



MONASH University

# Ultrasound based brachytherapy in the treatment of cervix cancer

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## Abstract

This thesis is comprised of studies that investigate incorporating ultrasound into brachytherapy programs for patients undergoing treatment for locally advanced cervix cancer. Radiotherapy and brachytherapy are the definitive treatments for this cancer and the use of soft tissue imaging, particularly magnetic resonance imaging (MRI), has enhanced their effectiveness and improved clinical outcomes. However, use of MRI is largely restricted to well- resourced centres in both the first and developing world and remains elusive to many less advantaged centres, particularly those in areas with a high burden of cervix cancer. Treatment for the majority of these patients continues to be planned with planar x-ray imaging and as such there is a crucial unmet need for an accessible economical soft tissue imaging modality in gynaecological brachytherapy. Ultrasound has the potential to meet this need.

This thesis opens with a paper comparing measurements of the cervix made with ultrasound and MRI. MRI is considered the gold standard imaging modality for planning gynaecological brachytherapy and so was used as the standard against which to compare ultrasound measurements. This study confirms the primary hypothesis of this thesis that use of ultrasound provides an accurate assessment of the cervix and uterine dimensions to facilitate target delineation for brachytherapy treatment.

A second study then used ultrasound in the planning and treatment process and investigated changes to the brachytherapy target dimensions measured with ultrasound over the course of brachytherapy. The impact of this is reduced reliance on external departments for imaging, and reduced patient waiting and discomfort.

Clinical outcomes achieved using serial ultrasound and a single MRI to plan and verify brachytherapy are reported in chapter 6. The outcomes achieved using the techniques and methods described in this thesis compare favourably to more resource intensive and costly protocols.

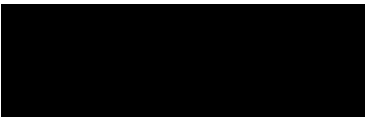
As use of ultrasound is not in the usual purview of brachytherapy staff, a reproducibility and reliability study was undertaken to confirm quality, accuracy and consistency of ultrasound imaging used for planning treatment. Ultrasound images and measurements were obtained by radiation therapists (RTs) rostered to brachytherapy and compared to a reference standard MRI. Inter-operator reliability agreement scores for measuring the cervix and uterine dimensions were excellent between MRI and RTs, and between RTs.

The work described in this thesis indicates that ultrasound can be used to accurately measure the brachytherapy target dimensions with the treatment applicator *in situ*. It can be used to complement existing imaging modalities or as a stand-alone imaging modality. Ultrasound can also be used to assess inter-fraction changes to the brachytherapy target volume. Real time application with immediate feedback makes it possible to reduce imaging time and overall procedure time. As described in this thesis, a concise training program aimed at brachytherapy personnel ensures consistent and accurate use of ultrasound for verifying treatment.

Incorporating an accessible, cost effective imaging modality such as ultrasound into brachytherapy protocols can result in treatment outcomes comparable to centres using more technically complex protocols. It is hoped the results in this thesis will confirm the usefulness of this protocol and encourage others to be innovative with the resources available to them and advance the cause of image guided brachytherapy for women with cervix cancer the world over.

## Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: ...  .....

Print Name: Elisabeth Sylvia van Dyk

Date: 30<sup>th</sup> May 2017

## Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers and one review published in peer reviewed journals. The core theme of the thesis is investigating the use of ultrasound for target delineation, treatment planning and verification in gynaecological brachytherapy. The ideas, development and writing of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Faculty of Medicine, Nursing and Health Sciences under the supervision of Associate Professor Michal Schneider; and at the Peter MacCallum Cancer Centre under the supervision of Associate Professor Kailash Narayan. Further supervision was provided by Associate Professor Srinivas Kondalsamy-Chennakesavan, Director of Research, Rural Clinical School, University of Queensland.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

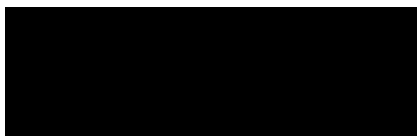
In the case of chapters 2, 4, 5, 6, 7, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent (%) of students contribution	Co-author names Nature and % of Co-author's contribution	Co-authors, Monash student Y/N
2	Ultrasound use in gynaecologic brachytherapy: Time to focus the beam	Published	100% of study concept and 100% of manuscript writing	Michal Schneider, input into manuscript; Srinivas Kondalsamy-Chennakesavan, input into manuscript; David Bernshaw, input into manuscript; Kailash Narayan, input into manuscript	N
4	Comparison of measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix cancer	Published	90% of data analysis, 90% of concept, design, data interpretation and manuscript writing, 100% of study conduct, data generation, and data collection.	Srinivas Kondalsamy-Chennakesavan, data analysis; Michal Schneider, input into manuscript; David Bernshaw, input into manuscript; Kailash Narayan, input into manuscript	N
5	Assessing changes to the brachytherapy target for cervical cancer using a single MRI and serial ultrasound	Published	90% of data analysis, 90% of concept, design, data interpretation and manuscript writing, 100% of study conduct, data generation, and data collection.	Srinivas Kondalsamy-Chennakesavan, data analysis; Michal Schneider, input into manuscript; David Bernshaw, input into manuscript; Kailash Narayan, input into manuscript	N
6	Clinical outcomes from an innovative protocol using serial ultrasound imaging and a single MRI image to guide brachytherapy for locally advanced cervix cancer	Published	90% of data analysis, 90% of concept, design, data interpretation, manuscript writing and study conduct. 30% of data generation and data collection.	Kailash Narayan, input into manuscript; David Bernshaw, input into manuscript; Srinivas Kondalsamy-Chennakesavan, data analysis; Pearly Khaw, input into manuscript; Ming Yin Lin, input into manuscript; Michal Schneider, input into manuscript.	N
7	Reproducibility and inter-operator reliability of obtaining images and measurements of the cervix and uterus with brachytherapy treatment applicators in situ using transabdominal ultrasound	Published	90% of data analysis, 90% of concept, design, data interpretation and manuscript writing, 100% of study conduct, data generation, and data collection.	Margaret Garth, input into manuscript; Amanda Oates, input into manuscript; Srinivas Kondalsamy-Chennakesavan, data analysis; Michal Schneider, input into manuscript; David Bernshaw, input into manuscript; Kailash Narayan, input into manuscript.	N

References and sections of published papers have been renumbered in order to generate a consistent presentation within the thesis.



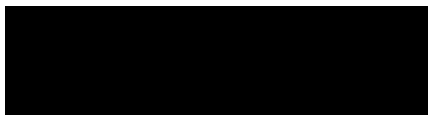
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Date: 30<sup>th</sup> May 2017

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work.

Main Supervisor signature:



ate: 30<sup>th</sup> May 2017

## Publications during enrolment

Sylvia van Dyk, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, David Bernshaw, Kailash Narayan

Comparison of measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix cancer

*International Journal of Radiation Oncology Biology Physics* 2014 88(4) pp 860-865

Sylvia van Dyk, Michal Schneider, Srinivas Kondalsamy-Chennakesavan, David Bernshaw, Kailash Narayan

Ultrasound use in gynecological brachytherapy: time to focus the beam

*Brachytherapy* 2015 14(3) pp.390-400

Sylvia van Dyk, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, David Bernshaw, Kailash Narayan

Assessing changes to the brachytherapy target for cervical cancer using a single MRI and serial ultrasound

*Brachytherapy* 2015 14(6) pp. 889-897

Sylvia van Dyk, Margaret Garth, Amanda Oates, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, David Bernshaw, Kailash Narayan

Reproducibility and interoperator reliability of obtaining images and measurements of the cervix and uterus with brachytherapy treatment applicators in situ using transabdominal ultrasound

*Brachytherapy* 2016 15(1) pp.71-78

Sylvia van Dyk, Kailash Narayan, David Bernshaw, Srinivas Kondalsamy-Chennakesavan, Pearly Khaw, Ming Yin Lin, Michal Schneider

Clinical outcomes from an innovative protocol using serial ultrasound imaging and a single MR image to guide brachytherapy for locally advanced cervix cancer

*Brachytherapy* 2016 15(6) pp. 817-824

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Finally, thank-you to the patients who placed their trust and belief in us. This is for you.

## Abbreviations

BMI	Body Mass Index
BT	Brachytherapy
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DVH	Dose Volume Histogram
D2cm <sup>3</sup>	Dose to 2 cm <sup>3</sup> of organ
D90	Dose to 90% of organ
EBRT	External Beam Radiotherapy
EMBRACE	European Study on <b>M</b> RI Guided <b>B</b> rachytherapy in Locally Advanced <b>C</b> ervical Cancer
EQD2	Equivalent Dose in 2 Gray
FIGO	Federation of Gynecology and Obstetrics
Fr	French (measure of the external diameter of a catheter)
Fx	Fraction
GEC-ESTRO	Groupe Européen de Curiétherapie and the European Society for Therapeutic Radiology and Oncology
Gy	Gray
HDR	High Dose Rate
HPV	Human Papilloma Virus
HRCTV	High Risk Clinical Target Volume
IC	Intracavitary
ICC	Intraclass Correlation Coefficient
IS	Interstitial
IUS	Intrauterine Ultrasound
ICRU	International Commission on Radiation Units
IRCTV	Intermediate Risk Clinical Target Volume
Kerma	Kinetic Energy Released per Mass
LDR	Low Dose Rate
MMMT	Malignant Mixed Müllerian Tumour
MHz	Megahertz

## Abbreviations

MRI	Magnetic Resonance Imaging
NCI CTCAE v3.0	National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0
PDR	Pulse Dose Rate
PMCC	Peter MacCallum Cancer Centre
PMCCTV	Peter MacCallum Cancer Centre Target Volume
Pt A	Point A
Pt M	Point M
RO	Radiation Oncologist
RTOG/WHO	Radiation Therapy Oncology Group/World Health Organisation
RT	Radiation Therapist
r	Roentgen
SPSS	Statistical Package for the Social Sciences
TRACE	<b>Trans</b> cervical Endosonography
TRAK	Total Reference Air Kerma
TRUS	Transrectal Ultrasound

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# Chapter 1

## Introduction

### 1.1 Incidence and mortality

Cervix cancer is the fourth most common cancer in women in the world, but it is a disease of disparities<sup>1,2</sup>. Cervix cancer is a largely preventable and curable disease if women have access to screening and treatment<sup>3</sup>. Screening detects precancerous and early stage cancers that can be safely treated with surgery alone. However, 85% of cervix cancers occur in women living in less developed regions of the world where access to screening is limited or non-existent<sup>2</sup>. Women in these regions tend to present with later stages of disease that require more resource intense treatments such as radiotherapy, chemotherapy and brachytherapy, resources that are also often limited, unaffordable or non-existent<sup>4,5</sup>. Eighty seven percent of deaths from cervix cancer occur in these parts of the world<sup>6</sup>. In contrast to this, the incidence of cervix cancer in developed countries has decreased dramatically due to the wide availability of screening tests such as the Papanicolaou test, and robust screening policies.

However, despite the wide availability of screening tests and programs, cervix cancer has not been eradicated in these regions as some women do not participate in screening programs, and there remain areas of disadvantage where women are unscreened or under screened<sup>7-9</sup>. These women too, present with later stage disease. It is the treatment and management of locally advanced cervix cancer with brachytherapy that is the focus of this thesis.

The societal impact of cervix cancer is keenly felt as women often present with this disease during child rearing years. Families and communities suffer enormously when the women who bear the burden of child care and home care are incapacitated due to illness or morbidity from treatment<sup>10</sup>. The cost of cancer care in developing regions can also put enormous strain on families, pushing them into poverty<sup>4</sup>.

## 1.2 Development of cervical cancer

Cervical cancer affects the cells of the uterine cervix. The cervix is the lower part of the uterus, Figure 1.1. The cervix is roughly cylindrical in shape and connects the vagina and uterus. The cervix is mainly comprised of fibromuscular tissue and consists of two main parts, the ectocervix and the endocervix. The ectocervix protrudes into the vagina and contains a central opening called the external os which allows passage between the uterus and vagina. The ectocervix is covered by stratified squamous epithelium. The endocervix is the passage running through the cervix from the external os into the uterus and is covered by columnar epithelium. The border between the endocervix and ectocervix is called the transformation zone<sup>11</sup>. The cervical transformation zone is a ring of active squamous metaplasia where the stratified squamous epithelium of the ectocervix progressively undermines and replaces the columnar epithelium of the endocervix<sup>12</sup>.

It is now known that persistent infections of human papillomavirus (HPV) causes cervical cancer, mainly at the transformation zone<sup>13</sup>. HPV infects epithelial cells and infections are transmitted by skin to skin or mucosa to mucosa contact, with sexual intercourse highly implicated<sup>14</sup>. The two most common strains of HPV implicated in cervix cancer are HPV 16, implicated in up to 70% of squamous cell carcinomas, and HPV 18, implicated in the development of adenocarcinoma and adenosquamous carcinoma<sup>13,15</sup>. Worldwide prevalence of HPV is 11.7% in women, causing 4.5% of new cancers each year<sup>16</sup>.

Cervical cancer arises via a series of four steps – HPV transmission, viral persistence, progression of a clone of persistently infected cells to precancer, and invasion<sup>12</sup>. Cervical cancer tends to occur earlier than other adult cancers. This is due to infections arising from sexual activity in late adolescence and early adulthood<sup>17</sup>. It is estimated that precancers result in a 20 - 30% risk of invasion over a 5-10 year time period<sup>12</sup>. Other factors such as smoking, multiparity, and long term use of oral contraceptives can double or triple the risk of precancer and cancer among women infected with carcinogenic types of HPV<sup>18</sup>.

### 1.3 Human papillomavirus vaccine

The first prophylactic vaccine against HPV was licensed in mid-2006<sup>15</sup>. There are three types of vaccine, the quadrivalent vaccine (which protects against high risk HPV types 16 and 18, and low risk types 6 and 11, which cause 90% of genital warts), a 9-valent vaccine (which prevents infection with the same four HPV types plus five additional high-risk types, 31,33,45,52, and 58), and a bivalent vaccine (which protects against HPV types 16 and 18).

The purpose of the vaccine is to prevent and reduce infection with the HPV and so reduce the incidence of precancerous and cancerous cervical, vulvar, vaginal and anal diseases; and genital warts<sup>19</sup>. The vaccine is aimed mainly at girls between the ages of 9 and 12 years because it is most effective when given before the onset of sexual activity.

In a study quantifying worldwide coverage of HPV programs implemented up to December 2014 it was found that vaccination programs have been implemented in more than 80 countries although worldwide coverage of women was estimated to be only 1.4% (95% CI) (1.1 -1.6)<sup>16</sup>. Most vaccinated females reside in high income countries (68%), or upper middle-income countries (28%). Only 1.4 million women from low-income and lower-middle-income countries were vaccinated. Australia has amongst the highest age-specific rates of vaccination along with Northern Europe and New Zealand (69%).

While the effect of vaccination on the incidence of cervix cancer is not expected to be known for some decades, modelling predicts declines in cervix cancer of between 70 – 90%<sup>19-21</sup>. Similar to screening programs, women in regions with a high burden of cervix cancer have less access to vaccinations and so the scourge of cervix cancer will remain for many years.

## 1.4 Presentation of cervix cancer

Precancerous and early stages of cervix cancer can be detected by both visual inspection of the cervix (with acetic acid to stain abnormalities) and the Papanicolou test in which a sample of cervical cells is examined under a microscope to detect cellular abnormalities. Patients with symptomatic cancers may present with intermenstrual bleeding, post coital or postmenopausal bleeding. Vaginal discharge is also often present. Other symptoms include abdominal pain,

dyspareunia, vesicovaginal or rectovaginal fistulas, renal failure secondary to ureteric obstruction, urinary retention and lymphedema<sup>22</sup>.

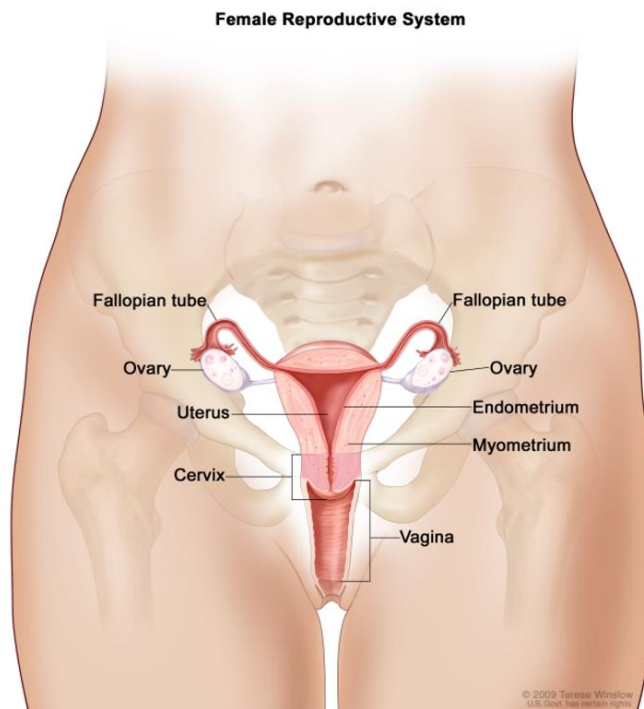


Figure 1.1 Female reproductive anatomy

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## 1.5 Staging of cervical cancer

The International Federation of Gynecology and Obstetrics (FIGO) has developed a staging system for cancer of the cervix. The FIGO staging system is based on clinical examination and was most recently updated in 2009<sup>6</sup>. Clinical examination includes a pelvic and digital rectal examination to assess whether the tumour has spread to the parametria, vagina and/or uterosacral ligaments. All tumours must be microscopically verified and histologic types included in the report. The clinical exam is supplemented by chest x-rays, intravenous pyelograms or renal ultrasound to assess ureteric dilatation, renal and liver function tests and a

cystoscopy to rule out occult bladder invasion. Information gained from exploratory surgery and investigations performed using computed tomography (CT), MRI and positron emission tomography (PET) scans cannot be used to alter the clinical stage of disease but can be used to select appropriate treatments<sup>23</sup>. FIGO staging for cancer of the cervix is detailed in Table 1.1.

## 1.6 Treatment of cervical cancer

Early stage cervix cancers including stages 1A1, 1A2, 1B1 and 1A1 are effectively treated with various surgical techniques which include conisation, trachelectomy, and hysterectomy. FIGO recommends adjuvant radiotherapy combined with chemotherapy for patients who have positive nodes, positive parametria, or positive surgical margins to reduce the risk of recurrence after surgery. However, if it is possible to predict the need for post-operative radiotherapy and chemotherapy due to identification of these adverse prognostic features, patients should be treated with combined radiotherapy and chemotherapy alone<sup>23-26</sup>. This approach reduces the increased morbidity caused by surgery in combination with radiotherapy and chemotherapy<sup>27</sup>.

Patients with grossly invasive cervix cancer staged as 1B2, 1A2, 1B, 1B and 1VA are said to have locally advanced cervix cancer and the standard of care is to treat with radiotherapy which includes external beam radiotherapy and concomitant platinum based chemotherapy followed by brachytherapy.

External beam radiotherapy consists of directing beams of radiation at the tumour. The beams traverse the patient from front to back and side to side. External beam radiation is used to shrink the bulky endocervical tumour and bring it within range of the high dose region of brachytherapy; shrink the ectocervical tumour that may distort anatomy and prevent optimal



brachytherapy; and sterilise paracentral and nodal disease that lies beyond the reach of the brachytherapy radiation dose region.

Table 1.1 FIGO staging of cancer of the cervix uteri<sup>6</sup>

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).
IA	Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers.) Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm
IA1	Measured invasion of stroma $\leq 3$ mm in depth and $\leq 7$ mm width.
IA2	Measured invasion of stroma $\geq 3$ mm and $\leq 5$ mm in depth and $\leq 7$ mm width.
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA.
IB1	Clinical lesions no greater than 4 cm in size.
IB2	Clinical lesions $\geq 4$ cm in size.
II	The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or to the lower third of vagina.
IIA	Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement.
IIA1	Clinically visible lesion $\leq 4$ cm
IIA2	Clinically visible lesion $> 4$ cm
IIB	Obvious parametrial involvement but not onto the pelvic sidewall.
III	The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
IVA	Spread to adjacent pelvic organs.
IVB	Spread to distant organs.

FIGO = Federation of Gynecology and Obstetrics

Brachytherapy delivers radiation via applicators placed on or in the target volume. When treating patients with cervix cancer an applicator facilitating passage of a radioactive isotope is placed inside the patients' uterus. The applicator is known as a tandem or intrauterine applicator. The ectocervix and upper vagina are treated by applicators called ovoids, cylinder or ring, Figure 1.2. Placement of these applicators within body cavities is known as intracavitary brachytherapy. The applicators are effectively placed within the target volume. This means radiation does not have to traverse through normal healthy tissue to reach and treat the target volume. The purpose of brachytherapy is to control the primary disease with extremely high doses of radiation that are in close proximity to the target tissues.

Isotopes used for brachytherapy typically include Iridium-192 and Cobalt-60 and exposure is governed by the inverse square law which sees a rapid fall-off of dose with increasing distance from the radioactive source. This limits the dose received by surrounding healthy tissues, Figure 1.3.

Brachytherapy for cervix cancer was first reported in 1903<sup>28</sup> and as such, has a long history. Due to the relative simplicity of placing applicators in a natural body cavity there has been little change in the administration of brachytherapy for cervix cancer for nearly 100 years. The last ten to fifteen years, however, have seen the emergence of new approaches in gynaecological brachytherapy. Practices based on 20th century empiricism are evolving and adopting 21st century imaging technologies. These imaging technologies include CT, PET and MRI, with MRI being considered the gold standard in soft tissue imaging of the cervix and uterus.

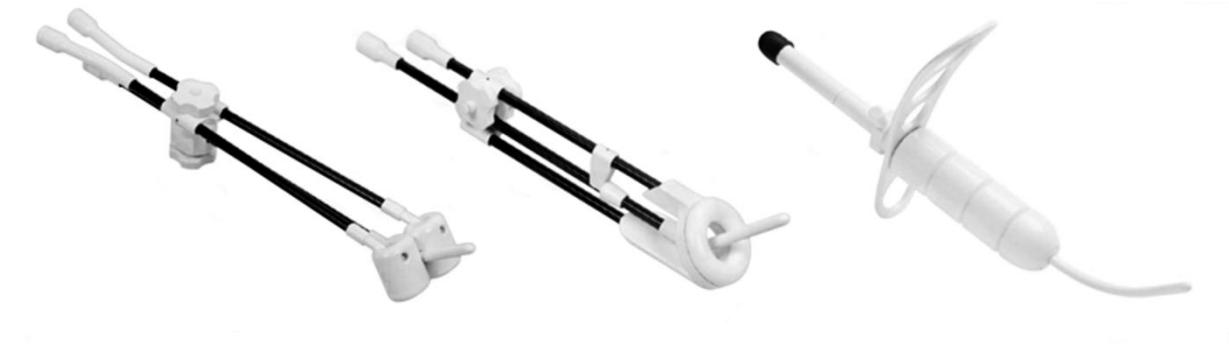


Figure 1.2 Brachytherapy intracavitary applicators

Tandem and ovoids; tandem and ring; tandem and cylinder

Source: Elekta Brachytherapy applicators and Accessories Guide 2015

## 1.7 Dosimetry systems

Dosimetry systems emerged for gynaecological brachytherapy as early as 1910. They were known as the Paris, Stockholm and Manchester systems. The original form of the Paris and Stockholm systems didn't allow dosage to be standardised and were not widely adopted. The Manchester system was developed in 1938 and reported absorbed dose in tissue rather than milligram hours of radium treatment and also standardised dose to a definable point<sup>29</sup>. Tenements of this system are the mainstay of much gynaecological brachytherapy today. The system described specific amounts of radium for all tandem and ovoid combinations so that a pre-calculable dose to a purposely defined point could be administered. This point is known as 'Point A' and was defined as a point in the paracervical triangle occurring 2.0 cm lateral to the central canal of the uterus and 2.0 cm from the mucous membrane of the lateral fornix of the vagina, in the axis of the uterus. Point A was said to represent the average dose throughout the paracervical triangle<sup>30</sup>. The definition of Point A was later modified to improve consistency of calculation and location on radiographs. Rather than measuring from the mucous membrane of

the lateral fornix, Point A was measured from the cervical stopper of the intrauterine applicator located at the external os<sup>31</sup>. Point A was originally intended to describe normal tissue tolerance and it was recommended to deposit not less than 7,000r and seldom more than 8,000r (r = roentgen, dosage unit) to this point, those doses being equivalent to 60.87 – 69.75 Gy in today's nomenclature respectively.

It is emphasised that Point A is a geometrical point linked to applicator geometry as visualised on x-ray imaging. Point A has no bearing on the size or location of the tumour within the cervix. Gilbert Fletcher from MD Anderson combined elements of the Paris and Manchester system to develop a more anatomical and volumetric approach to assessing the dose distribution in the pelvis. Through extensive work with *in vivo* measurements taken during brachytherapy he devised and published tables listing maximum amounts of radiation and time for intracavitary implants<sup>32</sup>. While intended to guide practitioners in conjunction with anatomical considerations made for each patient, the tables became formulaic for many.

These standardised systems were seen as advantageous as they enabled delivery of pre-calculated doses of radium that were considered accurate within the limits imposed by clinical variations. The Manchester system became the most widely used system as doses could be recorded at a simple point. While Point A was originally a tolerance point, over time it transformed into a prescription point. As clinicians tried to correlate treatment dose with outcome, they examined the dose at Point A. In an effort to improve clinical outcomes, ever more dose was prescribed to Point A with initial guidelines for high dose rate brachytherapy issued by the American Brachytherapy Society recommending 80 - 85 Gy for early stage and 85 - 90 Gy for advanced stages of disease<sup>33</sup>.

Due to the simplicity of prescribing treatment to this paracentral reference point, use of Point A has persisted since its inception in 1938. Until recently, the simplicity of applying this system has meant that intracavitary brachytherapy has not evolved to the same extent as external beam radiotherapy. The standards of efficacy, reproducibility and verification used in external beam treatment and other forms of brachytherapy, such as prostate brachytherapy, have not been applied to gynaecological brachytherapy.

## 1.8 Reporting

The International Commission on Radiation Units released report no. 38 (ICRU 38) in 1985 entitled “Dose and volume specification for reporting intracavitary therapy in gynaecology”<sup>34</sup>. The report recommended reporting requirements to enable comparisons of dosimetry between brachytherapy practitioners. It introduced a method to define reference points to describe dose received at organs at risk, namely, the ICRU 38 bladder and rectal reference points. The report stated that reporting dose to Point A was not appropriate due to the location of Point A in a high dose gradient region. The report recommended reporting a description of:

- the intracavitary technique used;
- total reference air kerma (TRAK cGy at 1 metre);
- a description of the reference volume (given by height, width, thickness described by a nominated dose level, usually 60 Gy);
- absorbed dose at reference points including bladder, rectal, lymphatic trapezoid, and pelvic wall;
- time dose patterns.

Adherence to these reporting recommendations has been sporadic with the majority of practitioners reporting Point A doses, bladder and rectal reference point doses and very few reporting TRAK or the 60 Gy reference volume<sup>35-37</sup>.

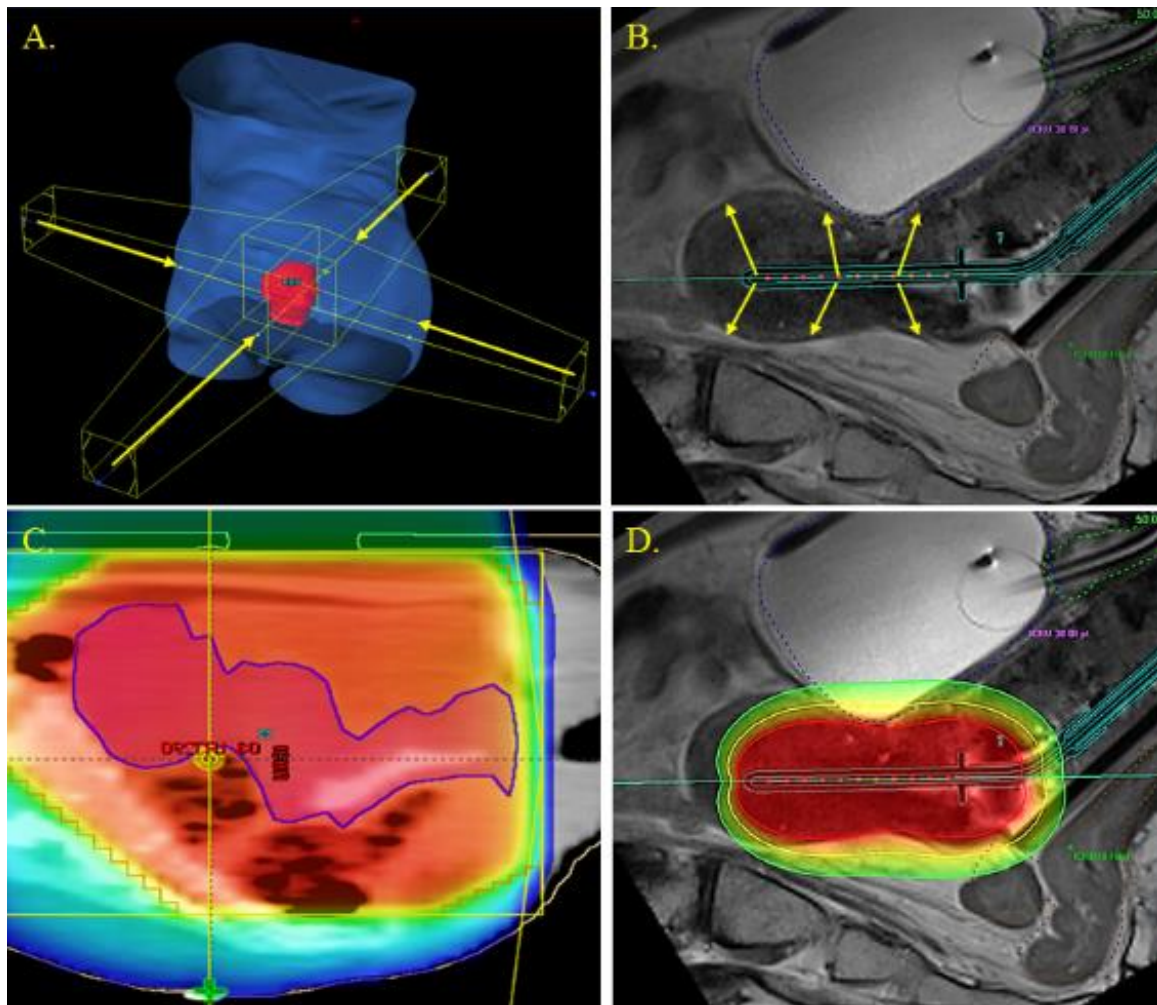


Figure 1.3 EBRT and brachytherapy fields and dose distributions

- A. EBRT fields
- B. Brachytherapy applicator *in situ*
- C. EBRT colour wash on sagittal view of pelvis
- D. Brachytherapy colour wash on longitudinal view of uterus

EBRT = external beam radiotherapy

Source: Peter MacCallum Cancer Centre

In June 2016 the ICRU and Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy and Oncology (ESTRO) released a joint report, ICRU report no. 89, called ‘Prescribing, recording and reporting cervix cancer brachytherapy’. The report highlights the advances made in imaging, planning and treatment technology and introduces and adopts concepts of image guided volumetric adaptive planning<sup>38</sup>.

## 1.9 Use of imaging in brachytherapy

The mainstay of brachytherapy treatment has been the Manchester system with reliance on planar orthogonal x-ray images for calculation and prescription of treatment doses<sup>39</sup>. The limitations of x-ray based planning are the inability to identify any soft tissue organs such as the cervix, which constitutes the target volume, and the surrounding healthy tissues such as bladder, rectum, sigmoid and bowel. Despite these limitations, use of x-rays to plan brachytherapy remains the most common imaging modality in use in the world today<sup>40</sup>. This is driven by the simplicity of the dosimetry system, widespread availability of x-ray units, and large numbers of patients presenting for treatment in disadvantaged regions of the world where resources are limited. The use of 3D soft tissue imaging for planning brachytherapy is increasing in the developed world and select centres in the developing world. GEC-ESTRO have been instrumental in promoting the use of 3D imaging in brachytherapy and published recommendations for use via four working group papers<sup>41-44</sup>. The purpose of using soft tissue imaging is to define the target volume, better direct radiation to these volumes while sparing normal surrounding tissues and thus improve the therapeutic ratio.

## 1.10 Concept of brachytherapy target volume

The purpose of visualising the anatomy on 3D soft tissue imaging is to define and delineate the target volume that will be treated with brachytherapy. The concept of a brachytherapy target volume is a recent development in gynaecological brachytherapy<sup>45</sup>. Prior to the introduction of soft tissue imaging the majority of treatments were prescribed to Point A and evaluated on 2D x-rays. When assessing 2D x-ray based plans on 3D soft tissue imaging data sets it quickly became apparent that small tumours and surrounding anatomy were likely over treated with Point A based dosimetry, while larger tumours were potentially under treated. Establishing exactly how much dose the tumour receives is not possible using 2D x-rays. It was also apparent that prescribing and reporting based on 3D imaging would encompass many new concepts, not the least being how to decide what to include in the treatment volume and how to describe what was being treated by the brachytherapy volume. In the first two GEC-ESTRO working group papers, terminology to describe target volumes and planning concepts were recommended. These papers were intended as a guide to allow consistent reporting of treatment volumes for comparison and analysis of techniques and clinical results<sup>41,42</sup>. The descriptions for reporting target volumes have now entered the lexicon of image guided brachytherapy, and were recently adopted by ICRU report no. 89<sup>38 46,47</sup>. GEC-ESTRO particularly encourages the use of MRI at each brachytherapy insertion to assess and report on changes to the target volume over the course of treatment. While the goal of using MRI at each brachytherapy insertion is desirable, it is unlikely to occur in many regions of the world, which means alternate forms of soft tissue imaging and target definition are needed.



## 1.11 Purpose of this thesis

The purpose of this thesis is to investigate the use of transabdominal ultrasound for guidance of applicator placement, target definition, conformal planning, verification, and treatment in brachytherapy for cervix cancer. The central theme of this research is the use of transabdominal ultrasound to enable image guided brachytherapy. The manuscripts included in this thesis are linked in a stepwise nature in terms of validating ultrasound against MRI, using ultrasound to assess temporal changes, and reporting clinical results achieved using ultrasound. The hypothesis is that use of transabdominal ultrasound provides an accurate assessment of the cervix and uterine dimensions that facilitates target definition and delineation for brachytherapy treatment. Use of transabdominal ultrasound to guide applicator insertion into the uterine canal is increasing but use of ultrasound to plan brachytherapy for cervix cancer does not occur and research into this modality is needed<sup>40,48</sup>. The results of this thesis will enable radiotherapy centres with limited access to sophisticated and expensive imaging devices, such as MRI and CT, to practice image-guided brachytherapy using ultrasound. Use of soft tissue imaging has been shown to lead to improved technical quality of brachytherapy treatments, resulting in better local control of disease and reduced toxicity. This has the potential to positively affect the quality of life of patients undergoing curative brachytherapy for cervix cancer.

The aims of this thesis are:

Aim 1. *Validation of ultrasound*: In order to introduce an alternative imaging modality into practice it must be validated against an accepted standard to prove its efficacy. The first aim of this thesis was to determine if ultrasound based cervix and uterine measurements show good agreement with MRI based cervix and uterine measurements. This aim is addressed in chapter

four and was published in the International Journal of Radiation Oncology Biology and Physics (van Dyk et al., 2014).

*Aim 2. Assessment of target volume:* Having validated ultrasound as a viable imaging modality to delineate and assess the brachytherapy target volume the second aim was to incorporate ultrasound into the brachytherapy procedure and use it to evaluate the magnitude of target volume changes over the course of treatment by comparing ultrasound based fraction one cervix dimensions with fraction two, three and four cervix dimensions. This aim is addressed in chapter five and was published in Brachytherapy (van Dyk et al. 2015).

*AIM 3. Impact of changes to the target volume:* Image guided fractionated brachytherapy is a resource intense treatment regime. We wanted to investigate the impact of changes to the target volume over time to see if they warrant replanning each fraction. The third aim was to investigate the frequency of adjustments made to the ultrasound plan, and the impact on resources within the Peter MacCallum Cancer Centre. This aim is addressed in chapter five and was published in Brachytherapy (van Dyk et al. 2015).

*AIM 4. Dose response:* Having based conformal treatment on the information obtained from ultrasound imaging it was important to assess the clinical outcomes of patients to ensure the therapeutic ratio of tumour control and morbidity were not compromised. The fourth aim of this thesis was to correlate the dose delivered to the ultrasound defined target volume with local control and toxicity. This aim is addressed in chapter six and was published in Brachytherapy (van Dyk et al. 2016).

AIM 5. *Reliability*: Basing important clinical decisions on the images obtained with ultrasound makes it imperative that consistent and reliable images are obtained. Even though education and training is provided for all radiation therapists undertaking ultrasound it is still recognised that the quality of the ultrasound images are somewhat user dependent. The fifth aim of this thesis was to validate the inter-operator reliability of obtaining measurements of the cervix and uterus with treatment applicators *in-situ* using transabdominal ultrasound in our clinical setting. This aim is addressed in chapter seven and published in Brachytherapy (van Dyk et al., 2016).



# Chapter 2

## Literature Review

This chapter represents a comprehensive review of the use of ultrasound in gynaecological brachytherapy based on the available literature until 2014. A condensed version of this review is attached in Appendix C and was published as:

### Ultrasound use in gynaecological brachytherapy: time to focus the beam

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*Brachytherapy, 2015 14 (3) pp. 390- 400*

An update to the review based on literature published between 2014 and April 2017 has been included in section 2.11

## Abstract

There is wide disparity in the practice of brachytherapy for cervix cancer around the world. While select well-resourced centres advocate use of MRI for all insertions, planar x-ray imaging remains the most commonly used imaging modality to assess intracavitary implants, particularly where the burden of cervix cancer is high. Incorporating soft tissue imaging into brachytherapy programs has been shown to improve the technical accuracy of implants, which in turn has led to improved local control and decreased toxicity. These improvements have a positive effect on the quality of life of patients undergoing brachytherapy for cervix cancer. Finding an accessible soft tissue imaging modality is essential to enable these improvements to be available to all patients. A modality that has good soft tissue imaging capabilities, is widely available, portable and economical, is needed. Ultrasound fulfils these requirements and offers the potential of soft tissue image guidance to a much wider brachytherapy community. While use of ultrasound is the standard of care in brachytherapy for prostate cancer it has only seen limited uptake in gynaecological brachytherapy. This chapter reviews the role of ultrasound in gynaecological brachytherapy and highlights the potential applications for use in brachytherapy for cervix cancer.

## 2.1 Introduction

Brachytherapy is an integral part of radiotherapy treatment for locally advanced cervix cancer. It has been used for well over one hundred years<sup>49</sup>. While other forms of radiotherapy evolved through innovation and advances in technology during the 20th century, brachytherapy techniques for cervix cancer remained largely static. The story of brachytherapy for cervix cancer is eloquently told by Erickson in which she outlines the reasons for this lack of progress<sup>50</sup>. Early dosimetry systems brought structure and standardisation to gynaecological brachytherapy but while other areas of radiotherapy progressed, gynaecological brachytherapy stalled within the confines of these dosimetric systems. Over time though, there has been growing awareness of the limitations of these standardized systems, the main being lack of use of modern imaging to appreciate and assess the individual nature of each women's anatomy and disease<sup>51-60</sup>. The release of the GEC-ESTRO recommendations for incorporating imaging, particularly MRI, into brachytherapy programs, is changing the way brachytherapy is being practiced<sup>41-44</sup>. Traditional dosimetry systems consisting of specific insertion techniques, applicators, prescribing and reporting, and planning and treatment methods, are all being challenged as soft tissue imaging is incorporated into practice. Sadozye and Reed provide the next chapter to Erickson's unfinished tale in which they describe the use of modern imaging such as CT and MRI and the beneficial effects this use has on clinical therapy outcomes<sup>39</sup>. These benefits include improvements in local control, overall survival and very significant reductions in normal tissue toxicity<sup>61-67</sup>. The chapter closes with the authors expressing hope that the uptake of image based brachytherapy will be much better in the next ten years than it has been in the previous decade. The most favoured imaging modality for image guided brachytherapy is MRI for its superior soft tissue definition but uptake is largely hampered by cost and lack of access. CT is more accessible and so has seen

greater uptake<sup>37,48,68-73</sup>. Incorporating these imaging modalities into brachytherapy programs is largely restricted to well-resourced centres in both the first and developing world and remains elusive to many less well-resourced centres, particularly those in areas with a high burden of cervix cancer<sup>74</sup>. The challenges of moving to 21st century image-guided brachytherapy treatment are faced by both the first and developing worlds in regards to resource procurement, resource allocation and healthcare costs<sup>68,74</sup>. Challenges are also encountered in terms of the implementation of image guidance and the implications imaging has on the traditional practices of gynaecological brachytherapy<sup>59,68,75,76</sup>, Table 2.1.

Ultrasound in gynaecological brachytherapy has featured from time to time over the years but has not found routine use and has tended to be overlooked in favour of more technically advanced imaging modalities.



Table 2.1 Properties of imaging modalities used in brachytherapy

	MRI	CT	Ultrasound
Image propagation	Magnetic field and radiofrequency (RF) transmit and receive pulses <sup>77</sup> .	High energy electromagnetic radiation absorption and detection <sup>78</sup> .	High frequency sound wave emission and reflected echoes Based on pulse echo principle <sup>79</sup> .
Soft tissue resolution	Excellent soft tissue contrast	Good bone contrast, good soft tissue resolution that can be enhanced through use of a contrast agent	Good soft tissue contrast
Imaging mechanism	Contrast resolution relies on behaviour of hydrogen nuclei in different tissues reacting under the influence of a magnetic field while an RF pulse is applied. As the RF pulse is applied the nuclei absorb energy and resonate. After a period of time the nuclei relax and flip back to their normal energy state. When they relax they emit a radio photon. The emitted photons form the signal received by the RF coil. Different relaxation and decay states of the hydrogen nuclei send back different RF pulses that relate to the different types of tissue, these form the basis of MRI images.	A narrow beam of x-rays are rotated around the patient. Digital x-ray detectors positioned opposite the x-ray source send information from the exposure to a computer that constructs a 2D slice of the patient. Slices can be viewed individually or stacked to form a 3D image of the patient. X-rays are differentially absorbed by different tissues depending on the radiological density of the tissues. Radiological density is determined by the density and atomic number of the tissues. Tissues with high atomic number such as bone absorb x-rays and produce high contrast on images. Less dense tissues with lower atomic numbers do not absorb the x-rays and are displayed as shades of grey in the image.	High frequency sound pulses are transmitted into the body. As the sound waves hit a boundary between different tissues with different acoustic impedance some sound is reflected back as an echo. Each reflected echo is displayed at a point in the image which corresponds to the relative position of its origin within the body cross section, resulting in a scaled map of anatomical features. The brightness of the image at each point is related to the strength of the echo. Brighter echoes result from great acoustic impedance mismatches e.g soft tissue bone interface. Clear fluid such as a full bladder is depicted as black as no echoes are reflected back to the transducer.
Slice orientation and image planes	Multi-planar Volumetric scan	Trans-axial Post processing can be used to obtain other orientations	Multi-planar Free hand acquisition Volumetric scan possible
FOV ROI	Skin to skin Needs to be within the receiving coil	Skin to skin	Keyhole Needs to be perpendicular to the beam
Time to obtain image	Minutes per sequence, multiple sequences usually acquired	Seconds	Minutes
Geometric accuracy	Inaccuracy increases away from the magnet isocentre. Careful choice of pulse sequence parameters is required for applications which rely on geometric integrity.	Good	Good but relies on accurate scanning planes and focal optimisation in region of interest.
Artifacts	Multiple types and causes <sup>80</sup>	Multiple types and causes <sup>81</sup>	Multiple types and causes <sup>82</sup>
Dose calculations for radiotherapy	Work underway to produce electron density estimates for RT applications	Based on electron density of tissue	Work underway to produce electron density estimates for RT applications
Possibility for intraoperative use	Extremely limited due to cost and safety considerations	Limited due to cost	Possible
Portability	MRI on rails available Safety considerations paramount	CT on rails available	Extensive range of sizes, all ultrasound units are portable
Image quality	Protocol and sequence dependent	Protocol and sequence dependent	Operator and protocol dependent
Cost of equipment	High	High	Low
Cost of scan	High	High	Low

This chapter reviews the role of ultrasound in gynaecological brachytherapy and highlights the potential applications for use in brachytherapy for cervix cancer. A search of the literature was performed in the bibliographic databases PubMed, Ovid Medline, and EMBASE using the

keywords ‘ultrasound,’ ‘gynaecology,’ ‘brachytherapy,’ ‘endometrial cancer,’ and ‘cervix cancer’ in various combinations, up to June 2014

## 2.2 Ultrasound use in brachytherapy to guide applicator placement

By far the greatest use of ultrasound in gynaecological brachytherapy has been to guide applicator placement to avoid perforation and optimise the position within the uterine canal. Carson et al. recognised the usefulness of ultrasound to reposition a misplaced tandem in 1975<sup>83</sup>. Rossmann et al. reported using ultrasound to diagnose a suspected perforation during a difficult insertion<sup>84</sup>. Ultrasound confirmed the applicator had perforated the posterior wall of the bladder and led this group to suggest that ultrasound may be useful in the diagnosis of unsuspected cases of uterine puncture during brachytherapy. Wong and Bhimji described four case studies illustrating the use of post-operative ultrasound while using a metal applicator<sup>85</sup>. The applicator was easily identified on both longitudinal and transverse scans. Perforations were detected in three cases and resulted in cessation of treatment and removal of applicators. Although patients in the study were scanned post-operatively the authors concluded that ultrasound could easily be performed intra-operatively which would render the procedure even safer. Granai et al. described applicator insertion ‘as blindly pushing a metal probe through an often distorted cervix to an unverifiable point’. They dispelled the prevailing thinking that ideal positioning of the intracavitary applicator is achieved using standard techniques of clinical palpation and x-ray confirmation<sup>86</sup>. In a two part study looking at ultrasound used post-insertion and during insertion, Granai et al. found 34% of insertions were inadequate when assessed post-insertion. This included frank perforations in 10% of insertions. In the second part of the study, 72 of 73 insertions assessed with intra-operative ultrasound were optimally

placed. The single case in which ultrasound did not facilitate placement involved cancer of the cervical stump, for which adequate imaging was not possible. Granai et al. found that ultrasound clearly visualized the procedure, allowing applicators to be positioned with confidence even in the most difficult cases. The immediate feedback from intraoperative ultrasound eliminated malplacements and thus the need for a second anaesthesia to reposition the applicator. McGinn et al. used ultrasound for 11 out of 237 procedures and detected perforation in seven instances (3%)<sup>87</sup>. They strongly recommended the use of portable intraoperative ultrasound during the placement of intrauterine applicators for difficult cases or any case in which perforation was suspected. Rotmensch et al. investigated use of intraoperative ultrasound for applicator placement in 20 implants<sup>88</sup>. Unsatisfactory placement was detected in nine implants (45%) including six (30%) perforations. These complications were unknown to the clinician inserting the applicators. The authors concluded that use of intraoperative ultrasound was helpful when difficulty was encountered in the placement of the applicator. Potential complications could be identified early without resorting to more invasive corrective procedures. Erickson et al. described their institutional technique of using transabdominal ultrasound to guide intra-uterine applicator placement along with interstitial needle placement during transperineal implants<sup>89</sup>. They found ultrasound readily established the relationships of the endocervical canal, cervico-uterine junction, intra-uterine applicator and first interstitial needles. Assessing needle depth with ultrasound ensured optimum tumour coverage while avoiding perforation of the bladder. Corn et al. investigated whether the inclusion of intraoperative ultrasound converted a more dangerous insertion into a procedure with relative safety, akin to that of a procedure not requiring ultrasound<sup>90</sup>. One hundred and forty-three implants were performed on 100 women. Ultrasound was used for 20 implants in patients with stenosis of the cervical os, radiation fibrosis, indeterminate orientation of the axis of the endometrial cavity, and previous perforation. There were five (3.5%) instances of

perforation (with two occurring in the ultrasound subset). It was noted that these two cases were among the first cases planned with ultrasound, implying the presence of a learning curve. Corn et al. found that use of ultrasound may compensate for the inherent risks of perforation harboured by patients with difficult anatomy. Mayr et al. evaluated the outcome of ultrasound guided applicator placement in retroverted uteri<sup>91</sup>. Thirty three insertions were performed to dilate the cervical canal and reposition the uterus to anteversion. Ultrasound guided anteversion of the applicator and uterus was achieved in all procedures with no evidence of perforation. Mayr et al. concluded that use of ultrasound was feasible and resulted in acceptable outcomes and complication rates in a population at high risk for uterine perforation. In a pictorial essay, Reuter reported the most frequent indication for intra-operative ultrasound was the difficult dilatation and curettage, but also described using ultrasound to aid in the placement of intracavitary applicators for patients with endometrial and cervix cancer<sup>92</sup>. Reuter concluded that use of ultrasound prevented the need for invasive procedures and resulted in timely completion of previously unsuccessful procedures, while minimising tissue damage. Watkins et al. conducted a retrospective review of 71 patients who underwent 110 ultrasound guided placements of applicators for low dose rate (LDR) brachytherapy<sup>93</sup>. The objective of the study was to determine if using ultrasound minimized the risk of perforation. Only one patient experienced infection that may have been attributable to perforation. Perforation was not verified clinically and symptoms resolved with antibiotics. Watkins et al. found that ultrasound guided applicator placement was associated with minimal risk of uterine perforation and offered an effective technique for minimizing morbidity. Phelps and Peteriet wrote a descriptive report of their technique using transabdominal ultrasound to facilitate applicator positioning and treatment planning<sup>94</sup>. They concluded that use of transabdominal ultrasound plays a critical role in accurate applicator positioning, radiation delivery and patient outcomes, by facilitating proper placement and decreasing perforation rates. The studies discussed range

from the 1990s to 2005; and although they all showed that use of ultrasound improved the technical quality of implants and contributed to a decrease in perforation, increased uptake in both the Australian environment and around the world has only been seen in the last few years<sup>37,48,70,95</sup>.

