and d); Transverse (e) and ragittal (f) CT at level of transition anteriorly into sigmoid colon (arrowed in e and f).

1.3: Kidney (Left and Right) (Fig. 1.3)

If either kidney is within 2 cm of the cranial border of the PTV both kidneys must be outlined. This is required in all patients receiving para-aortic nodal radiotherapy and some patients receiving pelvic radiotherapy alone. Outline the outer margin of the right kidney (dashed arrow in Fig. 1.3a and 1.3b) and left kidney (solid arrow in Fig. 1.3a and 1.3b) individually.
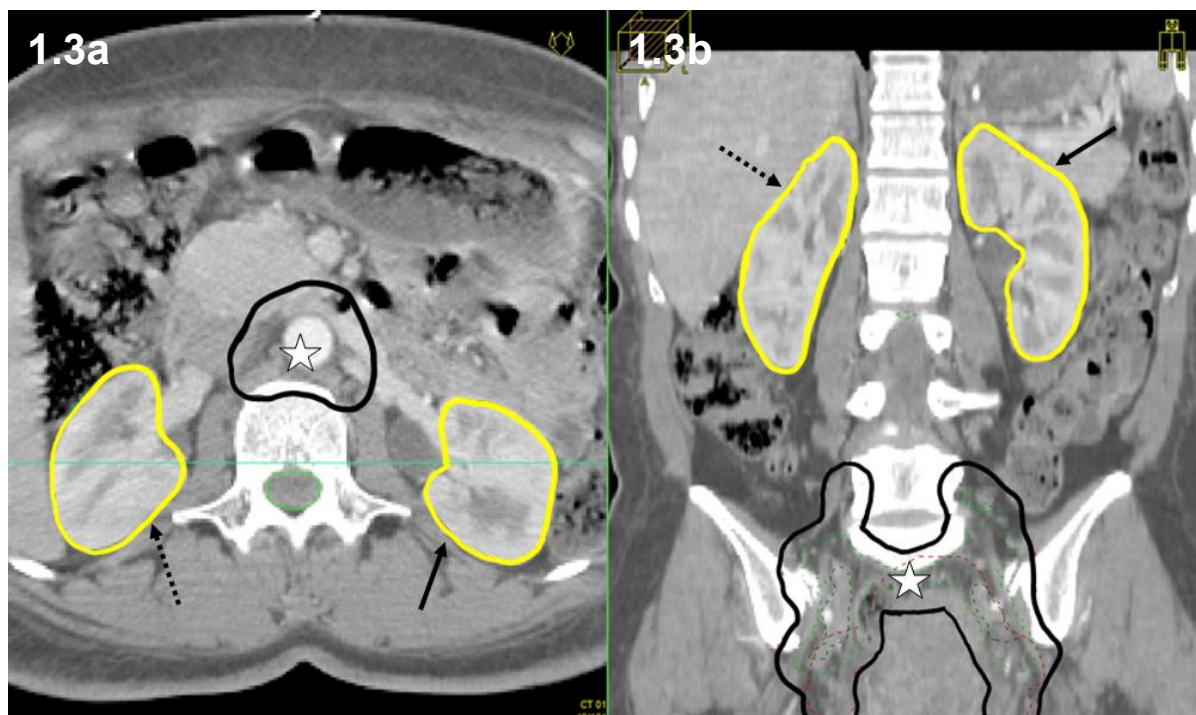
Fig. 1.3: Transverse (a) and coronal (b) CT of patient receiving para-aortic nodal radiotherapy (PTV starred) with left kidney (solid arrow) and right kidney (dashed arrow) outlined.

1.4: Spinal cord (Fig. 1.4)

If the cranial border of the PTV (starred in Fig. 1.4b) is within 2 cm of the L2/3 junction the spinal canal must be outlined. This will include all patients receiving para-aortic nodal radiotherapy and some patients receiving pelvic radiotherapy alone. Outline the whole spinal canal (solid arrow Fig. 1.4a and 1.4b) from at least 2 cm superior to the PTV to the inferior border of L2. The most inferior slice of the spinal cord outline will be level with the inferior border of the L2 vertebra (dashed arrow in Fig. 1.4b).

Fig. 1.4: Transverse (a) and sagittal (b) CT of patient receiving para-aortic radiotherapy where the PTV (star) extends to the superior border of L2. The spinal canal is outlined (solid arrow) with the most inferior level at the lower border of L2 (dashed arrow).

When Intensity-Modulated Radiotherapy is used, additional Organs At Risk must be outlined:

1.5: Bowel ('Bowel bag' if external beam radiotherapy; bowel loops if Brachytherapy. Fig. 1.5)

The RTOG recommendation (Gay et al. 2012) for patients receiving external beam radiotherapy for gynaecological cancers is to delineate the 'bowel bag'. The 'bowel bag' is the area within the abdominal cavity in which the bowel loops move around. For brachytherapy we recommend outlining all bowel loops which are close to the high dose region only.

For the bowel bag, contour the abdominal cavity excluding muscle, bone and great vessels (aorta and inferior vena cava) as seen in Fig. 1.5a and 1.5b. On transverse imaging, stop outlining inferiorly either at the level of the anorectum or when no bowel loops are seen, select whichever level is most inferior, as in Fig. 1.5b. The outline should extend at least 2 cm superiorly to the PTV. Using your treatment planning software (Boolean operations or subtraction), subtract out any overlapping structures including bladder (triangle in Fig. 1.5c-d), rectum (square in Fig. 1.5c-d), CTV1 (cross in Fig. 1.5c-d, includes uterus see section 2) and CTV2 (diamond on Fig. 1.5c, see section 3) from the bowel bag to create the final complete outline as seen in Fig. 1.5c.
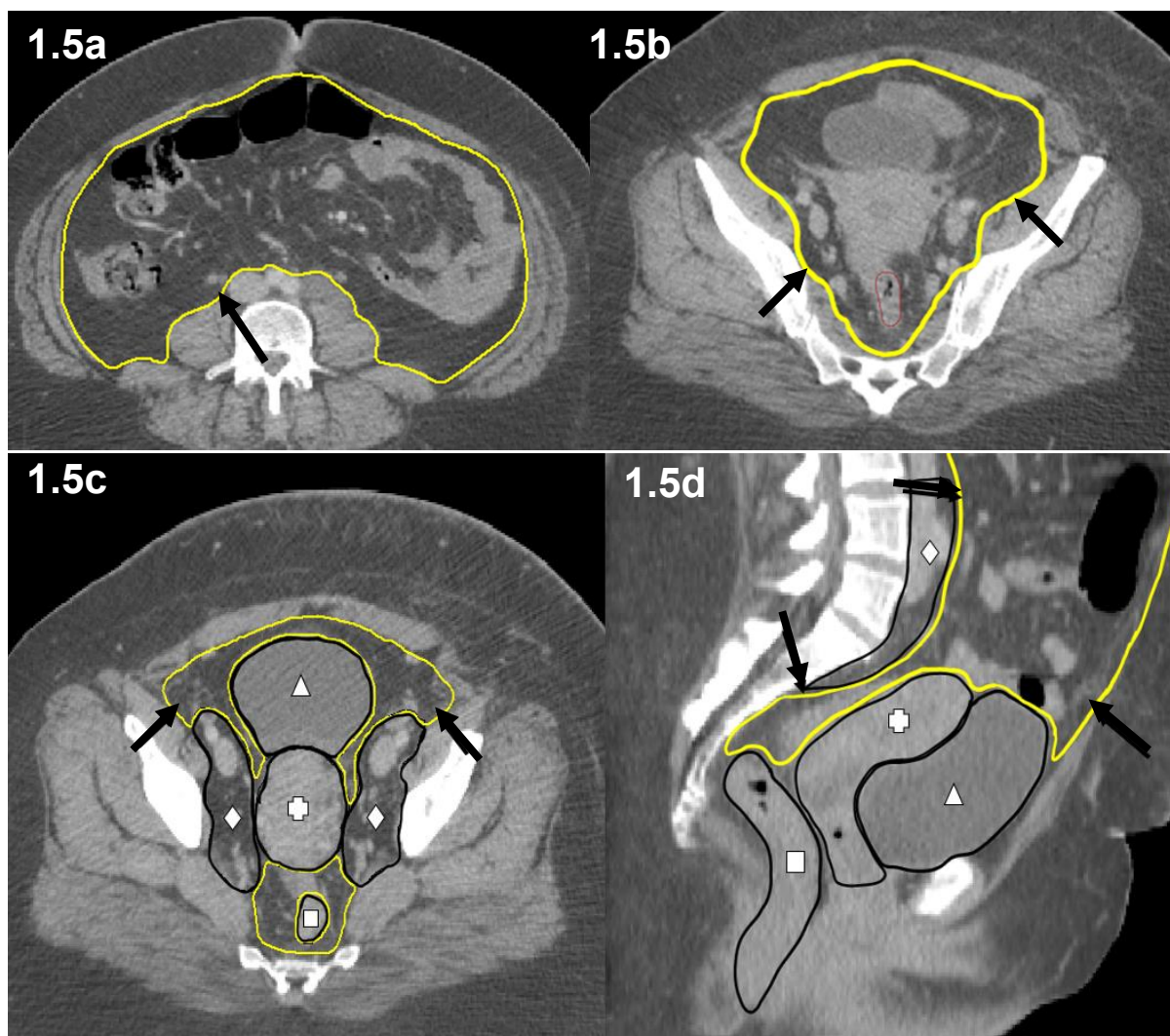
Fig. 1.5: Transverse (a, b and c) and sagittal (d) CT with bowel bag outlined (arrowed) and bladder (triangle on c and d), rectum (square c and d), uterus/CTV1 (cross on c and d) and CTV2 (diamond on c) edited out of the initial volume seen in c and d.

TIP: In sections where the abdominal cavity does not change shape rapidly between transverse slices, alternate CT slices can be outlined and interpolated by the treatment planning software. It is vital to review all CT slices once this has been performed and edit if necessary.

1.6: Femur (Left and Right)

Separately outline the left and right femoral heads and proximal femurs to the inferior margin of the lesser trochanter; left femur (solid arrows in Fig 1.6a and 1.6b), right femur (dashed arrows in Fig. 1.6a and 1.6b).
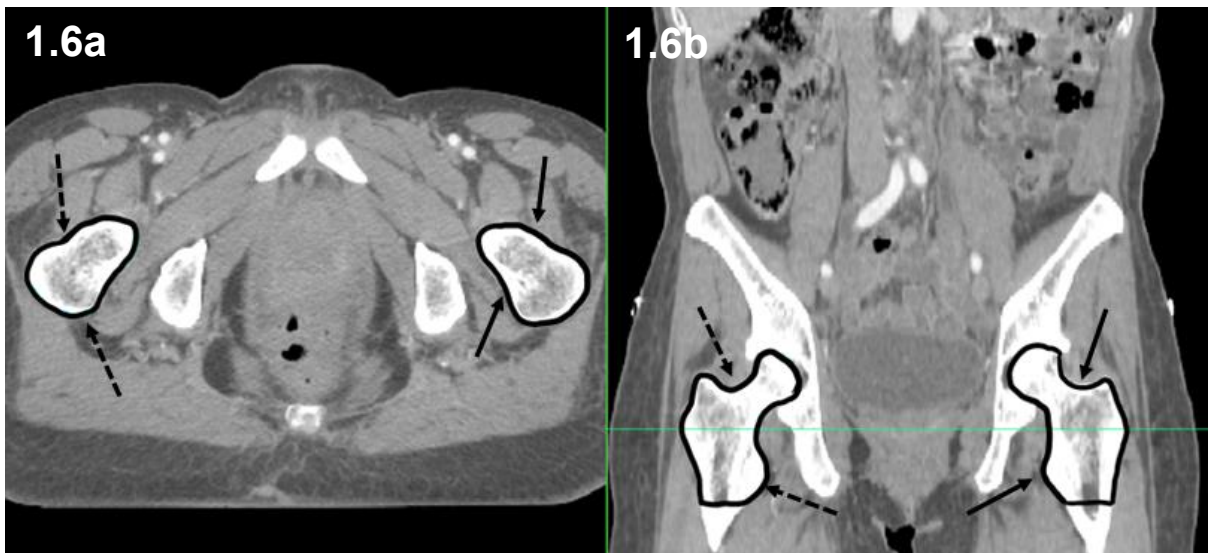
Fig. 1.6: Transverse (a) and coronal (b) CT with left femur (solid arrows) and right femur (dashed arrows) outlined.

Section 2: CTV1 guidelines (Lim et al. 2011; Toita et al. 2011):

CTV1 includes the tumour (GTV) and its local extent, the entire uterine cervix, entire uterine corpus, both parametria, ovaries if seen, proximal half of the uterosacral ligaments and at least the upper half of the vagina depending upon extent of disease. This volume is delineated as a single contiguous outline but for the purpose of these instructions, we have separated the structures to aid description.

Step 1 (Fig. 2.1): Outline the entire uterine corpus (arrowed in Fig. 2.1a and 2.1b). The sagittal images (Fig. 2.1b) will help determine the extent of this outline. The uterine cervix (star) and vagina (triangle) can be seen outlined on the sagittal CT (Fig. 2.1b)
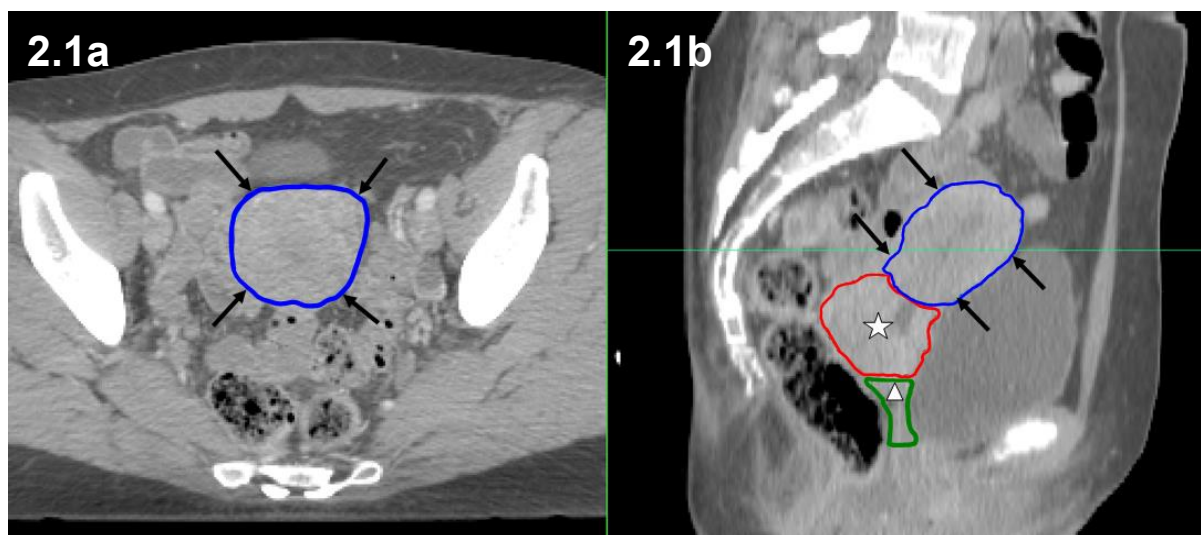
Fig. 2.1: Transverse (a) and sagittal (b) CT with the uterine corpus outlined (arrowed). The uterine cervix (star) and vagina (triangle) can also be seen in b.

Step 2 (Fig. 2.2): Outline the ovaries (arrowed in Fig. 2.2a and 2.2b) in continuity with the uterine corpus (cross) if they are visible on the radiotherapy planning CT.
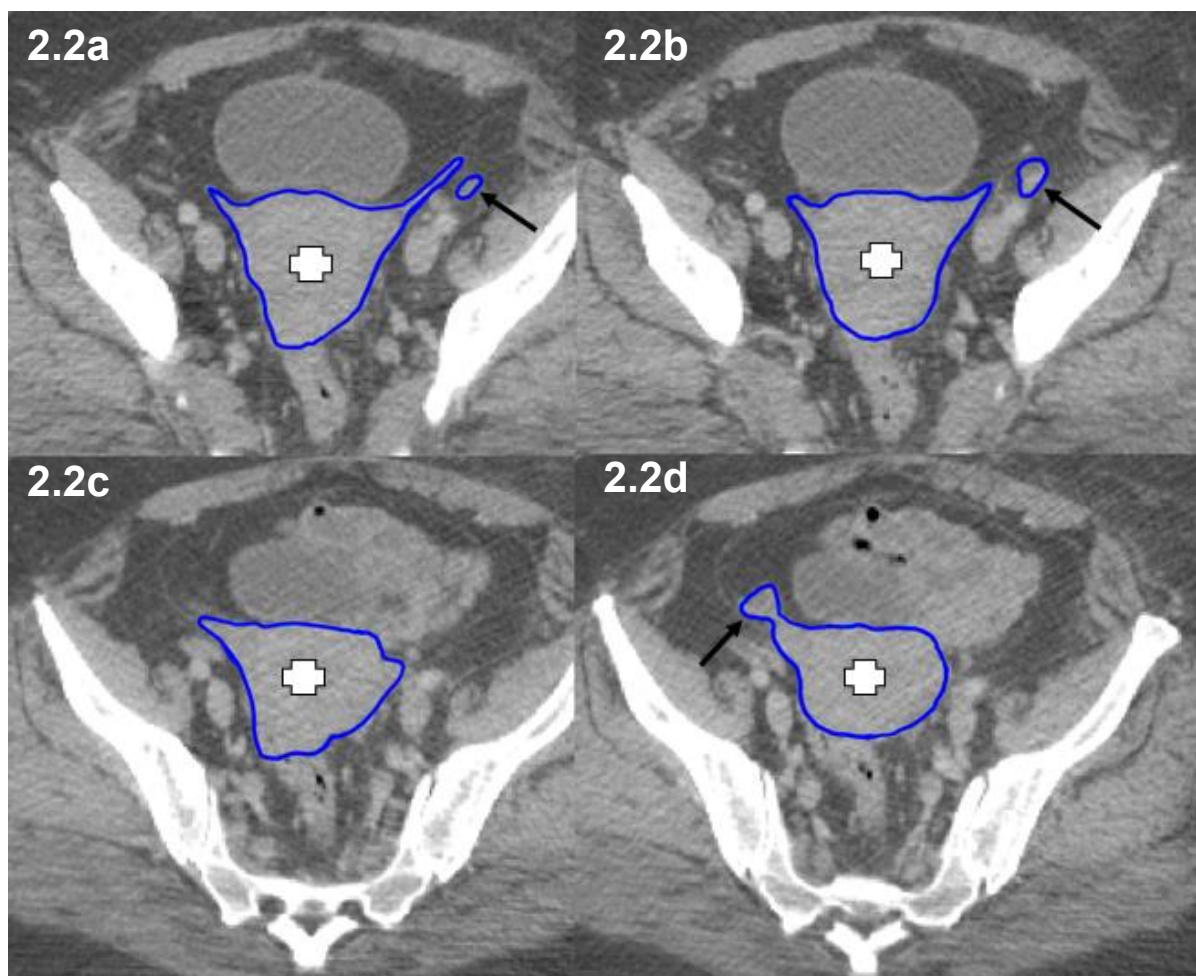
Fig. 2.2 a-d: Transverse CT with uterine corpus (cross) and ovaries (arrowed, a, b and d) outlined in continuity.

Step 3 (Fig. 2.3): Outline the entire uterine cervix including the local tumour extension (gross tumour volume) as arrowed in Fig. 2.3a and 2.3b. The uterine corpus (cross) and vagina (triangle) are also seen on the sagittal view (Fig. 2.3b)
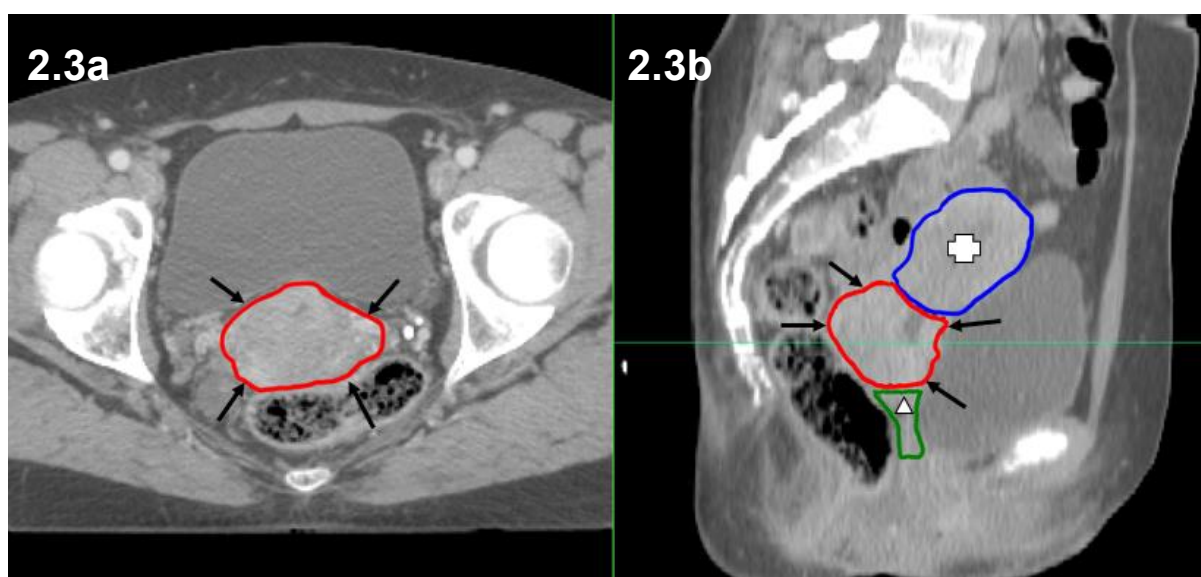
Fig. 2.3: Transverse (a) and sagittal (b) CT of the cervix and gross tumour outlined as a single structure (arrowed in a and b). The uterine corpus (cross) and vagina (triangle) outlines can also be seen on the sagittal image (b).

TIP: Use diagnostic imaging, especially the T2 weighted MRI, and examination under anaesthetic findings to determine the boundaries of CTV1 (gross tumour, uterine corpus and cervix).

TIP: The cranial margin of the cervix is at the level of the uterine arteries entering the uterus.

Step 4: Outline both parametria even if not involved with disease. The borders are described in table 1 and outlined in Fig. 2.4.

Border	Definition (arrowed and numbered in Fig. 2.4)
Superior	Fallopian tube or broad ligament (1)(RTOG) Uterine artery enters uterus (2) (JJCO)
Inferior	Levator ani/pelvic floor muscles (3)
Anterior	Posterior bladder (4) or posterior border of external iliac vessels (5)
Posterior	Mesorectal fascia and uterosacral ligaments(6)
Lateral	Medial internal obturator (7) / piriformis muscle(8) / ischial ramus (9) ie Pelvic sidewall
Medial	Cervix

Table 1: Definition of the borders of the parametrial outlines, which forms part of CTV1.
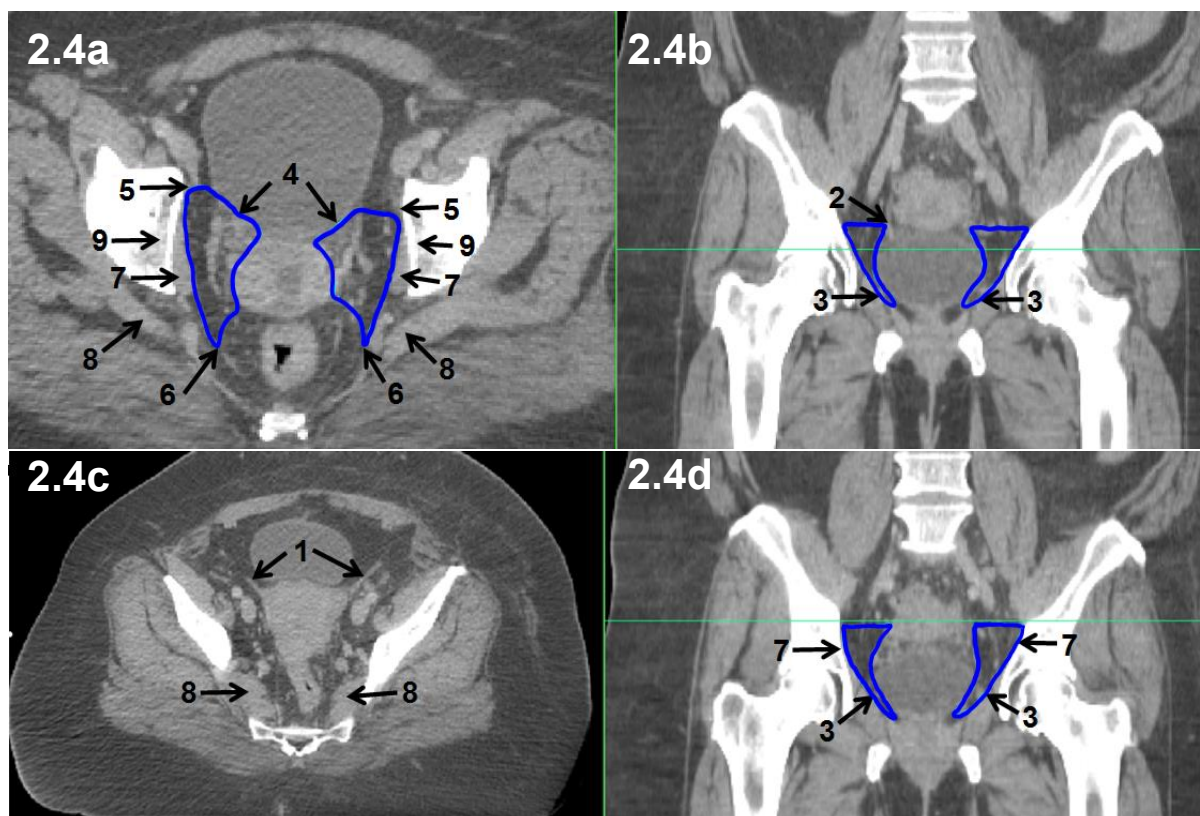
Fig. 2.4: Transverse (a and c) and coronal (b and d) CT with both parametrial borders outlined; see Table 1.

TIP: The most cranial margin of the parametrial outline is usually at the level where bowel is seen adjacent to the uterus on transverse imaging.

NB: Overlap of CTV1 and CTV2 due to the parametrial volume extending to the lateral pelvic sidewall does not need to be edited.

