The Dosimetric Consequences of Intensity Modulated Radiotherapy for Cervix Cancer

The Impact of Organ Motion, Deformation and Tumour Regression

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science
Institute of Medical Sciences
University of Toronto

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University of Toronto
2010

Abstract

Hypothesis: In intensity modulated radiotherapy (IMRT) for cervix cancer, the dose received by the tumour target and surrounding normal tissues is significantly different to that indicated by a single static plan. Rationale: The optimal use of IMRT in cervix cancer requires a greater attention to clinical target volume (CTV) definition and tumour & normal organ motion to assure maximum tumour control with the fewest side effects. Research Aims: 1) Generate consensus CTV contouring guidelines for cervix cancer; 2) Evaluate intra-pelvic tumour and organ dynamics during radiotherapy; 3) Analyze the dose consequences of intra-pelvic organ dynamics on different radiotherapy strategies. Results: Consensus CTV definitions were generated using experts-in-the-field. Substantial changes in tumour volume and organ motion, resulted in significant reductions in accumulated dose to tumour targets and variability in accumulated dose to surrounding normal tissues. Significance: Formalized CTV definitions for cervix cancer is important in ensuring consistent standards of practice. Complex and unpredictable tumour and organ dynamics mandates daily soft-tissue image guidance if IMRT is used. To maximize the benefits of IMRT for cervix cancer, a strategy of adaptation is necessary.
Acknowledgments

I wish to thank my supervisors Dr Michael Milosevic and Dr Anthony Fyles for their generous time, advice and mentorship through out this fantastic research adventure.

Special thanks to the members of my research team: Valerie Kelly, Jason Xie, James Stewart, Young-Bin Cho, Kristy Brock and Joanne Moseley.

Thanks to the Giovanni and Concetta Guglietti Family Cancer Fund, EIRR21 and the PMH Foundation for the financial support throughout my Masters and Fellowship.

Last but certainly not least, a heartfelt thanks to my wonderful husband Tony (I count my blessings every day) and my mischievous little daughter Mika (who keeps me grounded, figuratively & literally in the best possible way).
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List of Abbreviations

3D: Three dimensional

3DCRT: Three dimensional conformal radiotherapy

90PI: 90% prediction interval

95% CI: 95% confidence interval

CBCT: Cone-beam computer tomography

cGy: Centi-gray

CTCAE v3.0: Common Terminology Criteria for Adverse Events version 3.0

COM: Centre of mass

CT: Computed tomography

CTRT: chemoradiation

CTV: Clinical target volume

D98: Dose to 98% volume

DNA: Deoxyribonucleic acid

EFRT: Extended field radiotherapy

EM: Expectation maximisation algorithm

FDG-PET: Fluorine-18-labeled fluoro-2-deoxy-D-glucose positron emission tomography

FFB: Four-field box

FIGO: International Federation of Gynecology and Obstetrics
GI: gastrointestinal
GU: genitourinary
GTV: Gross tumour volume
Gy: Gray
IMRT: Intensity modulated radiotherapy
ITV: Internal target volume
kV: Kilovoltage
LM: Large margin
LN: Lymph nodes
MORFEUS: Multi-Organ Finite Element Model-based Deformable Image Registration
MRI: Magnetic resonance imaging
MV: Megavoltage
NCI CTCv2.0: National Cancer Institute Common Toxicity Criteria version 2.0
nCTV: Nodal clinical target volume
OAR: Organs at risk
ORBIT: Optimisation of Radiotherapy Beams by Iterative Techniques
POI: Point of interest
pCTV: Primary clinical target volume
RTOG/ EORTC: Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer
SD: Standard deviation

SM: Small margin

STAPLE: Simultaneous truth and performance level estimation

V45: Volume receiving 45 Gy

WPRT: Whole pelvis radiotherapy
Chapter 1
Introduction/ Literature Review
1 Overview

Advanced cervix cancer has traditionally been treated with concurrent chemoradiation (CTRT). The radiotherapy fields used have encompassed the entire pelvis, with little sparing of the normal tissues such as bladder and bowel. The toxicity associated with this treatment has limited the aggressiveness of the curative approach. Intensity modulated radiotherapy (IMRT), with its ability to sculpt radiotherapy fields to conform closely to the tumour target, potentially allows for greater sparing of normal tissues while escalating dose to the site of gross disease. However, any organ motion in the setting of such conformal treatment potentially risks geographical target miss and compromised outcomes. Cervix cancer is one site where primary tumour and normal organ motion can be substantial, both at the tumour target, and the surrounding normal tissues. In order to maximise the advantages of IMRT, a clearer understanding of the intra-pelvic organ dynamics that occur during radiotherapy is essential. Cervix cancer presents a particular challenge as the target volume is often large and complex, and the tumour often demonstrates marked regression, deformation and motion over a course of treatment. The surrounding normal tissues also display substantial motion during treatment and are often the dose limiting structures for the treatment plan. Being able to map the dose consequences of organ motion in the setting of an IMRT plan, would provide valuable information on how to safely and effectively institute IMRT for gynaecologic cancers.

1.1 Incidence and Mortality of Cervix Cancer

Cervix cancer remains a serious health problem among women worldwide despite advances in screening and management. It is the 7th most common cancer in the world and the 2nd most common cancer among women (1). Incidence and mortality rates vary widely across different countries. In less developed countries (such as in Africa), the incidence is as high as 29.3 per 100 000 person-years, with an associated mortality rate of 23.1 per 100 000 person-years. In contrast, more developed countries (such as North America) demonstrate an incidence rate of 7.7 per 100 000 person-years and a mortality rate of 2.3 per 100 000 person-years. (1) In Canada, the incidence and mortality of cervix cancer has been declining at 2.3% and 3.3% per year.
respectively, however it remains the 4th most common cancer in women aged 15-29 years (2). The lower rates seen in developed countries can largely be attributed to screening programs (Papanicolaou test). While the introduction of human papilloma virus (HPV) vaccines can contribute to further declines in the incidence and mortality, it will not eliminate cervix cancer entirely. As such, strategies to maximise the efficacy and minimise the toxicity of treatment remain important goals.

1.2 Treatment and Associated Morbidity

1.2.1 Surgery

Cervix cancer was traditionally treated with surgery alone (radical hysterectomy, bilateral salpingo-oophorectomy and lymph node dissection). For early stage disease, the outcomes are excellent, with 5-year overall survival rates of over 80% (3). Consequences of such surgery include infertility and menopausal symptoms (in pre-menopausal women), lymphodema and other surgical complications. Of late, there has been a trend toward lesser surgery such as trachelectomy (for early stage patients who wish to preserve their fertility) and minimally invasive robotic surgery (4-6). Surgical outcomes are substantially worse for patients with more extensive disease (with parametrial invasion, pelvic or para-aortic lymph node metastases), with survival rates approaching 50-70% (7). The risk of loco-regional recurrence when operating on more advanced stages of disease may be lessened with the addition of adjuvant radiation therapy, but at the increased cost of both acute and long term toxicity (8). In light of this, chemoradiation (CTRT) has been used to manage patients who are not considered operable candidates, with outcomes comparable to, or better than surgery alone (9, 10).

1.2.2 Radiation – Current status

1.2.2.1 External Beam and Chemotherapy

While non-bulky early stage cervix cancer can be treated with surgery, radiotherapy (external beam and brachytherapy) has formed an integral component of treating the more advanced stages of this disease since the 1930’s. Meig and Dresser first published their experience with kilovoltage external beam radiation in combination with brachytherapy in 1937, detailing their methodology and outcomes in 70 patients (11). While technological advances in radiotherapy
delivery (such as megavoltage linear accelerators and high dose rate brachytherapy) have occurred over the decades, the treatment fields and volumes have remained largely unchanged. A clinical alert was issued in 1999 by the National Cancer Institute. It recommended the addition of chemotherapy based on the results of five major randomized controlled trials (7, 12-15) that demonstrated a survival advantage to combined treatment with radiotherapy and concurrent cisplatin-based chemotherapy compared to radiation alone. Standard of care rapidly became CTRT, and remains the mainstay of treatment for more advanced stages. While there was no statistically significant difference in acute grade 1 and 2 gastrointestinal (GI) or genitourinary (GU) toxicity with CTRT, there was a significant two-fold increase in acute grade 3 or 4 GI and haematological toxicity with CTRT. Late grade 3 or 4 toxicity was reported to affect up to 23% of patients undergoing CTRT (16).

External beam radiotherapy treatment fields have not altered substantially for many years. The standard pelvic field irradiates the cervix, entire uterus, upper vagina, parametrial tissues and draining regional lymph nodes [Figure 1.1]. In order to encompass these tissues, significant portions of bowel, rectum and bladder are also included in the high dose volume. Loco-regional failure rates with CTRT approach 35% at 5 years for some of these patients (17). Overall, despite improved outcomes with the addition of chemotherapy, a substantial proportion of patients with cervix cancer continue to develop recurrent disease after treatment with radiotherapy, often in the pelvis (17). The morbidity and mortality associated with such events are substantial and salvage therapies remain limited. This highlights a persistent problem in the treatment of cervix cancer that in part reflects an inability to deliver sufficient dose to tumour-bearing regions without exceeding critical normal tissue tolerances.

1.2.2.2 Brachytherapy

Brachytherapy forms an intrinsic component of cervix cancer treatment. As the applicator is in close proximity to the tumour target, it is able to deliver high doses of radiation to adjacent tissues with the rapid dose drop-off potentially sparing surrounding normal organs. Motion issues are rarely a problem as the applicator housing the radiation source lies within the cervix and uterus and moves with the treatment target. A major constraint with brachytherapy, however, has been the delivery of sufficient dose to large tumours while at the same time limiting dose to surrounding normal tissues that lie in close proximity to the applicator. The emergence of image
Figure 1.1. Axial (top) and sagittal (bottom) images of a female pelvis demonstrating the dose distribution from a conventional four-field radiotherapy plan. Colourwash represents percentage of prescribed dose: 100% (red); 95% (orange); 90% (yellow); 80% (green); 60% (light blue); 40% (dark blue). Surface meshes represent intra-pelvic organs: bladder (green); uterus (dark blue); vagina (pink); gross tumour volume (red); cervix (khaki); recto-sigmoid (cyan).
guided brachytherapy has partially overcome this problem by enabling better characterisation of the normal tissue dose-volume relationships and optimisation of dose to tumour targets (18-21). However, there is still a limit to how well the brachytherapy dose can be optimised, particularly when normal tissues lie adjacent to the target volume.

Therefore, ‘protecting’ the critical normal tissue during the external beam portion of radiation treatment through the use of more conformal approaches opens the door to dose escalation leading to improved local control and survival. This is particularly so for those patients with more advanced disease.

1.3 Current Developments in External Beam Radiation Treatment for Cervix Cancer

Efforts to refine the external beam radiation used in treating cervix cancer have progressed from a simple four-field box (FFB) technique, irradiating the entire pelvic contents including the normal tissues, to more three-dimensionally conformal radiotherapy (3DCRT) through the use of computed tomography (CT) imaging and planning. While 3DCRT allows for greater normal tissue sparing, the field arrangements have remained largely unchanged. A substantial amount of bladder and bowel continue to be unnecessarily irradiated due to the limited ability of standard radiation beam arrangement to conform to complex target volumes. The emergence of intensity modulated radiotherapy (IMRT) has resulted in a paradigm shift in treatment techniques. It has been increasingly used in a number of tumour sites to enable dose escalation as well as sparing of normal tissues (e.g. head and neck cancer and prostate cancer). It has also been explored for cervix cancer treatment.

1.3.1 Imaging Modalities for Cervix Cancer

The International Federation of Gynecology and Obstetrics (FIGO) staging for cervix cancer is primarily based on clinical evaluation and the imaging modalities permitted for consideration are only intravenous urograms and radiographic evaluations of the lung and skeleton. Despite this, the value of additional imaging to determine extent of disease at the time of diagnosis is well recognised. The presence of regional or distant metastases at diagnosis can substantially alter treatment techniques and radiotherapy volumes. In the setting of highly conformal radiation
treatment, high quality soft tissue imaging becomes an essential tool in creating the optimal radiotherapy plan.

The predominant imaging modalities in this setting are CT, magnetic resonance imaging (MRI) and fluorine-18-labeled fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET).

1.3.1.1 Computed Tomography (CT)

CT has the advantage of being widely available and readily accessible in virtually all radiation treatment centres. The pelvic soft tissue image quality is acceptable for the purposes of radiotherapy planning. Added advantages of CT are the electron density data and the lack of image distortion, which makes it valuable for radiotherapy planning and dose calculation.

Unfortunately there are limitations to the degree of soft tissue discrimination possible with CT. It can be very difficult to identify boundaries between soft tissue structures in the pelvis, determining the extent of tumour invasion into surrounding normal tissues and identifying lymphatic metastases when the nodes are <1 cm in short axis dimension. CT scanning also exposes the patient to radiation, although this is many times less than the dose of radiation the patient will receive therapeutically for cancer treatment.

1.3.1.2 Magnetic Resonance Imaging (MRI)

MRI has largely replaced CT as the optimal soft tissue imaging tool for cervix cancer. [Figure 1.2] There is ample evidence of it’s superiority over CT when it comes to detecting soft tissue boundaries and the extent of tumour invasion into surrounding tissues (22-29). Comparisons between pre-operative MRI and histopathological assessments of tumour size have shown that MRI is up to 93% accurate in determining tumour size to within 5 mm (28). An overestimation of tumour size on MRI by up to 19% is possible due to the inability of MRI to distinguish between inflammation and oedema (28). Aside from the clear advantage of better image quality, MRI also has the advantage of not exposing the patient to radiation. On the other hand, MRI availability is more limited than CT and the cost can be prohibitive in some health care systems. The MRI scanner may be poorly tolerated by claustrophobic patients and the presence of internalized medical devices that are sensitive to strong magnetic fields excludes some patients from being scanned. There can be nonlinearities and distortion artefacts as inherent consequences of the imaging process and the quality of the image obtained can be degraded by
Figure 1.2. Comparison of CT (left) versus MRI (right) axial images of cervix cancer patient. Soft tissue details such as myometrial invasion (white arrows) and early parametrial invasion (black arrows) are much better appreciated on MRI.
motion artefacts such as breathing and bowel peristalsis. Patients undergoing radiotherapy will still need to have a CT scan done for the purposes of planning as current radiation treatment planning systems are unable to generate the information required for dose calculation from MRI data sets.

1.3.1.3 Fluorine-18-labeled fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG-PET)

FDG-PET exploits the high rate of glucose uptake that is characteristic of most tumours, including cervix cancer, to provide information about metabolism that complements anatomical data obtained using other imaging modalities. FDG-PET is increasingly being used in cervix cancer. Its main strength is in locally advanced disease, where the detection of regional or distant metastases can result in a significant alteration in the treatment plan (30, 31), or in the detection of recurrent disease (32). In early stage disease, its utility is less well defined due to the difficulties with image resolution (33, 34). The excretion of the imaging agent into the bowel, kidneys and bladder can also present difficulties in interpreting the extent of primary disease, although emptying the bladder (either voluntarily or with catheterization) helps. The spatial resolution of PET also limits its utility in providing anatomical soft tissue details of the primary tumour (30), although registering the PET images to CT images obtained at the same time can partially mitigate this problem.

1.3.2 Intensity Modulated Radiotherapy (IMRT)

The major advantage of IMRT is the ability to spatially and temporally modify the beam fluence, which introduces additional degrees of freedom for treatment planning and delivery in addition to field position, size and shape. This provides the ability to create sculpted conformal radiotherapy beams, which enable sparing of surrounding normal tissues due to steep dose gradients around target and normal tissue volumes. The treatment of concave target volumes, selective dose-painting and concurrent boosting of smaller targets within a larger target structure also becomes possible.

While traditional 3DCRT fields irradiated the entire pelvis at the cost of increased normal tissue dose, they were less sensitive to uncertainties in target localization at the time of planning and
target motion during treatment. The use of IMRT necessitates explicit contouring of the tumour target volume (CTV) as well as any normal tissues that need to be spared. In order to maximally exploit the advantages of dose escalation and normal tissue sparing with IMRT, smaller planning target volume (PTV) margins are necessary. As conformality increases, sensitivity to inter-fraction organ motion also increases. In order to deliver the complex beam arrangements associated with IMRT, treatment delivery times are prolonged, increasing the possibility that intra-fraction tumour or normal tissue motion will result in compromised dosimetry. A reduction in the margin that would normally allow for uncertainties in target positioning during treatment can result in geographical target miss in the event of unforeseen or unrecognised organ or target motion. The consequences of this are potentially disastrous for the patient. IMRT also increases the integral dose delivered to the tissues surrounding the target volume, potentially increasing the risk of secondary malignancies (35).

While IMRT has been investigated both in planning and clinical studies of cervix cancer, the cautions highlighted above mean that the adoption of this treatment technique is far from straightforward.

### 1.4 Tumour & Organ Dynamics

Tumour and normal organ motion and deformation remain an unexplored confounder in the planning studies that have compared IMRT with traditional pelvic radiotherapy fields. In addition, cervix cancer can regress substantially during a course of radiotherapy. As a result, estimates of tumour and normal tissue dose derived using a single image set prior to starting treatment, as in most studies to date, are likely to be quite different to those actually delivered in a clinical setting.

#### 1.4.1 Tumour Regression

Cervical tumour regression during external beam radiotherapy can be substantial (36-41). While often clinically assessable (42), the true extent of the regression can best be appreciated on repeat imaging, with MRI being the preferred modality (26, 38, 43-47). Volume reductions of 50% after 30 Gy (41) and up to 80% following 45-50 Gy have been reported (37, 40). This tumour
regression is often asymmetric (39), making predictions of volume and size changes during treatment difficult.