## 2.3 Rates of perforation detected with 3D imaging

While use of CT was being investigated for assessing dosimetry in intracavitary brachytherapy some practitioners observed unexpected perforations of the uterus<sup>51,54,64,96-102</sup>. Makin and Hunter described detecting 18 (3%) unexpected perforations in a cohort of 631 scans<sup>103</sup>. Milman and Goodman reported a case study of uterine perforation detected on CT<sup>104</sup>. These authors recognised that ultrasound was the most useful technique for demonstrating perforation and could be employed intra-operatively and so avoid a second procedure to remove or reposition an incorrectly located applicator. However, they were making the case for use of CT which they felt better determined the distance of the applicator from bowel and other normal pelvic structures. Barnes et al. conducted a prospective study comparing clinical assessment of perforation with actual placement determined on CT<sup>105</sup>. The incidence of CT detected perforation was 13.7% (17/124 insertions). CT detected perforation in 8.2% (8/98 insertions) where the clinician was clinically confident of correct applicator placement. After implementing 3D CT imaging for intracavitary brachytherapy Davidson et al. observed perforations in 10% of insertions, similar to the findings of Barnes et al. above<sup>106</sup>. In an effort to improve workflow, implant quality, and reduce re-implantation, they introduced routine use of intra-operative transabdominal ultrasound to guide applicator placement. In an initial analysis of 35 insertions all but one were successfully guided by ultrasound. One patient with an atrophic bladder could not be scanned as she could not retain sufficient water to provide an

adequate acoustic window into the pelvis. Davidson et al. demonstrated that use of intra-operative ultrasound could be practically integrated into the cervix brachytherapy program. Insertion time was reduced from 34 to 26 minutes, use of gynaecological services was reduced from 38% to 5.7%, and radiology was not required for any insertions.

Two retrospective studies using 3D imaging to plan brachytherapy for cervix cancer have been conducted to review the rate of perforation. Segedin et al. reviewed 496 insertions in 253 patients and identified perforation in 13 (3%) insertions in 10 (4.6%) patients<sup>107</sup>. Re-perforation occurred in three patients (without the use of ultrasound guidance). Ultrasound was used to successfully guide applicator placement for subsequent insertions in four patients. While recognising the benefits of intra-operative ultrasound to detect and correct applicator malplacements this group only uses ultrasound in challenging cases. Onal et al. reviewed 200 patients (626 insertions) who underwent 3D CT image guided brachytherapy<sup>108</sup>. They identified 30 (4.8%) perforations. The aim of their study was to assess an alternative modality to ultrasound to prevent or reduce perforations during applicator insertion. The authors investigated use of pre-brachytherapy MRI to assess uterine position. This information was then used to guide applicator insertion. One third of patients had pre brachytherapy MRI scans. There were three (4%) perforations in this subgroup as opposed to 14 (11%) perforations in the patients with no MRI evaluation before brachytherapy. The authors acknowledged evidence in the literature that use of intra-operative ultrasound decreases the perforation rate but countered with a survey result that indicated only 56% of brachytherapists have used ultrasound at some point in their practice<sup>69</sup>. They felt a further limitation of ultrasound was the need for experience. There was no comparative investigation into the use, availability or learning curve associated with MRI. They concluded that pre-operative MRI is a feasible and safe method and could be used preoperatively at centres where intra-operative ultrasound is not used in routine practice.

While a number of investigators recommend the use of ultrasound for complicated cases and when perforation is clinically suspected, Small et al. recommend using ultrasound for all applicator insertions after they detected an unexpected perforation at routine post implant CT<sup>109</sup>. They felt that uterine perforation was possible in any patient. Schaner et al. in a report on 10 years of experience using intra-operative ultrasound for both LDR and high dose rate (HDR) brachytherapy observed a perforation rate of 1.4%, also recommend routine use<sup>110</sup>.

## 2.4 Early ultrasound use in external beam radiotherapy

In the 1970's, an era before widespread use of CT, use of ultrasound was reported for acquiring anatomical information such as patient contours, and location and depth of tumours and normal structures<sup>111-113 114,115 83,116-118 119-121</sup>. Brascho described ultrasound as a major break-through in radiation treatment planning and predicted ultrasound would become a standard method of obtaining anatomical information in all modern radiotherapy departments<sup>114</sup>. While this prediction did not eventuate, largely due to the introduction of CT for radiotherapy planning<sup>122-125</sup>, ultrasound did see a small resurgence in the early 2000's with the development of ultrasound alignment systems. Examples of these systems are BAT® (B-mode Acquisition and Targeting, NOMOS, Sewickley, PA), Sonarray (Varian, Palo Alto CA), ExacTrac© (Brainlab AG, Feldkirchen, Germany), and more recently, Clarity™ (Resonant Medical Inc, Montreal, Canada)<sup>126</sup>. A desiderate feature of these systems is the use of non-ionising technology for localising targets and verifying treatments. The later systems have become highly sophisticated as they combine 3-D ultrasound imaging and optical technology for real-time tumour tracking, but once again ultrasound is competing with CT in the guise of on-board imaging systems such as cone-beam CT, and so has not enjoyed widespread uptake.

## 2.5 Ultrasound use in gynaecological brachytherapy planning

### Uterine cancer

Use of ultrasound to aid in planning brachytherapy for uterine cancer was first reported in 1975. Wenzel described use of ultrasound as a non-invasive method of obtaining uterine measurements to aid in dose determination in intracavitary treatment for endometrial cancer<sup>127</sup>. Wenzel recognised that while complex computer programs had been developed to calculate intracavitary dosimetry, there was no accurate method of measuring the uterus on which to evaluate dosimetry. Carson et al. described how longitudinal and transverse images of the uterus with an applicator in place could be combined with computerized treatment planning to yield meaningful estimates of the dose during intracavitary implants<sup>83</sup>. Brascho et al. also described use of ultrasound for planning intracavitary treatment for endometrial cancer<sup>128</sup>. The authors recognised that individualised treatment planning was possible with ultrasound imaging. Scanning before treatment facilitated applicator selection, while scanning after applicator insertion allowed for calculation of dose at critical points within and around the uterus. They also recognised the value of verifying the applicator position in relation to the uterus. This gave opportunity to adjust the plan in response to the anatomy reached by the radiation. Verification also detected poor applications that could be repositioned or abandoned. Englemeir et al. described use of an intrauterine ultrasound probe to obtain cross sections of the uterus<sup>129</sup>. The sections were combined to form pseudo three dimensional projections upon which dose coverage could be evaluated. Reuter described using ultrasound to obtain measurements of the uterus for planning brachytherapy treatment for endometrial cancer in obese patients<sup>92</sup>. Chun et al. reported using intra-operative ultrasound in patients undergoing brachytherapy for endometrial cancer<sup>130</sup>. Chun et al. recognised that myometrial invasion could not be evaluated by conventional CT scan or clinical examination and that each patient has a



different uterine thickness due to variations in normal anatomy and extent of disease. The authors used ultrasound to measure the thickness of the uterine wall in different directions to calculate the radiation dose delivered to the mid myometrium and serosal surface of the uterus. Gunter and Degenhardt described using simple ultrasound methods to localise the tumour, select suitable isodose curves, and estimate dose to surrounding loops of bowel<sup>131</sup>. They concluded that ultrasound could also be used to verify the position of the applicators making injury to the uterus and other organs less likely.

Nguyen et al. described introducing ultrasound into their endometrial brachytherapy program after analysing toxicity encountered over a six year period<sup>132</sup>. They recognised that use of ultrasound enabled them to confirm tandem placement and individually tailor radiation to each patient. Since implementing use of ultrasound and individualised planning they observed no late complications.

Similar to this time period in EBRT, ultrasound emerged as an aid to planning brachytherapy and then disappeared. Unlike in the EBRT world, however, use of CT for gynaecological brachytherapy while investigated<sup>96,98</sup>, did not replace ultrasound for planning. Plain film radiographs to assess applicator placement and dosimetry remained the standard<sup>133</sup>.

## Cervix cancer

Ultrasound has been widely used to guide applicator placement in brachytherapy for cervix cancer but unlike in brachytherapy for endometrial cancer, it has not been used to guide planning. While several authors have described and illustrated how measurements can be taken of the uterus to guide planning in endometrial cancer these methods have not been widely adopted in to cervix brachytherapy, Figure 2.1.

There have been two early studies looking at use of ultrasound to assist in calculating dose to the bladder during brachytherapy for cervix cancer. Rahim et al. found ultrasound to be the most appropriate method to evaluate the distance between the applicator and the bladder mucosa in brachytherapy implants for cervix cancer<sup>134</sup>. Using similar methodology, Barillot et al. also used ultrasound to measure the distance to the balloon of the Foley catheter which indicates the ICRU 38 bladder reference point<sup>34,135</sup>. Sixty nine measurements were performed on 58 patients. Barillot et al. also measured the minimum distances to the bladder in the axial and sagittal projections. These points were then transferred to orthogonal films and used to calculate the average dose to the bladder base. Barillot et al. found excellent correlation between the ultrasound and orthogonal film calculations for the ICRU 38 bladder point but found this point did not represent the mean and maximum bladder doses in over 75% of cases. Barillot et al. introduced routine ultrasound for all gynaecology applications to monitor bladder doses and while not stating specifically, inferred that adjustments to plans could be made to reduce bladder toxicity.

In 2008 we reported the first use of transabdominal ultrasound to guide applicator placement and plan conformal treatment for HDR brachytherapy treatment for both cervix and endometrial cancer<sup>136</sup>. Using two case studies, we showed how intra-operative ultrasound can be used to optimise the applicator position and shape the isodose distribution to individual anatomy. Our group further investigated use of ultrasound based planning in a number of studies. In 2009 we published a retrospective planning study comparing isodose distributions resulting from standard plans, ultrasound derived plans, 2D MRI derived plans, and final dosimetry based on the combination of planning methods actually used in treating patients<sup>137</sup>. There was no difference in target volume coverage between ultrasound and MRI derived plans ( $p=0.2$ ) nor between ultrasound and final dosimetry ( $p=0.075$ ). We concluded that ultrasound

can be seen to offer comparable anatomical detail to MRI, allowing sufficient dose to be delivered to the target area while sparing normal surrounding tissues. In a further study in 2009, we compared an historical series of patients treated with LDR brachytherapy to patients treated with ultrasound guided conformal HDR brachytherapy<sup>62</sup>. Patients who received ultrasound guided conformal brachytherapy received significantly less dose to Point A, but we found no significant difference in five year overall survival or five year relapse free survival between the groups. We also found significant differences in the dose received at ICRU 38 reference points

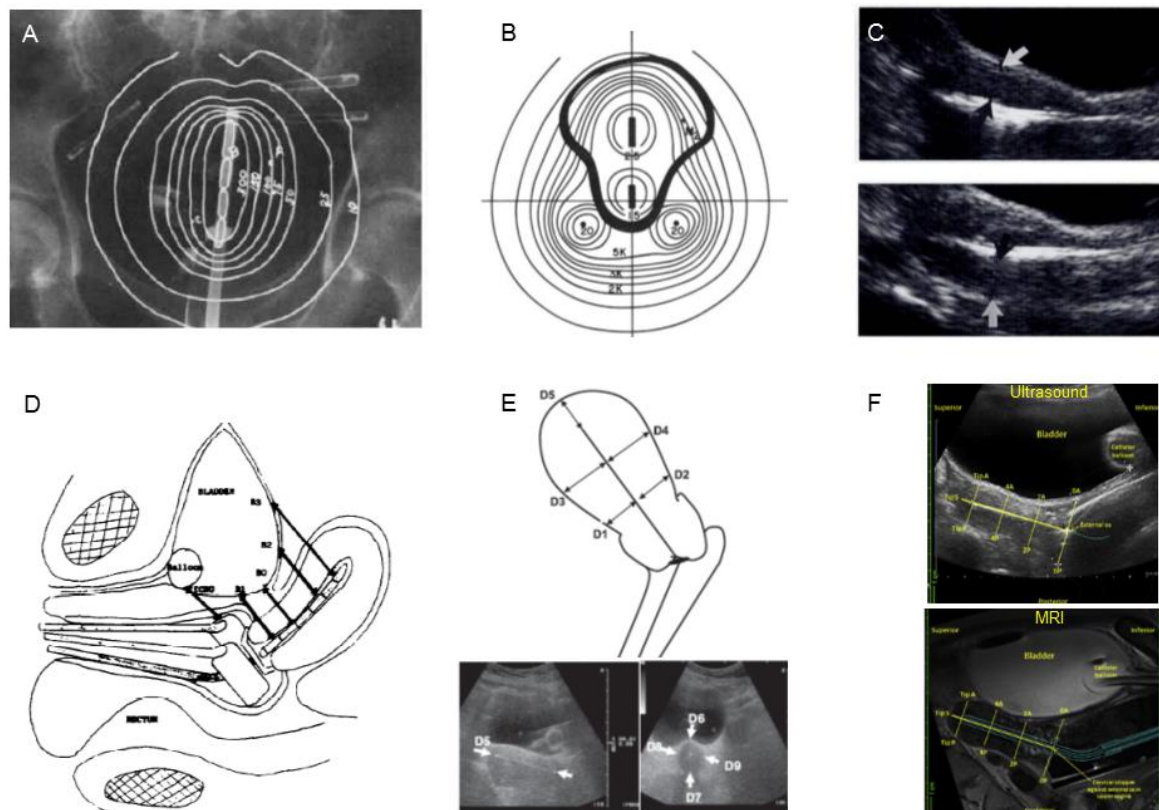


Figure 2.1 Examples of ultrasound measurements of uterus used to guide brachytherapy planning

- A. A-P Radiograph of the pelvis with tandem and sources in place. Serosal surface of uterus measured from ultrasound indicated by A in the image, isodose curves, labelled in rads per hour overlaid on radiograph <sup>127</sup>.
- B. Uterine outline superimposed over isodose curves for and tandem and ovoid applicator. The uterine size was determined from the ultrasound scan <sup>128</sup>
- C. Longitudinal transabdominal intraoperative sonograms of uterus show radiation applicators for caesium intracavitary treatment of endometrial carcinoma. Distance from applicators to uterine walls indicated by arrows <sup>92</sup>.
- D. Methodology of recording measurements obtained with ultrasound showing distance from radioactive source to bladder mucosa <sup>135</sup>.
- E. Definition of measurement points from intrauterine applicator to uterine wall obtained with ultrasound. Measurements taken to assess suitability of ultrasound to guide planning <sup>138</sup>.
- F. Nomenclature of measurement points on longitudinal ultrasound and MRI views of cervix and uterus. Measurements used to guide planning <sup>139</sup>.

for bladder and rectum. Patients who underwent ultrasound guided conformal HDR brachytherapy received significantly less dose at these points. The effect of these differences

was notable in that 68% of patients in the HDR group remained completely asymptomatic after treatment compared to 42% in the LDR group.

## Validation studies

There is a perception that ultrasound is difficult to interpret and produces less accurate depictions of anatomy than MRI. This is despite the widespread use of ultrasound in diagnostic medicine to visualize and measure many organs within the body not the least of which is the human foetus *in utero*. Ultrasound is considered the gold standard in obtaining milestone images and measurements of the foetus and yet has failed to find widespread use in identifying the uterus for planning brachytherapy. As there is increasing familiarity and acceptance of MRI in gynaecological brachytherapy, MRI has been used as the standard against which to validate ultrasound. Two validation studies looking at correlation and agreement between MRI and ultrasound have been reported.

Mahantshetty et al. compared ultrasound and MRI measurements of the uterus and cervix to assess the potential value of ultrasound for image-guided cervical cancer brachytherapy<sup>138</sup>. In a study of 20 patients and 32 applications utilizing repeated measurements, this group looked for correlation between the imaging modalities. While good correlation was found overall, the strongest correlation was found between measurements of the anterior surface of the cervix and uterus,  $R=0.92$  and  $R=0.94$  ( $p<0.01$ ). Measurements to the posterior surface had a moderate correlation,  $R=0.63$  and  $R=0.82$  ( $p<0.01$ ). They concluded that newer ultrasound systems could improve posterior wall identification and that ultrasound could be utilised in conformal brachytherapy but needed further evaluation. We conducted a similar study using data from 192 patients<sup>139</sup>. All measurements were recorded prospectively and only one pair of

measurements were analysed per patient (MRI vs ultrasound at fraction 1). We used Bland Altman methodology and looked for agreement between the imaging modalities rather than correlation<sup>140,141</sup>. We found good agreement between the imaging modalities. In particular, we found little difference between modalities when measuring the posterior surface of the cervix and uterus with mean differences of less than 1 mm. This was important as the organs at risk outside the posterior surface include the rectum and bowel. It was possible to obtain clear and detailed images of the uterus and cervix with the intra-uterine applicator in treatment position. We concluded that such detailed images make it possible to practice image-guided, conformal, and adaptive brachytherapy using transabdominal ultrasound.

These planning and validation studies have been limited to intracavitary implants. Although these form the bulk of brachytherapy treatments for cervical cancer, there has been a steady increase in the use of intracavitary applicators combined with interstitial needles. These hybrid applicators are used in centres with advanced imaging capabilities such as MRI and CT. Ultrasound has not been investigated for use with these applicators other than in a study investigating transrectal ultrasound (TRUS) discussed in the following sections.

## 2.6 Using transrectal ultrasound (TRUS)

Use of ultrasound in gynaecological brachytherapy has predominantly been performed with transabdominal ultrasound. Holm et al. developed TRUS in 1983 to perform transperineal seed implantation for prostate cancer<sup>142,143</sup>. The technique was adopted and refined by Radge and Blasko from Seattle and has become the definitive method for implanting catheters and radioactive seeds in both HDR and LDR brachytherapy for prostate cancer<sup>144-147</sup>. TRUS has been used in gynaecology to guide complicated procedures such as abscess draining, uterine

evacuation, and cerclage placement<sup>148-152</sup>. There has also been extensive work looking at TRUS to assess resectability of early stage cervical cancer<sup>153-159</sup>. Fischerova et al. evaluated the accuracy of TRUS in comparison to MRI in patients who underwent a surgical treatment (simple hysterectomy, radical hysterectomy, or radical trachelectomy). The group found TRUS to be comparable to, or superior to MRI in the identification of residual tumour following conisation, evaluation of small tumour volume, and initial parametrial infiltration<sup>158</sup>. Epstein et al. reported similar findings based on a European multicentre study<sup>159</sup>. These studies were conducted on patients with early stage disease (FIGO IA1 – IIA1) who were referred for surgery. The pathological specimen served as the gold standard against which comparisons could be made. Though TRUS was found to have a low false negative rate in predicting parametrial invasion in both these studies, it is important to note the small number of patients with actual parametrial involvement in these studies. The high sensitivity and specificity demonstrated by TRUS in these studies has not led to widespread adoption of TRUS to evaluate the extent of cervix cancer, nor has TRUS been widely used in treatment planning for cervix cancer.

## TRUS in gynaecological brachytherapy

In contrast to the investigative procedures above, TRUS is being used in more advanced disease during brachytherapy, primarily to guide insertion of both intra-uterine applicators and interstitial needles<sup>160-163</sup>. Stock et al. describe using interstitial implants to treat patients with significant parametrial or paracervical extension that could not be adequately treated with intracavitary brachytherapy<sup>161</sup>. They concluded that TRUS provided real time visualization of the target volume and normal tissues, and allowed for accurate needle placement. Sharma et al. reported on a series of 40 TRUS guided interstitial brachytherapy procedures for patients with

FIGO IIB and IIIB tumours, and found that TRUS assisted in avoiding needle injury of pelvic structures and reduced the risk of perioperative complications<sup>162</sup>.

Schmid et al. studied the feasibility of TRUS for the assessment of local target extension in patients undergoing brachytherapy for cervix cancer. They compared TRUS measurements of the cervix to MRI based measurements<sup>163</sup>. Two measurements were made, the width and thickness of the cervix on transverse planes. Height of the target was not examined. This was a small heterogeneous study of 17 patients, with measurements made at different time points in the patient's clinical journey. Pre-treatment imaging was used for five patients, imaging taken prior to brachytherapy was used for nine patients, and imaging taken with brachytherapy applicators *in-situ* was used for three patients. Cervical width measurements were able to be taken in all patients with corresponding good correlation between TRUS and MRI ( $R^2=0.842$ ). Measurements of cervical thickness also showed good correlation ( $R^2=0.934$ ), but with a systematic difference indicating an underestimation of thickness by TRUS. Cervical thickness could not be measured in the three patients with brachytherapy applicators *in-situ*. Artifacts from the interstitial needles obscured the anterior wall of the cervix. Although the study found that TRUS can potentially be used to identify the brachytherapy target volume in image guided brachytherapy, it did not confirm that TRUS can be used to guide planning using hybrid applicators. A further limitation of TRUS is the smaller focal length and field of view associated with endorectal probes. This will limit visibility of larger uteri requiring longer applicators.



## 2.7 *Pros et Contra* of transabdominal ultrasound

The advantages and disadvantages of using ultrasound in gynaecological brachytherapy are listed in Table 2.3. The most advantageous aspect of ultrasound is the ability to view structures in real time, while the most serious limitation seems to be the dependence on operators for a good image.

Ultrasound training does not form part of the core syllabus for radiation oncologists or radiation therapists so it is not surprising that there is a level of discomfort and unease in using ultrasound. However, these professions are exposed to constantly advancing technology in both hardware and software and recognise that training is needed to utilise these changes safely. So while ultrasound is often perceived as easy to use, these craft groups understand the need for specific training and education<sup>164</sup>. There is a role for limited scope training to educate and inform potential users about ultrasound. Similar training has been designed for specific use of ultrasound in a number of areas for other medical, paramedical and non-medical people<sup>165-173</sup><sup>174,175</sup>. These training programs are designed to impart very specific skills and examination techniques that are particularly relevant to the different groups. While most ultrasound use is concerned with diagnosis, another use is to enhance the practitioner's ability to perform their job more efficiently or safely<sup>176 177-179</sup>. These are two of the motivations for use of ultrasound in gynaecological brachytherapy.

Table 2.4 lists the personnel performing ultrasound for brachytherapy identified in the literature. While some mentioned a learning curve, none described the training required to perform the procedure. Davidson et al. certainly recognised the utility and efficiency of having a member of the brachytherapy team perform the ultrasound<sup>106</sup>. This reduced the reliance on

other expert resources such as radiologists or diagnostic sonographers. Mayadev et al. originally used a certified technician but transitioned to the radiation oncologist performing the ultrasound to save time and optimise the workflow<sup>76</sup>. Van Dyk et al. use a radiation therapist trained in ultrasound to assist with applicator insertion and treatment planning<sup>139</sup>.

The use of ultrasound to examine the obese patient can be challenging. Particular difficulties have been reported when using ultrasound to detect foetal abnormalities in obese pregnant women<sup>180</sup>. However, none of the literature describing use of ultrasound in brachytherapy reported difficulties in obtaining images of the uterus and cervix in obese patients. This may be attributable to ultrasound being used to insert the applicator while the patient is anaesthetised. This affords the sonographer ample opportunity to fill the bladder to ensure an optimal acoustic window into the pelvis and use of firm applicator contact without causing undue patient discomfort.

Although the uterus is easily visualised on ultrasound, there have been no reports describing the ability to see residual disease or gross target volume (GTV) at the time of brachytherapy. This ability may well be addressed in the future as advances are made in ultrasound capabilities. Identification of the GTV is not crucial at the time of brachytherapy as the brachytherapy target incorporates the whole cervix, which is readily identifiable<sup>41</sup>.

The literature describing use of ultrasound for planning brachytherapy for cervical cancer is very limited. There are still questions and areas of practice that need to be addressed, with training and education in ultrasound use being foremost. Once appropriate training has been obtained, guidelines for use need to be established that explain planning technique and reporting mechanisms.

There have been many advances in ultrasound technology progressing it from the gray fuzzy and indiscernible images from early machines to images that rival the detail of MRI, Figure 2.2. These advances include improved transducer sensitivity, faster image processing speed, higher resolutions, panoramic imaging, 3D/4D imaging, elastography, contrast imaging, and smaller portable units. The gains achieved from using these technologic advances in diagnostic examinations will also influence how ultrasound is used in brachytherapy.

## 2.8 Use of ultrasound around the world

The use of ultrasound in gynaecological brachytherapy was identified from patterns of care surveys, Table 2.5. There is reasonable availability of ultrasound in the USA, Europe and Canada, although not all surveys asked specific questions in relation to ultrasound use. Only one department in Australia reported using ultrasound for planning brachytherapy. This department and a further department from New Zealand reported using ultrasound for verification of the applicator position during the course of brachytherapy. While ultrasound is commonly available in hospitals and increasingly available in radiotherapy departments these surveys indicate limited uptake for brachytherapy. Planar x-ray images remain the most common imaging modality used to plan brachytherapy treatments, particularly in the developing world.

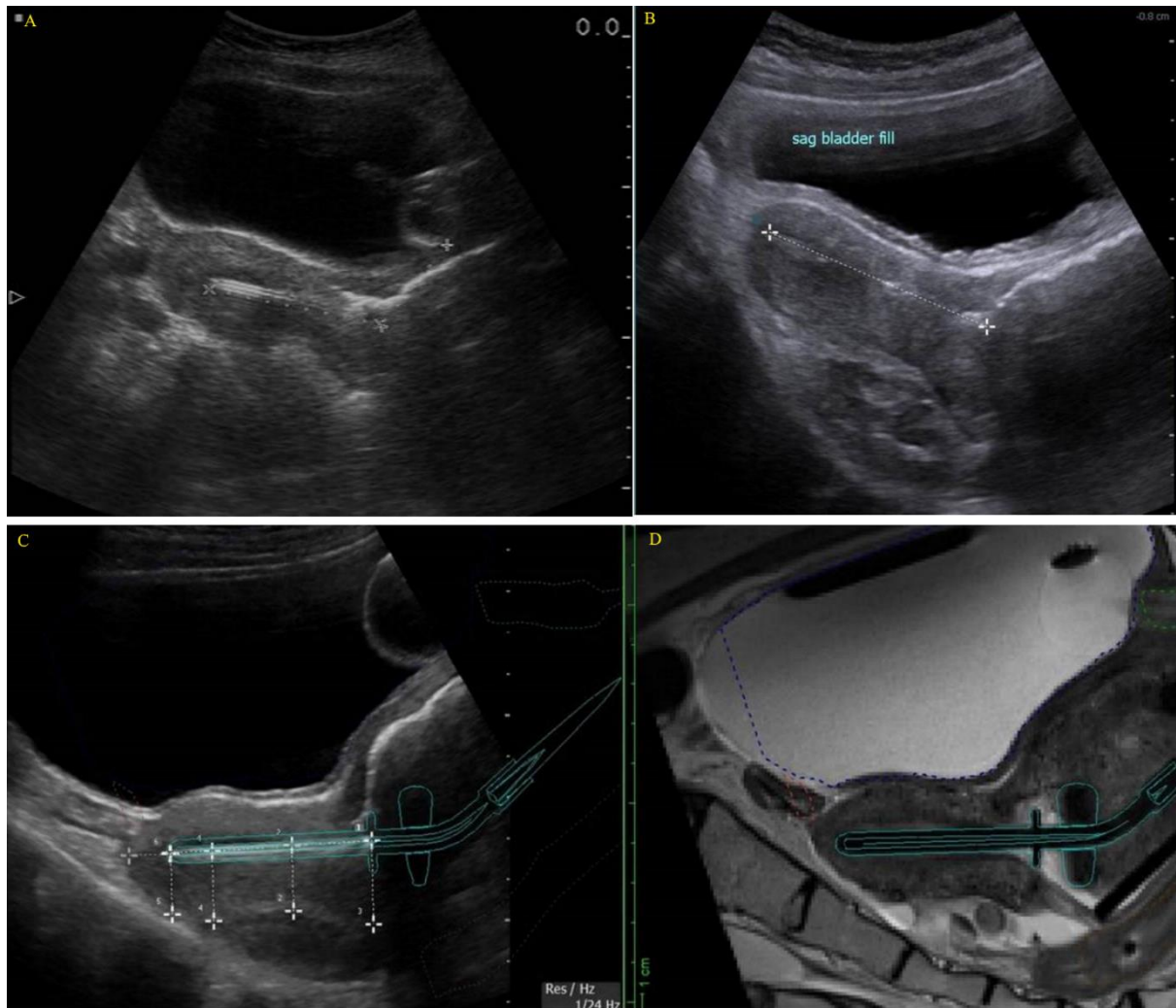


Figure 2.2 Example of improvements in quality of ultrasound images

- A. Longitudinal view of applicator in uterus taken in 2008 with Falcon ultrasound unit (BK-Medical, Herlev, Denmark)
- B. Longitudinal view of applicator in uterus taken in 2010 with Flex focus 400 ultrasound unit (BK-Medical, Herlev, Denmark).
- C. Longitudinal view of applicator in uterus taken in 2012 with Flex focus 400 ultrasound unit (BK-Medical, Herlev, Denmark)
- D. Longitudinal view of applicator in uterus on MRI taken in 2012, same patient as image C

Source: Peter MacCallum Cancer Centre

Table 2.3 *Pros et contra* of ultrasound use

<i>Pros</i>	<i>Contra</i>
Cost: <sup>86-88,105-109,135-138,181,182</sup> Low cost installation Economical (cheap to use)	Needs physical contact: <sup>183 138,139,163</sup> Potential tissue deformation
Portable: <sup>87,182 184 105 137</sup> Bring imaging to patient Able to integrate into OR easily	Learning curve: <sup>90 136 137 138 139</sup> Image acquisition Image orientation Image interpretation
Non-ionising: <sup>128 135</sup> Safer for patient and staff	No 3D co-ordinate system: <sup>139</sup> Can't spatially allocate image No fixed frame of reference
Real time intra-operative assessment : <sup>85,86,104,127,128 87,88,90,91,93,94,105-107,109,110,136,137,139</sup> Anatomy topography Guide applicator choice Diagnose perforation Correct applicator malplacements Optimise applicator placement	No volumetric analysis of target coverage or dose to OAR <sup>136,137</sup>
Speed : <sup>182 86 106 108</sup> Reduce time required for insertion	
Use for verification of applicator position at time of treatment <sup>128 132 106 136 109 110 139</sup>	
Use for verification of target volume <sup>127 128 129 130 132 136 94 139</sup>	
Can use full bladder as bowel displacement device <sup>135</sup>	
View adjacent organs (e.g. loops of bowel) <sup>131</sup>	
Reduced reliance on other expert resources: <sup>106 110 139</sup>	
Gynae Oncologist Radiologist Sonographer	
Applicator acts as fiducial marker & calibration device: Assists in understanding image orientation <sup>139</sup>	
Serial imaging gives 4D changes to perform adaptive brachytherapy <sup>136,137 139</sup>	

OAR = organs at risk

## 2.9 Future directions

At present ultrasound is largely limited to guiding applicator placement in brachytherapy for cervix cancer. Extrapolating use to plan brachytherapy has only been conceived by a few practitioners<sup>138,139</sup>. Incorporating soft tissue information obtained from 2D ultrasound can improve the technical quality of brachytherapy implants and has the potential to allow 3D conformal planning to be performed<sup>136,138</sup>. Two dimensional ultrasound images can be used to create 3D treatment plans as it is now possible to upload 2D images to some treatment planning systems<sup>139</sup>. It is also possible to upload 3D data sets. Three dimensional ultrasound acquires volume data of the pelvis that can be processed for display in multi-planar reconstructions similar to CT and MRI<sup>185</sup>. These volumes are very similar in orientation and quality to those of MRI and CT<sup>185</sup>. Use of 3D ultrasound can overcome some of the disadvantages of 2D ultrasound. Volumetric scanning may reduce the reliance on operator skill as a 3D volume can be acquired by a mechanical sweep of the transducer. Users would no longer need to mentally integrate 2D images to form an impression of the anatomy and pathology in three

Table 2.4 Personnel involved in performing ultrasound identified in the literature

Article (ref)	Personnel performing ultrasound for insertion of brachytherapy applicators
Wong and Bhimji <sup>85</sup>	Patient taken to radiology department
Rotmensch et al. <sup>88</sup>	Initially personnel trained in ultrasound (implies skill was later passed onto brachytherapy team)
Erickson et al. <sup>89</sup>	Radiologist
Davidson et al. <sup>106</sup>	Radiation Therapist/Physicist
Watkins et al. <sup>93</sup>	Ultrasound technician
Phelps and Petereit <sup>94</sup>	Sonographer
Schaner et al. <sup>110</sup>	Qualified technician
Mayadev et al. <sup>76</sup>	Sonographer with transition of skills to Radiation Oncologist
van Dyk et al. <sup>139</sup>	Radiation Therapist with ultrasound qualifications

Table 2.5 Patterns of Care studies

Indicating imaging modalities used during brachytherapy

Article (Ref)	Ultrasound used for insertion	Imaging modality used for planning	Imaging used for verification fx 2 3 4 5
van Dyk et al. 2010 <sup>186</sup> Australia New Zealand (ref period 2009)	15%	x-ray 30% CT 65% MRI 15% Ultrasound 5%	CT 55% X-ray 5% Ultrasound 10%
Viswanathan et al. 2010 <sup>69</sup> ABS USA (ref period 2007)	56% 42% routinely	CT 56% (US A only)	CT 60% (USA + Int)
Guedea et al. 2010 <sup>73</sup> Europe (ref period 2007)	48% available	x-ray 71% CT 54% MRI 15% PET-CT 5%	
Pavamani et al. 2011 <sup>71</sup> Canada (ref period 2008)	59% 24% routinely	x-ray 50% CT 45%	CT/MRI 44%
Tan et al. 2011 <sup>72</sup> United Kingdom (ref period 2010)		CT 51% MRI 20%	
Guedea et al. 2011 <sup>74</sup> Latin America (ref period 2007)	24% available	x-ray 97% CT 22% MRI 0.2%	
Viswanathan et al. 2012 <sup>70</sup> GCIC International (ref period 2008/9)	62% available 18% routinely	CT 57% MRI 25%	CT 37% MRI 11%

ABS = American Brachytherapy Society; USA = United States of America;  
GCIG = Gynecologic Cancer Intergroup

dimensions<sup>187</sup>. Although use of 3D ultrasound volumes to plan gynaecological brachytherapy has not been clinically tested, there is huge potential for this modality in limited resource settings. Use of 3D ultrasound would allow radiation coverage of the uterus and cervix to be

volumetrically assessed generating potentially similar analytical metrics to those obtained with CT and MRI.

Training and education of brachytherapy personnel in use of ultrasound also has to be addressed to obtain the maximum benefit from the many features of these machines and to ensure safe and efficacious use.

## 2.10 Conclusions

There is a large range in the resources used to plan brachytherapy for patients with cervix cancer. Progress is slowly being made as sophisticated imaging modalities are introduced into well-resourced centres, but the majority of patients with cervix cancer around the world continue to be planned with planar x-ray imaging. There is a crucial unmet need for soft tissue imaging capabilities in gynaecological brachytherapy. Ultrasound has the potential to meet this need by offering soft tissue imaging capabilities to all brachytherapy departments. Ultrasound is an accessible and economical imaging modality that can readily be incorporated into brachytherapy programs. Transabdominal ultrasound and TRUS can be used to guide placement of intracavitary and interstitial applicators, respectively. Transabdominal ultrasound can be used to guide intracavitary planning. Appropriate training for brachytherapy personnel is necessary to ensure safe and optimal use. Guidelines for planning and reporting treatment are also necessary. Ultrasound can be used to improve the technical quality of implants. These improvements have the potential to improve local control and reduce toxicity in these patients.



## 2.11 Recent progress of ultrasound usage in brachytherapy (2014 – 2017)

This section summarises recent progress in the literature that occurred in parallel with the studies presented in this thesis and after publications of the above review up until April 2017.

### Ultrasound use in gynaecological brachytherapy

A recent survey of brachytherapy practices in Australia and New Zealand has highlighted the increased use of ultrasound to guide applicator insertion<sup>48</sup>. Ultrasound use for applicator insertion was 86% which was an increase of 71% compared to a survey conducted four years previously. There is no doubt use of ultrasound makes insertion of the brachytherapy applicator a safer procedure. In a study of 96 patients undergoing intracavitary brachytherapy, Bramhananda et al. used ultrasound to confirm applicator placement in 78 patients, guide the applicator through a visible os but occluded canal in 12 patients, and identify the os and canal in a further four patients<sup>188</sup>. Use of ultrasound helped in identifying bulky disease only suitable for interstitial treatment in two patients. The authors found use of ultrasound decreased the overall time required for an intracavitary insertion and noted the benefit of this in their resource limited environment.

### Further investigations of ultrasound in gynaecological brachytherapy

Difficulty in obtaining MRI for every fraction of brachytherapy is well recognised and this has sparked an interest in exploring alternative imaging modalities for gynaecological brachytherapy. Similarly, recognition of the limitations of CT soft tissue contrast also make it necessary to investigate alternative modes of high resolution soft tissue imaging.

Schmid et al. had conducted a study evaluating the local extension of cervix cancer with TRUS with a view to determining the potential for using TRUS in image guided brachytherapy<sup>163</sup>. The authors found TRUS feasible for the assessment of local target extension. There was a systematic bias in underreporting of target thickness by TRUS attributed to probe pressure, but overall TRUS showed a high correlation with MRI in determining width and thickness of the target volume. TRUS could not depict the height of the target volume. The study used transverse slices of 5 mm thickness and was unblinded. In a recent updated study the authors investigated the use of 3D TRUS and compared it to MRI and CT<sup>189</sup>. This study included data from 19 patients who underwent TRUS prior to brachytherapy (14), TRUS with applicators *in situ* (16), MRI prior to brachytherapy (13), MRI with applicators *in situ* (19), and CT with applicators *in situ* (19). Images were analysed both quantitatively (cervix width and thickness), and qualitatively (grading system based on discrimination of HRCTV, parametria, uterine corpus, uterine fundus, rectum, bladder, sigmoid and bowel) in a blinded fashion. MRI with applicator *in situ* was used as the reference standard against which all imaging was compared. There were no statistically significant differences between MRI and TRUS with and without applicator *in situ* for target width. Target width on CT was statistically significantly wider with a mean (SD) difference of 13.8 mm (6.7) ( $p < 0.001$ ). Similar to the previous study, there were also statistically significant differences in target thickness between the imaging modalities. The qualitative analysis indicated that TRUS without applicators performed more accurately than TRUS with applicators *in situ*. Again, TRUS with applicators *in situ* performed less well than MRI particularly in determining the anterior border of the cervix and the posterior bladder wall. There was difficulty seeing through and beyond the artifacts caused by the applicator. There were three instances where TRUS could not be performed due to anatomical considerations, the probe could not pass beyond the recto-sigmoid curvature and so could not image the whole uterus. In fact, the height of the cervix was not imaged or measured at all due to limited

visibility on TRUS and CT. Overall the authors found TRUS to be within inter-observer variability of MRI and superior to CT in determining target volume width and thickness. They also recognised that they have not fully reconciled a full planning approach using TRUS, as the upper third of the uterus and some organs at risk were not visualised. They did suggest a combined approach of transabdominal ultrasound, as described by van Dyk et al., and TRUS might be used to overcome these limitations.

In an adjunct to the above work, Nescavil et al. recently published a proof of concept looking at incorporating 3D TRUS into a brachytherapy workflow for centres using CT to plan brachytherapy treatment<sup>190</sup>. Data from a single patient was used to illustrate the workflow and highlight both advantages and limitations of the process. The patient underwent TRUS prior to brachytherapy and TRUS, CT and MRI with applicators *in situ*. The main advantage of the concept is improved delineation of the cervix compared to CT. The main limitations are decreased ability to see beyond the applicators with TRUS and inability to determine the height of the target volume. Physical features of TRUS also contribute to limitations such as the relatively small field of view, the rigid fixed length probe that cannot negotiate beyond some applicators positioned above it in the vagina or beyond the recto-sigmoid junction. Variations in patient anatomy, such as a large uterus, will exacerbate these limitations. The study also highlighted some technical issues associated with obtaining a 3D acquisition. The 3D volume can be acquired by a pull back of the probe thereby obtaining a transverse volume akin to CT or by a rotation of the probe obtaining a longitudinal volume. The transverse method resulted in image distortions due to movement of the applicator and so was not used for planning. Applicator reconstruction was difficult on TRUS, as only parts of the applicator could be identified. This is in contrast to the views obtained with transabdominal ultrasound that can depict the whole applicator in the longitudinal plane and thus make applicator reconstruction

relatively quick while ensuring accuracy. CT overestimated the HRCTV volume and dimensions, while TRUS largely agreed with MRI, although the height of the HRCTV could not be delineated on TRUS. The group were able to achieve planning aims for TRUS/CT that would have fulfilled clinical acceptance criteria but they do concede there are a number of aspects to consider before full implementation of TRUS is possible. These aspects include customised software and hardware for volumetric image acquisition, DICOM export to the planning system, and applicator based image registration. It was also recognised that operational procedures such as ultrasound machine settings and training of users need to be considered to improve image quality, precision of target delineation and applicator reconstruction.

In another proof of concept study, Petric and Kirisits reported on the use of transcervical endosonography giving it the acronym TRACE (TRAnsCervical Endosonography)<sup>191</sup>. This was a single patient study exploring the possibility of using TRACE to guide brachytherapy planning. The patient underwent uterine canal dilatation and a 6.9 mm diameter ultrasound probe with a mechanically rotating array was inserted into the canal. The refreshment rate of the image allowed for clinically useful real time assessment of pathology and anatomy. The resultant image was a 360° transverse view of the cervix and uterus. The probe utilises a frequency of 10 MHz and so produces a high resolution image. The main limitation was gradual deterioration of image quality as the probe was progressed further into the uterine canal and this was thought to be due to removal of the coupling gel. This finding needs to be further explored. The uterine canal is quite small, it was dilated to permit probe insertion, there should have been good contact between the probe and the walls of the canal and resultant good images. The images permitted a good view of the uterus and cervix free from applicator artifacts. Correlation between MRI and TRACE was good for target volume dimensions and parametrial

involvement. The absence of applicator artifacts was seen as a positive feature although it can also be seen as detrimental, as the ultrasound image cannot be taken with the applicator *in situ*. While not considered in the study there is scope to use the probe per rectum once the applicator is in place and to investigate this modality for verification of applicator placement. Another limitation noted was the free hand nature of the image acquisition that made spatially allocating the axial views difficult. This is a similar limitation encountered when using transabdominal ultrasound and might be addressed by the addition of echo bright calibrations on applicators or use of a fixed co-ordinate system something akin to the original static B-mode scanners that could spatially allocate the transducer<sup>192</sup>. Overall, the authors demonstrated the potential of TRACE in pre-planning for brachytherapy. Several areas were recommended for further investigation and they included effective transducer tissue coupling, applicator reconstruction, imaging range, ultrasound contouring concepts and validation, OAR dose assessment, registration with other imaging methods, and real time dosimetry. The authors also indicated potential for TRACE to be used in conjunction with existing technologies such as MRI, CT, transabdominal, transrectal, and transvaginal ultrasound.

## The potential of 3D ultrasound in image guided brachytherapy

The potential of 3D ultrasound for use in brachytherapy is keenly anticipated especially by those who are familiar with good quality 2D ultrasound data sets. 3D ultrasound of the cervix and uterus is increasingly being used to assess anatomical abnormalities and diagnose and stage disease<sup>193,194</sup>. There have been some promising studies looking at the use of 3D ultrasound in gynaecological brachytherapy. Tamaki et al. conducted a phantom study comparing intrauterine ultrasound (IUS) to MRI and CT<sup>195</sup>. The phantom was specially constructed from chicken and agar. A polyethylene tube was inserted to mimic the uterine canal. The IUS probe

was inserted into the tube. Axial slices were obtained with CT, MRI and IUS in 1 mm slices and exported as DICOM files to an image processing software program to reconstruct the 3D images. The MRI and IUS images were visually registered to the CT data set using manual registration. Contouring was performed independently on each data set and a sample brachytherapy plan was calculated on the CT images. The dice similarity coefficients for contours were similar across the imaging modalities and dose volume histogram (DVH) metrics within 4%. Similar to Petric and Kirsits above, the authors proposed that IUS could be used to better identify soft tissue structures and assist in evaluating the brachytherapy treatment plan.

In a study involving eight patients Foster et al. examined the use of 3D ultrasound to determine if it can be used as an imaging modality for volumetric treatment planning<sup>196</sup>. Patients received an MRI scan prior to starting brachytherapy. The group used a 3D ultrasound unit (Clarity AutoScan, Elekta, Montreal) that consists of a transducer that performs a mechanical sweep to obtain a volume scan of the pelvis. The ultrasound was used to assist applicator insertion and treatment planning. The patients were then CT scanned and all data sets co-registered. Images were qualitatively assessed based on visualisation of the cervix, uterus, bladder, rectum and sigmoid and quantitatively assessed on HRCTV contouring. All organs could be clearly seen on all imaging modalities except the sigmoid and rectum on 3D ultrasound. The intrauterine applicator could be seen all on imaging modalities, but the ovoids were not clearly seen on 3D ultrasound. The HRCTV could be identified on 3D ultrasound, but with a wider standard deviation than the other imaging modalities. The 3D ultrasound data set improved the CT HRCTV contours and more closely approximated the MRI contours than CT alone. Overall, the authors did not find they could recommend 3D ultrasound as a sole modality for volumetric planning because of poorer reproducibility and sub-optimal visualisation of critical structures.

However, they did find that CT contouring was improved with CT-3D ultrasound fusion and could enable faster and more efficient treatment planning in the future. The authors also believe the results could improve over time as they recognised there was a learning curve associated with the use of 3D ultrasound. The same group further examined 3D ultrasound, CT and CT-3D ultrasound fusion and found similar results<sup>197</sup>. The 3D ultrasound provided additional information about the target volume that could improve treatment planning. The authors also believed that 3D ultrasound needs to be combined with CT for volume based 3D planning at the moment.

These are encouraging studies and open the door for further investigation of ultrasound use in gynaecological brachytherapy. One such investigation would be looking at the inclusion of 2D and 3D ultrasound in departments that currently only have access to x-ray to plan brachytherapy. There is a huge potential to confirm in-utero applicator placement and assess iso-coverage using these modalities.





# Chapter 3

## Methods and Materials

Methods and materials for chapters 4, 5, 6 and 7 were concisely reported within each manuscript, previous works were cited to avoid repetition and adhere to word counts when published. This chapter describes the methods and materials in detail, removing the need to refer to older published works.

All studies were approved by the Divisional Review Panel for Retrospective Studies at the Peter MacCallum Cancer Centre and by the Monash University Human Research Ethics Committee.

### 3.1 Study design

All patient data, ultrasound measurements, MR measurements, dosimetric data, and clinical outcomes were prospectively collected and recorded in a dedicated secure Gynaecological Unit data base.

### 3.2 Patient selection Criteria

Patients who presented to Peter MacCallum Cancer Centre between January 2007 and March 2012 with previously untreated cervical cancer were included in studies presented in chapters four, five and six. Patients who presented between May 2013 and October 2013 were included in the study presented in chapter seven. Patients had to have been staged according to the clinical FIGO staging system as Stage 1, 11, 111 or 1V, have had both a pre-treatment MRI and an MRI at the time of brachytherapy, and treated with curative intent.

### 3.3 External Beam Radiotherapy and concomitant chemotherapy

Patients with disease confined to the pelvis were prescribed 40 Gy EBRT in 2.0 Gy fractions using 3D conformal radiotherapy. The majority of patients were treated in the prone position on a belly board to displace small bowel from the treatment field. Patients with nodal involvement above the common iliac nodes were treated supine with 3D conformal extended field radiotherapy, and received 45 Gy in 25 fractions. Involved nodes were assessed with pre-treatment FDG-PET scans and were boosted with antero-posterior fields and were prescribed between 6 and 10 Gy depending on size and location.

Four to five cycles of concomitant cisplatin chemotherapy, 40 mg/m<sup>2</sup>, were routinely administered unless contraindicated.

### 3.4 Brachytherapy

The brachytherapy protocol consisted of three to four fractions of HDR brachytherapy following the completion of EBRT and chemotherapy. This was to achieve maximum tumour shrinkage to bring the target volume within reach of the brachytherapy field, and enable consistent and reproducible insertion of the applicator. Brachytherapy took place in an integrated theatre suite. This suite houses operating and anaesthetic facilities, ultrasound facilities and an HDR treatment unit. A 'control room' co-located with the operating room houses the brachytherapy planning and treatment control systems. There is audio and visual contact with the operating room and facilities to monitor the anaesthetic machine. The patients were anaesthetised during applicator insertion, imaging, planning, treatment and applicator removal. Patients only received one MR scan at the first insertion. At subsequent insertions ultrasound alone was used to guide applicator insertion, and verify the target dimensions and applicator position.