Step 5 (Fig. 2.5): Outline the proximal half of the uterosacral ligaments (arrowed in Fig. 2.5 and arrow number 6 in Fig. 2.4a). Extend the volume posteriorly along the uterosacral ligaments if they are involved.
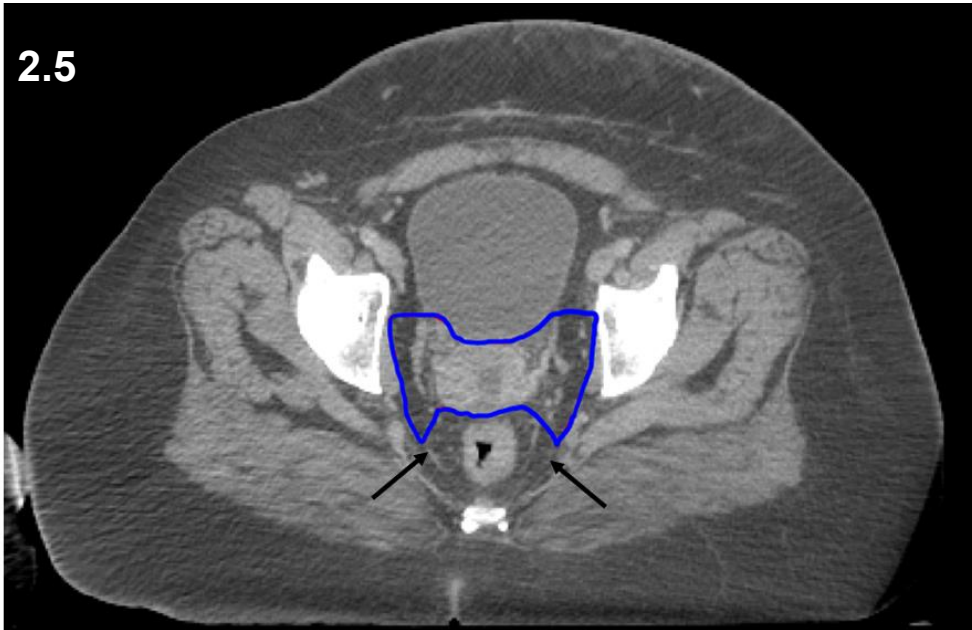
Fig. 2.5: Transverse CT demonstrating the uterosacral ligaments (arrowed) and CTV1 (outlined).

Step 6 (Fig. 2.6): Outline the upper half of the vagina (arrowed in Fig. 2.6a-d and 2.6f) if there is no vaginal involvement. If the vagina is involved with disease, outline to 2 cm below disease. The paravaginal tissue should be included in this outline (Fig. 2.6a and 2.6c). The introitus is difficult to see on CT and therefore an introital marker can be used. The level of the introitus is just proximal to the level of the clitoral crura (arrowed in Fig. 2.6e).
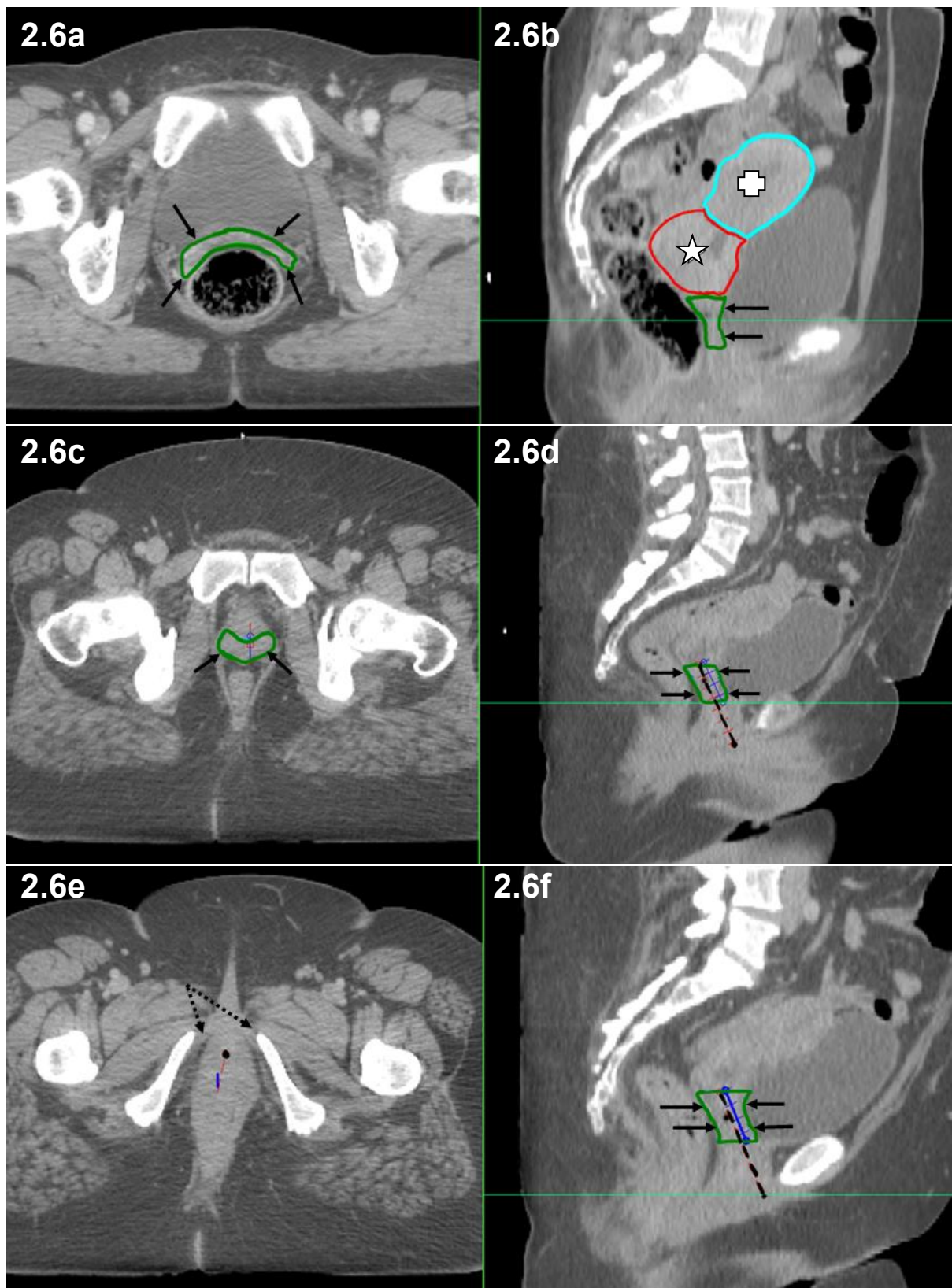
Fig. 2.6: Transverse (a, c, e) and sagittal (b, d, f) CT demonstrating outlining of the upper half of the vagina (arrowed in a-d and f); dashed line on d and f follows the full length of the vagina; arrow on e demonstrates the clitoral crura corresponding to the introitus. The uterus (cross) and cervix (star) are also outlined on the sagittal view (b).

Section 3: CTV2: Pelvic nodal guidelines (Taylor et al. 2005; Small et al. 2008):

The common iliac, internal and external iliac, obturator and presacral nodal groups are at risk of microscopic disease and are included in the nodal CTV (CTV2).

Step 1: Outline the iliac blood vessels (Fig. 3.1a, 3.2a and 3.6a). The cranial transverse margin is at the aortic bifurcation. The caudal transverse margin is at the superior border of the femoral head.

Step 2: Use the treatment planning software to add a circumferential 7mm margin to the blood vessels (Fig. 3.1b, 3.2b and 3.6b) except superiorly where 0mm is added. This ensures the cranial border of CTV2 is the level of the aortic bifurcation.

Step 3: Edit the outline using the rollerball, eraser or drawing tools to remove bone and muscle (Fig. 3.1c, 3.2c and 3.6c). Also edit the CTV, using the same tools, to include all visible nodes or lymphoceles. Involved nodes should be included in CTV2 with a minimum 3-5mm margin. Do not edit to exclude bladder or bowel.

Step 4: Extend the outline posterolaterally at the level of the common iliac vessels to ensure the space between the psoas muscle and vertebral body is included (Fig. 3.1d)
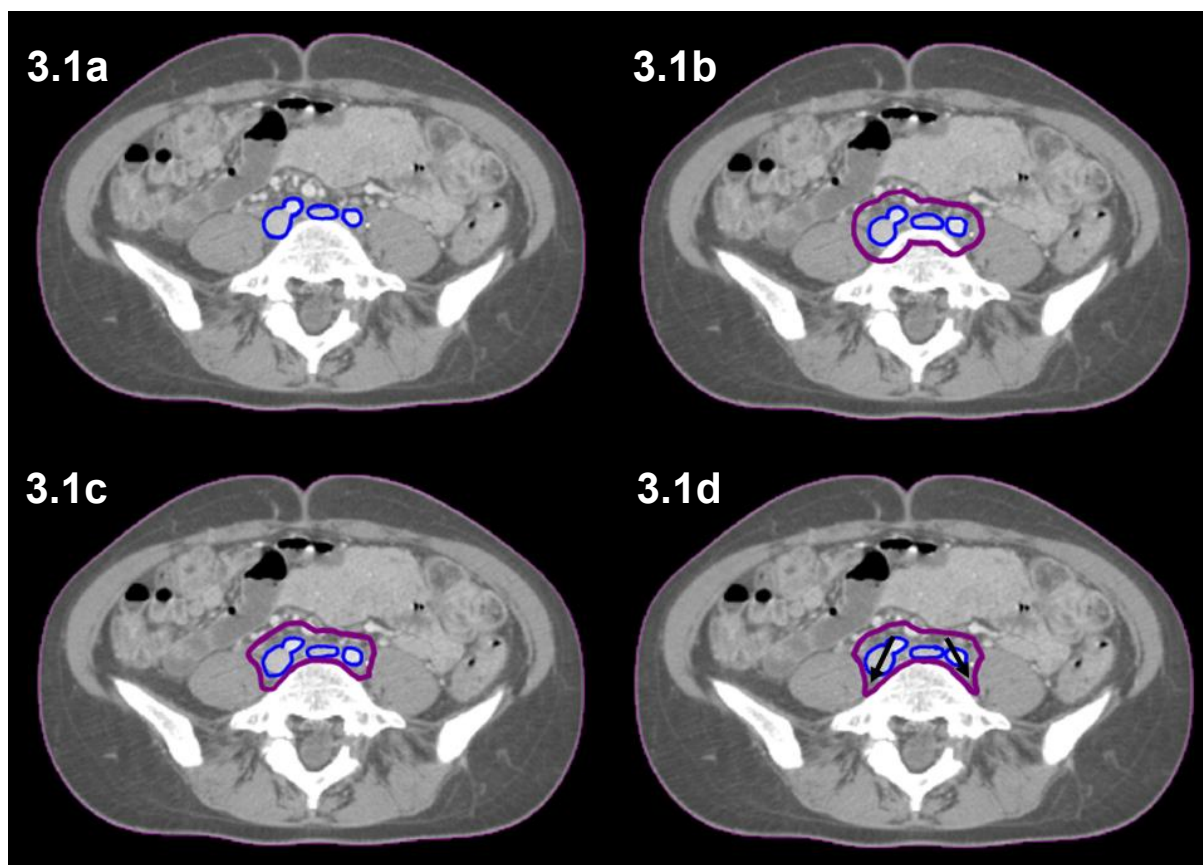
Fig. 3.1: Transverse CT image 1cm caudal to the aortic bifurcation showing the steps required to outline CTV2. The common iliac vessels are outlined (a), a circumferential 7mm margin added (b), muscle and bone is edited out (c) and the outline is extended to include the area between the psoas muscle and vertebral body (arrowed in d)**.** D illustrates the complete outline.

Step 5: Add a presacral strip by adding a 10mm strip joining the left and right outlines over the anterior sacrum (dashed arrow in Fig. 3.2d) to the lower level of S2. Do not extend into the sacral foramina (arrowed in Fig. 3.3) but do include the sacral notch.
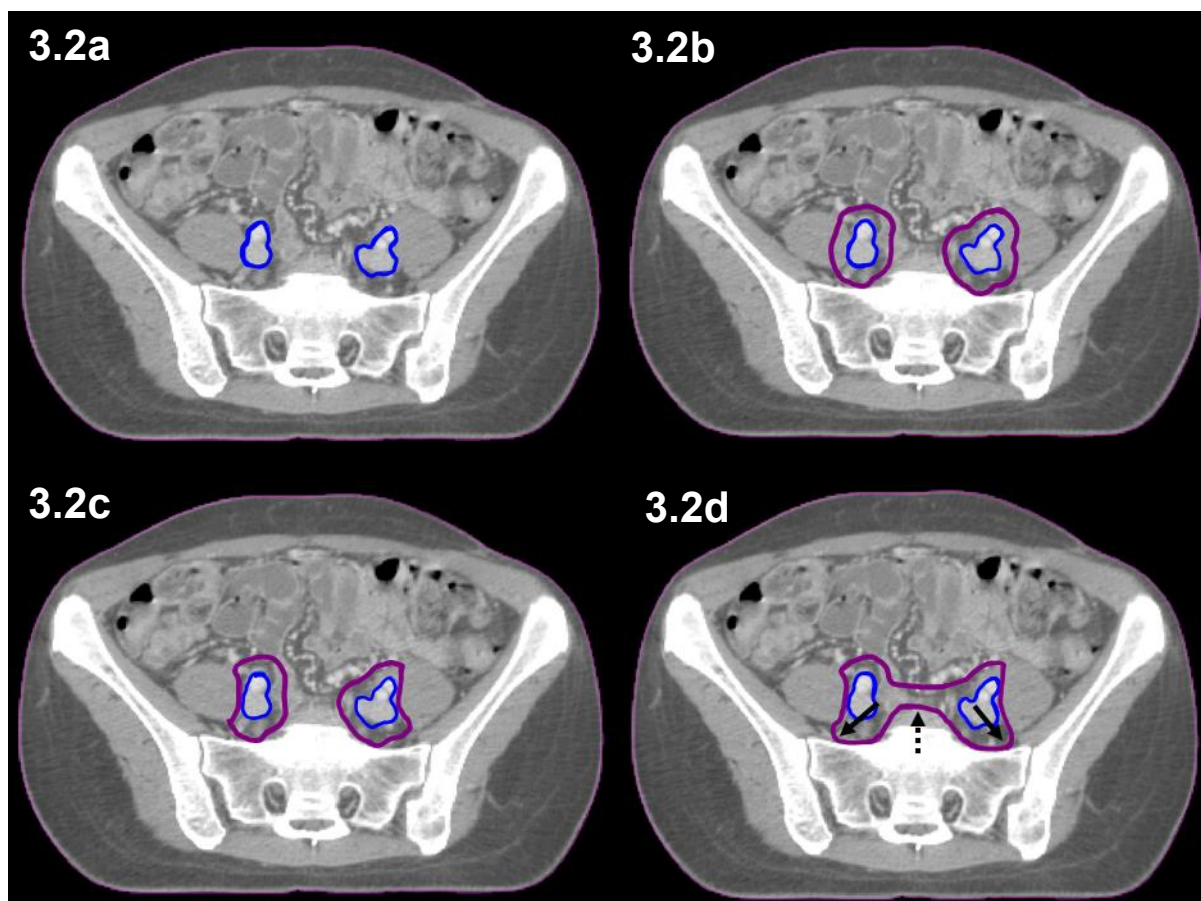
Fig. 3.2: Transverse CT image at the level of the iliac bifurcation showing the steps required to outline CTV2. The vessels are outlined (a), a circumferential 7mm margin is added (b), muscle and bone is edited out (c), the outline is extended posterolaterally to include the area between the psoas muscle and vertebral body (solid arrow, 3.2d) and a presacral strip is added (dashed arrow, d). D illustrates the complete outline.
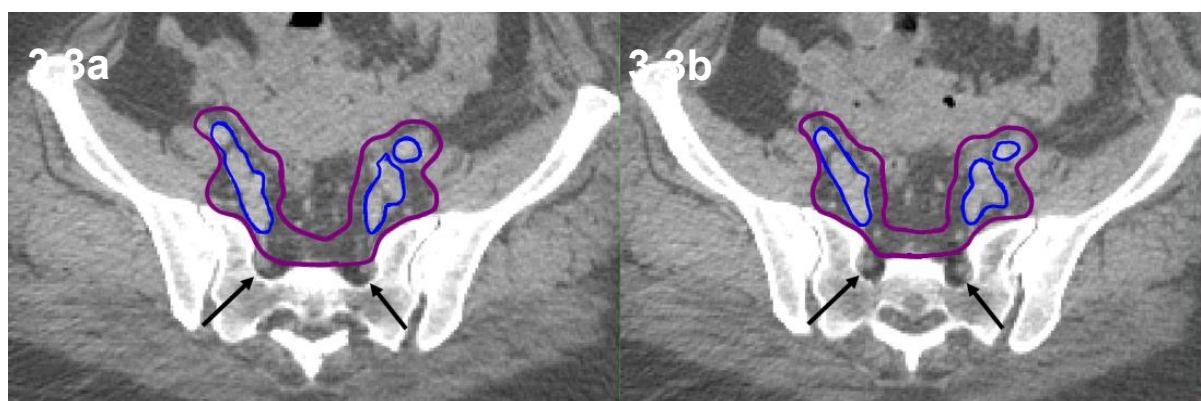
Fig. 3.3: Transverse CT with CTV2 outlined not including the sacral foramina (arrowed).

Step 6: Edit the outline to ensure there is no space between the outline and the pelvic bones and/or muscles. This ensures the outline extends to the pelvic sidewall (Fig. 3.4).
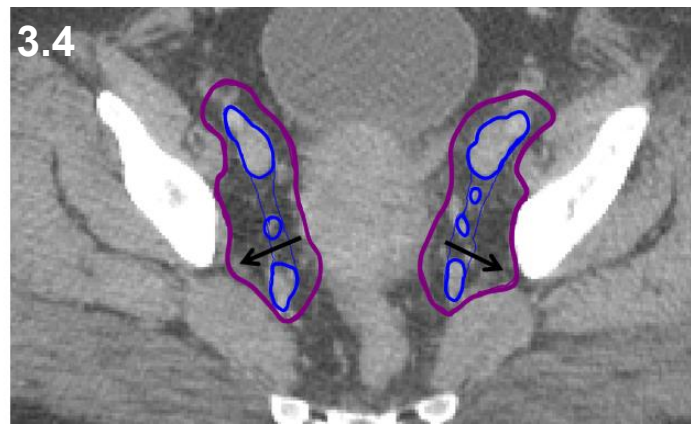
Fig. 3.4: Transverse CT showing the CTV2 outline extending fully to the pelvic sidewall (in direction of arrows).

Step 7: When external iliac nodes are involved with tumour extend the outline to include the lateral external iliac nodes (Fig. 3.5): Extend the outline 10mm antero-laterally along the ilio-psoas muscle in the region of the external iliac vessels (arrowed in Fig. 3.5a and 3.5b).
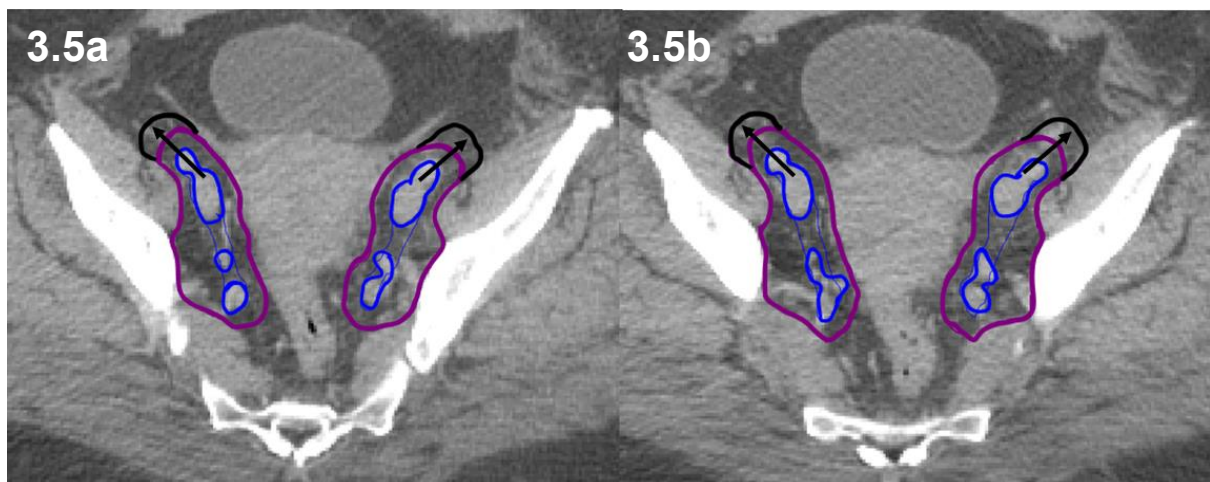
Fig. 3.5: Transverse CT at the level of the internal and external iliac vessels showing extension antero-laterally (arrowed) along the iliopsoas muscle to include the lateral external iliac nodes.

Step 8: Join the internal and external iliac outlines together with an 18mm strip parallel/medial to the pelvic sidewall (arrowed in Fig. 3.6d). This ensures the obturator and infra-iliac nodes are included.
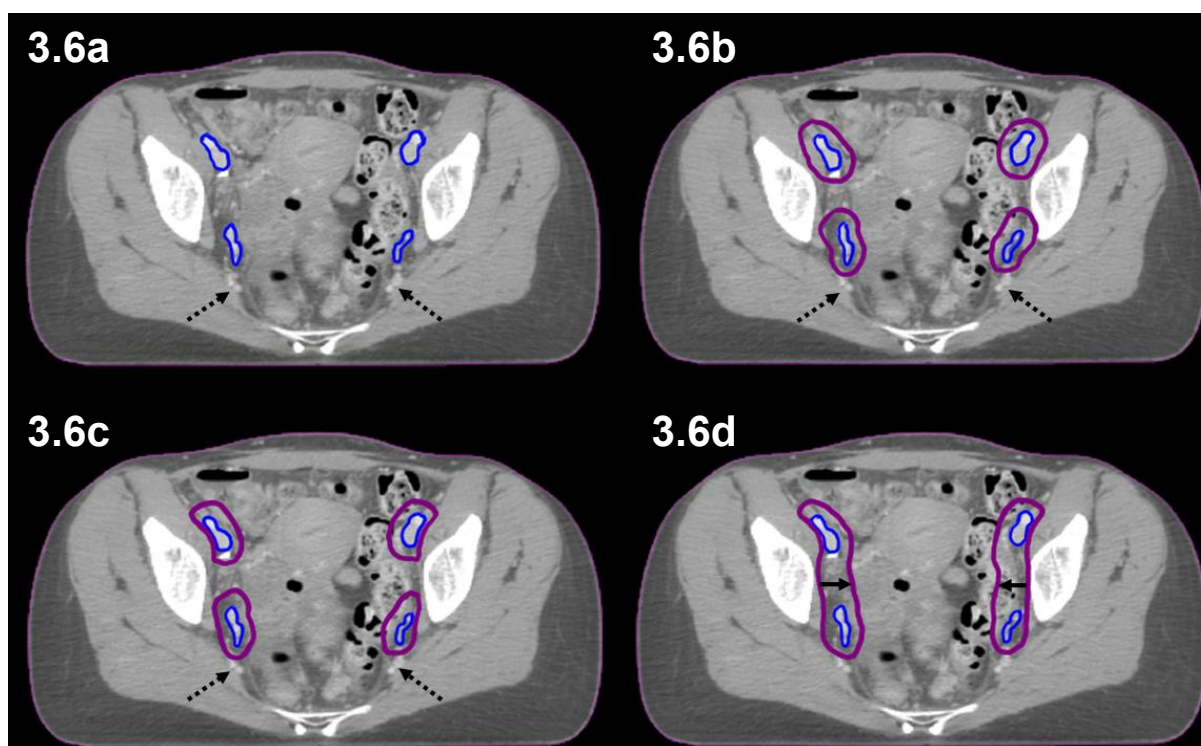
Fig. 3.6: Transverse CT at the distal level of the internal and external iliac vessels showing the steps required to outline CTV2. The vessels are outlined (a), a circumferential 7mm margin is added (b), muscle and bone is edited out (c) and an 18mm (solid arrows in d) strip is added to cover the obturator/infra-iliac nodal region. The gluteal vessels (dashed arrows) should not be included. D illustrates the complete outline.

TIP: Stop outlining the external iliac vessels when the femoral heads are visible or when the vessels are anterior to the pelvic bone. This ensures you do not include the inguino-femoral region.

TIP: Only outline the main internal iliac vessels. Do not outline the smaller branching vessels as this leads to unwanted coverage of pudendal and gluteal regions (dashed arrow in fig. 3.6a-c).

Step 9 (Fig. 3.7): Continue with a 10-18mm diameter strip inferiorly to cover the obturator nodes (Fig. 3.7d-f). The caudal transverse slice is at the level of mid-femoral heads or approximately 1cm cranial to the obturator foramen (demonstrated in Fig. 3.7a-d). This outline should not include muscle or bone. Do not edit to exclude bladder or bowel.
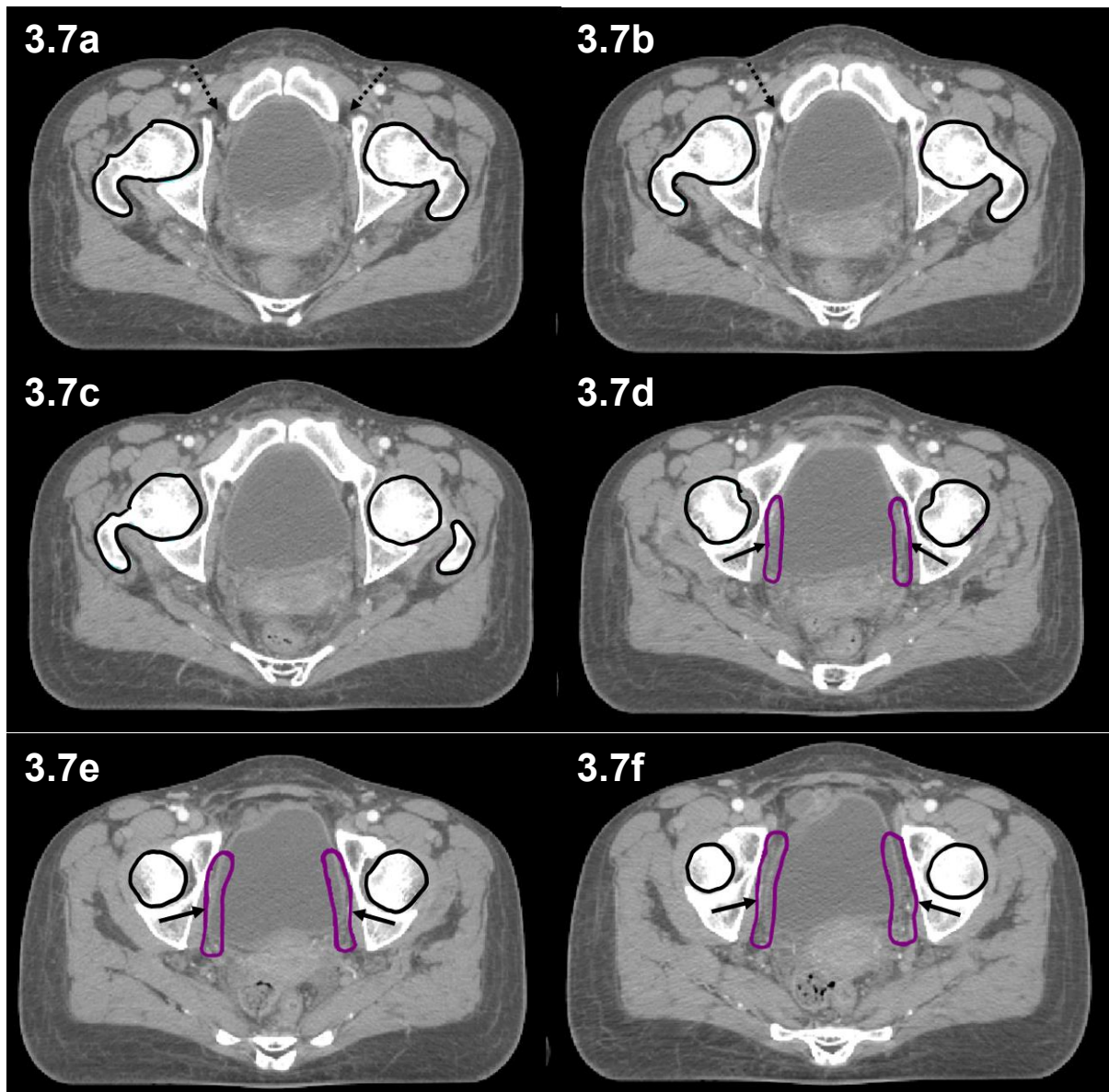
Fig. 3.7: Transverse CT showing the caudal slice of CTV2 (outlined and arrowed in d-f).This is at the level of the mid-femoral heads (outlined) and approximately 1cm superior from the top of the obturator foramen (dashed arrows in a and b).