Tumour regression can impact the movement of other parts of the CTV, particularly the uterus (48). As tumour shrinks, the formerly upright or retroverted uterus can attain an anteverted position, resulting in a substantial change in target shape. This is separate from the influence that surrounding normal organs (such as differences in bladder and rectal filling) may have on target positioning. [Figure 1.3]

Figure 1.3. This patient had a very upright uterus position at the start of radiation treatment (a). As treatment progressed, the tumour regressed and the uterus became more anteverted, despite little change in bladder filling (c). In the final week of treatment, the anteverted position of her uterus was exaggerated by an empty bladder (d).
1.4.2 Tumour (Uterus and Cervix) Motion

Several imaging modalities have been used to visualise uterus and cervix motion during radiotherapy including, orthogonal X-rays (42, 49, 50), CT (51-53) and MRI (48, 54-56). Different methodologies have been used to characterize uterus and/ or cervix motion, ranging from point of interest (POI) analyses (using tumour surrogates like fiducial markers (42, 49, 50) or anatomical landmarks (48, 52, 54, 55)), to centre of mass (COM) (51) and perimeter displacement techniques (51, 53, 56, 57). As imaging modalities have improved, a greater appreciation for the potentially large range of motion exhibited by the uterus and cervix has emerged.

Studies using orthogonal X-rays and fiducial markers (either gold seeds or a uterine sleeve) have reported random standard deviations for marker displacements up to 5.2 mm in the cranial-caudal direction (49, 50). Maximum inter-fraction displacements of the cervix of up to 36 mm have been seen during external beam radiotherapy (42). An obvious limitation to the use of fiducial markers is the inability to visualise the tumour directly. The reliance on fiducial markers means that only the tumour/cervix motion is able to be assessed. Fiducials often fall out or shift during treatment, further limiting their usefulness. Kaatee et al (49) reported that 42% of their markers were lost during the course of their study.

Studies using CT have focused on uterus or tumour/cervix motion, attempting to describe the movement through changes in COM or perimeter displacements (51-53). Buchali et al (52) investigated 29 women with cervical or endometrial cancer who were being treated either definitively or post-operatively with radiation. These women underwent two CT scans in the prone position. The initial scan was with the bladder and rectum empty, the second scan was with the bladder and rectum manually filled (mean volumes 190 cm$^3$ and 20 cm$^3$ respectively). In the 14 women with an intact uterus, they found the median movement of the cervix to be 4 mm superiorly and the median uterus movement to be 7 mm superiorly and 4 mm posteriorly, when referenced to bony landmarks. Lee et al (53) performed weekly CTs on 13 women undergoing definitive radiotherapy for cervix cancer. The position of the uterus at each weekly CT was compared to the planning CT. Measurements were taken from the isocentre to the boundary of the uterus. They found that uterus motion could range up to 4.5 cm in the sup-inf direction and 2.8cm in the ant-post direction. Beadle et al (51) in their study of 16 cervix cancer patients who
underwent weekly CT scanning during definitive radiotherapy, found mean maximum changes in COM for the cervix of 2.1 cm sup-inf and 1.6 cm ant-post. They noted that the COM of the cervix shifted by a mean of 0.55 cm inferiorly and 0.39 cm anteriorly when the bladder was emptied. While CT provides much greater soft tissue information than fiducial markers, discrimination between tumour/ cervix/ uterus and the other CTV components remains suboptimal compared to MRI (26, 38, 43-45, 58).

MRI has been used to comprehensively explore inter- and intra-fraction motion of the cervix and uterus during radiotherapy (48, 54-56). Huh et al (48) reported one of the few studies that looked at rotational changes in uterus position (changing from an anteverted to retroverted position) or changes in uterine angle of flexion (>30º variation). They found that up to 18% of cervix cancer patients undergoing radical radiotherapy demonstrated these changes. They only imaged their patients twice, once prior to starting treatment and again in the 3rd or 4th week of radiotherapy. Chan et al (54) measured inter- and intra-fractional motion of the cervix and uterus in 20 patients using weekly cine-MRIs. This was a POI analysis that traced the displacement of the cervical os, uterine canal and uterine fundus relative to bony reference points. They found intra-fraction organ motion to be relatively small (<10 mm) but inter-fraction motion ranged up to 4 cm for the uterine fundus, implying that large margins would be required to compensate for this motion unless daily soft tissue image guidance was used. Van de Bunt et al (56) did not characterize tumour motion per se, but rather assessed GTV and CTV perimeter change using serial MRI scans. An anisocentric margin of 8-24 mm around the CTV and 4-14 mm around the GTV was necessary to encompass all the observed motion in a cohort of 20 cervix cancer patients undergoing definitive radiotherapy. Taylor and Powell (55) performed MRI scans on 33 patients with gynaecological cancers on two consecutive days. Three POIs were identified on the anterior uterine body, posterior cervix and upper vagina. They found the mean displacement of the uterine body POI to be 7 mm ant-post and sup-inf. For the cervix POI, mean displacements were 4 mm sup-inf and 2.7 mm ant-post. Kerkhof et al (57) also measured intra-fractional motion of the CTV (GTV, uterus, vagina and parametrial tissues) in 22 patients using three MRI scans done at baseline and during weeks 1 and 4 of radiotherapy. A total of 60 MRI scans were analysed and the maximum residual CTV motion after bony registration for 90% of the scans was 9.9 mm. This motion was at the region of the uterine fundus.
These studies demonstrate that the range of motion exhibited by the tumour/cervix and uterus can be substantial. As imaging modalities have improved, the extent of motion (particularly for the uterus) has been better appreciated. This motion, if not anticipated and compensated for, could contribute to target miss with the use of highly conformal radiation treatment. Most of these studies have been limited in the number of scans acquired to measure organ motion, Chan et al (54) and van de Bunt (56) being the only two in which weekly MRI scans were obtained. While a number of authors have characterized tumour regression, few have looked at it in conjunction with tumour motion (42, 51). The asymmetric and highly individualized nature of cervix tumour regression during radiotherapy (39) would also confound some of the cervix motion reported from POI or COM displacements.

Table 1.1. Summary of studies looking at inter-fraction motion of the uterus and cervix.

Table 1.2. Summary of studies looking at intra-fraction motion of the uterus and cervix.
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Modality</th>
<th>Imaging Freq</th>
<th>Method</th>
<th>Inter-fraction Mean (SD) mm</th>
<th>PTV margin recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al, 2008</td>
<td>33</td>
<td>MRI</td>
<td>Day 1 &amp; Day 2</td>
<td>POI: uterine fundus cervix vagina</td>
<td>Fundus: 7.1 (6.8) 7 (9) 0.8 (1.3)</td>
<td>CTV-PTV internal margin: SI = 15mm AP = 15mm RL = 7mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cervix: 4.1 (4.4) 2.7 (2.8) 0.3 (0.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vagina: 2.6 (3) NR 0.3 (1)</td>
<td></td>
</tr>
<tr>
<td>Chan et al, 2008</td>
<td>20</td>
<td>MRI</td>
<td>Baseline &amp; weekly</td>
<td>POI: uterine fundus uterine canal cervical os</td>
<td>Fundus: 7.8 -4.6 NR</td>
<td>Inter-fraction 90PI suggested margins – fundus (10-40mm); canal (10-25mm) os (10-15mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ut canal: 5.7 -4.8 NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cervix: 1.5 2.4 NR</td>
<td></td>
</tr>
<tr>
<td>Beadle et al, 2008</td>
<td>16</td>
<td>CT</td>
<td>Baseline &amp; weekly</td>
<td>COM cervix (max change)</td>
<td>Cervix: 21 (7) 16 (6) 8 (3)</td>
<td>CTV-PTV 20-30mm</td>
</tr>
<tr>
<td>Yamamoto et al, 2004</td>
<td>10</td>
<td>orthog kV</td>
<td>Not stated. Likely daily</td>
<td>GTV/ cervix COM</td>
<td>Manual set-up: -0.6 (4.5) 0.9 (4.6) 0.4 (3.6)</td>
<td>PTV margin of 10-13mm with manual set up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluoros</td>
<td></td>
<td></td>
<td>Gold seed set-up: 0.3 (1.1) 0.9 (1.7) 1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Lee et al, 2004</td>
<td>15</td>
<td>MV portal</td>
<td>Weekly</td>
<td>GTV/ cervix POI</td>
<td>65 films from 11 patients: median (mm)</td>
<td>16 8 10</td>
</tr>
</tbody>
</table>

Table 1.1. Summary of Inter-fraction cervix & uterus motion.
N (number of patients); CT (computed tomography); MRI (magnetic resonance imaging); kV (kilovoltage); MV (megavoltage); POI (point of interest); COM (centre of mass); SI (superior-inferior); AP (anterior-posterior); LR (left-right); PTV (planning target volume); SD (standard deviation); CI (confidence interval); NR (not recorded).
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Modality</th>
<th>Imaging Freq</th>
<th>Method</th>
<th>Inter-fraction</th>
<th>SI</th>
<th>AP</th>
<th>LR</th>
<th>PTV margin recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaatee et al, 2002</td>
<td>10</td>
<td>MV portal films</td>
<td>Daily</td>
<td>8- or 11-mm tantalums fixed to cervix or vaginal vault imaged on 4 x MV port films per patient referenced to DRR</td>
<td>Marker movement relative to bony anatomy. Mean (SD) mm</td>
<td>3 (4.1)</td>
<td>1.7 (3.5)</td>
<td>1.3 (3.7)</td>
<td>CTV-PTV margin: approx 11mm</td>
</tr>
</tbody>
</table>

**STUDIES LOOKING AT MARGIN OR PERIMETER CHANGE**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Modality</th>
<th>Imaging Freq</th>
<th>Method</th>
<th>Inter-Fraction</th>
<th>PTV margin recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beadle et al, 2008</td>
<td>16</td>
<td>CT</td>
<td>Baseline &amp; weekly</td>
<td>Max cervix perimeter change</td>
<td>Perimeter change Mean (SD) mm S I A P L R</td>
<td>CTV-PTV margins of 2-3cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>23 (7) 13 (7) 17 (7) 18 (14) 9 (4) 8 (3)</td>
</tr>
<tr>
<td>Van de Bunt et al, 2008</td>
<td>20</td>
<td>MRI</td>
<td>Baseline &amp; weekly</td>
<td>Margins required to encompass GTV / CTV from week to week used as a surrogate for motion.</td>
<td>Max Margin Mean (mm) S I A P L R</td>
<td>CTV-PTV margins: Sup = 11mm; Inf = 8mm Ant = 24mm; Post = 17mm; Lt = 16mm Rt = 12mm;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GTV 4 8 12 14 11 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTV 11 8 24 17 16 12</td>
</tr>
</tbody>
</table>

Table 1.1. Summary of Inter-fraction cervix & uterus motion.
N (number of patients); CT (computer tomography); MRI (magnetic resonance imaging); kV (kilovoltage); MV (megavoltage); POI (point of interest); COM (centre of mass); SI (superior-inferior); AP (anterior-posterior); LR (left-right); PTV (planning target volume); SD (standard deviation); CI (confidence interval); NR (not recorded).
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Modality</th>
<th>Imaging Freq</th>
<th>Method</th>
<th>Inter-Fraction</th>
<th>PTV margin recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchali et al, 1999</td>
<td>14</td>
<td>CT</td>
<td>2 consecutive scans - bladder &amp; rectum empty vs bladder &amp; rectum full</td>
<td>Geometrical shift in contour of uterus &amp; cervix relative to bony landmarks</td>
<td>Median mm SI AP LR</td>
<td>CTV-PTV margin: Sup = 15mm Inf = 6mm AP = 9mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cervix</td>
<td>4 NR NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uterus</td>
<td>7 4 NR</td>
<td></td>
</tr>
</tbody>
</table>

**STUDIES LOOKING AT UTERUS ANGLE CHANGE**

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Modality</th>
<th>Imaging Freq</th>
<th>Method</th>
<th>Mean (SD) mm Length change</th>
<th>Angle change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huh et al, 2004</td>
<td>66</td>
<td>MRI</td>
<td>Baseline and 2nd scan in 3rd/4th week of RT</td>
<td>Six geometrical measures of uterus &amp; cervix position compared between baseline &amp; 2nd scan</td>
<td>Cervix 8.7 (7.8)</td>
<td>12.5 (12.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Uterus 5.5 (8.9)</td>
<td>15.4 (15.8)</td>
</tr>
</tbody>
</table>

Table 1.1. Summary of Inter-fraction cervix & uterus motion.
N (number of patients); CT (computer tomography); MRI (magnetic resonance imaging); kV (kilovoltage); MV (megavoltage); POI (point of interest); COM (centre of mass); SI (superior-inferior); AP (anterior-posterior); LR (left-right); PTV (planning target volume); SD (standard deviation); CI (confidence interval); NR (not recorded).
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Modality</th>
<th>Imaging freq</th>
<th>Method</th>
<th>Intra-fraction</th>
<th>PTV margin recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al, 2008</td>
<td>20</td>
<td>Cine-MRI</td>
<td>Baseline &amp; weekly</td>
<td>POI</td>
<td>Fundus -31</td>
<td>Intra-fraction 90PI suggested margins: fundus (10mm), canal (5mm), os (5mm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Yamamoto et al, 2004</td>
<td>10</td>
<td>Orthogonal kV fluoroscopes</td>
<td>Not stated, likely daily</td>
<td>105 POI measurements over 9.4 ± 4.7 min</td>
<td>SI 2.4-4.2</td>
<td>PTV margin of at least 7-8mm when setting up with gold seeds.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AP 1.9-2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR 1.4-3.4</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.2. Summary of Intra-fraction cervix & uterus motion.**

N (number of patients); MRI (magnetic resonance imaging); kV (kilovoltage); MV (megavoltage); POI (point of interest); SI (superior-inferior); AP (anterior-posterior); LR (left-right); PTV (planning target volume); CI (confidence interval); NR (not recorded); 90PI (90% prediction interval).
1.4.3 Normal Tissue Motion

The motion of surrounding normal tissues within the pelvis during radiotherapy for cervix cancer is poorly described in the literature. The bulk of the published literature that exists has focused on bladder and rectal movement in patients with prostate, bladder or rectal cancers. There is little information that is specific to patients with cervix cancer.

There are a number of reasons why characterizing normal tissue motion is particularly complex. Firstly, defining what constitutes an appropriate and relevant volume in relation to radiation dose-response relationships for normal tissues within the pelvis can be problematic. Although the bladder is a well defined organ, there continues to be debate about whether it should be defined as a solid organ (outer contour) versus hollow organ (wall contour) for the purposes of radiation treatment planning. Similarly, there is variability in the literature as to how the bowel is defined for the purposes of planning and dose constraints (i.e. individual loops of bowel vs. peritoneal space where loops of bowel reside) (59-63). Nor are there clear delineators or fascial planes at the interfaces between anus-rectum, and rectum-sigmoid, resulting in some subjectivity when defining these structures. Secondly, motion of hollow organs is often complex and asymmetric, requiring thorough three-dimensional evaluation at multiple time points to obtain a comprehensive picture. This is difficult to implement in practice and many of the studies to date have used simple COM or POI analyses. The motion of single points often is not representative of the complex motion of the organ as a whole or the motion of interface between the organ and the target volume. Many studies looking at OAR motion have focused on bladder or rectal volume change rather than motion per se.

Imaging modalities allowing high quality discrimination of soft tissues within the pelvis (such as CT or MRI) have become routine in the last few decades. Even with access to such modalities, repeated scanning over time to capture inter- or intra-fraction motion is often prohibitively time and labour intensive, in addition to being inconvenient for the patient. Consequently, the studies that have looked at organ motion have generally only managed weekly scanning, at best.

1.4.3.1 Bladder

Most of the studies exploring bladder motion during radiotherapy have been in bladder cancer patients, and thus, may not be strictly applicable to cervix cancer patients. Inter-fraction bladder
wall displacements have been noted primarily on the anterior and superior surfaces. These have been measured using serial CT scans during treatment referenced to the baseline planning CT. Inter-fraction displacements recorded have ranged from 5-36 mm in bladder cancer patients undergoing radical radiotherapy (63-65).

McBain et al (66) reported one of the few studies that looked at intra-fraction motion of the bladder using cine-MRI. More importantly, they included five normal controls in addition to ten bladder cancer patients. They measured bladder wall displacements over the course of a 28 minute cine-MRI scan and found wall displacements of up to 7 mm in controls and 58 mm in the cancer patients. They noted that bladder filling was much less symmetrical and wall displacements were larger in the cancer patients than in the controls.

1.4.3.2 Rectum

Muren et al (63) quantified rectal motion in a cohort of 20 bladder cancer patients receiving definitive radiotherapy. Using weekly CT scans, they measured rectal displacements at pre-specified anatomic levels using a 3D margin tool to determine the margins required to encompass the left, right, anterior and posterior displacements seen on the serial imaging. The authors noted that rectal displacements did not vary significantly between different anatomical levels correlating to the top, centre and bottom of the bladder. They did find that anterior and left displacements to be larger than right and posterior displacements, though no further details were given in the paper.

1.4.3.3 Bowel

No studies specific to gynaecological patients were found addressing the issue of bowel motion. It is well recognised that bowel is subject to motion, particularly in the un-operated abdomen. Nuyttens et al (67) measured small bowel movement in rectal cancer patients using the planning CT and weekly CTs during treatment. Bowel motion was quantified as the distance from the posterior bones of the pelvis to the nearest loop of small bowel on that axial slice. This distance was subtracted from the mean distance for that individual patient and the standard deviation calculated. In the pre-operative group, the standard deviation of small bowel motion was 2.7 cm anterior-posterior and 1.6 cm superior-inferior. They found a strong correlation between bladder filling and the volume of small bowel within the pelvis in the pre-operative group. The range of
motion seen in patients who had undergone surgery was much less. It was not stated in the paper how many patients in their study were women. Kvinnsland et al (68) calculated variations in the bowel DVHs obtained from weekly CT scans of 10 patients undergoing radiotherapy for bladder cancer. Their definition of bowel included the small and large intestine, excluding rectum. Not surprisingly, large variations in the calculated DVHs for individual patients were observed, reflecting the highly mobile nature of the organ. The pattern of movement exhibited by the loops of bowel was complex and not easily characterised. Hysing et al (69) examined weekly CT scans of 20 bladder cancer patients undergoing definitive radiotherapy. Individual loops of large and small bowel were contoured on each of the CT scans and location probability maps of the intestine were constructed for each patient. They found that isotropic margins of 3 cm around the bowel were required to encompass all intestinal motion for 90% of the patients.