### 3.5 Applicator insertion

It was the preference that patients were anaesthetized using spinal anaesthesia during the first brachytherapy insertion. This ensured anaesthetic coverage during transfer to and from the MR suite and during applicator removal. At subsequent insertions patients routinely underwent general anaesthesia but this was subject to patient and anaesthetist preference.

The patient's legs were supported in semi-lithotomy position for applicator insertion. Two examinations were carried out, a clinical exam and an ultrasound exam using transvaginal ultrasound (Endovaginal 8819 transducer, 9 - 5 MHz, Falcon ultrasound unit, BK Medical, Denmark). These were performed to assess tumour response to EBRT and to evaluate the cervix, uterus, parametria and vagina. The upper vagina was measured to determine the choice and size of ovoid or cylinder. The transvaginal ultrasound examination was also used to evaluate the topography of the pelvis. It was used to determine the position of the uterus and cervix and identify any anatomical variations such as ante-version and retroversion; and pathologies such as fibroids, cysts, clots, polyps, hydrometras and stenosis that may impede or affect applicator placement. The patient was prepped with iodine, and sterile surgical drapes were placed over their legs. An 18 – 20 French three-way urinary catheter was inserted into the bladder and connected to a double spike disposable urology set and a 500-ml bag of isotonic saline (0.9% sodium chloride intravenous infusion BP Viaflex). The balloon was filled with 20 ml saline and positioned against the bladder neck and the bladder was filled with sterile saline. A sterile fenestrated drape was placed over the perineum and pelvis. Transabdominal ultrasound (curved array 8820e, 6 – 2.5 MHz, BK Medical, Denmark) was used to confirm bladder filling. The bladder filling was continued until the fundus of the uterus was visible on the longitudinal view of the uterus. The saline bag was clamped once the bladder covered the uterus. Bladder filling is patient dependent and recorded for each patient but typically consists of 300 – 400 ml. The bladder filling moves bowel away from the uterus and acts as an acoustic window into the pelvis, through which to view applicator insertion into the uterine canal. Bladder filling also increases the angle between the cervix and vagina and facilitates applicator insertion. Once the uterine canal was identified on the longitudinal view the uterus was sounded to ascertain the required length of the intra-uterine applicator. The cervical canal was then further dilated under ultrasound guidance. The selected intra-uterine applicator was inserted

under ultrasound guidance and the ovoids and vaginal spatula were inserted under direct vision. A vaginal spatula was always used with tandem and ovoids to displace the posterior vaginal wall and rectum from the applicator system. Vaginal packing using radiopaque gauze moistened with 1% chlorhexidine obstetric examination cream was inserted to displace the bladder and stabilise the implant. The applicator was loosely sutured to the perineum and the position of the intra-uterine tandem was verified in the axial and longitudinal planes using ultrasound. Sterile drapes were removed and the patient's legs positioned flat on the bed in the treatment position. Figures 3.1 – 3.5 give a pictorial overview of the imaging and planning protocol.

### 3.6 Imaging, ultrasound and MRI

The patient was rescanned with transabdominal ultrasound after being placed in treatment position. The position of the applicator was assessed in the transverse and longitudinal planes of the uterus. The applicator may be gently manipulated to optimise its position in the uterine canal. Once the position of the applicator was optimised the sutures were secured. A longitudinal view of the intrauterine applicator and uterus was obtained. The position of the transducer was manipulated such that the whole applicator appeared across the ultrasound screen. This meant that the applicator was perpendicular to sound propagation and returning the best quality echoes possible. It also meant that measurements were taken in the direction of sound propagation which is the most accurate way to obtain them. The dimensions and geometry of the applicator are known so the applicator acts as both a fiducial marker and calibration device within the image. The visualised applicator was measured with digital calipers on the ultrasound unit screen. Measurement of the applicator in the ultrasound image which concurs with its actual length confirms the correct view has been obtained.

Measurements defining the uterus and cervix outline were obtained. The measurements were taken at the anterior and posterior surface of the cervix and uterus at 2.0 cm intervals along the applicator, from the external os to the tip of the applicator, and recorded at the time of ultrasound image acquisition to facilitate visual acuity. The uterus and cervix were also imaged in the transverse orientation. The width of the cervix and uterus were noted. The longitudinal ultrasound image was uploaded to the treatment planning system and a brachytherapy plan devised. The patient was readied for treatment within the operating room while planning took place. Although only planning on a single longitudinal view, the plan also takes into account the width of the cervix and uterus obtained from measurements taken in the transverse direction. The RT sonographer also conceptualises and builds a 3D view of the uterus and cervix in their mind by taking multiple sweeps of the transducer across the patient. This information also guides planning. Uploading the ultrasound image to the planning system, inserting the applicator model, planning and evaluation takes approximately 15 minutes. The brachytherapy target is the residual disease, whole cervix, and any clinically detected disease in the vagina and parametria. The target volume extends into the uterine corpus as dwell positions in the intra-uterine applicator were activated from cervical stopper to tip. The dwell times were modulated so that the 100% isodose line covered the cervix, while the serosa of the uterus received between 50-70%. Doses at the vaginal mucosa were monitored via points positioned on the surface of the ovoids in contact with the lateral vaginal wall. Doses to the target and OAR were extrapolated for the prescribed 3-4 fractions of brachytherapy using an EQD2 calculator that takes into account EBRT doses. The planning aim was to cover the target volume with 80 -84 Gy<sub>10</sub>, while restricting the ICRU 38 bladder point dose to less than 75 Gy<sub>3</sub>, the ICRU 38 rectum point dose to less than 70 Gy<sub>3</sub> and the vaginal mucosa points to 120 -130 Gy<sub>3</sub>. Once the plan was approved and cross checked it was sent to the treatment control station and the patient was treated.

After treatment the patient's bladder was emptied to a catheter bag and the amount of saline solution drained was noted. The patient was transferred to the MR suite with applicators fixed in treatment position. A brachytherapy radiation therapist accompanied the patient to the MR suite to monitor the applicator position. At the MR suite the bladder was refilled by attaching a new bag of saline to the double spike. MR (1.5T GE Signa, 2007-June 2008; 3T Siemens Magnetom Trio, June 2008 to January 2012) images were taken with the patient positioned supine and head first in the scanner. A body coil was placed over the pelvic area, and scout and T2 Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) localiser images obtained. Bladder filling and the position of the applicator were checked on the localiser images by the radiation therapist. Though rarely required, any adjustments to reproduce treatment conditions in regard to applicator position and bladder filling were made at this point. Further images using Turbo Spin Echo T2 axial (to bed) and parasagittal and paracoronaral (to the intrauterine applicator) were then taken with 3-4 mm slice thickness and 0-1mm slice gap. The typical field of view covered from 3.0 cm above the uterus to the perineum, and total scan time was approximately 20 minutes. After MR imaging the patient was returned to the theatre recovery suite where the sutures and applicators were removed. The patient was discharged from the recovery suite. MR images were transferred to the picture archiving and communications system (PACS) (Syngo version 35, Siemens, Erlangen, Germany) and then imported into the planning computer (Oncentra version 3.0, Nucletron, Veenendal, the Netherlands). The cervix and uterine dimensions were measured on the MR images on the PACs workstation. All measurements were recorded in the Gynaecological Unit database.

## 3.7 Planning

Later in the day the target volume and organs at risk were contoured on the MR data set and the ultrasound based plan was back projected onto the MR data set. The fraction one ultrasound based plan was evaluated on the MR data set using DVH metrics. Standard metrics were:

- target volume D90;
- maximum dose to D2 cm<sup>3</sup> of bladder, rectum, sigmoid, and bowel;
- vaginal mucosa doses;
- Point A doses; and ICRU report 38 reference points at bladder and rectum.

The plan was reviewed by the radiation oncologist at a designated chart round prior to the second fraction. Any suggested changes to the plan were calculated as a new plan in readiness for fraction two should they be needed.

## 3.8 Subsequent insertions

At subsequent insertions the patient was usually under general anaesthesia. A workflow as described in sections 3.5 – 3.7 occurred. At subsequent insertions the applicators were not sutured to the perineum as the patient was not moved from the operating room, as they did not undergo MR imaging. Ultrasound imaging took place as described in sections 3.5 and 3.6. The dimensions of the cervix and uterus were measured and compared to both fraction one ultrasound and MR measurements. If the measurements were within designated criteria, treatment using the original based ultrasound based plan went ahead. Replanning may occur based on the coverage assessed on the MR images at fraction one, or it may occur in response to changes detected with ultrasound at subsequent insertions, or to clinically detected changes. If the measurements were outside the designated criteria a new adapted plan may be calculated.



Clinically detected changes typically include narrowing of the vagina necessitating smaller ovoids. All ultrasound measurements were uploaded to the data base. If changes were made to the plan, a new total dose chart was calculated.

### 3.9 Clinical agreement criteria

A clinically relevant range of differences between MRI and ultrasound measurements was established in consultation with a gynaecological radiation oncologist. These differences were set at 3 mm for the cervix and 5 mm for the uterus. These cut-offs were validated from previous work using identical imaging and treatment methodology as described here<sup>62,137</sup>. In a study comparing dosimetry derived from MRI and ultrasound, there was no significant difference in dosimetric coverage of the brachytherapy target volume between plans<sup>137</sup>. The cut-offs were further validated by comparing clinical outcomes of an historical series of patients treated with low-dose-rate brachytherapy to patients who underwent ultrasound-guided conformal brachytherapy. Patterns of failure and survival were similar in both groups, but ultrasound guided conformal brachytherapy led to a large decrease in late radiation effects<sup>62</sup>. These clinical cut-offs were used to evaluate ultrasound measurements for studies in chapters 4, 5, 6, and 7.

### 3.10 Reporting

At the completion of brachytherapy treatment, data from all plans was assessed. Total radiobiological doses from EBRT and brachytherapy were recorded in regard to target coverage, Point A doses, OAR doses based on ICRU 38 reference points and the vaginal mucosa points, using the EQD2 spreadsheet. These doses were entered into the Gynaecological Unit database.

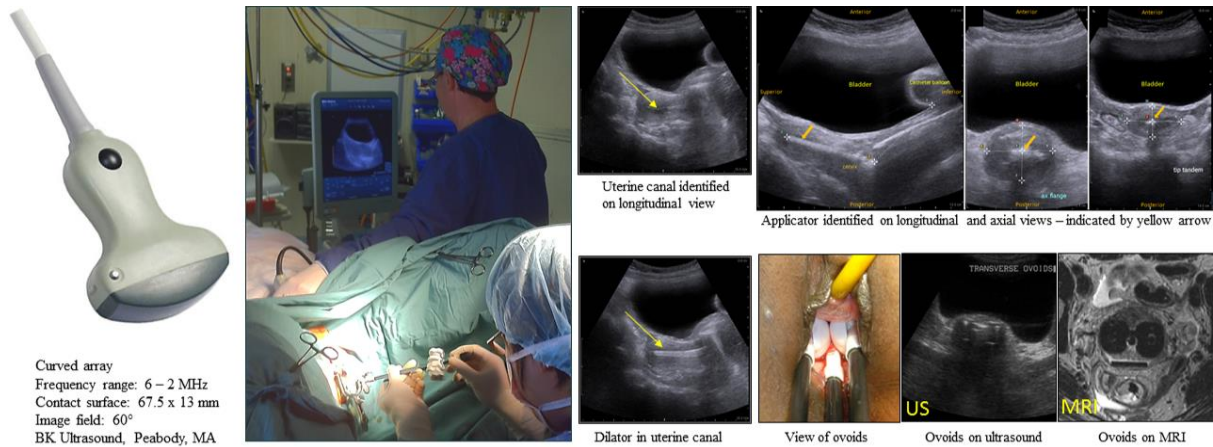


Figure 3.1 Pictorial overview of imaging and planning protocol

Patient anaesthetised, positioned in semi-lithotomy position, EUA to determine clinical response to EBRT, IDC inserted to fill bladder which acts as acoustic window into pelvis. Bladder filled until it covers fundus. Pelvis surveyed with transabdominal ultrasound, check uterus, cervix, parametria, adnexa.

Uterine canal sounded and dilated under ultrasound guidance. Applicator inserted under ultrasound guidance. Uterus and applicator identified on axial and longitudinal views. Applicator position optimised in axial and sagittal views. Ovoid separation confirmed. Uterine and cervix dimensions obtained in axial and longitudinal views.

Source: Peter MacCallum Cancer Centre

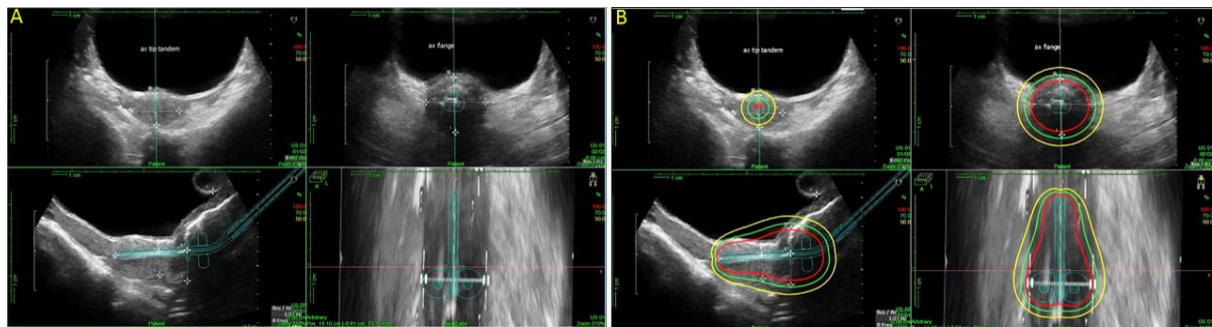


Figure 3.2 Ultrasound imaging and planning

Ultrasound images uploaded to planning computer. Applicator modelling (Nucletron, Elekta) used to translate applicator into ultrasound image. Dwell positions populated from library template. Prescription dose entered. Isolines conformed to cervix. Doses at vaginal mucosa, bladder and rectum monitored via nominated dose points and image on screen. Plan reviewed and approved by RO and brachytherapist. Plan transferred to treatment control system. Plan checked by physicist and brachytherapist. Treatment delivered.

A: ultrasound views with applicator superimposed into data set.

B: ultrasound views with applicator and isolines

Source: Peter MacCallum Cancer Centre

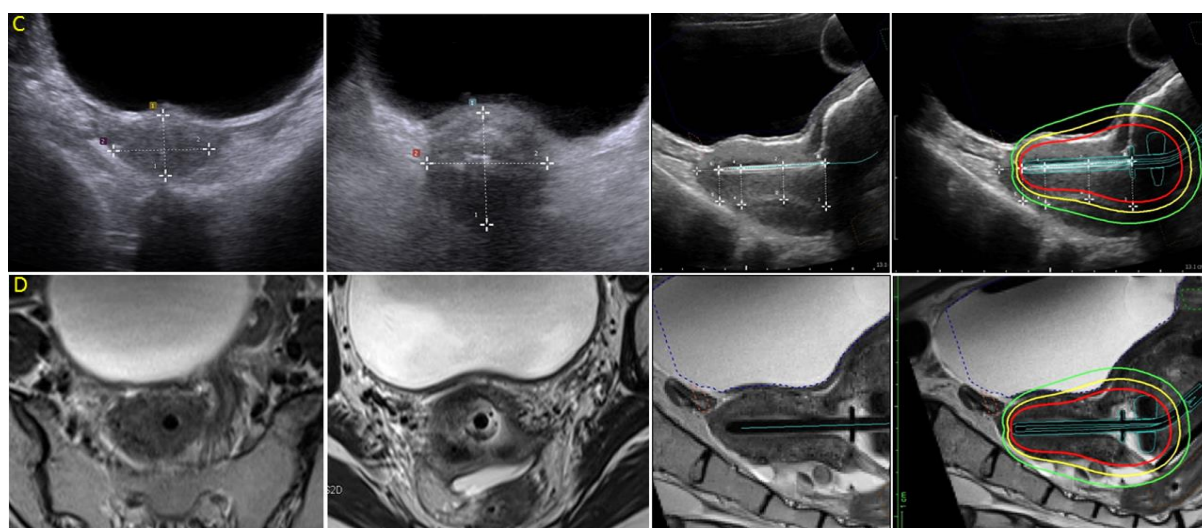


Figure 3.3 MRI and planning

After treatment, bladder drained and patient recovered in Post Anaesthetic Care Unit. Patient transferred to MRI suite for imaging with applicators *in-situ*. Bladder refilled to reproduce treatment conditions. Applicators removed after MRI. Ultrasound plan back projected onto MRI data set for review and evaluation.

- C: ultrasound views, transverse at tip of tandem, transverse at cervical stopper, longitudinal uterus, longitudinal uterus with isolines
- D: corresponding MRI views, transverse at tip of tandem, transverse at cervical stopper, longitudinal uterus, longitudinal uterus with isolines

Source Peter MacCallum Cancer Centre

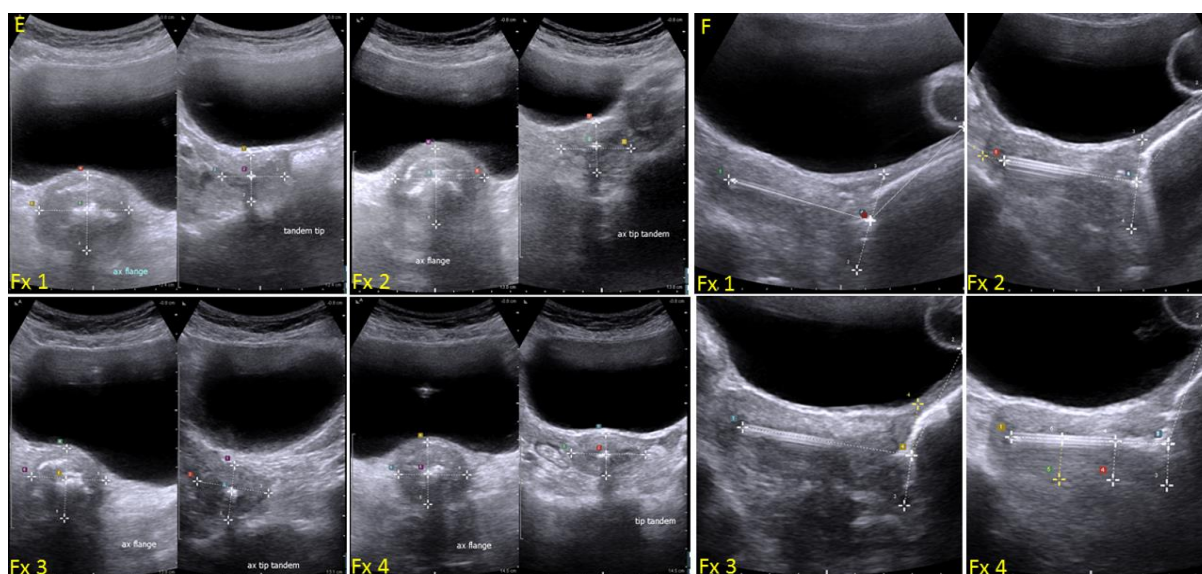


Figure 3.4 Interfraction ultrasound verification

Position of applicator and cervix and uterine dimensions verified at each insertion. First fraction conformal plan used for subsequent treatments in the majority of patients. Plan may be adapted for clinical reasons or if there is a clinically significant change to cervix dimensions.

E: Transverse views through cervical stopper at external os and tip of applicator in uterine canal

F: Longitudinal views of applicator in uterine canal

Source: Peter MacCallum Cancer Centre

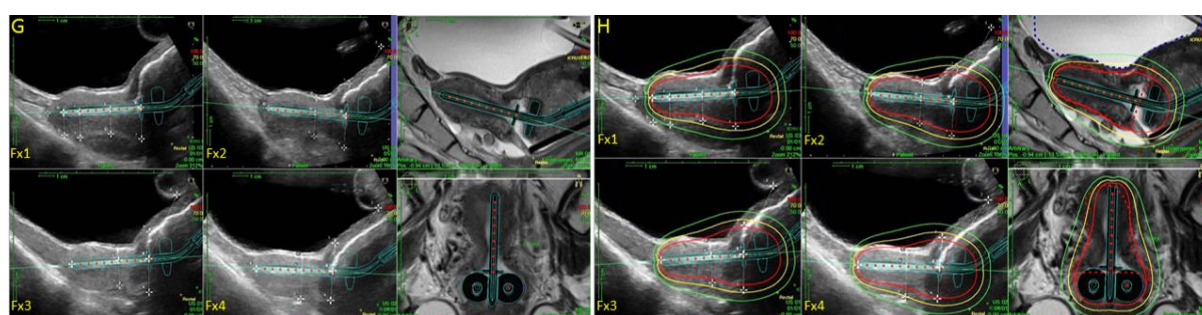


Figure 3.5 Ultrasound verification and MRI evaluation

G: Longitudinal ultrasound views of uterus co-registered to MRI data set.

H: Longitudinal ultrasound views of uterus with iso-lines of conformal plan used throughout treatment co-registered to MRI data set

Source: Peter MacCallum Cancer Centre

### 3.11 Statistical analyses

The purpose of the studies was to compare the measurements of the cervix and uterus made with ultrasound and MRI, and determine if MRI can be substituted by ultrasound. The aim was to determine the level of agreement between the two imaging modalities in measuring the dimensions of the cervix and uterus. Agreement is best tested by a method described by Bland and Altman known as Bland Altman plots<sup>140</sup>.

Chapter 4 includes data from 192 patients, examining measurements from nine points around the cervix and uterus made on MRI and ultrasound. Chapter 5 examines the same patients and measurements but also included ultrasound measurements repeated over time. The normality of the samples were tested with the D'Agostino and Pearson omnibus normality test. Continuous data were expressed as mean  $\pm$  SD. Agreement was assessed using Bland-Altman plots, which are a graphic representation of the data that illustrate the degree of agreement between the different imaging modalities used to measure the cervix and uterine dimensions. The graphs show the difference between the two methods plotted against their mean. Bias is the average difference between the methods and represents systematic error. The smaller the bias, the less the systematic error. The closer the mean of differences is to zero and the smaller the value of the SD of the differences, the better the agreement between measurements. The plots also included 95% limits of agreement that indicate random differences in measurements. These limits represent two values within which approximately 95% of the differences between paired measurements will lie. Agreement was confirmed if the mean measurements between MRI and ultrasound at each location were within the clinically relevant range. Repeated ultrasound measures were analysed with repeated-measures one-way analysis of variance. For analyses returning significant results with analysis of variance, post hoc analyses were

conducted. Multiple comparisons were analysed with Dunnett's multiple comparison test, comparing mean ultrasound measurements to mean MRI (control) measurements; and the Tukey test, comparing every ultrasound mean with every other mean (ultrasound).

Chapter 6 examines clinical outcomes of patients who underwent ultrasound guided brachytherapy. Kaplan-Meier estimates were used to calculate overall survival, cancer specific survival, failure free survival and local control. Descriptive statistics were used to present toxicities associated with treatment.

Chapter 7 examines data from 12 patients and measurements obtained by 3 operators, looking for reliability in obtaining measurements by ultrasound. Bland-Altman plots were calculated to compare MRI and ultrasound measurements. Multiple comparisons were calculated using repeated-measures two-way analysis of variance. For significant results, post hoc analyses using Dunnett's and Tukey's tests were carried out. Intraclass correlation coefficient (ICC) was used to compare reliability between measurements obtained from MRI and ultrasound (obtained by RT sonographers).



# Chapter 4

## Comparison of measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix cancer

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This chapter is an exact copy of the journal paper referenced on the previous page except the figure, table and reference numbers have been modified for the purpose of this thesis.

The main theme of this thesis is exploring the use of transabdominal ultrasound to facilitate image guided brachytherapy treatment for locally advanced cervix cancer. MRI is recognised as an accurate soft tissue imaging modality that can be used to identify the cervix, distinguish residual disease and delineate normal structures such as the bladder, rectum, sigmoid colon and bowel. For this reason MRI was the imaging modality chosen to validate ultrasound. This chapter describes work that confirms ultrasound is a viable alternative soft tissue imaging modality that can be used to identify and delineate the brachytherapy target volume.



# Abstract

**Purpose:** To compare measurements of the uterus and cervix obtained with magnetic resonance imaging (MRI) and transabdominal ultrasound to determine whether ultrasound can identify the brachytherapy target and be used to guide conformal brachytherapy planning and treatment for cervix cancer.

**Methods and Materials:** Consecutive patients undergoing curative treatment with radiation therapy between January 2007 and March 2012 were included in the study. Intrauterine applicators were inserted into the uterine canal while patients were anaesthetized. Images were obtained by MRI and transabdominal ultrasound in the longitudinal axis of the uterus with the applicator in treatment position. Measurements were taken at the anterior and posterior surface of the uterus at 2.0 cm intervals along the applicator, from the external os to the tip of the applicator. Data were analysed using Bland Altman plots examining bias and 95% limits of agreement.

**Results:** A total of 192 patients contributed 1668 measurements of the cervix and uterus. Mean ( $\pm$ SD) differences of measurements between imaging modalities at the anterior and posterior uterine surface ranged from 1.5 ( $\pm$ 3.353) mm to 3.7 ( $\pm$ 3.856) mm, and -1.46 ( $\pm$ 3.308) mm to 0.47 ( $\pm$ 3.502) mm, respectively. The mean differences were less than 3 mm in the cervix. The mean differences were less than 1.5 mm at all measurement points on the posterior surface.

**Conclusion:** Differences in the measurements of the cervix and uterus obtained by MRI and ultrasound were within clinically acceptable limits. Transabdominal ultrasound can be substituted for MRI in defining the target volume for conformal brachytherapy treatment of cervix cancer.

## 4.1 Introduction

**B**rachytherapy for cervix cancer is essential for controlling local disease by allowing high doses of radiation to be delivered to the residual disease from within the cervix and tumour<sup>198,199</sup>. The success of brachytherapy rests on accurate identification of the uterus, cervix, and residual disease; accurate placement of the intrauterine applicator within the uterine canal; and sparing of surrounding normal tissue<sup>133</sup>. Historically, brachytherapy applicators were placed under direct vision, and implant quality was assessed with x-rays. These traditional methods, however, do not enable evaluation of the uterine and cervical anatomy, the residual tumour, or the correct placement of the applicators within the cervical canal<sup>133</sup>. Although considered outdated in some parts of the world, traditional methods continue in many countries, particularly in those with a high incidence of cervix cancer. The use of soft tissue imaging for cervix brachytherapy is increasing in some advanced economies and well-resourced departments<sup>70</sup>. The Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) have been instrumental in advancing the use of soft tissue imaging with a particular emphasis on the use of MRI<sup>41</sup>. MRI has superior anatomy and tumour recognition when used in brachytherapy<sup>44</sup>. Unfortunately, MRI is expensive and difficult to access for many clinical centers. It is also not suitable for patients with implanted devices, those with claustrophobia, and those with large body habitus. These drawbacks make it necessary to find alternative imaging modalities that provide information of similar quality to MRI but are more readily accessible and affordable<sup>136,137</sup>. Ultrasound is an inexpensive imaging modality that offers good soft tissue information and is widely available. The aims of this study were to compare measurements of the uterus and cervix obtained with transabdominal ultrasound to those obtained using MRI to determine the level of agreement between the imaging modalities. The purpose was to

determine whether transabdominal ultrasound can be substituted for MRI in the application of conformal brachytherapy in cervix cancer.

## 4.2 Methods and materials

This study was approved by the Divisional Review Panel for Retrospective studies at the Peter MacCallum Cancer Centre and by the Monash University Human Research Ethics Committee (MUHREC).

### Patient selection criteria

Patients who presented to Peter MacCallum Cancer Centre between January 2007 and March 2012 with previously untreated cervical cancer, histologically diagnosed as either squamous cell carcinoma or adenocarcinoma (or 1 of their variants) were included in this study. Patients had to have been staged according to the clinical (International Federation of Gynecology and Obstetrics [FIGO]) staging system as stage IB, II, III, or IVA; have had an MRI at the time of brachytherapy; and have been treated with curative intent.

Patients received 40 - 45 Gy external beam radiation therapy (EBRT) in 1.8 - 2.0 Gy fractions and 3 - 4 fractions of high-dose-rate (HDR) intracavitary brachytherapy to achieve a total combined dose to the target volume in the order of 80 - 84 Gy<sub>10</sub> equivalent to doses in 2 Gy fractions (EQD2). The radiation therapy and brachytherapy technique have previously been described<sup>137</sup>. In brief, patients commence brachytherapy at the completion of EBRT. Brachytherapy was performed using an HDR microselectron after- loader (Nucletron, Veenendaal, the Netherlands), which is housed in a dedicated operating theatre. This study was limited to patients undergoing treatment with intracavitary applicators alone. Nucletron

Standard CT/MR and Vaginal CT/MR applicator sets were used for all treatments. The majority of patients underwent spinal anaesthesia for the first insertion. Patients were positioned in semi-lithotomy position, and an examination under anaesthesia was performed to determine clinical response to EBRT. An 18 - 20-Fr 3-way Foley catheter was inserted into the bladder. The catheter was connected to a double bag spike urology set, and the bladder was filled with isotonic saline solution (0.9% sodium chloride intravenous infusion BP Viaflex). Bladder filling provides the acoustic window into the pelvis. The bladder was filled until the entire uterus was visible. Average volumes used in this study were between 300 and 400 ml.

### Ultrasound and MR imaging protocol

The intrauterine applicator was positioned under transabdominal ultrasound guidance using a transabdominal transducer (curved array 8830, BK Medical, Denmark). After the intrauterine applicator, ovoids, vaginal spatula, and gauze packing were inserted; the applicator was loosely sutured to the perineum. The sutures were used to prevent movement of the applicator during transfer to the MR suite. The patient's legs were lowered during planning and treatment. The intrauterine applicator position was optimized within the uterus on the transverse and longitudinal ultrasound views and the sutures secured Figure 4.1. All ultrasound imaging was performed and/or supervised by a radiation therapist with ultrasound qualifications (S.v.D.). A treatment plan was devised using the ultrasound measurements. The brachytherapy target was the residual disease, whole cervix, vaginal fornices, and uterus<sup>62</sup>. Bladder filling was maintained during planning and treatment. The patient was treated while under anaesthesia. After completion of treatment, the patient's bladder was emptied and the amount of saline solution drained was noted. The patient was then transferred to the MRI suite with applicators fixed in treatment position. At the MRI suite the bladder was refilled via a new bag of saline connected to the double spike. MR (1.5T GE Signa, 2007-June 2008; 3T Siemens Magnetom

Trio, June 2008 to present) images were taken with the patient positioned supine and head first in the scanner. A body coil was placed over the pelvic area, and localizer and T2 haste images were obtained. Images using Turbo Spin Echo T2 axial (to bed) and parasagittal and paracoronal to the intrauterine applicator were then taken with 3 – 4 mm slice thickness and 0 - 1 mm slice gap. The MR images were transferred to the picture archiving and communication system (PACS) (Syngo version35, Siemens, Erlangen, Germany) and then imported into the planning computer (Oncentra version3.0, Nucletron, Veenendal, the Netherlands).

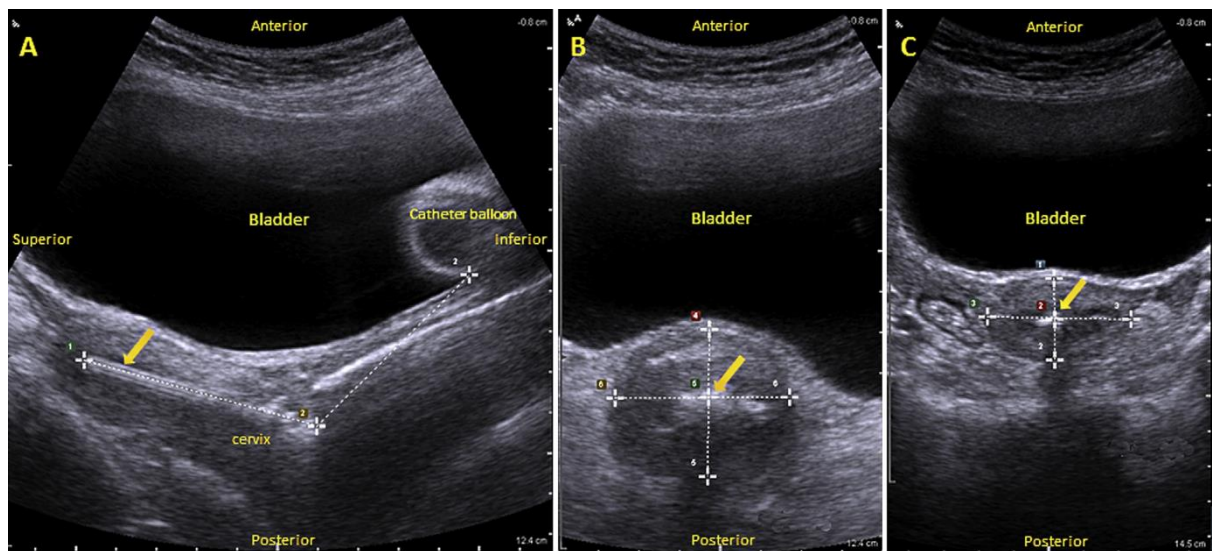


Figure 4.1 Longitudinal and transverse ultrasound image of uterus and cervix

- A. Longitudinal view of cervix and uterus with applicator in treatment position
- B. Transverse view at level of external os/vaginal fornices
- C. Transverse view at tip of applicator. Solid yellow arrow indicates applicator.

Source: Peter MacCallum Cancer Centre

## Study design

All data were prospectively recorded in the gynaecology service database and retrieved for this retrospective analysis.

A longitudinal view along the intrauterine applicator was obtained with both imaging modalities. Measurements defining the uterus and cervix outline were taken at the anterior and posterior surface of the uterus at 2.0 cm intervals along the applicator, from the external os, to the tip of the applicator. Measurements of the cervix and uterus obtained with ultrasound were made at the time of image acquisition to facilitate visual acuity. MRI measurements of the cervix and uterus were made on PACS. Measurements and their designated nomenclature are shown in Figure 4.2.

### Establishing clinical agreement between MRI and ultrasound

A clinically relevant range of differences between MRI and ultrasound measurements was established in consultation with a Gynaecological Radiation Oncologist (K.N.). These differences were set at 3 mm for the cervix and 5 mm for the uterus. These cut-offs were validated from previous work using identical imaging and treatment methodology as described here. In a study comparing dosimetry derived from MRI and ultrasound, there was no significant difference in dosimetric coverage of the brachytherapy target volume between plans<sup>137</sup>. The cut-offs were further validated by comparing clinical outcomes of an historical series of patients treated with low-dose-rate brachytherapy to patients who underwent ultrasound-guided conformal brachytherapy. Patterns of failure and survival were similar in both groups, but ultrasound guided conformal brachytherapy led to a large decrease in late radiation effects<sup>62</sup>.

Only 1 pair of measurements (MRI vs ultrasound at fraction 1) was analysed per patient.

## Power and sample size

With a sample size of 192, this study achieves 97% power to detect a mean of paired differences of 1 mm with a known standard deviation of differences of 3.5 mm and with a significance level ( $\alpha$ ) of 0.05 using a 2-sided paired  $z$  test. With a sample size of 172 (minimum for measurement points tip A, tip P, and tip S), this study achieves at least 99% power to detect a mean of paired differences of 2 mm with a known standard deviation of differences of 4.5 mm and with a significance level ( $\alpha$ ) of 0.05 using a 2 - sided paired  $z$  test.

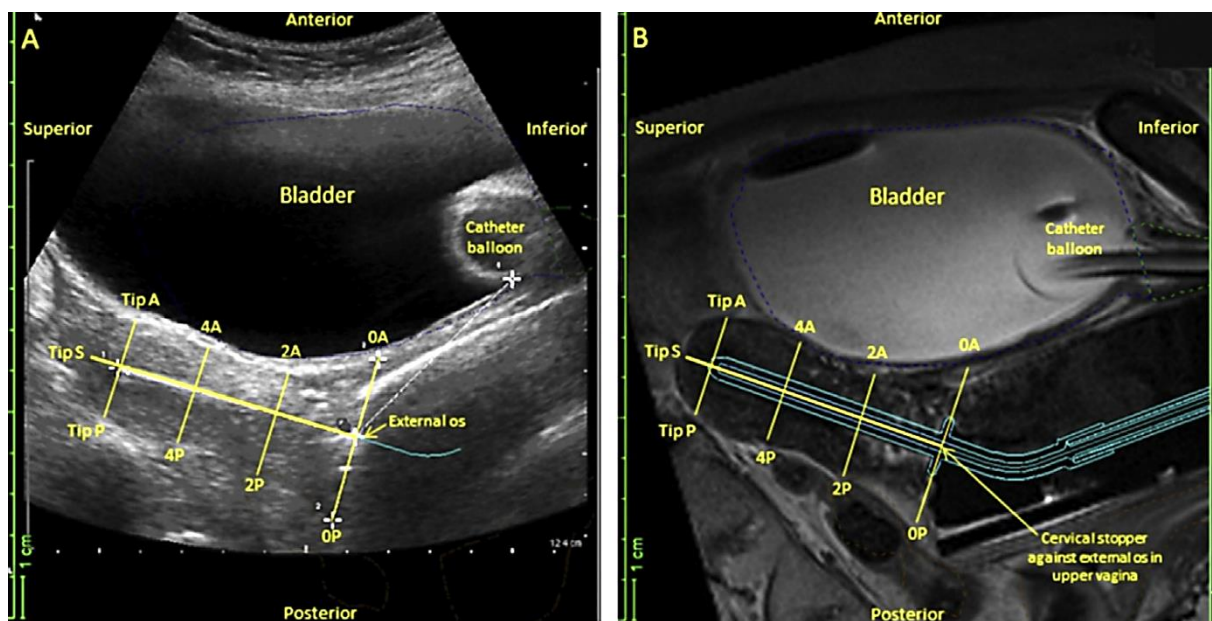


Figure 4.2 Nomenclature for measurement points

- A. Longitudinal ultrasound view
- B. Longitudinal magnetic resonance imaging view

The cervical stopper is 0,0 and abuts the external os in the vaginal fornices. Measurements were taken at the anterior and posterior surface of the cervix and uterus perpendicular to the applicator at the cervical stopper, 0A and 0P; 2.0 cm along the applicator, 2A and 2P; 4.0 cm along the applicator, 4A and 4P; and at the tip of the applicator, Tip A and Tip P. The distance from the tip of the applicator to the fundus was also recorded as Tip S.

Source: Peter MacCallum Cancer Centre.

## Statistical analyses

Data analysis was performed using Graphpad Prism, version 6.02 for Windows (Graphpad Software, La Jolla, CA). The normality of the samples was tested with D'Agostino and Pearson omnibus normality test. Continuous data were expressed as mean  $\pm$  SD. Agreement between MRI and ultrasound measurements was assessed using Bland-Altman analysis<sup>140,141</sup>. Bland-Altman plots are a graphic representation of the data, with the difference between the two methods plotted against their mean. Bias is the average difference between the methods and represents systematic error. The smaller the bias, the less the systematic error. The plots also included a 95% confidence interval (CI) that was expected to include 95% of the differences between measurements when set at  $\sim 2$  SD of the mean<sup>200</sup>. Agreement was confirmed if the mean measurements between MRI and ultrasound at each location were within the clinically relevant range.

## 4.3 Results

Data from 198 patients was included in this study. Six patients were excluded because of insufficient data; four of these had missing information for one or more measurements and two were excluded because of data fluctuations caused by large fibroids that were unable to be visualized in the ultrasound field of view. Measurements from the external os to 4 cm along the applicator were available for 192 patients. Measurements around the tip of the applicator were available for 172 of these patients. Patient demographic and tumour characteristics are shown in Table 4.1.

There were 1668 measurements available for analysis. Mean measurements at each point are outlined in Table 4.2 .



Bland-Altman analysis indicating the 95% limits of agreement between the 2 methods and the average of differences between the 2 methods (bias) is shown in Table 4.3.

Figure 4.3 is a summary of the Bland-Altman plots for each measurement point. The mean difference between MRI and ultrasound with 95% confidence intervals are plotted against the clinically determined cut-off points. The mean difference at all measurement points was less than 4 mm. Of particular note, the mean differences between imaging modalities at the posterior surface of the uterus and cervix, 0P, 2P and 4P were less than 1 mm.

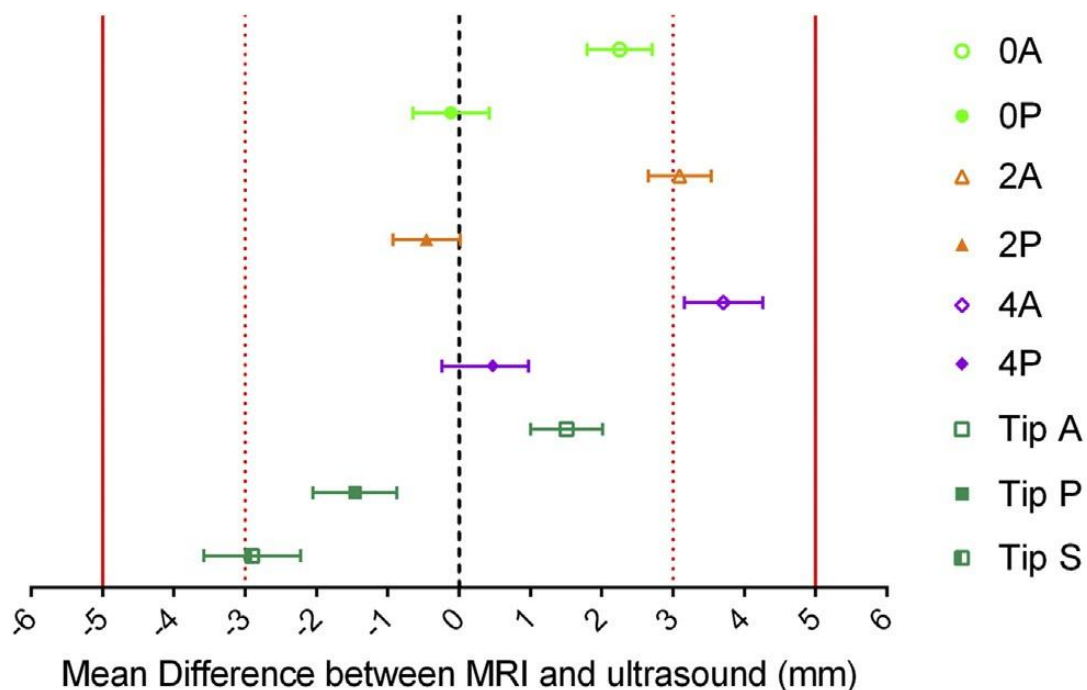


Figure 4.3 Summary of Bland-Altman plots,

Means of differences between magnetic resonance imaging (MRI) and ultrasound at each measurement point and 95% confidence interval limits of mean differences shown in relation to clinically relevant cut-off values at  $\pm 3$  mm (cervix cut-off; dotted vertical lines) and  $\pm 5$  mm (uterus cut-off; solid vertical lines). Refer to Figures 4.2 and 5.1 for nomenclature of measurement points and rationale for establishing clinical agreement between MRI and ultrasound.

Table 4.1 Patient and tumour characteristics (Total N=192)

Characteristic	
Age (years)	
Median	51
Range	21-91
FIGO stage, N (%)	
1	65 (33)
2	82 (43)
3	36 (19)
4	9 (5)
Histology, N (%)	
Squamous Cell Carcinoma	148 (77)
Adenosquamous	8 (4)
Endometriod/mucinous	22 (12)
MMMT	1 (0.5)
Small cell	8 (4)
Serous	1 (0.5)
Clear cell	4 (2)
Original Tumour volume (cm <sup>3</sup> )	
Median	33.3
Range	0.13 – 381.7

FIGO = Federation of Gynaecology and Obstetrics; MMMT = Malignant mixed Müllerian tumour

## 4.4 Discussion

Improving brachytherapy practices for patients with cervix cancer requires new avenues to make it possible for all treating clinicians to identify the brachytherapy target. This study has shown that ultrasound can be used to delineate the cervix and uterus to determine the target for use in planning conformal brachytherapy treatments for cervix cancer. The greatest potential of incorporating ultrasound into the brachytherapy program is the ability to improve accuracy of applicator placement and radiation delivery. Improved accuracy can potentially lead to better local control and reduced toxicity to surrounding normal tissues<sup>62,201,202</sup>.

Table 4.2 Mean measurements at each measurement point  
in the cervix and uterus for MRI and ultrasound

Measurement point	N	MRI Mean ( $\pm$ SD) mm	Ultrasound Mean ( $\pm$ SD) mm	Mean of	95% CI of
				differences MRI-US ( $\pm$ SD) mm	mean differences MRI-US mm
0A	192	17.5 ( $\pm$ 4.848)	15.25 ( $\pm$ 4.411)	2.25 ( $\pm$ 3.190)	1.8 to 2.7
0P	192	18.45 ( $\pm$ 4.150)	18.57 ( $\pm$ 4.335)	-0.12 ( $\pm$ 3.773)	-0.65 to 0.42
2A	192	13.95 ( $\pm$ 3.912)	10.85 ( $\pm$ 3.035)	3.09 ( $\pm$ 3.102)	2.65 to 3.54
2P	192	16.24 ( $\pm$ 4.238)	16.7 ( $\pm$ 4.448)	-0.46( $\pm$ 3.308)	-0.93 to 0.01
4A	192	17.79 ( $\pm$ 4.653)	14.08 ( $\pm$ 4.063)	3.71 ( $\pm$ 3.856)	3.16 to 4.26
4P	192	18.43 ( $\pm$ 4.837)	17.96 ( $\pm$ 4.089)	0.47 ( $\pm$ 3.502)	-0.24 to 0.97
Tip A	172	16.59 ( $\pm$ 5.291)	15.08 ( $\pm$ 4.254)	1.51 ( $\pm$ 3.353)	1.00 to 2.01
Tip P	172	16.29 ( $\pm$ 5.339)	17.75 ( $\pm$ 4.148)	-1.46 ( $\pm$ 3.903)	-2.05 to -0.87
Tip S	172	12.62 ( $\pm$ 5.982)	15.52 ( $\pm$ 6.614)	-2.90 ( $\pm$ 4.491)	-3.58 to -2.23

Table 4.3 Bland Altman analysis of MRI versus ultrasound measurements  
according to measurement locations in the cervix and uterus

Measurement Point	N	Bland-Altman Bias (average of difference) mm ( $\pm$ SD)	Bland-Altman 95% Limits of Agreement mm
0A	192	2.25 ( $\pm$ 3.190)	-4.00 to 8.50
0P	192	-0.12 ( $\pm$ 3.773)	7.51 to 7.28
2A	192	3.09 ( $\pm$ 3.102)	-2.99 to 9.17
2P	192	-0.46 ( $\pm$ 3.308)	-6.94 to 6.03
4A	192	3.71 ( $\pm$ 3.856)	-3.85 to 11.27
4P	192	0.47 ( $\pm$ 3.502)	-6.39 to 7.34
Tip A	172	1.51 ( $\pm$ 3.353)	-5.07 to 8.08
Tip P	172	-1.46 ( $\pm$ 3.903)	-9.11 to 6.19
Tip S	172	-2.90 ( $\pm$ 4.491)	-11.70 to 5.90

The use of ultrasound during applicator insertion has been shown to decrease the rate of uterine perforations<sup>106</sup>. Ultrasound is increasingly being used to select appropriate applicators and to guide placement in brachytherapy<sup>109,110</sup>. Such use relies on accurate identification of the uterus and cervix. This study illustrates that such identification is possible, and demonstrates good agreement with MRI.

Ultrasound is considered the ideal imaging modality for prostate brachytherapy because it is possible to image, insert applicators, plan, and verify placement in one location<sup>203,204</sup>. These benefits have not been used in gynaecological brachytherapy to the same extent as in prostate brachytherapy. The greatest deterrents have been the lack of a 3D coordinate system associated with free-hand transabdominal ultrasound, and reliance on the operator to obtain “good” images. We have found that training and education of operators results in good-quality images that allow us to use ultrasound for applicator insertion, target identification, conformal planning, and verification at each insertion. Although the images obtained are not referenced to a coordinate system, the applicator itself acts as a fiducial marker and calibration device, helping to define the spatial location of the anatomy being viewed.

Wenzel et al. and Brascho et al. described a method using ultrasound to plan brachytherapy for uterine cancer in the 1970s<sup>127,128</sup>. The methodology and rationale described are similar to our use of ultrasound, although the practice is not commonly adopted. In cervix brachytherapy, ultrasound is primarily used to ensure safe applicator placement<sup>136</sup>. There has been one prior study by Mahantshetty et al. comparing the use of MRI and trans- abdominal ultrasound for planning cervix brachytherapy<sup>138</sup>. These investigators compared measurements of 32 applications from 20 patients using methodology similar to that in this study<sup>138</sup>. Their study used MRI and repeated measurements of the cervix with ultrasound and looked for correlation between the imaging modalities. We used single measurements analysed with Bland-Altman

plots looking for agreement between the imaging modalities. Mahantshetty et al. found reasonably good correlations between MRI and ultrasound. Measurements to the anterior cervix had a strong correlation, with  $R=0.92$  and  $R=0.94$  ( $p<.01$ ), whereas measurements to the posterior surface of the cervix had a moderate correlation, with  $R^2=0.63$  and  $R^2=0.82$  ( $p<.01$ ). In contrast to our study, Mahantshetty et al. found that the anterior uterine cervix measurements showed better correlation between MRI and ultrasound than the posterior measurements. They attributed this to attenuation of echoes through the posterior uterine wall. Even though the anterior wall of the uterus is easier to visualize on ultrasound, we found larger mean differences between the imaging modalities on the anterior surface of the uterus and cervix. Mean ultrasound measurements were less than MRI measurements at 0A, 2A, and 4A, with mean differences of 2.2, 3.1, and 3.7 mm, respectively. Every effort was made to reproduce the patient position, the applicator position, and bladder filling at MRI. The main difference between image acquisitions was the use of a transabdominal transducer during ultrasound. The smaller anterior wall ultrasound measurements in our study were attributed to transducer pressure causing slight compression of the anterior uterine wall. Measurements to the posterior wall in our study, showed no differences between modalities with 0P, 2P and 4P having mean differences of less than 1 mm. Accurate identification of the applicator and the posterior surface of the uterus is crucial, as the organs at risk outside this surface include the rectum and bowel.