TIP: This step-by-step approach can be time consuming. Clinicians with extensive experience may therefore delineate the final CTV2 as a freehand structure rather than follow each step. This must be done using a tool, e.g. pearl, to ensure a 7mm margin from vessels to edge of CTV2.

Section 4: CTV3: Para-aortic nodal volume

Step 1 (Fig. 4.1a): With the aid of intravenous contrast outline the aorta (Fig. 4.1a, solid arrow) and medial half of the inferior vena cava ((IVC; Fig 4.1a, dashed arrow). Lymphadenopathy lateral to the IVC (paracaval) is uncommon and extension in this direction may increase kidney doses. The aortocaval space (between aorta and IVC) is a common location for nodal disease and must be included.

Step 2 (Fig. 4.1b): Add a circumferential margin of 7mm to the blood vessels using your treatment planning software.

Step 3 (Fig. 4.1c): Edit to exclude muscle and bone.

Step 4 (Fig. 4.1d): Extend the outline postero-laterally along the vertebral body (arrowed in Fig. 4.1d) to cover the left para-aortic area. Edit to include any lymphoceles.
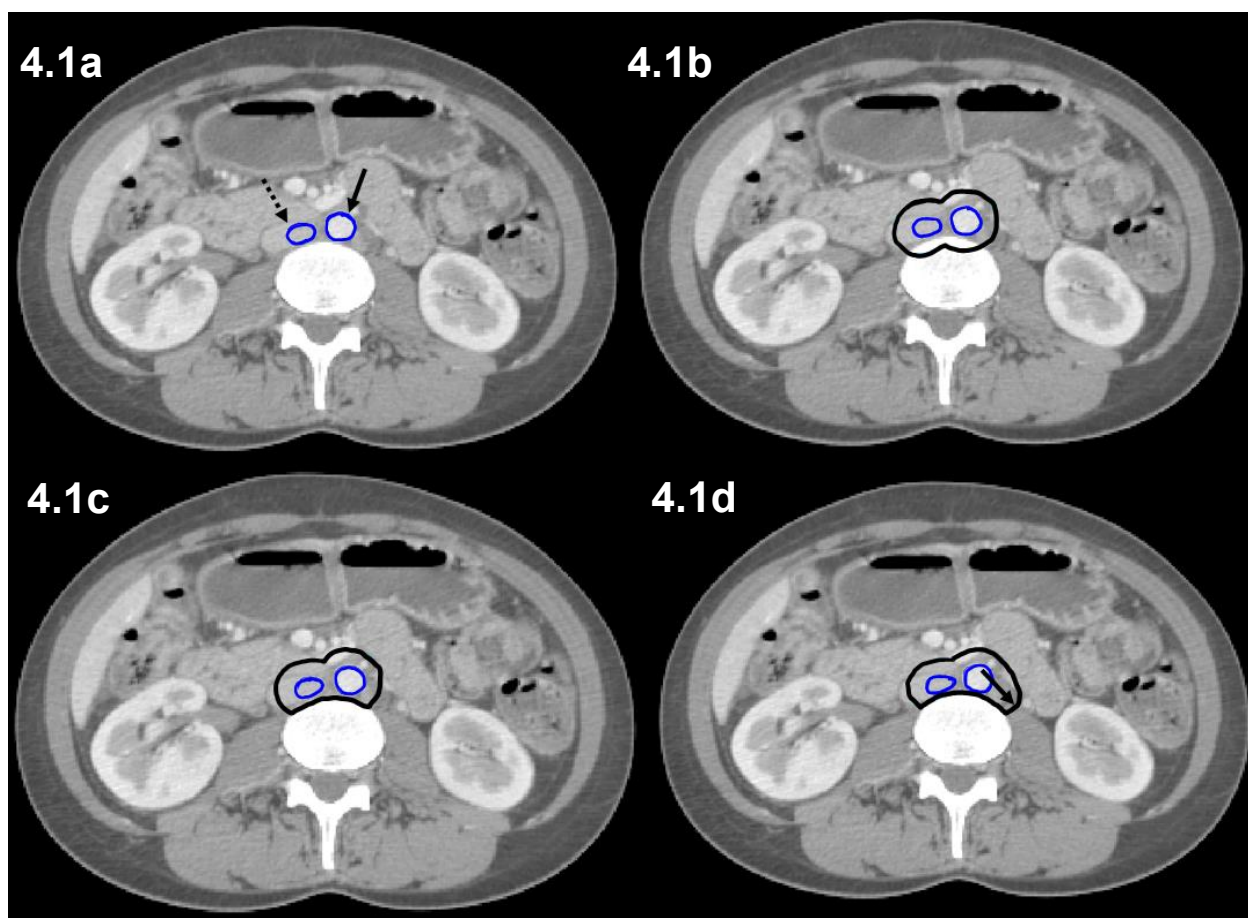
Fig. 4.1: Transverse CT at level of kidneys showing the steps required to outline CTV3; vessels (aorta, solid arrow; IVC, dashed arrow) outlined in a, circumferential 7mm margin added (b) and the outline is edited for bone and muscle (c) and extended along the vertebrae to the psoas muscle (d, arrowed). D illustrates the complete outline.

NB: Before treating the para-aortic region differential function of each kidney should be assessed.

Section 5: Pelvic nodal regions and anatomy
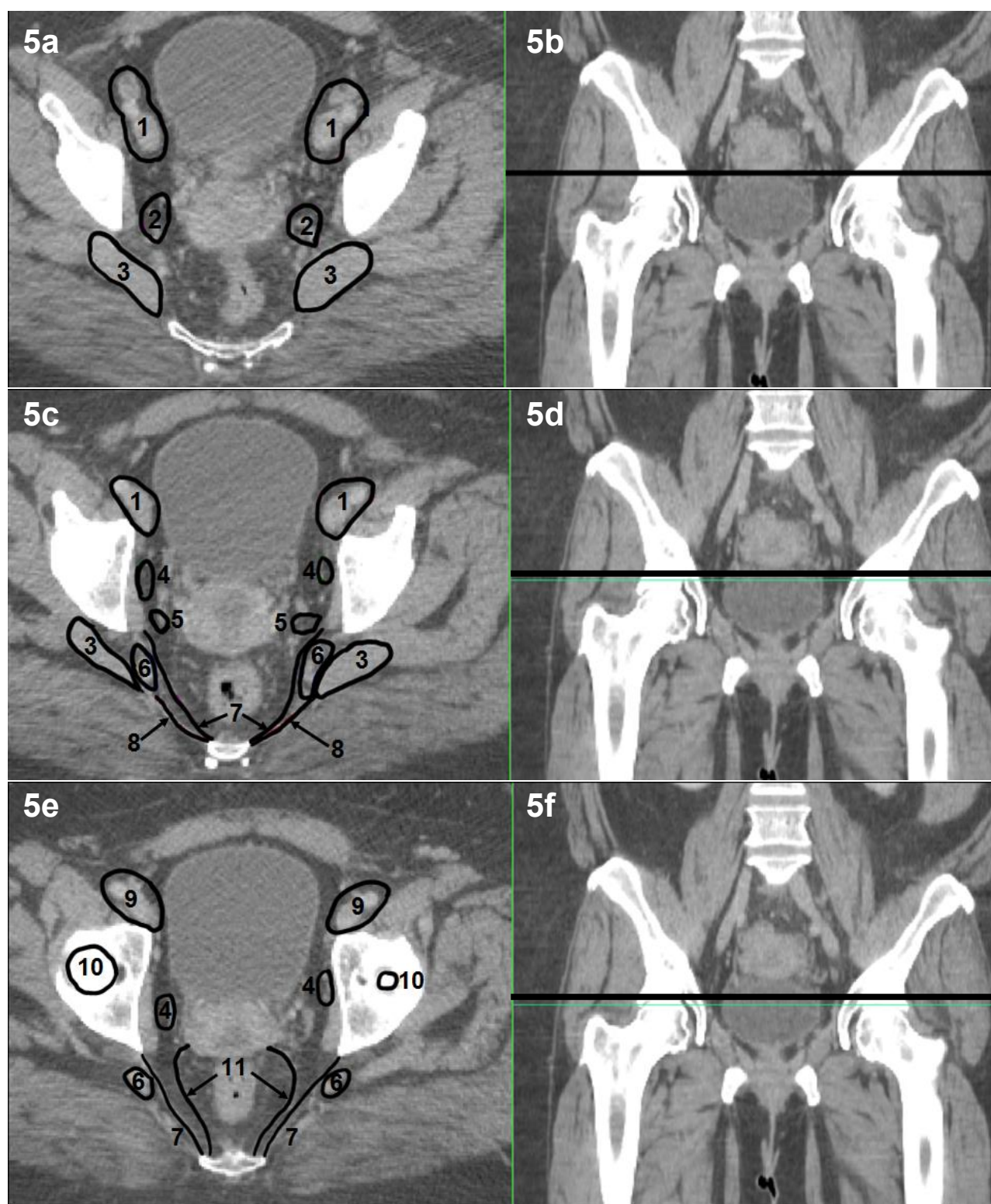
Figure 5: Transverse pelvic CT images (a,c,e) with the corresponding level shown on the coronal images (b with a, d with c and f with e). Anatomical areas: 1=external iliac vessels; 2=junction of gluteal and internal iliac vessels; 3=piriformis muscle; 4=obturator vessels/infra-iliac region; 5=internal iliac vessels; 6=gluteal vessels; 7= sacrospinous ligament; 8=sacrotuberous ligament; 9=inguinal vessels; 10=femoral head; 11=uterosacral ligaments

4.3.6 Impact of atlas implementation

64 outlined cases were reviewed before incorporation of the guidelines within the RTQA pack and 30 after. Mean score (maximum of 4) was 1.8 pre implementation and 2.7 post. This is a statistically significant difference of 0.9 (95%CI 0.3-1.5 p=0.003). There also appeared to be a difference in the distribution of scores for the cases. Before implementation of the atlas 67% scored 0-2 and after only 40% (see Table 4.3). 25% less cases scored 0 after, compared to before, atlas implementation and 19% more cases scored 3 after, compared with before, implementation. All four structures' compliance improved significantly (p=0.004). Rectum improved most (33%) and CTV1 least (18%). As expected, CTV1 and CTV2 were less compliant than bladder and rectum.

		No before (64)	% before	No after (30)	% after	Difference (%)
Total score (max 4)	0	18	28	1	3	-25
	1	12	19	3	10	-9
	2	13	20	8	27	7
	3	9	14	10	33	19
	4	12	19	8	27	8
Structure Compliance	Bladder	38	59	25	83	24
	Rectum	30	47	24	80	33
	CTV1	25	39	17	57	18
	CTV2	16	25	15	50	25

Table 4.3: Proportion of protocol compliant outlines represented by total score per case out of 4 (rows 2-6) and by specific structures (row 7-10) before and after atlas implementation in absolute numbers (column 3, 5) and percentage (column 4,6) and percentage difference (column 6).

Exclusion of centres which did not submit cases before and after the atlas implementation showed very similar results as seen in Table 4.4.

		No before (34)	% before	No after (17)	% after	Difference (%)
Structure Compliance	Bladder	19	56	16	94	38
	Rectum	18	53	13	76	24
	CTV1	14	41	13	76	35
	CTV2	6	18	9	53	35

Table 4.4: Proportion of protocol compliant outlines before and after atlas implementation excluding centres not represented both before and after implementation.

These results suggest an improvement in delineation standards with atlas use. CTV2 is least compliant pre and post atlas despite existing guidance and substantial detail. This may represent differences in usual practice.

Clinician's confidence in identifying set anatomical areas did not statistically change as seen in Table 4.5.

Anatomical area	Mean score PRE	Mean score POST	95%CI for difference
Aortic bifurcation	3.9	3.8	-0.1 to 0.3
Iliac bifurcation	3.8	3.7	-0.2 to 0.4
Inferior obturator	3.2	3.2	-0.4 to 0.6
Ilio-inguinal region	3.4	3.2	-0.2 to 0.5
Uterosacral ligament	2.7	2.8	-0.7 to 0.4
Mesorectum	3.5	3.4	-0.5 to 0.6
Superior parametria	2.6	3	-0.8 to 0.1
Posterior parametria	2.7	3.1	-0.9 to 0.1
Inferior parametria	2	3	-0.9 to 0.1
Upper vagina	3.4	3.4	-0.4 to 0.5
Total	31.5	32.4	

Table 4.5: Mean scores for clinicians' self-reported confidence levels in identifying set anatomical areas before and after atlas implementation. Max score is 4 with 1 equating to 'unable to identify', 2 'can occasionally identify', 3 'confident with most cases' and 4 'confident in all cases with rare exceptions'. No differences were statistically significant.

4.4 Discussion

The delineation atlas detailed here is the first to provide a summary of all the available published guidelines along with such detailed pictorial step-by-step instructions for delineation of all target organs and OARs. By attempting to address the eleven identified areas of discrepancy between different guidelines and clinical practice I have, to some degree, reduced the likelihood of different practice between centres if this atlas is used. This atlas is useful for educational and training purposes as well as for daily practice attempting to minimise the witnessed inter-observer variation. By pictorially detailing each step of the processes necessary to create CTVs and OARs this facilitates improved compliance versus the published guidelines which often depicts the final outline but not the detail of the steps necessary to create that outline. This step-by-step approach also eliminates the variation due to lack of anatomy training as anatomical landmarks and regions are visually demonstrated.

UK clinicians in general are aware of a lack of adequate training and hence confidence as evidenced by the questionnaire results. From my experience, clinicians are keen to learn and use guidance such as this delineation atlas. This is especially true in the UK as many centres only treat 5-10 cases of cervical cancer a year. This means a clinician may only be delineating a cervical cancer case once every other month. This is arguably not frequent enough to maintain the expertise necessary. Furthermore, when real time review within INTERLACE was made voluntary the vast majority of centres still requested review even though it meant a faster than usual turn-around in the clinical setting. This supports my experience of clinicians being willing to collaborate and use guidance.

The comparison of test and real time review cases before and after implementation of the atlas within the INTERLACE RTQA pack does suggest an improvement in the delineation standards. A higher proportion of the outlines complied with protocol after implementation. However, many factors should be considered when interpreting my results. Firstly, I cannot be sure that these centres were using the atlas when outlining. Secondly, the post implementation outlines were proportionately more real time reviews and it is therefore likely that the clinicians were more familiar with the protocol and therefore more likely to be compliant. However, often when outlining test cases for a trial, more time is spent referring to protocol to ensure compliance and therefore one would expect that compliance to protocol should not be less because of this. Thirdly and finally, I have not compared cases outlined by the same clinicians as these are random according to what was submitted and therefore the results could represent the inter-observer variation that we have already documented. However, the analysis of only centres which were represented in both groups shows similar improvements and this provides confidence that these observed improvements are real. In contrast, the overall confidence of clinicians did not improve following atlas implementation. This is self-reported and may therefore not be a reliable indicator. It may also suggest that the atlas was not widely used or that the questionnaire was not answered by the clinicians using the atlas as not all of the responders would have recruited many, if any, patients. On detailed review of each anatomical area there is a suggestion of improvement in the definition of the parametrial borders but this is not statistically significant. With a higher response rate after implementation we may have found this to be significant and this would increase the evidence

of an improvement in relation to atlas use. As INTERLACE keeps growing, with more than half of UK centres now open, the use of this atlas will increase and repeated use will lead to established practice. The ideal method of redoing the two test cases applying the atlas directly to show its potential benefits will not be possible due to clinician's time constraints. Without this option available we can continue to encourage use of the atlas within the INTERLACE setting and with time will continue to collect data to validate its use. It must be noted that in more contentious and less evidence based areas this guidance is still experience based and therefore may be disagreed with. Consequently, this further validation work is essential before this atlas could be implemented nationally.

In this Chapter, I have attempted to refine practice for cervical cancer target and OAR delineation by combining data from 7 published guidelines and an in-depth analysis of the INTERLACE RTQA. This step by step pictorial atlas to aid delineation can provide an additional resource for oncologists and reduce inter-observer variation as it includes more detailed images than previously available. So far, an improvement has been documented in the delineation standards of test and real cases since implementation of this atlas within the INTERLACE RTQA which, in part, may be due to use of this atlas. This provides support for ongoing use and validation of this delineation atlas.

Chapter 5

Bladder and rectum filling variation during radiotherapy, their impact on clinical target volume (CTV) coverage and methods to reduce or compensate for variation observed.

5.1. Introduction

In cervical RT the primary CTV lies between bladder and rectum which fill and empty throughout the day. Margins around CTV aim to account for daily uncertainties during RT including organ motion. It is therefore important to understand and quantify the effects of organ filling on target position and coverage, especially in the current era of IMRT due to increased conformality to PTV.

Many studies have investigated cervical and uterine movements during RT as discussed in Chapter 1, section 1.9.2. (Lee et al. 2007; Chan et al. 2008; Taylor et al. 2008; Beadle et al. 2009; Collen et al. 2010; Ahmad et al. 2011; Haripotepornkul et al. 2011). Jadon et al systematically reviewed the organ motion literature in 2014 identifying 39 heterogeneous studies, 12 of which were conference abstracts (Jadon et al. 2014). Each study used different methods to characterise motion and therefore established slightly different conclusions. Overall, the cervix and uterus moved by up to 4-6cm (Lee et al. 2007; Chan et al. 2008; Taylor et al. 2008; Beadle et al. 2009; Ahmad et al. 2011; Jadon et al. 2014).

Adequate margins to account for all of this motion would negate the benefits of more conformal RT and are therefore not applicable (Jadon et al. 2014). However, asymmetrical margins of maximum 15mm were deemed adequate to cover uterine and cervical motion in patients who underwent consecutive day MRI scans (Taylor et al. 2008). This may not represent changes that occur during a course of RT but is often what is applied in clinical practice, including in the DEPICT, INTERLACE and EMBRACE trial protocols. Similar measurements of 16-20mm margins have been suggested for postoperative patients around the vaginal cuff (Harris et al. 2011; Ahmad et al. 2013). Uterine movements are larger than vaginal and cervical implying that the cervical RT margin necessary should be larger than for post-operative RT. Supporting this, when 15mm margins were applied during chemoradiation for cervical cancer, CTV fell outside of PTV for 32% of fractions (Tyagi et al. 2011). Other weekly imaging during chemoradiation studies have reported margins up to 24mm are necessary (van de Bunt et al. 2008). Through analysis of variable bladder filling CTs, 38mm margins were necessary to cover the full range of bladder filling (Bondar et al. 2012). This is probably larger than necessary during RT as patients should not experience the full range of bladder filling if

following instructions daily. Again, margins this large will negatively impact the benefit of more conformal RT (Jadon et al. 2014). It therefore remains unclear what margins are truly necessary to ensure CTV coverage without adaptive techniques. Furthermore, if margins alone are to be used to account for this motion, measures to reduce the magnitude are vital to maintain the benefits of advanced RT techniques.

What is clear is that bladder and rectal filling affect CTV motion, and I propose that this could be controlled. However, no published guidance on bladder or bowel preparation exists. Most centres aim for a 'comfortably full bladder' to push bowel out of the radiation field but a full bladder leads to unacceptably large set-up errors (Chan et al. 2008; Ahmad et al. 2011). Most centres do not have specified bowel preparation protocols.

Due to the variation observed and the advanced imaging and technology available alternative compensatory approaches to large margins have been sought. Proposals include daily soft tissue imaging and matching, adaptive RT with variable bladder filling scans, or individualised margins (Bondar et al. 2012; Heijkoop et al. 2014). These are discussed further in Chapter 7.

The aim of this chapter is to analyse bladder and rectal filling patterns for a cohort of patients undergoing a course of cervical chemoradiation, assess the impact on CTV coverage, calculate the margins necessary to account for this movement and attempt to produce some clinical proposals for patient preparation to minimise this variation.

Outlining of CBCTs, described in section 5.2.3, was undertaken by myself and Dr Carla Perna. Justhna Motlib and Sabina Khan, radiographers, completed the offline Automatching described in 5.2.3. All other work including analysis and interpretation of the data is my own. Some of the work presented in this Chapter has been accepted for publication in Clinical Oncology (Eminowicz et al. 2016).

5.2. Methods

5.2.1. Patient selection and preparation

I retrospectively analysed ten consecutive patients undergoing a course of radical cervical chemoradiation at UCLH. Patients followed the standard bowel and bladder preparation for gynaecological patients treated with RT at UCLH.

For bowel preparation, laxatives were prescribed, either movicol or sodium docusate, for a minimum of 5 days before planning and treatment to achieve Bristol stool chart type 5 stool. Patients used an information leaflet which detailed the Bristol stool chart with an adjacent table to direct the amount of laxatives to be taken as seen in Figure 5.1.

Bristol Stool Chart

Type 1-3: 1 DOSE OF LAXATIVE X 2 DAILY	**Type 1** — Separate hard lumps, like nuts (hard to pass)
	Type 2 — Sausage-shaped but lumpy
	Type 3 — Like a sausage but with cracks on its surface
Type 4: 1 DOSE OF LAXATIVE X 1 DAILY	**Type 4** — Like a sausage or snake, smooth and soft
Type 5: IDEAL CONTINUE AS RECOMMENDED	**Type 5** — Soft blobs with clear-cut edges (passed easily)
Type6-7: NO LAXATIVE REQUIRED

Tell radiotherapy if you experience this for more than 2days | **Type 6** — Fluffy pieces with ragged edges, a mushy stool |
| | **Type 7** — Watery, no solid pieces. **Entirely Liquid** |

Figure 5.1: Illustration of Bristol stool chart with laxative recommendations.

For bladder preparation, patients were asked to empty their bladder on arrival in the RT department then to drink 3 cups of water 30 minutes before both the planning CT scan and each daily treatment. The aim was a 'comfortably full' bladder'.

5.2.2. CBCT acquisition

Twice weekly CBCTs, as per the agreed departmental imaging protocol, were acquired one day and three days post chemotherapy. Varian On-Board Imaging (OBI) acquired a 16cm length CBCT with 2mm slices around the isocentre. This was shifted to ensure the entire bladder and rectum were captured. An example CBCT image can been seen in Fig. 5.2.

Figure 5.2: Example CBCT axial (top) and sagittal (bottom) images.

5.2.3. Data collection and analysis

At time of RT, actual bladder filling time was recorded by the treating radiographers.

Retrospective CBCT review was performed on Eclipse v11 Contouring and ARIA Offline Review v11.

Bony matching to the planning CT was performed to establish and eliminate set up errors. The Automatch function was applied using a region of interest which included the coccyx posteriorly, pubic symphysis anteriorly, neck of femur laterally, ischium inferiorly and L5

superiorly. This Automatch was verified by visual assessment of the bone match. The resultant measures of translational discrepancy, i.e. shifts necessary to bone match, were recorded as the setup errors.

CTV1 (cervix, tumour, bilateral parametria, entire uterus and upper vagina), CTV2 (pelvic nodes), bladder and rectum were outlined by experienced clinicians on the planning CT. These outlines would have been reviewed by one of two known clinicians who follow the same protocol. This inter-observer variation introduces potential bias which could impact on results due to our small numbers. However, on visual review of the outlines the only difference was inclusion of the ovaries and fallopian tubes based on whether or not they could be visualised. This may affect the lateral movements calculated, discussed later. No ITV was created. PTV was created by adding 8mm to CTV2 and 15mm to CTV1 except laterally where 10mm was added. Rectum, Bladder and CTV1 were outlined on all CBCTs by two independent clinicians. These two outlines were summed to create a final Rectum, Bladder and CTV1. Along the uterine axis, the upper two thirds represents uterus and lower third represents cervix. Where the CBCT failed to capture the entire bladder the planning bladder volume was used to complete the outline, ensuring total bladder volume was available for each CBCT. This was only applied for 11 CBCT, 10% overall.

Maximum distances on axial imaging between the planning CTV and CBCT CTV were measured in the anterior, posterior, right lateral and left lateral directions. This was recorded at the level of the mid-cervix (approximately S5) and at the level of the mid-uterus (approximately S2/3). For superior motion, the distance was measured on the midline sagittal image directly inferior from the L5/S1 bony prominence.

Bladder volume, rectal volume, length, and maximum anterior-posterior (AP) diameter, and whether PTV covered the entirety of CTV1 was recorded for all scans (planning and CBCTs). Where CTV was not fully covered by PTV the maximum distance (mm) from PTV edge to CTV was recorded. The deviation from planning was then calculated for bladder volume and rectal AP diameter.

Mean, SD and 95%CI were calculated following QQ plots review confirming normality using IBM SPSS Statistics 22. Scatter plots and Pearson's correlation was analysed for overall

patterns and relationships. P values were derived from one sample t-tests, and independent samples t-tests assuming equal variance. Linear mixed regression modelling was used to analyse patterns through time. Fixed effects binary logistic regression was used to assess the organ size impact on CTV1 coverage resulting in odds ratios.

5.2.4. Estimated margin calculation

Van Herk et al proposed a mathematical margin calculation model to account for random and systematic errors using a patient cohort (van Herk et al. 2000). In 2008 the RCR, Institute of Physics and Engineering in Medicine (IPEM) and Society and College of Radiographers (SCoR) collaborated to produce a document on ensuring geometric accuracy in RT explaining these errors, calculations and compensation techniques in detail (RCR IPEM SCoR 2008). This Van Herk formula to derive CTV to PTV margins is:

$$\text{CTV-PTV margin} = a\Sigma + b\sigma + c$$

Σ is systematic error, σ is random error and a, b and c are constants. C accounts for parameters that affect margins in a linear manner e.g. breathing and is therefore not applicable in this patient cohort. A and b depend upon beam coverage and chosen coverage probability. To ensure a minimum dose of 95% for 90% of the cases a = 2.5 and b = 0.7 and therefore the calculation I will apply is:

$$\text{CTV-PTV margin} = 2.5\Sigma + 0.7\sigma$$

Despite my results from Chapter 2 regarding delineation variation I will only calculate margins here to ensure coverage of set-up and organ motion. The following definitions were therefore applied for set-up error and organ motion error independently:

Individual mean error ($M_{individual}$) = sum of error for each fraction ÷ no of fractions

Overall population mean error (M_{pop}) = mean of $M_{individual}$ (ideally = 0)

Population systematic error (Σ_{setup}) = SD of $M_{individual}$ around overall population mean

Individual random error ($\sigma_{individual}$) = SD of errors around corresponding individual mean

Population random error (σ_{error}) = mean of individual random errors

For set-up, the distances shifted for bony match were the errors. For organ motion the errors were the OAR distances between the CBCT and planning CT.