1.4.3.4 Vagina

There is very little published data looking at vaginal motion. The vagina is intimately located between the bladder and rectum. Intuitively, one would expect the filling status of these organs to influence its motion.

Taylor and Powell (55) noted that upper vaginal motion was subject to bladder and rectal filling. They found mean ant-post displacements of 2.6 mm but noted maximal displacements of up to 10 mm. However, their motion estimates were based on a single point (2 cm below the cervix) which may not be representative of the entire organ. In addition to this, they only imaged their patients on two consecutive days. Ahamad et al (59) reported anecdotally that, in post-hysterectomy patients, the vaginal apex could move by as much as 3 cm depending on bladder filling status. This led to the recommendation for an internal target volume (ITV) construct in the recent Phase 2 RTOG 0418 study investigating IMRT in post-hysterectomy patients. The ITV was defined as the volume of vagina on two fused consecutive planning scans; one with the bladder was full and the other with the bladder empty, in order to account for this wide range in motion.

1.4.4 Planning Target Volume (PTV) Margins

A number of groups have attempted to provide PTV margin recommendations based on measured tumour motion (49-52, 54-56). The problem with a universal class solution for PTV
margins lies in the highly individualized nature of intra-pelvic tumour and organ motion. The margin recommendation would necessarily have to be large to encompass potential outliers, negating any advantageous normal tissue sparing (48, 51, 54, 59). Alternatively, if the PTV margins are too small, geographical target miss may occur during treatment due to unpredictable motion such as uterus angle change (48). Not surprisingly, margin recommendations across the literature have ranged from 6–40 mm (49-52, 54-56), while PTV margins used in various planning and clinical IMRT studies for this site have ranged from 5-15 mm (41, 70-76).

1.5 Planning Studies

A number of groups have been exploring IMRT for the treatment of gynaecological cancers over the last decade. Generally all have demonstrated the potential of IMRT to provide excellent tumour coverage and substantial normal tissue sparing. However, all of these studies have failed to take into account organ motion and deformation as one of the major confounding factors for this tumour site.

The heterogeneity of the patient population and target volumes in the IMRT planning studies published to date, make it difficult to draw anything but very broad conclusions from their findings. All of the studies included patients with cervix cancer, a third of them also included post-hysterectomy patients (either cervix or uterine cancer) (61, 76, 77). This implies potentially important differences in the CTV definition among these studies, leading to differences in OAR dosimetry and toxicity. While the majority of IMRT planning studies for cervix cancer have focused on the pelvis alone (41, 61, 72, 74, 76-79) some have included extended field radiotherapy (EFRT) volumes (60, 75).

Table 1.3 summarizes the planning IMRT studies for cervix cancer reported to date.
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Tumour site</th>
<th>Imaging modality</th>
<th>Treatment field</th>
<th>Tumour CTV definition</th>
<th>PTV margins</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roeske et al, 2000; Lujan et al, 2003</td>
<td>10</td>
<td>Cervix, Post-op endometrium</td>
<td>CT</td>
<td>Pelvis</td>
<td>Upper ½ vagina, whole uterus (if present), parametria</td>
<td>10 mm</td>
<td>98% PTV to receive 100% dose (45 Gy)</td>
</tr>
<tr>
<td>Portelance et al, 2001</td>
<td>10</td>
<td>Cervix</td>
<td>CT</td>
<td>Pelvis + PAN</td>
<td>Uterus + cervix</td>
<td>4 mm (12.4 mm around cervix)</td>
<td>100% PTV to receive ≥ 95% prescribed dose (45 Gy)</td>
</tr>
<tr>
<td>Kavanagh et al, 2002</td>
<td>2</td>
<td>Cervix</td>
<td>CT</td>
<td>Pelvis</td>
<td>GTV, cervix, uterus</td>
<td>5 mm</td>
<td>Not stated. 40 Gy to CTV</td>
</tr>
<tr>
<td>Heron et al 2003</td>
<td>10</td>
<td>Post-op cervix and Post-op endometrium</td>
<td>CT</td>
<td>Pelvis</td>
<td>Upper 4 cm vagina</td>
<td>5 mm</td>
<td>Not stated. 45 Gy to PTV</td>
</tr>
<tr>
<td>Ahmed et al, 2004</td>
<td>5</td>
<td>Cervix</td>
<td>CT</td>
<td>Pelvis (4F box) + PAN</td>
<td>Whole pelvis (4F box) + PAN (IMRT)</td>
<td>5 mm around PAN</td>
<td>99% PTV to receive ≥ 95% prescribed dose (45 Gy)</td>
</tr>
<tr>
<td>Georg et al, 2006</td>
<td>20</td>
<td>Cervix, Post-op endometrium</td>
<td>CT</td>
<td>Pelvis</td>
<td>Upper ½ vagina, whole uterus (if present), parametria</td>
<td>10 mm</td>
<td>95% PTV to get 95% prescribed dose (50.4Gy)</td>
</tr>
<tr>
<td>Han et al, 2006</td>
<td>10</td>
<td>Cervix</td>
<td>CT</td>
<td>Pelvis</td>
<td>Upper ½ vagina, whole uterus, parametria</td>
<td>15 mm</td>
<td>100% PTV to get prescribed dose (50Gy)</td>
</tr>
<tr>
<td>Van de Bunt et al, 2006</td>
<td>14</td>
<td>Cervix</td>
<td>MRI</td>
<td>Pelvis</td>
<td>GTV, whole uterus, upper ½ vagina, parametria</td>
<td>15 mm</td>
<td>100% PTV to get 95-107% prescribed dose (45 Gy)</td>
</tr>
<tr>
<td>Kerkhof et al, 2008</td>
<td>11</td>
<td>Cervix</td>
<td>MRI</td>
<td>Pelvis</td>
<td>GTV, whole uterus, upper ½ vagina, parametria</td>
<td>15 mm</td>
<td>100% PTV to get 95-107% prescribed dose (45 Gy)</td>
</tr>
<tr>
<td>Taylor et al, 2008</td>
<td>40</td>
<td>Cervix</td>
<td>CT</td>
<td>Pelvis</td>
<td>GTV, whole uterus, upper vagina, parametria, proximal uterosacral ligaments</td>
<td>15 mm</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

Table 1.3. Summary of IMRT planning studies. N (number of patients); CT (computer tomography); MRI (magnetic resonance imaging); PAN (para-aortic lymph nodes); 4F (four-field); CTV (clinical target volume); PTV (planning target volume).
1.5.1 Clinical Target Volume (CTV) coverage

CTV coverage has been universally reported as excellent in all of the IMRT planning studies (41, 60, 61, 72, 74-79). This is not particularly surprising given that most of these have been based on single static planning images. Three of the studies investigated the influence of organ motion on CTV coverage using limited re-imaging (41, 72, 78). However, that CTV coverage was in the context of either very generous PTV margins (15 mm) (41, 78) and/ or re-imaging at only one time point during treatment (41, 72). All three studies found CTV coverage to be maintained.

1.5.2 OAR sparing

Results of OAR sparing in EFRT planning studies comparing IMRT to conventional two- or four-field plans have been encouraging (60, 75). Portelance et al (75) noted a 2-fold reduction in the volume of small bowel irradiated to the prescribed dose and significant sparing of rectum and bladder. Dose reductions to bone marrow, kidneys and spinal cord have also been noted (60). In the pelvis-alone setting (41, 61, 72, 74, 76-80), almost half of the planning studies included patients who had undergone hysterectomy for either cervix or uterine cancer (61, 76, 77, 80). The reports of OAR sparing using IMRT in this setting have been particularly striking. Relative reductions in the volume of bladder and rectum receiving the prescribed dose have ranged from 23-44% (41, 76, 79) up to 70% (72) when comparing IMRT to conventional radiotherapy plans. Georg et al (61) reported that the mean dose reduction to rectal wall with IMRT versus conventional four-field plans was 3-3.5 Gy, while the reduction to bladder was 5.5-6 Gy. Bone marrow sparing was also realised using IMRT or specific bone marrow-sparing IMRT plans compared to conventional fields (80). Volumes of bowel (either large or small) receiving the prescribed dose were also reduced by 60-84% with the use of IMRT planning (41, 79). Heron et al (77) reported that the volumes of small bowel, bladder and rectum receiving 45 Gy or more were reduced by factors of 10, 15 and 56 respectively with the use of IMRT compared to 3DCRT. However it should be noted that all the patients in this study were post-hysterectomy. The absence of a uterus potentially biases the reported bowel-sparing advantages of IMRT, as the uterus tends to help keep bowel out of the pelvis. In addition, the CTV would be substantially smaller than for radically treated cases and comprise of only the residual vaginal stump, as opposed to the entire uterus and upper-half or one-third of vagina.
Georg et al (61) attempted to address the heterogeneity of the patient population in these planning studies by assessing the influence of an intact uterus on IMRT vs. 3DCRT plans. They found that the average volume of small and large bowel receiving the prescribed dose decreased by a factor of 6 and 2 respectively using IMRT techniques. When they looked only at the patients with an intact uterus, they found the effect of small bowel sparing with IMRT correlated with bladder volume. The benefits of IMRT in reducing bowel dose diminished as bladder volume increased. Intuitively, this makes sense as a full bladder will push the uterus up, thereby also pushing bowel out of the pelvis. In the post-operative situation, a similar relationship was demonstrated for large bowel but not for small bowel. The authors reasoned that it was because loops of small bowel remained in the pelvis despite bladder filling in the post-hysterectomy setting.

A significant weakness in most of these planning studies is their use of only a single static planning image to compare dosimetry between standard radiation plans and IMRT plans. Given the large amount of tumour regression and organ motion that can occur during radiotherapy for cervix cancer, the dosimetric advantages reported with IMRT may not be realized when applied to the clinical setting. The three studies that performed limited re-imaging for organ motion during treatment either did so in the context of very generous PTV margins (15 mm) (41, 78) and/or only re-imaged once during treatment (41, 72). Han et al (78) performed weekly CT scans on 10 cervix cancer patients during radiotherapy and found statistically significant increases in the volume of small bowel included in the treatment field at weeks 3 and 4 of treatment compared to the first week. The authors found a correlation between the volume of small bowel in the radiation treatment field and the bladder volume, in line with Georg et al (61). Van de Bunt et al (41) re-imaged 14 cervix cancer patients after approximately 30 Gy had been delivered. They compared CTV and OAR coverage between the pre-treatment and intra-treatment scans for conventional, 3DCRT and IMRT plans. They found persistent gains in OAR sparing with IMRT compared to conventional or 3DCRT plans. A replan based on the contours from the intra-treatment MRI resulted in significant sparing of the rectum with both the conformal and IMRT plans. In 5 patients who demonstrated substantial GTV regression (>30 cc) after 30 Gy, an IMRT replan resulted in further bowel sparing. Kavanagh et al (72) selected three patients to undergo repeat CT imaging once during their treatment course to determine if target
coverage was adequate with the IMRT plans. It is not clear at what time point the re-imaging occurred and only CTV coverage was assessed; OAR coverage was not analyzed.

The planning target volume (PTV) margins used by various groups were meant to take into account organ motion as well as set-up errors. As seen in Table 1.3, these PTV margins are highly variable. The size of the PTV margin is integral in the trade-off between target coverage and normal tissue sparing and differences among studies could result in different conclusions and recommendations (59). In addition, the conformality of the IMRT plan to the prescribed PTV can vary substantially as a function of many factors, including patient-specific anatomy and the skill and experience of the planning team. Poor plan conformality in essence increases the PTV margin beyond what was specified, which potentially reduces OAR sparing and makes the interpretation of results from different studies even more difficult.

1.6 Clinical Studies

The majority of clinical studies using IMRT for cervix cancer have reported similar tumour control with similar or less acute toxicity compared to traditional pelvic fields. This is confounded by the heterogeneous patient population and differences in the CTV and PTV definitions among these studies. Data on chronic toxicity are scarce and while target coverage appears to be adequate, data on sites of relapse and survival with longer follow-up are still maturing.

Table 1.4 summarises the current cohort of clinical studies exploring IMRT for the treatment of cervix cancer
<table>
<thead>
<tr>
<th>Study</th>
<th>N patients</th>
<th>Tumour site</th>
<th>Treatment field</th>
<th>Tumour CTV definition</th>
<th>PTV margin</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mundt et al, 2001</td>
<td>15</td>
<td>Cervix and endometrium</td>
<td>Pelvis</td>
<td>uterus (if present), upper ½ vagina, parametria</td>
<td>10 mm</td>
<td>Not stated. Prescribed dose 45 Gy</td>
</tr>
<tr>
<td>Brixey et al, 2002; Mundt et al 2003</td>
<td>36</td>
<td>Cervix and endometrium</td>
<td>Pelvis</td>
<td>uterus (if present), upper ½ vagina, parametria</td>
<td>10 mm</td>
<td>Not stated. Prescribed dose 45 Gy</td>
</tr>
<tr>
<td>Kavanagh et al, 2002</td>
<td>7</td>
<td>Cervix, Recurrent</td>
<td>Pelvis +/- PAN</td>
<td>GTV, cervix, uterus</td>
<td>5 mm</td>
<td>Not stated. Prescribed dose 45 Gy</td>
</tr>
<tr>
<td>Roeske et al, 2003</td>
<td>50</td>
<td>Cervix, endometrium, other</td>
<td>Pelvis</td>
<td>uterus (if present), upper ½ vagina, parametria</td>
<td>10 mm</td>
<td>Not stated. Prescribed dose 45 Gy</td>
</tr>
<tr>
<td>Gerszten et al, 2006; Varlotta et al, 2006</td>
<td>21</td>
<td>Cervix</td>
<td>Pelvis + PAN</td>
<td>Cervix + uterus + upper vagina + 20mm margin, parametria</td>
<td>5 mm</td>
<td>95% PTV to get 100% prescribed dose (45 Gy)</td>
</tr>
<tr>
<td>Mell et al, 2006</td>
<td>37</td>
<td>Cervix</td>
<td>Pelvis + PAN</td>
<td>uterus, upper ½ vagina, parametria</td>
<td>10 mm</td>
<td>Not stated. Prescribed dose 39.6-50.4 Gy</td>
</tr>
<tr>
<td>Salama et al, 2006</td>
<td>13</td>
<td>Cervix, Endometrium, Recurrence</td>
<td>Pelvis + PAN</td>
<td>uterus (if present), upper ½ vagina, parametria</td>
<td>10 mm</td>
<td>Not stated. Prescribed dose 45 Gy</td>
</tr>
<tr>
<td>Beriwal et al, 2007</td>
<td>36</td>
<td>Cervix</td>
<td>Pelvis + PAN</td>
<td>Cervix + uterus + parametria + upper vagina + 1-2cm margin</td>
<td>5-10mm</td>
<td>Not stated. Prescribed dose 45 Gy</td>
</tr>
<tr>
<td>Kidd et al, 2009</td>
<td>135</td>
<td>Cervix</td>
<td>Pelvis +/- PAN</td>
<td>“Metabolically active” primary cervical tumour</td>
<td>7 mm</td>
<td>100% PTV to get 95% prescribed dose</td>
</tr>
</tbody>
</table>

Table 1.4. Summary table of clinical IMRT studies. PAN (para-aortic lymph nodes); CTV (clinical target volume); PTV (planning target volume).
1.6.1 CTV coverage

In terms of CTV coverage, the generous CTV definitions and large PTV margins used in most of the studies to date appear to be adequate based on early reports regarding in-field failures. Beriwal et al (70) reported in-field failures in 2 of 36 patients receiving cervix cancer IMRT (one pelvic, one pelvic and para-aortic lymph node). The majority of failures (9 of 11) were at distant sites remote from the irradiated volumes. Similarly, Kidd et al (81) found a lower recurrence rate in the IMRT group compared to the non-IMRT group, 29% versus 44%, although this failed to reach statistical significance (p = 0.0738). For both arms, one third of the recurrences were local and two-thirds failed distantly. A caveat to these impressive results is the mean duration of follow-up, which was more than 3 times longer in the non-IMRT arm compared to the IMRT group (72 months versus 22 months respectively) (81).

1.6.2 Acute and Late Toxicity

The impressive OAR sparing predicted by IMRT planning studies appears to be attainable, particularly in the EFRT setting. One study reported a substantial reduction in severe grade 3 GI toxicity with IMRT compared to historical studies (3% versus 50% respectively) (70). However, with treatment of the pelvis alone, the benefits of IMRT are less obvious. Rates of grade 1 and 2 GI toxicity have ranged from 28-92% depending on the study, as summarized in Table 1.5 (70-73, 82). The wide range of reported GI toxicity is, in part, a consequence of the generous PTV margin expansions (up to 10mm) used by a number of groups due to concerns about geographical miss (41, 80, 82-84). While this may still result in sparing of OAR within the pelvis in the post-operative setting, the need to treat the uterus in patients without prior hysterectomy would increase the overall target volume substantially, making any OAR sparing less likely. This is reflected in the experience of Gerszten et al who noted that their pelvic IMRT fields closely approximated traditional whole pelvis radiotherapy (WPRT) fields due to their inability to clearly delineate areas at risk using CT (71). Similarly, Roeske et al reported a grade 1-2 GI toxicity rate of 28%, which was comparable to their standard WPRT cohort (82).

In terms of late toxicity, Mundt et al reported an 11% incidence of late grade 1 and 2 GI toxicity in their IMRT cohort compared to 50% with their historical WPRT controls (83). Kidd et al (81) have published the largest cohort to date of definitive cervix cancer patients treated with IMRT. They treated 135 patients with pelvis +/- para-aortic lymph nodes using an IMRT technique and
compared the results with 317 non-IMRT historical controls. They found significantly improved late grade 3 GI/ GU toxicity in the IMRT group (6%) versus 17% in their non-IMRT arm. (p = 0.0351, Table 1.6). A small but significant reduction in creatinine clearance has also been found in women receiving extended field (para-aortic) IMRT for gynaecological malignancies, however this did not result in any clinical renal toxicity (85).