Mahantshetty et al. comment that the presence of uterine pathologies such as pyometra, haematometra, fibroids, retroversion, and uterus off axis may influence image acquisition. The presence of these anatomical variations and pathologic conditions makes accurate visualization of the uterus extremely important. This is crucial to ensure correct placement of the applicator, and to achieve adequate identification and coverage of the target volume and dose sparing of surrounding normal tissues. It is the very presence of these variations that necessitates the use

of an imaging modality that can be used at the time of applicator insertion. Applicator insertion then becomes a dynamic process that responds to the anatomical information made available from imaging. We encountered pathologic conditions and anatomical variations similar to those described by Mahantshetty et al. and did not find them to be a hindrance to image acquisition in the majority of our patients. Only two patients were unable to be included in this study because of the presence of extremely large fibroids. The fibroids were 9.7 cm and 8.5 cm in diameter, and the plane containing the applicator and fibroids could not be fully imaged within the ultrasound field of view. Although these two patients were excluded from the study, the applicator was correctly inserted, and the patients underwent successful planning using transabdominal ultrasound.

Schmid et al. discussed using transrectal ultrasound (TRUS) to assess cervix cancer during radiation therapy<sup>163</sup>. The cervix was examined in 17 patients using TRUS and the findings compared with those of MRI. Examinations were conducted at diagnosis and at the time of brachytherapy with and without applicators *in situ* in 5, 3, and 9 patients, respectively. The study found good agreement with mean ( $\pm$ SD) absolute differences in cervix width between TRUS and MRI of 0.0 ( $\pm$ 0.3) cm and means ( $\pm$ SD) absolute differences in antero-posterior cervical thickness of -0.2 ( $\pm$ 0.3) cm. It was deemed that the anterior border of the cervix could not be detected in the three patients who underwent imaging with applicators *in situ*, because of applicator artifacts. This is a finding similar to that outlined by Mahantshetty et al. and, again, is in contrast to our findings. We attribute our ability to clearly see both the applicator and posterior uterine surface to appropriate training in scanning technique and optimization methods.

A possible limitation of TRUS imaging is the smaller field of view that may not accommodate the whole uterus, particularly once the applicators have been inserted. Our study focused on

measurements in the longitudinal view. This view gives information about the applicator, its fit and position; the uterus, size, and shape, and the surrounding anatomy. At the time of brachytherapy, images para-axial to the uterus were also examined along the applicator. Two cardinal views, para-axial at the tip of the applicator and at the external os, were also recorded for each patient, Fig. 4.1. Brachytherapy target delineation and isodose coverage were planned using information from these views, as well as live scanning information. The present limitations of 2-dimensional ultrasound scanning are well recognized; however, through collation of scan information from multiple orientations, we are able to successfully plan isodose coverage.

This study has shown that it is possible to obtain clear and detailed images of the uterus and cervix with the intrauterine applicator in treatment position using transabdominal ultrasound. The information obtained from ultrasound shows good agreement with that obtained from MRI. It is important that the imaging modality can be used with the applicator in treatment position. This makes it possible to practice image-guided, conformal, and adaptive brachytherapy for all insertions across all resource settings. In well-resourced settings, ultrasound can be used as a verification aid in conjunction with MRI or computed tomography to verify applicator position after patient transfers and before commencing treatment. In limited-resource settings, ultrasound can be used as the primary imaging modality, providing sufficiently accurate soft tissue information to insert the applicator, identify the brachytherapy target, plan conformal treatment, and verify target volumes and applicator position at each insertion





# Chapter 5

## Assessing changes to the brachytherapy target for cervical cancer using a single MRI and serial ultrasound

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This chapter is an exact copy of the journal paper referenced on the previous page except the figure, table and reference numbers have been modified for the purpose of this thesis. Supplementary figures and tables have been included as part of the main text.

The work in chapter 4 validated ultrasound measurements of the cervix and uterus against MRI measurements. This indicates that ultrasound is a viable alternative to MRI to measure the cervix and uterus and can be used to both plan treatment and verify the target volume. The following chapter illustrates how ultrasound can be used as the sole imaging modality to monitor changes to the brachytherapy target over time. This chapter describes how ultrasound can be used not only as a tool to verify applicator placement but also to monitor and verify interfraction changes to treatment volumes. The findings of this chapter have important ramifications for resource management, rates of replanning and patient wellbeing.

# Abstract

**Purpose:** To assess changes to the brachytherapy target over the course of treatment and the impact of these changes on planning and resources.

**Methods and materials:** Patients undergoing curative treatment with radiotherapy between January 2007 and March 2012 were included in the study. Intrauterine applicators were positioned in the uterine canal while patients were under anaesthesia. Images were obtained by MRI and ultrasound at Fraction 1 and ultrasound alone at Fractions 2, 3, and 4. Cervix and uterine dimensions were measured on MRI and ultrasound and compared using Bland-Altman plots and repeated measures one-way analysis of variance.

**Results:** Of 192 patients who underwent three fractions of brachytherapy, 141 of them received four fractions. Mean differences and standard error of differences between MRI at Fraction 1 and ultrasound at Fraction 4 for anterior cervix measurements were 2.9 (0.31), 3.5 (0.25), and 4.2 (0.27) mm and for posterior cervix 0.8 (0.3), 0.3 (0.3), and 0.9 (0.3) mm. All differences were within clinically acceptable limits. The mean differences in the cervix over the course of brachytherapy were less than 1 mm at all measurement points on the posterior surface. Replanning occurred in 11 of 192 (5.7%) patients, although changes to the cervix dimensions were not outside clinical limits.

**Conclusions:** There were small changes to the cervix and uterus over the course of brachytherapy that were not clinically significant. Use of intraoperative ultrasound as a verification aid accurately assesses the target at each insertion, reduces uncertainties in treatment delivery, and improves efficiency of the procedure benefiting both the patient and staff.

## 5.1 Introduction

There is increasing awareness of the need to incorporate soft tissue imaging into brachytherapy protocols for cervical cancer. Use of serial imaging evaluates each implant on its own merits, and early studies recommended that imaging be performed at each applicator insertion to account for variations in applicator geometry and positioning within the patient<sup>205,206</sup>. Similarly, imaging is now also recommended to assess the dosimetric coverage of the target and organs at risk (OAR)<sup>207</sup>. The Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology recommended using MRI at each brachytherapy insertion<sup>41,42</sup>. Significant gains in tumour control and reduced toxicity have been reported by centres using such advanced imaging<sup>64,65,67</sup>. Select centres around the world have investigated the use of MRI to assess and confirm the brachytherapy target volumes but have also recognized the difficulties of obtaining an MRI for every fraction of brachytherapy, even in well-resourced departments<sup>208-210</sup>. Alternative imaging modalities have to be investigated so that gains made by centres using advanced imaging can be replicated in lower resource settings. We previously investigated the use of ultrasound to identify the brachytherapy target and guide conformal planning<sup>139</sup>. In that investigation, we validated ultrasound as a viable alternative to MRI in identifying the cervix and uterus with intracavitary applicators *in situ*. In the present study, we describe the use of a single MRI taken at Fraction 1 and use of ultrasound for verification of applicator position and target dimensions in subsequent insertions. The purpose of the study was to investigate the change in target dimensions detected with ultrasound over the course of brachytherapy and the impact on planning and departmental resources.

## 5.2 Methods and materials

This study was approved by the Divisional Review Panel for Retrospective studies at the Peter MacCallum Cancer Centre and the Monash University Human Research Ethics Committee.

### Patient selection criteria

Patients who presented to Peter MacCallum Cancer Centre between January 2007 and March 2012 with previously untreated cervical cancer. Patients had to have been staged according to the clinical (International Federation of Gynaecology and Obstetrics [FIGO]) staging system as Stage IB, II, III, or IVA; had an MRI at the time of brachytherapy, and been treated with curative intent.

### Radiotherapy

Patients received 40 (2 Gy/fx) to 45 Gy (1.8 Gy/fx) external beam radiation therapy (EBRT) and three to four fractions of high-dose-rate brachytherapy to achieve a total combined dose to the target in the order of 80 - 84 Gy<sub>10</sub> equivalent to doses in 2 Gy fractions. The radiation therapy, brachytherapy technique, and imaging protocols have previously been described<sup>137,139</sup>.

### Brachytherapy

Brachytherapy was always given after the completion of EBRT. All patients in this study were treated with intracavitary applicators (Standard CT/MR and Vaginal CT/MR applicators; Nucletron, Veenendaal, The Netherlands). Applicator insertion, ultrasound imaging, planning, and treatment took place in a single session in a dedicated operating theatre. All patients were anesthetized for the whole procedure. Most patients were under spinal anaesthesia for Fraction 1 and general anaesthesia for Fractions 2 - 4. The brachytherapy target was the residual disease,

whole cervix, vaginal fornices, corpus uterui, and any clinical detected disease at the time of brachytherapy. Parametrial involvement was assessed clinically (visualization with transvaginal ultrasound and palpation at the first insertion before applicator insertion and visualization with transabdominal ultrasound after applicator insertion). Parametrial coverage was then assessed on MRI after the first treatment had been delivered. Clinical assessment of parametria was performed at each subsequent insertion using palpation and visualization with transabdominal ultrasound. Figure 3.1 – 3.5 outline the steps in the procedure.

## Study design

All data were prospectively recorded in the gynaecology service database and retrieved for this analysis.

Longitudinal and axial views along the intrauterine applicator were obtained with MRI and ultrasound at Fraction 1, and ultrasound alone at subsequent fractions. Measurements and their designated nomenclature are shown in Figure 5.1 and Figure 5.2.

Clinical agreement criteria between MRI and ultrasound were set at 3 mm for the cervix and 5 mm for the uterus. These criteria were established in a previous study<sup>139</sup>; see Table 5.1.

Cervix and uterine dimensions obtained at each measurement point with MRI and ultrasound were analysed for each patient (MRI vs. ultrasound at Fractions 1 2, 3, and 4).

The analysis looked at agreement between MRI and the ultrasound measurements and compared ultrasound measurements obtained at each fraction.

Table 5.1 Establishing clinical agreement between MRI and ultrasound

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Excerpt from van Dyk *et al.* Comparison of measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix cancer <sup>139</sup>

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A clinically relevant range of differences between MRI and ultrasound measurements was established in consultation with a Gynaecological Radiation Oncologist (KN). These differences were set at 3 mm for the cervix and 5 mm for the uterus. These cut-offs were validated from previous work using identical imaging and treatment methodology as described here. In a study comparing dosimetry derived from MRI and ultrasound there was no significant difference in dosimetric coverage of the brachytherapy target volume between plans <sup>137</sup>. The cut-offs were further validated by comparing clinical outcomes of an historical series of patients treated with low dose rate brachytherapy to patients who underwent ultrasound guided conformal brachytherapy. Patterns of failure and survival were similar in both groups but ultrasound guided conformal brachytherapy led to a large decrease in late radiation effects <sup>62</sup>.

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## Power and sample size

With a sample size of 141 (number of patients who received four fractions of treatment), this study achieves at least 92% power to detect a mean of paired differences of 1 mm with a known standard deviation (SD) of differences of 3.5 mm with a significance level ( $\alpha$ ) of 0.05 using a two-sided paired z test.

## Statistical analyses

Data analysis was performed using Graphpad Prism, version 6.02 for Windows (Graphpad Software Inc, La Jolla, CA). The normality of the samples was tested with the D'Agostino-Pearson omnibus normality test. Continuous data were expressed as mean  $\pm$  SD. Agreement between MRI and ultrasound measurements was assessed using Bland-Altman analysis<sup>140,141</sup>. Bland-Altman plots are a graphic representation of the data with the difference between the two methods plotted against their mean. Bias is the average difference between the methods

and represents systematic error. The closer the mean of differences is to zero and the smaller the value of the SD of the differences, the better the agreement between measurements. The plots also included a 95% confidence interval range that was expected to include 95% of the differences between measurements when set at  $\sim 2$  SD of the mean<sup>200</sup>. Agreement was confirmed if the mean measurements between MRI and ultrasound at each location were within the clinically relevant range<sup>139</sup>.

Repeated ultrasound measures were analysed with repeated-measures one-way analysis of variance. For analyses returning significant results with analysis of variance, post hoc analyses were conducted. Multiple comparisons were analysed with Dunnett's multiple comparison test, comparing mean ultrasound measurements to mean MRI (control) measurements; and the Tukey test, comparing every ultrasound mean with every other mean (ultrasound)<sup>211</sup>

## 5.3 Results

Data from 192 patients were included in this study. Brachytherapy consisted of three or four fractions, and measurements were obtained from all patients, 192 for three fractions of treatment, and 141 patients for four fractions of treatment. Patient demographic and tumour characteristics are shown in Table 5.2

Good clinical agreement between MRI and ultrasound measurements at Fraction 1 was established in a previous study conducted at our centre<sup>139</sup>. The mean cervix and uterine dimensions measured with ultrasound showed a slight decrease in magnitude over the course of three and four fractions, but the differences were within the clinically acceptable limits for both the third and fourth fractions. Figure 5.3 depicts the mean measurements of the cervix and uterus at each measurement point over four fractions.



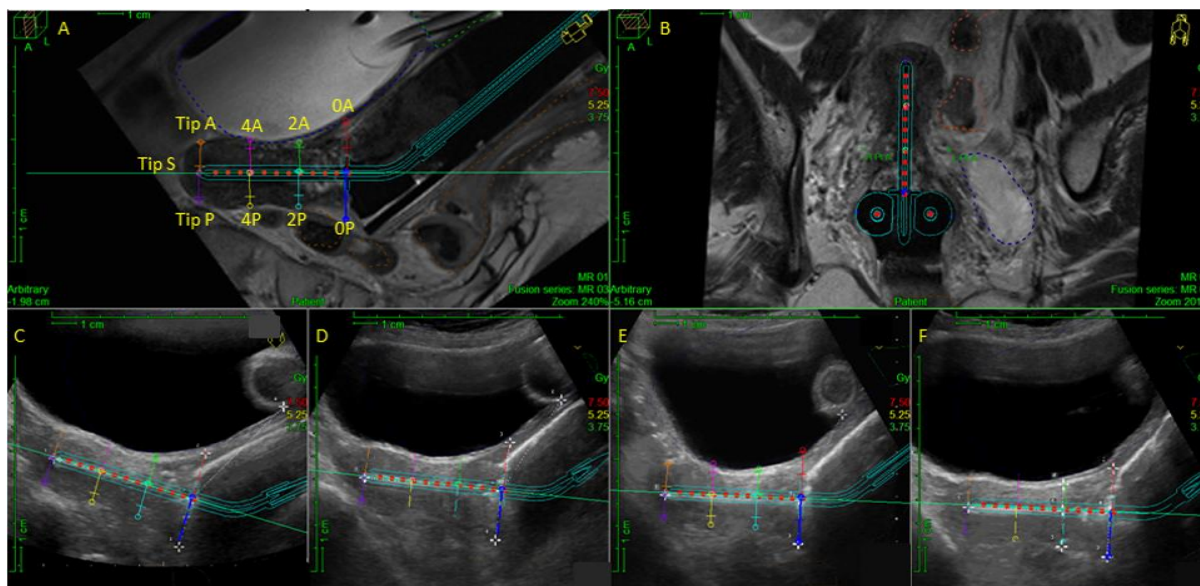


Figure 5.1 Measurements and designated nomenclature

- A. longitudinal MRI view
- B. corresponding coronal MRI view

The cervical stopper is 0, 0 and abuts the external os. Measurements were taken at the anterior and posterior surfaces of the cervix and uterus perpendicular to the applicator at the cervical stopper, 0A and 0P; 2.0 cm along the applicator, 2A and 2P; 4.0 cm along the applicator, 4A and 4P; and at the tip of the applicator, Tip A and Tip P. The distance from the tip of the applicator to the fundus was also recorded as Tip S.

- C, D, E, F. Longitudinal ultrasound images from Fractions 1, 2, 3, and 4 co-registered to MRI. Note correlation of MRI measurements on the ultrasound images

Source: Peter MacCallum Cancer Centre

The mean differences between MRI and ultrasound measurements on the anterior surface indicated that ultrasound underestimated the anterior cervix dimensions and uterine dimensions by between 2 and 4 mm. The largest difference was found at measurement point 4A, which is the lower part of the corpus uteri.

Figure 5.4 is a summary of the Bland-Altman plots for each measurement point at Fractions 1 and 4. The mean difference at all measurement points was  $\leq 4$  mm. Of particular note, the mean differences between imaging modalities at the posterior surface of the uterus and cervix, 0P, 2P, and 4P, were less than 1 mm over the course of brachytherapy.

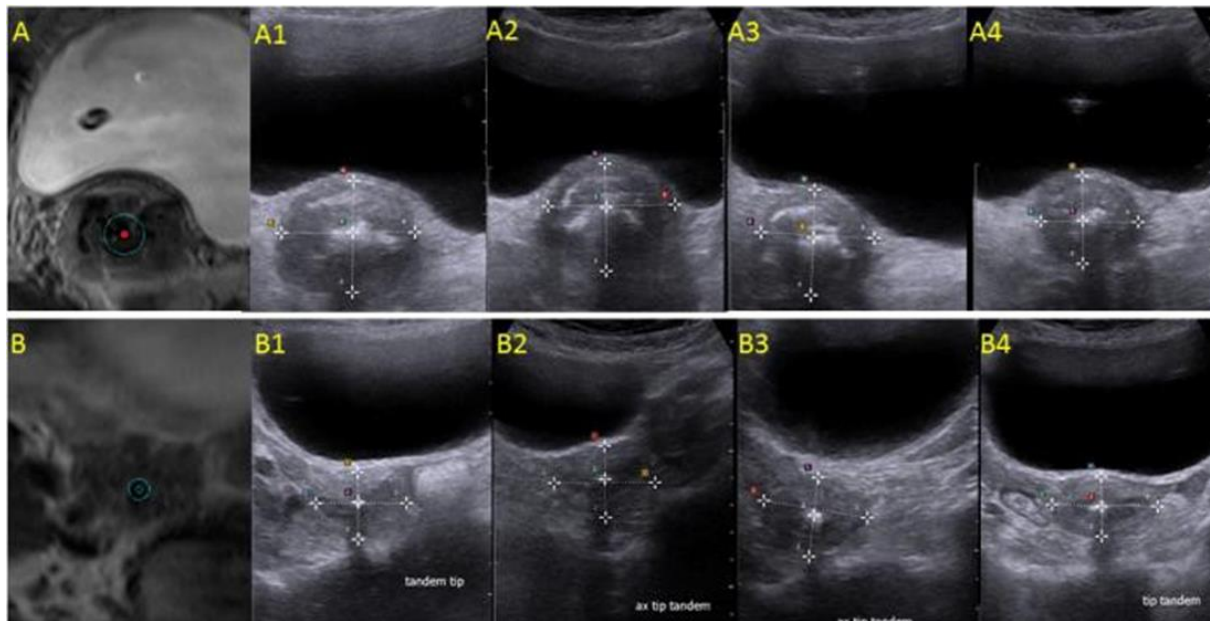


Figure 5.2 MRI and ultrasound verification images

Depicting applicator position and dimensions of cervix and uterus in the axial orientation.

A, A1, A2, A3, A4: axial views of applicator at level of cervical stopper at external os on MRI and ultrasound for fractions 1, 2, 3, 4 respectively

B, B1, B2, B3, B4: axial views of tip of applicator on MRI and ultrasound for fractions 1, 2, 3, 4 respectively

Source: Peter MacCallum Cancer Centre

Results from multiple comparisons, MRI vs. ultrasound at Fractions 1, 2, 3, and 4 (Dunnett's test), are shown in Figure 5.5. Each ultrasound measurement at each fraction was compared with a control (MRI taken at Fraction 1). Mean differences between MRI and ultrasound were within 1 mm across all fractions at measurement points on the posterior surface of the cervix and uterus indicating clinically insignificant changes in the cervix dimensions over the course of treatment. Mean differences at the anterior measurement points were within the 3-5 mm clinical cutoff, and therefore, although statistically significant, were not clinically significant.

The mean differences between ultrasound measurements over the course of treatment were all submillimeter, indicating little change in the size and shape of the cervix and uterus over the course of brachytherapy, Table 5.3

Table 5.2 Patient and tumour characteristics (total N=192)

Characteristic	
Age (years)	
Median	51
Range	21-91
FIGO stage, N (%)	
1	65 (33)
2	82 (43)
3	36 (19)
4	9 (5)
Histology, N (%)	
Squamous Cell Carcinoma	148 (77)
Adenosquamous	8 (4)
Endometrioid/mucinous	22 (12)
MMMT	1 (0.5)
Small cell	8 (4)
Serous	1 (0.5)
Clear cell	4 (2)
Original Tumour volume (cm <sup>3</sup> )	
Median	33.3
	0.13 –
Range	381.7

FIGO: Federation of Gynecology and Obstetrics; MMT: Malignant Mixed Müllerian Tumour

Eleven patients, 4 of 51 treated with three fractions, and 7 of 141 treated with four fractions, underwent replanning during their course of brachytherapy.

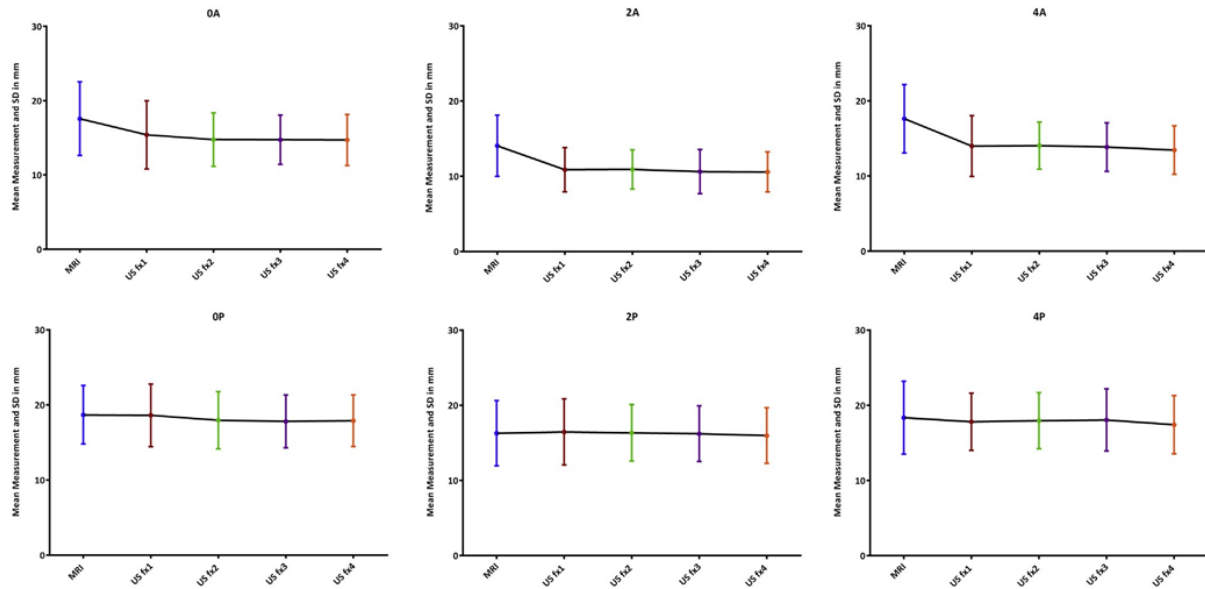


Figure 5.3 Mean measurements ( $\pm$  standard deviation) of cervix and uterus

At measurement points 0A, 0P, 2A, 2P, 4A, and 4P, taken with MRI at Fraction 1 and ultrasound at Fractions 1, 2, 3, and 4 (141 patients) Refer to Figure 4.2 for nomenclature of measurement points

There were no statistically or clinically significant differences in cervix dimensions in these patients over the course of treatment, apart from measurement point 0A. This measurement point is at the external os and is influenced by packing in the vagina.

Analysis for a subgroup of 30 patients with FIGO IIIB tumours also indicated no clinically significant change in cervix and uterus dimensions over the course of brachytherapy. Three patients in this group had replans.

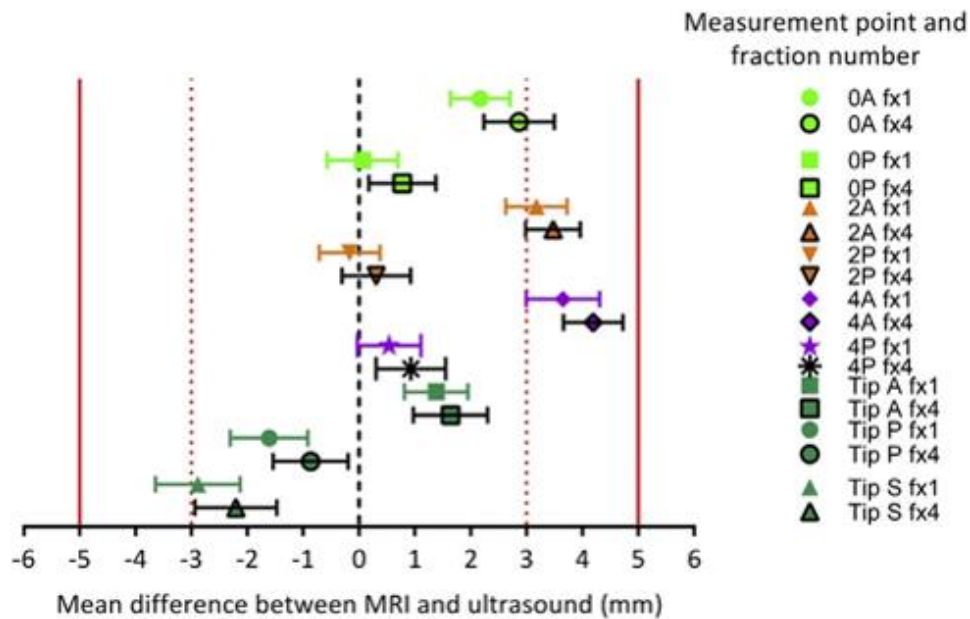


Figure 5.4 Summary of Bland-Altman plots

Means of differences between MRI and ultrasound at each measurement point, and 95% confidence interval of mean differences for Fractions 1 and 4 measurements (141 patients) shown in relation to clinically relevant cutoff values at  $\pm 3$  mm (cervix cut-off; dotted vertical lines) and  $\pm 5$  mm (uterus cutoff; solid vertical lines). Refer to Figures 4.2 and 5.1 for nomenclature of measurement points and rationale for establishing clinical agreement between MRI and ultrasound

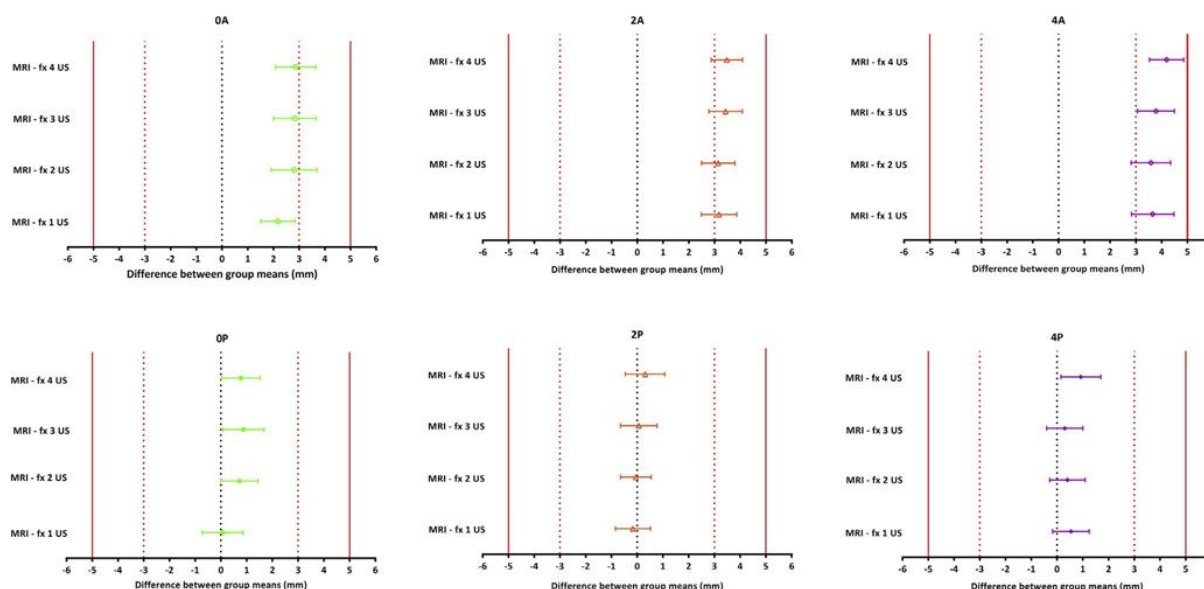


Figure 5.5 Mean differences between MRI and ultrasound at each measurement point

and 95% confidence interval of mean differences over four fractions (141 patients) shown in relation to clinically relevant cutoff values at  $\pm 3$  mm (cervix cutoff: dotted vertical lines) and  $\pm 5$  mm (uterus cutoff: solid vertical lines). Refer to Figure 4.2 for nomenclature of measurement points

## 5.4 Discussion

Inclusion of soft tissue imaging facilitates applicator insertion, identification of the treatment volume, and assessment of the relationship between the applicator, the target volume, and normal surrounding anatomy. Imaging is also increasingly being used to assess both intrafraction and interfraction changes over the course of brachytherapy<sup>212-216</sup>. The first objective of this study was to investigate changes to the dimensions of the cervix and uterus over the course of brachytherapy. There was no clinically significant change to the dimensions of the cervix (target) in 192 patients receiving three fractions of brachytherapy. Similarly, there was no clinically significant change in cervix dimensions over the course of brachytherapy for 141 of these patients who underwent four fractions of treatment. These findings have important implications for planning resources. Treatment plans were individualized for each patient at the first fraction, and 181 patients received this plan for the whole course of brachytherapy.

Use of a single plan for a course of brachytherapy has been investigated by a number of centres using three-dimensional imaging, with earlier studies recommending imaging and replanning for each insertion<sup>208,217</sup>. Mohamed et al.<sup>214</sup> investigated the feasibility of applying a single plan for two fractions of pulsed-dose-rate brachytherapy, and found comparable mean dose- volume histogram parameters for both target volume and OAR. This group concluded that use of a single plan was feasible when intracavitary brachytherapy was used for small-volume tumours (FIGO IB-IIB). In contrast, our study included 30 patients with FIGO Stage IIIB disease and in a sub analysis of these patients; there were no statistical or clinically significant differences in the dimensions of the cervix over the course of brachytherapy. Three patients in this subgroup had replans, although replanning was not made based on changes to the target dimensions.

A number of aspects of the protocol used at our institution influences our ability to apply the same treatment plan at each insertion see Table 5.4. Brachytherapy always commences at the completion of EBRT. This takes advantage of maximum tumour regression that occurs during EBRT. Dimopoulos et al.<sup>218</sup> examined serial MRI examinations over a course of EBRT and brachytherapy and found that tumours regressed during EBRT in the order of 75% with only minor regression occurring during brachytherapy. In that study, the first brachytherapy insertion occurred before the completion of EBRT, after patients had received a mean dose of 37 Gy. The results of the study demonstrated only a minor decrease in the absolute tumour volume during brachytherapy, with the target volume reducing from 16 cm<sup>3</sup> at the first insertion to 10, 9, and 8 cm<sup>3</sup> at the second, third, and fourth fractions, respectively. The greatest reduction was seen between first and second insertions (6 cm<sup>3</sup>) while the patients were still undergoing EBRT, with subsequent changes during brachytherapy of the order of 1 cm<sup>3</sup> per fraction. Our study did not quantify changes in target volume, but rather dimensions of the cervix and the

associated residual tumour (which constitutes the brachytherapy target) and did not see the magnitude of change detected by Dimopoulos et al.

Our patient cohort contained both good and poor responders, and all had serial measurements performed. The 95% confidence interval of differences in cervix dimensions give an indication that regression was not significant over the course of brachytherapy, Figure 5.4. We suggest that this is because of completion of all EBRT before starting brachytherapy. Dimopoulos et al. felt that minor modifications to subsequent brachytherapy plans may be expected because of the small regression in tumour volume over the course of brachytherapy. We concur with this, as we found only small changes in the target over time that required few modifications to the brachytherapy plans in our patient cohort.

In our protocol, patients were anesthetized for all fractions of treatment and remained under anaesthesia throughout the whole procedure. This included applicator insertion, ultrasound imaging, planning, and treatment.

Although a perceived advantage of high-dose-rate brachytherapy is the ability to perform the procedure in an outpatient setting, this may come at a technical cost. Hoskin et al.<sup>205</sup> commented that the ability to manipulate the applicator and packing may be limited compared with the results obtained under anaesthesia. Optimal applicator placement and technical accuracy are highly achievable throughout the procedure while the patient is under anaesthesia. Patients are not moved at all during the procedure, which reduces intrafraction uncertainties. Tanderup et al.<sup>219</sup> modelled the effect of applicator shifts in patients undergoing intracavitary treatment and showed that antero-posterior displacement of the applicator can result in mean changes to the bladder and rectum of 5% and 6% per mm for D2cc and D0.1cc, respectively. However, Lang et al.<sup>220</sup> found that with standardized bladder filling, geometric differences of



the applicator position relative to the target and OAR had minor overall dosimetric effect within a 16-20 h time interval of a single insertion treatment. On an anecdotal level, we have noted changes in applicator position between ultrasound imaging and MRI (which takes place within an hour of completing ultrasound imaging) and believe that restricted movement for subsequent insertions contributes to the accuracy of treatment delivery. Only intracavitary applicators were used in this study. Tandem and ovoids, and tandem and cylinder, were used in 85% and 15% of patients, respectively. The tandem and ovoid applicators are part of a locked system and so are less subject to variation during insertion.

Table 5.3 Comparison of ultrasound measurements at Fractions 1,2,3 and 4 (141 patients)

Measurement point	Tukey multiple comparisons test	Mean differences (mm)	95% CI of differences (mm)	Adjusted P Value <sup>a</sup>
0A	US fx1 vs. US fx2	0.6383	-0.1738 to 1.450	0.1964
	US fx1 vs. US fx3	0.6667	-0.1026 to 1.436	0.1227
	US fx1 vs. US fx4	0.695	-0.07635 to 1.466	0.0987
	US fx2 vs. US fx3	0.02837	-0.6868 to 0.7435	> 0.9999
	US fx2 vs. US fx4	0.05674	-0.5937 to 0.7072	0.9992
	US fx3 vs. US fx4	0.02837	-0.4972 to 0.5539	0.9999
0P	US fx1 vs. US fx2	0.6522	-0.06525 to 1.370	0.0937
	US fx1 vs. US fx3	0.8116	0.01875 to 1.604	0.042
	US fx1 vs. US fx4	0.7101	-0.09917 to 1.519	0.1147
	US fx2 vs. US fx3	0.1594	-0.5302 to 0.8490	0.9684
	US fx2 vs. US fx4	0.05797	-0.5497 to 0.6656	0.9989
	US fx3 vs. US fx4	-0.1014	-0.7330 to 0.5301	0.9919
2A	US fx1 vs. US fx2	-0.03546	-0.5005 to 0.4295	0.9996
	US fx1 vs. US fx3	0.2553	-0.2624 to 0.7731	0.6523
	US fx1 vs. US fx4	0.2979	-0.2334 to 0.8291	0.5323
	US fx2 vs. US fx3	0.2908	-0.1530 to 0.7346	0.3716
	US fx2 vs. US fx4	0.3333	-0.09552 to 0.7622	0.2059
	US fx3 vs. US fx4	0.04255	-0.4042 to 0.4893	0.9989
2P	US fx1 vs. US fx2	0.1151	-0.6029 to 0.8331	0.9919
	US fx1 vs. US fx3	0.2302	-0.5623 to 1.023	0.9293
	US fx1 vs. US fx4	0.4748	-0.3921 to 1.342	0.5552
	US fx2 vs. US fx3	0.1151	-0.6306 to 0.8608	0.993
	US fx2 vs. US fx4	0.3597	-0.3698 to 1.089	0.6523
	US fx3 vs. US fx4	0.2446	-0.4088 to 0.8980	0.8388
4A	US fx1 vs. US fx2	-0.07092	-0.7999 to 0.6580	0.9988
	US fx1 vs. US fx3	0.1277	-0.5677 to 0.8230	0.9865
	US fx1 vs. US fx4	0.539	-0.1595 to 1.238	0.2122
	US fx2 vs. US fx3	0.1986	-0.3168 to 0.7139	0.8241
	US fx2 vs. US fx4	0.6099	0.06568 to 1.154	0.0197
	US fx3 vs. US fx4	0.4113	-0.1054 to 0.9281	0.1858
4P	US fx1 vs. US fx2	-0.1367	-0.7513 to 0.4779	0.9725
	US fx1 vs. US fx3	-0.2374	-0.9308 to 0.4560	0.8782
	US fx1 vs. US fx4	0.3885	-0.4086 to 1.186	0.6622
	US fx2 vs. US fx3	-0.1007	-0.6842 to 0.4827	0.9893
	US fx2 vs. US fx4	0.5252	-0.08368 to 1.134	0.1258
	US fx3 vs. US fx4	0.6259	-0.02222 to 1.274	0.0638
Tip A	US fx1 vs. US fx2	-0.392	-0.9852 to 0.2012	0.3616
	US fx1 vs. US fx3	-0.088	-0.8453 to 0.6693	0.9977
	US fx1 vs. US fx4	0.256	-0.5052 to 1.017	0.8843
	US fx2 vs. US fx3	0.304	-0.3922 to 1.000	0.7463
	US fx2 vs. US fx4	0.648	-0.08562 to 1.382	0.1103
	US fx3 vs. US fx4	0.344	-0.4295 to 1.118	0.7333
Tip P	US fx1 vs. US fx2	0.328	-0.5062 to 1.162	0.8122
	US fx1 vs. US fx3	0.328	-0.4252 to 1.081	0.7482
	US fx1 vs. US fx4	0.744	-0.03704 to 1.525	0.0699
	US fx2 vs. US fx3	0	-0.8140 to 0.8140	> 0.9999
	US fx2 vs. US fx4	0.416	-0.4349 to 1.267	0.6584
	US fx3 vs. US fx4	0.416	-0.2901 to 1.122	0.4806
Tip S	US fx1 vs. US fx2	0.1228	-1.009 to 1.254	0.9982
	US fx1 vs. US fx3	0.4825	-0.6906 to 1.656	0.7848
	US fx1 vs. US fx4	0.6842	-0.5036 to 1.872	0.5024
	US fx2 vs. US fx3	0.3596	-0.7990 to 1.518	0.9106
	US fx2 vs. US fx4	0.5614	-0.4726 to 1.595	0.5613
	US fx3 vs. US fx4	0.2018	-0.7169 to 1.120	0.9734

CI = confidence interval; US = ultrasound;

<sup>a</sup>Multiplicity-adjusted p-values<sup>211</sup>

Datta et al.<sup>221</sup> investigated applicator geometry of flexible tandems and unfixed ovoids and found significant variations over a course of brachytherapy. A rectal retractor is used in conjunction with vaginal packing for every patient undergoing treatment with tandem and ovoids. Although the rectal retractor is primarily used to displace the rectum, its use also contributes to stability and reproducibility of the implant. Use of the rectal retractor has been found to reduce the variability of packing, particularly with regard to rectal proximity to the applicator<sup>222</sup>.

Bladder filling was kept consistent throughout the procedure and the course of treatment. A full bladder is required to provide an acoustic window into the pelvis. The protocol stipulates that the bladder must cover the fundus during ultrasound scanning, which means that the amount of bladder filling is patient dependent. Consistent bladder filling is primarily used to reduce dose to the bowel and contribute to reproducibility of the implant across fractions, Figure 5.6. In a study looking at the effect of bladder distension on dose distribution, Cengiz et al.<sup>223</sup> found that the small bowel received significantly greater doses when the bladder was empty.

These stringent quality control measures contribute to the accuracy of applying a single individualized plan at most insertions. Numerous studies attest to the need for reimaging and planning at each insertion, but most still experience a time lag between imaging, planning, and treatment. Our protocol verifies applicator position and target dimensions just minutes before administering treatment. Anderson et al.<sup>212</sup> reimaged patients during a single insertion to ascertain intrafraction changes to the position of OAR. The average time between planning MRI and pretreatment MRI was 4.75 hours (range, 3.2 - 9.9 hours). During this time, the position of the OAR changed and dose constraint compliance reduced by 13.9%. The time

between pretreatment MRI and treatment was not recorded but was in the region of 20 min. Although stating that it is advisable to plan the patient as quickly as possible, they also recommended re-evaluation of anatomy at the time of treatment. In a similar study, Simha et al.<sup>216</sup> took a planning MRI followed by CT to evaluate intrafraction motion of OAR. There was an average of 2 hours (range, 1.5 - 3.5 hours) between MRI and CT and 7 h (5 - 8 hours) between applicator placement and treatment delivery. Although variations between D2cc, D1cc, and D0.1cc for bladder and rectum were not statistically significant, there was significant variation in dose-volume histogram parameters for the sigmoid colon, with an average change of nearly 10% for D2cc and much higher changes in D0.1cc.

There is still considerable patient movement and time required if using MRI or CT to evaluate the applicator position and the anatomy before treatment. We used ultrasound to do this at the point of care reducing both patient movement and overall procedure time. Overall procedure time, including applicator insertion, ultrasound imaging, planning, treatment, and applicator removal, is 1.5 hours for a new patient and between 1 and 1.5 hours for patients undergoing a repeat insertion. The conformal ultrasound-based plan is back projected onto the MRI data set later in the day by the dosimetrists. The target volume and OAR are contoured on the MRI data set at this time. This takes less than an hour. The contours and plan are reviewed by the radiation oncologists in a designated chart round before the next insertion. Ultrasound verification images from subsequent insertions are registered to the MRI data set by the dosimetrists. Isodose coverage is assessed at each insertion Figure 5.7. This protocol reduces the planning burden on the dosimetrists, the need to recall radiation oncologists throughout the day, and greatly reduces the time patients spend in the hospital

Table 5.4 Aspects of brachytherapy protocol and explanatory notes

Protocol	Explanatory notes
Brachytherapy always commences after EBRT has been completed	Ensures maximum tumour regression has occurred.
Brachytherapy occurs in an integrated operating suite	Anaesthetic services, ultrasound imaging, HDR unit, patient monitoring (CCTV, audio, remote anaesthetic monitoring), planning facilities in treatment control room co-located with theatre
Patients are anesthetized for the whole procedure at each insertion	Fx1 spinal anaesthesia, fx 2-4 general anaesthesia (depending on patient condition)
Patient preparation	Bowel preparation – fasting from midnight before procedure, Oral Microlax® night before and morning of procedure
Consistent bladder filling	Bladder acts as acoustic window into pelvis. Bladder is filled until fundus of uterus is covered. Amount of filling is patient dependent.
Use of locked system tandem and ovoids	Reduces uncertainties and contributes to reproducibility of insertion across fractions
Use of rectal retractor	Reduces uncertainties and contributes to reproducibility of packing across fractions
Use of intra-operative ultrasound to guide applicator placement	Real time feedback of applicator placement avoids perforation, allows for optimal placement of applicator
Intra-operative verification of brachytherapy target	Real time assessment of applicator – uterus cervix relationship. Uterine and cervix dimensions are verified and suitability of fraction 1 plan is assessed. Presents opportunity for adaptive planning if cervix dimensions have changed.
No patient movement after planning images have been taken	Patients are imaged in treatment position and are not moved until planning and treatment have been completed
Expedited planning	Planning takes place in co-located room while patient is under anaesthetic. Planning on ultrasound image takes 15 minutes.
Short overall procedure time	Total time for fraction 1 procedure is 1 ½ hours Total time for subsequent fractions is 1 – 1 ½ hours
Brachytherapy personnel trained in ultrasound	All Radiation Therapists rostered to brachytherapy undergo a limited scope ultrasound training course. All therapists perform ultrasound under clinical supervision for a number of months.

EBRT = external beam radiotherapy

In contrast to most studies looking at intrafraction and interfraction differences in the positions of OAR, the anatomical assessment made with ultrasound is focused on the applicator-target relationship. The cervix and uterine dimensions are verified at each insertion to check if the original conformal plan still fits. We cannot quantify the differences to OAR doses using ultrasound verification, but we can verify the coverage of the target and ensure that the isodose coverage beyond the target is safe for surrounding tissues, whatever they are, Figure 5.7. Although we cannot quantify dose volumes to OAR, we can see OAR near the cervix and uterus on axial and sagittal two- dimensional projections and consider these relationships when we apply isodose coverage, Figure 5.1, Figure 5.2, and Figure 5.7. We do not conclude that the bladder, sigmoid, and rectal dosimetry are comparable from fraction to fraction. By verifying the applicator position, the cervix and uterine dimensions, and iso-coverage at each insertion, we are ensuring that OAR beyond these structures do not receive toxic doses. In a previous study, we validated the use of ultrasound to identify the cervix, which is the brachytherapy target<sup>139</sup>. Cervix dimensions measured with ultrasound were not significantly different to measurements made on MRI, particularly at the posterior border of the cervix, which showed mean agreement within 1 mm of MRI. In a study comparing CT-and MRI-based contouring, Viswanathan et al.<sup>209</sup> found significant differences in the width of the cervix identified on CT and MRI. Cervix width on CT was wider than on MRI and resulted in statistically significant differences in the volume treated to the prescription dose. Beriwal et al.<sup>210</sup> found similar significant differences between the cervix contoured on MRI and CT. These centres recommend using MRI for the first insertion to contour the high-risk clinical target volume and CT for subsequent insertions to monitor the OAR. Given our data, ultrasound may well be a feasible alternative to CT to monitor the high-risk clinical target volume and by inference, protect the OAR.

Another feature of our protocol is the use of brachytherapy staff trained in ultrasound. All radiation therapists rostered to brachytherapy undergo a limited scope training course that teaches ultrasound skills for brachytherapy. They also perform ultrasound under clinical supervision for a number of months under a radiation therapist with postgraduate ultrasound qualifications. This ensures consistency and reliability of the results obtained with ultrasound. If the target dimensions are within clinically acceptable limits of the first day dimensions, then the first day plan is delivered to subsequent insertions. If the target dimensions are not within clinically acceptable limits, then a new adaptive plan is calculated.

The second objective of this study was to ascertain the amount of replanning required. Of 192 patients, 11 (5.7%) received replans. The changes in cervix dimensions over the course of treatment were not statistically or clinically significant for these patients. Although changes were made to the plans, other clinical factors contributed to the decision to modify the plans. The reasons for plan changes and the magnitude of changes were not recorded.

The findings of this study are limited to intracavitary brachytherapy. At this time, use of ultrasound as a verification tool does not allow us to assess dosimetric variations to the OAR.