5.3. Results

In total, 10 planning CTs and 109 treatment CBCTs (between 9 and 12 per patient) were analysed. Actual bladder filling time was recorded for 98 scans.

5.3.1. Bladder filling

Bladder volume ranged from 45-664cc overall, mean 200cc. Bladder volume at planning was 73-664cc, mean 289cc and through treatment was 45-578cc, mean 192cc. During RT, bladder volume was on average smaller by 96cc, 95%CI 9-184, p=0.031. For individual cases the range of bladder volume through radiotherapy varied between 116cc and 416cc, mean 306cc. 9/10 had a minimum bladder volume less than 100cc (Table 5.1).

Bladder volume increased with increased interval after drinking by approximately 4cc per minute.
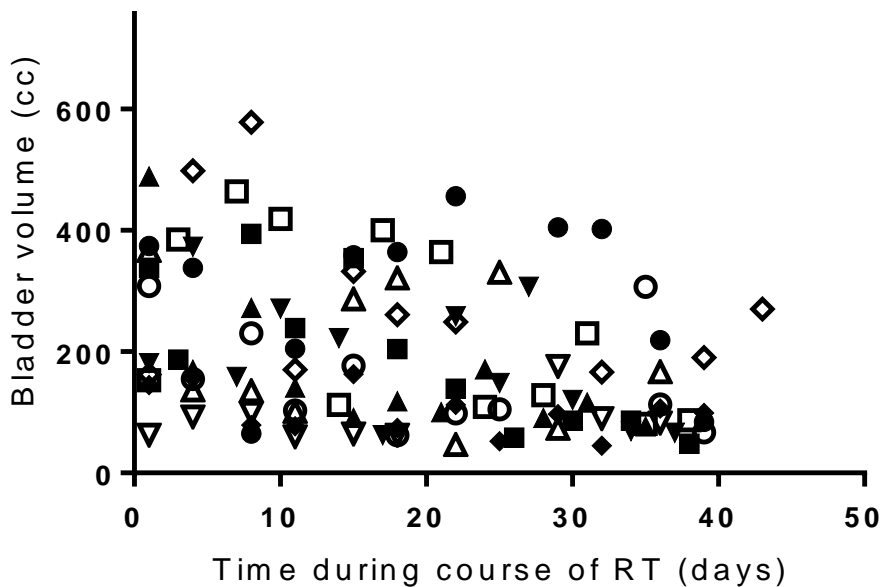
Figure 5.3: Scatter plot of bladder volume (cc) vs time through treatment (days) [each symbol=each individual patient]

case	CBCT no	plan BV(cc)	min;max	cc/day (95%CI)	p value	plan AP	min;max	>1cm dev (%)	No CTV out (%)	Max out(mm)	Mean out(mm)	No Cx out (%)	Max (mm)	Mean (mm)
		Bladder volume				**Rectum**			**CTV**			**Cervix**		
1	11	197	65;456	-1(6.7;-8.6)	0.776	3.2	3.3;5.9	7(73)	10(91)	31	20	2(18)	14	13
2	11	664	48;394	-8(3.5;12.5)	0.003	3.6	4.7;6.7	11(100)	11(100)	50	33	11(100)	25	11
3	11	560	77;489	-7(1.6;13.3)	0.018	2.9	2.7;5.3	3(27)	10(91)	46	29	7(64)	12	8
4	12	430	62;373	-4(0.9;-9.4)	0.094	4.4	3.8-8.7	3(25)	11(92)	29	17	3(25)	20	12
5	12	355	45;163	-1.4(0.6;-3.3)	0.145	3.1	2.4;5.3	1(8)	12(100)	38	26	0	-	-
6	11	143	62;308	-2(2.7;-6.9)	0.348	4.8	3.3;4.4	4(36)	9(82)	39	8	4(36)	20	9
7	12	113	81;464	-7(0.7;-13.8)	0.052	2.9	2.8;4.5	2(17)	10(83)	31	11	0	-	-
8	10	180	46;366	-2(6.1;-10.6)	0.546	3.9	3.5;6.2	2(20)	7(70)	45	8	0	-	-
9	9	73	60;176	1(3.5;-1.3)	0.303	5.3	1.6;4.3	8(89)	0(0)	0	0	0	-	-
10	10	183	162;578	-4(3.6;-11.3)	0.264	3.6	3.5;6.3	6(60)	10(100)	23	12	2(20)	10	8

Table 5.1: Individual case data showing planning and treatment bladder volumes (column 3-6) with trend through time (cc/day, including 95%CI and p value for trend through time) , rectal AP diameter (column 7-9) at planning and range through treatment, how frequently CTV was outside PTV (column 10-12) including maximum and mean distances and how frequently the lower third (cervix) was outside PTV (column 13-15) including maximum and mean distances.

Bladder volume decreased with time through treatment by 3.6cc per day (Fig.5.3), leading to an approximate average 150cc decrease throughout the course of treatment. This decrease was larger (5cc per day) in patients with planning bladder volume >300cc. On individual case analysis, bladder volume reduced through treatment in 9/10 cases, 1-8cc/day. One case, which had a small bladder volume in general, ranging from 60cc to 176cc, displayed a stable volume through treatment (95%CI +3 to -1cc/day) (case 9 Table 5.1).

Mean bladder volume on non-chemotherapy days was 170cc and 219cc on the first day post-chemotherapy; 49cc increase (95%CI 1-96cc, p=0.045). Analysing each patient independently, mean bladder volume difference between post-chemotherapy and non–chemotherapy days ranged from 0 to 115cc. Therefore, all patients had a larger mean bladder volume on post-chemotherapy days.

5.3.2. Bladder filling effect on CTV coverage

Fig.5.4 displays bladder volume deviation from planning (y axis) against whether CTV1, uterus (upper CTV1) or cervix (lower CTV1) are covered by PTV (x axis). In all cases where deviation from planning volume exceeded 130cc CTV1 was not covered by PTV. A deviation exceeding 130cc was most likely to compromise the superior aspect (uterus) whereas bladder volumes much smaller than at planning (>400cc smaller) were most likely to compromise the inferior aspect (cervix).

Mean bladder volume when CTV1 was not covered by PTV was 203cc compared with 150cc when CTV1 was covered; 53cc difference (95%CI -9-116, p=0.097). When uterus was not covered by PTV mean bladder volume was 209cc versus 147cc when uterus was covered; 61cc difference (95%CI 7-116cc, p=0.028). When cervix was not covered by PTV mean bladder volume was 197cc versus 189cc when cervix was covered; 7cc difference (95%CI -47-62, p=0.785). This is tabulated in Table 5.2 and again demonstrates bladder volume has less impact on cervix coverage than uterine coverage. Despite this lack of difference, on visual qualitative review some cases of very large deviation (>200cc) in bladder volume from planning the cervix was pulled anteriorly out of PTV.
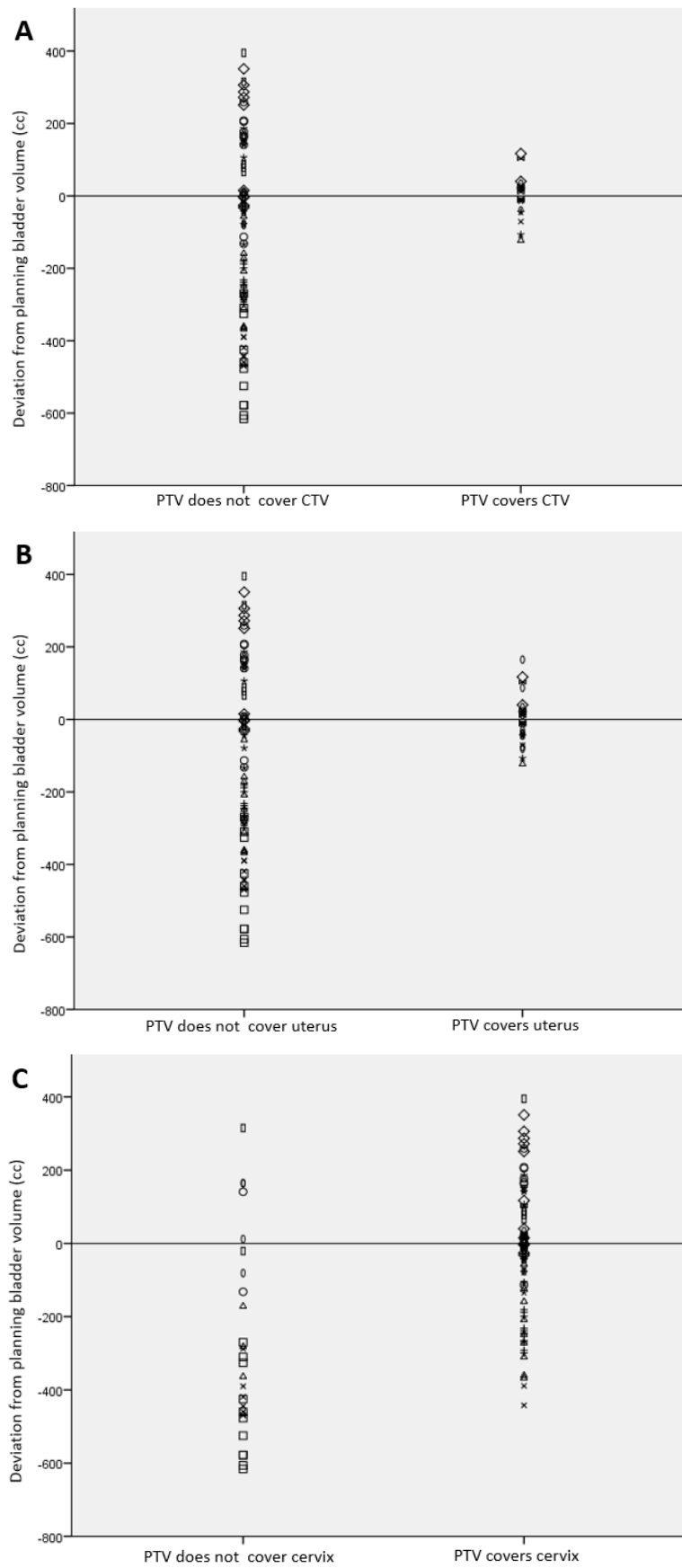
Figure 5.4: Deviation from bladder planning volume (in cc) for when target (CTV1 a, uterus b or cervix c) covered or not by PTV. The horizontal line represents no difference from planning volume.

		Target in/out PTV		Difference IN vs OUT		
	Target	IN	OUT		95%CI	P value
Bladder volume (cc)	CTV	150	203	53	-9 to 116	0.097
	Uterus	147	209	61	7 to 116	0.028
	Cervix	189	197	7	-47 to 62	0.0785
Rectal AP diam (cm)	CTV	3.6	4.5	0.9	0.3 to 1.5	0.002
	Uterus	3.7	4.6	0.9	0.4-1.4	0.0004
	Cervix	4.1	5.1	1	0.5 to 1.4	0.0002

Table 5.2: Mean bladder volumes and rectal AP diameters when target was covered by PTV (IN) or not (OUT).

Using fixed effects binary logistic regression modelling, the probability of CTV1 being covered by PTV decreased by 1.9% for every cc deviation from bladder planning volume. This effect was greater for the uterus compared with the cervix, 2.1% and 0.6% respectively.

5.3.3. Rectal filling

Total rectal volume and volume per centimetre length correlate well with rectal AP diameter (Pearson's correlation coefficient 0.635, $p=8 \times 10^{-15}$, Fig.5.5).

There was no identifiable relationship between rectal volume and time through treatment or chemotherapy timing.

There was an inverse relationship between rectal AP diameter and bladder volume (Pearson's correlation coefficient -0.261, p=0.006).
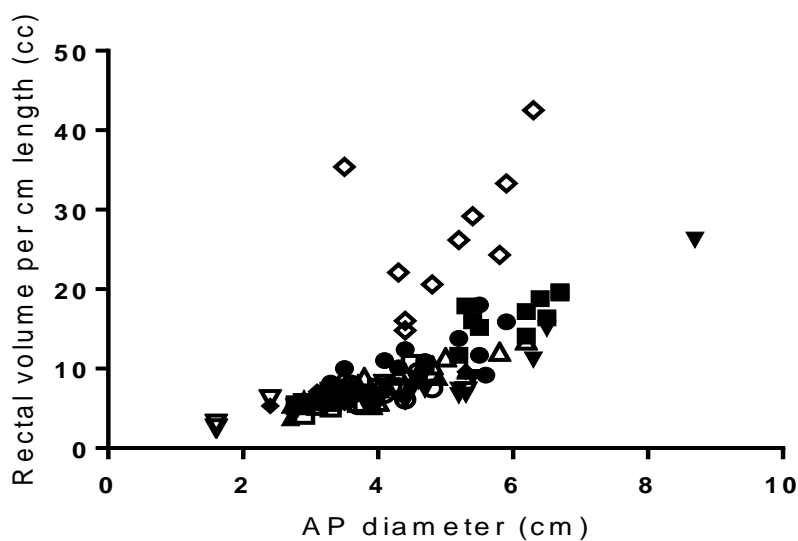
Figure 5.5: Rectal AP diameter correlates with rectal volume [each symbol=each patient]

Individual case analysis showed an AP diameter range of 1.1 to 4.9cm, mean 2.6cm. 3 cases had a planning AP diameter >4cm; 4.4cm, 4,8cm, 5.3cm. One case (case 9 Table 5.1) with 5.3cm rectum at planning maintained good coverage through treatment as bladder volume was well maintained within 116cc. For the other two cases CTV was outside PTV, maximum 20mm, in 25% and 36% of CBCTs. On visual review it was difficult to distinguish if this was due to bladder or rectal changes.

5.3.4. Rectal filling effect on CTV coverage

Fig.5.6 illustrates that a larger rectal AP diameter during treatment was more common when CTV1 was not covered by PTV compared to when CTV1 was covered. This is true for the whole CTV1 (uterus and cervix).

The mean AP diameter was 0.9cm (95% CI 0.3-1.5cm, p=0.002) larger in patients with compromised CTV1 coverage compared with satisfactory CTV1 coverage; 4.5cm versus 3.6cm respectively. This difference was consistent at the superior (uterus) and inferior (cervix) aspect of CTV; difference 0.9cm (95%CI 0.4-1.4, p=0.0004) and 1cm (95%CI 0.5-1.4, p=0.0002) respectively, tabulated in Table 5.2.

Using fixed effects binary logistic regression modelling, the probability of CTV1 being covered by PTV reduced by 5.6% for each mm deviated from rectal planning AP diameter. The probability of uterus and cervix being covered by PTV for every mm deviation from planning AP diameter decreased by 2.2% and 5.8% respectively.

Maximum distances which CTV extended outside of PTV were 50mm for the whole CTV and 25mm for the inferior CTV (cervix) (Table 5.1). Six cases had some area of the inferior CTV (cervix) extending outside of PTV, three of which were for a quarter of CBCTs or less. The two cases where the cervix was outside PTV for 64% and 100% of CBCTs had very large (>500cc) planning bladder volumes; 560cc and 664cc respectively. These two cases had a rectal AP diameter range during treatment of 2 and 2.7cm with one case only having a rectal AP diameter >1cm different from planning for 27% of the CBCTs. On visual review for both of these cases the uterus is so anteverted that it looks as if the cervix is pulled anteriorly out of PTV by this movement.
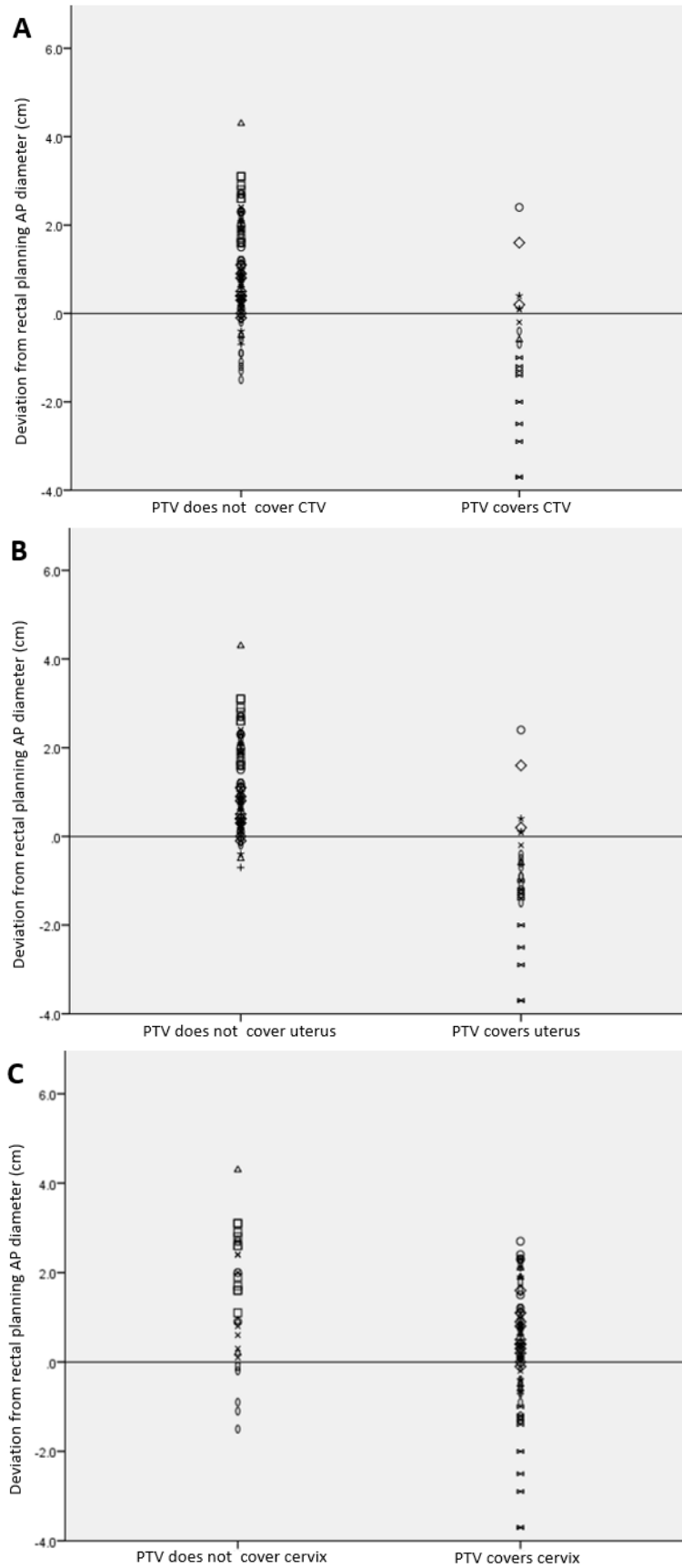
Figure 5.6: Deviation from rectal AP diameter (in cm) for when target (CTV1 a, uterus b or cervix c) covered or not by PTV. The horizontal line represents no difference from planning AP diameter.

5.3.5. Margin calculation

Appendix 4 tabulates the raw data used for these margin calculations. In this section, I only present the resultant estimated errors (random and systematic) and subsequent margins for set-up and organ motion variation.

Taking set-up error alone, i.e. shifts necessary to bony match, margins of 4mm vertically and 5mm longitudinally and 5mm laterally ensure a minimum 95% dose for 90% of this patient cohort as seen in Table 5.3.

	vert	long	lat
Σ_{setup}	0.12	0.14	0.15
σ_{set-up}	0.13	0.19	0.22
Margin (mm)	4	5	5

Table 5.3: Population systematic error (Σ) and random error (σ) for set-up.

For organ motion, with the same probability of minimum 95% dose for 90% of cases, margins are as large as 3.7cm superiorly, 4.2cm anteriorly and 3.8cm posteriorly for the uterus and 3cm anteriorly and 2.3cm posteriorly for the cervix.

In the superior and anterior-posterior directions at the level of the uterus exclusion of patients with very large bladders at planning (>300cc) led to a large drop in the calculated systematic errors and a small drop in the random errors (see Table 5.4). Use of 300cc as a cut-off follows on from the results of sections 5.3.1 to 5.3.4. Margins are therefore less for the uterus as seen in Table 5.5; 1.6cm superiorly, 1.8cm anteriorly and 2cm posteriorly. Interestingly, the effect on cervical margins is of a much smaller magnitude.

	Σ	Σ if blad<300	σ	σ if blad<300cc
SI	1.189667	0.377864	0.996898	0.970108
rightUT	0.428572	0.369583	0.690098	0.79927
leftUT	0.693815	0.814185	0.809421	0.736291
antUT	1.378516	0.449026	1.02652	0.828566
postUT	1.237222	0.501387	1.079984	0.735029
rightCX	0.168973	0.138662	0.280756	0.300057
leftCX	0.417894	0.434994	0.330512	0.336452
antCX	1.033699	0.977853	0.585862	0.624323
postCX	0.757687	0.856214	0.605692	0.595167

Table 5.4: Population systematic error (Σ) and random error(σ) for organ motion using all cases and cases with planning bladder volume<300cc.

138

	Organ motion margin (cm)	margin if Σ bl<300cc (cm)	Set-up margin (cm)	Total margin (cm)	Total margin if bl<300cc (cm)
SI	3.7	1.6	0.5	4.2	2.1
rightUT	1.6	1.4	0.5	2.1	1.9
leftUT	2.3	2.6	0.5	2.8	3.1
antUT	4.2	1.8	0.4	4.6	2.2
postUT	3.8	2.0	0.4	4.2	2.4
rightCX	0.6	0.5	0.5	1.1	1.0
leftCX	1.3	1.3	0.5	1.8	1.8
antCX	3.0	2.9	0.4	3.4	3.3
postCX	2.3	2.6	0.4	2.8	3.0

Table 5.5: Calculated margin using van Herk equation for all cases and cases with planning bladder volume<300cc.

Table 5.5 summarises all of the margins calculated for organ motion and set-up and the combined total margin to account for both errors. If planning bladder volume is below 300cc, overall margins of 2-2.5cm appear large enough to cover uterine motion. Concerningly, in this patient cohort, the anterior and posterior margins around the cervix need to be 3cm.

No difference was seen in these results if patients with large deviations in rectum from planning were excluded.

5.4. Discussion

This study confirms that, despite a bladder protocol aiming for a 'comfortably full bladder', large bladder filling variations are seen. However, definite bladder filling patterns were identified. These facilitate refinement of patient preparation protocols hopefully leading to increasing volume reproducibility.

With time through treatment bladder volume decreased. This is consistent with published data (Lee et al. 2007; Ahmad et al. 2008; Jadon et al. 2014). The magnitude of decrease seen in my data (approx. 3.6cc per day, from 248cc in first week to 153cc in final week) was less than the 269cc over six weeks Ahmad et al reported in 2008 but is in keeping with Jadon et al who described a 44% decrease versus my 38% decrease. Ahmad et al did not report their planning bladder volumes and it is therefore difficult to propose possible reasons for this difference. Jadon et al's conclusions are based on a systematic review of published literature and are therefore more likely to be truly representative of the population. My data shows a consistent decrease in bladder volume week on week. This is different to that reported by Lee et al who

noted a similar reduction by week 2 and by week 3 but their data is incomplete in comparison to mine as they only analysed bladder volume at weeks 1, 2 and 3.

Inadequate hydration secondary to poor fluid intake, nausea, diarrhoea and other treatment toxicities including radiation cystitis as patients progress through the course of treatment is likely to explain the decreasing volume through RT. Bladder volume was smaller on days which were not post-chemotherapy. This can also be explained by inadequate hydration as intravenous fluids administered with chemotherapy temporarily increased hydration status.

Planning bladder volumes greater than 300cc were less reproducible and led to greater variation during treatment with an increased likelihood of CTV not being covered by PTV. This mostly affected uterine position. However, in cases with planning bladder volume >500cc the cervix was consistently pulled anteriorly out of PTV due to such large uterine movements.

To my knowledge, no previously published data has described this effect of chemotherapy timing on bladder size nor of a large bladder (>300cc) at planning leading to increased variation. These two factors are potentially modifiable factors and could be controlled to reduce the magnitude of CTV1 motion. Therefore, a 10 minute shorter waiting time on chemotherapy and post-chemotherapy days, due to bladder filling increasing by 4cc/minute, and a bladder volume of 150-300cc at planning is proposed to optimise CTV1 coverage. This novel concept of strictly maintaining an upper limit is key and can be facilitated by use of bladder scanners at planning as detailed in Table 5.6.

Other findings, such as bladder volume deviations from planning predominantly compromising uterine coverage rather than cervical, are in line with previously published data (Jadon et al. 2014). These findings emphasise the need for regular monitoring of bladder volume as part of a treatment pathway, as well as regular monitoring of organ position. Ideally soft tissue matching using CBCTs should be undertaken daily if this is possible. This has inevitable resource implications for example CBCT availability, radiographer training and confidence to analyse online CBCT, patient throughput and cost. Monitoring of bladder volume using ultrasound bladder scanners may be effective. Bladder scanner results correlate well with CT volumes and can be used at planning and during treatment without any additional radiation exposure for the patient (Ahmad et al. 2008).

It is very important to highlight that my results strongly suggest that control of bladder volume will not significantly reduce daily variation of position of the cervix. This is of concern as it is the location of the primary tumour. However, by controlling the bladder volume strictly and applying the preparation suggested here it may be that additional patterns will expose themselves regarding non-bladder related cervical motion.

Overall, variation in rectal AP diameter was less predictable than the variation in bladder volume. No pattern was seen with time through treatment or following chemotherapy. Many variables can affect bowel function which may explain why patterns are less identifiable in this small cohort of patients. A clear correlation exists between rectal volume and AP diameter which is good for clinical practice as radiographers at planning can measure AP diameter in seconds. A rectal AP diameter increase correlated with a bladder volume decrease. This could be explained clinically by dehydration and again emphasises the importance of hydration throughout treatment. This is also a potential confounding factor when considering my results.

Larger rectal AP diameter than at planning resulted in increased likelihood of CTV not being covered by PTV, affecting the cervix more than the uterus, again consistent with published data (Jadon et al. 2014). From my data, patients with a smaller rectum size through treatment were more likely to have better CTV coverage. I therefore suggest laxatives to maintain small rectal sizes during treatment, aiming for a rectal AP diameter of less than 4cm at all times. If necessary, microenema use should be considered to empty the lower part of the rectum. In patients where large variations are seen, an alternative approach is to increase the posterior margin in the region of the cervix. This can compensate for the less predictable rectal changes which impact on cervix and tumour coverage but does increase the rectal dose. However, in a lot of cases most of the rectum is within the PTV even without the larger margins.

The variation in rectal size and lack of clear patterns is most concerning as it appears from my data, as well as the published literature, that rectum predominantly affects the cervical motion and hence cervical (primary tumour) coverage. It is therefore essential to continue investigating this further.