The same weaknesses noted in the planning studies generally apply to the clinical studies. While the majority of clinical IMRT studies have concentrated on EFRT volumes, some have looked at treating the pelvis alone. The inclusion of post-hysterectomy patients is another confounding factor for OAR toxicity, as this substantially alters both the CTV and the amount of bowel residing in the pelvis (73, 82-84, 86). The inclusion of “GTV”, “cervix” or “parametria”, as well as the length of vagina in the CTV definition, has not been uniform across the studies. Different acute and late toxicity scoring systems have been used among these studies, including RTOG/ EORTC (70-73, 82), CTCAE v3.0 (73, 81), NCI CTCv2.0 (70, 84) and study-specific scoring schemes (83, 86), making strict comparisons difficult.
<table>
<thead>
<tr>
<th>Study</th>
<th>N patients</th>
<th>Tumour site</th>
<th>Treatment field</th>
<th>GI</th>
<th>GU</th>
<th>Haem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gd 1-2</td>
<td>Gd 3-4</td>
<td>Gd 1-2</td>
</tr>
<tr>
<td>Mundt et al, 2001</td>
<td>15</td>
<td>Cervix, post-op endometrium</td>
<td>Pelvis</td>
<td>10 (67%)</td>
<td>0</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Brixely et al, 2002</td>
<td>36</td>
<td>Cervix, post-op endometrium</td>
<td>Pelvis + PAN</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kavanagh et al, 2002</td>
<td>7</td>
<td>Cervix, post-op, recurrent</td>
<td>Pelvis +/- PAN</td>
<td>5 (70%)</td>
<td>2 (28%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Roeske et al, 2003</td>
<td>50</td>
<td>Cervix, post-op endometrium</td>
<td>Pelvis</td>
<td>14 (28%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gerszten et al, 2006</td>
<td>21</td>
<td>Cervix</td>
<td>Pelvis + PAN</td>
<td>10 (48%)</td>
<td>0</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Salama et al, 2006</td>
<td>13</td>
<td>Cervix, post-op endometrium</td>
<td>Pelvis + PAN</td>
<td>11 (85%)</td>
<td>1 (6%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Beriwal et al, 2007</td>
<td>36</td>
<td>Cervix</td>
<td>Pelvis + PAN</td>
<td>33 (92%)</td>
<td>1 (3%)</td>
<td>23 (64%)</td>
</tr>
</tbody>
</table>

Table 1.5. Summary table of reported acute toxicity with IMRT. PAN (para-aortic lymph nodes); GI (gastrointestinal); GU (genitourinary); Haem (haematological); Gd (grade); NR (not reported)
<table>
<thead>
<tr>
<th>Study</th>
<th>N patients</th>
<th>Tumour site</th>
<th>Treatment field</th>
<th>GI Gd 1-2</th>
<th>GI Gd 3-4</th>
<th>GU Gd 1-2</th>
<th>GU Gd 3-4</th>
<th>Haem Gd 1-2</th>
<th>Haem Gd 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mundt et al, 2003</td>
<td>36</td>
<td>Cervix, post-op endometrium</td>
<td>Pelvis</td>
<td>4 (11%)</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Salama et al, 2006</td>
<td>13</td>
<td>Cervix, post-op endometrium</td>
<td>Pelvis + PAN</td>
<td>0</td>
<td>1 (8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Beriwal et al, 2007</td>
<td>36</td>
<td>Cervix</td>
<td>Pelvis + PAN</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kidd et al, 2009</td>
<td>135</td>
<td>Cervix</td>
<td>Pelvis +/- PAN</td>
<td>NR</td>
<td>7 (5%)</td>
<td>NR</td>
<td>1 (0.7%)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 1.6. Summary table of reported chronic toxicity with IMRT. PAN (para-aortic lymph nodes); GI (gastrointestinal); GU (genitourinary); Haem (haematological); Gd (grade); NR (not reported)
1.7 Clinical Target Volume (CTV) Definition

1.7.1 Current definitions

CTV definitions for the treatment of cervix cancer have been derived in an ad hoc manner on a centre by centre basis largely by extrapolating from the surgical experience. Therefore, the CTV is often ill-defined and highly variable among studies, as summarized in Tables 1.3 (planning studies) and 1.4 (clinical studies). Most include the gross tumour volume (GTV), cervix, uterus (variable amount), parametria (variable amount), upper vagina (variable amount) and the draining regional lymph nodes.

A number of questions remain unanswered with regards to the definition of the CTV. Is it necessary to include the entire uterus in the CTV? How much vagina should be treated? Does the presence of lymphovascular space invasion influence the target volume at risk? This is particularly the case when target volumes become so prohibitively large that they nullify the normal tissue sparing advantages that IMRT might provide. Surgico-pathological data, which would ideally provide the gold-standard for informing us of the CTV, are not always applicable in a radiotherapy cohort as the tumours are often much more advanced (hence not appropriate for surgery). Much of the histopathological data concerning issues such as parametrial or vaginal involvement is dichotomised to present/absent without any details regarding the explicit distance of invasion from the gross tumour. In addition, many of these series present patients who have had neoadjuvant chemotherapy or radiotherapy, thus muddying the histopathological waters (26, 87-89).

Areas of controversy regarding defining a target volume are as follows:

1.7.1.1 Parametria

The parametria defines a tissue space adjacent to the cervix and uterus, encompassed by the broad ligament. It contains blood vessels, lymphatics and connective tissue and is a predictable route of direct invasion by cervix tumours. From a surgical perspective, the radicality of hysterectomy determines the amount of cardinal, uterosacral, utero-vesical, vesicovaginal and paravaginal ligament and vagina removed. However these definitions for different classes of
hysterectomy were not uniformly defined (90, 91). A precise definition of this tissue space is not necessary if the entire pelvis is irradiated, as with a traditional four-field box plan. However, with the advent of IMRT, more explicit CTV definitions are necessary. Within the radiotherapy literature, not all groups using IMRT have explicitly included the parametria in the CTV (72, 81, 92). Others have identified the parametria as part of the CTV but failed to described how it was demarcated, thus making it difficult to rigorously apply their methodology in other studies or routine clinical practice (41, 60, 61, 70, 71, 73, 74, 76, 82-84, 93). The parametrial tissue space is not always well seen on axial imaging and little is known about inter- and intra-fractional motion dynamics from a radiotherapy standpoint.

1.7.1.2 Uterus

Traditionally, the entire uterus has been treated with a four-field pelvis plan. Empirically this target volume is extrapolated from the tissues that would be removed in a surgical setting. While most groups have included the entire uterus in the CTV, it is debatable whether this is truly necessary, particularly in the setting of early stage disease. While isolated fundal recurrences are unusual, it could be argued that this is because the fundus has always been included in the target volume. The fundus is the most mobile part of the uterus and substantial motion is often seen between radiotherapy fractions (48, 54). Excluding the uterine fundus from the CTV would decrease the target volume and result in greater sparing of surrounding normal tissues.

1.7.1.3 Vagina

Little data exist on the ideal length of vagina which should be included in the CTV for an IMRT plan. Traditionally, inferior pelvic field borders have been positioned at the bottom of the obturator foramen or pubic rami, ensuring that at least the upper half of the vagina was included in the high dose volume. Whether it is necessary to treat that length, with its attendant long term morbidity (adhesions, dryness, stricture), is unknown. However, lower vaginal recurrences are unusual, which supports this practice.

1.7.1.4 Ovaries

None of the groups who have published either planning or clinical studies using IMRT for cervix cancer have explicitly included ovaries within the CTV, and ovaries are often preserved at radical hysterectomy for young patients with early stage disease. However, the ovaries would
have been included in the traditional pelvic radiotherapy fields although with more conformal radiotherapy, theoretically ovarian sparing might be possible. In young women with early stage disease, ovarian sparing surgery is beneficial for the purposes of maintaining fertility and hormonal levels. The ovaries are exquisitely sensitive to radiation with doses of 2 to 3 Gy often being sufficient to cause ovarian failure. Patterns of ovarian involvement in surgical cervix cancer cases demonstrated an increased risk for patients with adenocarcinoma histology and those with clinical stage 2B or greater (94). As such, it could be argued that they should be included in the CTV.

1.8 CTV assessment

Contours defining the CTV should ideally be both accurate (the contours truly encompass the CTV) and precise (the inter- and intra-observer differences in the contours are minimal). Achieving this in a clinical context is difficult for a number of reasons. In a clinical scenario, the “true CTV” can never be objectively known with 100% certainty, thus the closest estimate achievable is one where experts-in-the-field all agree. Within the limits of knowledge and expertise, it is expected that there is some congruence among different participants as to what should and should not be encompassed in the CTV as a reference standard. As such, using experts should theoretically minimize the differences of opinion and be closer to the “truth” (that is, “accurate”). However in reality, the closest surrogate we have for accuracy is “precision” (do their contours all agree).

Numerous different methods exist for trying to determine and clarify the reference CTV. One could compare the volumes of the contoured structures between experts. However, volume concordance does not guarantee that the actual contours are the same. An alternative strategy would be to look at the amount of overlap between the various contours or assess the boundary differences between the contours. Another way of measuring agreement among contouring experts would be to use the voting rule, where the CTV is comprised of the voxels which the majority of experts have included in their contours. This is generally only good for binary (yes/no) situations but not so useful when there are multiple contouring categories involved. What constitutes a “majority” is also somewhat arbitrary. A variant of the voting rule is a Borda count, which allows for multiple categories and theoretically selects the most broadly acceptable
agreement rather than just majority wins, however it still may not be particularly precise. Kappa statistics have also been used in an attempt to quantify levels of agreement between experts against agreement which might be expected by chance alone. None of these methods provide any detail regarding the quality of each participant’s contours. Consensus has sometimes been achieved through more qualitative methods such as roundtable discussions among a representative sample of experts (95-98).

More recently, a better way of determining contour agreement and thus target definition guidelines has been suggested.

1.8.1 STAPLE – Expectation-Maximization Algorithm

One strategy that has been used by a number of groups is through the use of a variant of the expectation-maximisation (EM) algorithm (99), known as the Simultaneous Truth and Performance Level Estimation (STAPLE) method (100-102). STAPLE (Simultaneous Truth and performance Level Expectation) is a pixel-based statistical algorithm developed specifically for comparing image segmentation among observers in situations where the true segmentation is not known. The algorithm uses an iterative approach to estimate both the “true segmentation” and the performance of the observer contours relative to the true estimate. At each step of the iteration, a new estimate of the true segmentation is made based on the prior estimate and the observer contours, each of which is weighted according to its performance in the previous iteration. The final result provides the best estimate of the “true segmentation” as a binary map in the same imaging space as the original contours: an individual pixel is defined as 1 if part of the true segmentation and 0 if not. The original contours can be defined in the same way. Sensitivity and specificity for each observer are then calculated by comparing the original and true segmentations pixel by pixel. The ability to provide a measure of contour quality (in terms of sensitivity and specificity for each observer), is advantageous compared to previously stated methods of contour assessment (102). There are a number of assumptions when STAPLE is used: 1. Observers derive their contours on the same image set independently from one another; 2. Observers have all been trained to interpret the images in a similar way; 3. Segmentation decisions may differ due to systematic or random rater differences; 4. A probabilistic estimate of the “true segmentation” can be formulated as an optimal combination of the observed differences.
1.9 Technical Innovations

With such wide variations in patient population, CTV definition, OAR definitions and PTV margins, it is hardly surprising that the acute toxicity experienced with IMRT has been so varied. Awareness of the intra-pelvic organ dynamics that occurs during radiotherapy for cervix cancer (such as tumour regression, tumour motion and normal tissue motion and deformation), gives one pause when considering IMRT for this tumour site. What minimum PTV margins are adequate in the setting of normal tissue motion and concurrent tumour regression?

Understanding the dose consequence of this organ motion in the setting of an IMRT plan would be valuable. The emergence of technical innovations, such as deformation software (to model organ motion more accurately) and dose accumulation software (to provide a more realistic model of the actual dose delivered to the organs in the setting of such motion), provides us with the opportunity to do so.

1.9.1 Deformation Modeling (MORFEUS)

The increasing use of imaging modalities other than CT, in addition to the different time points at which these images are acquired, have raised the issue of image registration in order to maximize the benefits of the information provided. The difficulty with using different imaging modalities has been one of matching images sets from different time points and potentially different organ positions. In many of these instances, simple rigid translations are not sufficient to accurately compensate for differences in organ position. Various deformation algorithms have been created to overcome this problem.

Fluid flow is one algorithm where the deformations in the images are modeled as a fluid. Optical flow uses differences between the images and the intensity gradient inherent in the image to drive the registration. Both of these are limited by their inability to accommodate non-continuous motion (e.g. stationary spine next to moving lung). They are also unable to provide intensity correspondence (e.g. registering full rectum with empty rectum).

Thin-plate spline and B-plate spline are algorithms where the image is deformed using control points that are placed in specific locations (thin-plate) or on a regular grid (B-plate). These control points guide the deformation. Thin-plate control points affect deformation of the entire
organ and so are best for single organ registration. B-plate control points only affect the local area, thus allowing for multiorgan registration. However, spline deformation algorithms also have the same problems with non-continuous motion and lack of intensity correspondence as fluid and optical flow algorithms.

The biomechanical method deforms according to the material properties of the tissue. Boundary conditions describing the motion and deformation of parts of the model are required, in this case, the surface of the organ. A limitation of this method is its dependence on contours to provide these boundary conditions and uncertainty in defining material properties of the anatomy being modeled. MORFEUS is an example of a finite-element biomechanical deformable registration algorithm. MORFEUS stands for Multi-Organ Finite Element Model-based Deformable Image Registration. It has been used extensively for image registration in the thorax, abdomen and pelvis in the research setting (103-113).

1.9.2 Dose tracking/ Dose accumulation

The organ motion described in Section 1.4, can impact significantly on the doses of radiation received by both the target and normal tissues during highly conformal fractionated radiotherapy. While it is inherently understood within the radiation oncology community that what you plan is not necessarily what you treat, this has not been formally demonstrated in the context of IMRT for cervix cancer (114, 115). When more generous treatment fields were used (such as a 4-field box), this was not an issue as sharp dose gradients near moving organs were less likely to occur. The more pressing question is whether the dosimetric differences between what is planned and what is delivered with IMRT are clinically significant, particularly in light of its increasing usage for gynaecological malignancies (116).

Models to quantify the accumulated fractionated dose in deforming organs have been proposed for more than 10 years (117, 118). While planning studies utilizing organ deformation and dose accumulation have been performed for prostate cancer (114, 115), there have been none published looking at cervix cancer. Cervix cancer provides a particularly challenging prototype, more so than prostate cancer. This is because the target volume is often larger and more complex and subject to considerable deformation during treatment as the tumour regresses. Different parts of the target may move in different ways over a course of treatment and even during a single
radiation fraction. In addition to this, the surrounding normal tissues (bowel, bladder, rectum) are often located in close proximity to large portions of the CTV.

ORBIT Workstation (Optimisation of Radiotherapy Beams by Iterative Techniques; RaySearch Laboratories) is one such research software platform which uses organ deformation maps to model dose accumulation (119).

1.10 Hypothesis & Aims

The hypothesis is that the dose received by tumour targets and surrounding normal tissues during radiotherapy for cervix cancer, is significantly different to that indicated by the static pre-treatment plan.

1.10.1 Aim 1: Generate consensus guidelines on CTV definitions for cervix cancer

In order to address this hypothesis, the target must be accurately defined. Therefore, developing a consensus guideline for CTV definition in the setting of definitive cervix cancer radiotherapy forms the first aim. Determining what should comprise the CTV and establishing broad international agreement about this definition with a number of radiation oncology experts in the field is an important first step. To do this, CTV contours generated by the experts on a representative clinical cervix cancer case will be analyzed using STAPLE. Inter-observer agreement on the CTV delineated will be summarised using kappa statistics and the 95% volume of agreement contours will form the basis of the consensus contours.

1.10.2 Aim 2: Analyze tumour and organ dynamics (regression, motion, deformation) within the pelvis during radiotherapy

The next aim is to quantify tumour and organ dynamics in a cohort of twenty women undergoing definitive radiotherapy for cervix cancer. This will address a current gap in the literature surrounding normal tissue motion and deformation for this tumour site. In addition, it will provide valuable insight into the impact of such organ motion on highly conformal radiotherapy strategies such as IMRT.
1.10.3  Aim 3: Analyze the dose consequences of tumour and organ dynamics on currently used IMRT strategies

The intra-pelvic organ dynamics analyzed in Aim 2 lead directly to modeling of the dose consequence of such motion during a fractionated course of highly conformal radiotherapy. This will provide a better appreciation of whether the target is under-dosed and whether the surrounding normal tissues are over-dosed. To do this, two software platforms will be used. MORFEUS, a finite element deformable registration algorithm to model inter-fraction organ motion in a cohort of cervix cancer patients, and ORBIT Workstation (RaySearch Laboratories), a research software platform used to calculate the accumulated delivered dose over a course of fractionated radiotherapy in the setting of organ motion.
1.11 References


Chapter 2 Consensus CTV Definition

Aim 1: Consensus Guidelines for Delineation of Clinical Target Volume for Intensity Modulated Radiotherapy for the Definitive Treatment of Cervix Cancer

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I was directly and intimately involved with every aspect of the development of these consensus guidelines. My contribution as lead author involved spear-heading the consensus guideline working group meetings; creating the survey to assess patterns of practice among working group members; writing the draft consensus guideline document; researching available literature on contentious issues related to the CTV definition; selecting the clinical case used for contouring by the working group members (including creating the tasklist for contouring, clinical details, feedback forms); liaising with collaborators at the Image-Guided Therapy Centre (ITC) on the statistical analysis of the contours; collating and incorporating the feedback from participants regarding the draft guideline document and contouring case; creating the pictures and figures used in the manuscript and ultimately, liaising with all 29 co-authors in achieving a formalized consensus CTV definition.