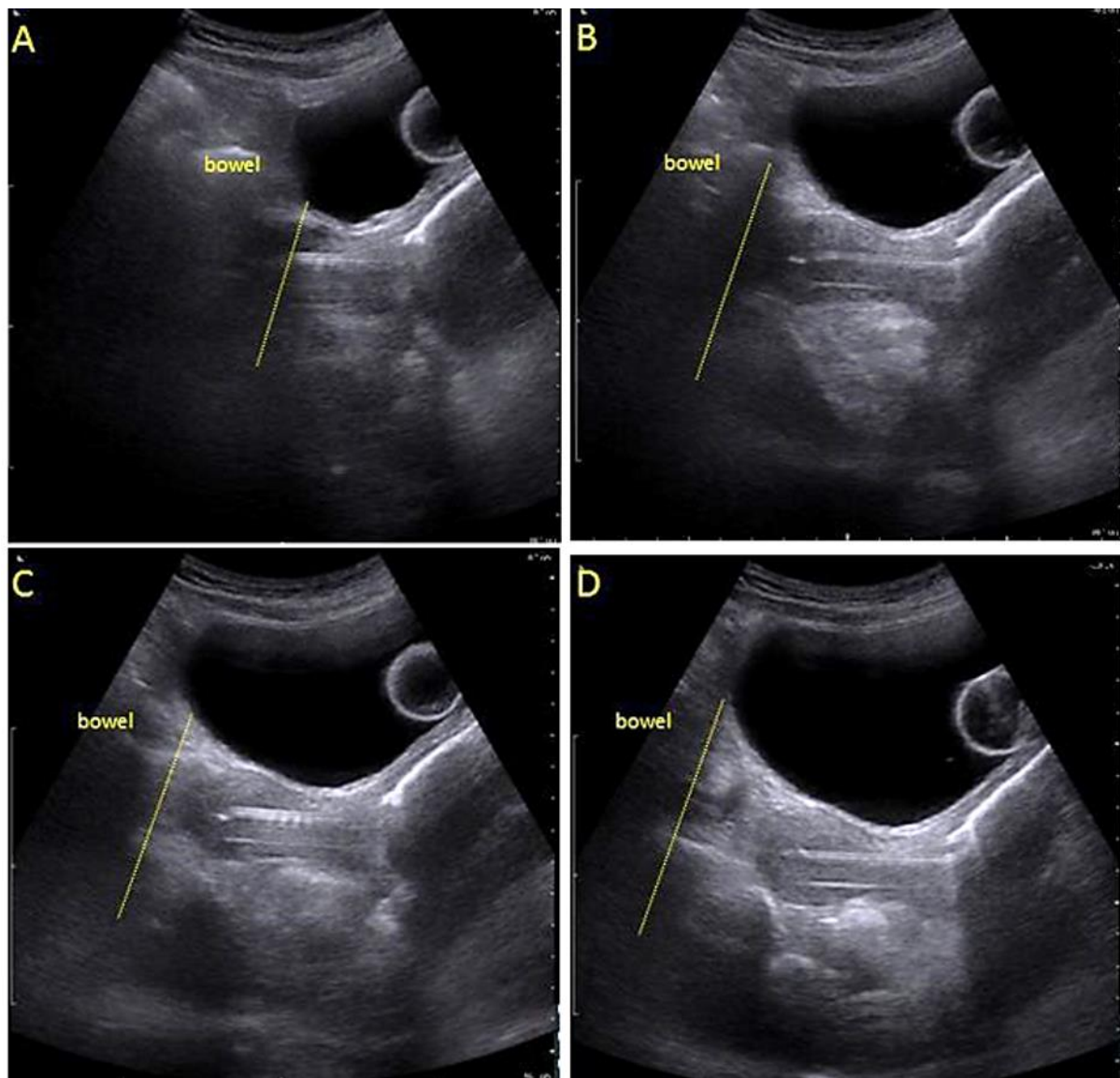


Figure 5.6 Bladder filling

provides an acoustic window into the pelvis and moves the bowel away from the uterus

- A. Transabdominal ultrasound – longitudinal view of uterus. Note small amount of bladder filling. The top of the uterus is obstructed by bowel.
- B. Transabdominal ultrasound – longitudinal view of uterus. Bladder filling increasing, fundus of uterus is now visible, there is far less bowel visible.
- C. Transabdominal ultrasound – longitudinal view of uterus. Bladder filling is sufficient to clearly view whole uterus.
- D. Transabdominal ultrasound-longitudinal view of uterus. Optimal bladder filling giving clear line of site to uterus with applicator in-situ. Bowel superior to uterus has moved out of field of view.

Note line of acoustic enhancement indicated by dashed yellow lines

Source: Peter MacCallum Cancer Centre



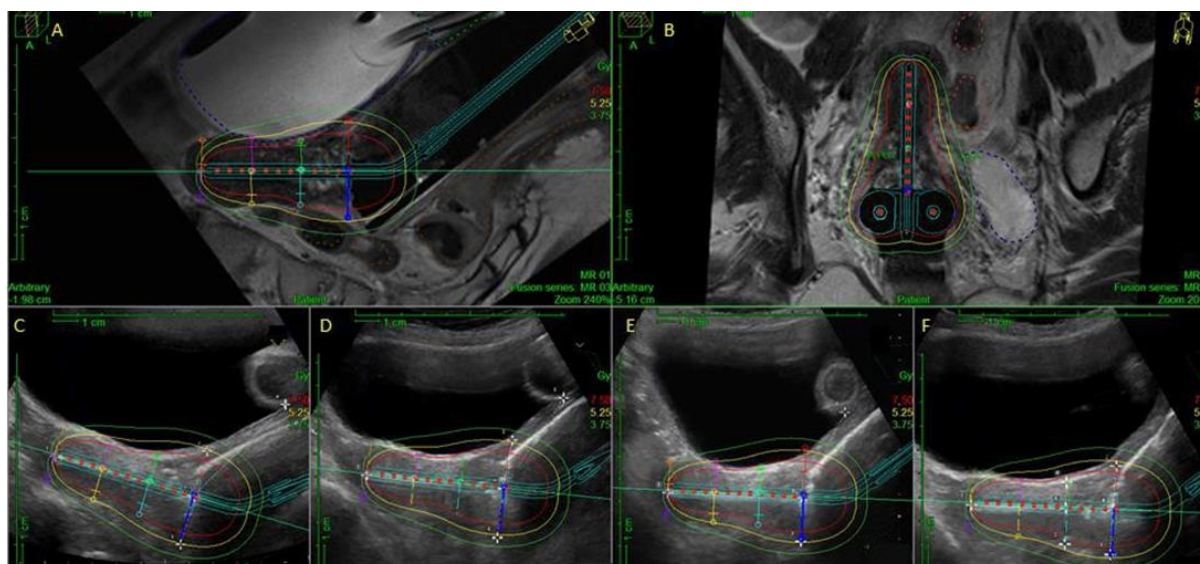


Figure 5.7 Treatment plan evaluated on ultrasound and MRI

Ultrasound images taken at each insertion and co-registered with fraction 1 MRI data set to evaluate iso-coverage of cervix and uterus

- A. T2 para-sagittal MRI – longitudinal view of uterus with applicator (taken at fx1) Isodose coverage was devised on sagittal ultrasound views and back projected onto MRI after treatment had been delivered
- B. T2 para-coronal MRI – coronal view of uterus with applicator (taken at fx1) Isodose coverage was devised on axial ultrasound views and back projected onto MRI after treatment had been delivered
- C. Transabdominal ultrasound – longitudinal view of uterus with applicator in-situ at fx1 showing ultrasound based isodose coverage
- D. Transabdominal ultrasound – longitudinal view of uterus with applicator in-situ at fx2 showing same isodose distribution as fx1, there was no change to treatment volume or isodose coverage
- E. Transabdominal ultrasound – longitudinal view of uterus with applicator in-situ at fx3 showing same isodose distribution as fx1, there was no change to treatment volume or isodose coverage
- F. Transabdominal ultrasound – longitudinal view of uterus with applicator in-situ at fx4 showing same isodose distribution as fx1, there was no change to treatment volume or isodose coverage

Source: Peter MacCallum Cancer Centre

## 5.5 Conclusion

We have found little change in the dimensions of the brachytherapy target over the course of treatment. These findings are based on adherence to a strict protocol with a number of important quality control measures. They include commencement of brachytherapy after EBRT is completed; use of intraoperative ultrasound imaging for applicator guidance and pretreatment applicator and anatomy verification; bladder- and rectal-filling protocols; minimal patient movement; and treatment in an integrated brachytherapy suite. The impact of these findings are that we are able to reduce reliance on external departments for imaging, reduce patient waiting and discomfort, and reduce the amount of time brachytherapy personnel are needed for replanning. We have described a novel protocol of using a single MRI in combination with serial ultrasound that enables image guidance for applicator insertion, individualized dosimetric optimization, and verification before treatment for all patients. We strongly recommend the use of imaging at each insertion to verify treatment and allow for adaptive planning should it be required.

# Chapter 6

## Clinical outcomes from an innovative protocol using serial ultrasound imaging and a single MR image to guide brachytherapy for locally advanced cervix cancer

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This chapter is an exact copy of the journal paper referenced on the previous page except the figure, table and reference numbers have been modified for the purpose of this thesis. Supplementary figures and tables have been included as part of the main text.

The work presented in Chapters 4 and 5 described the technical aspects of incorporating ultrasound into a brachytherapy program. Technical innovation and applicability can only truly be proven by examining the clinical results achieved when using a technique. This chapter describes the excellent clinical outcomes of patients who were treated for locally advanced cervix cancer with ultrasound guided brachytherapy at the Peter MacCallum Cancer centre.

# Abstract

**Purpose:** The aim of this study was to report clinical outcomes in a series of patients who underwent serial ultrasound and a single MRI to plan and verify intracavitary brachytherapy.

**Methods and materials:** Data for patients who were referred for curative intent radio therapy with International Federation of Gynecology and Obstetrics (FIGO) Stage 1-1V cervix cancer between January 2007 and March 2012 were analysed. All patients received external beam radiotherapy with concurrent chemotherapy and sequential high-dose rate brachytherapy. Brachytherapy was planned and verified using serial ultrasound imaging and a single MRI.

**Results:** Data from 191 patients were available for analyses. The median (range) follow-up time was 5.08 (0.25-8.25) years. Five-year local control, failure-free survival, cancer-specific survival, and overall survival were 86%, 57.3%, 70% and 63%, respectively. Mean (standard deviation) combined external beam radiotherapy and brachytherapy target doses, equivalent to doses in 2 Gy fractions were 80.4 Gy<sub>10</sub> (3.89), median (range) 80 (49 - 96) Gy<sub>10</sub>. Grade 3 or greater gastrointestinal, genitourinary, or vaginal late toxicity occurred in 3%, 1.6%, and 2% of patients, respectively. Survival, patterns of failure, and late complication rates were similar to published series of MRI/CT based brachytherapy practices.

**Conclusions:** This large study demonstrates that favourable treatment outcomes can be obtained using a pragmatic and innovative combination of ultrasound and MR imaging.

## 6.1 Introduction

It is now well established that use of image-guided brachytherapy improves local control (LC) and reduces toxicity for patients undergoing treatment for locally advanced cervix cancer<sup>65-67,224-233</sup>. The majority of these studies use advanced imaging technologies such as CT and MRI, Table 6.1. Access to these technologies on a per fraction basis is difficult for many centres and may not be possible at all for some<sup>228,234-236</sup>. In our institution, we do not have access to MRI for every fraction of brachytherapy and so have developed a protocol that uses serial ultrasound imaging and a single MRI scan to guide, plan, and verify treatment. From January 2007, all measurements taken with ultrasound were recorded systematically to serve as both a record of treated volumes and verification of treatment delivery. Over the past few years, ultrasound has been validated against MRI, and that validation has been used as a basis on which to continue employing ultrasound in daily practice<sup>139,237</sup>. The aim of this study is to present clinical outcomes achieved with an innovative protocol of using ultrasound imaging and a single MRI to guide brachytherapy for cervix cancer.

## 6.2 Methods and materials

This study was approved by the Divisional Review Panel for Retrospective Studies at the Peter MacCallum Cancer Centre and by the Monash University Human Research Ethics Committee

### Study design

All patient data, ultrasound measurements, MR measurements, dosimetric data, and clinical outcomes were prospectively collected and recorded in a dedicated Gynaecological Unit data base

Table 6.1 Literature review of image based brachytherapy  
with at least 2-year follow-up

Reference	No. of patients	Patients with positive nodes %	FIGO 3B %	Median Follow up months	Technique IC intracavitary IC/IS intracavitary/interstitial		Imaging	Mean target dose Gy <sup>10</sup>	3 years	Local Control %		Cancer Specific Survival %		Overall survival %	
										5 years	3 years	5 years	3 years	5 years	5 years
Potter <i>et al</i> <sup>67</sup> 2011	156	48	21	42	IC 56%	IC/IS 44%	MRI	93	95			74		68	
Petit <i>et al</i> <sup>230</sup> 2013	226	40	12	82	IC 100%		X-ray CT	45 EBRT + 16 PDR		80					67
Sturdza <i>et al</i> <sup>238</sup> 2012 Retro-EMBRACE	454	53	18	36.5	IC 86%	IC/IS 14%	CT/MRI	84	91.4						
Nomden <i>et al</i> <sup>225</sup> 2013	54	44	15	41	IC 75%	IC/IS 25%	MRI	84	93		74			65	
Lindegaard <i>et al</i> <sup>226</sup> 2013	140	50	20	36	IC 57%	IC/IS 43%	MRI	92	91		87			79	
Rijkman <i>et al</i> <sup>227</sup> 2014	93	35	20	42	IC 77%	IC/IS 13%	CT/MRI	80.8	93					86	
Narayan <i>et al</i> <sup>166</sup> 2014	309	45	16	48	IC 100%		US/MRI	80.1		87.5				77	66
Gill <i>et al</i> <sup>232</sup> 2015	128	46	16	24	IC 95%	IC/IS 5%	CT/MRI	82.7	91.6		85.4			77	
Castelnau-Marchand <i>et al</i> <sup>229</sup> 2015	225	51	11	39	IC 98%	IS 2%	CT/MRI	82.5	86.4	85.5				76	
Choong <i>et al</i> <sup>233</sup> 2015	76	54	1.3	47	IC 65%	IC/IS 35%	CT/MRI	96.5	91.4					74	
van Dyk <i>et al</i> 2016	191	43	16	60	IC 100%		US/MRI	79.7	86	86	79	70	75	63	

FIGO = Federation of Gynecology and Obstetrics; EBRT = external beam radiotherapy;  
IC = intracavitary; IS = interstitial; PDR = pulse dose rate; US = ultrasound

## Patient selection criteria

Patients who presented to Peter MacCallum Cancer Centre between January 2007 and March 2012 with previously untreated cervical cancer were included in this study. Patients had to have been staged according to the clinical FIGO staging system as Stage I, II, III, or IV, have had both a pretreatment MRI and an MRI at the time of brachytherapy, and been treated with curative intent.

## Treatment

Patients were prescribed 40-45 Gy external beam radiotherapy (EBRT) in 1.8 - 2.0 Gy fractions using three- dimensional (3D) conformal radiotherapy. Nodal involvement was assessed on pretreatment fluorodeoxyglucose positron emission tomography (FDG-PET) scans. Involved nodes were treated with antero-posterior fields of 6 - 10 Gy depending on size and location. Four to five cycles of concomitant cisplatin chemotherapy, 40 mg/m<sup>2</sup>, were routinely administered unless contraindicated. Image guided brachytherapy was delivered using intracavitary applicators, tandem and ovoids, or tandem and cylinder. The high-dose rate brachytherapy schedule consisted of three to four applications (7 - 8.9 Gy per fraction) to achieve a total combined dose to the target volume of 80 - 84 Gy<sub>10</sub> equivalent to doses in 2 Gy.

Brachytherapy was performed in a dedicated theatre suite. Patients had two fractions per week for 1½ to 2 weeks after completion of EBRT. Patients were anesthetized for the whole brachytherapy procedure which included applicator insertion, imaging, planning, treatment, and applicator removal. The brachytherapy target consisted of the whole cervix, residual disease, and upper vagina and extended into the corpus uteri<sup>62</sup>. This target was identified on ultrasound, and iso-coverage was later confirmed on MRI after the first fraction was treated. The ultrasound treatment plan was back projected onto the MR data set and evaluated with respect to target coverage and normal tissue doses. Subsequent insertions relied on intraoperative ultrasound alone for applicator guidance and volume and iso-coverage verification. The target volume was measured at each insertion with ultrasound using the dimensions of width, height, and length and compared to the similarly derived MRI target volume. If the target volume was within stated clinical limits, treatment proceeded as planned<sup>139,237</sup>. See Figure 3.1 to Figure 3.5 for overview of ultrasound use and planning protocol. Doses to organs at risk (OAR) were assessed on the initial 3D MRI and subsequent



ultrasound imaging and were recorded using International Commission of Radiation Units (ICRU) and Measurements report 38 reference points<sup>34</sup>. It was not possible to report dose volume histogram parameters for OAR as the volume of these structures cannot be measured on two-dimensional (2D) ultrasound projections. The planning techniques for EBRT and BT have previously been described<sup>139,237</sup>. It is important to note that using 2D ultrasound projections is somewhat akin to using x-rays, but with soft tissue information. Evaluation of iso-coverage is limited to organs that can be imaged in the longitudinal and transverse planes within the ultrasound field of view. This is possible for the uterus and cervix but less so for the bladder, rectum, and sigmoid colon. This is why ICRU report 38 reference points were used to describe doses to OAR.

## Imaging

EBRT planning was guided by pretreatment MRI and FDG-PET, on planning CT scans. All patients underwent MRI and transabdominal ultrasound imaging with applicators *in situ* at the first brachytherapy fraction and ultrasound imaging alone at subsequent fractions.

## Clinical outcomes

LC, overall survival (OS), cancer-specific survival (CSS), and failure-free survival (FFS) were calculated.

The follow-up schedule for these patients was clinical review six weeks after completing treatment, followed by an FDG-PET scan at six months. If there was a complete metabolic response, patients were reviewed six monthly for four years, then yearly up to seven years.

After seven years, patients had the option of 12 monthly telephone follow-up or clinic attendance.

## Toxicity

Doses to normal tissues were assessed on the first fraction MR images and all ultrasound images. Cumulative volume doses to normal tissues were not able to be recorded as the 3D MR images were only obtained at Fraction 1. Doses were reported using ICRU report 38 methodology for bladder and rectum. The dose to vaginal mucosa was measured at a standardized point on the ovoid or cylinder surface. All reference dose points were able to be assessed on ultrasound images<sup>237</sup>.

## Statistics

Statistical analysis was performed using Graphpad Prism version 6.05 for windows, GraphPad Software, La Jolla, California, USA.

Closeout date of the study was the earliest of the last appointment dates for patients who are alive and not lost to follow-up. This was March 15, 2014. All events after this date were censored to minimize potential bias.

OS and CSS were defined as the period from date of diagnosis to date of any death and death by cervical cancer, respectively.

FFS was defined as the period from date of diagnosis to date of local, regional, para-aortic, distant failure, or any failure.

LC was defined as absence of disease at the primary site and uterus.

All failures were determined by combining clinical investigations (FDG-PET, MRI) and/or by pathological findings and were classified as recurrence or persistent disease. Kaplan-Meier estimates were used to calculate OS, CSS, FFS, and LC.

Median follow-up was calculated using the Kaplan- Meier estimate of potential follow-up (KM-PF) method as described in Schemper and Smith<sup>239</sup>.

Late morbidity occurring at least 91 days after radiotherapy was scored using World Health Organization/ Radiation Therapy Oncology Group criteria. The relationship between late morbidity  $\geq 3$  (crude rates) and the ICRU report 38 reference point doses was evaluated. Descriptive statistics were used to present toxicities associated with treatment.

## 6.3 Results

Two hundred thirty-one patients were treated with radical intent during the study period. Thirty patients were excluded as they did not receive an MRI scan at the fraction of brachytherapy. This was due to a variety of reasons: lack of scanner availability, patient condition, patient refusal, and machine breakdowns. Eight patients were excluded because of insufficient data, which included poor-quality MR images due to patient movement. Data from two further patients were excluded because of incomplete ultrasound views due to large fibroids. Data from 191 patients were available for analyses. Patient and tumour characteristics are presented in Table 6.2. The median (range) follow-up time was 5.08 (0.26 - 8.6) years. Data of patients were analysed with and without those with histologies other than squamous cell, adeno and

adenosquamous carcinoma. There was no significant difference in LC, CSS, FFS, and OS when these groups were analysed separately, Figure 6.1.

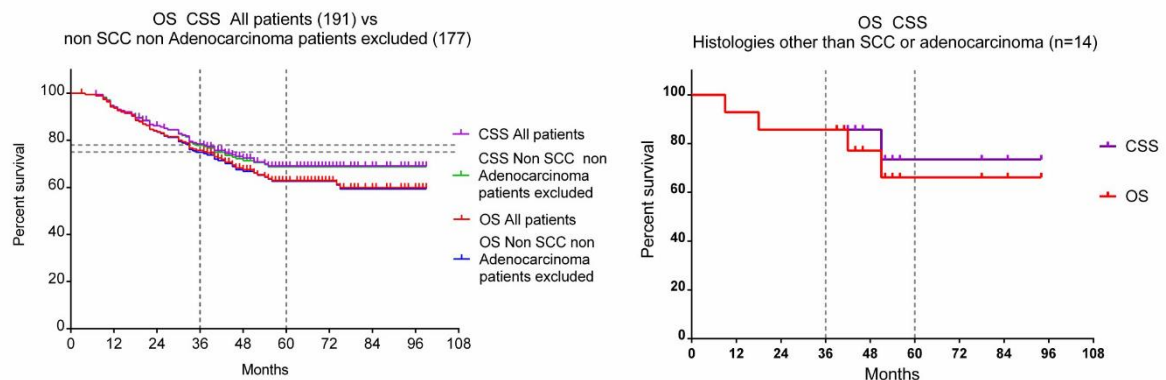


Figure 6.1 Kaplan-Meier estimates of Overall Survival (OS) and Cancer Specific Survival (CSS)

On Left: all patients (191) vs excluding patients with histologies other than squamous cell carcinoma or adenocarcinoma ( $191 - 14 = 177$ )

On Right: patients with histology other than SCC or adenocarcinoma (14)

Seven patients were lost to follow-up at 0.26, 1.7, 4.3, 6.6, 7.4, and 8.6 years, respectively.

Median (range) tumour volume at presentation was 33.6 (0.5-381) cm<sup>3</sup>. Eighty-three (43%) patients presented with involved nodes, with 45 (23%) patients receiving a pelvic nodal boost and 38 (20%) patients receiving extended field radiotherapy and nodal boosts.

## Treatment

The median (range) overall treatment time was 45 (30 - 100) days. All patients completed EBRT with median (range) physical dose of 40 (38 - 46.4) Gy and mean (standard deviation)

dose of 41.3 (2.22) Gy. All but 2 patients received concurrent chemotherapy with EBRT (four cycles, 149 [78%] patients; five cycles, 38 [20%] patients).

All patients received ultrasound-guided high-dose rate conformal brachytherapy. All patients underwent intracavitary brachytherapy, with 85% treated with tandem and ovoids and 15% treated with tandem and cylinder. Tandem and cylinder were used in patients with a narrow vaginal vault due to atrophy and old age.

## Dose parameters

Dose parameters for all patients and per FIGO stage are presented in Table 6.3. Target coverage was initially assessed on the MRI obtained at Fraction 1. At subsequent insertions, target dimensions were obtained with ultrasound and compared to the MRI target dimension to assess coverage

## Clinical outcomes

Kaplan-Meier estimates for OS, CSS, FFS, and LC are shown in

Figure 6.2. The 3 and 5 year rates for OS and CSS were 75%, 63%, 79%, and 70%, respectively.

Three and 5 year LC was 86%.

Sixty-eight (36%) patients have died, 52 from disease, 12 from other causes, and 4 from unknown causes.

## Sites of failure

Failures occurred in 70 (37%) patients. Six of these patients had histology other than SCC or adenocarcinoma. Twenty-six (13.6%) patients had local failures. Thirty-two patients had pelvic failures, 42 had para-aortic nodal failures, 16 had supraclavicular nodal failures, 3 had inguinal failures, and 42 had distant failures.

Figure 6.3 illustrates the local and pelvic patterns of failure. There were 19 isolated failures; one local, two pelvic, three para-aortic nodes, and 13 distant locations. The 3 and 5 year FFS rates were 63% and 58%, respectively.

## Late toxicity

No patients progressed within 91 days after treatment, so late toxicity was analyzed for 191 patients. Overall late Grade  $\geq 3$  morbidity was seen in 12 (6%) patients, Table 6.4 and Table 6.5.

One patient experienced Grade 4 bladder toxicity. This patient presented with FIGO IVA disease. This patient developed a vesicovaginal fistula four months after completing radiotherapy. The fistula developed in response to tumour resolution after treatment. The patient refused corrective surgery and manages with continence pads. Similarly, this patient also experienced Grade 4 vaginal toxicity.

Table 6.2 Patient and tumour characteristics N= 191

Characteristic	
<b>Age (y)</b>	
Mean (SD)	52 (15.9)
Median	50.8
Range	21 - 89
<b>FIGO stage, N (%)</b>	
1	64 (33)
2A	19 (10)
2B	62 (32)
3A	5 (3)
3B	31 (16)
4A	5 (3)
4B	5 (3)
<b>Histology, N (%)</b>	
Squamous cell carcinoma	147 (77)
Adenosquamous	8 (4)
Endometrioid/mucinous	22 (12)
Malignant mixed Müllerian tumour	1 (0.5)
Small cell	8 (4)
Serous	1 (0.5)
Clear cell	4 (2)
<b>Original tumour volume (cm<sup>3</sup>)</b>	
Mean (SD)	48.9 (56.21)
Median	33.56
Range	0.5 - 381
<b>Radiotherapy field, N (%)</b>	
pelvic radiotherapy	153 (80)
extended field radiotherapy	38 (20)

SD = Standard deviation; FIGO = Federation of Gynecology and Obstetrics

Two patients experienced Grade 3 bladder toxicity. One of these patients also experienced Grade 3 bowel toxicity. This patient underwent multiple hyperbaric treatments for cystitis, proctitis, and rectal bleeding. The proctitis and bleeding have resolved, and the cystitis is decreasing with Mirabegron (b3-Adrenergic Receptor Agonist).

The remaining patient presented with urinary incontinence and is managing this with exercises.

One patient experienced Grade 4 bowel toxicity. She developed metastases to the rectum and anus and underwent surgery.

Five patients experienced Grade 3 bowel toxicity. One underwent hyperbaric treatment (described above); one presented with small bowel obstruction but was lost to follow-up in 2011; one presented with acute bowel syndrome in 2009, but was alive with no disease in 2011 but has since been lost to follow-up; one presented with bowel obstruction after recurrence and is alive with disease; one presented with small bowel obstruction, diarrhoea, and bowel metastases but was lost to follow-up in 2012.

One patient experienced Grade 4 vaginal toxicity, described above. This patient developed a vesicovaginal fistula due to tumour resolution during treatment. She is unable to tolerate vaginal examination. Four patients experienced Grade 3 vaginal toxicity. All but one of these patients presented with stenosed vagina after radiotherapy. None of the patients used the vaginal cylinder.



Table 6.3 Dosimetric outcomes for all patients and FIGO stages

Total doses: EBRT + BT expressed in EQD2							
			Point A	Target dose	ICRU 38 Bladder point	ICRU 38 Rectum point	Vaginal mucosa point
		N	Gy10	Gy10	Gy3	Gy3	Gy3
All patients	191	Mean (SD)	66.8 (9.29)	80.4 (3.89)	53.8 (10.17)	56.2 (8.28)	120.9 (17.12)
		Median	65	80	50.8	54.4	122.4
		Range	40.5 - 114	49 - 96	41.7 - 120	42.4 - 120	62 - 162
		<u>Mean</u>					
		<u>Pre-tx vol</u>					
<u>FIGO stage</u>	<u>N</u>	<u>cm3 (SD)</u>	<u>Mean dose Gy (SD)</u>				
1	64	26.7 (52.21)	66.1 (10.15)	80.31 (2.94)	49.6 (8.08)	53 (4.43)	119.7 (17.56)
2A	19	29.3 (26.9)	64.6 (8.33)	79.9 (1.87)	53.6 (7.89)	54.6 (4.29)	125.3 (13.43)
2B	62	58.6 (57.10)	67.5 (8.53)	81.49 (2.72)	54.6 (8.65)	56.8 (5.71)	124.5 (14.16)
3A	5	46.13 (36.26)	61.1 (7.76)	80.8 (1.79)	61.5 (10.23)	63.3 (10.34)	119.3 (17.01)
3B	31	65.2 (41.82)	68.2 (9.88)	80.1 (3.65)	57.71 (14.38)	56.9 (8.42)	115.7 (22.58)
4A	5	163 (93.63)	72.8 (8.94)	72.0 (15.41)	65.3 (7.46)	78.48 (28.43)	119.9 (18.98)
4B	5	57.74 (26.17)	64.5 (4.72)	80.3 (2.17)	58.7 (9.45)	58.9 (7.11)	na

SD = standard deviation; FIGO = Federation of Gynecology and Obstetrics; BT = brachytherapy; EBRT = external beam radiotherapy; EQD2 = equivalent to doses in 2 Gy; ICRU = International Commission of Radiation Units.

## 6.4 Discussion

This large modern series of patients imaged with serial ultrasound and a single MRI has reported excellent clinical outcomes that compare favourably to groups using more technically complex imaging and treatment protocols. There is no doubt serial soft tissue imaging improves the accuracy of implant positioning and iso-coverage, which leads to improved local control

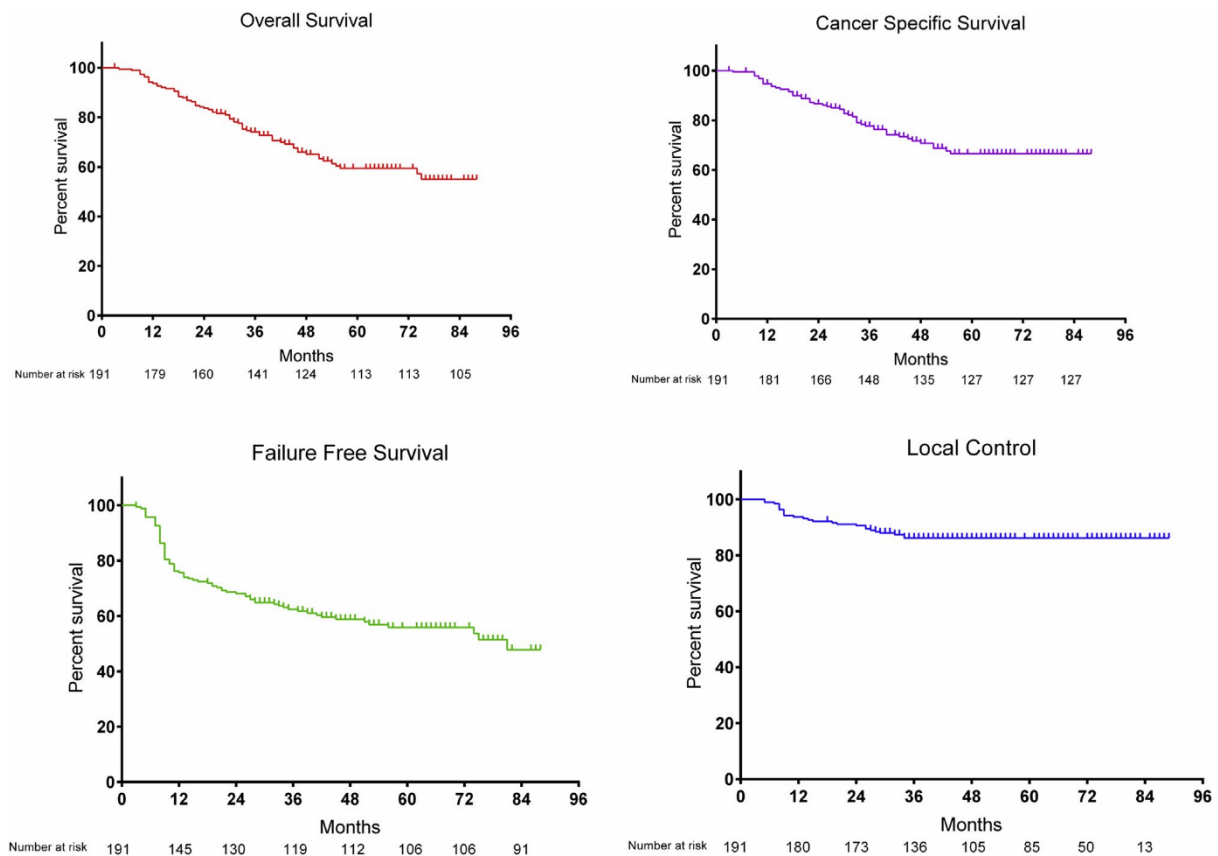


Figure 6.2 Kaplan-Meier estimates for overall survival, cancer-specific survival, failure-free survival, and local control for 191 patients.

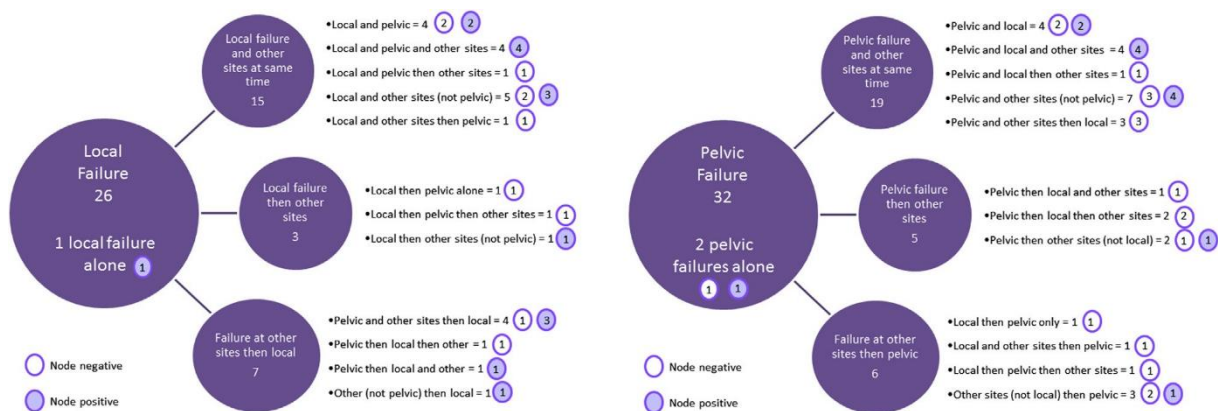


Figure 6.3 Patterns of failure and nodal status at presentation

The small spheres indicate the number of patients who were node positive and node negative at presentation. Left panel, local failure; right panel, pelvic failure.

Table 6.4 Incidence of late toxicity at bladder rectum and vaginal mucosa

Total doses from EBRT and brachytherapy expressed in EQD2 at corresponding ICRU 38 bladder and rectal reference points and vaginal mucosal reference point

	# of Grade 0	# of Grade 1	# of Grade 2	# of Grade 3	# of Grade 4
N = 191	(%)	(%)	(%)	(%)	(%)
Reference point	mean (SD) Gy <sub>3</sub>	mean (SD) Gy <sub>3</sub>	mean (SD) Gy <sub>3</sub>	mean (SD) Gy <sub>3</sub>	mean (SD) Gy <sub>3</sub>
Bladder	142 (74)	39 (20)	7 (4)	2 (1)	1 (0.5)
	53.9 (9.26)	52.86 (13.21)	58 (10.08)	48.80 (2.54)	84
Rectum	133 (70)	43 (23)	9 (5)	5 (3)	1 (0.5)
	56.2 (8.96)	56.1 (6.46)	57.5 (7.95)	53.90 (5.13)	50.9
Vaginal mucosa	68 (36)	37 (19)	20 (10)	2 (1)	2 (1)
	121.3 (16.99)	119.7 (16.31)	121.5 (19.27)	139.5 (6.36)	130 (9.89)

SD = standard deviation; BT = brachytherapy; EBRT = external beam radiotherapy; EQD2 = equivalent to doses in 2 Gy; ICRU = International Commission of Radiation Units.

Table 6.5 Toxicity per individual patient

Doses at Point A, target volume and corresponding ICRU 38 bladder and rectal reference points and vaginal mucosal reference point

Date of diagnosis	FIGO stage	Minimum		ICRU38		ICRU38		Vaginal	Vaginal
		Point A	iso-coverage	Bladder	Bladder	Bowel	Rectal	mucosa	mucosa
		Gy <sub>10</sub>	of target Gy <sub>10</sub>	toxicity	dose Gy <sub>3</sub>	toxicity	dose Gy <sub>3</sub>	toxicity Gy <sub>3</sub>	dose Gy <sub>3</sub>
May-07	2B	71.3	79.3	0	49	3	54	0	na
Jul-07	3B	64	80	0	68	0	69	3	na
Sep-07	1B	65.3	80	3	47	1	51	1	na
Oct-07	1B	52.7	69.8	0	47.3	3	49.2	0	na
Jun-09	1B	72.8	80	1	53.6	4	57.4	0	128
Nov-09	1B	58.1	79.7	0	72.7	3	50.1	0	125
Feb-10	3B	85	80	0	48	3	54	0	153
Feb-10	2B	71.3	80	0	59	1	61	3	135
Apr-11	4A	63.7	49	4	84	0	65	4	120
Jun-11	1B	114	68.6	3	50.6	3	62.2	2	134.7
Jul-11	2B	60.1	78	0	59	0	54.4	3	144
Oct-11	2B	71.4	83.9	0	54.4	0	56.8	4	137

FIGO = Federation of Gynecology and Obstetrics ICRU = International Commission of Radiation Units

and sparing of normal tissues and structures. This protocol was conceived in response to existing infrastructure limitations and logistics. The lack of access to daily MRI and limited access to the brachytherapy suite have led to an innovative and accessible protocol that is now seen as desirable and advantageous. Similar developments have evolved elsewhere with Simpson et al.<sup>236</sup> finding CT-based planning with guidance from a single MRI offering a good alternative for practices with limited access to MRI in the developed world. We hypothesize that ultrasound-based planning with guidance from a single MRI may find wider applicability in both developing and advanced parts of the world.

The greatest differences in clinical outcomes between this study and the series listed in Table 6.1 were seen in the local control rates. Local control in our patients was 86% at 3 and 5 years for a mean target dose of 79.7 Gy<sub>10</sub>. These results are similar to a study reporting on clinical results from an earlier period when ultrasound use was evolving<sup>66</sup>. The definitive dose to achieve optimal local control has not been determined, although work from the Vienna group has suggested that high-risk clinical target volume D90 doses in excess of 87 Gy are required to reach local control rates in excess of 95%<sup>63</sup>. Potter et al.<sup>67</sup> reported the highest 3-year local control at 95% with a mean target dose of 93 Gy<sub>10</sub>. Similarly, Lindegaard et al.<sup>226</sup> and Choong et al.<sup>233</sup> also reported 3-year local control rates and mean target doses of 91% and 91.4% and 92 and 96.5 Gy, respectively. However, equally good local control was demonstrated by Nomden et al.<sup>225</sup>, Rijkmans et al.<sup>227</sup>, Gill et al.<sup>232</sup>, and Sturdza et al.<sup>231</sup> while delivering lower mean target doses of 81-84 Gy<sub>10</sub>.

Many of the groups discussed above achieved the higher target doses by using intracavitary applicators modified to accommodate interstitial needles. These hybrid applicators helped cover bulky and/or asymmetric disease not adequately covered with intracavitary applicators

alone. The use of these applicators ranged from 5% to 44% of patients. Although we see a need for improved applicator geometry, the rate of use seems high in some series. Twenty-six (13.6%) patients failed locally in our series. The mean target volume dose in these patients was 80.1 Gy<sub>10</sub> and ranged from 49 to 84 Gy<sub>10</sub>. Although not all of these patients had bulky or asymmetric disease, we do recognize that it can be difficult to cover such disease satisfactorily with intracavitary applicators alone and have purchased hybrid applicators for future use. Greater flexibility in applicator geometry may enable us to better conform dose in these patients in the future.

Grade 3 and 4 toxicity was limited to 12 patients in this series (crude rate of 6%), and this compares well to the other image-guided series listed in Table 6.1. A feature of this study was the use of ultrasound verification at each insertion. The applicator position was optimized within the uterus and confirmed minutes before treatment. This verification in combination with conformal brachytherapy minimizes uncertainties encountered when patients undergo multiple transfers from theatre to imaging to treatment.

This protocol combines 2D and 3D imaging modalities. At present, it is not possible to produce 3D metrics for OAR using ultrasound. It is possible to report ICRU report 38 reference points using ultrasound and this was done. It is noted that the Grade 3 and 4 toxicities reported are not related to particularly high doses at the ICRU 38 reference points. The protocol calls for treatment with a full bladder, and we can see on both ultrasound and MRI that the ICRU 38 bladder point underestimates the dose to bladder. Although the ICRU 38 rectal point is generally more closely correlated with maximum rectal doses, it too is limited. Similarly, it is possible to accurately calculate a point dose on the vaginal mucosa with ultrasound, but such an assessment does not take into account the effect of volume of irradiated tissue. These are

recognized limitations of using 2D imaging. However, by incorporating 2D ultrasound at the time of each insertion and using it to check and optimize the tandem position within the uterus and check and confirm the target dimensions around the tandem, doses to surrounding OAR are minimized. The low toxicity rates in this study bear this out. Ultrasound use at each insertion does allow for adaptive planning when changes to the target dimension are noted. A previous study highlighted the rate of replanning based on changes to the target dimensions measured with ultrasound for this series of patients as being 5.7%<sup>237</sup>.

There are limitations in this study. The study only contains data from a single institution. Although the study is retrospective in nature, all data were prospectively collected in the Gynaecological Unit data base, ensuring high-quality data not subject to the usual biases inherent in such studies. Rates of toxicity and recurrence were meticulously recorded prospectively. It is recognized that this study is not a 3D study and as such does not report 3D metrics. The message is that safe and effective treatment can be achieved using accessible imaging modalities and an innovative approach.

## 6.5 Conclusion

The use of soft tissue imaging helps to verify both the applicator position and the target volume when conforming isolines to a target volume. We have found using ultrasound to guide, plan, and verify each intracavitary brachytherapy treatment has produced safe and effective treatment for patients with locally advanced cervix cancer. Ultrasound provides good organ definition and is an economical and accessible imaging modality especially for those with limited access to more complex technologies such as CT and MR imaging.

# Chapter 7

## Reproducibility and interoperator reliability of obtaining images and measurements of the cervix and uterus with brachytherapy treatment applicators *in situ* using transabdominal ultrasound

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This chapter is an exact copy of the journal paper referenced on the previous page except the figure, table and reference numbers have been modified for the purpose of this thesis. Supplementary figures and tables have been included as part of the main text.

As described in chapters 4, 5, and 6, ultrasound is used extensively in our practice. We are cognisant that it is a user dependent imaging modality. We have sought to provide training and education to the RT sonographers to standardise use of ultrasound. The study described in this chapter was undertaken to validate the use of ultrasound in our department, and illustrate that good reproducibility and reliability can be obtained with robust protocols, training and education. We have followed the guidelines for reporting reliability and agreement studies (GRRAS) as described by Kottner et al.<sup>240</sup> and analysed our data with relevant statistical tests. This chapter is an important addition to the brachytherapy world as it emphasises training, education and protocol requirements when introducing new imaging modalities. It is hoped this work may help dissipate some of the doubts associated with using ultrasound and encourage wider use in limited resource settings.



# Abstract

**Purpose:** To validate interoperator reliability of brachytherapy radiation therapists (RTs) in obtaining an ultrasound image and measuring the cervix and uterine dimensions using transabdominal ultrasound.

**Methods and materials:** Patients who underwent MRI with applicators *in situ* after the first insertion were included in the study. Imaging was performed by three RTs (RT1, RT2, and RT3) with varying degrees of ultrasound experience. All RTs were required to obtain a longitudinal planning image depicting the applicator in the uterine canal and measure the cervix and uterus. The MRI scan, taken one hour after the ultrasound, was used as the reference standard against which all measurements were compared. Measurements were analysed with intraclass correlation coefficient and Bland-Altman plots.

**Results:** All RTs were able to obtain a suitable longitudinal image for each patient in the study. Mean differences (SD) between MRI and ultrasound measurements obtained by RTs ranged from 3.5 (3.6) to 4.4 (4.23) mm and 0 (3.0) to 0.9 (2.5) mm on the anterior and posterior surface of the cervix, respectively. Intraclass correlation coefficient for absolute agreement between MRI and RTs was >0.9 for all posterior measurement points in the cervix and ranged from 0.41 to 0.92 on the anterior surface. Measurements were not statistically different between RTs at any measurement point.

**Conclusions:** RTs with variable training attained high levels of interoperator reliability when using transabdominal ultrasound to obtain images and measurements of the uterus and cervix with brachytherapy applicators *in situ*. Access to training and use of a well-defined protocol assist in achieving these high levels of reliability.

## 7.1 Introduction

The use of ultrasound to guide applicator insertion in the treatment of cervix cancer with brachytherapy is increasing around the world. Patterns of care studies indicate that ultrasound is available in more than 50% of radiotherapy departments in the United States, Canada and parts of Europe, and to a lesser extent Latin America<sup>69,71,73,74</sup>. In a recent survey of Australia and New Zealand, ultrasound was identified as being used to guide applicator insertion in 74% of brachytherapy departments<sup>241</sup>. Although ultrasound is heralded for its ready access and relative low cost, a number of factors that enhance its appeal also confound use. Ultrasound is perceived as being easy to use. It is possible to obtain an image immediately if a transducer is placed against the skin. However, understanding that image can be difficult and lack of understanding can quickly dissuade use. Because of easy availability and portability, ultrasound use in radiotherapy is often delegated to radiation oncologists (ROs) and radiation therapists (RTs) who have no formal education or training in its use<sup>242</sup>. Ultrasound is an operator-dependent imaging modality so it is important to ensure adequate education, training, and scanning protocols are provided to optimize use and limit interoperator variability<sup>40,243,244</sup>. In our department, ultrasound is used to guide insertion of brachytherapy applicators into the uterine canal, verify applicator placement, verify cervix and uterine dimensions, and plan treatment. RTs primarily perform the ultrasound imaging and, together with ROs, view and interpret the images for applicator insertion and planning decisions. To adequately perform and interpret ultrasound in brachytherapy, users are required to be familiar with anatomy, ultrasound theory and practice, and applicator construction, Figure 7.1.

These requirements are built into a detailed protocol that is followed at our institution, Table 7.1. As part of our quality assurance program, we validated the reproducibility and

interoperator reliability of brachytherapy RTs in obtaining the ultrasound image and measuring the cervix and uterine dimensions using transabdominal ultrasound.

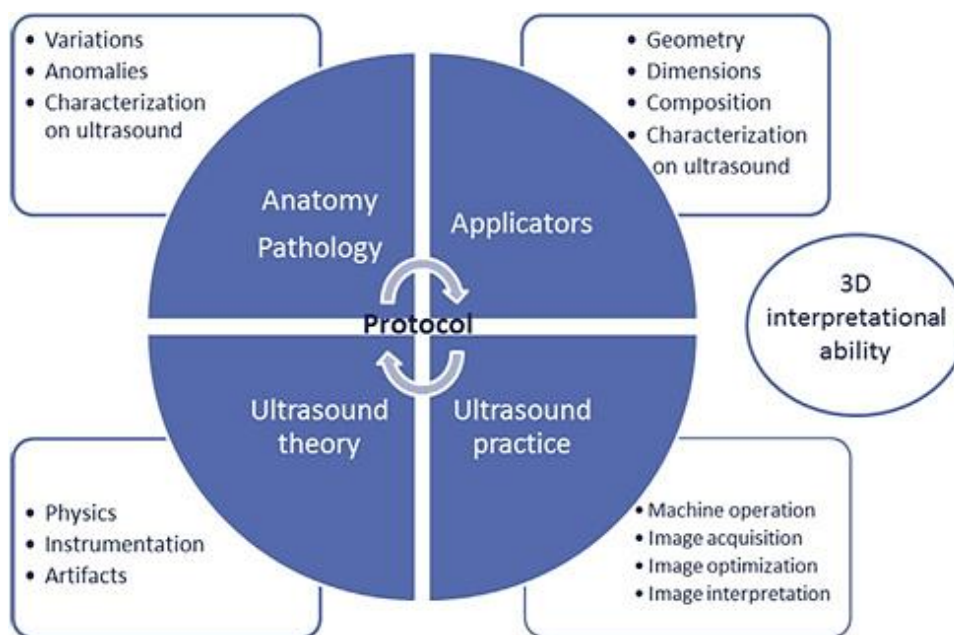


Figure 7.1 Knowledge requirements for using transabdominal ultrasound in brachytherapy.

Source: Peter MacCallum Cancer Centre

## 7.2 Methods and materials

### Study population

The study consisted of patients who presented for curative intent brachytherapy for cervix cancer between May 2013 and October 2013 and who underwent MRI with applicators in situ after the first insertion. Data obtained from patients were part of a hospital-based quality assurance program and audit.

Table 7.1 Protocol for use of transabdominal ultrasound

During gynaecological brachytherapy

Protocol elements
Patient preparation: fasting, empty bowel, bladder filling
Sufficient coupling medium (gel) used
Bladder covers fundus of uterus
Bladder does not compress anterior uterine wall
Volume scan undertaken in longitudinal and transverse directions to confirm location of cervix uterus and vagina
Assess cervix, uterus, parametria, adnexa
Uterus, cervix and vagina identified on longitudinal and transverse view
Uterine canal identified on longitudinal view
Applicator inserted under ultrasound guidance, watched on screen
Applicator identified on longitudinal and transverse views
Patient placed in treatment position
Applicator position optimized in uterus and cervix on longitudinal and transverse views
Ovoid separation confirmed on transverse view
Applicator imaged perpendicular to ultrasound beam
Whole applicator viewed in longitudinal view
Applicator length confirmed with digital callipers
Anterior and posterior cervix and uterine walls visible
Anterior and posterior wall of cervix and uterus measured in direction of ultrasound propagation
Image acquisition and measurements repeated to confirm orientation and dimensions
Image optimized throughout procedure with respect to frequency, depth, focus, gain, TGC, probe position, probe pressure
Gel refreshed throughout procedure
Images periodically saved and appropriately annotated throughout procedure
All measurements saved on image, recorded on hard copy and compared to any previous MRI & ultrasound measurements
All MRI and ultrasound measurements entered into gynae unit database for assessment, verification, audit
Ongoing credentialing of RT sonographers, peer to peer review

TGC = time gain compensation; RT = radiation therapist

## Interoperator reliability and reproducibility analysis

Three RT sonographers were recruited to participate in the study. All three had to be present at the first brachytherapy insertion to obtain images and measurements on the same patients in the same clinical setting. RTs were designated as RT1, RT2, or RT3. RT1 had postgraduate qualifications in ultrasound and more than 10 years clinical experience in brachytherapy; RT2 received on the job training in ultrasound and had more than 7 years clinical experience in brachytherapy; RT3 attended a weekend workshop on ultrasound use in brachytherapy and had 10 months clinical experience in brachytherapy at the time of the study.