By maintaining an upper limit of 300cc for bladder volume at planning, 2-2.5cm margins appear large enough to cover uterine motion in my patient cohort but 3cm is still needed

anterior and posterior around the cervix. One can argue that some of this would be covered by the 'rolling ball effect', i.e. the inferior margin around the uterus positioned anterior to the cervix will actually create a larger margin around the cervix. Therefore, 2.5cm may be adequate. I therefore propose margins of 2cm superior, inferior, left lateral and right lateral and 2.5cm anterior and posterior. As already stated, this is only applicable if the bladder volume at planning is smaller than 300cc. If all cases are included with no maximum planning volume applied, margins as large as 4.6cm are necessary. This is not clinically appropriate as there is evidence showing that increasing CTV to PTV margins reduces the normal tissue sparing benefit of IMRT (Ahamad et al. 2005; Gordon et al. 2011). The margins of 3.4-4.6cm anterior, 2.8-4.2 posterior and 4.2 superior would make the PTV so large that the benefit of IMRT would be negated. Even with controlling the upper limit of bladder volume at planning, proposed margins are 2.2-3.3cm anterior, 2.4-3.0cm posterior and 2.1cm superior, much larger than the 0.5-1cm margins that have been applied in the majority of articles demonstrating IMRT benefit.

Of note, when analysing CBCTs at the level of the cervix in patients with large bladder volume reductions, the uterus was positioned directly anterior to the cervix which may have biased the measurements taken leading to an overestimation of margins necessary.

It is very important to highlight the limitation of these data being based on only ten cases. Four out of the ten patients had large planning bladder volumes (>300cc), two of which were very large, exceeding 500cc. This is clearly much larger than would be achieved daily during treatment. However, it can be argued that this is representing true practice as it happened in a substantial proportion of my cases.

Another limitation of this type of study is the CBCT quality and lack of clarity. The poor resolution of linear accelerator based CBCTs can lead to distortion and difficulties with reliably outlining CTV. To minimise the impact of this on my results two experienced clinicians independently outlined all CBCTs. On qualitative review of these two sets of outlines no substantial or systematic discrepancies were observed, and therefore the poor CBCT resolution is unlikely to have affected our results greatly. These outlines were also summed

together to ensure that all the extreme points were included. However, the ovaries were not visualised on any CBCTs which may impact the lateral margin calculations.

Following on from my results I have proposed bladder and bowel preparation for patients undergoing cervical chemoradiation, seen in Table 5.6. These proposed instructions are likely to have a larger impact on standardising bladder size than rectal size. However, by controlling bladder size consistently, further patterns of the impact of rectal size may emerge and modifications may be necessary to control rectal size further. These proposals will therefore need further validation.

All of the patients in this study were treated with 3D-CRT and therefore the CTV was always adequately covered even when outside PTV. This is due to the brick-like distribution of dose delivered which gives a margin around PTV in certain areas. If these patients had been undergoing treatment with IMRT this may not be the case. Every time that CTV was out of PTV there would be a potential drop in the dose delivered as the benefit of IMRT is the tight dose conformity to PTV. This could potentially have dosimetric implications and subsequent survival implications. Studies have investigated this with varying conclusions as discussed in Chapter 1, section 1.9.2. In view of these conflicting results I analyse the dosimetric effect of the observed variation within these cases in Chapter 6.

Even without knowing the true dosimetric consequence of this data, actions need to be taken to reduce the motion observed before moving forward with IMRT and more conformal techniques as many centres and countries are doing.

As discussed, potential solutions, in addition to strict patient preparation, is anisotropic margins (Jadon et al. 2014). Non uniform margins, with the largest in the direction of greatest movement, allow increased normal tissue sparing than generalised large margins. However, from my small cohort of patients the margins derived to ensure minimum 95% dose in 90% of cases are still too large as they will reduce the normal tissue sparing benefit gained from IMRT.

Adaptive RT, as discussed in Chapter 7, is another alternative. This includes creation of an ITV or weekly replanning. The ITV combines the CTVs from bladder full and empty scans and has been investigated extensively in Rotterdam (Bondar et al. 2012). This does not account for rectal changes and requires significant resources and training to be implemented safely.

Currently, these compensatory techniques all need further validation before being implemented as standard practice. At this time therefore, measures to reduce and monitor this motion must be utilised. The patient preparation proposals detailed here and the introduction of robust and regular monitoring of patients with cervical cancer undergoing radical RT are some significant first steps.

General preparation   • Throughout the entire course of treatment and for at least 5 days before the planning CT scan, maintain adequate hydration and drink 2 litres of water spread throughout the day.   • Monitoring of organ motion is essential. Weekly CBCTs is a minimum requirement providing the first 3-5 days imaging does not show significant variation which is unpredictable.   • Daily monitoring with the use of bladder scanner or CBCTs is recommended.
Bladder preparation   • Before planning and all treatments drink 3 cups of water and wait for 30 minutes. The volume of bladder achieved should ideally be 150-300cc. If the bladder does not fall in that range at planning, especially if larger, consider rescanning having waited for a different time period e.g. 10 minutes shorter if bladder large than 300cc. A bladder scanner can be used to facilitate this without extra radiation exposure for patients.   • On the day of and one day after when patients receive chemotherapy they should drink 3 cups and wait 10 minutes less than usual.   • Use of bladder scanners are strongly recommended as these are a non–invasive quick imaging method which can improve the likelihood of reproducing similar bladder volumes across the radiotherapy course. Record the average of three bladder scanner readings. This approximates to 50cc below the CT outlined bladder volume.   • At planning a bladder scanning volume of 100-250cc should be the trigger for scanning, then within 100cc of planning volume for treatment. If a patient is overfull, emptying then re-drinking is necessary. As patients progress through treatment this will be less frequently required as bladder volume decreases and the individual preparation will become more adapted.   • Patient education and tailoring of bladder preparation through treatment is helpful.
Rectal preparation   • Regular laxatives should be administered (sodium docusate preferred) to ensure Bristol stool type 5; laxatives twice daily if type 1-3 stool, once daily if type 4-5 stool and none if type 6-7 stool. Patients can be given a copy of the Bristol stool chart with instructions if this is helpful for them.   • As patients progress through treatment they may develop diarrhoea and should be monitored carefully for this if taking laxatives.   • If the AP diameter of the rectum is still>4cm at planning, consider micro-enemas and if done, do this for all treatments.   • The posterior margin should be increased by 1cm in the region of the cervix if repeatedly large or variable diameters are seen despite these measures.

Table 5.6: Proposed patient preparation protocol

Chapter 6

The dosimetric impact of the observed organ motion variation on clinical target volume (CTV) coverage in cervical cancer radiotherapy.

6.1. Introduction

Large movements in CTV position, such as those discussed in Chapter 5, raise concern that target coverage may be compromised if IMRT is delivered using conventional margins. Understanding the dose impact, if any, is therefore essential before implementing resource intense compensatory techniques such as adaptive radiotherapy (Heijkoop et al. 2014).

Few studies have investigated this dose impact, perhaps due to difficulties in calculating delivered dose to each point of tissue, especially when an organ changes shape and dimensions as well as position, as the uterus does. To derive accurate solutions, high contrast imaging coupled to an accurate dose calculation algorithm and mathematical process to sum doses from different geometric sets is necessary. Deformable dose algorithm software, such as MORFEUS, can track anatomical changes and transform and add dose clouds from multiple image sets. Even using this software produces varying results as demonstrated by Lim et al and Stewart et al (Lim et al. 2009; Stewart et al. 2010). The dosimetric impact of this organ position variation therefore remains unclear.

Within our CBCT analysis during chemo-radiation for cervical cancer (Chapter 5) large organ filling variations were seen with subsequent target position variations. Up to 5cm of CTV extended beyond PTV for some treatment days. This Chapter therefore aims to understand the dosimetric effect of this variation observed and what factors trigger poor coverage, thereby allowing definition of methods to reduce any effect.

The RapidArc planning within this Chapter was completed by Lisa Hall and Vasilis Rompokos. The novel vector based method for analysing dosimetric effects was created by Vasilis Rompokos and verified by Chris Stacey. Vasilis performed the data extraction from the RapidArc plans using his novel technique and the analysis of data and all other work was completed by me.

6.2. Methods

CBCT acquirement and analysis including the delineation of CTV1, bladder and rectum are detailed in Chapter 5 section 5.2.3.

6.2.1. Planning process

Dual arc RapidArc treatment plans were created based on the planning PTV using Eclipse v11 [Varian Medical Systems, Palo Alto] TPS. Plans were inversely optimised, prioritising PTV coverage and optimising OARs outside of PTV only. Calculation used the Anisotropic Analytical Algorithm. Additional plans were created for the four cases which demonstrated greatest variation. These cases had planning bladder volumes exceeding 300cc and were replanned based on the CBCT CTV1 with bladder volume closest to but not more than 300cc.

6.2.2. Dose distribution analysis

All CBCT generated volumes were copied to the planning CT after bone matching. RapidArc plan CTV1 dose coverage was evaluated assuming that each CBCT represented the organ position for an equal proportion of fractions. CBCTs were excluded if the entire CTV1 was not captured.

To approximate dose delivered within each CBCT we applied a novel vector-based approach. Vectorised DVH methods have been recommended due to different dose distributions resulting in overlapping curves limiting the reliability of summing DVH parameters (Mayo et al. 2013). This means that summing DVH parameters dilutes the potential dosimetric effect as it is not know if the same point is consistently underdosed (clinical concern) or the dose detriment is spread across a larger area (less clinical concern). Our point dosimetry method presented here is therefore likely to reliably represent doses to specified points of tissue.

Three vectors were drawn on the central sagittal slice of the uterus on the planning CT relative to the angle between uterus and cervix (Fig. 6.1). The uterus vector follows the central uterine canal cranio-caudally with the pivot point at the cervix base. The mid-uterus vector is perpendicular to the uterus vector at its midpoint. This is in the lower third of the uterus close to the superior cervix. The cervix vector lies between the posterior and anterior pivot points of the cervix. The length of each vector was linearly deformed to match the planning CT length. Dose delivered continuously along these vectors was extracted from Eclipse v11. An average vector was then derived representing the integrated treatment effect from the average amplitude.
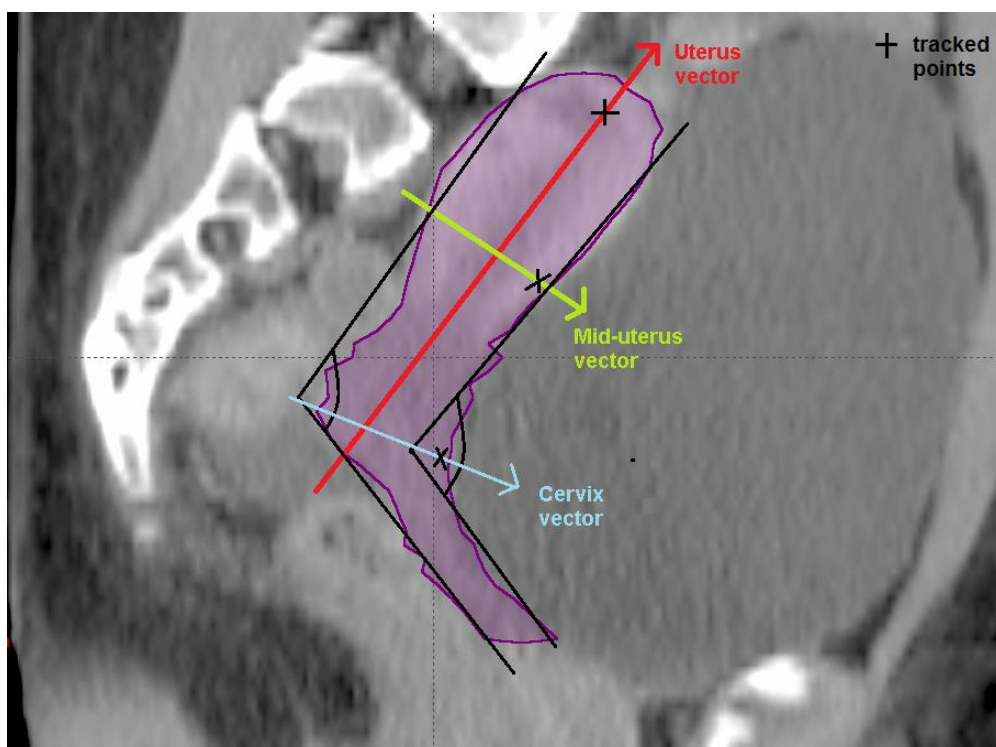
Figure 6.1: Central sagittal CT showing CTV vectors and dose points; uterine vector (red), mid-uterus vector (yellow) and cervix vector (blue) with the three dose points marked as Xs.

Respective dose points were calculated along the three vectors; 10mm caudally from the uterine tip (uterus point); 2mm posterior to the anterior CTV surface along the mid-uterus vector (anterior mid-uterus point) and cervix vector (anterior cervix point). These points represent areas of greatest dose variation along the vectors. Similar points posteriorly and inferiorly did not show as much dose discrepancy from planning. Repeated vector delineation in the TPS showed 3mm intra-observer reproducibility in point placement. Dose delivered to these dose points was calculated for all RapidArc plans.

6.2.3. Statistical analysis

All doses are reported as percentage of prescribed dose (50.4Gray/28#). This is because dose prescriptions for cervical cancer varies across countries and studies, ranging from 45 to 50Gy in 25 to 30 fractions. Median and ranges were calculated using IBM SPSS Statistics 22 following visual review of data confirming non-normal distribution. P values were derived from Wilcoxon signed rank test.

6.3. Results

105 scans were analysed for 10 cases with 6 to 13 scans per case.

Vector analysis revealed CTV1 under-dosing for some fractions if RapidArc treatment is delivered using 10mm-15mm margins (10mm laterally, 15mm in all other directions). This dose detriment led to less than 95% average vector coverage for all vectors in 2 cases and one vector (mid-uterus) in 1 case.

Absolute minimum doses along the individual average uterus vector was 75%, mid-uterus 80% and cervix 89%.

D99 was less than 95% in 50/105 (48%) fractions.

Patients with the largest variation had over-filled bladders (>300cc) at planning. Replanning of these cases using the CTV acquired with the bladder volume closest to, but not larger than, 300cc led to statistically significantly improved coverage along the vectors (Fig. 6.2) and dose points (Table 6.1). These replanned bladder volumes were 239cc, 258cc, 291cc and 163cc.

		Planning PTV % prescribed dose			Replanned with BV <300cc			
		min;max	median	IQ range	min; max	median	IQ range	p value
uterus	all	49.0;102.9	99.4	98.4-100.7				
	BV<300cc	89.5;102.9	99.9	98.8-101				
	BV>300cc	49.0;101.9	98.9	82.9-100.2	86.2; 102.4	100	99.4-100.7	<0.001
ant mid-uterus	all	61.8;103.3	98.7	93.5-99.7				
	BV<300cc	96.2;103.3	99.3	98.3-100.6				
	BV>300cc	61.3;100.1	91.4	83.1-97.8	94.0; 101.6	99.2	98.4-100.4	<0.001
ant cervix	all	85.5;103.1	99.3	97.8-100.6				
	BV<300cc	96.9;103.1	99.8	98.8-101.2				
	BV>300cc	85.5;101.7	98.2	95.3-99.6	94.8;101.5	99.4	98.4-100.7	<0.001

Table 6.1: Range, median and interquartile (IQ) range for bladder volume (BV) and percentage doses delivered to uterus, anterior mid-uterus and anterior cervix points for all cases and those with BV below or above 300cc. Replanning led to statistically improved coverage most prominent for the anterior mid-uterus point.

A — Analysis of vectors for uterus

Legend: CT_plan, 1.11th_March, 2.13th_March, 3.18th_March, 4.21st_March, 5.25th_March, 6.28th_March, 7.1st_April, 8.4th_April, 9.9th_April, 10.13th_April, 11.17th_April, •••• average, end of ctv

Y-axis: Normalised plan dose / %
X-axis: Length of vector / cm

B — Analysis of vectors for uterus, planned at bladder near 300ml

Legend: CT_plan, 1.11th_March, 2.13th_March, 3.18th_March, 4.planningCT, 5.25th_March, 6.28th_March, 7.1st_April, 8.4th_April, 9.9th_April, 10.13th_April, 11.17th_April, •••• average, end of ctv

Y-axis: Normalise plan dose / %
X-axis: Length of vector / cm

C Analysis of vectors for mid-Uterus

Normalised plan dose / %

Length of vector / cm

CT_plan
1.11th_March
2.13th_March
3.18th_March
4.21st_March
5.25th_March
6.28th_March
7.1st_April
8.4th_April
9.9th_April
10.13th_April
11.17th_April
•••• average
end of ctv

D Analysis of vectors for mid-Uterus,planned at bladder near 300ml

Normalised plan dose / %

Length of vector / cm

CT_plan
1.11th_March
2.13th_March
3.18th_March
4.21st_March
5.25th_March
6.28th_March
7.1st_April
8.4th_April
9.9th_April
10.13th_April
11.17th_April
•••• average
end of ctv

E Analysis of vectors for cervix

F Analysis of vectors for cervix, planned at bladder near 300ml

Figure 6.2: Percentage dose delivered (y axis) along uterus (A,B), mid-uterus (C,D) and cervix (E,F) vectors in cm along the CTV length (x axis) for case with large planning bladder volume; red vertical line is end of CTV; 0cm (x axis) is posterior or inferior aspect. Dose decreases anteriorly and superiorly. Improvement in coverage is seen when replanning with bladder volume closest to but less than 300cc (B,D,F) with the average vector (dotted line) remaining above 95% dose coverage.

The range and medians of dose delivered to the uterus, anterior mid-uterus and anterior cervix points are presented in Table 6.1. Planning bladder volumes larger than 300cc were associated with lower dose coverage for all three points, most prominently within the anterior mid-uterus point. These all significantly improved with replanning, corroborating the suggested patient preparation at planning in Chapter 5.

Smaller bladder volumes during treatment increased the likelihood of below 95% dose coverage for all cases. This pattern was more prominent with large planning bladder volumes (diamonds on Fig. 6.3), and improves with replans (crosses on Fig. 6.3). This is as expected due to the larger difference between the planning and treatment bladder volumes. CTV dose coverage was maintained when bladder volume during treatment was closely matched to the planning bladder volume. 99% of CTV volume received minimum 95% dose (D99>95%) in 93% of cases if bladder volume was between 50cc below and 150cc above planning. This fell to 24% if bladder volume was outside of this range. Similarly, D95 was maintained above 95% in all cases when bladder volume was within this range and fell to 84% outside of this range (see Table 6.2).

	Bladder deviation-50 to +150cc		Outside -50-+150cc	
	total no	%	total no	%
no fractions	43		62	
D99>95%	40	93%	15	24%
D95>95%	43	100%	52	84%

Table 6.2: Proportion of fractions maintaining D99>95%dose and D95>95%dose with bladder volume close to planning (-50cc to +150cc)(column 2,3) compared to outside this bladder range (column 4,5).
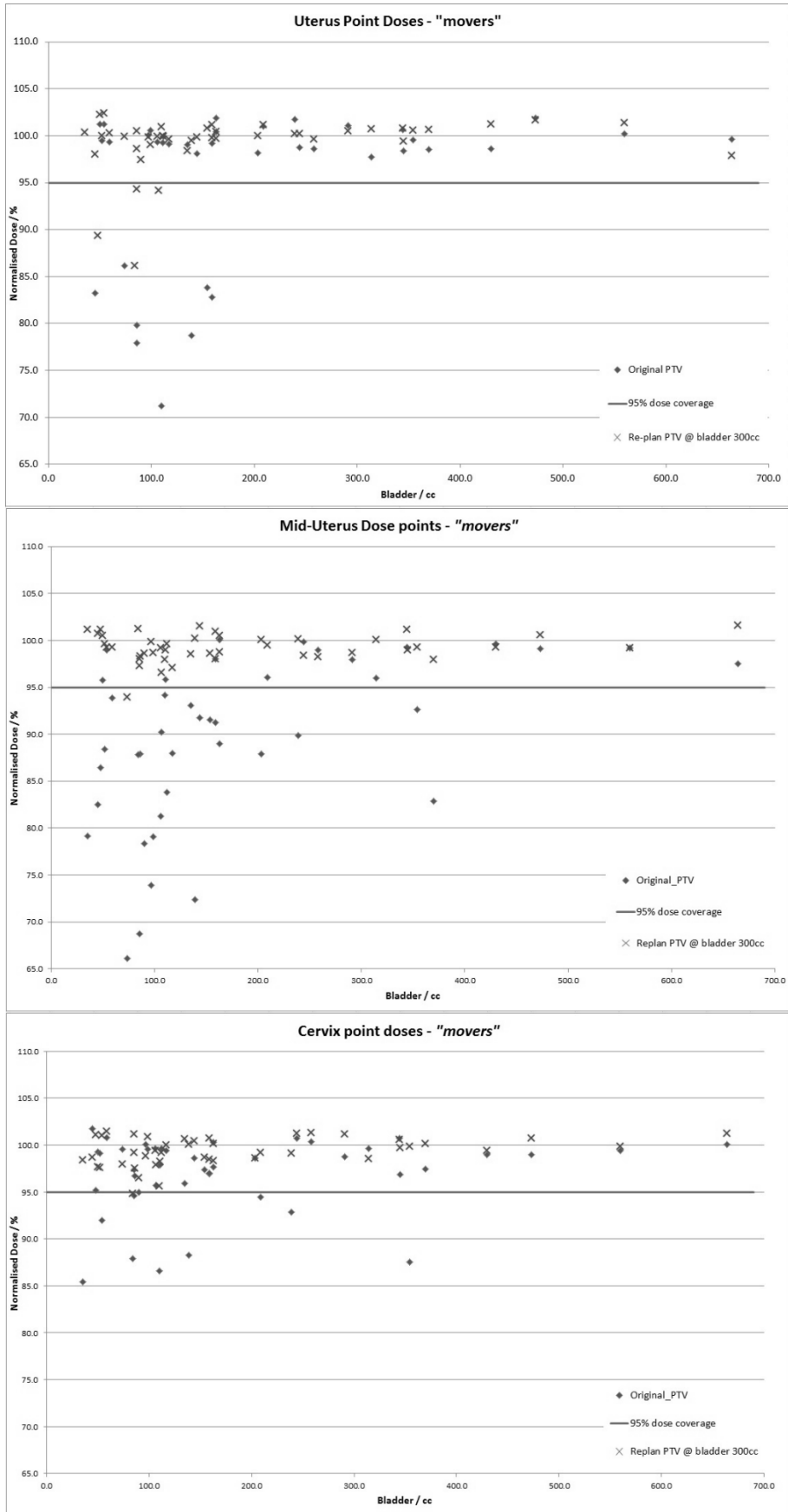
Figure 6.3: Bladder volume (x axis) and normalised dose (% prescribed dose, y axis) for all fractions in cases with planning bladder volume>300cc (movers).

6.4.   Discussion

My results demonstrate clinically significant changes in dose to uterus, mid uterus and cervix related to bladder volume changes, correlating well with my findings and recommendations within Chapter 5. This is greatest in cases with large planning bladder volumes and is corrected with replanning at a bladder volume closer to but not exceeding 300cc. Control of bladder volume is therefore key to reducing geometric discrepancies. No pattern was observed with regards to rectal volume, again in keeping with my findings in Chapter 5.

Dose point assessment concluded that the anterior mid-uterus point was the most variable regarding dose delivered. This is initially surprising, as one might expect the uterus tip to be least covered as it is most mobile. However, this point was more anterior than the uterus point and only 2mm from edge of CTV which may explain the difference. Also, outliers significantly affect the dose delivered to uterus point as the mean and median values varied widely (90.5 and 98.9 for BV>300cc respectively) and absolute minimum values are lower for uterus than anterior mid-uterus. With replanning, the minimum values for anterior mid-uterus are much improved to 94.0% but minimum uterus dose remains at 86.2%. This suggests that the uterus tip, an area of less clinical concern, is corrected less by our proposed bladder volume control strategy but the more critical variations (mid uterus/cervix) are corrected by these strategies. This increases the importance of bladder volume control.

Through analysis of cumulative dose delivery using weekly MRIs and MORFEUS software for 33 cases, Stewart et al found that 27% of fractions did not achieve 95% dose coverage to 98% target volume during treatment (Stewart et al. 2010). This was using small CTV to PTV margins of only 3mm. Despite the differences in sample size and margins, my results of 48% of fractions not achieving 95% dose coverage to 99% volume are in broad agreement with Stewart et al. This is in contrast to Lim et al, who applied a similar methodology using MORFEUS with only 20 patients and found no difference between planned and delivered dose, despite only 5mm margins (Lim et al. 2009). My cohort is smaller than both of these studies with only 10 cases but this is a similar sized cohort as several other published studies (Han et al. 2006; Gordon et al. 2011; Jensen et al. 2015). My results are in strongest agreement with Stewart et al who analysed the largest patient cohort of 33 cases. I also

analyse twice weekly imaging which is more frequent than many published studies (Han et al. 2006; Lim et al. 2009; Stewart et al. 2010) adding to the strength of our data. Two studies, which analysed DVH parameters rather than using dose deformation software, concluded adequate coverage of uterus was maintained with 5mm and 15mm margins despite an observed trend of decreased coverage with time through treatment (Han et al. 2006; Jensen et al. 2015). In contrast, Gordon et al reported an approximate 5Gy reduction in dose delivered for 10 patients having summed DVHs using coverage probabilities and uterine motion modelling with a 1cm margin (Gordon et al. 2011), in keeping with my results. Applying a tapered margin (1cm cervix, 2.4cm fundus) to this cohort did improve uterine coverage but increased normal tissue doses, suggesting that increasing CTV to PTV margins is not an adequate solution to this dose reduction observed. Alternative compensation methods are therefore necessary.

From my data, I reinforce the strict bladder volume monitoring proposed in Chapter 5 to reduce this organ motion magnitude. This dosimetric data supports my recommendation that the bladder should be as close to but not more than 300cc at planning then between 50cc below and 150cc above the planning volume throughout treatment. This strategy should reduce target position variation and subsequent dosimetric deficit related to bladder filling without the intensive resources necessary for adaptive radiotherapy (Heijkoop et al. 2014). These prescriptive recommendations can be implemented using ultrasound bladder scanners or CBCTs as previously discussed (Ahmad et al. 2008).

It is important to note that this novel vector and point dose approach guides understanding of coverage patterns. It does not represent accurate total dose coverage and is therefore insufficient to determine clinical decisions during treatment. For this study, however, it gives some insight into the areas and magnitude of dose detriment to allow generalisation of my results. Deformable registration between CT and CBCT images for pelvic areas can also introduce significant errors when tracking the bladder and rectum (Thor et al. 2011; Zambrano et al. 2013). These errors can be even greater if unfavourable CBCT contrast to noise ratio is observed. On comparison of the two clinicians' CBCT outlines in my ten cases no gross differences were observed. It is therefore unlikely that the CBCT quality detrimentally affected the results in my cohort.

Many assumptions have been made when applying our vector approach. This includes twice weekly imaging reliably representing daily position. This is a consistent assumption across many publications. However, by having up to 12 scans for a single patient allows this data to represent the whole treatment course with some confidence. Having one scan close to and one longer since chemotherapy administration also attempts to increase the generalisability of these results and these CBCTs are likely to represent the whole treatment course. The process of linear deformation assumes that tissue deforms equally across its length. If this is not true the differences are unlikely to be large enough to affect my results but should be considered. Our applied mathematical model only uses a single pivot point which may not fully describe the true target motion but again this is a reasonable simplification as the differences in results due to this are unlikely to be large.