This chapter was electronically published ahead of print in the International Journal of Radiation Oncology, Biology, Physics. 2010 May 14.
2 ABSTRACT

Purpose: Accurate target definition is vitally important for definitive treatment of cervix cancer with intensity-modulated radiotherapy (IMRT), yet Clinical Target Volume (CTV) definitions remain variable within the literature. The aim of this study is to develop a consensus Clinical Target Volume (CTV) definition in preparation for a Phase 2 clinical trial being planned by the Radiation Therapy Oncology Group (RTOG).

Methods and Materials: A consensus guidelines working group meeting was convened in June 2008 for the purposes of developing target definition guidelines for IMRT in the intact cervix. A draft document of recommendations for CTV definition was created and used to aid in contouring a clinical case. The clinical case was then analyzed for consistency and clarity of target delineation using an expectation-maximization algorithm for simultaneous truth and performance level estimation (STAPLE), with Kappa statistics as a measure of agreement between participants.

Results: Nineteen experts in gynaecologic radiation oncology generated contours on axial magnetic resonance (MR) images of the pelvis. Substantial STAPLE agreement sensitivity and specificity was seen for Gross Tumour Volume (GTV) delineation (0.84 and 0.96 respectively) with a kappa statistic of 0.68 (p<0.0001). Agreement for delineation of cervix, uterus, vagina and parametria was moderate.

Conclusion: This document provides guidelines for CTV definition in the definitive cervix cancer setting for the purposes of IMRT, building on previously published guidelines for IMRT in the post-operative setting.

2.1 INTRODUCTION

Intensity-modulated radiotherapy (IMRT) is being increasingly explored as a means to reduce normal tissue toxicity in cervix cancer with or without treatment intensification (such as extended-field radiotherapy or concomitant boost) (1-6). Reductions in acute and late toxicities with the use of IMRT have been reported in conjunction with low rates of in-field failures (2, 3,
Accurate target definition is vitally important to ensure the target is not under-treated and to limit the dose to surrounding normal tissues. There are published guidelines on clinical target volume (CTV) definitions for a number of tumour sites including the post-operative gynaecological and prostatectomy setting (8, 9). However, CTV definitions for IMRT for the radical treatment of cervix cancer remain variable within the literature (2, 3, 5, 6, 10). The amount of organ motion, tumour regression and deformation that cervix cancer patients demonstrate is more substantial than in prostate cancer (11-18). These complex intra-pelvic organ dynamics imply greater caution when using highly conformal radiotherapy (such as IMRT) for this site as compared to prostate cancer. In order for IMRT to be delivered safely, adequate PTV margins are necessary to account for CTV motion.

The aim of this paper is to provide consensus guidelines in CTV definition for the intact cervix in order to achieve safe clinical IMRT practice in preparation for a planned RTOG (Radiation Therapy Oncology Group) Phase 2 clinical trial. This would supplement currently published consensus guidelines on post-operative IMRT for endometrial and cervix cancer (9).

2.2 METHODS & MATERIALS

A proposal for a prospective RTOG trial evaluating the role of IMRT in the definitive cervix cancer setting was the impetus behind the development of these guidelines. Representatives from the following groups participated in the Gyn IMRT Consortium: RTOG; National Cancer Institute of Canada; the Japan Clinical Oncology Group and the European Society of Therapeutic Radiology and Oncology.

An electronic survey among Consortium members was undertaken prior to the June 2008 RTOG meeting to determine patterns of practice for IMRT in definitive cervix cancer. The survey explored the current prevalence of IMRT usage in definitive cervix cancer treatment; imaging modalities used for target delineation; CTV definition; planning margins; prescriptions and target verification during treatment. Specific questions detailing the more controversial aspects of CTV definition were also explored, including the amount of uterus to include in the CTV, how to define the parametrium, and how much vagina to treat. At the meeting, current data on organ motion, tumour regression and examples of current IMRT practice was reviewed.
Following this, a draft document describing contouring boundaries for CTV structures was circulated. Consortium members were provided with magnetic resonance (MR) images (axial and sagittal T2-weighted) and axial computed tomography (CT) images from a clinical case and asked to contour the gross tumour volume (GTV); cervix (if seen); uterus; vagina and parametria on the axial MR images using these guidelines. It was assumed that the “true” CTV existed within the collection of contours generated by the Consortium members. A pixel-based, iterative expectation-maximization algorithm, called Simultaneous Truth and Performance Level Estimation (STAPLE), was used to determine an estimation of this “true” CTV contour. Using the estimated “true” CTV, sensitivity and specificity were calculated for each consortium member, on each CTV component, \((8, 19)\). The average of all the sensitivities and specificities for each CTV component was then calculated, along with standard deviations Generalized kappa statistics were used to correct for contour agreement that occurred by chance alone. Values between +1 (perfect agreement) to 0 (no agreement above chance) and -1 (complete disagreement) were generated for each of the CTV components \((20)\). The p-value for the kappa statistic is the probability that the result is due to chance alone. Ninety-five percent agreement contours were also generated, representing volumes where consensus was reached. These contours were reviewed at a second RTOG meeting in June 2009 and areas of controversy or discordance in the contours discussed and resolved.

A teaching atlas was also felt to be a valuable addition to the guidelines. Consortium members were asked to contour several cases representing different clinical scenarios. The 95% agreement contours would then form the basis for the “gold standard” contours in the teaching atlas. This comprehensive magnetic resonance imaging (MRI) atlas would be available on-line through the RTOG website.

2.3 RESULTS

A total of 16 members from the Consortium were surveyed with a response rate of 75% \((12/16)\). There was general consensus on the structures to be included in the CTV (such as GTV, cervix, uterus, parametria, vagina and regional lymph nodes), but less agreement regarding the definition of these structures for the purposes of contouring. All respondents agreed that the lateral boundary of parametria should be at the pelvic sidewall, and the medial boundary of parametria
should abut the GTV, cervix, uterus and vagina. The superior and inferior boundaries of the parametria were more varied [Figure 2.1]. The amount of normal tissues (such as the uterus and vagina) to include in the CTV also differed. Forty-two percent of survey respondents felt that it was not always necessary to include the entire uterus in the CTV. Reasons for this included the observation that isolated uterine recurrences are rare, and the fundus is not always included in patients with small, cervix-confined tumours and large fibroid uteri. The length of normal vagina included in the CTV varied from 1.5 cm to the bottom of the pubic symphysis (approximately 4 cm below tumour). CT was the most prevalent imaging modality used to determine the tumour CTV (91%), though most respondents used multiple imaging modalities (MRI 55%; PET 46%). Planning target volume (PTV) margins for tumour CTV and nodal CTV ranged from 1-5 cm and 0.5-1 cm respectively. Based on these findings, some guidelines on target delineation were felt to be important in achieving consistent, safe standards of practice.

Figure 2.1. Sagittal and coronal T2-weighted MR images of a patient showing the different definitions of superior and inferior parametrial boundaries from survey respondents. Gross tumour volume (GTV; red contour).
Nineteen experts in the field of gynaecologic radiation oncology used the draft guidelines to contour a clinical case. These Consortium members demonstrated high specificity but lower sensitivity, particularly in relation to the parametrial contours (Table 2.1). Substantial STAPLE agreement sensitivity and specificity was seen for GTV delineation (0.84 and 0.96 respectively) with a kappa statistic of 0.68 (p<0.0001). Kappa values for cervix, uterus, vagina and parametria indicated moderate agreement (0.42-0.57). On the whole, the 95% agreement contours were felt to be quite consistent with the intention of the guideline document [Figure 2.2]. Areas of controversy included anatomical boundaries for the parametrial tissue; the volume of uterus to include in the CTV; the length of normal vagina to treat; PTV margin recommendations; and the use of bladder and/or bowel preparation. The majority of these issues were resolved in the June 2009 meeting and the finalized document circulated for comment prior to publication.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Sensitivity (Average ± SD‡)</th>
<th>Specificity (Average ± SD‡)</th>
<th>Kappa measure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>0.84 ± 0.14</td>
<td>0.96 ± 0.04</td>
<td>0.68†</td>
</tr>
<tr>
<td>Cervix</td>
<td>0.55 ± 0.24</td>
<td>0.98 ± 0.03</td>
<td>0.42†</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.68 ± 0.22</td>
<td>0.97 ± 0.03</td>
<td>0.57†</td>
</tr>
<tr>
<td>Vagina</td>
<td>0.58 ± 0.13</td>
<td>0.99 ± 0.01</td>
<td>0.53†</td>
</tr>
<tr>
<td>Parametria</td>
<td>0.48 ± 0.27</td>
<td>0.99 ± 0.02</td>
<td>0.42†</td>
</tr>
</tbody>
</table>

Table 2.1. STAPLE analysis results of participants clinical target volume (CTV) contours.  
* corrected for chance; † p-value < 0.001; ‡ standard deviation
Figure 2.2. Axial and reconstructed sagittal & coronal views of T2-weighted MR image from clinical contouring case showing the 95% agreement contours for gross tumour volume (GTV, red); cervix (pink); vagina (yellow); parametria (green) and uterus (blue).
2.3.1 Consensus guidelines for delineation of CTV for IMRT for the intact cervix

This document is not meant to be prescriptive since clinical judgment remains an important aspect of determining extent of disease. There are also aspects of the CTV and suggested minimum planning target volume (PTV) margins which remain areas of active research. Further refinement of these areas is likely as data regarding patterns of failure in cervix cancer patients treated with non-conventional pelvic fields accrues.

2.3.1.1 Simulation

While the majority of survey respondents used CT as a clinical imaging modality, this was in the context of generous PTV margins and relatively large field sizes. In the setting of more conformal treatment, MRI was strongly recommended by the group to aid in target delineation due to the difficulty in distinguishing soft tissue components on CT. Either a diagnostic MR scan, or an MR simulation scan (with the patient in the same treatment position), were recommended if resources allowed. Fusion of the T2-weighted axial MR images to the planning CT was recommended. Ideally, the MRI would occur close to the time of planning to minimize discrepancies in organ positioning.

The use of patient immobilization at planning and during treatment is necessary to help minimize set-up error.

2.3.1.2 CTV components

It was agreed that the CTV should include the gross tumour volume (GTV), cervix (if not already encompassed by the GTV), uterus, parametria, ovaries and vaginal tissues. The rationale for the inclusion of these structures is extrapolated from the surgical management of cervix cancer (21-23). Details on the extent of uterus, parametria and vagina to be included in the CTV are as follows. [Figure 2.3a-e)] Table 2.2.
Figure 2.3a-b). T2-weighted MR axial (left-hand-side) and sagittal (right-hand-side) images of one patient demonstrating GTV (red), cervix (pink), uterus (blue), vagina (yellow), parametrium (green), bladder (purple), rectum (light blue), sigmoid (orange) at different levels. Black arrow heads refer to uterosacral ligaments and mesorectal fascia. Open arrow heads refer to the broad ligament and top of fallopian tube.
Figure 2.3c-d. T2-weighted MR axial (left) and sagittal (right) images of one patient demonstrating GTV (red), cervix (pink), uterus (blue), vagina (yellow), parametrium (green), bladder (purple), rectum (light blue), sigmoid (orange) at different levels.
Figure 2.3e. T2-weighted MR axial (left-hand-side) and sagittal (right-hand-side) images of one patient demonstrating GTV (red), cervix (pink), uterus (blue), vagina (yellow), parametrium (green), bladder (purple), rectum (light blue), sigmoid (orange) at different levels. Black arrow heads refer to uterosacral ligaments and mesorectal fascia. Open arrow heads refer to the broad ligament and top of fallopian tube. Dashed white line represents the clinical target volume (CTV).

<table>
<thead>
<tr>
<th>GTV</th>
<th>Entire GTV (intermediate/ high signal seen on T2-weighted MR images)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>Entire cervix (if not already included within GTV contour)</td>
</tr>
<tr>
<td>Uterus</td>
<td>Entire uterus</td>
</tr>
<tr>
<td>Parametrium</td>
<td>Entire parametrium including ovaries (include entire mesorectum if uterosacral ligament involved)</td>
</tr>
<tr>
<td>Vagina</td>
<td>Minimal or no vaginal extension: upper ½ of vagina</td>
</tr>
<tr>
<td></td>
<td>Upper vaginal involvement: upper ¾ of vagina</td>
</tr>
<tr>
<td></td>
<td>Extensive vaginal involvement: entire vagina</td>
</tr>
</tbody>
</table>

Table 2.2. Clinical Target Volume (CTV) components.
2.3.1.2.1 Uterus

The group consensus was that the entire uterus should be included in the CTV for the following reasons. The uterus and cervix are embryologically one unit with interconnected lymphatics and no clear separating fascial plane (25). Secondly, determination of myometrial invasion radiologically or clinically can be difficult. While published outcomes of radical trachelectomy for early stage disease have demonstrated overall recurrence rates of less than 5% and mortality rates of less than 3% (26), uterine recurrences have been reported (2%), although the exact location of these (fundal vs corpus) have not been stated (27-29). Recurrence rates after radical trachelectomy have been substantially higher (up to 10%) for patients with tumour size greater than 2 cm (more comparable to a radiotherapy patient cohort) or with the presence of lymph-vascular invasion (26, 30). The possibility of excluding the uterine fundus in selected cases may be revisited in the future once more data has been collected.

2.3.1.2.2 Parametria

Explicit boundaries defining the extent of parametrial tissue have been lacking within the radiotherapy literature. Efforts were made at the working group meeting to reach a consensus on the anatomical boundaries of this tissue space. The parametrial tissue is encompassed by the broad ligament but is not always well demarcated on axial imaging. The boundaries of the parametrium are as described in Table 2.3.

<table>
<thead>
<tr>
<th>Anteriorly</th>
<th>Posterior wall of bladder or posterior border of external iliac vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posteriorly</td>
<td>Uterosacral ligaments and mesorectal fascia</td>
</tr>
<tr>
<td>Laterally</td>
<td>Medial edge of internal obturator muscle/ischial ramus bilaterally</td>
</tr>
<tr>
<td>Superiorly</td>
<td>Top of fallopian tube/ broad ligament. Depending on degree of uterus flexion, this may also form the anterior boundary of parametrial tissue.</td>
</tr>
<tr>
<td>Inferiorly</td>
<td>Urogenital diaphragm</td>
</tr>
</tbody>
</table>

Table 2.3. Anatomical boundaries of parametrium
The superior boundary of the parametria is at the top of the fallopian tube and contours should stop once loops of bowel are seen next to the uterus as this is clearly above the broad ligament. For the very anteverted uterus, particularly where the fundus lies below the cervix, the parametrial volume should stop once the cervix is seen. Inferiorly, the parametrial tissue finishes at the muscles of the pelvic floor [Figure 2.4]. Anteriorly, the parametrial boundary lies at the posterior wall of the bladder. In patients with a very small bladder (which lies deep in the pelvis), it was decided to set the anterior parametrial boundary in line with the posterior border of the external iliac vessels. Posteriorly, the parametrial tissue is bounded by the mesorectal fascia and uterosacral ligaments. Care must be taken to include the entire uterosacral ligaments if they are either clinically or radiologically involved with disease. If this is the case, an argument can be made to include the entire mesorectum as pararectal lymph nodes would also be at risk. In that case, parametrial volumes would extend up to the rectal contour [Figure 2.5]. Patients with FIGO stage 3B or greater disease and those with extensive nodal involvement should also have the entire mesorectum included in the parametrial volume. Laterally the parametrial volume should extend to the pelvic sidewall (excluding bone and muscle). It is acknowledged that there would be some overlap of this volume with the nodal CTV, particularly along the obturator strip. The pelvic sidewall was considered a more consistent and reproducible boundary and any overlap between the two volumes could be dealt with during treatment planning. [Figure 2.6]
Figure 2.5. Axial T2-weighted MR image of a different patient, GTV (red), modified parametrium (green), rectum (light blue), red arrows indicate right proximal uterosacral ligament invasion.

Figure 2.6. Same image as Figure 2.3b, showing overlap (purple shaded) between nodal clinical target volume (orange contour) and lateral portion of parametrial volume (green contour).
2.3.1.2.3 Vagina

For tumours with minor or no extension into the vaginal fornices, the upper half of the vagina should be included in the CTV. For those with upper vaginal involvement, the upper 2/3 of vagina should be treated. Those with extensive involvement should have the entire vagina encompassed in the CTV. This would be in conjunction with clinical judgment as vulva and perineum would not be included unless they were grossly involved [Figure 2.3e].

2.3.1.2.4 Nodal CTV

The nodal CTV must include involved nodes and relevant draining nodal groups (common, internal and external iliac; obturator and presacral lymph nodes). Inclusion of para-aortic lymph nodes will depend on the extent of disease and results of staging investigations. Details of nodal CTV delineation will not be addressed in this document as a number of guidelines already exist (9, 31, 32).

2.3.1.2.5 Organs at Risk

While the majority of published literature on IMRT for this site report contouring of normal structures such as pelvic bone marrow, femoral heads, bladder, rectum and bowel, the exact definition of how some of these organs were contoured remains vague. While bladder is straightforward, the extent of rectum and bowel contoured can substantially influence planning dose constraints and subsequent reported outcomes. The controversies regarding organ at risk (OAR) definition and delineation for IMRT in this setting are beyond the scope of this paper.

2.3.1.2.6 PTV Margins & Image-Guidance

The survey of patterns of practice indicated that PTV margins were variable among group members, largely as a function of available data on organ motion for this site. A number of groups have published CTV-PTV margin recommendations which have ranged from 0.6-4 cm, depending on their methodology for assessing organ motion (11, 12, 14, 18, 33, 34). The combination of unpredictable organ motion and substantial tumour regression resulted in conservative margin recommendations by the group. Margins of 1.5-2 cm around the CTV were recommended if good quality daily soft tissue verification was available during treatment. A
PTV margin of 7 mm around the nodal CTV was agreed upon, in line with previous recommendations in the post-operative cervix cancer setting (e.g. RTOG 0418 protocol). If bone matching alone was being used, more generous margins would be necessary, due to the uncertainty of tumour CTV position in relation to nodal CTV position. The use of IMRT without any form of daily soft-tissue verification risks geographical target miss and should be approached with caution. Even the use of fiducial markers is not always reliable as they may shift over the course of treatment.