All scans were performed using the Flex Focus 400 ultrasound unit and a transabdominal curved array transducer 8820e, 2.5-6 MHz (BK Medical, Denmark). Only intracavitary applicators were used in this study, standard CT/MR tandem and ovoids and Vaginal CT/MR tandem and cylinder (Elekta, Nucletron, Veenendaal, The Netherlands).

## Imaging protocol

Patients underwent spinal anaesthesia and were placed in the semi-lithotomy position. An 18-20 French three-way urinary catheter was inserted into the bladder and connected to a double bag spike disposable urology set and a 500-ml bag of saline (0.9% sodium chloride intravenous infusion BP Viaflex). The RT sonographer commenced ultrasound scanning and watched the screen as the bladder filled. The full bladder acts as an acoustic window into the pelvis. Once the bladder covered the superior border of the uterus, the saline bag was clamped. The RT sonographer volume scanned the pelvis in the longitudinal and transverse orientations to identify the uterus and cervix. Once identified, the RT then focused on identifying the uterine canal in the longitudinal plane of the uterus to assist the RO to insert the intrauterine applicator.

The applicator geometry and dimensions are known and so act as a fiducial marker and calibration device within the image. Vaginal applicators were inserted under direct vision. After the applicators were inserted, the RT confirmed optimal placement in the uterus and vagina with ultrasound. The patient's legs were lowered to lie flat on the bed, which is the treatment position, and the ultrasound scans were repeated. The position of the brachytherapy applicator was optimized and confirmed in the longitudinal and transverse planes. The applicator was secured in position using perineal sutures. A longitudinal planning image was then taken which had to identify the whole applicator and the anterior and posterior borders of the cervix and uterus. The position of the transducer was manipulated such that the whole applicator appeared across the ultrasound screen. The length of the intrauterine applicator was measured with digital calipers available on the ultrasound machine to confirm that the true longitudinal plane of the applicator and uterus was being viewed. Orientating the applicator and uterus across the screen ensures that measurements to the anterior and posterior surface of the uterus and cervix are made in the direction of sound propagation<sup>79</sup>. Uterine and cervix dimensions were measured and recorded on the ultrasound image along with the initials of the RT, Figure 7.2. The remaining RTs then repeated image acquisition and measurements as described previously. All RTs were blinded to each other's images and measurements.

## Reference standard for ultrasound images

Ultrasound images and measurements were compared with MRI images taken an hour after the ultrasound images were obtained. The MRI images were also taken with brachytherapy applicators *in situ*. MR images were taken with the patient-positioned supine and head first in the scanner (3T Magnetom Trio, Siemens, Munich, Germany). A body coil was placed over the pelvic area, and localizer and T2 haste images were obtained. Images using Turbo Spin

Echo T2 axial (to bed) and parasagittal and paracoronal to the intrauterine applicator were taken with 3 to 4 mm slice thickness and 0 to 1 mm slice gap. The typical field of view covered from 3.0 cm above the uterus to the perineum, and scan time was approximately 20 minutes. Measurements from the applicator to the anterior and posterior surface of the cervix and uterus were made on a picture archiving and communication system (Syngo version 35, Siemens, Munich, Germany) <sup>139</sup>

## Statistical analyses

Graphpad Prism, version 6.02 for windows (Graphpad Software, La Jolla, CA), was used to test for normality and mean, SD, and standard error of mean and to calculate Bland-Altman plots with 95% confidence interval. Multiple comparisons (MRI as control vs. RT1, RT2, and RT3 measurements) using repeated-measures two-way analysis of variance with a Dunnet's post hoc test were performed. Multiple comparisons (RT1 vs. RT2 vs. RT3) using repeated-measures two-way analysis of variance and Tukey's post hoc test were also calculated. Intraclass correlation coefficient (ICC) was used to compare reliability between MRI and RT sonographers. Stata (version 12.1 for Mac, StataCorp LP, College Station, TX) was used to calculate ICC.

The ICC is a descriptive statistic used to assess agreement of quantitative measurements in the sense of consistency and conformity. Consistency refers to interoperator reproducibility of measurement scales, and conformity refers to agreement of a first measurement with a reference that is well established<sup>245</sup>. In this study, MRI was used as the reference. Reliability was determined using ICC (3,1) using a two-way mixed-effects model as described by Shrout and Fleiss<sup>246</sup>. This formula was used as we were interested in assessing the reliability of

incumbent RTs who will continue performing ultrasound in our institution. ICCs are reported in terms of consistent and absolute agreement per McGraw and Wong<sup>247</sup>, and on a scale of 0-1, with zero meaning all the variability in measurements is due to measurement error and one

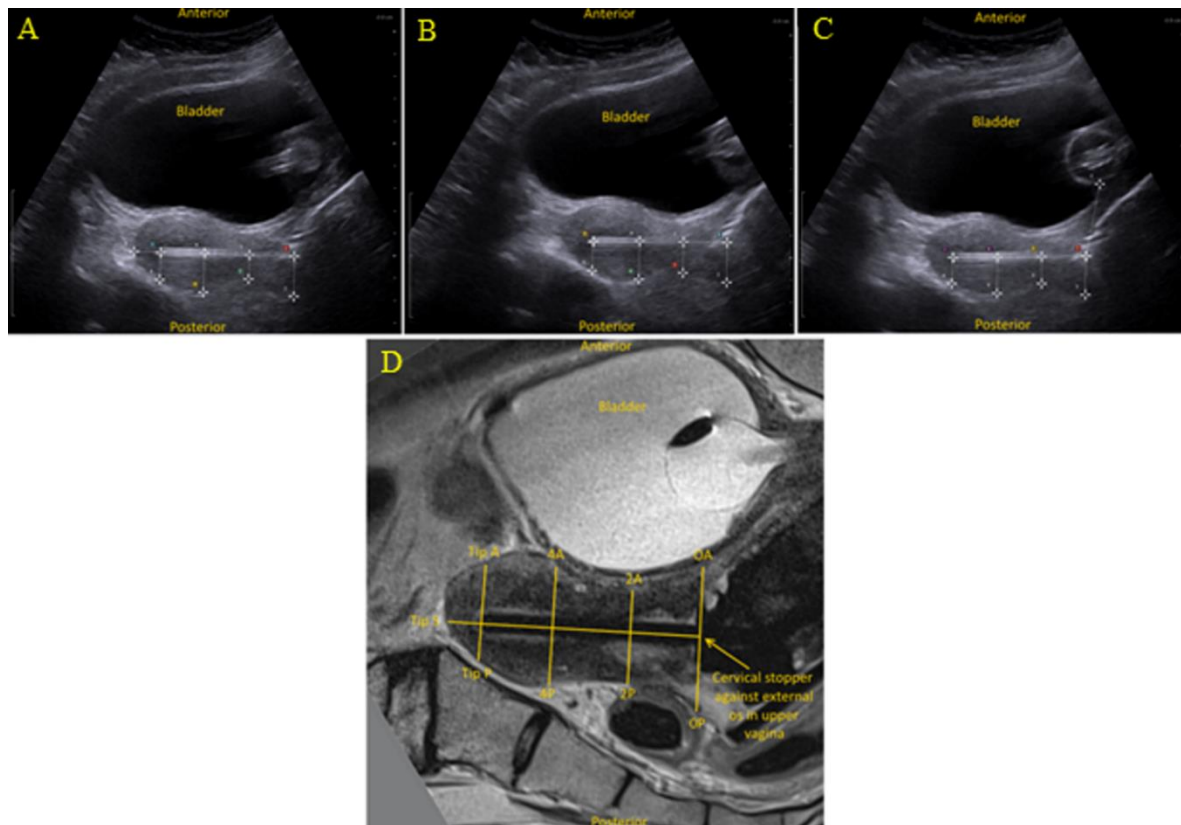


Figure 7.2 Nomenclature for measurement points on longitudinal ultrasound views

- A. Image taken by RT1
- B. Image taken by RT2
- C. Image taken by RT3
- D. Longitudinal MRI view

The cervical stopper is 0, 0 and abuts the external os in the vaginal fornices. Measurements were taken at the anterior and posterior surface of the cervix and uterus perpendicular to the applicator at the cervical stopper, 0A and 0P; 2.0 cm along the applicator, 2A and 2P; 4.0 cm along the applicator, 4A and 4P; and at the tip of the applicator, Tip A and Tip P.

RT = radiation therapist

Source: Peter MacCallum Cancer Centre



corresponding to no measurement error<sup>248</sup>. In this study, an ICC < 0.4 represents poor reliability, values above 0.75 represent excellent reliability, and values between 0.4 and 0.75 represent fair to good reliability<sup>246</sup>.

Bland-Altman plots are graphical representations of data that illustrate the degree of agreement between the different imaging modalities (MRI and ultrasound) used to measure the cervix and uterine dimensions. The plots also indicate any systematic biases between the modalities<sup>141,249</sup>.

### 7.3 Results

Thirteen patients commenced treatment in this period, one patient was excluded because she was unable to tolerate the MRI scan. Data from 12 patients were therefore included in this study. Patient demographic characteristics are shown in Table 7.2.

Ultrasound images were obtained, optimized, and presented according to the protocol. All images displayed the whole applicator with length confirmed by digital calipers. The posterior surface of the uterus and cervix was also visible. The average time taken to perform each ultrasound imaging study was 6.5 minutes (range, 3 - 9 minutes). Each MRI scan takes 15 - 20 minutes. RTs obtained suitable images for all patients regardless of patient body mass index (BMI).

The means ( $\pm$ SD) of measurements taken with MRI and ultrasound are shown in Figure 7.3. Overall, there was a 3 - 5 mm discrepancy between MRI and ultrasound measurements on the anterior surface of the cervix and uterus ( $p = 0.0007$ ).

Table 7.2 Patient demographic characteristics

Characteristic	
Age (years)	
Median	48
Range	25 - 77
FIGO stage, N (%)	
1	4 (33)
2	7 (58)
3	1 (8)
4	
Histology, N (%)	
Squamous Cell Carcinoma	10 (83)
Adenosquamous	2 (17)
Original Tumour volume (cm <sup>3</sup> )	
Median	51
Range	0.1 - 179
Body Mass Index	
Median	27
Range	23 - 41

FIGO = International Federation of Gynecology and Obstetrics

Measurements of the anterior cervix and uterus made on ultrasound images were less than measurements made on MRI. The mean differences between the ultrasound measurements made by RTs on the anterior surface were  $\leq 1$  mm ( $p = 0.35$ ). There was much less discrepancy between measurements made with MRI and ultrasound on the posterior surface of the uterus and cervix. Mean differences between MRI and ultrasound were  $\leq 1$  mm ( $p = 0.37$ ). Mean differences between ultrasound measurements made by RTs were also  $\leq 1$  mm ( $p = 0.33$ ).

Interobserver reliability scores for measuring the cervix and uterine dimensions were excellent between MRI and RTs using ultrasound with scores ranging from 0.595 to 0.936 for

consistency of agreement. Absolute agreement scored between 0.418 and 0.928. Scores between RTs alone were also excellent and ranged from 0.916 to 0.944 for consistency of agreement and 0.89 to 0.947 for absolute agreement, Table 7.3.

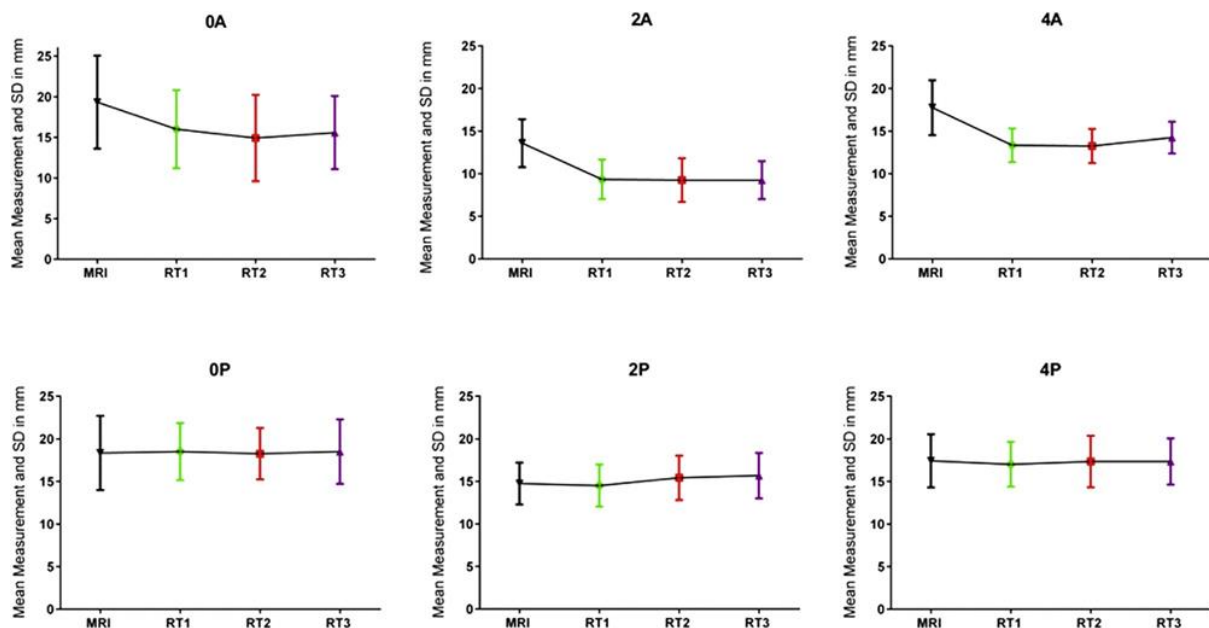


Figure 7.3 Mean measurements ( $\pm$ SD) of anterior and posterior cervix and uterus dimensions made with MRI and ultrasound at each measurement point

A summary of the Bland-Altman plots for interobserver agreement is shown in Figure 7.4. These summary plots show the mean differences and 95% confidence interval between measurements obtained with MRI and ultrasound. A clinically relevant range of differences between MRI and ultrasound measurements was established in an earlier study<sup>139</sup>. These differences were set at 3 mm for the cervix and 5 mm for the uterus. The anterior cervix measurements were just outside the cut-off of 3 mm. This is probably due to the small sample, as we did not see such results in a larger study of 192 patients performed earlier<sup>139</sup>.

Table 7.3 Intraclass correlation coefficients for interoperator reliability  
in measuring the dimensions of the cervix and uterus

		Consistency of agreement		Absolute agreement	
		Correlation between Individual measurements	Correlations between average measurements	Absolute agreement between individual measurements	Absolute agreement between average measurements
0A	MRI + 3 RT's	0.7845	0.9357	0.694	0.9007
	3 RT's	0.8499	0.9444	0.8499	0.9444
0P	MRI + 3 RT's	0.7471	0.9219	0.7623	0.9276
	3 RT's	0.7968	0.9216	0.809	0.9271
2A	MRI + 3 RT's	0.7287	0.9148	0.4219	0.7448
	3 RT's	0.8384	0.9396	0.8495	0.9442
2P	MRI + 3 RT's	0.7853	0.936	0.7637	0.9282
	3 RT's	0.8349	0.9381	0.8007	0.9233
4A	MRI + 3 RT's	0.2694	0.5959	0.1527	0.4189
	3 RT's	0.7849	0.9163	0.7382	0.8943
4P	MRI + 3 RT's	0.729	0.9149	0.7427	0.9203
	3 RT's	0.8497	0.9443	0.8563	0.947
Tip A	MRI + 3 RT's	0.5633	0.8376	0.5315	0.8194
	3 RT's	0.7315	0.891	0.7149	0.8826
Tip P	MRI + 3 RT's	0.7439	0.9207	0.7442	0.9208
	3 RT's	0.9353	0.9806	0.9353	0.9774
Tip S	MRI + 3 RT's	0.92	0.9787	0.9007	0.9731
	3 RT's	0.9764	0.992	0.9773	0.9923

RT = radiation therapist; CI = confidence interval; ICC = intraclass correlation coefficient.

Note. ICC < 0.4 = poor reliability, ICC > 0.4 and < 0.75 = fair-to-good reliability, ICC > 0.75 excellent reliability<sup>248</sup>

## 7.4 Discussion

This study has shown that RTs with variable training and experience were able to obtain consistent and reliable images and measurements of the cervix and uterus with brachytherapy applicators *in situ* using transabdominal ultrasound. As ultrasound is increasingly relied on to guide and optimize brachytherapy applicator placement, it is imperative that there is consistency and accuracy in its use. In our gynecologic brachytherapy program, ultrasound was

initially performed by diagnostic sonographers but as reliance on ultrasound grew the time commitment became too onerous for the sonographers. RTs started to undertake the scans with some preliminary training by the diagnostic sonographers. In an effort to formalize and

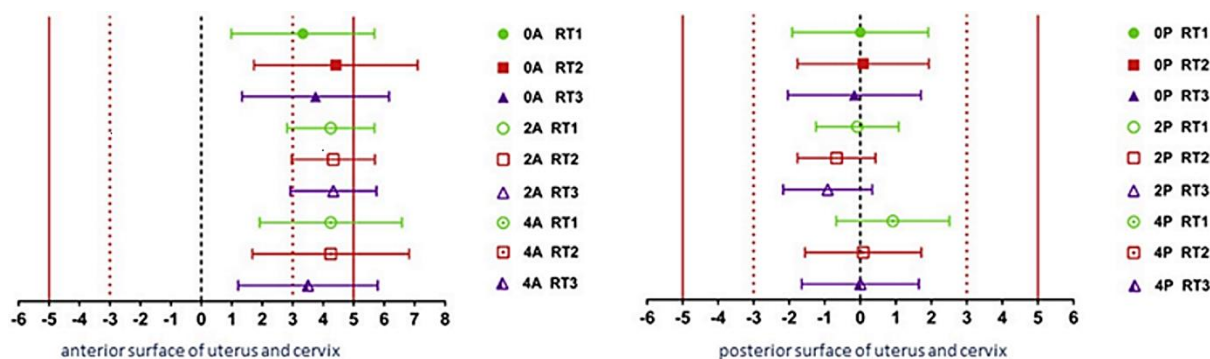


Figure 7.4 Summary of Bland-Altman plots

Means of differences between MRI and RT measurements made with ultrasound at each measurement point and 95% CI limits of mean differences shown in relation to clinically relevant cutoff values at  $\pm 3$  mm (cervix cutoff; dotted vertical lines) and  $\pm 5$  mm (uterus cutoff; solid vertical lines).

RT = radiation therapist; CI = confidence interval.

credential RT use of ultrasound, RT1 undertook a university-based post-graduate certificate in medical sonography. This course was specifically tailored to RT use of ultrasound for male and female pelvic brachytherapy. RT1 then trained other RTs during clinical sessions. RT2 undertook this training while “on the job.” To improve efficiency and fast track competency, a short training course was developed by RT1 with an Australian-based ultrasound school to give RTs the opportunity to learn in a nonclinical setting. This course covers basic ultrasound physics, “knobology,” scan techniques, and extensive scanning of live models over a 2-day period. The course has proven invaluable in enabling an undiluted transfer of knowledge, with

its most attractive feature being the opportunity to learn and practice scanning in a nonclinical setting. RT3 undertook this training course.

Competent use of ultrasound in brachytherapy relies on four main factors: understanding of ultrasound physics; good knowledge of anatomy and pathology; good knowledge of applicator geometry, dimensions, and composition; and transducer skills. RTs involved in this study had good anatomical and applicator knowledge, as these are prerequisites for working in brachytherapy. Transducer skills have to be developed through applying ultrasound physics, practicing scanning under guidance of a trained sonographer and through scanning a wide range of patient types<sup>79</sup>. A strength of this study was that it was conducted under clinical conditions with all the attendant pressures usually present during routine work. RTs had to scan all patients, the patients were prepared according to protocol, and scans had to be completed in a defined period.

RTs routinely work with 3D image data sets that combine the applicator and anatomy and so have an opportunity to spatially conceptualize the applicator and anatomy. We think this greatly assists in their understanding of ultrasound anatomy and the ability to perform ultrasound scans. Vollman et al. undertook a study using fusion of MRI with ultrasound images to assess medical students' ability to understand ultrasound images<sup>250</sup>. This group found that knowledge of ultrasound anatomy was facilitated by pre-acquired knowledge of CT and MRI anatomy. In our department, MRI is used to assess the tumour volume before treatment and at the time of brachytherapy. RTs are very familiar with identifying anatomy on MRI data sets as most patients undergoing brachytherapy for cervix cancer undergo an MRI scan with applicators *in situ* after the first brachytherapy session. We have used MRI to validate the use of ultrasound in this study, as the multi-planar reconstructions available on MRI make it possible to view the cervix, uterus, and applicators in orthogonal planes relative to the

applicator and organs. Taking measurements in these planes ensured we were not underestimating or overestimating the true dimensions of the organs. In an exploratory study of spatial ability and student achievement in sonography, Clem et al. found a significant relationship between medical students' spatial ability scores and scanning performance scores<sup>251</sup>. We believe visualizing the applicator and anatomy on MRI assists RTs spatial awareness and helps them acquire the correct orientations using freehand ultrasound.

Another important component of our practice is the implementation of a well-defined protocol. This specifies the image quality and orientations that need to be obtained. In a reliability study of quantitative measurements of the patellar tendon obtained with ultrasound, Gellhorn and Carlson<sup>252</sup> recommend the establishment of a protocol before imaging and found high levels of interoperator reliability when measuring the patellar tendon using strict scanning protocols. A well-defined protocol ensures consistency of both image quality and scan planes presented for documentation and verification. All RTs in this study obtained the required image planes and measurements. Outside this study, the images are used to guide treatment planning and serve as a verification record of the applicator position during treatment. Hence, consistent presentation is important.

Although there were no significant differences between measurements made by RTs in this study, there was a systematic bias in the measurement of the anterior cervix and uterus between MRI and ultrasound measurements which ranged between 3 and 4 mm, particularly noticeable at measurement point 4A. We found a similar bias in two larger studies looking at the differences between MRI and ultrasound measurements although the magnitude of bias was smaller (less than 3 mm in the cervix)<sup>139,237</sup>. Every attempt is made to reproduce the scanning conditions between ultrasound and MRI for patients undergoing brachytherapy. Bladder filling

is recorded at the time of ultrasound and reproduced as closely as possible at the time of the MRI scan. The MRI scan is timed to occur while the patients are still covered by the spinal anaesthetic. If the spinal anaesthetic is wearing off, the patients can experience discomfort when the bladder is filled. In these circumstances, we try to balance patient comfort and scanning conditions to achieve the best outcome for both. A factor we cannot reproduce is the probe pressure used to obtain the ultrasound images. We surmise that bladder filling may contribute to the differences between MRI and ultrasound at measurement point 4A, but we attribute the differences at measurement points 0A and 2A to probe pressure. Exerting pressure on the probe can help dissipate bowel gas, compress abdominal fat, and improve the clarity of the image. The need for probe pressure varies from patient to patient and between sonographers. Use of probe pressure is a recognized strategy to improve image quality and is recommended during training<sup>79</sup>. Although recognizing the need for some probe pressure, our protocol incorporates a number of strategies to minimize it. All patients are scanned with a full bladder to displace the bowel from the uterus, affording the best possible acoustic window into the pelvis. Gel is periodically refreshed throughout the scan to minimize artifacts. RTs are trained to obtain the best possible images and then periodically reassess probe pressure during each scan to see if it can be reduced without loss of image quality.

The quality of the ultrasound images obtained was not compromised by patient body habitus. Median BMI of patients in this study was 27 (range, 23-41) which included normal; Grade 1 (BMI, 25-29.9 kg/m<sup>2</sup>) and Grade 2 (BMI, 30-39.9 kg/m<sup>2</sup>) obese patients; and morbidly obese patients (BMI  $\geq$  40 kg/m<sup>2</sup>)<sup>253</sup>. Obese patients are challenging to scan with ultrasound, but a number of strategies exist that can help optimize the image. These strategies have been developed through training and experience and include use of low frequency probes, tissue harmonics, and speckle reduction filters. Further strategies involve elevation of the pannus, use



of full bladder, adjustment of transducer position, and optimization of gain and focal zones. These are strategies similarly recommended and used in diagnostic scanning of obese patients<sup>254,255</sup>.

The high correlation between RT scans is testament to a well-defined training program that includes regular peer review. At present, the peer review is not formally documented, but this will form part of ongoing credentialing in the future. In a study to identify whether peer audit is a suitable method of assessing the diagnostic quality of gynecologic ultrasound images, Cantin et al. reviewed a number of parameters such as scope of imaging, equipment usage, image quality, and study difficulty using Likert scales and heuristics for image quality assessment. The study found that peer audit is a promising tool in maintaining and improving the quality of an ultrasound service<sup>256</sup>. Although this study found good interoperator reliability among RT sonographers with different levels of experience and training, it cannot answer an oft-asked question of “how long does it take to become an independent RT sonographer?” This is a vexed question throughout ultrasound training, as there are large differences in the learning curves for different people and different types of examinations. What has to be recognized is that the RT sonographers undertook very limited scope ultrasound training for a specific purpose. This puts their training in the realm of competency-based learning for which reliable and valid assessments have been developed. We have not used formal assessments to date, but are considering them as part of our credentialing processes. Tolsgaard et al.<sup>243</sup> developed an instrument for assessment of ultrasound operator competence, the Objective Structured Assessment of Ultrasound Skills. This group found that ultrasound competence can be assessed in a reliable and valid way using the Objective Structured Assessment of Ultrasound Skill scale and may help to determine when trainees are qualified for independent practice.

We have undertaken a number of measures to ensure continual improvements to RT sonography skills. All RTs rostered to brachytherapy now undergo the weekend training course. Practice scanning sessions on phantoms and each other are conducted out of the clinical setting when time permits, and novice RT sonographers scan all new patients under guidance of more experienced RTs. There are other strategies available that show promise in helping to facilitate scanning skills, such as use of simulators, live models, and cadavers<sup>257-259</sup>.

This study has some limitations. The number of RT sonographers is limited as ultrasound training is only provided to RTs rostered to brachytherapy. A rotation to brachytherapy typically lasts for 12-18 months, so throughput is relatively slow. Measurements were confined to patients undergoing brachytherapy with intracavitary applicators. We were unable to measure intra-observer reliability due to the time constraints of scanning patients while under anaesthetic.

## 7.5 Conclusion

Ultrasound is used in brachytherapy to guide applicator insertion, which improves the technical quality of implants and ensures accuracy of treatment. Improved technical quality and accuracy have been shown to improve local control of disease. Because of operator input, it is imperative that there is consistency and reliability in obtaining and interpreting the ultrasound image. RTs with variable training attained high levels of interoperator reliability when using transabdominal ultrasound to obtain images and measurements of the uterus and cervix with brachytherapy applicators *in situ*. Access to training and use of a well-defined protocol appears to assist in achieving these high levels of reliability. All RTs rostered to brachytherapy now undertake the specially designed training course. Training is limited in scope to meet a specific

purpose, that of identifying the cervix, uterus, and brachytherapy applicator. By focusing on these aspects, a very particular set of skills can be learnt in a short period of time. The high interoperator reliability was also based on good existing anatomical and applicator knowledge. The high interrater reliability contributes to the ongoing quality of our brachytherapy service. The findings of this study may encourage further use of ultrasound in settings where access to advanced imaging modalities is limited.



# Chapter 8

## Discussion

**B**rachytherapy has been and remains an integral component of treatment for locally advanced cervix cancer<sup>260</sup>. Development of early dosimetry systems brought structure and some measure of reproducibility for reporting treatments, but they ultimately relied on empiricism and standardised points and tables to guide dose prescription. These dosimetry systems did not relate the dose distribution from the applicators to the surrounding anatomy. In many respects gynaecological brachytherapy is undergoing a renaissance as it moves from standardised 2D x-ray based planning to individualised 3D soft tissue image based planning. Incorporating soft tissue imaging into gynaecological brachytherapy, particularly MRI, is proving to be difficult in both the developing world and parts of the developed world because of lack of resources and limited access to infrastructure. There is a crucial need for an accessible, economical and safe imaging modality that can be widely employed across many resource settings. This thesis is concerned with the introduction of such an imaging modality, ultrasound, and how it can be employed in gynaecological brachytherapy. It presents a logical development of validating ultrasound against an accepted standard imaging modality, MRI, to illustrating how ultrasound can be used to monitor, verify and adapt brachytherapy treatment for cervix cancer. This thesis concludes with clinical

outcomes achieved using this imaging modality that compare favourably to treatment protocols using more complex imaging technologies. This discussion follows the flow of the thesis and chapters are discussed in turn. In this context, the main research findings are integrated into the current scientific knowledge and implication for clinical practice is discussed (where appropriate), as well as recommendations and suggestions for future work in this field.

## 8.1 Comparison of measurements of the uterus and cervix obtained by MRI and transabdominal ultrasound

In seeking a soft tissue imaging modality that can be readily incorporated into a gynaecological brachytherapy program a number of criteria have previously been developed<sup>137</sup>, Table 8.1. These criteria were developed in reference to the infrastructure and resources used at our treatment facility.

Ideally, an imaging modality should be available for each brachytherapy insertion; it should be performed intra-procedurally, offer good organ and applicator definition, and be able to delineate residual tumour. Ultrasound fulfilled the first two points and most of the remaining criteria. Fortunately, both traditional metal and newer CT/MR compatible (plastic) applicators are able to be visualised on ultrasound as both are echogenic. The metal applicators can create large reverberation artifacts that can obscure information, while the plastic applicators are sufficiently echogenic to be identifiable in the ultrasound image whilst producing fewer artefacts. The CT/MR compatible (plastic) applicators are the most desirable to use with ultrasound. Having met most of our established criteria for use, ultrasound then needed to be validated against a recognised reference standard. There are three methods available to compare anatomical volumes such as those of the cervix and uterus. These are clinical

examination, reference imaging studies and surgical specimens. Clinical examination plays a defining role in the staging of cervix cancer but its accuracy has been frequently questioned<sup>261-263</sup>. When compared to surgical staging, clinical examination has been shown to have an error rate of 26 – 66%<sup>261,262,264</sup>. The ultimate or gold standard for determining anatomical and tumour volumes is through examination of surgical specimens. However, it is not possible to obtain histopathologic proof of tumour response during radiotherapy, so evaluation of tumour response using imaging must be relied upon during and after treatment.

Table 8.1 Imaging modality criteria in order of importance to brachytherapy protocol for imaging modalities available at our institution

	X-ray	Ultrasound	CT	PET†	MRI
Accessible for each insertion	*	*			
Ability to image intra-procedurally	*	*			
Visualise cervix uterine outline		*	*	*	*
Visualise applicator					
CT/MRI applicators available	*	*	*	*	*
Visualise surrounding organs	*§	*	*	*	*
Visualise residual tumour				*‡	*

† in conjunction with CT (PET/CT available at our institution)

§ limited – can visualise vagina with addition of radio-opaque gauze packing

can visualise part of rectum with radio-opaque contrast or applicator

can visualise bladder with radio-opaque contrast

‡ depends on threshold image intensity percentage of peak tumour intensity

## Ultrasound versus surgical specimens

There are many studies comparing ultrasound to surgical specimens to determine the accuracy of ultrasound in evaluating the size and weight of the uterus, primarily to guide the surgical approach for hysterectomy<sup>265-274</sup>. The majority of these studies used measurements of length, width and thickness of the uterus obtained from 2D ultrasound images and then applied formulas to calculate the volume and weight of the uterus. The volume and weight of the uteri were then compared to the weight of pathology specimens. All showed good correlation for uterine dimensions but there were some disagreements between uterine volumes. These disagreements were largely attributed to coarse methods of volume calculation. Correlation of ultrasound and histo-pathology was further refined by Rovio et al. who calculated uterine volume using a combination of the prolate ellipsoid and cylinder formulas<sup>271</sup>. The authors found this combination of formulae to be the most accurate means of estimating the uterine volume, finding no significant differences between actual weight and calculated weight when using these formulae. The study concluded that 2D transvaginal ultrasound gave an accurate estimate of uterine volume. Another study compared 2D and 3D ultrasound measurements of the uterus to pathology specimens in 31 patients and found two 2D calculation methods to be acceptable for clinical use<sup>272</sup>. The authors also demonstrated that these two 2D calculation methods measured the uterus with similar precision to 3D ultrasound. 3D ultrasound was found to offer better results in cases of unclear and complicated structures. A further study compared *in vivo* imaging using transvaginal ultrasound and MRI to surgico-pathologic findings of tumour dimension, tumour volume, parametrial invasion and vaginal extension in 46 patients<sup>274</sup>. Thirty three patients had early stage disease and 13 had advanced stage disease. There was strong correlation between the performance of MRI and transvaginal ultrasound in the assessment of tumour volume, ( $p < 0.0001$ ). There was no significant difference between the performance of MRI and transvaginal ultrasound in the assessment of stromal or parametrial



invasion. In other studies employing transvaginal ultrasound alone, accuracy rates of 90-92% agreement between imaging and pathology have been reported<sup>193,275,276</sup>. While these studies were primarily conducted to assess ultrasound use for guiding surgical decisions the results illustrate good agreement between ultrasound and anatomic-pathology. The results indicate that ultrasound accurately identifies the cervix and uterus in both early and advanced cancer patients and so by extension can also be used to identify the cervix and uterus to guide brachytherapy treatment. In our institution, transvaginal ultrasound is used at the first brachytherapy insertion to assess the response of tumour to EBRT. It cannot be used during applicator insertion to verify applicator placement or plan brachytherapy treatment by virtue of the probe being in the space the applicator must transgress. Transabdominal ultrasound is used to verify applicator placement and plan treatment.

### MRI versus surgical specimens

There are a number of studies comparing MRI to surgical specimens<sup>263,264,277-283</sup>. These studies were conducted on hysterectomies from patients who were suitable for surgery and hence had early stage cancer of the cervix. The studies looked at the size of the actual anatomical organ (the cervix), or the extent and location of tumour (histopathology). All of the studies confirmed high correlations of tumour volumes between *in vivo* MRI, MRI of surgical specimens and morphometry in the order of 80 – 88%. Most discrepancies between surgical staging and MRI were not statistically significant and were attributed to oedema around the cervix *in situ* and/or shrinkage of the specimen after fixation. These studies have paved the way for MRI to be accepted as the gold standard against which to measure the cervix in the absence of surgical specimens.

## Ultrasound and MRI versus surgical specimens

A current review of the literature illustrates that ultrasound is as accurate as MRI in assessing the uterine dimensions and on occasion has been shown to be more accurate than MRI, particularly in assessment of tumour size. In a study comparing diagnostic accuracy of ultrasound and MRI in the pre-operative assessment of early-stage cervical cancer, transvaginal and transrectal ultrasound were significantly better in assessing residual tumour ( $p<0.001$ ) and parametrial invasion ( $p<0.001$ ) than MRI<sup>159</sup>. Similarly, transrectal ultrasound correlated better with pathological tumour volumetry than MRI when assessing tumour response after neoadjuvant chemotherapy in patients with cervix cancer<sup>284</sup>. While ultrasound has been shown to accurately measure dimensions of the uterus, volume calculations have relied on formulas that approximate ellipsoids rather than true volume. This disadvantage may well be overcome by the use of more robust calculation methods as described by Rovio et al. or through use of 3D ultrasound in the future. In gynaecological brachytherapy it is important to identify the uterus and cervix, which constitutes the target volume. This enables accurate assessment of iso-coverage. Ultrasound has been proven to accurately assess uterine and cervix dimensions and is thus suitable to use in place of MRI.

In chapter 4 measurements of the uterus and cervix obtained with transabdominal ultrasound were compared to those obtained with MRI. Measurements reported in the study were confined to the longitudinal view of the uterus and cervix with the treatment applicator *in situ*<sup>139</sup>. This projection gives a view of the whole uterus and cervix and surrounding anatomy allowing changes in consistency, size and organ outline to be easily seen<sup>285</sup>. Identifying the anterior surface of the uterus and cervix was not difficult due to the close apposition of the full bladder. There was, however, an inherent bias found in the measurements of the anterior cervix and uterus. Ultrasound systematically underestimated the thickness of the anterior wall by 2 – 3

mm in the cervix and 2 – 4 mm in the uterine corpus. This was attributed largely to transducer pressure which compressed the full bladder and anterior uterine wall. While every effort was made to reproduce bladder filling during the MR scan, transducer pressure could not be simulated. So while the planning conditions were slightly different, the MRI scan more accurately represented actual treatment conditions as the patients were treated with a full bladder and without transducer pressure. (Provided there is no applicator movement during transfer to the MRI unit.) The bias in anterior measurements has to be taken into consideration in our environment, as the longitudinal ultrasound view is used to plan the first fraction of brachytherapy prior to seeing the MR scan. To ensure coverage of the posterior cervix overtreatment of the anterior cervix is accepted. This involves conscientiously accepting ingress of isodose lines into the bladder on ultrasound. While not a blanket rule, the magnitude of allowable ingress is to permit the 110 – 120% isoline to cover the bladder mucosa. This ensures the whole cervix is covered by 100% during treatment. Later examination on MRI has confirmed these decisions, as do the clinical outcomes detailed in chapter 7 which reported only 1.6% of patients in our study experienced grade 3 or greater genitourinary toxicity<sup>286</sup>. It is acknowledged that the ability to perform this procedure with high accuracy is due to experience gained over a number of years.

The measurements of the posterior wall thickness of the cervix and uterus obtained with transabdominal ultrasound showed much greater agreement with MRI measurements than the anterior wall thicknesses. Mean differences between ultrasound and MRI were less than 1 mm. These measurements were taken with the applicator *in situ*. It is vitally important to achieve this level of accuracy. The applicator acts as a fiducial marker, its length is known. Having verified the applicator position in the transverse views, identification of the whole applicator on the longitudinal view confirms correct visualisation of the longitudinal plane of the uterus

and cervix. This in turn leads to correct measurement of the posterior thickness of the cervix. In a study comparing measurements of the cervix made with transrectal ultrasound and MRI, the anterior border of the cervix could not be identified in the three patients studied with the applicator *in situ*<sup>163</sup>. In a further study comparing TRUS, MRI and CT for delineating the brachytherapy target volume the same authors again found difficulty in identifying the anterior border of the target volume with the applicator *in situ* on TRUS imaging<sup>189</sup>. The authors similarly found it difficult to identify the posterior bladder wall and the uterine corpus. Inability to accurately identify any border of the cervix severely compromises the ability to perform conformal brachytherapy planning. Transrectal ultrasound appears to perform well in assessing tumour response to EBRT but may not be as useful as transabdominal ultrasound for planning treatment.

## Defining and delineating the brachytherapy target volume

The purpose of identifying the cervix and uterus is to define and delineate the target volume that will be treated with brachytherapy. The definition of the target volume used for planning with ultrasound was developed independently from GEC-ESTRO<sup>136</sup>. While there are some notable differences in approach, there are also some significant similarities Table 8.2.

A notable difference is the concept of the intermediate risk clinical target volume (IRCTV). This is predominantly used by French schools of radiotherapy for treatment planning and evaluation<sup>65</sup>. Other centres that record IRCTV doses do so retrospectively for reporting purposes only<sup>287,288</sup>.

The main difference between the definitions of the brachytherapy target volume is our routine inclusion of part of the uterine corpus. Historically, the longest intra-uterine applicator was used to ensure consistent depth dose at Point A and contribution to pelvic nodal stations<sup>30</sup>. This also meant that a good portion of the corpus was irradiated though not necessarily the entire corpus<sup>289</sup>. The rationale to continue including part of the corpus which is now visualised on imaging is based on previous work by Narayan et al. that has highlighted the prognostic significance of corpus invasion<sup>290</sup>. This work indicated that both the volume of the tumour and uterine involvement were strongly related to overall survival and failure free survival. Having previously verified MRI against surgical specimens in 13 cases of squamous cell carcinoma and 19 cases of adenocarcinoma, it was acknowledged that determination of corpus invasion in small tumours and adenocarcinomas can be difficult<sup>281</sup>. These advanced infiltrative tumours often present with a non-distinct tumour border making delineation difficult on MRI. The border between cervix and corpus becomes even more difficult to discern on MRI after EBRT. While the borders of the cervix and uterus can be clearly delineated *in toto* using transabdominal ultrasound, it is not always possible to definitively discern the cervical uterine border. For this reason the ultrasound based target volume includes activating dwell positions up to the tip of the intrauterine applicator to cover any vestiges of corpus invasion. This practice is also used in corpus negative patients as it is safe to do so using ultrasound verification of the brachytherapy target volume and applicator placement.

The isodose lines are conformed to the ultrasound derived uterine shape and tumouricidal doses contained well within the serosa, effectively leaving a safety rind of myometrium to spare surrounding tissues. A pragmatic approach is needed when considering use of ultrasound to define the brachytherapy target volume until advances in ultrasound technology facilitate the ability to distinguish corpus invasion on ultrasound. This is borne out by the inability to

measure the height of the HRCTV with transrectal ultrasound<sup>189</sup>. This issue was also recognised in an exploratory study of trans-cervical endosonography (TRACE)<sup>191</sup>. While demonstrating the potential role of TRACE the authors conceded that ultrasound based contouring concepts need to be developed.

Difficulty in delineating the extent of disease in the uterus is not confined to ultrasound. The majority of departments treating cervix cancer with brachytherapy in the developed world use CT<sup>40,48</sup>. Numerous studies have attested to the inability of CT to accurately distinguish the cervix, parametrial involvement and corpus invasion<sup>209,291,292</sup>. In a study comparing CT and MRI, contours of the cervix were shown to be wider on CT ( $p = 0.05$ )<sup>209</sup>. In fact all CT contours were typically larger, except for height as it was not always possible to see the cervical apex on CT. In patients with cervix confined tumours, the authors recommended using the sagittal reconstruction to ensure the superior extent of the cervix encompasses the average cervical height of 3 cm. This is a somewhat generic recommendation that could potentially over or under estimate both the extent of the actual cervix and the upper border of the infiltrating residual tumour. The authors also assert that, if MRI is not available, the entire uterine canal should be contoured to ensure the HRCTV covers the extent of potential areas at risk. While these two recommendations are somewhat contradictory, the second recommendation does make sense. This approach is also advocated by the American Brachytherapy Society who recommend that the entire length of the intrauterine applicator should be treated in patients planned with CT<sup>293</sup>. Another group discussed improvements to CT contouring by incorporating detailed information from clinical gynaecological examinations and use of a standard height for the HRCTV of at least two thirds of the uterine cavity<sup>292</sup>. Unfortunately, this type of standardisation is another form of generic brachytherapy that may well blur results of GEC-ESTRO reporting volumes and still does not ensure that all corpus invasion has been included.

A proof of concept study investigated the feasibility of incorporating TRUS ultrasound into the brachytherapy workflow in conjunction with CT to better delineate the cervix and HRCTV<sup>190</sup>. The authors still found it difficult to identify the height of the HRCTV with TRUS and used the height of the tumour from a pretreatment MRI to avoid a geographical miss at the time of brachytherapy. The inability to ‘see’ the top of the cervix was largely due to limitations of the transrectal probe, and anatomical considerations such as rectal capacity and natural tilt of the cervix and uterus away from the probe. Target volume height was pragmatically delineated based on pretreatment extent in order to ensure adequate coverage.

Although we can clearly see the cervix and uterine corpus up to the fundus using transabdominal ultrasound, these are similar rationales for inclusion of part of the uterine corpus into the ultrasound defined target volume in our practice. We concur with inclusion of the uterine corpus for the length of the uterine canal.

### Impact of imaging and guidelines on uterine dwell position activation

The GEC-ESTRO guidelines were originally developed to create a common language for reporting 3D volumes, however, they are now recognised as prescription volumes and dose distributions are being modified based on them<sup>38,46,294</sup>.

Despite some practitioners recognising the need to include at least part of the corpus when using indeterminate imaging, others are being influenced by the height of the HRCTV and reducing coverage of the corpus. A group investigated the safety of dwell length adjustment to the uterine corpus based on an MRI specified GTV at the time of brachytherapy in 95 patients<sup>295</sup>. There were 22 pelvic recurrences but no evidence of recurrence at the corpus. The

Table 8.2 Target volume definitions

Based on Peter MacCallum Cancer Centre, GEC-ESTRO and American Brachytherapy Society Guidelines

Peter MacCallum Cancer Centre	GEC-ESTRO working group 1 <sup>41</sup> ICRU 89 <sup>38</sup>	Consensus guidelines for CT contoured CTV volumes Viswanathan et al. <sup>209</sup> American Brachytherapy Society guidelines 2012 <sup>293</sup>
Microscopic disease	LRCTV	
EBRT 40 -45 Gy	Potential tumour spread EBRT 40 -45 Gy	
	IRCTV	Disease extension on clinical exam and MRI at the time of diagnosis should be contoured as IRCTV
	Significant microscopic disease Encompass HRCTV with a safety margin of 5-15 mm (limited by natural anatomic borders) depending on response to EBRT EBRT + BT 60 Gy	
PMCCTV	HRCTV	Contour from level of ring or ovoids
Whole cervix	Whole cervix	Add vaginal tissue adjacent to ring or ovoids if involved at time of brachytherapy
Residual disease	Residual macroscopic tumour load	Superiorly, contour to the level where the uterus indents (internal os), draw the next 1 cm as a pointed shape (cone). The approximate dimension (height) of the cervix should be 3 cm.
Infiltrative disease	Presumed extracervical extension of tumour at time of brachytherapy (the grey zones)	Laterally, parametrial extension should be included if it appears 'grey/white' on CT (i.e. similar density to cervix). Include tumour present on clinical examination.
Dwell positions in applicator are activated to treat into the corpus uteri	EBRT + BT 80 – 90 Gy	Include pathologic residual tissues identified in the uterus, vagina, rectum, and/or bladder. For CT only plans – activate whole length of intrauterine applicator as precise determination of the superior extent of disease is not feasible.
Clinically detected disease		
EBRT + BT 80 – 84 Gy		

LRCTV = low risk clinical target volume; IRCTV = intermediate risk clinical target volume HRCTV = high risk clinical target volume; PMCCTV = Peter MacCallum Cancer Centre clinical target volume; EBRT = external beam radiotherapy; BT = brachytherapy



decision to deactivate dwell positions was made to reduce dose to surrounding OAR, as dwell weightings were part of a standard plan.

An alternative method that could be considered for use in image guided brachytherapy is the modulation of dwell weights to ensure dose is contained within the uterine corpus, similar to our practice. In another study, cranial dwell positions in uterine applicators were reduced in 45 patients based on clinical examinations and some use of MRI or PET/CT<sup>296</sup>. This infers that response of the tumour was largely based on clinical examination. It is not clear from this study how the upper extent of tumour extension into the corpus was estimated by clinical examination. Dwell positions were retracted if patients exhibited a rapid rate of response or imaging showed absence of a large superior extent of disease. The authors found no local failures in these patients. The original plans were based on standard dosimetry and while the results gave the authors confidence to perform more aggressive adaptive brachytherapy, greater inclusion of imaging might lead to dwell weight modulation rather than elimination.

Dose to the non-involved uterus was evaluated in a study of 84 patients demonstrating a reduction in dose to the corpus in optimised plans based on contouring of the HRCTV<sup>294</sup>. Of the 84 patients investigated there were seven local failures within the HRCTV. In one patient with mid uterine involvement at diagnosis and no uterine involvement detected on MRI at brachytherapy, there was uterine corpus failure along with cervical and parametrial failure. The authors point out that uterine infiltration can only be assessed on MRI and that care should be taken when evaluating the impact of reduced tandem loading. Given the difficulties in determining corpus invasion even when MRI is used at each brachytherapy fraction it may be prudent to maintain dose in the uterine corpus through dwell point modulation.

Accepting that corpus invasion is difficult to assess at the time of brachytherapy be it clinically, by CT, ultrasound or MRI, we believe it is important to maintain some coverage of the corpus, and imaging should be used to direct modulation of coverage rather than elimination of dwell positions. Late toxicity is not increased by irradiating the corpus provided tumouricidal doses are contained within the serosa of the uterus. The longitudinal ultrasound image clearly depicts the uterus, cervix and applicator and facilitates dose shaping to treat into the corpus while protecting surrounding organs at risk. The width of the uterus and cervix are well appreciated on transverse images and can also be used to guide iso-shaping.

### Target volume delineation – parametrial involvement

An important component of target volume delineation for brachytherapy is the ability to distinguish residual parametrial involvement after EBRT to ensure adequate iso-coverage. In section 8.1.3 it was noted that accurate detection of parametrial involvement by MRI was 88% compared to histopathology<sup>283</sup>. That study included 19/57 (33%) patients with advanced disease, (FIGO stage IIB-IIIB). In another study comparing preoperative MRI and TRUS with histopathology in 68 patients, 51% of whom had locally advanced cancer, there was low sensitivity in both modalities in regard to five patients with histopathologically confirmed parametrial infiltration, although agreement between TRUS and MRI was 87%<sup>297</sup>. This indicates that while MRI and ultrasound imaging are not as sensitive as histopathology in detecting parametrial invasion, the two imaging modalities are at least comparable to each other in measuring tumour diameter and volume in locally advanced cervix cancer. In a study comparing diagnostic accuracy of transvaginal ultrasound or transrectal ultrasound and MRI in patients undergoing preoperative assessment of early cervix cancer, ultrasound was shown to be more accurate than MRI<sup>159</sup>. Ultrasound showed 97% agreement with histopathology in

detecting parametrial invasion, compared to 90% for MRI ( $p=0.001$ ). Detection of early parametrial invasion is crucial for determining surgical margins. Detection of gross parametrial invasion influences treatment modality. Patients with gross parametrial invasion are normally recommended to have radiotherapy and brachytherapy. MRI and ultrasound appear to have similar accuracy when assessing parametrial invasion and this justifies the approach in use. In our practice a thorough clinical gynaecological examination is conducted along with transvaginal ultrasound examination and transabdominal ultrasound examination to determine the extent of parametrial involvement<sup>237</sup>. These findings are considered when the brachytherapy target volume is determined. Similar to the authors of the aforementioned studies, Testa et al. and Epstein et al., the need for specially trained ultrasound operators is recognised<sup>159,297,298</sup>.