With respect to the site of greatest dose variation there is very little published data. The Gordon study shows dose detriment at the uterine fundus, which is slightly different to my findings. The fundus is an area of lower relapse risk and is therefore less clinically relevant and concerning. Compromise of 5Gy may therefore be accepted. If this was the cervix however, dose detriment would be less acceptable. My study suggests that dose detriment for cases with large planning bladder volumes is seen in the cervix and anterior uterus. This is of greater concern and would be especially important in cases with uterine invasion. None of my ten cases had uterine or myometrial invasion so it is difficult to comment further but my data suggests a risk of under-dosage especially anteriorly. Perhaps, in the clinical situation of uterine invasion this area may be more fixed and therefore less mobile.

Of interest, within my small cohort, large tumours (CTV1 volume>210cc) maintained good dosimetric coverage, perhaps due to local tumour fixation limiting movements. Also, as the tumour shrinks the large initial CTV1 ensured large margins to account for additional movements. One of my cases also had a very small bladder at planning but, as this was consistent throughout treatment, good coverage was maintained.

The dosimetric findings within this Chapter do support the suggestions within Chapter 5, especially the impact of having a maximum planning bladder volume of 300cc. The reduced variation seen with replanning is of significant interest but this is a small cohort. Ongoing

analysis of patients whose bladder volume is strictly controlled using my recommendations is therefore necessary to assess if the dosimetric observations in this cohort are sustained. With strict bladder volume control it will also be important to monitor for rectal patterns as these may be revealed once bladder volume impact is minimised. The next steps of applying strict bladder volume control will be key to assess feasibility. I have practical concerns regarding how to apply this strict control in a busy clinical unit but I am convinced of it's importance if IMRT is to be routinely applied for cervical cancer radiotherapy.

Chapter 7:

Discussion

Cervical cancer remains a significant health burden worldwide despite the introduction of primary and secondary prevention. Ongoing efforts to improve the current treatment and outcomes are therefore necessary. Chemo-radiation remains the mainstay of curative treatment for locally advanced disease which is the focus of this collection of work. Survivorship is an important aspect of patient care and minimising late sequelae from cancer treatment is a clinical priority. Advanced RT techniques are therefore being applied to reduce the volume of irradiated normal tissue and hence minimise normal tissue toxicity.

In Chapter 1 I reviewed the evidence for use of IMRT in cervical cancer concluding that IMRT reduces acute gastrointestinal toxicity and is likely to also reduce genitourinary toxicity and late gastrointestinal toxicity. In addition, it has been shown to increase the likelihood of administering all prescribed chemotherapy concurrently which in turn may improve cure rates. Furthermore, IMRT can be used to boost doses to improve outcomes, the feasibility of which is being investigated in the DEPICT study. This is a phase 1/2 multicentre dose escalation simultaneous boost with IMRT study sponsored by Cancer Research UK (CRUK) and has recently completed recruitment. Despite these proven and potential benefits of IMRT, caution must be applied in view of such tight conformity to the outlined targets. This tight conformity increases the importance of accurate delineation and CTV position reproducibility. Currently, there is no evidence to suggest a change in recurrence rates but as IMRT is more widely implemented this must be monitored.

This collection of work has investigated two major uncertainties within the delivery of radical EBRT for cervical cancer that are fundamental to the delivery of safe RT and become increasingly important with IMRT. Chapter 2, 3 and 4 investigated target volume delineation variation, and Chapter 5 and 6 investigated daily organ and CTV position variation.

Delineation variation is well described to be one of the largest uncertainties and sources of error within EBRT in many tumour sites. My analysis of the RTQA delineation cases from the INTERLACE trial represents approximately half of the UK centres that treat cervical cancer. It is therefore the largest number of observers analysed for cervical cancer delineation variation. Large inter-observer variations were described with up to two fold volume differences and up to 4cm and 3.5cm discrepancies in the superior and inferior borders respectively (Chapter 2).

Encouragingly JCI was not unacceptable (≤0.5) for any cases compared with gold standard but only 14% and 32% achieved acceptable concordance (JCI≥0.7).

These differences did translate into large dosimetric differences with no plans achieving D98%≥95% or D95%≥95% for the GSPTV (Chapter 3). The GSPTV volume receiving 95% dose (V95%) was below 95% for all cases and up to 458cc of GSPTV was outside of the 95% isodose. This dosimetric effect of delineation variation has never been previously assessed for cervical cancer EBRT. The areas with reduced dose were mostly nodal rather than primary CTV. This was initially reassuring as primary CTV is the primary tumour location. However, in view of brachytherapy delivering a high proportion of the dose to the primary tumour and EBRT being the sole source of nodal treatment, we should not be reassured by this. We must therefore continue to strive to develop our training and radiology support when outlining.

INTERLACE (https://clinicaltrials.gov/ct2/show/NCT01566240) is a phase 3 multicentre trial of weekly induction chemotherapy followed by standard chemo-radiation versus standard chemo-radiation alone in patients with locally advanced cervical cancer. This follows on from a phase 2 feasibility study showing manageable toxicity and complete or partial response in 70% of patients treated with dose dense weekly carboplatin and paclitaxel before chemoradiation (McCormack et al. 2013). The radiotherapy delivered within the INTERLACE trial is the subject of an intensive prospective RTQA programme as described in Chapter 2 despite this being a trial investigating the role of chemotherapy. My work here demonstrates the importance of delineation consistency and has emphasised the importance of this on-going RTQA programme.

The EMBRACE2 study, a large multicentre European study currently in set-up, will focus on standardising adaptive EBRT techniques, building on EMBRACE which set the standards for image guided brachytherapy. Within EMBRACE2 prospective RTQA with test delineation cases are mandatory before patient accrual can start. This supports the conclusions drawn from my work regarding the importance of delineation standardisation and strict RTQA.

Within my qualitative review of delineation variation well defined anatomical areas were inconsistent, such as the aortic bifurcation. This again is very concerning. However, for other tumour sites, such as prostate and rectum (Mitchell et al. 2009; Lobefalo et al. 2013), which

similarly treat nodal areas, delineation variation significantly improved with use of education or descriptive guidance. After a thorough evaluation of published guidance I identified areas of discrepancies between individual guidelines and RTQA experience and discussed these within the INTERLACE TMG to formulate a consensus. Subsequently I produced the detailed pictorial delineation atlas seen in Chapter 4. This was added to the RTQA resources within INTERLACE and was found to reduce the delineation variation observed, supporting the hypothesis of reduced variation with descriptive guidance. This again sets the standards for delineation guidance in future trials involving pelvic radiotherapy for gynaecological cancers.

Prior to implementation of this atlas within the INTERLACE RTQA, published guidelines were available. Therefore, an underlying question, not addressed within this work, is why these resources have not already improved the delineation standards observed. Perhaps there is not enough time to access these resources in an already busy RT planning session. What my work shows is that we must make the time. RT centres can upload atlases or guidance onto the computer systems within the department which facilitates speedy access. Another important consideration is whether Clinical Oncology trainees should have formal radiology teaching incorporated into their training programme within the UK. As radiotherapy techniques develop our training needs also expand and maybe even a radiology placement will be beneficial in the future. My atlas is the first pictorial atlas giving complete guidance for nodal target, primary target and OARs in cervical cancer. Publication of this ensures it is readily available for use and it is a unified atlas that covers all areas. I am hopeful that clinicians will refer to this as my work shows this is of great value.

Publication of my findings highlighting the extent of delineation variation and its impact at a time of increasing IMRT use has hopefully increased awareness of the need to be conscientious. This will ensure the potential benefit gained from these advanced RT techniques will not be lost due to the detrimental dosimetric effects that I have shown. The ongoing INTERLACE trial RTQA, as well as the newly introduced EMBRACE2 RTQA, will continue to drive standardisation of delineation across the UK and internationally.

In clinical practice there will always be inter-observer variation despite improvements with atlas implementation and trial RTQA. This should be taken into consideration by the entire

radiotherapy team and monitoring of delineation accuracy should be on-going. This is especially true as some research groups such as EMBRACE are proposing that 95% dose does not need to cover all of the delineated PTV. My hesitation with this is that the areas with compromised dose coverage will be the nodal areas at the edge of field where delineation variation appeared greatest in the cases which I reviewed. An example that immediately comes to mind is the anterior inferior external iliac region just cranial to the inguinal region. When creating the RapidArc plans for Chapter 3, coverage of this area was often tight due to the sudden change in contour. If overall coverage is relaxed this is likely to be an area under-dosed and, along with this being an area where I qualitatively observed large variation in delineation, actual under-dosage may be considerably greater than expected.

Future implications of potential target under-dosage on locoregional control rates are currently uncertain but with on-going efforts to reduce OAR dose and minimise toxicity at some point recurrences may reveal themselves due to reduced target dose. We therefore need to balance what toxicity is really unacceptable because if we keep striving to reduce OAR dose and compromise on our target coverage how much benefit are we truly gaining?

The second major uncertainty addressed within this work is target organ daily position variation. This is a problem specific to pelvic radiotherapy due to rectal and bladder filling. It is especially prominent in intact cervical cancer due to the mobility of CTV.

Some European centres use adaptive RT routinely to compensate for the effects of bladder filling. One approach is to create an ITV by summing the bladder full CTV and bladder empty CTV from multiple planning scans. This was introduced for the RTOG trials investigating IMRT in the post-operative setting for cervical and endometrial patients (RTOG 0418) and adjuvant chemotherapy after post-operative chemo-radiation in cervical cancer (RTOG 0724). For intact cervical cancer, compared to post-operative cases, the ITV can become much larger due to uterine movements.

The Rotterdam group have been pivotal in the application of ITV and variable bladder filling plans for intact cervical cancer (Bondar et al. 2011; Bondar et al. 2012; Heijkoop et al. 2014). Their protocol is to separate patients according to magnitude of uterine movement by performing two planning CT scans; bladder full and bladder empty. If the uterus moves more

than 2.5cm between these scans two IMRT plans are created; empty-to-half-full and half-full-to-full. If the uterine movement is less than 2.5cm a single ITV plan is created. ITV to PTV margin is 1cm. All patients have a backup 3D-CRT plan. Using daily CBCT, bony matching is performed, then the appropriate plan is selected to ensure coverage of vaginal fornix markers and uterus. Approximately 18% of fractions are treated with 3D-CRT. This is due to uterus being out of PTV (27.5%), markers out (21.3%), both out (21.7%) and poor CBCT quality (10.5%). Therefore approximately 13% apply the backup 3D-CRT plan due to either uterus or cervix being out of PTV. As with most of these advanced techniques, resource implications exist and a significant amount of skill and teaching is necessary. Within the UK, CBCT and clinician availability is limited but we can use this data to evidence the need to build on the resources that we have and to develop teams of highly skilled radiographers who can ensure its safe application.

Due to the complexity and resource intensity of these techniques I analysed twice weekly CBCTs in ten patients undergoing cervical chemo-radiation to understand the extent and patterns of CTV position variation and organ filling with a view to reducing this variation. This work is presented in Chapter 5 and 6. I demonstrated large variations in target position related to bladder and rectum filling (Chapter 5), consistent with published data. My analysis revealed patterns already documented such as decreasing bladder volume through treatment, large deviations (>130cc) from planning increasing the likelihood of PTV not covering CTV and bladder predominantly affecting uterine coverage compared to rectum affecting cervical coverage. I also made novel observations of increased variation if bladder volume at planning was too large, specifically more than 300cc, and an increased bladder volume on days immediately post chemotherapy. Additional work confirmed that these observed changes have a clinically significant impact on dose delivered to CTV (Chapter 6). D99≤95% for CTV in 48% of fractions overall, and median dose to the uterus point in cases with planning bladder volume more than 300cc was 98.9%, mid uterus point 91.4% and cervix point 98.2%. These dosimetric findings correlated well with the movement data analysis. Subsequently I replanned the cases with large initial bladder volumes using the CTV position from the CBCT with the bladder closest to but not more than 300cc. This led to significant improvements in coverage. The mean point doses for uterus, mid-uterus and cervix were increased to 100%, 99.2% and

99.4% respectively. This corroborated the suggested planning bladder volume range of 150-300cc rather than a 'comfortable full bladder'. Of note, the application of newer RT techniques increase avoidance of bowel reducing the need for an overfull bladder to spare bowel.

The recommended patient preparation and bladder monitoring in Chapters 5 and 6 are potentially a more feasible intervention than adaptive RT for less resource rich environments such as the UK National Health Service (NHS). This is not 'resource neutral' however, as I do recommend the use of bladder scanners daily to monitor bladder volume. An audit within my department showed that bladder scanners are useful to control bladder volume, and can be used at planning and during treatment (Ahmad et al. 2013). They also do not expose patients to additional radiation, do not need interpretation and are quicker to acquire than CBCTs. However, they do not give additional anatomical information such as rectal size. My next project is to apply this patient preparation protocol using bladder scanners to a larger cohort of patients whilst collecting further data. More experience may allow less frequent imaging (bladder scanner or CBCT) during treatment or selection of certain patient cohorts requiring less imaging during RT. Building experience will also show that use of bladder scanners on the treatment floor by radiographers is feasible and will aid bladder volume control.

Other approaches for adaptive RT include weekly replanning. Due to tumour shrinkage through treatment replanning weekly can reduce the irradiated volume size, improve CTV coverage and minimise normal tissue dose whilst using small margins (Kerkhof et al. 2008; Stewart et al. 2010; Oh et al. 2014). This approach again has significant resource implications and does not really account for organ filling changes. In my patient cohort I observed that significant tumour shrinkage can lead to increases in daily target position variation in patients with large planning CTV volumes. It would be important to ensure conforming closer to the CTV each week is not detrimental to dose delivered to CTV due to CTV motion. The main reason that these patients achieved adequate coverage in our cohort was that the initial CTV was so large that this ensured larger margins as they progressed through RT. The application of my proposed patient preparation to control organ filling may therefore facilitate safe introduction of techniques such as this once my proposal has been validated.

In clinical practice, adaptive RT is an ideal goal for the future but deciding which approach is best clinically and from a health economics perspective is complex. These approaches all need further validation before being considered as standard of care. The EMBRACE2 study may set these standards across Europe and facilitate a unanimous approach. In the meantime, my findings and proposals provide the basis for introducing IMRT safely, providing monitoring is ongoing, with less resource intensity of other interventions.

Moving forward from this work, prospective RTQA will carry on within the INTERLACE and EMBRACE2 trials striving to continue to improve the EBRT standards across the world. This RTQA has also set standards for future trials involving RT for cervical cancer. Regarding my clinical practice, I will implement the strict patient preparation protocol presented in Chapter 5 and monitor its impact. I will also educate the radiotherapy team regarding the importance of controlling bladder volume and will focus my teaching to clinical oncology trainees on delineation utilising the atlases available for many tumour sites. Finally, it is essential that we track RT patient outcomes to monitor for changing relapse patterns as RT techniques advance. Most clinicians do this independently but perhaps it is also time to do this collaboratively at a national level.

As the standards of cervical radiotherapy improve due to the increased understanding of delineation and organ motion within this work, IMRT can be applied with increased confidence of its safety. We can then investigate exciting avenues of optimising IMRT delivery, such as using radiological biomarkers, FDG-PET/CT and DW-MRI, to tailor treatment according to response. In current practice, FDG-PET/CT can be used to aid delineation of tumour or involved nodes with good outcomes. In theory, FDG-PET/CT and DW-MRI can also give functional information regarding tumour response throughout RT to enable dose painting and escalation (Esthappan et al. 2004; Kidd et al. 2010). Alongside this collection of work I have set up a feasibility study using PET-MRI in this situation. However, to successfully demonstrate the therapeutic gain of these exciting advanced approaches we still rely on standardisation of delineation and target position to ensure safe delivery.

References

Ahamad, A., D'Souza, W., Salehpour, M. et al. (2005). "Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size." Int J Radiat Oncol Biol Phys **62**(4): 1117-1124.

Ahmad, R., Bondar, L., Voet, P. et al. (2013). "A margin-of-the-day online adaptive intensity-modulated radiotherapy strategy for cervical cancer provides superior treatment accuracy compared to clinically recommended margins: a dosimetric evaluation." Acta oncologica **52**(7): 1430-1436.

Ahmad, R., Hoogeman, M. S., Bondar, M. et al. (2011). "Increasing treatment accuracy for cervical cancer patients using correlations between bladder-filling change and cervix-uterus displacements: proof of principle." Radiother Oncol **98**(3): 340-346.

Ahmad, R., Hoogeman, M. S., Quint, S. et al. (2008). "Inter-fraction bladder filling variations and time trends for cervical cancer patients assessed with a portable 3-dimensional ultrasound bladder scanner." Radiother Oncol **89**(2): 172-179.

Ahmed, R. S., Kim, R. Y., Duan, J. et al. (2004). "IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk." Int J Radiat Oncol Biol Phys **60**(2): 505-512.

Al Feghali, K. A. and Elshaikh, M. A. (2016). "Why brachytherapy boost is the treatment of choice for most women with locally advanced cervical carcinoma?" Brachytherapy **15**(2): 191-199.

Albuquerque, K., Giangreco, D., Morrison, C. et al. (2011). "Radiation-related predictors of hematologic toxicity after concurrent chemoradiation for cervical cancer and implications for bone marrow-sparing pelvic IMRT." Int J Radiat Oncol Biol Phys **79**(4): 1043-1047.

Aoki, T., Nagata, Y., Mizowaki, T. et al. (2003). "Clinical evaluation of dynamic arc conformal radiotherapy for paraaortic lymph node metastasis." Radiother Oncol **67**(1): 113-118.

Balleyguier, C., Sala, E., Da Cunha, T. et al. (2011). "Staging of uterine cervical cancer with MRI: guidelines of the European Society of Urogenital Radiology. ." Eur Radiol **21**: 1102-1110.

Banerjee, R., Chakraborty, S., Nygren, I. and Sinha, R. (2013). "Small bowel dose parameters predicting grade 3 acute toxicity in rectal cancer patients treated with neoadjuvant chemoradiation: an independent validation study comparing peritoneal space versus small bowel loop contouring techniques." Int J Radiat Oncol Biol Phys **85**(5): 1225-1231.

Bansal, A., Patel, F. D., Rai, B. et al. (2013). "Literature review with PGI guidelines for delineation of clinical target volume for intact carcinoma cervix." J Cancer Res Ther **9**(4): 574-582.

Barrett, A., Dobbs, J., Morris, S. and Roques, T. (2009). Practical Radiotherapy Planning., Hodder Arnold.

Beadle, B. M., Jhingran, A., Salehpour, M. et al. (2009). "Cervix regression and motion during the course of external beam chemoradiation for cervical cancer." Int J Radiat Oncol Biol Phys **73**(1): 235-241.

Beadle, B. M., Jhingran, A., Yom, S. S. et al. (2010). "Patterns of regional recurrence after definitive radiotherapy for cervical cancer." Int J Radiat Oncol Biol Phys **76**(5): 1396-1403.

Benedet, J. L., Bender, H., Jones III, H. et al. (2000). "FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers FIGO Committee on Gynecologic Oncology." Int J Gynecol Obstet **70**(2): 209-262.

Beriwal, S., Gan, G. N., Heron, D. E. et al. (2007). "Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer." Int J Radiat Oncol Biol Phys **68**(1): 166-171.

Bondar, L., Hoogeman, M., Mens, J. W. et al. (2011). "Toward an individualized target motion management for IMRT of cervical cancer based on model-predicted cervix–uterus shape and position." Radiother Oncol **99**(2): 240-245.

Bondar, L., Hoogeman, M. S., Mens, J. W. et al. (2012). "Individualized nonadaptive and online-adaptive intensity-modulated radiotherapy treatment strategies for cervical cancer patients based on pretreatment acquired variable bladder filling computed tomography scans." Int J Radiat Oncol Biol Phys **83**(5): 1617-1623.

Brixey, C. J., Roeske, J. C., Lujan, A. E. et al. (2002). " Impact of intensity modulated radiotherapy on acute haematologic toxicity in women with gynecologic malignancies." Int J Radiat Oncol Biol Phys **54**(5): 1388-1396.

Buchali, A., Koswig, S., Dinges, S. et al. (1999). "Impact of the filling status of the bladder and rectum on their integral dose distribution and the movement of the uterus in the treatment planning of gynaecological cancer." Radiother Oncol **52**: 29-34.

Buis, D. R., Lagerwaard, F. J., Dirven, C. M. et al. (2007). "Delineation of brain AVMs on MR-Angiography for the purposes of stereotactic radiosurgery." Int J Radiat Oncol Biol Phys **67**(1): 308-316.

Camisão, C. C., Brenna, S. M. F., Lombardelli, K. V. P. et al. (2007). "Magnetic resonance imaging in the staging of cervical cancer." Radiol Bras [online] **40**(3): 207-215.

Cazzaniga, L. F., Marinoni, M. A., Bossi, A. et al. (1998). "Interphysician variability in defining the planning target volume in the irradiation of prostate and seminal vesicles." Radiother Oncol **47**(3): 293-296.

CCCMAC (2008). "Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomised trials. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. ." J Clin Oncol **26**: 5802-5812.

Cengiz, M., Dogan, A., Ozyigit, G. et al. (2012). "Comparison of intracavitary brachytherapy and stereotactic body radiotherapy dose distribution for cervical cancer." Brachytherapy **11**(2): 125-129.

Chan, P., Dinniwell, R., Haider, M. A. et al. (2008). "Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study." Int J Radiat Oncol Biol Phys **70**(5): 1507-1515.

Chan, P., Yeo, I., Perkins, G. et al. (2006). "Dosimetric comparison of intensity-modulated, conformal, and four-field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study." Radiat Oncol **1**: 13.

Chao, K. S. C. and Lin, M. (2002). "Lymphangiogram-assisted lymph node target delineation for patients with gynecologic malignancies." Int J Radiat Oncol Biol Phys **54**(4): 1147-1152.

Chen, C.-C., Lin, J.-C., Jan, J.-S. et al. (2011). "Definitive intensity-modulated radiation therapy with concurrent chemotherapy for patients with locally advanced cervical cancer." Gynecol oncol **122**(1): 9-13.

Chen, L. A., Kim, J., Boucher, K. et al. (2015). "Toxicity and cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for postoperative treatment of gynecologic cancers." Gynecol Oncol **136**(3): 521-528.

Chen, M. F., Tseng, C. J., Tseng, C. C. et al. (2007). "Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy." Int J Radiat Oncol Biol Phys **67**(5): 1438-1444.

Collen, C., Engels, B., Duchateau, M. et al. (2010). "Volumetric imaging by megavoltage computed tomography for assessment of internal organ motion during radiotherapy for cervical cancer." Int J Radiat Oncol Biol Phys **77**(5): 1590-1595.

Cozzi, L., Dinshaw, K. A., Shrivastava, S. K. et al. (2008). "A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy." Radiother Oncol **89**(2): 180-191.

De Sanjose, S., Quint, W. C., Alemany, L. et al. (2010). "Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study (Retrospective International Survey and HPV Time Trends Study Group)." Lancet Oncol **11**: 1048-1056.

Deasy, J. O., Blanco, A. I. and Clark, V. H. (2003). "CERR: a computational environment for radiotherapy research." Med Phys **30**(5): 979-985.

Debois, M., Oyen, R., Maes, F. et al. (1999). "The contribution of magnetic resonance imaging to the three-dimensional treatment planning of localised prostate cancer." Int J Radiat Oncol Biol Phys **45**(4): 857–865.

Deurloo, K. E., Steenbakkers, R. J., Zijp, L. J. et al. (2005). "Quantification of shape variation of prostate and seminal vesicles during external beam radiotherapy." Int J Radiat Oncol Biol Phys **61**(1): 228-238.

Dimopoulos, J. C., De Vos, V., Berger, D. et al. (2009). "Inter-observer comparison of target delineation for MRI-assisted cervical cancer brachytherapy: application of the GYN GEC-ESTRO recommendations." Radiother oncol **91**(2): 166-172.

Dinniwell, R., Chan, P., Czarnota, G. et al. (2009). "Pelvic lymph node topography for radiotherapy treatment planning from ferumoxtran-10 contrast-enhanced magnetic resonance imaging." Int J Radiat Oncol Biol Phys **74**(3): 844-851.

Downey, K. and deSouza, N. M. (2011). "Imaging cervical cancer: recent advances and future directions." Curr Opin Oncol **23**: 519-525.

Du, X.-l., Sheng, X.-g., Jiang, T. et al. (2010). "Intensity-modulated Radiation Therapy Versus Para-aortic Field Radiotherapy to Treat Para-aortic Lymph Node Metastasis in Cervical Cancer: Prospective Study." Croat Med J **51**(3): 229-236.

Du, X.-l., Tao, J., Sheng, X.-g. et al. (2012). "Intensity-modulated radiation therapy for advanced cervical cancer: A comparison of dosimetric and clinical outcomes with conventional radiotherapy." Gynecol oncol **125**(1): 151-157.

Duane, F. K., Langan, B., Gillham, C. et al. (2014). "Impact of delineation uncertainties on dose to organs at risk in CT-guided intracavitary brachytherapy." Brachytherapy **13**(2): 210-218.

Eminowicz, G., Hall-Craggs, M. A., Diez, P. and McCormack, M. (2016). "Improving target volume delineation in intact cervical carcinoma: literature review and step-by-step pictorial atlas to aid contouring." Prac Radiat Oncol **In press**: doi:10.1016/j.prro.2016.1001.1006.

Eminowicz, G. and McCormack, M. (2015). "Variability of clinical target volume delineation for definitive radiotherapy in cervix cancer." Radiother Oncol **117**: 542-547.

Eminowicz, G., Motlib, J., Khan, S. et al. (2016). "Pelvic organ motion during radiotherapy for cervical cancer: understanding patterns and recommended patient preparation." Clin Oncol **pii. S0936-6555(16)30078-4**: doi:10.1016/j.clon.2016.1004.1044[Epub ahead of print].

Eminowicz, G., Rompokos, V., Stacey, C. and McCormack, M. (2016). "The dosimetric impact of target volume delineation variation for cervical cancer radiotherapy." Radiother Oncol **pii:S0167-8140(16)31074-X**: doi:10.1016/j.radonc.2016.1004.1028.[Epub ahead of print].

Erpolat, O. P., Alco, G., Caglar, H. B. et al. (2014). "Comparison of hematologic toxicity between 3DCRT and IMRT planning in cervical cancer patients after concurrent

chemoradiotherapy: a national multi-center study." Eur J Gynaecol Oncol **35**(1): 62-66.

Eskander, R. N., Scanderbeg, D., Saenz, C. C. et al. (2010). "Comparison of computed tomography and magnetic resonance imaging in cervical cancer brachytherapy target and normal tissue contouring." Int J Gynecol Cancer **20**(1): 47-53.

Esthappan, J., Mutic, S., Malyapa, R. S. et al. (2004). "Treatment planning guidelines regarding the use of CT/PET-guided IMRT for cervical carcinoma with positive paraaortic lymph nodes." Int J Radiat Oncol Biol Phys **58**(4): 1289-1297.

Fleiss, J. L., Slakter, M. J., Fischman, S. L. et al. (1979). "Inter-examiner reliability in caries trials." J Dent Res **58**(2): 604-609.