2.4 DISCUSSION

Traditional whole pelvis radiotherapy fields based on bony landmarks encompasses targets within the pelvis with little sparing of OAR. The benefit of these large treatment volumes is that geographical miss is minimized. In the era of more conformal treatment, where target delineation becomes critical, one of the major difficulties in pelvic IMRT for the radical treatment of cervix cancer lies in the definition of the CTV components. While there is general agreement on what constitutes the CTV, defining these different components becomes more problematic. Explicit radiological boundaries of pelvic targets such as parametrial tissue are lacking, and there is little data to guide our choice as to the extent of uterus and vagina that should be included in the CTV.

It is evident from the clinical contouring case, that while experts in the field were reasonably certain about what should not be in the CTV (high specificity values, Table 2.1), the sensitivity was generally less, reflecting the difficulty in determining the interface between the different CTV components. The moderate agreement (as evidenced by the Kappa measures from Table 2.1) for cervix, uterus, vagina and parametrial contours reflects some of the problems inherent with contouring for this particular clinical case, where the extreme anteversion of the uterus made identifying various CTV components challenging [Figure 2.2].

These CTV components are also subject to organ motion, deformation and tumour regression, resulting in highly individualized and unpredictable organ dynamics (12, 13, 16, 18, 34). The potential differential in motion between the tumour CTV (which is relatively mobile) and the nodal CTV (which remains largely fixed to bone) means a combined CTV encompassing both...
would require generous margins since any isocentre shift to cover one component could compromise coverage of the other [Figure 2.7].

Figure 2.7. Sagittal T2-weighted MR images of one patient one week apart, demonstrating the marked difference in uterus and cervix position with altered bladder filling. Primary tumour CTV (red) and nodal CTV (green) contours overlaid. Left panel: Solid lines represent targets at week 1. Right panel: Dashed lines represent the targets at week 2. Orange colour wash represents dose distribution for combined CTV. If a direct translational shift is made to compensate for the change in the primary tumour CTV position in week 2, the nodal CTV and portions of the tumour CTV are underdosed (not covered by orange colour wash).

As a consequence, margin recommendations are difficult and any class solution would need to be generous in order to encompass unpredictable outliers. With PTV margins of 1.5-2 cm, OAR sparing with IMRT becomes more difficult. While planning and clinical studies have all shown that there is indeed some OAR sparing using IMRT, even with generous margins, the toxicity experienced by patients can be variable (2, 10, 35).

Integrated boost strategies for primary cervical tumours should be approached with caution as the large PTV margins currently required to compensate for organ motion are also likely to result in increased doses being delivered to surrounding normal tissues thereby increasing toxicity.
For IMRT to be given safely for the intact cervix, daily soft-tissue image guided verification is required to prevent geographical miss. Minimizing the motion of the tumour CTV through bladder and bowel preparation might help, though the highly individualized nature of the organ motion and tumour regression means that this is not a safe-guard against significant shifts in target position.

While the potential for normal tissue sparing is one of the motivations behind the move toward IMRT for this site, achieving good target coverage remains the primary objective. Further refinement of PTV margins will continue to evolve as the results of ongoing research mature.

2.4.1 CONCLUSION

This is the first consensus document attempting to clarify target definitions for whole pelvis IMRT for the intact cervix. It was felt that clear target definition guidelines would be useful in achieving consistency across different treatment centers. This paper does not attempt to address issues of minimizing organ motion or adaptation to organ motion or tumour regression. The value of this document lies in providing groundwork for safe practice, building on previously published guidelines for IMRT in the post-op setting, and for future trials of IMRT in cervix cancer.

2.5 ACKNOWLEDGEMENTS

The following radiation oncologists contributed to this work as part of the Gyn IMRT Consortium:

Anamaria Yeung, M.D. & Robert Amdur, M.D. (Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL); Ivy Petersen, M.D. (Department of Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN); Penny Anderson, M.D. (Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA); Melanie Powell, M.D., F.R.C.R. (Department of Radiotherapy, St Bartholomew’s Hospital, London, UK); Mahesh Varia, M.D. (Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC); Tracey Schefter, M.D. (Department of Radiation Oncology, University of Colorado, Aurora, CO); Satoshi Ishikura, M.D., Ph.D. (Clinical Trials and Practice Support
Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan; Gillian Thomas, M.D. (Odette Cancer Centre, Sunnybrook Health Sciences Centre and Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada)
2.6 References


Chapter 3 Dosimetric impact of organ motion during IMRT

Aim 2: Analyze tumour and organ dynamics

Aim 3: Analyze the dose consequences of these tumour and organ dynamics on currently used IMRT strategies


My contribution as lead author in this research includes the creation of formalized target definitions for the clinical target volume (as explicit ones were lacking in the literature). This led directly to my role in leading the drive for consensus guidelines (Chapter 2). I was intimately involved in all aspects relating to the contouring, planning and dose accumulation, including review and quality assurance of all the contours and plans generated. The wide range of interdisciplinary expertise required to make this research a reality meant that I needed to chair weekly/fortnightly research meetings to co-ordinate contouring of cases; surface meshing of contours; planning; dose accumulation of plans; trouble-shooting on various aspects of the research progress; strategizing on publication and abstract goals, in addition to determining the future directions this research could take. It was my responsibility to ensure that research goals were met and to achieve a comprehensive, coherent synthesis of the research results within a meaningful clinical context.

This chapter was published as “Pelvic IMRT for Cervix Cancer: Is what you plan actually what you deliver?” in the International Journal of Radiation Oncology, Biology, Physics. 2009 May1;74(1):304-12.
3 ABSTRACT

Purpose: Whole pelvic IMRT is increasingly being used to treat cervix cancer and other gynaecologic tumours. However, tumour and normal organ movement during treatment may substantially detract from the benefits of this approach. This study explores the impact of internal anatomic changes on the dose delivered to the tumour and organs-at-risk (OARs) using a strategy integrating deformable soft tissue modeling with simulated dose accumulation.

Methods and Materials: Twenty patients with cervix cancer, had baseline and weekly pelvic MRI scans during treatment. Inter-fraction organ motion and delivered (accumulated) dose was modeled for three treatment scenarios: four-field box (FFB), large margin whole pelvic IMRT (LM; 20 mm PTV but 10 mm inferiorly) and small margin IMRT (SM; 5 mm PTV).

Results: Individually, planned dose was not the same as simulated delivered dose, but when taken as a group, this was not statistically significant for FFB and LM plans. Surprisingly, SM IMRT plans yielded adequate target coverage in most patients, however, significant target underdosing occurred in one patient who displayed excessive, unpredictable internal target movement. Delivered doses to the OAR were significantly reduced with the SM plan, although there was substantial variability among patients.

Conclusion: Simulated dose accumulation may provide a more accurate depiction of target and OAR coverage during fractionated whole pelvic IMRT for cervix cancer. The adequacy of primary tumour coverage using 5mm PTV margins is contingent on the use of daily image-guided set-up.

3.1 INTRODUCTION

Whole pelvis radiation treatment for cervix cancer has remained largely unchanged for decades, and the associated gastrointestinal (GI), genitourinary (GU) and haematological toxicities due to these large fields have been accepted as unavoidable. Further dose escalation to gross disease is often achieved with brachytherapy, with the understanding that its highly conformal nature will help to limit long-term toxicity to surrounding normal structures. The introduction of concurrent
chemoradiation (CTRT) improved overall survival rates for cervix cancer, at the cost of increased acute toxicity (1). Late grade 3 or 4 toxicity is estimated to affect up to 20% of patients, however the incidence is generally under-reported (2).

A number of groups have explored intensity-modulated radiotherapy (IMRT) in the gynaecological setting as a means to minimize GI, GU and bone marrow (BM) toxicity (3-7). Planning studies have reported up to a 2-fold reduction in the dose delivered to small bowel and a 23% reduction in the volume of rectum and bladder receiving the prescribed dose compared to conventional radiotherapy fields (4). However, concerns about tumour movement during treatment and geographical target miss have resulted in generous PTV margins for most of these studies (up to 2.5 cm), which can increase the volume of normal tissue irradiated (8). Toxicity could probably be reduced even further if radiation treatment planning and delivery were optimized.

Current assessment of IMRT plans and dose volume histograms (DVHs) are based on the planning CT, a single image set taken at one time point prior to the start of treatment. The dosimetry and DVHs do not necessarily represent the actual dose delivered to the tumour and organs at risk (OARs) during treatment, as intra- and inter-fraction organ motion are not accounted for. In addition, the tumour often regresses and deforms during treatment (9), which may cause the OARs to move into the high dose region, resulting in greater dose being delivered to these structures than anticipated based on the initial plan.

The purpose of this study in cervix cancer patients, is to demonstrate the dosimetric impact of tumour regression and inter-fraction tumour and OAR motion for three different clinically relevant planning scenarios: standard four-field box pelvic RT (FFB); a large margin IMRT plan (LM; 20 mm PTV margin except 10 mm inferiorly) and a small margin IMRT plan (SM; 5 mm PTV margin). This is the first study to model dose accumulation over the course of fractionated treatment in the setting of pelvic IMRT for cervix cancer, thus presenting a more realistic scenario of actual dose delivery.
3.2 METHODS & MATERIALS

Twenty women with cervix cancer, participating in a research ethics board approved prospective study involving weekly MRI scans during treatment, were selected for this planning study. These were consecutive patients who had completed a minimum of 5 weekly MRI scans. The patients had stage IB-IIIB disease, and all underwent whole pelvis radiotherapy (45-50Gy in 1.8-2 Gy fractions over 5 weeks) with concurrent weekly cisplatin chemotherapy (CTRT) prior to intra-cavitary brachytherapy (Table 3.1).

<table>
<thead>
<tr>
<th>Category</th>
<th>Number (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>44 (31-70) years</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>11 (55%)</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma/Adenosquamous carcinoma</td>
<td>7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Small cell or Glassy cell</td>
<td>2 (10%)</td>
<td></td>
</tr>
<tr>
<td><strong>FIGO stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB and IIA</td>
<td>10 (50%)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>4 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>MRI tumour volume</strong></td>
<td></td>
<td>46.4 (8.0-199.4) cm³</td>
</tr>
<tr>
<td><strong>EBRT dose</strong></td>
<td></td>
<td>4780 (4500-5040) cGy</td>
</tr>
<tr>
<td><strong>Courses of cisplatin</strong></td>
<td></td>
<td>4.8 (2-5)</td>
</tr>
</tbody>
</table>

Table 3.1. Patient and treatment characteristics. FIGO International Federation of Gynecology and Obstetrics; EBRT external beam radiotherapy

3.2.1 Imaging

Each patient had an initial computerized tomography (CT) scan and pelvic magnetic resonance imaging (MRI) scan for radiotherapy planning, then weekly MRI scans during external beam radiotherapy using a protocol described previously (10). In an attempt to minimize internal organ motion, patients were instructed to use a mild laxative 12 to 24 hours prior to each scan and to drink 500 ml of water one hour in advance after voiding completely. Five of the twenty patients had six MRI scans and 15 patients had five scans.
3.2.2 Target Delineation

Contouring occurred on the planning MR and each of the weekly MR image sets. The MRI scans were fused to the baseline planning CT images using bone matching. Clinical target volumes were contoured on the fused axial MR slices following ICRU 50 (11) & 62 (12) recommendations. All contours were created by one individual who was experienced in MR imaging (JX), and reviewed by a second investigator (KL).

Two clinical target volumes were contoured, namely the primary tumour clinical target volume (pCTV) and the nodal clinical target volume (nCTV). There were five components to the pCTV definition: the gross tumour (GTV, high signal on T2 weighted MRI, plus a 7 mm expansion to account for microscopic spread, excluding bowel, bladder and rectum if they were not clinically involved); the parametria; the remaining normal cervix; the lower uterus (2 cm above gross tumour) or entire uterus (if tumour invaded myometrium) and the upper vagina (2 cm below gross tumour).

The radiographic boundaries of parametrial tissue are poorly described in the literature in relation to radiotherapy volume definition and treatment planning. Following consultation with experienced gynaecologic MR imaging and surgical colleagues, we defined parametria as the soft tissue lateral to the cervix and uterus, encompassed by the broad ligament. This is bounded laterally by the bony pelvis; anteriorly by the posterior wall of the bladder and the peritoneal reflection; posteriorly by the mesorectal fascia and uterosacral ligaments; inferiorly by the pelvic diaphragm and superiorly by the appearance of sigmoid crossing over the uterus or fallopian tube. Parametrial boundaries were seen to vary substantially with bladder filling, particularly for the anteverted uterus [Figure 3.1a & b].

The nCTV encompassed internal, external and common iliac lymph nodes. The corresponding vessels were contoured and expanded by 7 mm; this expanded volume was then modified as per Taylor et al. (13) with a 10 mm presacral strip and an 18 mm lateral sidewall strip. In the low pelvis, the nCTV often overlapped with the parametrial aspect of the pCTV [Figure 3.1c].
Figure 3.1. Axial T2-weighted MR images with coronal and sagittal reconstructions of one patient. 3.1a & b shows the same axial level a week apart. The gross tumour volume (red), bladder (green) and parametrial volume (cyan) are shown at week 1. Parametrial volume defined at week 2 (pink) with empty bladder (green) demonstrates a marked difference. 3.1c shows axial image through the pelvis at a higher level, nodal CTV contour (nCTV, orange) overlaps with the parametrial contour (cyan).
OAR were contoured (bladder, rectum, sigmoid, small bowel and femoral heads) as solid organs. Small bowel was defined as a contiguous volume encompassing the peritoneal cavity to 1.5 cm above the most superior vessel contour. The recto-sigmoid junction was defined as the point where rectum was seen to be moving anteriorly, away from the pre-sacral space, which generally occurred around S2/3. For consistency, the rectum was contoured inferiorly to the bottom of the pubic symphysis.

3.2.3 Margins

Planning target margins were based on previous work at our institution, which described the inter- and intra-fractional cervix and uterus motion in detail using cine-MRI (10). Intra-fraction motion was found to be relatively small, averaging 4 mm for the cervix. Inter-fraction motion was significantly more variable ranging up to 15 mm for the cervix and 40 mm at the fundus. For the purpose of this study, three nominal plans were generated. The first was a traditional four-field box (FFB) based on the pCTV and bony landmarks. Field borders and corner shielding were placed based on standard clinical practice (14). A large margin (LM) IMRT plan was created using a 20 mm PTV margin except 10 mm inferiorly around the vaginal portion of the pCTV. It was anticipated that this margin size would be large enough to account for both inter- and intra-fraction organ motion at the cost of higher than necessary doses to the OARs. A small margin (SM) IMRT plan was also created using a 5 mm PTV margin around the pCTV, anticipating that this would only account for intra-fractional organ motion and would be insufficient to achieve good target coverage in the setting of large inter-fraction motion. However, the SM plan was anticipated to provide better OAR sparing.

3.2.4 Radiotherapy Treatment Planning

The contoured weekly MR image sets and the pre-treatment planning CT images were imported into specialized research software (ORBIT Workstation, RaySearch Laboratories AB) for the purposes of IMRT planning and assessment of accumulated dose from day to day over a course of fractionated radiotherapy. The baseline MRI contours were used to generate the nominal plan. A direct machine parameter optimization method for step and shoot IMRT was used with 6 MV photons, 7 beams (maximum of 120 segments in total), a minimum MU/segment of 2 and a
multi-leaf collimator leaf size of 5 mm. A single, experienced dosimetrist (VK), generated all the plans.

The primary objective was adequate target coverage, with OAR sparing being secondary. The prescribed dose was 5000 cGy and hot spots of up to 110% were allowed provided that they did not occur in any critical organs. The primary planning objective was for 98% of the pCTV and nCTV to be covered by the 98% isodose (4900 cGy). To allow direct comparison between the FFB and IMRT plans, the FFB plans were normalised to ensure that 98% of the target also received at least 4900 cGy. Dose constraints for the OARs were conservatively based on the current RTOG 0418 protocol for post-operative IMRT of endometrial and cervix cancer, and are summarized in Table 3.2.

<table>
<thead>
<tr>
<th>Minor deviations</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>Less than 35% volume to get 4500 cGy or more</td>
</tr>
<tr>
<td>Rectum</td>
<td>Less than 60% volume to get 3000 cGy or more</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>Less than 60% volume to get 3000 cGy or more</td>
</tr>
<tr>
<td>Femoral heads</td>
<td>Up to 15% volume to get 3000 cGy or more</td>
</tr>
</tbody>
</table>

Table 3.2. Plan optimization criteria and dose constraints; GTV gross tumour volume; pCTV primary tumour clinical target volume; nCTV nodal clinical target volume; PTV planning target volume
3.2.5 Deformable Dose Accumulation

The difficulty with dose accumulation in the setting of changing organ geometry (motion, deformation, regression), is trying to resolve where dose has been deposited at one time point versus another. A simple overlay of contours and summation of dose does not provide an accurate picture of dose delivered when organ geometry has changed over time. We chose to approach this problem using two different software components, MORFEUS (a finite-element model-based deformable registration algorithm) and ORBIT Workstation. MORFEUS was used to resolve the geometric discrepancy of changing organ geometry over time, while ORBIT was used to calculate dose accumulation in light of this organ motion.