## Target volume delineation using CT

Computed tomography is not used in our brachytherapy protocol but it is used extensively throughout Australia and the radiotherapy world, and is increasingly being used in developed countries<sup>40,48</sup>. It is so widely used that consensus guidelines for contouring the brachytherapy target volumes on CT have been developed<sup>207</sup>. The consensus guidelines were based on a study of contours drawn on three sample cases by 23 physicians. All physicians received pretreatment MR imaging, brachytherapy MR and CT imaging with applicator *in situ*, and clinical diagrams indicating extent of disease at diagnosis and at the time of brachytherapy. Brachytherapy target volumes were contoured by each physician for each case according to instructions listed in Table 8.2. The mean tumour volumes were smaller on MR than on CT for all three cases ( $p<0.001$ ). Agreement between contours was higher for CT compared to MR ( $p=0.048$ ). Contours drawn on CT tended to overestimate the target volume, particularly if the patients

presented with large tumours and parametrial involvement and then showed a good response to EBRT. A study examining the utility of pre-brachytherapy MRI without applicators *in situ* also demonstrated the difficulty in identifying parametrial involvement and response on CT<sup>299</sup>. Patients underwent pre-EBRT MRI, pre-BT MRI without applicators, MRI with applicators and CT with applicators *in situ*. CT over-estimated the HRCTV volume in instances of involved parametria that had a good response to EBRT. In instances of partial response both CT and pre-BT MRI without applicators indicated a trend to underestimate parametrial involvement and potentially cause a geographic miss. Similarly, a study of 37 patients found the HRCTV to be larger on CT (44.1 cm<sup>3</sup>) than MRI (35.1 cm<sup>3</sup>;  $p < 0.0001$ ) This group found that a higher body mass index and tumour size  $\geq 5$  cm with parametrial invasion on the MRI scan at diagnosis were associated with an increased discrepancy in volumes at the time of brachytherapy<sup>300</sup>. Few studies have compared ultrasound and CT, but a prospective study looking at measurements of the uterus and cervix obtained by CT, transabdominal ultrasound and surgical specimens for planning intracavitary brachytherapy found ultrasound to be significantly more accurate than CT in measuring the dimensions of the cervix<sup>301</sup>.

The advice given in the consensus guidelines by Viswanathan et al. is that in centres where only a CT is available, the CT suffices to cover adequate parametrial extension in all scenarios if the contours extend to the most lateral aspect of the parametrial tissue<sup>207</sup>. Again, this seems to be quite generic advice and may result in over treatment of paracervical space for no clinical reason. Other authors recommended that in instances where parametrial involvement is underestimated by CT, further imaging such as TRUS, be included in the workflow<sup>299</sup>. This implies that TRUS should be included in all workflows, as practitioners will not know if parametrial involvement is underestimated. Given the high correlation of ultrasound and MRI in detecting parametrial extension and the lack of MR in some centres, inclusion of any form

of ultrasound may prove to be a useful imaging modality to improve contouring of the brachytherapy target volume on CT.

## Contouring

In 2005, GEC-ESTRO released contouring recommendations for MRI guided brachytherapy<sup>41</sup>. These guidelines were based on consensus statements from a number of practitioners from different schools of radiotherapy, hence the inclusion of different clinical target volumes. A new body of knowledge had to be acquired, as the brachytherapy practitioners learnt how to interpret MR images<sup>302</sup>. Similarly, studies looking at interpretation of MR imaging and the contouring recommendations needed to be conducted to validate the recommendations. The bulk of these interobserver studies illustrated learning phases and variations in contouring within the studies<sup>303-307</sup>. Although all ultimately reported fair to good agreement in contouring, the clinical significance of dosimetric variations resulting from contouring variations needs to be considered<sup>303,304,306-308</sup>.

The recommendations and their nomenclature have percolated into brachytherapy practices even where MRI is not used for treatment planning. This has raised a number of questions, particularly when image guidance is performed using CT which has poorer soft tissue contrast resolution than MRI<sup>209,234,291,309,310</sup>. As discussed previously, the main difficulty with CT based planning is the inability to distinguish the superior border of the HRCTV and parametrial involvement after EBRT. As the potential of ultrasound is slowly being realised based on its superior soft tissue contrast, compared to CT, its use will also raise questions about how to implement the GEC-ESTRO reporting recommendations for users of ultrasound<sup>189,191,286,311</sup>.

Given the difficulties in identifying the superior extent of the involved cervix on all forms of imaging it is not surprising that variations in the contouring of the HRCTV are seen. These variations can potentially blur dose responses estimated from GEC-ESTRO reporting recommendations, as the delineation of the height of the HRCTV is being modified based on the imaging modality used. It might be prudent to make the definition consistent across all modes of imaging to ensure robustness of both contouring and reporting.

## Reporting intracavitary brachytherapy

Dose reporting for intracavitary brachytherapy has until recently been based on recommendations from the ICRU report 38 published in 1985<sup>34</sup>. Dose reporting was based on 2D x-ray film based planning and specified methodology to determine uniform reference points for calculating dose in the bladder and rectum. These reference points described dose at a single point due to the 2D nature of planning, as no volumetric dosimetry could be calculated from x-ray films. The ICRU report 38 recommended against reporting the Point A dose. With the advent of 3D image based brachytherapy a new report has been released describing prescribing, recording and reporting of brachytherapy for cancer of the cervix, namely, ICRU report 89<sup>38</sup>. This comprehensive report recognises the variations in resources and infrastructure across the world, and has devised a three tier reporting system that recognises basic, advanced and investigative practices. Level 1 reporting describes the minimum requirements, which should be followed in all centres for all patients and represents the minimum standard of treatment; level 2, indicates advanced volumetric planning and treatment; and level 3 describes new forms of planning related to research and development. Reporting recommendations are made within each level based on clinical practice, be it 3D image based or 2D x-ray based planning, see excerpt from ICRU report 89 in appendix D.

Quite separately, PMCC guidelines have been developed based on use of 2D and 3D imaging which closely mirror the recommendations of ICRU report 89, Figure 8.1. Target reporting is volumetric and based on measuring the dimensions of the target on ultrasound using width, thickness and height. These dimensions are compared to the dimensions of the target on the MRI. The target is volumetrically contoured on MRI and as long as the dimensions of the target measured each fraction with ultrasound are within clinically acceptable limits the D90 of the target volume is extrapolated from MRI for reporting purposes.

There have been a number of studies investigating the relationship between ICRU report 38 reference points and volumetric indices<sup>135,312-315</sup>. These studies aimed to determine how closely the reference points correlated with volumes, to establish if the reference points can indeed be used as surrogates for volumes. As ICRU report 89 points out, there is a relationship between the ICRU report 38 rectal reference point and the maximum dose to 2 cm<sup>3</sup> of the rectum (D2cm<sup>3</sup>). In a recent report from the prospective EMBRACE study, the rectal D2cm<sup>3</sup> was reasonably close to the ICRU 38 rectal point with a mean difference of  $-3.4 \pm 7.1$  Gy<sup>287</sup>. However, there is considerable variation among individual patients, which means the ICRU 38 rectal point may not be a good predictor of D2cm<sup>3</sup> in the individual patient.

The ICRU 38 bladder reference point measured at the bladder base has been shown to have poorer correlation to the maximum D2cm<sup>3</sup> of bladder irradiated<sup>135</sup>. The bladder point typically underestimates the maximum dose to the bladder and this has been noted in the work carried out at PMCC. The discrepancy between the ICRU 38 bladder reference point and the bladder D2cm<sup>3</sup> is greater than that of the rectal reference point, and is well appreciated on both ultrasound and MR imaging, Figure 8.2.

The dose to the vagina was not considered in ICRU report 38, but has been included in ICRU report 89. Numerous ways to report vaginal doses have been proposed in ICRU report 89, including points based on the surface of the applicator, points 5 mm from the surface of the applicator, and by using the ICRU 38 rectal point<sup>38</sup>. The vagina can be both a target tissue and an OAR depending on the likelihood of disease infiltration. The upper and middle vagina are often included in the target volume and treated to a therapeutic dose whereas the lower vagina is excluded from both EBRT fields and brachytherapy.

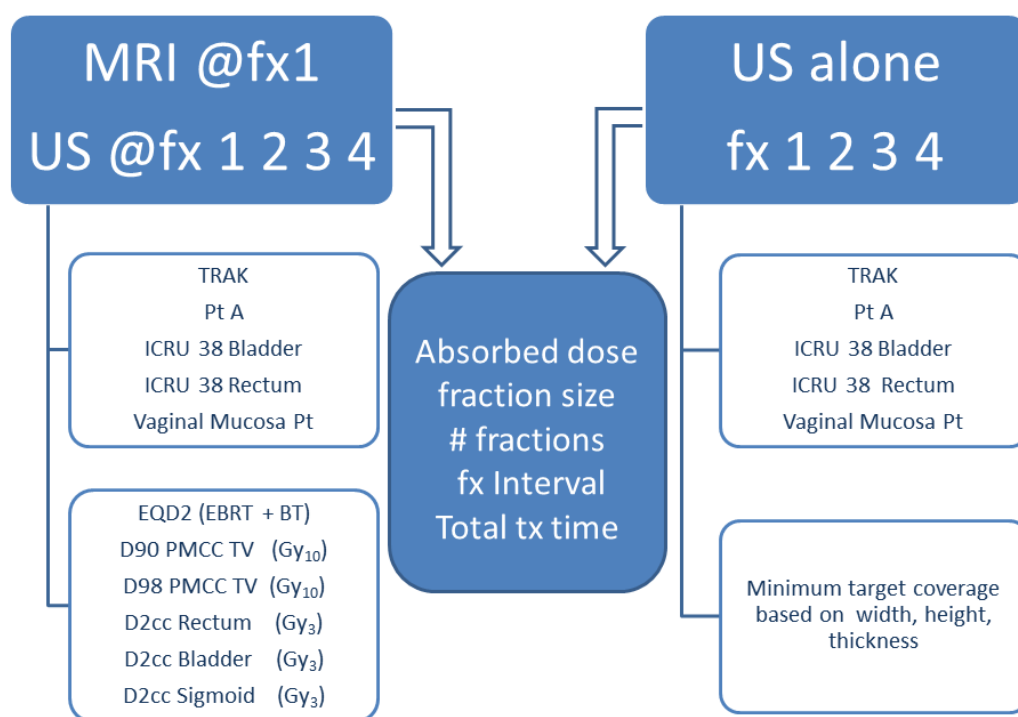


Figure 8.1 Brachytherapy treatment parameters

Reported by Peter MacCallum Cancer Centre

TRAK = treatment reference air kerma; D90 = dose to 90%; D98 = dose to 98%;  
PMCC TV = Peter MacCallum Cancer Centre target volume; D2cm<sup>3</sup> = dose to 2cm<sup>3</sup>

Source: Peter MacCallum Cancer Centre



More dose points have been described to monitor dose to the uninvolved vagina. These points are based on work by Westerfeld et al. who proposed a way of segmenting the vagina based on the relationship of the vagina to the pubic symphysis<sup>316</sup>. At PMCC an applicator based point located on the surface of the ovoid or cylinder is always used to monitor dose to the upper vagina. It is possible to do this using x-ray, ultrasound, MRI and CT<sup>286,317</sup>. In ICRU report 89, the dose to the upper vagina is monitored via the ICRU 38 rectal point, which is renamed the ICRU 89 recto-vaginal point.

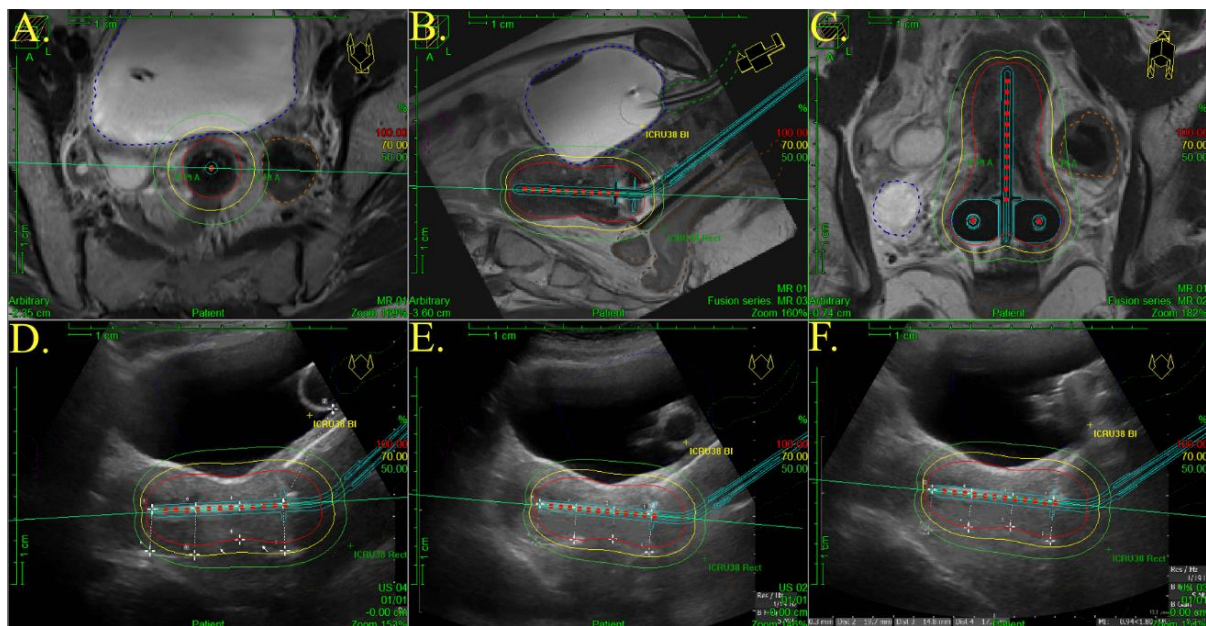


Figure 8.2 ICRU 38 bladder and rectal points on MRI and ultrasound images

- A. Axial MRI through Point A
- B. Longitudinal MRI view. The ICRU 38 bladder point is some distance from the radiation field and does not represent the dose to the bladder wall
- C. Coronal MRI view
- D. Longitudinal ultrasound verification image taken at fraction 1
- E. Longitudinal ultrasound verification image taken at fraction 2
- F. Longitudinal ultrasound verification image taken at fraction 3

Source: Peter MacCallum Cancer Centre

This reassignment of nomenclature is based on work by Kircheiner et al. analysing data from the prospective EMBRACE study, which correlated vaginal stenosis and shortening with doses received at the ICRU 38 rectal reference point<sup>318</sup>.

Other organs at risk include bowel, particularly the sigmoid colon. ICRU report 38 did not define a point for reporting the dose to the sigmoid colon as this organ is not visible on x-ray. In our practice the bowel and sigmoid colon can be seen on individual ultrasound views is taken into consideration when planning isodose coverage of the cervix and uterus, Figure 8.3. The sigmoid is contoured and dose received is assessed on the MRI scan. There is often reasonable correlation between the bowel position on MRI and ultrasound, in the region surrounding the uterus, but differences are also noted, Figure 8.4 . The differences in intrafraction and interfraction bowel position have also been observed with sequential MR imaging<sup>38,216</sup>. This highlights the uncertainties of calculating and recording a dose on a mobile structure. At the moment it is only possible to report point doses to the sigmoid if the sigmoid is captured on the 2D ultrasound image used for planning, see Figure 8.3 and Figure 8.4.

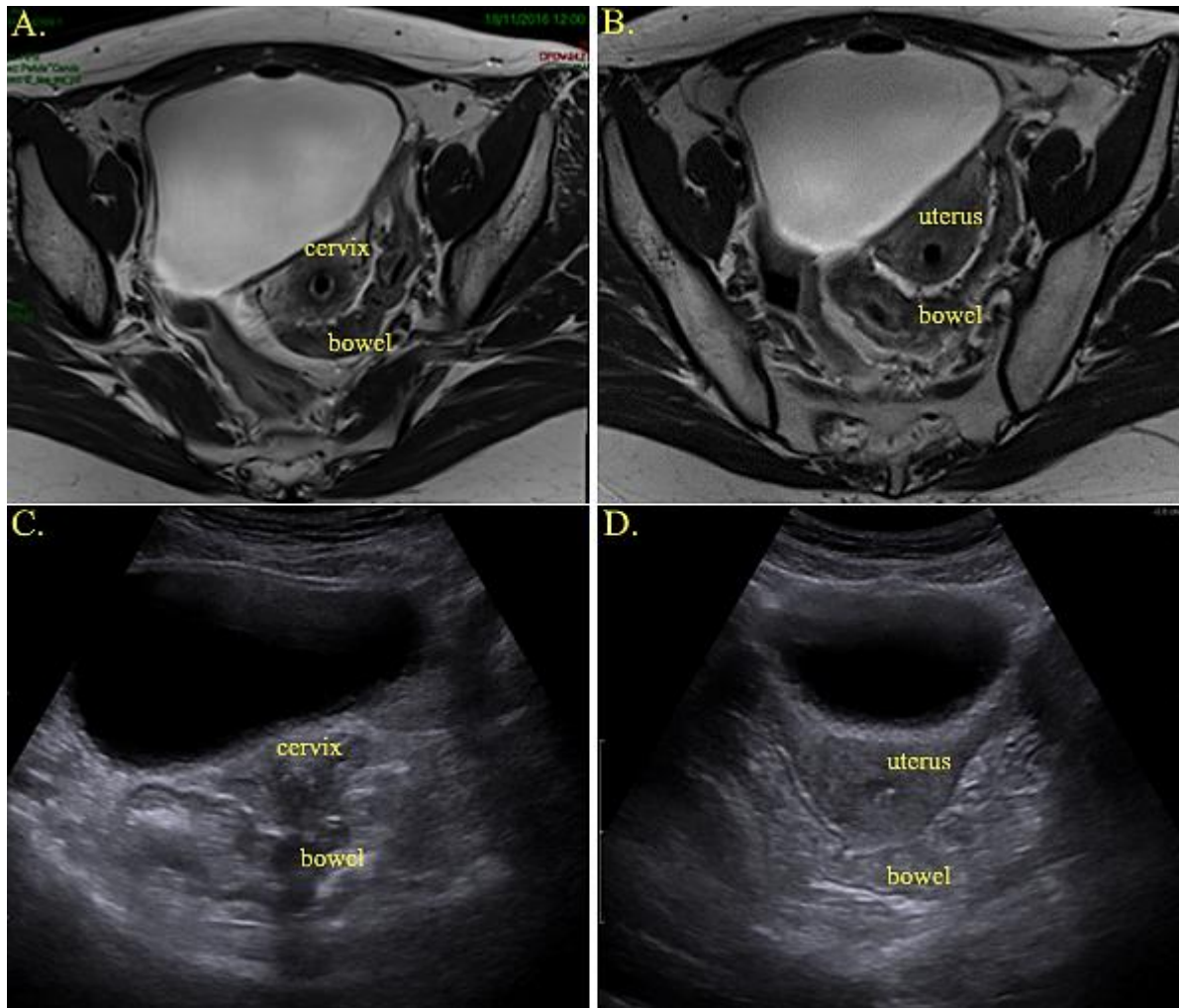


Figure 8.3 Bowel surrounding cervix and uterus

- A. Transverse MRI view of bowel surrounding cervix
- B. Transverse MRI view of bowel surrounding uterus
- C. Transverse ultrasound view of bowel surrounding cervix taken 1 ½ hours prior to MRI
- D. Transverse ultrasound view of bowel surrounding uterus taken 1 ½ hours prior to MRI

Source: Peter MacCallum Cancer Centre

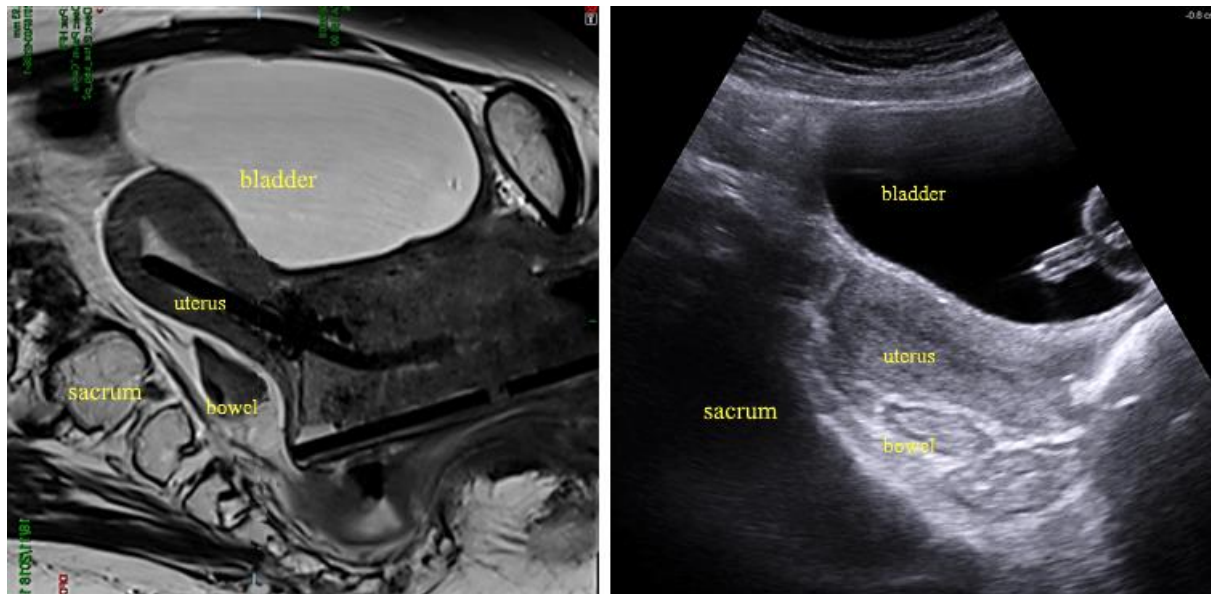


Figure 8.4 MRI and ultrasound views of uterus and bowel

Left: Longitudinal MRI view of uterus and bowel taken 1 ½ hours after ultrasound image

Right: Longitudinal ultrasound view of uterus and bowel taken just prior to applicator insertion and treatment

Source: Peter MacCallum Cancer Centre

## 8.2 Assessing changes to the brachytherapy target for cervical cancer using a single MRI and serial ultrasound

In EBRT, field coverage is verified through use of periodic imaging over the course of treatment. This serves to ensure that the target volume is within the radiation field and a geographic miss is not occurring. It also ensures that doses to surrounding normal tissues are kept to a minimum. In many centres this verification is becoming a daily occurrence prior to treating the patient. Such verification is also necessary in brachytherapy. In brachytherapy it is imperative to check both the applicator placement, which is akin to field placement in EBRT; and the volume of the target around the applicator, as this confirms adequate dose coverage to the target volume and avoidance of surrounding critical structures. This type of verification can

only be done with soft tissue imaging such as CT, MRI or ultrasound. As the range of isodose coverage from brachytherapy is typically short, the assessment of target volume topography before treatment is important. For patients with small tumours brachytherapy can commence during EBRT, as the tumour volume is small and can be encompassed easily with typical brachytherapy applicators and source loadings. For patients with large tumours, brachytherapy should not commence until the tumours have regressed significantly during the course of EBRT such that they are adequately covered by radiation provided by the brachytherapy system. This of course has to be balanced with overall treatment time. Serial assessment of applicator placement and target volume over the course of brachytherapy is necessary to avoid geographic miss of the tumour and overdosing of surrounding organs at risk.

A number of studies have been conducted evaluating tumour shrinkage during EBRT. Evaluation was by clinical examination or serial soft tissue imaging<sup>319-322</sup>. There was good concordance between the studies showing around a 50% reduction in tumour size over 20 days. Lee et al. conducted clinical exams on 17 patients who underwent EBRT and chemotherapy and found a 50% reduction in tumour volume at 30.8 Gy<sup>319</sup>. Likewise, Beadle et al. used CT to monitor tumour regression in 16 patients who had chemo-RT and found the median time to 50% reduction of tumour was 20 days with mean volume reduction at 45 Gy to be 62.3%<sup>321</sup>. Studies using MR imaging found greater rates of regression. In an evaluation of 14 patients, mean tumour volume reduced 46% after 30 Gy or 23 days<sup>323</sup>. In an assessment of 43 RT patients and 38 chemo-RT patients, somewhat higher mid RT regression rates of 69 and 79% were observed<sup>320</sup>. In a larger study of 175 patients using MRI, tumour regression of 78.5% was observed over the course of EBRT<sup>324</sup>. These findings were similar to other studies that evaluated regression with MRI and found regression rates of 74%; 71%; and 89%<sup>325-327</sup>. These studies suggest that maximum tumour regression occurs between 30 and 45 Gy. From this we

can infer that brachytherapy is best started very late in a course of EBRT or after EBRT has been completed, as greater tumour regression leads to better geometry of the brachytherapy application.

At PMCC brachytherapy always commences at the end of EBRT and as discussed in chapter 5, significant changes to the brachytherapy target volume during brachytherapy have not been observed. When analysing reports of changes to the target volume during brachytherapy it is therefore necessary to distinguish when brachytherapy commenced in relation to EBRT. Patients in a study conducted by Dimopolous et al. commenced brachytherapy after receiving a mean dose of 37 Gy with EBRT<sup>218</sup>. The mean tumour volume at diagnosis was 61 cm<sup>3</sup> (range: 1 - 381 cm<sup>3</sup>) and at first brachytherapy treatment was 16 cm<sup>3</sup>. Target volume changes between fraction one and fraction two were 8 cm<sup>3</sup> but only 1 cm<sup>3</sup> for the remaining fractions. It can be inferred that there would have been less target volume change between fraction one and fraction two had brachytherapy commenced at the completion of EBRT. Similarly, Cooper et al. found the mean reduction of HRCTV was less than 1 cm<sup>3</sup> per fraction in five patients who underwent sequential MR planning when patients commenced brachytherapy late during EBRT<sup>328</sup>. Sun et al. obtained other results, with an average tumour (GTV) regression of 39% after EBRT and reductions of the brachytherapy target volume of 27% between fraction one and fraction two and 9% between fraction three and fraction four<sup>309</sup>. Although tumour regression was evaluated by MRI, evaluation was not volumetric but rather based on point H based planning, which infers regression was evaluated only in one dimension. Brachytherapy did commence after EBRT had finished, but the response to EBRT observed in this study was certainly less than in the earlier studies mentioned. The findings of Carvalho et al. were more in line with Dimopolous et al. Carvalho et al. found a 75% reduction in tumour volume after EBRT in 13 patients assessed with MRI at the first brachytherapy insertion<sup>329</sup>. The authors

found a modest reduction of the GTV between the first and third brachytherapy insertions. Half the patients commenced treatment during EBRT and half after EBRT. Interestingly, there were no statistically significant differences observed in tumour volumes when patients were evaluated according to the dose of EBRT received at the third brachytherapy insertion. While replans might be necessary for fractions one and two of brachytherapy based on when patients commence treatment, changes to the brachytherapy volume plateau and less adaptive planning may be sufficient for later insertions. The rate of replanning may be further reduced if brachytherapy commences after EBRT as found in chapter 5<sup>237</sup>. GEC-ESTRO guidelines recommend that each brachytherapy insertion be imaged and planned using MRI, as reimaging is necessary to evaluate tumour shrinkage and replanning is necessary to limit doses to OAR. This recommendation is obviously based on situations where brachytherapy is commenced during EBRT. The studies cited above, along with our own, suggest that there is minimal change to the brachytherapy target volume over the course of brachytherapy if brachytherapy commences after EBRT has been completed. The implications for resource management and planning workload are immense if less intense imaging and planning are required than recommended by GEC-ESTRO. Serial image based assessment must be conducted to confirm tumour shrinkage, ensure OAR are safe, and optimise applicator position over the course of treatment. The work in chapter 5 indicates that ultrasound is eminently suited for this type of verification.

## Hybrid imaging protocols

The routine use of MRI for each brachytherapy fraction as recommended by GEC-ESTRO guidelines is not feasible for many centres. This is due to the prohibitive costs of multiple MRI scans, difficult logistics and inaccessibility<sup>210,235,236,300,328,330,331</sup>. In an attempt to introduce

image guided brachytherapy, many departments have developed hybrid approaches to treatment planning similar to that introduced at PMCC. Indeed, the large European study on MRI guided brachytherapy in locally advanced cervical cancer (EMBRACE), which seeks to validate the GEC-ESTRO guidelines in a multi-institutional setting, allowed hybrid approaches to attract greater participation by more centres around the world<sup>332</sup>. Most hybrid approaches employ combinations of MR and CT imaging<sup>210,234-236,291,309,328</sup>. There are a number of aspects to this approach that might be improved by inclusion of ultrasound. In contrast to the understanding that the dose to the HRCTV should increase over the course of treatment as the target volume shrinks, a group from Pittsburgh found that the HRCTV dose reduced with time as CT overestimated the target volume<sup>210,234,333</sup>. The authors did not use information from MRI to guide target volume contouring on CT and admitted that the CT-HRCTV at subsequent insertions was larger than the MRI-HRCTV at the first insertion. The authors did not use the fraction one MRI plan for all insertions, as they found applicator geometry and OAR positions to be different at subsequent insertions. CT information did improve dosimetry based on the changes to applicator geometry and OAR positions. Similarly, Eskander et al. studied data from 11 patients who underwent one MRI per course of brachytherapy and CT at each fraction and found CT overestimated the HRCTV in the coronal dimension but underestimated HRCTV height in the sagittal dimension<sup>291</sup>. Axial dimensions were not statistically significantly different but showed a trend to be wider on CT. There were instances where CT contours mistakenly included ovary or fallopian tubes in the HRCTV. Five of the patients were prescribed to Pt A and six patients received volume based planning. The main differences in Pt A based plans were higher doses to the D2cm<sup>3</sup> bladder on the CT plan. There were no statistically significant differences in dose parameters for HRCTV or OAR in the MRI and CT volume based plans. The authors found CT acceptable but recommended at least one MRI be obtained at fraction one to guide GTV and soft tissue delineation, particularly of the uterine



adnexa<sup>236</sup>. The main limitation of CT is the less accurate estimation of the HRCTV, CT mostly overestimates the HRCTV but has also been shown to underestimate the HRCTV<sup>209,299</sup>. Sun et al. recommended a new hybrid approach of MRI based planning for fractions one and three and CT based planning for remaining fractions to better evaluate changes detected during the course of brachytherapy<sup>309</sup>. As limited access to MRI is the main driver for hybrid approaches to image guided brachytherapy, implementation of this approach may still not be feasible in many centres. Nesvacil et al. conducted a feasibility study testing a combination of a single MRI for the first brachytherapy fraction and CT for the remaining fractions<sup>235</sup>. Twenty plans were included in the study where hybrid plans were compared to MRI scans and plans for each fraction. The authors found hybrid planning a feasible alternative to the full MRI approach in the case of small tumours, but for larger tumours with complex applications and unfavourable OAR topography they found MRI based adaptive planning to be superior.

The findings from our study might help improve HRCTV delineation on CT as ultrasound shows greater agreement with MRI than CT in delineating the HRCTV in all directions with the exception of the caudal extent. Another advantage of ultrasound is that it is used to guide and optimise applicator insertion and reproduce the applicator position at subsequent insertions. From our studies we know that use of ultrasound at point of care improves implant geometry, as it allows us to obtain and reproduce the optimal applicator position within the uterus at each insertion. This in turns makes it feasible to use the MR based plans for subsequent insertions. In a study of nine patients undergoing three fractions of brachytherapy who received MRI at fraction one and CT for all three fractions, Cooper et al. examined the effect of applicator position on HRCTV coverage<sup>328</sup>. The authors assumed the HRCTV to be fixed with respect to the applicator which is an assumption many make when using hybrid approaches. They found the applicator HRCTV relationship to be relatively stable with regard to the cervix

and lower uterine body over the three fractions, but variable in the uterine corpus and near the fundus. This could have implications for coverage of the HRCTV that extends to the uterine corpus and the authors recommended using MRI with each fraction when the corpus was involved. As shown in our study, it is possible to use ultrasound to optimise and reproduce the applicator position within the cervix and uterus at each insertion at the time of treatment. This is an important consideration as all of the hybrid studies experience a time lag between imaging and treatment that also involves patient movement. The evaluations of applicator position are all made on imaging that occurs some time prior to treatment and nearly always necessitates movement of the patient from the imaging suite to the treatment suite. Use of ultrasound in the treatment suite, just prior to treatment commencement, ensures accurate placement of the applicator, confers accurate coverage of the target volume, sparing of OAR, and potentially reduces overall planning and treatment time while also minimising patient discomfort.

## Treatment planning and verification using ultrasound

Chapter five discussed and listed the benefits of using ultrasound to assess the brachytherapy target over time, and the use of ultrasound to verify and optimise the applicator position at each fraction of treatment. Two of these benefits were reduced replanning time and verification of applicator position just prior to treatment. The number of patients presenting for treatment varies throughout the world, with many centres in developed countries experiencing a plateau or downturn in patient numbers, while centres in less developed regions continue to see very high numbers of patients. As MR or CT guided brachytherapy typically takes anywhere from 5 - 10 hours from insertion to treatment, the benefits of reduced planning and replanning rates might be best appreciated in regions where the burden of cervix cancer is high<sup>76,212,216</sup>. A group from a high volume treatment centre in Thailand studied 29 patients who underwent ultrasound

guided brachytherapy and analysed the use of portable ultrasound and early results of treatment. The authors found ultrasound to be beneficial during applicator insertion, treatment planning and treatment verification due to portability of the unit<sup>228</sup>. They also found the cost of ultrasound to be clearly more economical than MR or CT. Importantly for this group, the duration of one application of ultrasound guided brachytherapy was shown to be between 40 - 60 minutes compared with two hours for CT and four hours for MR based planning. Such time savings are crucial in their high volume centre that treats more than 250 patients per year. The time spent verifying and treating patients was similar to the PMCC protocol which takes 2 ½ hours for a new treatment (includes insertion, ultrasound imaging, planning, treatment and MRI scan), and 1 – 1 ½ hours for subsequent insertions and treatment. Importantly, the portable nature of the ultrasound unit meant it could be taken to the loading room to verify applicator placement just prior to treatment. Brachytherapy suites with in-room imaging typically utilise x-ray, but portable ultrasound can add a soft tissue dimension to in-room imaging. This is a very important quality assurance consideration. Verifying the applicator at the time of treatment ensures it is in the correct position or at the very least gives an accurate depiction of where it is. We have seen differences between the applicator position on ultrasound (taken at the time of treatment) and the applicator position on the MRI. This indicates that the applicator can move during patient transfer to and from the scanner and means the planning MRI may not be indicative of the treatment conditions. In this instance the position of the applicator on the ultrasound image taken just prior to treatment is the most accurate record of that treatment. The group from Thailand found use of ultrasound improved both the dose distribution for the brachytherapy target and OAR when compared to standard x-ray based planning as was the norm in their department<sup>228</sup>. While appreciating the limitations of 2D ultrasound guided brachytherapy, such as lack of full volumetric analysis of tumour and OAR coverage, lack of evaluation of residual tumour at the time of brachytherapy, and the need for training and

education in the use of ultrasound, the authors found ultrasound based brachytherapy to be feasible. They also demonstrated use of ultrasound made image guided conformal brachytherapy possible in limited resource settings.

### 8.3 Clinical outcomes from image guided brachytherapy

Clinical outcomes have improved and toxicity has been reduced in patients who receive image based brachytherapy. The gains made by the inclusion of imaging, which provide an opportunity for dose optimisation and individualised planning, are well illustrated by the mono-institutional clinical studies listed in Table 6.1. There have also been a number of large multicentre studies that are contributing to this body of knowledge. The French multicentre study [Soutien aux Techniques Innovantes et Coûteuses (STIC)] compared 2D (x-ray based) and 3D (CT based) brachytherapy and demonstrated improved local control, disease free survival, and overall survival for all patients who underwent 3D image based planning<sup>65</sup>. The rate of grade  $\geq 3$  toxicity was reduced by a factor of two in patients enrolled in the 3D arm of the study. The optimisation used in the 3D arm was modest compared to more recent studies but still illustrates how visualisation of the applicator and anatomy can improve implant quality, facilitate optimisation and improve clinical outcomes. Another study employing simple imaging was that of Tharavichitkul et al. from Thailand who used transabdominal ultrasound to guide optimisation<sup>228</sup>. With a median follow up time of 19 months, local control and disease free survival rates were 93% and 86% respectively. This group were able to substantially reduce dose to organs at risk based on the measurements of the cervix and uterus obtained using transabdominal ultrasound. Both these studies reported outcomes similar to ours in chapter 6<sup>286</sup>. It is the virtue of ‘seeing’ that improves the technical quality and provides the ability to optimise both applicator position and isodose coverage that improves outcomes. The ability to

‘see’ is not exclusive to any imaging modality but can come from ultrasound, CT or MRI, individual pros and cons of each modality notwithstanding. The advantage of ultrasound is the ability to provide real time assessment of the applicator position and the target volume at the time of treatment.

A recent update of clinical outcomes from the retro-EMBRACE study reported on data from 731 patients from 12 participating departments<sup>334</sup>. Patients were treated between January 1998 and August 2012, planned according to departmental protocol, had to have been planned with MRI or CT and reported doses according to GEC-ESTRO guidelines. The time period was similar to the time this PMCC study took place<sup>286</sup>. Mean target doses were somewhat higher than ours, 87 Gy vs 79.7 Gy. Three and five year local control was also higher, 91% versus 86%, but five year cancer specific survival (73% versus 70%) and overall survival (65% versus 63%) were similar. As discussed in chapter 6 the ability to dose escalate originated from use of hybrid applicators combining intracavitary and interstitial components for at least one fraction. There is no doubt these applicators enable greater dose shaping to asymmetric or eccentric tumours. In a further study from retro-EMBRACE examining data from 610 patients, 310 of whom received intracavitary treatment and 300 who received at least one intracavitary/interstitial treatment, Fokdal et al. showed a significant increase in the HRCTV D90 from  $83 \pm 14$  Gy to  $92 \pm 13$  Gy ( $p < 0.01$ )<sup>335</sup>. Local control was 5% higher ( $p = 0.06$ ) in the intracavitary/interstitial group.

Another study from a similar time period reported on 170 patients who underwent pulse dose rate brachytherapy (PDR)<sup>336</sup>. Patients were planned with MRI (95%) or CT (5%), and treated using intracavitary (84%) or intracavitary/interstitial (16%) applicators. The mean HRCTV dose was 84.8 Gy. The three and five year local control was 95% and overall survival at three

and five years was 73% and 65% respectively. Mean doses to the target volume were higher than ours, 84.8 Gy versus 79.7 Gy, and local control was 9% higher, 95% versus 86%.

The reports from retro-EMBRACE do support the case for a dose response. Reporting HRCTV doses  $\geq 85$  Gy resulted in 3 year local control rates of  $>94\%$  in limited size (20 cm<sup>3</sup>),  $>93\%$  in intermediate size (30 cm<sup>3</sup>) and  $>86\%$  in large size (70 cm<sup>3</sup>) tumours<sup>288</sup>. The authors also found doses of 90 - 95 Gy advantageous, as they added 1 – 4% to local control depending on tumour volume. These figures are valid for treatment occurring within a seven week window.

A separate study excluding patients reported in retro-EMBRACE conducted an analysis of dose-volume effects published in the literature to establish the veracity of single institution claims and reduce the uncertainties present in published data<sup>310</sup>. According to their model a significant dose-volume effect relationship was confirmed between the CTV and the probability of achieving local control. The D90 HRCTV warranting a 90% rate of local control was 81.4 Gy CI (78.3 – 83.8 Gy).

While there does seem to be a dose response effect for local control, as shown in ours and other reported studies, this effect is less evident in cancer specific survival and not yet evident in overall survival.

## Toxicity

Though the protocol used at PMCC is simpler than most, it yielded comparable outcomes for patients, similar to those treated with more resource intense practices. While it is difficult to compare toxicity outcomes with other published data due to different reporting mechanisms

the overall crude rate of late grade  $\geq 3$  bladder and rectal morbidity (using modified RTOG/WHO criteria) was seen in 8/191 (4%) patients. Other 3 year crude and actuarial rates range from 7 – 12% and 7 – 11% respectively. See Table 8.3 comparisons from IGBT studies.

## Rectal toxicity

Reporting of gastrointestinal toxicity is often all encompassing and it can be difficult to attribute toxicity to specific organs. This discussion is specific to toxicity that has been identified as rectal toxicity. The reported incidences of rectal toxicity for HDR brachytherapy vary from 5% to 30%, with a notable decrease since the advent of image guided brachytherapy<sup>337</sup>.

Six out of 191(3%) patients in our series experienced grade  $\geq 3$  rectal toxicity. The mean ICRU 38 rectal dose in these patients was 67.2 Gy<sup>3</sup>, while the mean (SD) dose for the whole patient cohort was 56.2 Gy<sup>3</sup> (8.28). Volumetric indices were unable to be reported for this group of patients due to the 2D nature of ultrasound and the single MRI taken. The ICRU 38 rectal point has been shown to reasonably correlate with the D2cm<sup>3</sup> although it is appreciated that this point is not a surrogate for the D2cm<sup>3</sup> as there is considerable variation among individual patients<sup>38</sup>. However, a recent report from the prospective EMBRACE study reported the D2cm<sup>3</sup> to be reasonably close to the ICRU 38 rectal point (mean difference of  $-3.4 \pm 7.1$  Gy)<sup>287</sup>. Overall, the authors found a rectal D2cm<sup>3</sup>  $\geq 75$  Gy to be associated with a 30% risk of grade 2-4 overall rectal morbidity at three years, whereas D2cm<sup>3</sup>  $\leq 65$  Gy had an actuarial rate of <10%. The EMBRACE study examined data from 960 patients and reported actuarial 2.1% grade  $\geq 3$  rectal

Table 8.3 Clinical outcomes and toxicity

Reference	No. of patients	Patients with positive nodes %	FIGO 3B %	Median Follow up months	Technique IC intracavitary IC/IS intracavitary/interstitial		Imaging	Mean target dose Gy <sup>10</sup>	Local Control %		Morbidity Crude and actuarial rates Grade ≥3	
									3 year	5 year		
Potter <i>et al.</i> <sup>67</sup> 2011	156	48	21	42	IC 56%	IC/IS 44%	MRI	93	95		7%	Crude LENT SOMA
Petit <i>et al.</i> <sup>230</sup> 2013	226	40	12	82	IC 100%		X-ray/CT	45 EBRT+ 16 PDR		80	9.7%	Crude CTCAE v3.0
Sturdza <i>et al.</i> <sup>238</sup> 2012 Retro-EMBRACE	454	53	18	36.5	IC 86%	IC/IS 14%	CT/MRI	84	91.4			
Nomden <i>et al.</i> <sup>225</sup> 2013	54	44	15	41	IC 75%	IC/IS 25%	MRI	84	93		9.5%	Crude CTCAE v3.0
Lindegard <i>et al.</i> <sup>226</sup> 2013	140	50	20	36	IC 57%	IC/IS 43%	MRI	92	91		7%	Actuarial
Rijkman <i>et al.</i> <sup>227</sup> 2014	93	35	20	42	IC 77%	IC/IS 13%	CT/MRI	80.8	93		8.4%	Actuarial CTCAE v3.0
Narayan <i>et al.</i> <sup>66</sup> 2014	309	45	16	48	IC 100%		US/MRI	80.1		87.5		Crude WHO/RTOG
Gill <i>et al.</i> <sup>232</sup> 2015	128	46	16	24	IC 95%	IC/IS 5%	CT/MRI	82.7	91.6		0.9%	Actuarial
Castelnau-Marchand <i>et al.</i> <sup>229</sup> 2015	225	51	11	39	IC 98%	IS 2%	CT/MRI	82.5	86.4	85.5	6.2%	Crude CTCAE v3.0
Choong <i>et al.</i> <sup>233</sup> 2015	76	54	1.3	47	IC 65%	IC/IS 35%	CT/MRI	96.5	91.4		11.8%	Crude CTCAE v4.0
van Dyk <i>et al.</i> <sup>286</sup> 2016	191	43	16	60	IC 100%		US/MRI	79.7	86	86	6%	Crude WHO/RTOG
Ribeiro <i>et al.</i> <sup>336</sup> 2016	170	50.6	15	37	IC 84%	IC/IS 16%	MRI/CT	84.8	95	95	12%	Crude CTCAE v4.03
Charra-Brunaud <i>et al.</i> <sup>65</sup> 2012 STIC (Group 3)	117	19		24	IC 100%			73.1	78.5 (2 yr)		2.6%	Crude CTCAE v3.0
Tharavichitkul <i>et al.</i> <sup>228</sup> 2015	29	NA	31	19	IC 100%		US/x-ray	82.6	93 (1.6 yr)		3.4%	Crude RTOG/EORTC
Sturdza <i>et al.</i> <sup>334</sup> 2016 Retro-EMBRACE	731	40.5	20	43	IC 77%	IC/IS 23%	MRI/CT	87	91	89	11%	Actuarial CTCAE v3.0

FIGO = Federation of Gynecology and Obstetrics; IC = intracavitary; IS = interstitial; EBRT = external beam radiotherapy; PDR = pulse dose rate; LENT SOMA = Late Effects Normal Tissue Task Force – Subjective, Objective, Management, Analytic; WHO/RTOG = World Health Organisation/Radiation Therapy Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; RTOG/EORTC = Radiation Therapy Oncology Group/ European Organisation for Research and Treatment of Cancer



toxicity. Interestingly, if we use our mean (SD) ICRU 38 rectal point doses of 56.2 (8.28) Gy as surrogates for  $D_{2cm^3}$ , our results concur with the findings of EMBRACE. An important point is that these results were obtained with far fewer resources than those used in the EMBRACE study.

## Urinary toxicity

Urinary grade  $\geq 3$  toxicity was experienced by 3/191 (1.5%) patients. What is rather extraordinary about this is that all patients were treated with a full bladder. This means a substantial portion of the posterior bladder wall was in close proximity to the anterior wall of the cervix and uterus. Careful dose shaping and a static set up made possible by using ultrasound, contributed to the low rates of toxicity experienced by patients. Similar to the rectum, only the ICRU 38 bladder reference point was reported in our study. The mean (SD) bladder point for all patients was 50.8 Gy<sup>3</sup> (10.17), but we know from viewing the ultrasound images that the  $D_{2cm^3}$  is usually a good deal higher, Figure 8.2. This is proven by volumetric measurements taken from the MR images. We have not identified a relationship between the ICRU 38 bladder reference point and the  $D_{2cm^3}$  bladder volume, although this is only an observation and has not been quantified in our practice. In a study examining the usefulness of the ICRU 38 bladder reference point, Barillot et al. found the ICRU 38 bladder reference point to be representative of the maximum bladder dose in less than 25% of cases<sup>135</sup>. The maximum bladder dose was assessed with ultrasound using similar methodology to ourselves. Notably the Barillot study was conducted in 1994 but unfortunately did not result in widespread uptake of ultrasound. We concur with the Barillot findings and judge iso-coverage not by the value of the ICRU 38 bladder point, but by visualising and assessing ingress of isolines into the bladder as seen on the ultrasound planning image. The Vienna group found the incidence of bladder

toxicity to be dependent on DVH parameters<sup>338</sup>. Incidence rates of 10% and 20% for grade 2 - 4 side effects were estimated for D2cm<sup>3</sup> doses (CI) between 101 (29-137) – 134 (110-371) Gy<sup>3</sup>. In their retrospective study of 141 patients with a median follow-up of 51 months, three (2%) patients experienced grade  $\geq 3$  toxicity. These are similar results to ours with the main difference being the full MRI approach used by the Vienna group and our ultrasound guided approach.