Fontanilla, H. P., Klopp, A., Lindberg, B. S. et al. (2013). "Anatomic distribution of (^{18}F) fluorodeoxyglucose-avid lymph nodes in patients with cervical cancer." Prac Radiat Oncol **3**: 45-53.

Forrest, J., Presutti, J., Davidson, M. et al. (2012). "A Dosimetric Planning Study Comparing Intensity-modulated Radiotherapy with Four-field Conformal Pelvic Radiotherapy for the Definitive Treatment of Cervical Carcinoma." Clin Oncol **24**: e63-e70.

Forrest, J. L., Ackerman, I., Barbera, L. et al. (2010). "Patient outcome study of concurrent chemoradiation, external beam radiotherapy, and high-dose rate brachytherapy in locally advanced carcinoma of the cervix." Int J Gynecol Cancer **20**(6): 1074-1078.

Fotina, I., Lutgendorf-Caucig, C., Stock, M. et al. (2012). "Critical discussion of evaluation parameters for inter-observer variability in target defintion for radiaiton therapy." Strahlenther Onkol **188**: 160-167.

Franco, E. L., Villa, L. L., Sobrinho, J. P. et al. (1999). "Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer." J Infect Dis **180**(5): 1415-1423.

Gandhi, A. K., Sharma, D. N., Rath, G. K. et al. (2013). "Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study." Int J Radiat Oncol Biol Phys **87**(3): 542-548.

Gay, H. A., Barthold, H. J., O'Meara, E. et al. (2012). "Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas." Int J Radiat Oncol Biol Phys **83**(3): e353-362.

Georg, P., Georg, D., Hillbrand, M. et al. (2006). "Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies." Radiother Oncol **80**(1): 19-26.

Gerszten, K., Colonello, K., Heron, D. E. et al. (2006). "Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for carcinoma of the cervix." Gynecologic oncology **102**(2): 182-188.

Gill, B. S., Lin, J. F., Krivak, T. C. et al. (2014). "National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements." Int J Radiat Oncol Biol Phys **90**(5): 1083-1090.

GLOBOCAN. (2012). "Cancer factsheet:Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012." Retrieved 2015 April 15, from http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Gordon, J. J., Weiss, E., Abayomi, O. K. et al. (2011). "The effect of uterine motion and uterine margins on target and normal tissue doses in intensity modulated radiation therapy of cervical cancer." Phys Med Biol **56**(10): 2887-2901.

Gwynne, S., Spezi, E., Sebag-Montefiore, D. et al. (2013). "Improving radiotherapy quality assurance in clinical trials: assessment of target volume delineation of the pre-accrual benchmark case." Br J Radiol **86**(1024): 20120398.

Gwynne, S., Spezi, E., Staffurth, J. et al. (2011). "Inter-observer Variation in Outlining of Pre-trial Test Case in the SCOPE1 Trial: A United Kingdom Definitive Chemoradiotherapy Trial for Esophageal Cancer." Int J Radiat Oncol Biol Phys **81**: S67-68.

Haas, J. A., Witten, M. R., Clancey, O. et al. (2012). "CyberKnife boost for patients with cervical cancer unable to undergo bracytherapy." Front Oncol **2**: 25.

Haie-Meder, C., Pötter, R., Van Limbergen, E. et al. (2005). "Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV." Radiother Oncol **74**(3): 235-245.

Hall, E. J. and Wuu, C.-S. (2003). "Radiation-induced second cancers: the impact of 3D-CRT and IMRT." Int J Radiat Oncol Biol Phys **56**(1): 83-88.

Han, Y., Shin, E. H., Huh, S. J. et al. (2006). "Interfractional dose variation during intensity-modulated radiation therapy for cervical cancer assessed by weekly CT evaluation." Int J Radiat Oncol Biol Phys **65**(2): 617-623.

Haripotepornkul, N. H., Nath, S. K., Scanderbeg, D. et al. (2011). "Evaluation of intra- and inter-fraction movement of the cervix during intensity modulated radiation therapy." Radiother Oncol **98**(3): 347-351.

Harris, E. E., Latifi, K., Rusthoven, C. et al. (2011). "Assessment of organ motion in postoperative endometrial and cervical cancer patients treated with intensity-modulated radiation therapy." Int J Radiat Oncol Biol Phys **81**(4): e645-650.

Hasselle, M. D., Rose, B. S., Kochanski, J. D. et al. (2011). "Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix." Int J Radiat Oncol Biol Phys **80**(5): 1436-1445.

Heijkoop, S. T., Langerak, T. R., Quint, S. et al. (2014). "Clinical implementation of an Online Adaptive Plan-of-the-Day Protocol for Nonrigid Motion Management in Locally Advanced Cervical Cancer IMRT." Int J Radiat Oncol Biol Phys **90**(3): 673-679.

Hellebust, T. P., Tanderup, K., Lervag, C. et al. (2013). "Dosimetric impact of interobserver variability in MRI-based delineation for cervical cancer brachytherapy." Radiother Oncol **107**(1): 13-19.

Heron, D. E., Gerszten, K., Selvaraj, R. N. et al. (2003). "Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose–volume histograms." Gynecol Oncol **91**(1): 39-45.

Herrera, F. G., Callaway, S., Delikgoz-Soykut, E. et al. (2013). "Retrospective feasibility study of simultaneous integrated boost in cervical cancer using Tomotherapy: the impact of organ motion and tumor regression." Radiat Oncol **8**: 5.

Higham, C. E. and Faithfull, S. (2015). "Bone Health and Pelvic Radiotherapy." Clin Oncol **27**(11): 668-678.

Hsieh, C. H., Tien, H. J., Hsiao, S. M. et al. (2013). "Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result." Onco Targets Ther **6**: 59-66.

Hui, B., Zhang, Y., Shi, F. et al. (2014). "Association between bone marrow dosimetric parameters and acute hematologic toxicity in cervical cancer patients undergoing concurrent chemoradiotherapy: comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy." Int J Gynecol Cancer **24**(9): 1648-1652.

Igdem, S., Ercan, T., Alco, G. et al. (2009). "Dosimetric comparison of intensity modulated pelvic radiotherapy with 3D conformal radiotherapy in patients with gynecologic malignancies." Eur J Gynaecol Oncol **30**(5): 547-551.

Ikushima, H., Osaki, K., Furuntani, S. et al. (2006). "Pelvic bone complications following radiation therapy of gynaecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures." Gynecol oncol **103**: 1100-1104.

Ioffe, Y. J., Hillen, T. J., Zhou, G. et al. (2014). "Postradiation damage to the pelvic girdle in cervical cancer patients: is intensity-modulated radiation therapy safer than conventional radiation?" Int J Gynecol Cancer **24**(4): 806-812.

Jaakkola, S., Pukkala, E., H, K. L. and Ylikorkala, O. (2012). "Postmenopausal estradiol-progestagen therapy and risk for uterine cervical cancer." Int J Cancer **131**(4): E537-543.

Jaccard, P. (1901). "Etude comparative de la distribution florale dans une portion des Alpes et des Jura." Bull Soc Vaud Sci Nat **37**: 547-579.

Jadon, R., Pembroke, C. A., Hanna, C. L. et al. (2014). "A systematic review of organ motion and image-guided strategies in external beam radiotherapy for cervical cancer." Clin Oncol **26**(4): 185-196.

Jameson, M. G., Holloway, L. C., Vial, P. J. et al. (2010). "A review of methods of analysis in contouring studies for radiation oncology." J Med Imaging Radiat Oncol **54**(5): 401-410.

Jameson, M. G., Kumar, S., Vinod, S. K. et al. (2014). "Correlation of contouring variation with modeled outcome for conformal non-small cell lung cancer radiotherapy." Radiother Oncol **112**(3): 332-336.

Jena, R., Kirkby, N. F., Burton, K. E. et al. (2010). "A novel algorithm for the morphometric assessment of radiotherapy treatment planning volumes." Br J Radiol **83**: 44-51.

Jensen, N. B. K., Nyvang, L., Assenholt, M. S. et al. (2015). "EP-1515: Evaluation of organ motion and uterine dose summation for IMRT in locally advanced cervical cancer." Radiother Oncol **115**: S826-S827.

Jhingran, A., Salehpour, M., Sam, M. et al. (2012). "Vaginal motion and bladder and rectal volumes during pelvic intensity-modulated radiation therapy after hysterectomy." Int J Radiat Oncol Biol Phys **82**(1): 256-262.

Jia, M. X., Zhang, X., Yin, C. et al. (2014). "Peripheral dose measurements in cervical cancer radiotherapy: a comparison of volumetric modulated arc therapy and step-and-shoot IMRT techniques." Radiat Oncol **9**: 61.

Kabolizadeh, P., Fulay, S. and Beriwal, S. (2013). "Are Radiation Therapy Oncology Group para-aortic contouring guidelines for pancreatic neoplasm applicable to other malignancies- Assessment of nodal distribution in gynecological malignancies." Int J Radiat Oncol Biol Phys **87**(1): 106-110.

Kerkhof, E. M., Raaymakers, B. W., van der Heide, U. A. et al. (2008). "Online MRI guidance for healthy tissue sparing in patients with cervical cancer: An IMRT planning study." Radiother Oncol **88**(2): 241-249.

Keys, H. M., Bundy, B. N., Stehman, F. B. et al. (1999). "Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma." New Engl J Med **340**(15): 1154-1161.

Kidd, E. A., Siegel, B. A., Dehdashti, F. et al. (2010). "Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer." Int J Radiat Oncol Biol Phys **77**(4): 1085-1091.

Klopp, A. H., Moughan, J., Portelance, L. et al. (2013). "Hematologic toxicity in RTOG 0418: a phase 2 study of postoperative IMRT for gynecologic cancer." Int J Radiat Oncol Biol Phys **86**(1): 83-90.

Kouwenhoven, E., Giezen, M. and Struikmans, H. (2009). "Measuring the similarity of target volume delineations independent of the number of observers." Phys Med Biol **54**(9): 2863-2873.

Krishnatry, R., Patel, F. D., Singh, P. et al. (2012). "CT or MRI for image-based brachytherapy in cervical cancer." Jpn J Clin Oncol **42**(4): 309-313.

Landoni, F., Maneo, A., Colombo, A. et al. (1997). "Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer." Lancet **350**(9077): 535-540.

Lee, C. M., Shrieve, D. C. and Gaffney, D. K. (2004). "Rapid involution and mobility of carcinoma of the cervix." Int J Radiat Oncol Biol Phys **58**(2): 625-630.

Lee, J. E., Han, Y., Huh, S. J. et al. (2007). "Interfractional variation of uterine position during radical RT: weekly CT evaluation." Gynecol Oncol **104**(1): 145-151.

Lesnock, J. L., Farris, C., Beriwal, S. and Krivak, T. C. (2013). "Upfront treatment of locally advanced cervical cancer with intensity modulated radiation therapy compared to four-field radiation therapy: a cost-effectiveness analysis." Gynecol Oncol **129**(3): 574-579.

Li, X. A., Tai, A., Arthur, D. W. et al. (2009). "Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG Multi-Institutional and Multiobserver Study." Int J Radiat Oncol Biol Phys **73**(3): 944-951.

Lim, K., Erickson, B., Jürgenliemk-Schulz, I. M. et al. (2015). "Variability in clinical target volume delineation for intensity modulated radiation therapy in 3 challenging cervix cancer scenarios." Pract Radiat Oncol **5**(6): e557-565.

Lim, K., Kelly, V., Stewart, J. et al. (2009). "Pelvic radiotherapy for cancer of the cervix: Is what you plan actually what you deliver?" Int J Radiat Oncol Biol Phys **74**(1): 304-312.

Lim, K., Small, W., Jr., Portelance, L. et al. (2011). "Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer." Int J Radiat Oncol Biol Phys **79**(2): 348-355.

Lobefalo, F., Bignardi, M., Reggiori, G. et al. (2013). "Dosimetric impact of inter-observer variability for 3D conformal radiotherapy and volumetric modulated arc therapy: the rectal tumor target definition case." Radiat Oncol **8**: 176.

Logue, J. P., Sharrock, C. L., Cowan, R. A. et al. (1998). "Clinical variability of target volume description in conformal radiotherapy planning." Int J Radiat Oncol Biol Phys **41**(4): 929-931.

Loiselle, C. and Koh, W. J. (2010). "The emerging use of IMRT for treatment of cervical cancer." J Natl Compr Canc Netw **8**(12): 1425-1434.

Loo, S. W., Martin, W. M. C., Smith, P. et al. (2012). "Interobserver variation in parotid gland delineation: a study of its impact on intensity-modulated radiotherapy solutions with a systematic review of the literature." Br J Radiol **85**: 1070-1077.

Louie, K. S., Castellsague, X., de Sanjose, S. et al. (2011). "Smoking and passive smoking in cervical cancer risk: pooled analysis of couples from the IARC multicentric case-control studies. (International Agency for Research on Cancer Multicenter Cervical Cancer Study Group.)." Cancer Epidemiol Biomarkers Prev **20**(7): 1379-1390.

Lu, B., Kumar, A., Castellsague, X. and Giuliano, A. R. (2011). "Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis." BMC Infect Dis **11**: 13.

Lv, Y., Wang, F., Yang, L. and Sun, G. (2014). "Intensity-modulated whole pelvic radiotherapy provides effective dosimetric outcomes for cervical cancer treatment with lower toxicities." Cancer Radiother **18**(8): 745-752.

Ma, D. J., Michaletz-Lorenz, M., Goddu, S. M. and Grigsby, P. W. (2012). "Magnitude of interfractional vaginal cuff movement: implications for external irradiation." Int J Radiat Oncol Biol Phys **82**(4): 1439-1444.

Mayo, C. S., Zankowski, C., Herman, M. et al. (2013). "A method to vectorize the dose distribution, the dose volume histogram and create a dose vector histogram." Med Phys **40**(1): 011717.

McCormack, M., Brown, R. S. D. and Birtle, A. J. (2001). "A national audit of chemo-radiation practice for cervical carcinoma in the United Kingdom. Royal College of Radiologists Annual Scientific Meeting 2001." Clin Oncol **13**: 318-319.

McCormack, M., Kadalayil, L., Hackshaw, A. et al. (2013). "A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer." Brit J Cancer.

McCormish, E. (2011). "Cervical cancer: who's at risk?" Nurs Womens Health **15**(6): 476-483.

Mehmood, Q., Beardwood, M., Swindell, R. et al. (2014). "Insufficiency fractures in patients treated with pelvic radiotherapy and chemotherapy for uterine and cervical cancer." Eur J Cancer care **23**(1): 43-50.

Meijer, G. J., Rasch, C., Remeijer, P. and Lebesque, J. V. (2003). " Three-dimensional analysis of delineation errors, setup errors, and organ motion during radiotherapy of bladder cancer." Int J Radiat Oncol Biol Phys. **55**(5): 1277-1287.

Mitchell, D. M., Perry, L., Smith, S. et al. (2009). "Assessing the effect of a contouring protocol on postprostatectomy radiotherapy clinical target volumes and interphysician variation." Int J Radiat Oncol Biol Phys **75**(4): 990-993.

Morris, M., Eifel, P. J., Lu, J. et al. (1999). "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiaition for high-risk cervical cancer." New Engl J Med **340**(15): 1137-1143.

Mundt, A., Roeske, J. C., Lujan, A. E. et al. (2001). "Initial Clinical Experience with Intensity-Modulated Whole-Pelvis Radiation Therapy in Women with Gynecologic Malignancies." Gynecol oncol **82**(3): 456-463.

Mundt, A. J., Lujan, A. E., Rotmensch, J. et al. (2002). "Intensity-modulated whole pelvic radiotherapy in women with gynaecologic malignancies." Int J Radiat Oncol Biol Phys **52**(5): 1330-1337.

Mundt, A. J., Mell, L. K. and Roeske, J. C. (2003). "Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy." Int J Radiat Oncol Biol Phys **56**(5): 1354-1360.

Mutch, D. G. (2009). "The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas." Gynecol Oncol **115**(3): 325-328.

Nakamura, M., Fujii, T., Imanishi, N. et al. (2014). "Surgical anatomy imaging associated with cervical cancer treatment: A cadaveric study." Clin Anat **27**(3): 503-510.

NCI. (1999, cited 22nd Feb 1999). "NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival.", from http://www.nih.gov/news/pr/feb99/nci-22.htm.

Nogami, Y., Iida, M., Banno, K. et al. (2014). "Application of FDG-PET in Cervical Cancer and Endometrial Cancer: Utility and Future Prospects." Anticancer Res **34**(585-592).

O'Connell, H. E. and DeLancey, J. O. L. (2005). "Clitoral anatomy in the nulliparous, healthy, premenopausal volunteers using unenhanced magnetic resonance imaging." J Urol **173**: 2060-2063.

Oakeshott, P., Aghaizu, A., Reid, F. et al. (2012). "Frequency and risk factors for prevalent, incident, and persistent genital carcinogenic human papillomavirus infection in sexually active women: community based cohort study." BMJ **344**: e4168.

Oh, S., Stewart, J., Moseley, J. et al. (2014). "Hybrid adaptive radiotherapy with on-line MRI in cervix cancer IMRT." Radiother Oncol **110**(2): 323-328.

ONS. (2013). "Cancer Registration Statistics, England 2011.", from http://www.ons.gov.uk/ons/dcp171778_315795.pdf.

Peterson, R. P., Truong, P. T., Kader, H. A. et al. (2007). "Target volume delineation for partial breast radiotherapy planning: clinical characteristics associated with low interobserver concordance." Int J Radiat Oncol Biol Phys **69**(1): 41-48.

Peto, J., Gilham, C., Fletcher, O. and Matthews, F. E. (2004). "The cervical cancer epidemic that screening has prevented in the UK." Lancet **364**: 249-256.

Petric, P., Dimopoulos, J., Kirisits, C. et al. (2008). "Inter- and intraobserver variation in HR-CTV contouring: intercomparison of transverse and paratransverse image orientation in 3D-MRI assisted cervix cancer brachytherapy." Radiother oncol **89**(2): 164-171.

Petric, P., Hudej, R., Rogelj, P. et al. (2013). "Uncertainties of target volume delineation in MRI guided adaptive brachytherapy of cervix cancer: a multi-institutional study." Radiother Oncol **107**(1): 6-12.

Portelance, L., Chao, K. S. C., Grigsby, P. W. et al. (2001). "Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation." Int J Radiat Oncol Biol Phys **51**(1): 261-266.

Rai, B., Bansal, A., Patel, F. et al. (2014). "Pelvic nodal CTV from L4-L5 or aortic bifurcation? An audit of the patterns of regional failures in cervical cancer patients treated with pelvic radiotherapy." Jpn J Clin Oncol **44**(10): 941-947.

Rao, M., Stough, J., Chi, Y. Y. et al. (2005). "Comparison of human and automatic segmentations of kidneys from CT images." Int J Radiat Oncol Biol Phys **61**(3): 954-960.

Ray, A. and Sarkar, B. (2013). "Small bowel toxicity in pelvic radiotherapy for postoperative gynecological cancer: comparison between conformal radiotherapy and intensity modulated radiotherapy." Asia-Pac J Clin Oncol **9**(3): 280-284.

RCR (2008). Implementing image-guided brachytherapy for cervix cancer in the UK. The Royal College of Radiologists.

RCR IPEM SCoR (2008). On target: ensuring geometric accuracy in radiotherapy. London, The Royal College of Radiologists.

Roeske, J. C., Bonta, D., Mell, L. K. et al. (2003). "A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy." Radiother Oncol **69**(2): 201-207.

Roeske, J. C., Lujan, A. E., Rotmensch, J. et al. (2000). "Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies." Int J Radiat Oncol Biol Phys **48**(5): 1613-1621.

Ronco, G., Dillner, J., Elfström, K. M. et al. (2014). "Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials." Lancet **383**(9916): 524-532.

Rose, P. G., Bundy, B. N., Watkins, E. B. et al. (1999). "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer." New Engl J Med **340**(15): 1144-1153.

Roura, E., Castellsagué, X., Pawlita, M. et al. (2014). "Smoking as a major risk factor for cervical cancer and pre-cancer: results from the EPIC cohort. ." Int J Cancer **135**(2): 453-466.

Salama, J. K., Mundt, A. J., Roeske, J. and Mehta, N. (2006). "Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies." Int J Radiat Oncol Biol Phys **65**(4): 1170-1176.

Salama, J. K., Roeske, J. C., Mehta, N. and Mundt, A. (2004). "Intensity-modulated Radiation Therapy in Gynecologic Malignancies." Curr Treat Options Oncol **5**(2): 97-108.

Salz, H., Eichner, R. and Wiezorek, T. (2012). "Does IMRT increase the peripheral radiation dose? A comparison of treatment plans 2000 and 2010." Z Med Phys **22**(1): 6-12.

Sanguineti, G., Little, M., Endres, E. J. et al. (2008). "Comparison of three strategies to delineate the bowel for whole pelvis IMRT of prostate cancer." Radiother Oncol **88**: 95-101.

Saslow, D., Solomon, D., Lawson, H. W. et al. (2012). "American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer." CA: Cancer J Clin **62**(3): 147-172.

Schefter, T. E., Kavanagh, B. D., Wu, Q. et al. (2002). "Technical considerations in the application of intensity-modulated radiotherapy as a concomitant integrated boost for locally-advanced cervix cancer." Med Dosim **27**(2): 177-184.

Schreurs, L. M. A., Busz, D. M., Paardekooper, G. M. R. M. et al. (2010). "Impact of 18-fluorodeoxyglucose positron emission tomography on computed tomography defined target volumes in radiation treatment planning of esophageal cancer: reduction in geographic misses with equal inter-observer variability." Dis Esoph **23**: 493-501.

Screening and Immunisations team Health and Social Care Information Centre. (2013). "Cervical Screening Programme, England, 2012-13." Retrieved V1.0, from http://www.hscic.gov.uk/catalogue/PUB11889/cerv-scre-prog-eng-2012-13-rep.pdf.

Seddon, B., Bidmead, M., Wilson, J. et al. (2000). "Target volume definition in conformal radiotherapy for prostate cancer: quality assurance in the MRC RT-01 trial." Radiother Oncol **56**: 73-83.

Shaikh, T., Chen, T., Khan, A. et al. (2010). "Improvement in interobserver accuracy in delineation of the lumpectomy cavity using fiducial markers." Int J Radiat Oncol Biol Phys **78**(4): 1127-1134.

Sharfo, A. W., Voet, P. W., Breedveld, S. et al. (2015). "Comparison of VMAT and IMRT strategies for cervical cancer patients using automated planning." Radiother Oncol **114**(3): 395-401.

Shih, H. A., Harisinghani, M., Zietman, A. et al. (2005). "Mapping of nodal disease in locally advanced prostate cancer: rethinking the clinical target volume for pelvic nodal irradiation based on vascular rather than bony anatomy." Int J Radiat Oncol Biol Phys **63**(4): 1262-1269.

Shih, K. K., Folkert, M. R., Kollmeier, M. A. et al. (2013). "Pelvic insufficiency fractures in patients with cervical and endometrial cancer treated with postoperative pelvic radiation." Gynecol Oncol **128**(3): 540-543.

Simpson, D. R., Song, W. Y., Moiseenko, V. et al. (2012). "Normal tissue complication probability analysis of acute gastrointestinal toxicity in cervical cancer patients undergoing intensity modulated radiation therapy and concurrent cisplatin." Int J Radiat Oncol Biol Phys **83**(1): e81-86.

Small, W., Bosch, W. R., Strauss, J. B. et al. (2014). "Consensus Guidelines for Delineation of Clinical Target Volume for Intensity-Modulated Pelvic Radiation Therapy in Postoperative Treatment of Endometrial and Cervical Cancer- An Update." Int J Radiat Oncol Biol Phys **90**(1, Supplement): S109.

Small, W., Jr., Mell, L. K., Anderson, P. et al. (2008). "Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer." Int J Radiat Oncol Biol Phys **71**(2): 428-434.

Smith, J. S., Lindsay, L., Hoots, B. et al. (2007). "Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update." Int J Cancer **121**(3): 621-632.

Song, W. Y., Chiu, B., Bauman, G. S. et al. (2006). "Prostate contouring uncertainty in megavoltage computed tomography images acquired with a helical tomotherapy unit during image-guided radiation therapy." Int J Radiat Oncol Biol Phys **65**(2): 595-607.

Stewart, J., Lim, K., Kelly, V. et al. (2010). "Automated weekly replanning for intensity-modulated radiotherapy of cervix cancer." Int J Radiat Oncol Biol Phys **78**(2): 350-358.

Takiar, V., Fontanilla, H. P., Eifel, P. J. et al. (2013). "Anatomic distribution of fluorodeoxyglucose-avid para-aortic lymph nodes in patients with cervical cancer." Int J Radiat Oncol Biol Phys **85**(4): 1045-1050.

Tay, S. K. and Oon, L. L. (2014). "Prevalence of cervical human papillomavirus infection in healthy women is related to sexual behaviours and educational level: a cross-sectional study." Int J STD AIDS **25**(14): 1013-1021.

Taylor, A. and Powell, M. (2006). Uterus. Radiotherapy in practice: External beam therapy. P. J. Hoskin. Oxford, Oxford University Press**:** 235-243.

Taylor, A. and Powell, M. E. (2008). "An assessment of interfractional uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer." Radiother Oncol **88**(2): 250-257.

Taylor, A., Rockall, A. G. and Powell, M. E. (2007). "An atlas of the pelvic lymph node regions to aid radiotherapy target volume definition." Clin Oncol **19**(7): 542-550.

Taylor, A., Rockall, A. G., Reznek, R. H. and Powell, M. E. (2005). "Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy." Int J Radiat Oncol Biol Phys **63**(5): 1604-1612.

Tewari, K. S., Sill, M. W., Long, H. J., 3rd et al. (2014). "Improved survival with bevacizumab in advanced cervical cancer." New Engl J Med **370**(8): 734-743.

Thor, M., Petersen, J. B., Bentzen, L. et al. (2011). "Deformable image registration for contour propagation from CT to cone-beam CT scans in radiotherapy of prostate cancer." Acta Oncol **50**(6): 918-925.

Toita, T., Ohno, T., Kaneyasu, Y. et al. (2011). "A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer." Jpn J Clin Oncol **41**(9): 1119-1126.

Toita, T., Ohno, T., Kaneyasu, Y. et al. (2010). "A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer." Jpn J Clin Oncol **40**(5): 456-463.

Tsunoda, A. T., Andrade, C. E., Vieira, M. A. and Reis, R. D. (2015). "Laparoscopy in uterine cervical cancer. Current state and literature review." Rev Col Bras Cir **42**(5): 345-351.

Tyagi, N., Lewis, J. H., Yashar, C. M. et al. (2011). "Daily online cone beam computed tomography to assess interfractional motion in patients with intact cervical cancer." Int J Radiat Oncol Biol Phys **80**(1): 273-280.

Valley, J., Bernier, J., Tercier, P. A. et al. (1998). "Quality assurance of the EORTC radiotherapy trial 22931 for head and neck carcinomas: the dummy run." Radiother Oncol **47**(1): 37-44.

van de Bunt, L., Jurgenliemk-Schulz, I. M., de Kort, G. A. et al. (2008). "Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need?" Radiother Oncol **88**(2): 233-240.

van de Bunt, L., van der Heide, U. A., Ketelaars, M. et al. (2006). "Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression." Int J Radiat Oncol Biol Phys **64**(1): 189-196.

van Herk, M., Remeijer, P., Rasch, C. and Lebesque, J. V. (2000). "The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy." Int J Radiat Oncol Biol Phys **47**(4): 1121-1135.