MORFEUS was used to convert the tumour and OAR contours from the baseline and each weekly MR image set into representative 3-dimensional surface meshes. Each weekly surface mesh was then deformed using MORFEUS to match the baseline mesh representing the pre-treatment anatomic state [T0] [(Figure 3.2). Tumour and OAR delivered dose accumulation over a five-week course of treatment was simulated by applying the nominal isodose distribution generated using the baseline MR contours to each of the subsequent weekly image sets, ignoring internal soft tissue anatomy changes, thereby simulating delivered dose in the presence of interfraction organ motion [Figure 3.3a-e]. Using the surface mesh data from MORFEUS, organ geometry at each time point was then deformed back to match the baseline geometry. By doing so, the simulated delivered dose to each tumour and OAR voxel, at each time point, was mapped to the corresponding voxel in the baseline image set [Figure 3.3f]. The fractional doses to each voxel were then summed to determine the total accumulated dose over the course of treatment.
Figure 3.2. Schema for modeled delivered dose accumulation during fractionated radiotherapy. MRI_0: Baseline (planning) MR images and contours, MRI_n: MR images and contours from week n of treatment, T0: Baseline surface meshes representing tumour and organ geometry, Tn: Surface meshes of tumour and organ geometry from week n of treatment, FFB: Four-field box plan, LM: Large margin plan, SM: Small margin plan.
Figure 3.3. Sagittal images with superimposed surface meshes for the patient with significant underdosing of the pCTV during treatment with SM plan. The images show the organ geometry with the planning dose distribution overlaid at (a) baseline, (b) week 1, (c) week 2, (d) week 3 and (e) week 4. Note the variation in bladder (green) volume, tumour (red) regression and the change in uterine (blue) position from upright to anteverted. The last image (f) shows the final accumulated dose, with the organ geometry deformed back to the baseline geometry. Dose distribution: red 5000 cGy, orange 4900 cGy, yellow 4750 cGy, green 4500 cGy, blue 3000 cGy
Dose accumulation was performed for the FFB, LM and SM plans. Perfect daily image-guided set up to bone was assumed for the purposes of this planning study. The delivered tumour and OAR doses derived from each of the weekly MR image sets was assumed to apply for five fractions to allow simulation of accumulated dose over a typical five-week course of treatment. There was no re-calculation of dose based on the MR images or any bulk attenuation correction. Nominal and accumulated doses for all three plans were compared using the Student t-test with a significance value of p<0.05. The accumulated doses to the GTV, pCTV and OARs from the three plans were compared using one-way ANOVA with a Bonferroni correction. Statistical analysis was performed using SPSS v16. Target coverage was assessed on accumulated dose to GTV D98 ≥ 5000 cGy and pCTV D98 ≥ 4900 cGy. Dose to GTV and pCTV D98 below 95% of prescribed dose (4750 cGy) was also assessed as this was felt to be a clinically relevant dose threshold. The accumulated nCTV dose was not assessed in this study as the nodal volume is relatively fixed to bone and was assumed to have received nominal dose.

3.3 RESULTS

3.3.1 Tumour and OAR Volume and Position during Radiotherapy

The mean GTV for all patients at baseline was 46 cm³ (range 8–199 cm³). The relative reduction in GTV from baseline to the end of external beam radiotherapy ranged from 48-96%. The mean pCTV at baseline was 232 cm³ (range 110-479 cm³) and the relative reduction in pCTV from baseline to the end of treatment ranged from 8-77%. Despite the use of a bowel and bladder regimen intended to minimize day-to-day differences in normal organ filling, there was substantial variation in bowel and bladder volume during treatment in some patients. The maximum change in bladder volume in individual patients relative to baseline was between 7% and 450%, and the maximum relative change in rectal volume was between 39% and 380%.

Organ motion was measured as the relative displacement of all the surface nodes of each weekly surface mesh relative to baseline using data from MORFEUS. The results are summarized in Table 3.3. The Euclidean vector displacement motion ranged up to 3 cm for the GTV, cervix and bladder, 4.5 cm for the uterus and 4 cm for the rectum-sigmoid.
<table>
<thead>
<tr>
<th>ROI</th>
<th>Grand Mean ± SD (range) in cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left-Right</td>
</tr>
<tr>
<td>GTV</td>
<td>0.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(-0.5-0.8)</td>
</tr>
<tr>
<td>Cervix</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>(-0.5-1.0)</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>(-0.0-1.8)</td>
</tr>
<tr>
<td>Upper Vagina</td>
<td>0.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>(-0.2-0.2)</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.1 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(-0.5-0.5)</td>
</tr>
<tr>
<td>Rect-Sig</td>
<td>0.1 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>(-0.5-0.8)</td>
</tr>
</tbody>
</table>

Table 3.3. Summary of organ motion based on MORFEUS surface mesh deformations. ROI region of interest; GTV gross tumor volume; SD standard deviation

### 3.3.2 Delivered (Accumulated) Dose to GTV and pCTV

Taken as a group, there were no statistically significant differences between the planned and delivered (accumulated) doses to the GTV or pCTV with either the FFB or LM plans. However, there was a significant reduction in delivered dose with the SM plan, as shown in Figure 3.4. The SM mean GTV D98 decreased from 5017 cGy to 4987 cGy (p = 0.005) and the mean pCTV D98 decreased from 4920 cGy to 4865 cGy (p = 0.001). The SM accumulated GTV dose was ≥95% of the prescribed dose in all patients, and the pCTV accumulated dose was ≥95% in all but one patient, despite the small 5 mm PTV margin. In the single case where the pCTV was significantly underdosed (4656 cGy), the uterus at baseline was relatively upright but became antverted as treatment progressed and the tumour regressed, resulting in a lower than expected dose (4473 cGy) to the lower uterus [Figure 3.3a-e]. This shift in anatomy during treatment was not predictable based on pre-treatment clinical characteristics or the baseline planning images.
Figure 3.4. Box plots of nominal and accumulated dose to 98% of the gross tumour volume (GTV) and primary tumour clinical target volume (pCTV) for four-field box (FFB), large margin (LM) and small margin (SM) plans. One patient (red arrow) demonstrated clinically significant underdosing to pCTV with the SM plan on dose accumulation.
3.3.3 Delivered (Accumulated) Dose to OARs

The planned and delivered (accumulated) doses to the OARs for each of the three plans were not significantly different when all patients were considered as a group. However, from Figure 3.5 it is evident that individually, some patients demonstrated markedly greater OAR doses with organ motion factored in, while others demonstrated lower doses. It was also evident that as the margin size decreased, the variability in the accumulated OAR doses increased.

There were significant differences in the delivered OAR doses among the three plans, as shown in Figure 3.6. There was a progressive decline in the median dose to the bladder, rectum and sigmoid with the decrease in PTV margins associated with the FFB, LM and SM plans [Figure 3.6a]. The median bladder, rectum and sigmoid doses were reduced by 770 cGy, 300 cGy and 390 cGy respectively with the SM plan compared to the FFB plan (p<0.001 for all comparisons), although there was substantial variability among patients with some realizing even greater benefit. Similarly, the volume of the OARs receiving 90% or more of the prescribed dose (4500 cGy) was reduced with the SM compared to the FFB plans [Figure 3.6b]. There was a 55% reduction in bladder volume receiving the highest doses (p<0.001), a 30% reduction in rectal volume (p<0.001) and a 23% reduction in sigmoid volume (p=0.001). In general, the bladder dose was reduced the most with the use of small 5 mm PTV margins, followed by the sigmoid and rectal doses. Small bowel was defined in this study as a potential space that individual loops could occupy during treatment. There were no significant differences in the median small bowel dose among the three plans.
Figure 3.5. Normalized delivered doses for four-field box (FFB), large margin (LM) and small margin (SM) plans for rectum, sigmoid and bladder. Nominal OAR doses for each patient has been normalized to 1.0. If delivered dose was similar to planned dose, the normalized delivered OAR doses should lie close to 1.0.
Figure 3.6. Box plots of nominal and delivered (accumulated) dose to organs at risk (OARs) for the three plans - (a) Median dose, (b) V45 (volume of the organ receiving 4500cGy).
3.4 DISCUSSION

Tumour and normal tissue movement, deformation and volume change, are recognized to occur during pelvic radiotherapy for cervix cancer, potentially limiting the benefits of new highly conformal treatment approaches (3-7). Primary tumour PTV margins of 1.5-2.5 cm have been advocated based on the results of previous studies measuring inter-fractional tumour and organ movement (10, 15). This study is the first to simulate delivered dose to the tumour and OARs during a fractionated course of whole pelvic IMRT for cervix cancer. Using an approach integrating deformable soft tissue modeling with dose accumulation, we could account for many of the important factors known to influence dose delivery, including changes in anatomy during treatment and the characteristics of the treatment plan in individual patients. The results, surprisingly, suggest that smaller PTV margins on the order of 5 mm may be sufficient in many, although not all patients, and that these smaller margins may be associated with reduced dose to critical normal tissues.

A prerequisite for this work was an unambiguous definition of the pCTV for whole pelvic IMRT, including the tissues at high risk of microscopic tumour extension, which had not been addressed explicitly previously. Our pCTV definition was developed by reviewing the limited available literature, supplemented by discussion with experts in surgical gynaecologic oncology and medical imaging. It included the primary tumour with a 7 mm margin, entire cervix, parametria to the pelvic sidewall, 2 cm of vagina below gross tumour and 2 cm of uterus above gross tumour or the entire uterus if gross tumour involved the uterus. Traditionally, the entire uterus was incorporated in the high dose volume in all patients, although we could find little objective evidence to support this approach. The fundus is the most mobile aspect of the uterus (10) and could contribute to the adoption of excessive PTV margins. Overall, this pCTV definition is consistent with recent guidelines for image-guided brachytherapy (16). It is important to recognize that the results of our study depend heavily on this definition and may not translate directly to other situations.

There are several factors in addition to the pCTV definition that might explain why smaller PTV margins than previously advocated were found to be sufficient for the majority of cervix cancer patients in this study undergoing whole pelvic IMRT. Many of the prior studies based PTV
margins recommendations on the movement of representative uterine points (10, 15) rather than on the composite movement of the entire pCTV. Movement of a point within a larger target volume that moves in an asymmetric manner may lead to an overestimate of the required PTV margin. We have previously reported that the external cervical os may move 1 cm or more between fractions (10). However, in the context of this study, much of this movement was contained within the larger pCTV that included the lower uterus, upper vagina and parametria (fixed to the pelvic sidewall and relatively immobile laterally), thereby minimizing the PTV requirement. In addition, previous PTV estimates were often based on geometric considerations alone without regard for the characteristics of the treatment plan, and in particular dose gradients near the edge of the target volume. Portions of the CTV that transiently move outside the PTV continue to receive at least some dose, reducing the adverse dosimetric consequences of this movement. IMRT plan conformality can be challenging to optimize, particularly with the complex shapes seen in whole pelvic IMRT for cervix cancer, and can significantly influence the required PTV margin. In addition, our very conservative prescription parameters (GTV D98 to receive 100% dose; CTV D98 to receive 98% dose) would have contributed to more forgiving dose gradients and further reduced the adverse consequences of target movement.

While a 5 mm PTV margin around the pCTV was adequate for most patients in this study, one patient exhibited excessive target movement that resulted in clinically significant reductions in dose. This movement could not have been predicted from the planning images alone. The relationship between organ motion, organ filling and tumour regression during fractionated radiotherapy is complex and multifactorial, as witnessed by the generally poor correlations between bladder or rectal filling and organ motion that have previously been reported (10, 15). Despite attempts to maintain consistent bladder and rectal volumes through explicit instructions to patients about fluid consumption and laxative use, there was still marked intra-individual variation. Changes in bladder volume were noted to alter the configuration of the parametrial tissues (Figure 3.1) and tumour regression resulted in a substantial change in the position of the uterus in at least one patient. Therefore, the use of small PTV margins on the order of 5 mm should only be contemplated in the setting of daily soft tissue imaging of internal tumour and OAR anatomy with isocentre correction to minimize random targeting errors. Systematic changes in tumour and OAR position, shape and volume during radiotherapy for cervix cancer imply that adaptive strategies, whereby the treatment plan is repeatedly revised based on updated
imaging to account for these changes, have the potential to both improve target coverage and reduce side effects.

Our study has several limitations. MRI scans were performed weekly during external beam radiotherapy, providing information about target and OAR movement for only 20% of the treatment fractions. Extrapolation over the whole course of radiotherapy might have biased our findings by over-estimating systematic errors and under-estimating random errors in tumour and organ motion. Work is currently underway at our institution to recruit a validation cohort where cervix cancer patients will have MRI scans done three-times per week during treatment, thereby allowing more accurate modeling of motion and deformation. The delivered (accumulated) dose to pelvic lymph nodes (nCTV) was not evaluated, but rather the nodes were assumed to be fixed to the pelvic sidewall and to receive the planned dose with each fraction. Set-up errors were assumed to be zero. If we were to factor in random set-up errors, our PTV margin requirements would likely be larger. Our dose accumulation relies on accurate modeling of soft tissue deformation. While MORFEUS has been validated in other tumour sites (lung, prostate, liver), work is currently underway to validate it for cervix cancer using intra-uterine fibroids and cervical cysts as internal anatomic surrogates.

3.4.1 CONCLUSION

Tumour and OAR movement, deformation and change in volume can be substantial over a course of fractionated whole pelvic IMRT for cervix cancer. The unpredictable, individualized nature of these organ dynamics makes delivery of highly conformal therapy complicated. PTV class solutions derived from simplified geometric analyses of the movement of discrete points might yield margin estimates that are larger than necessary for most patients. The more comprehensive approach used in this study, which integrates deformable soft tissue modeling with simulated delivered dose accumulation from fraction to fraction, suggests that smaller PTV margins on the order of 5 mm can be used in most, although not all patients. Random variation in internal anatomy may be substantial in individual patients, mandating the use of daily soft tissue imaging with correction for targeting errors. Overall, the ability to reliably model dose accumulation is a powerful tool in understanding and optimizing our planning strategies in order to maximize local control while minimizing normal tissue toxicity. It will facilitate the future
development of adaptive radiotherapy strategies, with the expectation of further improvement in outcome for patients with cervix cancer.

3.5 ACKNOWLEDGEMENTS

Grateful acknowledgements to Dr. Masoom Haider and Dr. Jason Dodge for their advice and expertise. This work is supported through funding from a CIHR Strategic Fellowship in the Excellence in Radiation Research for the 21st Century Program, RaySearch Laboratories and the Giovanni and Concetta Guglietti Family Trust.
3.6 References


4 General Discussion

The value of IMRT in the treatment of cervix cancer lies in the ability to target the CTV while sparing surrounding normal tissues. This presumes accurate target definition at the time of planning and accurate target localisation throughout treatment.

The broad range of CTV definitions used for IMRT treatment of cervix cancer in studies performed to date points towards a need for consensus guidelines. The high specificity but only moderate sensitivity demonstrated by the experts in the contouring case (Chapter 2), reflects the challenges of target delineation for this site. While it is relatively clear what tissues should not be included in the CTV, discriminating between the different primary CTV components (particularly the cervix and parametria) is more difficult. The formalization of a primary CTV consensus definition helps to alleviate these problems by minimizing variability among experienced oncologists routinely involved in the care of these patients.

The tumour and organ motion that occurs during a course of radiotherapy for cervix cancer can be substantial, both as a function of tumour regression and deformation as well as differences in organ filling (such as bladder and rectum). This motion is complex, highly individualised and unpredictable. As such, any highly conformal radiotherapy plan for cervix cancer is fraught with the potential for geographical target miss unless daily soft tissue imaging and motion correction is utilized.

Not surprisingly, the tumour and organ motion demonstrated in this work translated to statistically significant differences in “planned” versus “delivered” dose when dose accumulation was modeled (Chapter 3). There was little difference between “planned” and “delivered” dose for the FFB and LM plans (both in primary CTV coverage and OAR sparing), but based on POI motion studies from previous work (1), it was anticipated that the SM plans would demonstrate greater OAR sparing but at the cost of primary CTV under-dosing with dose accumulation. While the smaller PTV margins did indeed result in OAR sparing for the patient group as a whole, it conversely resulted OAR over-dosing in more than one patient [Figure 3.5; pp 87]. In terms of primary CTV coverage, surprisingly, only one patient demonstrated clinically significant under-dosing.
The development of primary CTV definition guidelines for radiation treatment of cervix cancer was a collaborative effort involving international experts in the field of gynaecological radiotherapy and forms an important foundation for further development of image-guided radiotherapy and translation into clinical practice. It is based on the best evidence available within the literature and is intended to provide radiation oncologists in the wider community with guidance and facilitate more consistent practice in target delineation for cervix cancer. Consistency in target definition is valuable in the auditing of treatment outcomes and assessment of plan quality. It is anticipated that these guidelines will form the basis of target definition in future prospective IMRT studies for cervix cancer (such as RTOG 0918). The boundaries and PTV margins recommended in the guidelines were necessarily conservative to minimize target miss, particularly if the guidelines were going to be used in a non-academic setting where experience with image-guidance was not as well established. The guidelines were not meant to be prescriptive and I anticipate that they will evolve over time as information from ongoing studies mature.

Pelvic, and sometimes para-aortic, lymph nodes are an important target for definitive radiotherapy in cervix cancer. These draining lymph nodes form a nodal CTV which is usually amalgamated with the primary CTV for treatment purposes. Near the pelvic sidewalls the nodal CTV overlaps with the lateral parametrial volume [Figure 2.6; pp 63]. The focus of this work was the development of the primary CTV definition as comprehensive pelvic lymph node CTV definitions have already been published by a number of authors using CT and MR based techniques (2-4). Similarly, for the purposes of the dose accumulation study, the nodal CTV (comprising of the internal, external and common iliac nodal groups) was included as part of the composite CTV, but assumed to be fixed from day to day by virtue of their position along the pelvic sidewall. Unpublished studies (personal communication, Chan and Dinniwell) have shown that the PTV margin required to encompass inter-fraction motion of the pelvic lymph nodes is 3-4mm. As such, the nodal CTV was assumed to receive nominal dose in the dose accumulation study.

More accurate estimations of organ and target motion for cervix cancer have been achieved in this study using more frequent state of the art imaging (with MRI) and surface deformation meshes, rather than isolated COM/POI representations as in previous work. Deformable surface meshes provide a more comprehensive three dimensional picture of the complex motion that
occurs over a course of fractionated radiotherapy, one that explicitly accounts for the interactions between tumour and normal tissues as well as changes in shape and size of these structures. COM /POI techniques only provide limited information about the motion of a single point rather than an entire volume (and its relationship to other adjacent volumes), thereby potentially overestimating the necessary PTV margin. This is borne out to some extent by our dose accumulation results. The complex interplay between normal OAR motion during treatment, combined with concurrent tumour regression, resulted in substantial target motion.

The ability to take this tumour and organ motion data and model the dosimetric consequences of it in twenty cervix cancer patients provides important insights into the use of highly conformal radiotherapy for cervix cancer. The wide range of acute toxicity associated with the use of pelvic IMRT in the clinical studies to date has contrasted sharply with the clear dosimetric advantages reported in earlier planning studies. One reason for this might lie in the PTV margins used for many of these studies, which ranged from 5-10mm, sometimes in conjunction with a 20 mm expansion of the GTV to form the CTV. It stands to reason that larger margins around prescribed targets for sub-clinical disease extension or motion will result in less normal tissue sparing. It was anticipated that the 5 mm PTV margin would be insufficient for primary CTV coverage based on work by Chan et al, but in fact, only one patient demonstrated clinically significant under-dosing. This would imply that PTV margins used in previous IMRT studies may be too generous. A reduction in the PTV margin might greatly improve the treatment toxicity profile for these patients. However, it should be noted that our findings are dependent on a number of factors including CTV definition used; prescription specified; plan conformality; as well as the deformation and dose accumulation modelling performed.

The conservative target definitions (explicit definitions of the parametria) resulted in a potentially larger CTV than that defined by previous studies. This large primary CTV encompasses tumour components which demonstrate complex organ motion. The central structures (such as the uterus, cervix, GTV, medial parametrial tissue) move much more (due to tumour regression and variation in bladder and rectal filling) than the soft tissues of the lateral parametria which remain fixed to the bony pelvic sidewalls. Therefore, it is more likely that the extreme motion exhibited by the primary CTV in the central pelvis will remain within the defined primary CTV, resulting in less target-miss. The exclusion of the uterine fundus (most mobile portion of the CTV), from the target volume in the dose accumulation study, may have
also contributed to the lack of target under-dosing seen in the results. The necessity of treating the uterine fundus is an area of controversy which was debated among experts-in-the-field during the process of generating consensus guidelines for the CTV definition. While traditionally, the entire uterus is included in the pelvic radiotherapy volume, it is not clear if this is always necessary. Although isolated fundal recurrences appear rare, it could be argued that this is due to the fundus always being included in the target volume. However current knowledge of the large extent of uterine fundal motion makes it likely that this organ is not always situated within the high dose volume throughout treatment (1, 5, 6). In addition to this, the uterine fundus is sometimes intentionally excluded from standard pelvic radiotherapy fields in cases where the uterus is expanded due to large fibroids and the tumour is confined to the cervix. Excluding the uterine fundus potentially decreases the target volume and results in greater sparing of surrounding normal tissues. Conservative dose prescriptions (98% of GTV to get 100% of prescribed dose and 98% of CTV to get 98% of prescribed dose) also meant the dose gradient around the CTV was more forgiving. Disease regression might also have contributed to an increased tolerance for target motion towards the end of treatment, particularly in situations where the initial tumour volume was large and represented a substantial proportion of the CTV [Figure 4.1a]. Our imaging was limited to once a week, potentially under-estimating the random organ motion which might occur over a 5 week course of radiotherapy.
Figure 4.1. Sagittal images of a cervix cancer patient at the start of treatment (a) and in the last week of treatment (b). A patient with a very large CTV at the start of treatment (a) undergoes substantial tumour regression during external beam radiotherapy. Despite a large change in the position of her uterus (blue surface mesh), her primary CTV remains well within the high dose region. Unfortunately, her bowel (arrows) also moves into the high dose region (b).

Colourwash represents percent prescribed dose: red (100%); orange (95%); yellow (90%); green (80%); light blue (60%); dark blue (40%). Surface meshes represent organs: bladder (green); uterus (dark blue); gross tumour volume (GTV, red); cervix (khaki); upper vagina (pink); recto-sigmoid (cyan). Bowel (pale yellow contour).
Due to the large, complex target volumes inherent in the radical treatment of cervix cancer, it can be difficult to achieve tight dose conformality. Thus, while the PTV margin may be 5mm, the actual distance from the primary CTV to the 95% isodose line may be several millimetres more, [Figure 4.2] allowing for greater tolerance for organ motion. While the issue of dose conformality is routinely considered in the setting of stereotactic radiotherapy, it’s implications in the setting of IMRT and PTV margins are only starting to be recognised. Most PTV margin recipes taking into account geometrical uncertainties (7, 8) assume perfect dose conformality with the PTV, when in fact, the dosimetric margin can be larger than the geometric PTV margin (9). The distance of the 95% isodose line beyond the PTV margin can have significant implications on the plan’s tolerance of inter- and intra-fraction tumour and organ motion. Only one IMRT planning study assessed dose conformality in gynaecological patients receiving radiotherapy to the pelvis. While Georg et al found that IMRT plans achieved better dose conformity than WPRT, the impact of this conformity on tolerance to target motion was not assessed (10).

The normal tissue sparing seen in this study also highlights the unpredictable, individualistic nature of organ motion in patients with cervix cancer. While a general trend for greater OAR sparing with smaller PTV margins was seen, there were some patients who demonstrated marked increases in OAR dose with the small margin IMRT plan [Figure 3.5; pp 87]. There are many possible reasons for this. A shrinking GTV over the course of treatment can result in the surrounding OARs moving into the high dose region [Figure 4.1b], systematic shifts during treatment in the position of the CTV (due to an overly full or empty bladder or rectum on the initial planning scan, for example) could also cause over-dosing of these normal tissues. Our past understanding of dose constraints for surrounding normal tissues was based on dose-volume histograms derived from single static planning images. The dosimetric consequences of organ motion, (as demonstrated in [Figure 3.5]) were not appreciated in these earlier studies. The ability to model organ motion and accumulate delivered dose over a course of fractionated radiotherapy, as was done in this study, provides a more accurate representation of dose-volume relationships for tumour and normal tissues, paving the way to a greater understanding of tumour control and normal tissue complication probabilities (11).
Colourwash represents percent prescribed dose: red (100%); orange (95%); yellow (90%); green (80%); light blue (60%); dark blue (40%). Surface meshes represent organs: uterus (dark blue); gross tumour volume (GTV, red); cervix (khaki); upper vagina (pink); recto-sigmoid (cyan). Primary CTV (blue contour); primary PTV with 5 mm margin (green contour); nodal CTV (orange contour).

Figure 4.2. Axial (a) and sagittal (b) images of a cervix cancer patient. Achieving dose conformality with a complex target volume is challenging. The 95% isodose line (black arrows) can lie some distance from the edge of the PTV (white arrows), effectively increasing the therapeutic dosimetric margin.
This study is among the first to formally document the dosimetric consequences of tumour and organ anatomic changes during radiotherapy on the actual doses received by these structures. An important finding is that, while IMRT appears to cover the target and spare surrounding normal tissues based on the initial anatomy from the planning image set, this may not always be the case during treatment. Without daily soft tissue image guidance, highly conformal radiotherapy risks target miss and OAR overdosing due to the substantial organ motion that often occurs. The conundrum lies in the use of an adequate uniform PTV class solution. PTV margins large enough to encompass the extremes of target motion in all patients substantially reduce normal tissue sparing and the benefit of IMRT in terms of reduced acute and late toxicity. Therefore the only way to be assured of adequate target coverage while still maximising OAR sparing in the setting of IMRT, would be through a process of treatment adaptation in conjunction with smaller PTV margins (12, 13).

Adaptation can take a number of forms, the simplest being adaptation to changes in target position through volume translation and/or rotation. The difficulty with this in cervix cancer lies in the differential motion between the nodal CTV and the primary CTV. The immobility of the nodal CTV along the bony pelvic sidewall, compared to the substantially more mobile primary CTV within the central pelvis, can lead to a major problem with simple translational shifts for soft tissue matching. When the IMRT plan consists of a combined nodal and primary CTV, if the primary CTV has altered position due to inter-fraction motion, simple translational shifts to compensate for this could cause the nodal CTV to be under-dosed. [Figure 2.7; pp 66] One may think the solution to this problem would be to divide the nodal CTV and primary CTV into two separate IMRT plans. The difficulty lies in achieving dose homogeneity where the two plans intersect or overlap in the low pelvis. The interface between lateral parametrial tissues and the medial nodal CTV is difficult to distinguish. Ensuring that there are no areas of under- or overdosing in the low pelvis in the setting of a changing primary CTV and relatively fixed nodal CTV can present a substantial problem from both a planning and physics quality assurance perspective. [Figure 4.3a-b)] For these reasons, simple translational shifts are unlikely to be the answer to the problem of inter-fraction motion for this tumour site. For the purpose of this work, nodal CTV was assumed to have received the nominal dose as no translational shifts were made to compensate for the inter-fraction primary CTV motion.
Figure 4.3a-b). Axial T-2 weighted images of cervix cancer patient during week 1 (a) and week 2 (b) of radiation treatment. Planning nodal CTV (orange) and primary CTV (red solid) are shown. Week 2 primary CTV (green solid) is shown in (b). A simple translational shift (red arrows) of the planning primary CTV (red dashed) is unable to achieve adequate target coverage (green arrows).
Adaptation could incorporate daily image guidance, dose accumulation and triggered replanning when pre-specified dose thresholds are reached, both for the targets and OARs. The most efficient way to achieve this has yet to be determined and many questions remain regarding the frequency of imaging and what dose thresholds are clinically relevant. The substantial workload involved with contouring, dose accumulating and replanning on the re-imaging datasets means that it is not currently a viable option outside of a research setting. However, as technology advances, automated segmentation will become more accurate and refined, high quality soft tissue imaging at the time of treatment will become standard (such as with hybrid MR linear accelerators) and software to rapidly accumulate dose and replan in real time will enable flexible optimisation of a patient’s treatment.

The limitations of this work include the imaging frequency of only once weekly, accounting for only 20% of the external beam radiotherapy fractions and limitations inherent in the deformation and dose accumulation software. The anatomy from each weekly image data set was applied across the entire five fractions of that week, until the next imaging session occurred. This strategy may have resulted in the introduction of a systematic error in our organ motion modeling, potentially presenting a “worst-case” scenario in uncorrected soft tissue target positioning.

MORFEUS, the software algorithm used to model organ motion and deformation has not been validated for cervix cancer. While MORFEUS deformations have been validated for the thorax, liver and prostate, with measured accuracy of 2.5-3 mm, it has not been quantified yet for cervix cancer. The difficulty in cervix cancer lies in the absence of a suitable anatomic fiducial for validating the deformations. For the thorax, the surface deformations of the lung from one image set to another can be checked against the deformed position of the carina, which provides an anatomic reference point for validation. An accurate deformation would result in little or no discrepancy in the position of the carina between the image sets. In the liver, the portal veins can be used as fiducials and implantable gold seeds provide a means of validating the technique in patients with prostate cancer. There are no vessels or easily identified internal structures within the body of the uterus or cervix that can be used as validation fiducials and implanted gold seeds are frequently lost during treatment as the tumour regresses (14). Validation of the deformations modelled by MORFEUS, in the absence of any consistent internal fiducial within the cervix or uterus, is difficult. However, during the course of this study, it was noted that some patients had
cervical cysts or uterine fibroids. These cysts and fibroids were not affected by the radiation treatment and remained relatively constant in size and location within the cervix/uterus, thus serving as naturally occurring internal fiducials. The only problem is that these cysts and fibroids are not ubiquitous in our patients. Initial estimates of MORFEUS deformation accuracy using cervical cysts in one patient revealed vector displacements of approximately 4mm. This is preliminary work and further patients are being recruited. Given that the dose grid size for dose accumulation in ORBIT Workstation is also 4 mm, it suggests that the deformations modelled by MORFEUS are reasonable within the framework of this research. However, the accuracy of the dose accumulation algorithm in the setting of extreme deformation between fractions (as occurred at the uterine fundus in some of our patients) has not been extensively studied. When deformations are very large, interpolation of dose along the deformation can be very important, but the behaviour of ORBIT Workstation and how it interpolates in this situation has not yet been reviewed.

4.1 Significance & Future Directions

The safe use of highly conformal radiotherapy necessitates accurate and unambiguous target definitions. Maximizing the therapeutic ratio of such treatment also necessitates daily image guidance and real-time individualized treatment adaptation.

The significance of the consensus CTV definition guideline document lies in its influence on clinical practice and in the research arena. Explicit definitions of the target tissues help to minimize ambiguity in volume delineation for clinical practice and in the research setting. This in turn, results in more consistent applications when auditing plans for quality assurance and dose-volume consequences. The translation of the knowledge gleaned from experts in the field and formalization of this knowledge through publication of these guidelines (Chapter 2) is valuable. Some variability in contouring the primary CTV is unavoidable due to the absence of any “gold standard” contours in the clinical setting, however knowledge translation through contouring workshops and the development of a teaching atlas will help minimize inter- and intra-observer variability and improve consistency of target delineation.
The process of adaptation would require re-imaging during treatment to acquire information about organ motion and target response; dose accumulation to assess how much the target and OARs have received to that point in treatment; and a strategy for real-time replanning and optimization to correct for errors in accumulated dose to the tumour and OAR’s.

Current workloads for an adaptive strategy are prohibitively large to be used routinely outside of a well resourced academic institution. Repeated imaging during treatment is inconvenient and time consuming for the patient. As CT and MRI image quality have improved, the ability to accurately discriminate between different soft tissues within the pelvis has also increased. This in turn, provides a better framework with which to study the impact of organ motion. However, repeated CT or MR imaging during treatment is time consuming and confounded by the time lag between imaging and actual treatment delivery. The recent developments of CBCT certainly reduce this time lag, whereby re-imaging occurs at the time of treatment, but the generally poor image quality compared with diagnostic CT or MRI currently limits its utility in terms of reliable dose accumulation.

Before any adaptive strategy can be instituted, contouring of the image data sets must also occur to enable accurate dose accumulation. This in itself can potentially take hours if done manually by an experienced radiation oncologist. Replanning, if required, also takes time. Then initiation of replanning with new IMRT plan optimisation constraints followed by quality assurance of the new plan can also be time-consuming. Improvements in the therapeutic ratio with adaptive radiotherapy are most likely to be achieved when all of these activities are performed in real time. Any delay potentially contributes to a diminution of the benefits as target and OARs continue to move and deform.

Strategies to overcome these logistical issues and help with labour-intensive manual tasks are currently being developed. Real-time online imaging of patients while on the treatment couch can be achieved either through high quality CBCT or ideally with an MR scanner integrated with the linear accelerator. A number of research groups around the world are in the process of developing or have already developed hybrid MR linear accelerators (15-20). While these MR linear accelerators are currently only used in the research setting, the leap to clinical implementation is likely only a matter of time. The image quality obtainable with MRI is far superior to that of CT or CBCT and would greatly facilitate soft tissue image guidance in the
pelvis. Once these images have been obtained, automated segmentation of the target and OARs could be instituted using deformable meshes obtained from the planning imaging. This would substantially reduce the contouring time. Dose accumulation could be calculated and delivered dose to target and OARs determined. Automated weekly online replanning has been explored as a planning study (21) and has demonstrated excellent tumour target coverage. However, in order to maximise the potential OAR sparing possible with replanning, further refinement of the optimization criteria is required. Replanning could be triggered based on pre-specified delivered dose thresholds and implemented when necessary using an automated algorithm with scripting to fine-tune optimization criteria based on the updated imaging.

Future directions for this work include: the development of an online teaching atlas (through collaboration with RTOG) showcasing the consensus contours in a number of different clinical scenarios (such as parametrial invasion; pelvic lymph node involvement; retroverted uterus); the validation of the MORFEUS deformation modeling and a more intensive imaging protocol with MR scans three times weekly during radiotherapy. Also being explored is whether it is necessary to image so intensively throughout the treatment course or whether there is an optimal imaging schedule which captures the most significant organ motion without being too labor/resource/time intensive. Further exploration of triggered replanning, by recognizing when the target is being under-dosed (due to organ motion) or surrounding OARs are being over-dosed (due to target shrinkage) is also being studied. It would hopefully provide a more realistic and feasible workload.

It is increasingly becoming apparent that the residual cervix cancer bulk at the end of a course of external beam radiotherapy has prognostic significance for local control and disease-specific survival (22). Some studies have reported good correlation between local control and residual tumour volume at the end of treatment (22-24). The key would be identification of likely non-responders or slow-responders, earlier in the treatment course, enabling modification of the treatment strategy for more effective cell kill. Future directions for such biological adaptation include tools such as contrast agents which allow for functional real-time imaging of tumour response to treatment. A contrast agent which renders tumour visible on CBCT and which gradually depletes as tumour cells die, would allow for more accurate dose targeting and potentially, alteration of treatment strategies earlier during therapy to increase effectiveness. Other areas of biological adaptation involve using highly focused IMRT to escalate dose to
specific radioresistant sub-volumes of the tumour. The robust detection of these radioresistant regions is currently challenging. A number of planning studies (predominantly involving Head and Neck cancers) have demonstrated the feasibility of biologic image-guided dose escalation using hypoxia imaging as a marker for radioresistant tumour cells (25-33). In the future, it is anticipated that it will be possible to image other molecular processes which contribute to radioresistance (such as rapid cellular proliferation or altered DNA repair). These molecular processes can change rapidly over time, both in the natural state and also in response to treatment. The ability to adapt radiation treatment to respond to these dynamic changes through re-imaging and replanning, using an adaptive model similar to that described here, will be essential to the future success of this approach.

4.2 Conclusion

While it is intuitively recognized that “what you plan is not necessarily what you treat”, it is only recently that technology has advanced to the point where we can explicitly look at the dose consequence of target and OAR motion during radiotherapy to the pelvis. In the era of generous treatment fields, this was not an issue. However as the push toward greater dose conformality proceeds, the influence of intrapelvic organ dynamics will necessarily rise to the forefront. This work sets the stage for further refinement of adaptive strategies, laying the foundation for future strategies and highlighting various pitfalls associated with IMRT. You cannot treat what you do not contour, thus target definition guidelines form in integral part of ensuring quality assurance during the planning process. Understanding target and organ dynamics is essential to the safe and effective delivery of IMRT for this tumour site.
4.3 References