Verma, J., Sulman, E. P., Jhingran, A. et al. (2014). "Dosimetric predictors of duodenal toxicity after intensity modulated radiation therapy for treatment of the para-aortic nodes in gynecologic cancer." Int J Radiat Oncol Biol Phys **88**(2): 357-362.

Villeirs, G. M., Van Vaerenbergh, K., Vakaet, L. et al. (2005). "Interobserver delineation variation using CT versus combined CT + MRI in intensity-modulated radiotherapy for prostate cancer." Strahlenther Onkol **181**(7): 424-430.

Vorwerk, H., Beckmann, G., Bremer, M. et al. (2009). "The delineation of target volumes for radiotherapy of lung cancer patients." Radiother Oncol **91**(3): 455-460.

Wagner, A., Jhingran, A. and Gaffney, D. (2013). "Intensity modulated radiotherapy in gynecologic cancers: hope, hype or hyperbole?" Gynecol Oncol **130**(1): 229-236.

Walboomers, J. M., Jacobs, M. V., Manos, M. M. et al. (1999). "Human papillomavirus is a necessary cause of invasive cervical cancer worldwide." J Pathol **189**: 12-19.

Warfield, S. K., Zou, K. H. and Wells, W. M. (2004). "Simultaneous truth and performance level estimation (STAPLE): an algorithm for the validation of image segmentation." IEEE Trans Med Imaging **23**(7): 903-921.

Weiss, E., Richter, S., Krauss, T. et al. (2003). "Conformal radiotherapy planning of cervix carcinoma: differences in the delineation of the clinical target volume." Radiother Oncol **67**(1): 87-95.

Wijesooriya, K., Weiss, E., Dill, V. et al. (2008). "Quantifying the accuracy of automated structure segmentation in 4D CT images using a deformable image registration algorithm." Med Phys **35**(4): 1251-1260.

Wu, D. H., Mayr, N., Karatas, Y. et al. (2005). "Interobserver variation in cervical cancer tumor delineation for image-based radiotherapy planning among and within different specialties." J App Clin Med Phys **6**(4).

Yu, C., Zhu, W., Ji, Y. et al. (2015). "A comparative study of intensity-modulated radiotherapy and standard radiation field with concurrent chemotherapy for local advanced cervical cancer." Eur J Gynaecol Oncol **36**(3): 278-282.

Zambrano, V., Furtado, H., Fabri, H. et al. (2013). "Performance validation of deformable image registration in the pelvic region." J Radiat Res **54**(Suppl 1): i120-128.

Zeng, X. T., Xiong, P. A., Wang, F. et al. (2012). "Passive smoking and cervical cancer risk: a meta-analysis based on 3,230 cases and 2,982 controls. ." Asian Pac J Cancer Prev **13**(6): 2687-2693.

Zwahlen, D. R., Ruben, J. D., Jones, P. et al. (2009). "Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer." Int J Radiat Oncol Biol Phys **74**(2): 539-545.

Appendices

Appendix 1: Table of articles on delineation variation quantification methods

Appendix 2: INTERLACE RTQA pack v1.4

Appendix 3: INTERLACE clinician experience/confidence questionnaire

9th June 2014

Dear Consultant Clinical Oncologist,

Whilst working with the INTERLACE RTQA team we appreciate that there are many areas of uncertainty with respect to contouring for 3D planning in cervical cancer. We are therefore updating the RTQA pack with detailed pictoral information regarding contouring and anatomy to help minimise the uncertainties.

To ensure we are including all relevant information we would be very grateful if you would complete this anonymised questionnaire, which will take less than 2 minutes, on the contouring for cervical cancer and return it to the clinical trials office in the enclosed self-addressed envelope.

Yours sincerely

Dr Gemma Eminowicz
Radiotherapy Research Fellow
University College London Hospital

Questionnaire regarding contouring for cervical cancer:

Date of completion	
Specialist Tumour sites	

No of years specialising in gynaecology oncology at consultant level	
Approximate no of cervical cancer cases treated with radiotherapy per year	
Have you completed the RTQA contouring cases for INTERLACE?	Yes	No
Do you already treat cervical cancer patients with IMRT?	Yes	No
Do you have a radiologist who can dedicate time to review cases with you?	Yes	No

Previous training on gynaecology anatomy or contouring:

Radiologist led session	Yes	No	if yes details:
Online course	Yes	No	If yes details:
Attended local course	Yes	No	if yes details:
Attended national course	Yes	No	if yes details:
Attended international course	Yes	No	if yes details:
Attended course for other tumour site	Yes	No	If yes details:
Self taught	Yes	No	

Level of confidence in identifying the following anatomical structures

Please score numerically

1 no confidence/unable to identify

2 minimal confidence/can occasionally identify

3 confident with most cases

4 confident in all cases with rare exceptions

	1	2	3	4	Please define if possible
aortic bifurcation					
iliac bifurcation					
inferior level of obturator nodes					
external iliac and inguinal node junction					
uterosacral ligaments					
mesorectum					
superior border of parametrium					
posterior border of parametrium					
inferior border of parametrium					
upper half of vagina					

Please list any particular areas of uncertainty that you would like us to address in the updated RTQA pack which has not been mentioned here already:

Appendix 4: Raw data for CTV to PTV margin analysis

SET UP ERROR

patient no	vertical	longitudinal	lateral	vert from mean	long from mean	lateral from mean
1	0	-0.1	0.1	0.089	-0.033	-0.122
1	-0.2	-0.1	0.5	-0.111	-0.033	0.278
1	-0.5	0.2	-0.1	-0.411	0.267	-0.322
1	-0.1	0	0.3	-0.011	0.067	0.078
1	0	-0.1	-0.1	0.089	-0.033	-0.322
1	-0.1	-0.1	0.2	-0.011	-0.033	-0.022
1	-0.1	-0.2	0.8	-0.011	-0.133	0.578
1	0.1	-0.3	0	0.189	-0.233	-0.222
1	0.1	0.1	0.3	0.189	0.167	0.078
2	0.1	-0.2	0.1	0	-0.318	0.19
2	0	0	-0.4	-0.1	-0.118	-0.31
2	0.2	0	0	0.1	-0.118	0.09
2	0.2	0.2	0	0.1	0.082	0.09
2	0.1	0.2	0.2	0	0.082	0.29
2	0.2	0.2	0.2	0.1	0.082	0.29
2	0	0	0.1	-0.1	-0.118	0.19
2	0.1	0.2	0.1	0	0.082	0.19
2	0	0.1	-0.2	-0.1	-0.018	-0.11
2	0.1	0.2	-0.1	0	0.082	-0.01
2	0.1	0.4	-0.1	0	0.282	-0.01
3	0	-0.2	0.1	0.1	-0.092	-0.15
3	-0.1	-0.3	0	0	-0.192	-0.25
3	-0.3	-0.1	0	-0.2	0.008	-0.25
3	-0.1	-0.1	0.2	0	0.008	-0.05
3	-0.1	-0.2	0.1	0	-0.092	-0.15
3	-0.2	-0.1	0.3	-0.1	0.008	0.05
3	-0.1	-0.1	0.1	0	0.008	-0.15
3	-0.1	0.2	-0.2	0	0.308	-0.45
3	-0.1	-0.2	0	0	-0.092	-0.25
3	-0.1	0.1	-0.2	0	0.208	-0.45
3	0	-0.1	-0.2	0.1	0.008	-0.45
3	0	-0.2	0.1	0.1	-0.092	-0.15
4	-0.1	-0.1	0.1	-0.14	-0.12	0.28
4	-0.2	-0.2	0	-0.24	-0.22	0.18
4	0.1	0	-0.5	0.06	-0.02	-0.32
4	0.1	-0.2	-0.3	0.06	-0.22	-0.12
4	0	0	-0.3	-0.04	-0.02	-0.12
4	0.1	0.4	0.1	0.06	0.38	0.28
4	0.2	0.1	0.1	0.16	0.08	0.28
4	0.1	0.5	-0.5	0.06	0.48	-0.32

4	0.1	-0.2	-0.4	0.06	-0.22	-0.22
4	0	-0.1	-0.1	-0.04	-0.12	0.08
5	-0.1	-0.3	-0.1	-0.39	-0.05	-0.06
5	0.4	-0.3	-0.3	0.11	-0.05	-0.26
5	0.5	-0.7	0	0.21	-0.45	0.04
5	0.3	0.1	0.5	0.01	0.35	0.54
5	0	0.1	0	-0.29	0.35	0.04
5	0.3	-0.1	-0.2	0.01	0.15	-0.16
5	0.2	-0.3	-0.1	-0.09	-0.05	-0.06
5	0.5	-0.1	-0.2	0.21	0.15	-0.16
5	0.3	-0.7	0	0.01	-0.45	0.04
5	0.5	-0.2	0	0.21	0.05	0.04
6	0.1	0	0.1	0.125	-0.025	-0.108
6	-0.1	-0.1	0	-0.075	-0.125	-0.208
6	0	-0.2	0.4	0.025	-0.225	0.192
6	0	0	0	0.025	-0.025	-0.208
6	0.1	0.3	0.5	0.125	0.275	0.292
6	0.1	0.2	0.2	0.125	0.175	-0.008
6	-0.2	0	0.4	-0.175	-0.025	0.192
6	0	0	0	0.025	-0.025	-0.208
6	-0.1	0.1	0.2	-0.075	0.075	-0.008
6	0.1	-0.1	0.1	0.125	-0.125	-0.108
6	-0.2	-0.5	0.3	-0.175	-0.525	0.092
6	-0.1	0.6	0.3	-0.075	0.575	0.092
7	-0.2	0	0	-0.15	0.158	-0.033
7	0	-0.1	-0.1	0.05	0.058	-0.133
7	-0.2	-0.1	0.1	-0.15	0.058	0.067
7	-0.2	-0.2	0.2	-0.15	-0.042	0.167
7	-0.1	0	-0.1	-0.05	0.158	-0.133
7	0	-0.4	0.3	0.05	-0.242	0.267
7	0.2	0	-0.1	0.25	0.158	-0.133
7	0.1	0	-0.1	0.15	0.158	-0.133
7	0	-0.3	-0.1	0.05	-0.142	-0.133
7	0.1	-0.2	0.3	0.15	-0.042	0.267
7	0.3	-0.1	0	0.35	0.058	-0.033
7	-0.6	-0.5	0	-0.55	-0.342	-0.033
8	0.1	-0.1	0.3	-0.02	-0.32	0.15
8	0.2	0.1	0.1	0.08	-0.12	-0.05
8	0	0.4	-0.4	-0.12	0.18	-0.55
8	0	0.3	0.2	-0.12	0.08	0.05
8	0.2	0.5	0.4	0.08	0.28	0.25
8	0.1	0.3	0.2	-0.02	0.08	0.05
8	0.1	-0.2	0.2	-0.02	-0.42	0.05
8	0.1	0.7	0.2	-0.02	0.48	0.05
8	0.3	0	0.2	0.18	-0.22	0.05

8	0.1	0.2	0.1	-0.02	-0.02	-0.05
9	0.2	-0.2	0.1	0.13	-0.13	0.06
9	0.3	-0.2	0.1	0.23	-0.13	0.06
9	0.1	-0.3	0.2	0.03	-0.23	0.16
9	0	0.2	0	-0.07	0.27	-0.04
9	0.2	0.4	-0.2	0.13	0.47	-0.24
9	0	0	0	-0.07	0.07	-0.04
9	0	-0.4	0.1	-0.07	-0.33	0.06
9	-0.3	0.6	-0.1	-0.37	0.67	-0.14
9	0.1	-0.1	0.1	0.03	-0.03	0.06
9	0.1	-0.7	0.1	0.03	-0.63	0.06
10	0.1	-0.2	0.1	0.027	-0.145	-0.08
10	0.1	-0.2	0.1	0.027	-0.145	-0.08
10	0.1	-0.1	0	0.027	-0.045	-0.18
10	0	0	0.1	-0.073	0.055	-0.08
10	0.1	-0.1	0.1	0.027	-0.045	-0.08
10	0.1	0.1	0	0.027	0.155	-0.18
10	0.1	0	0.1	0.027	0.055	-0.08
10	0.2	-0.1	0	0.127	-0.045	-0.18
10	0	-0.2	-0.1	-0.073	-0.145	-0.28
10	0	0.1	-0.1	-0.073	0.155	-0.28
10	0	0.1	-0.1	-0.073	0.155	-0.28

Individual mean set up errors ($m_{individual}$)

mean vert	mean long	mean lateral
0.1	0.118	-0.09
0.073	-0.055	0.18
0.12	0.22	0.15
-0.05	-0.158	0.033
0.29	-0.25	-0.04
-0.1	-0.108	0.25
0.04	0.02	-0.18
-0.089	-0.067	0.222
0.07	-0.07	0.04
-0.025	0.025	0.208

Individual random error ($\sigma_{individual}$):

vert	long	mean
0.17	0.29	0.17
0.08	0.18	0.14

0.09	0.18	0.13
0.16	0.24	0.23
0.16	0.21	0.28
0.11	0.16	0.27
0.25	0.16	0.18
0.10	0.22	0.29
0.16	0.12	0.32
0.06	0.11	0.22

	vert	long	lat
M_{pop}	0.04	-0.03	0.08
Σ_{setup}	0.12	0.14	0.15
σ_{set-up}	0.13	0.19	0.22
Margin (mm)	4	5	5

ORGAN MOTION ERROR

pt	SI	rightUT	leftUT	antUT	postUT	rightCX	leftCX	antCX	postCX
1	0.3	-0.2	0.3	1.2	-2.2			2.3	-1.3
1	0	-0.1	0.4	1.2	-2.1			-0.8	0.5
1	-1.4	-1.2	-3.8	-4.3	1.2			1.2	-0.95
1	0.4	1.2	-0.6	1.5	-2.1			1.2	-0.7
1	-1.4	1.6	-1.2	0.4	-0.4			1.1	-1.3
1	-1.3	1.7	-1.3	1.5	-1.9			0.5	-1.8
1	-1	0.7	-1	0.3	-1.1			1.5	-1
1	1.3	1	-0.8	0.8	-1.9			1.5	0.5
1	1.2	1.2	-1.7	0.3	-1.1			0.3	-0.6
1	0	-1.2	-3.8	-2.6	-0.1			1.4	-3.1
2	1.5	3.6	1.6	2.1	-1	3.2	4.2	1.4	0.1
2	2.2	3.3	1.3	3.1	-0.8	2.8	3.7	1.8	0.5
2	1.4	3.3	2.3	3	-1.7	2.9	3.8	2	-0.1
2	2.5	3.1	3.6	3.3	-1.3	2.6	3.5	2.2	-1.4
2	1.3	3.5	1.9	2.8	-1.8	2.7	3.5	1.7	-1
2	3.1	3	2.8	3.5	-2.2	2.7	3	1.8	0.1
2	3	2.8	1.9	6	-2.9	2.7	3.9	2.3	-1.4
2	3.9	3	1.7	6.2	-2.2	2.9	0	5.3	-2.5
2	2.7	2.8	0.7	5.7	-2.4	2.9	3.5	2.2	-0.5
2	3.8	3.6	0	6	-3.2	2.9	3.5	2.5	-0.8
2	4.7	3.3	0.7	5.8	-2.4	3	3.6	5.8	-1.5
3	2	0.9	4.9	4.3	-0.3				
3	1.3	-0.4	3.4	2.3	-0.5				
3	1.3	0.7	4.6	3.2	-0.8				
3	2.8	0.2	4.2	4.6	-0.3				
3	1.4	0.2	4.5	2.8	-0.1			0.2	0.6
3	3.4	0.1	3.4	5.2	-0.6	0.8	3	0.9	-0.7
3	2	0.3	4.1	3.6	-0.9	2	3.7	0.9	-0.1
3	1.6	0.6	3.6	2.9	-0.1	0	0	-0.2	-0.2
3	1.6	0.1	2.7	4.7	0.4	3.4	3.8	0.8	-0.2
3	3.9	0.4	1.6	4.5	-2.1	0.4	1.3	4.2	-0.1
3	2.8	0.4	2.8	4.3	-1	3	4	1.4	-1.4
3	3.2	0.1	1.7	5	-1.9	2.7	4.7	0.9	-0.2
4	0			-1.1	-0.2			1.1	0.6
4	1.6			3.7	-2.6			1.7	0
4	0.5			1.5	-1.4			0.2	0.9
4	2.1			2.2	-2.6			1.7	-0.4
4	3.1	2.9	1.3	6	-4.6			1.9	0.2
4	2.7	1.9	0.2	4.9	-1.5			1.4	0
4	2.8	2.8	1.2	6	-4.6			1.7	-1.11
4	-2.4							0.5	1.4
4	2.2			3.8	-4.7			2.4	-0.4

4	3.2	2.6	1	5.6	-4.8	1.7	0.1	3.8	0
4	3.8	3.5	0.4	5.5	-6.5			2.4	-0.4
5	1.4	0.7	1.3	3.1	-1.1	0	3.9	1.5	-1.1
5	-0.6	1	2.3	1.9	-0.1	0.4	2.9	1	-0.4
5	0	0	1.9	2	-1.8	0.2	3.8	1.8	0.2
5	-0.3	0.2	2.8	1	-1	0	3.5	1.1	-0.9
5	1	0.7	0.4	2.5	-2.9	0.2	2.5	1.8	-1.8
5	0.7	1.3	0.8	2.1	-2.2	-0.2	2.4	1.6	-1.4
5	1.1	0.8	1.5	1.6	-2.1	0	0.5	0.3	-1.7
5	-1.5	0.8	0.5	3.1	-3	1.3	-0.1	1.4	-3.8
5	1.4	0.3	2.2	0.5	-2.1	0.9	2.2	0.4	-0.8
5	1.2	-0.5	1.6	0.7	-2.3	0.2	3.2	0.9	-2.4
5	2.2	-0.9	0.5	1	-2.9	0.5	3.6	1.3	-2.4
5	0.8	0	1.2	1.4	-3.3	1	3.7	1.7	-3.6
6	-0.8	-3.9	-4	-1.2	2.3		0	-0.3	1.1
6	0	-3	-2.6	-0.4	1.4			-0.5	0.8
6	-1	-3.9	-6.8	-1.7	2			-0.8	0.6
6	0	-4.3	-2.9	-1.5	-2			-0.7	0.3
6	-0.4	-3.5	-2.5	-0.7	-1.6			-0.8	0.3
6	1							-0.8	1.4
6	0.2	-4.3	-4.2	-0.9	-3.3			-1.3	0.7
6	0.5	-4.7	-4.4	-1.4	-1.4			-1.6	1.1
6	-3.6			-3.6	2.5			0.2	-0.6
6	-0.6	-4.3	-4.3	-1.8	-0.1			-1.7	0.1
6	0.9							-0.5	1.4
7	0.6			-0.6	-0.5	-0.2	0	-0.6	-0.5
7	-0.3			0.9	-0.2	0.1	-0.5	-0.4	-2.2
7	-0.6			1.2	-0.1	-0.1	0	-0.7	-2
7	-0.2			0.9	0.2	-0.2	0.2	-1.2	-1.6
7	1			-1.2	-0.3	-0.3	0.2	-0.3	-1.2
7	-0.3			1	0.2	-0.2	0.8	-2	-2.6
7	-0.6			0.7	0.6	-0.2	-0.8	-1.9	-1.3
7	2.3			-1.1	-1.4	0.6	0.4	3.8	-0.6
7	0.5			-1.3	0.2	0.1	0.5	-0.8	-1.2
7	0.6			-0.2	0.1	0.3	0	-1	-3
7	0.6			-1.1	0.4	0.7	0	1.8	-1.5
7	0.4			-1.2	0.5	0.2	0.4	1.8	-1.2
8	-1.1			-3.4	-1.9	-0.1	-0.5	0	-0.2
8	0.9	2.1	0	2.5	-2.3	0.1	-0.4	0.6	-0.9
8	-0.4	4.7	-0.5	0.3	-1.1	0.7	-0.5	1.6	-0.4
8	0.4	4.3	-0.3	-1.2	-3.7	-0.4	-1.2	1.3	-2.5
8	-1.1			-2.5	-0.9	0.6	-0.7	0.4	-0.3
8	-0.6	-0.2	0.5	-1.8	-3	0.5	0.4	0.6	0.1
8	-0.2	0.5	-0.2	-1.3	-2.5	0.1	-0.2	0.5	-1.1
8	0.1			-3	-1.5	1.4	0.4	0.2	-0.7

8	0.2	4.5	-0.4	-1.4	-0.8	-0.7	-1.8	1.8	-1.5
8	0.4	0	-0.1	-1	-2	-0.7	-1.3	1.3	-1.4
9	-0.2	-2.7	-1.2	-4.2	-0.9			1.3	-0.9
9	-0.5		-3.9	-6.3	-1.1			1.3	-2.5
9	0	0.2	1.4	0.7	-1.3	2.6	3.6	6.2	-1.5
9	-1.3	-0.9	-0.1	-2.4	-0.4			1.5	-1.1
9	-0.6	-2.9	-1.3	-4.9	-0.7			0.3	-1.9
9	-0.2			-7.4	-1			0.7	-1.7
9	-2.4			-7.9	-0.2			0.3	-1.1
9	-0.6			-6.8	-0.7			0.7	-1.5
9	-1.3			-8	-0.5			0.4	-1.2
9	0.6	-0.3	1.2	0.2	-0.8			0.8	-1
9	1.6	0.6	-0.9	0.9	-2.6	2.8	3.5	6.6	-1.2
10	-0.2					0.4	0.1	0.3	0.6
10	0.1					2.2	0.3	0	0.2
10	-0.1					4.5	0.4	0.5	-0.3
10	1					4.1	0.4	0.6	-0.3
10	0.1					0	-1.8	0.3	0.2
10	0.8					4.5	0.5	0.5	0
10	-0.8							-1.1	0.6
10	0.1							-0.8	0.5
10	0					-0.9	0.5	-0.3	0.2

individual means

patient	rightUT	leftUT	antUT	postUT	rightCX	leftCX	antCX	postCX	SI
	-1.709	0.5	-4.191	-0.927	0	-0.218	1.827	-1.418	-0.445
	3.209	1.682	4.318	-1.991	0.164	-0.464	2.636	-0.773	2.736
	-1.05	0.25	0.2	-0.8	-0.318	0.291	1.709	0.72	1.782
	0.367	1.417	1.742	-2.067	0.375	2.675	1.233	-1.675	0.617
	-1.1	-1.05	3.95	-0.683	-0.163	-0.375	1.138	-0.288	-0.345
	-0.6	-0.34	-0.78	0.06	-1.527	-1.245	0.573	0.509	0.333
	0.175	-1.025	-0.167	-0.025	0.67	0.1	-0.125	-1.575	-0.14
	-0.28	1.37	0.05	-0.28	0.15	-0.58	0.83	-0.89	0.111
	-0.378	0.222	0.489	0.122	-0.189	-0.367	-0.067	0.111	-0.19
	0.47	-1.35	0.03	-1.17	0.06	0.22	0.46	-0.66	2.275
pop mean	-0.0896	0.1676	0.5641	-0.7761	-0.0778	0.0037	1.0214	-0.5939	0.6734

deviation from pop mean

patient	rightUT	leftUT	antUT	postUT	rightCX	leftCX	antCX	postCX
	-1.6194	0.3324	-4.7551	-0.1509	0.0778	-0.2217	0.8056	-0.8241
	3.2986	1.5144	3.7539	-1.2149	0.2418	-0.4677	1.6146	-0.1791
	-0.9604	0.0824	-0.3641	-0.0239	-0.2402	0.2873	0.6876	1.3139
	0.4566	1.2494	1.1779	-1.2909	0.4528	2.6713	0.2116	-1.0811
	-1.0104	-1.2176	3.3859	0.0931	-0.0852	-0.3787	0.1166	0.3059
	-0.5104	-0.5076	-1.3441	0.8361	-1.4492	-1.2487	-0.4484	1.1029
	0.2646	-1.1926	-0.7311	0.7511	0.7478	0.0963	-1.1464	-0.9811
	-0.1904	1.2024	-0.5141	0.4961	0.2278	-0.5837	-0.1914	-0.2961
	-0.2884	0.0544	-0.0751	0.8981	-0.1112	-0.3707	-1.0884	0.7049
	0.5596	-1.5176	-0.5341	-0.3939	0.1378	0.2163	-0.5614	-0.0661
pop mean	1.350641	1.099799	2.417147	0.792008	0.584726	1.039398	0.871703	0.847727

individual random errors:

ID	SI	rightUT	leftUT	antUT	postUT	rightCX	leftCX	antCX	postCX
	1.04534	1.33900	0.87977	3.502129	0.63889	0.228035	0.188776	2.29917	0.472902
	1.10749	0.29139	1.01569	1.595505	0.75558	0.269343	0.874383	1.477344	0.895646
	1.79767					0.423835	0.398634	0.978217	0.692952
	1.03030	0.64149	0.78257	0.871215	0.94708	0.465393	1.294832	0.508712	1.213653
	0.90667	0.42817	0.42238	0.954892	0.72843	0.290637	0.363068	1.200347	0.477605
	1.2612	0.73361	0.29449	0.43212	0.26492	0.601815	0.914728	0.945612	0.590685
	0.8195	0.51720	0.66895	1.027206	0.5429	0.331205	0.43275	1.719474	0.754532
	0.6637	0.71771	0.74841	0.865705	0.9235	0.667083	0.708363	0.620125	0.77093
	0.53020	0.47900	0.29907	0.355121	0.35629	0.261937	0.141421	0.421307	0.169148
	1.03435	1.0822	1.45010	1.932212	1.11659	0.183787	0.311983	0.794705	0.952424
mea	1.01964	0.69220	0.7290	1.281789	0.69714	0.372307	0.562894	1.096501	0.699048
	SI	rightUT	leftUT	antUT	postUT	rightCX	leftCX	antCX	postCX
	1.01964	0.69220	0.72905	1.281789	0.69714	0.372307	0.562894	1.096501	0.699048

	Σ	Σ if blad<300	σ	σ if blad<300cc
SI	1.189667	0.377864	0.996898	0.970108
rightUT	0.428572	0.369583	0.690098	0.79927
leftUT	0.693815	0.814185	0.809421	0.736291
antUT	1.378516	0.449026	1.02652	0.828566
postUT	1.237222	0.501387	1.079984	0.735029
rightCX	0.168973	0.138662	0.280756	0.300057
leftCX	0.417894	0.434994	0.330512	0.336452
antCX	1.033699	0.977853	0.585862	0.624323
postCX	0.757687	0.856214	0.605692	0.595167

Margin (cm)	margin if Σ bl<300	Set-up margin (cm)	Total margin (cm)

SI	3.7	1.6	0.5	2.1
rightUT	1.6	1.4	0.5	1.9
leftUT	2.3	2.6	0.5	3.1
antUT	4.2	1.8	0.4	2.2
postUT	3.8	2.0	0.4	2.4
rightCX	0.6	0.5	0.5	1.0
leftCX	1.3	1.3	0.5	1.8
antCX	3.0	2.9	0.4	3.3
postCX	2.3	2.6	0.4	3.0

Publications