### Vaginal toxicity

There is no ICRU 38 reference point for reporting vaginal toxicity, and as such, this structure has been under-reported and often not considered either in practice or in reporting. Despite this we have always reported vaginal doses via a self-determined point created on the lateral surface of the ovoid. This point and dose constraint of 120 -130 Gy<sup>3</sup> was extrapolated from our previous LDR practice. We appreciate this point does not indicate a volumetric dose, but it has served us well in maintaining vigilance, and is possible to calculate using both ultrasound and MRI. We recorded vaginal doses and toxicity in our previous LDR practice and continue to do so in HDR brachytherapy. It is only with the advent of 3D imaging that an attempt has been made to report vaginal dosimetry and toxicity<sup>316,339-343</sup>. As discussed in section 8.1, numerous ways to report vaginal doses have been proposed in ICRU report 89, including an applicator surface point and the ICRU 38 rectal point renamed the recto-vaginal point<sup>38</sup>. In our study, five (2.6%) patients experienced grade  $\geq 3$  vaginal toxicity, which included entire vaginal stenosis and ulceration. None of these patients used the vaginal cylinder to administer Ovestin cream (Oestriol 0.1%). Mean doses to the vaginal point were 134 Gy<sup>3</sup> and mean doses to the ICRU 38 rectal point were 61.2 Gy<sup>3</sup>. A further outcome paper from the prospective EMBRACE study has reported on vaginal toxicity data from 630 patients accrued from eight centres, with a

median follow-up time of 24 months<sup>343</sup>. Toxicity was graded using the NCI CTCAE v3.0 criteria (Appendix D). Toxicity grade  $\geq 2$  is similar to toxicity grade  $\geq 3$  as scored by the modified RTOG/WHO criteria we use (Appendix D). The crude incidence of vaginal stenosis grade  $\geq 2$  was found to be 18%, the two year actuarial rate was 21% with rates varying dramatically across the eight participating centres, 1%, 14%, 16%, 16%, 23%, 26%, 41%, and 41% respectively. The study found increasing dose to the recto-vaginal reference point significantly increased the probability of grade  $\geq 2$  vaginal stenosis. Based on a calculated dose-effect model, the probability of developing such stenosis is 16% with a recto-vaginal point dose of 55 Gy, 20% with 65 Gy, 27% with 75 Gy, 34% with 85 Gy and 43% with 95 Gy. The study suggested a planning aim of  $\leq 65$  Gy EQD2 (combined EBRT and brachytherapy dose) to the recto-vaginal reference point be used, to decrease the risk of vaginal stenosis. The mean recto-vaginal point doses for patients with grade  $\geq 3$  vaginal toxicity in our study was 61.2 Gy<sup>3</sup> and the overall mean dose to this point for all patients was 56.2 Gy<sup>3</sup>. Our calculation methods and vigilance have resulted in outcomes similar to those predicted by the EMBRACE study.

## 8.4 Interoperator study

The use of ultrasound in gynaecological brachytherapy is increasing with 86% of brachytherapy departments throughout Australia and New Zealand using it to guide applicator insertion<sup>48</sup>. The high level of operator input into this imaging modality means training, education and protocols must be robust to minimise discrepancies in image quality that can lead to erroneous decisions. In chapter 7 the reproducibility and interoperator reliability of brachytherapy RTs obtaining an ultrasound image and measuring the cervix and uterine dimensions using transabdominal ultrasound was validated<sup>298</sup>. The high level of reliability observed was attributed to access to appropriate training, good supervision and use of a well-

defined protocol. These factors were supported by recognition that knowledge of anatomy, pathology, and ultrasound theory and practice underpins competent use<sup>244</sup>.

The World Federation of Ultrasound in Medicine and Biology has recognised the emergence of point of care ultrasound<sup>344 345</sup>. These forms of ultrasound are used to achieve specific procedural aims or answer focussed questions, and do not involve comprehensive diagnostic examinations. Ultrasound use is crossing traditional specialty boundaries and being adapted to specific clinical questions. As noted in chapter 7, the use of ultrasound in gynaecological brachytherapy is limited in scope which places it in the realm of a goal focussed or competency based procedure. Many other fields of medicine are experiencing a similar increase in specialised use of ultrasound and are also grappling with the training and education needed to use it safely<sup>346,347 344,345</sup>. As discussed in chapter 7, a specialist brachytherapy radiation therapist undertook a postgraduate limited training course to credential use of ultrasound in the brachytherapy environment, and then developed a short commercial based course for personnel rotating through brachytherapy. This approach has been identified by Royce et al. as goal focussed ultrasound as opposed to full diagnostic knowledge based ultrasound<sup>347</sup>. Training for this type of ultrasound use is based on limited but specific knowledge, use of pattern recognition to identify anatomy and pathology and a smaller number of training cases to achieve competency. A successful sonographer based ultrasound service incorporates recognised training, continuing education, regular frequent ultrasound practice, delegation by appropriately qualified person in charge, use of protocols or schemes of work, and regular audit and quality control procedures. In the PMCC a number of initiatives to facilitate training and ongoing consistent use of ultrasound have been introduced. These include access to a weekend training course, clinical mentorship, clinical supervision, practice scanning, peer to peer review and quality measures such as correlation of ultrasound scans with previous scans and MRI

scans. These initiatives will be enhanced by development of e learning modules and a formalised in-house credentialing program. Ultimately, it is hoped professional societies such as the Australian Society of Medical Imaging and Radiation Therapy (ASMIRT) and the Royal Australian and New Zealand College of Radiology (RANZCR) will set competency standards and develop courses to offer uniform education and training across the workforce.



# Chapter 9

## Conclusions and future directions

Ultrasound is a proven soft tissue imaging modality that has excellent image resolution, can be viewed in real time, and performed at point of care. The use of ultrasound is being progressively incorporated into gynaecological brachytherapy programs, primarily to guide the treatment applicator into the uterine canal and improve the technical quality of implants. The main aim of this body of work was to demonstrate how ultrasound can be incorporated into gynaecological brachytherapy to enhance the planning, treatment and clinical outcomes of patients with locally advanced cervix cancer.

The move to image guided brachytherapy necessitates inclusion of an accessible soft tissue imaging modality into the brachytherapy workflow. Chapter 4 has demonstrated that ultrasound shows excellent agreement with MRI in identifying the cervix and uterus. An important finding was the uterine cervix dimensions were not obscured by imaging with the

applicator *in situ*, indicating the images are suitable for planning treatment. Current single 2D ultrasound projections offer more information than x-rays alone and contribute to the conceptualisation of 3D volumes that facilitates conformal planning.

Replanning each brachytherapy insertion, as recommended by international guidelines, involves many resources and much infrastructure, but may be alleviated through judicious use of imaging and delaying commencement of brachytherapy until EBRT has finished. Chapter 5 examined changes to the brachytherapy target volume assessed with ultrasound over the course of treatment and found minimal changes in target volume dimensions. This has important implications for workload management and patient throughput particularly in regions with high numbers of patients and limited resources. Planning time is of the essence to both clinicians and patients, and one of the most significant achievements observed using ultrasound to guide brachytherapy was the reduced time taken to plan and administer treatment. This has enormous benefits for departmental efficiency and patient well-being.

The clinical outcomes achieved with this protocol were comparable to more resource intense treatment protocols and indicate that highly conformal doses of radiation can be safely delivered to the uterus and cervix using ultrasound guidance. The clinical outcomes reported in Chapter 6 were likewise predicted by recent dose response studies that also forecast that higher local control rates can be achieved with even higher doses. The ability to further isoshape and increase coverage of eccentric or asymmetric tumours is possible with hybrid applicators and an ultrasound based workflow needs to be developed to facilitate this. The overall toxicity profile of the patients undergoing ultrasound guided brachytherapy was comparable to other image guided studies. Overall survival was consistent with other studies



and indicates that other mechanisms are implicated in the spread of disease and this remains an area of research and investigation.

Use of ultrasound is not only recommended for low resource environments. Use of serial MR imaging is proving difficult even in developed regions and many practices rely on CT to plan fractionated brachytherapy. The deficiencies of CT in discriminating the borders of the cervix, uterus and parametria make it less accurate than MRI. The high correlation and excellent agreement of ultrasound with MRI make ultrasound a potential viable adjunct to CT based planning that will improve uterine and cervix delineation and thus treatment accuracy.

While user dependence is an often cited criticism of ultrasound, the results in Chapter 7 indicate that development of robust protocols, and specific training and education for brachytherapy sonographers' results in high quality scans across practitioners. This adds to the appeal of using ultrasound.

The main challenges in furthering use of ultrasound lie in making it less user dependent and enabling greater quantification of dosimetry metrics. This may be achieved by exploring 3D volumetric ultrasound which allows greater automation of image acquisition. Volumetric data sets will allow for multi-planar reconstructions, similar to MRI that will facilitate applicator placement and contouring of the target volume and possibly surrounding organs at risk. It will be possible to conduct validation studies of 3D ultrasound as it is a non-ionising modality, and can be utilised in conjunction with MRI and CT studies without compromising patient safety.



# Chapter 10

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## Appendices

### Appendix A: Dissemination of findings

The following is a list of publications presentations and awards arising from work undertaken for the purposes of this thesis.

#### Publications

Sylvia van Dyk, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, David Bernshaw, Kailash Narayan

Comparison of measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix cancer

*International Journal of Radiation Oncology Biology Physics* 2014 88(4) pp. 860-865

Sylvia van Dyk, Kailash Narayan

In reply to Coza and Ordeanu

*International Journal of Radiation Oncology Biology Physics* 2014 90(2) pp. 472-473

Kailash Narayan, Sylvia van Dyk, David Bernshaw, Pearly Khaw, Linda Mileshtkin, Srinivas Kondalsamy-Chennakesavan

Ultrasound guided conformal brachytherapy of cervix cancer: survival, patterns of failure, and late complications

*Journal of Gynecologic Oncology* 2014 25(3) pp. 206-213

Kailash Narayan, Linda Mileshtkin, Sylvia van Dyk, David Bernshaw, Pearly Khaw, Srinivas Kondalsamy Chennakesavan

We should not settle for low-level evidence but should always use the best available. Response to editorial by Dr Mirza

*Journal of Gynecologic Oncology* 2014 25(4) pp. 349-351



## Appendix A: Dissemination of findings

Sylvia van Dyk, Michal Schneider, Srinivas Kondalsamy-Chennakesavan, David Bernshaw, Kailash Narayan

Ultrasound use in gynecological brachytherapy: time to focus the beam

*Brachytherapy* 2015 14(3) pp.390-400

Sylvia van Dyk, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, David Bernshaw, Kailash Narayan

Assessing changes to the brachytherapy target for cervical cancer using a single MRI and serial ultrasound

*Brachytherapy* 2015 14(6) pp. 889-897

Sylvia van Dyk, Kailash Narayan

In response to Swamidas and Kirisits

*Journal of Medical Physics* 2015 40 pg.246

Sylvia van Dyk, Kailash Narayan, David Bernshaw, Pearly Khaw, Ming Yin Lin

In reponse to Kirisits, Schmid, Beriwal, and Potter

*Brachytherapy* 2016 15(2) pp.205-206

Sylvia van Dyk, Margaret Garth, Amanda Oates, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, David Bernshaw, Kailash Narayan

Reproducibility and interoperator reliability of obtaining images and measurements of the cervix and uterus with brachytherapy treatment applicators in situ using transabdominal ultrasound

*Brachytherapy* 2016 15(1) pp.71-78

Sylvia van Dyk, Kailash Narayan, David Bernshaw, Srinivas Kondalsamy-Chennakesavan, Pearly Khaw, Ming Yin Lin, Michal Schneider

Clinical outcomes from an innovative protocol using serial ultrasound imaging and a single MR image to guide brachytherapy for locally advanced cervix cancer

*Brachytherapy* 2016 15(6) pp.817-824

## Presentations

### **2012**

Sylvia van Dyk, Michal Schneider, Kailash Narayan, Srinivas Kondalsamy-Chennakesavan  
Using ultrasound to guide radiotherapy for women with cervical cancer  
*Research Seminar, Monash University, 27th November 2012, Melbourne, Australia,*

### **2013**

Sylvia van Dyk, Srinivas Kondalsamy-Chennakesavan, Kailash Narayan, Michal Schneider  
Comparison of measurements of the uterus and cervix obtained by MRI and ultrasound  
imaging used for planning radiotherapy for cervix cancer  
*International Society of Ultrasound in Obstetrics and Gynecology, 23rd World Congress on  
Ultrasound in Obstetrics and Gynecology incorporating ASUM 43rd Annual Scientific  
Meeting; 6<sup>th</sup> – 9<sup>th</sup> October 2013, Sydney Convention Centre, Sydney, Australia*

Sylvia van Dyk

Using ultrasound and MRI imaging for planning and verification in brachytherapy  
*Elekta User Group Meeting 16<sup>th</sup> - 18<sup>th</sup> August 2013, Sofitel on Collins, Melbourne,  
Australia **Invited speaker***

Sylvia van Dyk, Michal Schneider, Kailash Narayan, Srinivas Kondalsamy-Chennakesavan  
Using ultrasound to guide radiotherapy for women with cervical cancer  
*Research Seminar, Monash University, 26<sup>th</sup> November 2013, Melbourne, Australia*

### **2014**

Sylvia van Dyk, Srinivas Kondalsamy-Chennakesavan, Michal Schneider, Kailash Narayan  
Using MRI and integrated ultrasound to guide brachytherapy for cervix cancer  
*ESTRO 33 4<sup>th</sup> – 8<sup>th</sup> April 2014, Vienna, Austria*  
Abstract published in the ESTRO 33 Congress report

## Appendix A: Dissemination of findings

Sylvia van Dyk, Michal Schneider, Sri Kondalsamy-Chennakesavan, Kailash Narayan

Using MRI and integrated ultrasound to guide brachytherapy for cervix cancer

*Excellence in Research Seminar, Monash University, 16<sup>th</sup> August 2014, Melbourne, Australia*

### **2015**

Sylvia van Dyk, Margaret Garth, Amanda Oates, Sri Kondalsamy-Chennakesavan, Michal Schneider

Inter-observer reliability of obtaining measurements of the cervix and uterus with brachytherapy applicators in-situ using transabdominal ultrasound

*Australasian Brachytherapy Group Scientific Meeting, 12<sup>th</sup> – 14<sup>th</sup> March 2015, Sydney, Australia*

### **2016**

Sylvia van Dyk, Kailash Narayan, David Bernshaw, Pearly Khaw, Ming Yin Lin, Sri Kondalsamy-Chennakesavan, Michal Schneider

Clinical outcomes of ultrasound and MRI guided brachytherapy for cancer of the cervix: The Peter Mac experience

*Australasian Brachytherapy Group Scientific Meeting 3rd – 5<sup>th</sup> March 2016, Perth, Australia*

## **Awards**

2013 Best Oral Communication in Ultrasound in Oncology

*International Society of Ultrasound in Obstetrics and Gynecology, 23rd World Congress on Ultrasound in Obstetrics and Gynecology incorporating ASUM 43rd Annual Scientific Meeting; 6<sup>th</sup> – 9<sup>th</sup> October 2013*

*Sydney Convention Centre, Sydney, Australia*

2015 Best proffered paper, oral presentation

*Australasian Brachytherapy Group Scientific Meeting, 12<sup>th</sup> – 14<sup>th</sup> March 2015, Sydney, Australia*

## Appendix B: Approvals



**MONASH** University

Monash University Human Research Ethics Committee (MUHREC)  
Research Office

### Human Ethics Certificate of Approval

**Date:** 15 January 2013

**Project Number:** CF13/115 - 2013000037

**Project Title:** Using ultrasound to guide radiotherapy for women with cervical cancer

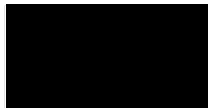
**Chief Investigator:** Assoc Prof Michal Schneider

**Approved:** From: 15 January 2013 To: 15 January 2018

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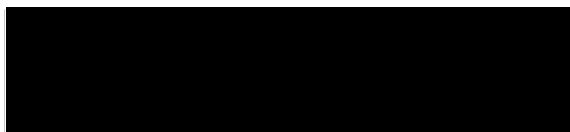
#### Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.**
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. **Complaints:** The researchers are required to inform MUHREC promptly of any complaints made about the project, whether the complaint was made directly to a member of the research team or to the primary HREC.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.



Professor Ben Canny  
Chair, MUHREC

cc: Ms Elisabeth Sylvia van Dyk, Assoc Prof Kailash Narayan, Dr Srinivas Kondalsamy-Chennakesavan



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**Divisions of Radiation Oncology & Cancer Imaging and Cancer Medicine**

**Divisional Review Panel for Retrospective Studies**

**MEMO**

**To:** Sylvia van Dyk  
**From:** Divisional Review Panel for Retrospective Studies  
**CC:** Dianne Snowden  
**Date:** 19 December 2012  
**Re:** **12/161 – Transabdominal Ultrasound Use for Image Guidance, Target Delineation, Conformal and Adaptive Planning, Verification and Treatment of Cervix Cancer Treated with Brachytherapy**

The DROCI & CM Divisional Retrospective Review Panel has reviewed the above research project.

**We are pleased to advise that the Version Dated December 2012 of your Study has been approved with no changes required.**

The Peter MacCallum Cancer Centre Ethics Committee will now issue a certificate of approval.

We wish you well with this study.



A/Prof Michael Mac Manus  
Chair, Divisional Review Panel for Retrospective Studies

## Appendix C: Other publications

### Chapter 2: Literature review as published in Brachytherapy Journal



BRACHYTHERAPY

Brachytherapy 14 (2015) 390–400

## Ultrasound use in gynecologic brachytherapy: Time to focus the beam

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### ABSTRACT

There is wide disparity in the practice of brachytherapy for cervical cancer around the world. Although select well-resourced centers advocate use of MRI for all insertions, planar X-ray imaging remains the most commonly used imaging modality to assess intracavitary implants, particularly where the burden of cervical cancer is high. Incorporating soft tissue imaging into brachytherapy programs has been shown to improve the technical accuracy of implants, which in turn has led to improved local control and decreased toxicity. These improvements have a positive effect on the quality of life of patients undergoing brachytherapy for cervical cancer. Finding an accessible soft tissue imaging modality is essential to enable these improvements to be available to all patients. A modality that has good soft tissue imaging capabilities, is widely available, portable, and economical, is needed. Ultrasound fulfils these requirements and offers the potential of soft tissue image guidance to a much wider brachytherapy community. Although use of ultrasound is the standard of care in brachytherapy for prostate cancer, it only seems to have limited uptake in gynecologic brachytherapy. This article reviews the role of ultrasound in gynecologic brachytherapy and highlights the potential applications for use in brachytherapy for cervical cancer. Crown Copyright © 2015 Published by Elsevier Inc. on behalf of American Brachytherapy Society. All rights reserved.

### Keywords:

Ultrasound; Gynecologic cancers; Cervical cancer; Brachytherapy

### Introduction

Brachytherapy is an integral part of radiotherapy treatment for locally advanced cervical cancer. It has been used for well over 100 years (1). Although other forms of radiotherapy evolved through innovation and advances in technology during the 20th century, brachytherapy techniques for cervical cancer remained largely static. The story of brachytherapy for cervical cancer is eloquently told by Erickson (2) in which she outlines the reasons for this lack of progress. Early dosimetry systems brought structure and standardization to gynecologic brachytherapy; but while

other areas of radiotherapy progressed, gynecologic brachytherapy stalled within the confines of these dosimetric systems. Overtime, although there has been a growing awareness of the limitations of these standardized systems, the main drawback was the lack of use of modern imaging to appreciate and assess the individual nature of each women's anatomy and disease (3–12). The release of the Groupe Europeen de Curietherapie and European Society for Radiotherapy and Oncology recommendations for incorporating imaging, particularly MRI, into brachytherapy programs, is changing the way brachytherapy is being practiced (13–16). Traditional dosimetry systems consist of specific insertion techniques, applicators, prescribing and reporting, planning, and treatment methods; are all being challenged as soft tissue imaging is incorporated into practice. Sadozye and Reed (17) provide the next chapter to Erickson's unfinished tale in which they describe the use of modern imaging such as CT and MRI and the beneficial effects this use has on brachytherapy outcomes. These benefits include improvements in local control, overall survival, and very significant reductions in normal tissue

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toxicity (18–24). The chapter closes with Sadozye and Reed expressing hope that the uptake of image-based brachytherapy will be much better in the next 10 years than it has been in the previous decade. The most favored imaging modality for image-guided brachytherapy is MRI for its superior soft tissue definition, but uptake is largely hampered by cost and lack of access. CT is more accessible and so has seen greater uptake (25–31). Incorporating these imaging modalities into brachytherapy programs is largely restricted to well-resourced centers in both the first and developing world and remains elusive to many less well-resourced centers, particularly those in areas with a high burden of cervical cancer (32). The challenges of moving to 21st century image-guided brachytherapy treatment are faced by both the first and developing worlds in regard to resource procurement, resource allocation, and health care costs (25, 32). Challenges are also encountered in terms of the implementation of image guidance and the implications imaging has on the traditional practices of gynecologic brachytherapy (11, 25, 33, 34).

Ultrasound in gynecologic brachytherapy has featured from time to time over the years but has not found routine use and has tended to be overlooked in favor of more technically advanced imaging modalities. This article reviews the role of ultrasound in gynecologic brachytherapy and highlights the potential applications for use in brachytherapy for cervical cancer.

A search of the literature was performed in the bibliographic databases PubMed, Ovid Medline, and EMBASE using the keywords “ultrasound,” “gynecology,” “brachytherapy,” “endometrial cancer,” and “cervix cancer” in various combinations, up to June 2014.

#### Ultrasound use in brachytherapy to guide applicator placement

By far, the greatest use of ultrasound in gynecologic brachytherapy has been to guide applicator placement to avoid perforation, optimize the position within the uterine canal, and improve the technical quality of implants. Use of ultrasound to reposition a misplaced tandem was recognized as early as 1975 by Carson *et al.* (35). A number of prospective studies investigated the benefits of using ultrasound to guide applicator placement. Granai *et al.* (36) described applicator insertion “as blindly pushing a metal probe through an often distorted cervix to an unverifiable point.” They dispelled the prevailing thinking that ideal positioning of the intracavitary applicator is achieved using standard techniques of clinical palpation and X-ray confirmation. In a two-part study looking at ultrasound used during and after insertion, Granai *et al.* (36) found that 34% of the insertions were inadequate when assessed after insertion. This included frank perforations in 10% of the insertions. In the second part of the study, 72 of the 73 insertions assessed with intraoperative ultrasound were

optimally placed. The single case in which ultrasound did not facilitate placement involved cancer of the cervical stump, for which adequate imaging was not possible. Granai *et al.* (36) found that ultrasound clearly visualized the procedure, allowing applicators to be positioned with confidence even in the most difficult cases. The immediate feedback from intraoperative ultrasound eliminated misplacements and thus the need for a second anesthesia to reposition the applicator. Rotmensch *et al.* (37) investigated the use of intraoperative ultrasound for applicator placement in 20 implants. Unsatisfactory placement was detected in nine implants (45%) including six (30%) perforations. These complications were unknown to the clinician inserting the applicators. Rotmensch *et al.* (37) concluded that use of intraoperative ultrasound was helpful when difficulty was encountered in the placement of the applicator. Potential complications could be identified early without resorting to more invasive corrective procedures. Corn *et al.* (38) investigated whether the inclusion of intraoperative ultrasound converted a more dangerous insertion into a procedure with relative safety, akin to that of a procedure not requiring ultrasound. A total of 143 implants were performed on 100 women. Ultrasound was used for 20 implants in patients with stenosis of the cervical os, radiation fibrosis, indeterminate orientation of the axis of the endometrial cavity, and previous perforation. There were five (3.5%) instances of perforation (with two occurring in the ultrasound subset). It was noted that these two cases were among the first cases planned with ultrasound, implying the presence of a learning curve. Corn *et al.* (38) found that use of ultrasound may compensate for the inherent risks of perforation harbored by patients with difficult anatomy. Mayr *et al.* (39) evaluated the outcome of ultrasound-guided applicator placement in retroverted uteri. Thirty three insertions were performed to dilate the cervical canal and reposition the uterus to anteversion. Ultrasound-guided anteversion of the applicator and uterus was achieved in all procedures with no evidence of perforation. Mayr *et al.* (39) concluded that use of ultrasound was feasible and resulted in acceptable outcomes and complication rates in a population at high risk for uterine perforation. The technical quality of implants has been shown to impact on clinical outcomes for patients (40). The studies discussed range from the 1990s to 2005; and although they all showed that use of ultrasound improved the technical quality of implants and contributed to a decrease in perforation, they have not had a widespread impact on practices to date.

#### Rates of perforation detected with three-dimensional imaging

Although use of CT was being investigated for assessing dosimetry in intracavitary brachytherapy, some practitioners observed unexpected perforations of the uterus

(6). Barnes *et al.* (41) conducted a prospective study comparing clinical assessment of perforation with actual placement determined on CT. The incidence of CT-detected perforation was 13.7% (17/124 insertions). The CT detected perforation in 8.2% (8/98 insertions) where the clinician was clinically confident of correct applicator placement. After implementing three-dimensional (3D) CT imaging for intracavitary brachytherapy, Davidson *et al.* (42) observed perforations in 10% of insertions, similar to the findings of Barnes *et al.* (41). The rate of perforations detected is considerable and may account for unexplained toxicities detected in the past. Both groups recognized that imaging is needed at multiple points in the brachytherapy procedure, during applicator positioning, and for dosimetry calculation. Both groups identified ultrasound as the ideal imaging modality to ensure optimal applicator placement as it can be used intraoperatively. Davidson *et al.* (42) illustrated this concept when they sought to decrease perforations detected at CT by introducing routine use of intraoperative transabdominal ultrasound to guide applicator placement. In an initial analysis of 35 insertions, all but one were successfully guided by ultrasound. Although a number of investigators recommend the use of ultrasound for complicated cases and when perforation is clinically suspected, Small *et al.* (43) recommend using ultrasound for all applicator insertions after they detected an unexpected perforation at routine postimplant CT. They felt that uterine perforation was possible in any patient.

### Ultrasound use in planning

Ultrasound has been used to guide planning for patients with endometrial cancer since the 1970s. Ultrasound was specifically used to map the uterus, shape the isodoses,

and evaluate dosimetry, studies describing this use are summarized in Table 1.

Although ultrasound has been widely used to guide applicator placement in brachytherapy for cervical cancer, it has not been used to guide planning. This is probably due to the almost universal use of the Manchester prescribing system for cervical brachytherapy. Emphasis was on prescribing to a geometric point (Point A) rather than focusing on the individual patient's anatomy and pathology (2). Several authors have described and illustrated how ultrasound can be used to obtain measurements of the uterus to guide planning in endometrial cancer, but these methods have only recently been used in cervical brachytherapy (Fig. 1).

In general, two approaches have been used to investigate the use of ultrasound for planning cervical brachytherapy. These approaches consist of planning studies using ultrasound to guide treatment and validation studies comparing ultrasound against an accepted imaging modality, namely MRI.

### Using transabdominal ultrasound to guide treatment planning

Using ultrasound to plan treatment enables the cervix and uterus to be visualized and makes sparing of normal tissues possible. Two early studies looked at the use of ultrasound to assist in calculating dose to the bladder during brachytherapy for cervical cancer. Rahim *et al.* (54) found ultrasound to be the most appropriate method to evaluate the distance between the applicator and the bladder mucosa in brachytherapy implants for cervical cancer. Using similar methodology, Barillot *et al.* (51) also used ultrasound to measure the distance to the balloon of the Foley catheter, which indicates the International Commission on Radiation Units and Measurements Report 38 (ICRU-38)

Table 1  
Reports of use and benefit of ultrasound to plan brachytherapy treatment for endometrial cancer

Article (Ref)	Year of publication	Benefit of ultrasound
Carson <i>et al.</i> (35)	1975	Yield meaningful estimates of dose during intracavitary implants
Brascho <i>et al.</i> (44)	1978	Individualized treatment planning possible Facilitated applicator selection Calculation of dose at critical points within and around uterus Verification of applicator position in relation to the uterus Adaptation of plan
Englemeir <i>et al.</i> (45)	1985	Obtained cross-sections of the uterus using intrauterine ultrasound Sections were combined to form pseudo 3D projections on which dose coverage could be evaluated
Chun <i>et al.</i> (46)	1990	Recognized myometrial invasion could not be detected by CT or clinical examination Uterine wall thickness measured in different directions to calculate dose delivered to the mid-myometrium and serosal surface
Gunter and Degenhardt (47)	1995	Used ultrasound to localize the tumor Select suitable isodose curves and estimate dose to surrounding loops of bowel Verify position of applicator making injury to uterus and other organs less likely
Reuter (48)	1997	Ultrasound used to obtain measurements of the uterus for treatment planning in obese patients
Nguyen and Peteret (49)	1998	Ultrasound confirmed applicator placement Individually tailored radiation to each patient Noted decrease in toxicity



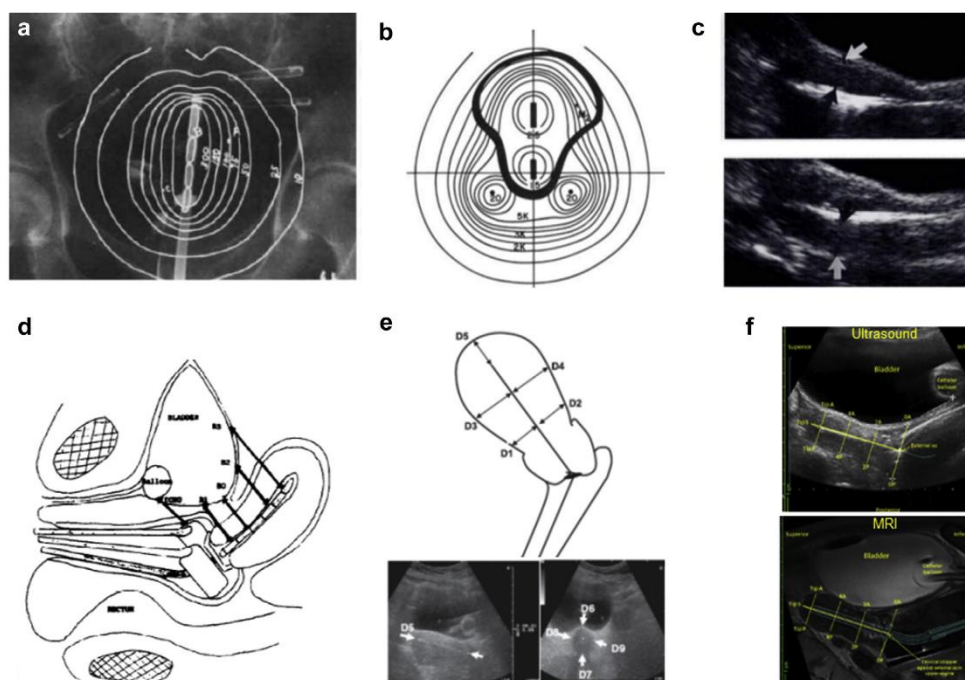


Fig. 1. Examples of ultrasound measurements of uterus used to guide brachytherapy planning. (a) Anteroposterior radiograph of the pelvis with tandem and sources in place. Serosal surface of uterus measured from ultrasound indicated by A in the image, isodose curves, labeled in rads per hour overlaid on radiograph [Wenzel (50)]. (b) Uterine outline superimposed over isodose curves for and tandem-and-ovoid applicator. The uterine size was determined from the ultrasound scan [Brascho *et al.* (44)]. (c) Sagittal transabdominal intraoperative sonograms of uterus show radiation applicators for cesium intracavitary treatment of endometrial carcinoma. Distance from applicators to uterine walls indicated by arrows [Reuter (48)]. (d) Methodology of recording measurements obtained with ultrasound showing distance from radioactive source to bladder mucosa [Barillot *et al.* (51)]. (e) Definition of measurement points from intrauterine applicator to uterine wall obtained with ultrasound. Measurements taken to assess suitability of ultrasound to guide planning [Mahantshetty *et al.* (52)]. (f) Nomenclature of measurement points on longitudinal ultrasound and MRI views of cervix and uterus. Measurements used to guide planning [van Dyk *et al.* (53)].

bladder reference point (55). Sixty-nine measurements were performed on 58 patients. Barillot *et al.* (51) also measured the minimum distances to the bladder in the axial and sagittal projections. These points were then transferred to orthogonal films and used to calculate the average dose to the bladder base. Barillot *et al.* (51) found excellent correlation between the ultrasound and orthogonal film calculations for the ICRU-38 bladder point, but found this point did not represent the mean and maximum bladder doses in more than 75% of the cases. Barillot *et al.* (51) introduced routine ultrasound for all gynecology applications to monitor bladder doses and while not stating specifically, inferred that adjustments to plans could be made to reduce bladder toxicity.

Van Dyk and Bernshaw (56) reported use of transabdominal ultrasound to guide applicator placement and plan conformal treatment for high-dose-rate (HDR) brachytherapy treatment of gynecologic cancers. Using two case

studies, one cervical and one endometrial cancer, van Dyk and Bernshaw (56) showed how intraoperative ultrasound can be used to optimize the applicator position and shape the isodose distribution to individual anatomy. This group further investigated use of ultrasound-based planning in a number of studies. In 2009, they published a retrospective planning study comparing isodose distributions resulting from standard plans, ultrasound-derived plans, 2D MRI-derived plans, and final dosimetry based on the combination of planning methods actually used in treating patients (57). Plans were based on 2D sagittal projections produced with ultrasound and MRI. There was neither any difference in target volume coverage between ultrasound and the 2D MRI-derived plans ( $p = 0.2$ ) nor between ultrasound and final dosimetry ( $p = 0.075$ ). The group concluded that ultrasound can be seen to offer comparable anatomical detail to the 2D MRI projections used in the study, allowing sufficient dose to be delivered to the target

area while sparing normal surrounding tissues. In a further study in 2009, Narayan *et al.* (19) compared an historical series of patients treated with low-dose-rate brachytherapy to patients treated with ultrasound-guided conformal HDR brachytherapy. Patients who received ultrasound-guided conformal brachytherapy received significantly less dose to Point A, but Narayan *et al.* (19) found no significant difference in 5-year overall survival or 5-year relapse-free survival between the groups. The authors also found significant differences in the dose received at ICRU-38 reference points for bladder and rectum. Patients who underwent ultrasound-guided conformal HDR brachytherapy received significantly less dose at these points. The effect of these differences was notable in that 68% of patients in the HDR group remained completely asymptomatic after treatment compared with 42% in the low-dose-rate group.

#### Validation studies

There is a perception that ultrasound is difficult to interpret and produces less accurate depictions of anatomy than MRI. This is despite the widespread use of ultrasound in diagnostic medicine to visualize and measure many organs within the body not the least of which is the human fetus *in utero*. Ultrasound is considered the gold standard in obtaining milestone images and measurements of the fetus and yet has failed to find widespread use in identifying the uterus for planning brachytherapy. As there is increasing familiarity and acceptance of MRI in gynecologic brachytherapy, MRI has been used as the standard against which to validate ultrasound. Two validation studies looking at the correlation and agreement between MRI and ultrasound have been reported.

Mahantshetty *et al.* (52) compared ultrasound and MRI measurements of the uterus and cervix to assess the potential value of ultrasound for image-guided cervical cancer brachytherapy. In a study of 20 patients and 32 applications using repeated measurements, this group looked for correlation between the imaging modalities. Although good correlation was found overall, the strongest correlation was found between measurements of the anterior surface of the cervix and uterus ( $R = 0.92$  and  $R = 0.94$ ;  $p < 0.01$ ). Measurements to the posterior surface had a moderate correlation ( $R = 0.63$  and  $R = 0.82$ ;  $p < 0.01$ ). They concluded that newer ultrasound systems could improve posterior wall identification and that ultrasound could be used in conformal brachytherapy but needed further evaluation. Van Dyk *et al.* (53) conducted a similar study using data from 192 patients. All measurements were recorded prospectively and only one pair of measurements were analyzed per patient (MRI vs. ultrasound at Fraction 1). This group used Bland–Altman methodology and looked for agreement between the imaging modalities rather than correlation (58, 59). Van Dyk *et al.* (53) found good agreement between the imaging modalities. In contrast to

Mahantshetty *et al.* (52), they found little difference between modalities when measuring the posterior surface of the cervix and uterus with mean differences of less than 1 mm. This was important as the organs at risk outside the posterior surface include the rectum and bowel. They were able to obtain clear and detailed images of the uterus and cervix with the interuterine applicator in treatment position. They concluded that such detailed images make it possible to practice image-guided, conformal, and adaptive brachytherapy using transabdominal ultrasound.

These planning and validation studies have been limited to intracavitary implants. Although these form the bulk of brachytherapy treatments for cervical cancer, there has been a steady increase in the use of intracavitary applicators combined with interstitial needles. These hybrid applicators are used in centers with advanced imaging capabilities such as MRI and CT. Ultrasound has not been investigated for use with these applicators other than in a study investigating transrectal ultrasound (TRUS) discussed in the following sections.

#### TRUS in gynecologic brachytherapy

Use of ultrasound in gynecologic brachytherapy has predominantly been performed with transabdominal ultrasound, although TRUS is being used in more advanced disease, primarily to guide insertion of both intrauterine applicators and interstitial needles (60–63). Stock *et al.* (61) describe using interstitial implants to treat patients with significant parametrial or paracervical extension that could not be adequately treated with intracavitary brachytherapy. They concluded that TRUS provided real-time visualization of the target volume and normal tissues, and allowed for accurate needle placement. Sharma *et al.* (62) reported on a series of 40 TRUS-guided interstitial brachytherapy procedures for patients with the International Federation of Gynecology and Obstetrics (FIGO) IIB and IIIB tumors, and found that TRUS assisted in avoiding needle injury of pelvic structures and reduced the risk of perioperative complications.

Schmid *et al.* (63) studied the feasibility of TRUS for the assessment of local target extension in patients undergoing brachytherapy for cervical cancer. They compared TRUS measurements of the cervix to MRI-based measurements. Two measurements were made, the width and thickness of the cervix on transverse planes. Height of the target was not examined. This was a small heterogeneous study of 17 patients, with measurements made at different time points in the patient's clinical journey. Pretreatment imaging was used for 5 patients, imaging taken before brachytherapy was used for 9 patients, and imaging taken with brachytherapy applicators *in situ* was used for 3 patients. Cervical width measurements were able to be taken in all patients with corresponding good correlation between TRUS and MRI ( $R^2 = 0.842$ ). Measurements of cervical thickness also showed good correlation ( $R^2 = 0.934$ ) but

with a systematic difference indicating an underestimation of thickness by TRUS. Cervical thickness could not be measured in the 3 patients with brachytherapy applicators *in situ*. Artifacts from the interstitial needles obscured the anterior wall of the cervix. Although the study found that TRUS can potentially be used to identify the brachytherapy target volume in image-guided brachytherapy, it did not confirm that TRUS can be used to guide planning using hybrid applicators. A further limitation of TRUS is the smaller focal length and field of view associated with endorectal probes. This will limit visibility of larger uteri requiring longer applicators.

#### Pros and cons of transabdominal ultrasound in gynecologic brachytherapy

The advantages and disadvantages of using ultrasound in gynecologic brachytherapy identified from the literature are listed in Table 2. The most advantageous aspect of ultrasound is the ability to view structures in real-time, whereas the most serious limitation seems to be the dependence on operators for a good image.

Ultrasound training does not form part of the core syllabus for radiation oncologists or radiation therapists, so it is not surprising that there is a level of discomfort and unease in using ultrasound. However, these professions are exposed to constantly advancing technology in both hardware and software, and recognize that training is needed to use these changes safely. So, although ultrasound is often perceived as easy to use, these craft groups understand the need for specific training and education (76). There is a role for limited scope training to educate and inform potential users about ultrasound. Similar training has been designed for specific use of ultrasound in a number of areas for other medical, paramedical, and nonmedical people (77–87). These training programs are designed to impart very specific skills and examination techniques that are particularly relevant to the different groups. Although most ultrasound use is concerned with diagnosis, other use is to enhance practitioner's ability to perform their job more efficiently or safely (88–91). These are two of the motivations for use of ultrasound in gynecologic brachytherapy. Table 3 lists the personnel performing ultrasound for brachytherapy identified in the literature. Although some mentioned a learning curve, none described the training required to

Table 2  
Pros and cons of ultrasound use identified from the literature

Pros (Ref)	Cons (Ref)
Cost (36, 37, 41–43, 51, 52, 56, 57, 64–68)	Needs physical contact (52, 53, 63, 69)
Low cost installation	Potential tissue deformation
Economical (cheap to use)	
Portable (41, 57, 64, 68, 70)	Learning curve (38, 52, 53, 56, 57)
Bring imaging to patient	Image acquisition
Able to integrate into OR easily	Image orientation
	Image interpretation
Nonionizing (44, 51)	No 3D co-ordinate system (53)
Safer for patient and staff	Cannot spatially allocate image
	No fixed frame of reference
Real-time intraoperative	No volumetric analysis of target coverage or dose to OAR (56, 57)
assessment (36–38, 40–44, 50, 53, 56, 57, 64, 66, 71–75)	
Anatomy topography	
Guide applicator choice	
Diagnose perforation	
Correct applicator misplacements	
Optimize applicator placement	
Speed (36, 42, 67, 68)	
Reduce time required for insertion	
Use for verification of applicator position at time of treatment (42–44, 49, 53, 56, 73)	
Use for verification of target volume (44–46, 49, 50, 53, 56, 74)	
Can use full bladder as bowel displacement device (51)	
View adjacent organs (e.g., loops of bowel) (47)	
Reduced reliance on other expert resources (42, 53, 73)	
Gynecologist	
Oncologist	
Radiologist	
Sonographer	
Applicator acts as fiducial marker and calibration device (53)	
Assists in understanding image orientation	
Serial imaging gives 4D changes to perform adaptive brachytherapy (53, 56, 57)	

OR = operating room; OAR = organ at risk.

Table 3

Personnel involved in performing ultrasound identified in the literature

Article (Ref)	Personnel performing ultrasound for insertion of brachytherapy applicators
Wong and Bhimji (71)	Patient taken to radiology department
Rotmensch <i>et al.</i> (37)	Initially, personnel trained in ultrasound (implies skill was later passed onto brachytherapy team)
Erickson <i>et al.</i> (92)	Radiologist
Davidson <i>et al.</i> (42)	Radiation therapist/physicist
Watkins <i>et al.</i> (75)	Ultrasound technician
Phelps and Peterit (74)	Sonographer
Schaner <i>et al.</i> (73)	Qualified technician
Mayadev <i>et al.</i> (34)	Sonographer with transition of skills to Radiation Oncologist
van Dyk <i>et al.</i> (53)	Radiation therapist with ultrasound qualifications

perform the procedure. Davidson *et al.* (42) certainly recognized the utility and efficiency of having a member of the brachytherapy team perform the ultrasound. This reduced the reliance on other expert resources such as radiologists or diagnostic sonographers. Mayadev *et al.* (34) originally used a certified technician but transitioned to the radiation oncologist performing the ultrasound to save time and optimize the workflow. Van Dyk *et al.* (53) used a radiation therapist trained in ultrasound to assist with applicator insertion and treatment planning.

The use of ultrasound to examine the obese patient can be challenging. Particular difficulties have been reported when using ultrasound to detect fetal abnormalities in obese pregnant women (93). However, none of the literature describing use of ultrasound in brachytherapy reported difficulties in obtaining images of the uterus and cervix in obese patients. This may be attributable to ultrasound being used to insert the applicator while the patient is anesthetized. This affords the sonographer ample opportunity to fill the bladder to ensure an optimal acoustic window into the pelvis and use of firm applicator contact without causing undue patient discomfort.

Although the uterus is easily visualized on ultrasound, there have been no reports describing the ability to see residual disease or gross target volume at the time of brachytherapy. This ability may well be addressed in the future as advances are made in ultrasound capabilities. Identification of the gross target volume is not crucial at the time of brachytherapy as the brachytherapy target incorporates the whole cervix (13), which is readily identifiable.

The literature describing use of ultrasound for planning brachytherapy for cervical cancer is very limited. There are still questions and areas of practice that need to be addressed, with training and education in ultrasound use being foremost. Once appropriate training has been obtained,

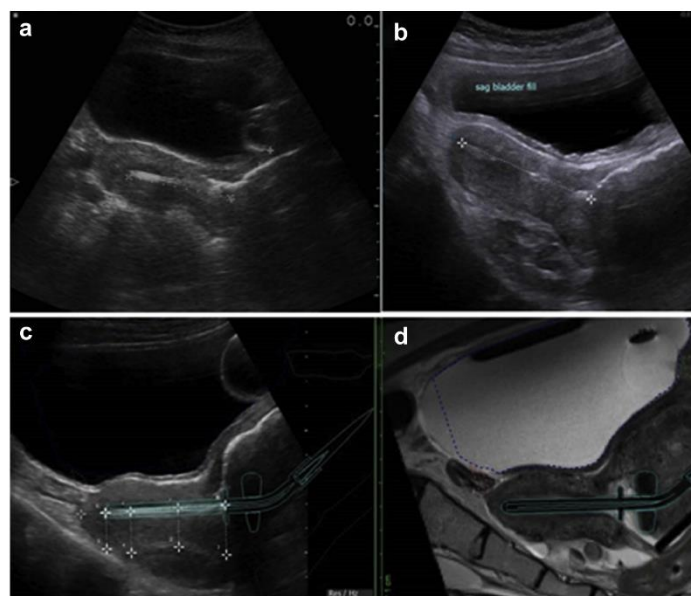


Fig. 2. Example of improvements in quality of ultrasound images with new ultrasound technology. (a) Sagittal view of applicator in uterus taken in 2008 with Falcon ultrasound unit (BK-Medical, Herlev, Denmark). (b) Sagittal view of applicator in uterus taken in 2010 with Flex focus 400 ultrasound unit (BK-Medical, Herlev, Denmark). (c) Sagittal view of applicator in uterus taken in 2012 with Flex focus 400 ultrasound unit (BK-Medical, Herlev, Denmark). (d) Sagittal view of applicator in uterus on MRI taken in 2012 same patient as image c. Source of all images: Peter MacCallum Cancer Center.



Table 4  
Patterns of care studies indicating imaging modalities used during brachytherapy for cervical cancer

Article (Ref)	Ultrasound used for insertion	Imaging modality used for planning	Imaging used for verification fx 2 3 4 5
van Dyk <i>et al.</i> (94) Australia and New Zealand (Ref period: 2009)	15%	X-ray: 30% CT: 65% MRI: 15% US: 5%	CT: 55% X-ray: 5% US: 10%
Viswanathan <i>et al.</i> (27) ABS United States (Ref period: 2007)	56% 42% routinely	CT: 56% (United States only)	CT: 60% (USA + International)
Guedea <i>et al.</i> (31) Europe (Ref period 2007)	48% available	X-ray: 71% CT: 54% MRI: 15% PET-CT: 5%	
Pavamani <i>et al.</i> (29) Canada (Ref period: 2008)	59% 24% routinely	X-ray: 50% CT: 45%	CT/MRI: 44%
Tan <i>et al.</i> (30) United Kingdom (Ref period: 2010)		CT: 51% MRI: 20%	
Guedea <i>et al.</i> (32) Latin America (Ref period: 2007)	24% available	X-ray: 97% CT: 22% MRI: 0.2%	
Viswanathan <i>et al.</i> (28) GCIG International (Ref period: 2008/2009)	62% available 18% routinely	CT: 57% MRI: 25%	CT: 37% MRI: 11%

ABS = American Brachytherapy Society; US = ultrasound; PET = positron emission tomography; GCIG = Gynecologic Cancer Intergroup.

guidelines for use need to be established that explain planning technique and reporting mechanisms.

There have been many advances in ultrasound technology progressing it from the gray fuzzy and indiscernible images from early machines to images that rival the detail of MRI (Fig. 2). These advances include improved transducer sensitivity, faster image processing speed, higher resolutions, panoramic imaging, 3D/4D imaging, elastography, contrast imaging, and smaller portable units. The gains achieved from using these technologic advances in diagnostic examinations will also influence how ultrasound is used in brachytherapy.

#### Use of ultrasound around the world

The use of ultrasound in gynecologic brachytherapy was identified from patterns of care surveys (Table 4). There is reasonable availability of ultrasound in the United States, Europe, and Canada, although not all surveys asked specific questions in relation to ultrasound use or availability. Only one department in Australia reported using ultrasound for planning brachytherapy. This department and a further department from New Zealand reported using ultrasound for verification of the applicator position during the course of brachytherapy. Although ultrasound is commonly available in hospitals and increasingly available in radiotherapy departments, these surveys indicate limited uptake for brachytherapy. Planar X-ray images remain the most common imaging modality used to plan brachytherapy treatments, particularly in the developing world.

#### Future directions

At present, ultrasound is largely limited to guiding applicator placement in brachytherapy for cervical cancer. Extrapolating use to plan brachytherapy has only been conceived by a few practitioners (52, 53). Incorporating soft tissue information obtained from 2D ultrasound can improve the technical quality of brachytherapy implants and has the potential to allow 3D conformal planning to be performed (52, 56). The 2D ultrasound images can be used to create 3D treatment plans as it is now possible to upload 2D images to some treatment planning systems (53). It is also possible to upload 3D data sets. The 3D ultrasound acquires volume data of the pelvis that can be processed for display in multiplanar reconstructions similar to CT and MRI (95). These volumes are very similar in orientation and quality to those of MRI and CT (95). Use of 3D ultrasound can overcome some of the disadvantages of 2D ultrasound. Volumetric scanning may reduce the reliance on operator skill as a 3D volume can be acquired by a mechanical sweep of the transducer. Users would no longer need to mentally integrate 2D images to form an impression of the anatomy and pathology in three dimensions (96). Although use of 3D ultrasound volumes to plan gynecologic brachytherapy has not been clinically tested, there is huge potential for this modality in limited resource settings. Use of 3D ultrasound would allow radiation coverage of the uterus and cervix to be volumetrically assessed generating similar analytical metrics to those obtained with CT and MRI.

Training and education of brachytherapy personnel in use of ultrasound also has to be addressed to obtain the

maximum benefit from the many features of these machines and to ensure safe and efficacious use.

### Conclusions

There is a large range in the resources used to plan brachytherapy for patients with cervical cancer. Progress is slowly being made as sophisticated imaging modalities are introduced into well-resourced centers, but most patients with cervical cancer around the world continue to be planned with planar X-ray imaging. There is a crucial unmet need for soft tissue imaging capabilities in gynecologic brachytherapy. Ultrasound has the potential to meet this need by offering soft tissue imaging capabilities to all brachytherapy departments. Ultrasound is an accessible and economical imaging modality that can readily be incorporated into brachytherapy programs. Transabdominal ultrasound and TRUS can be used to guide placement of intracavitary and interstitial applicators, respectively. Transabdominal ultrasound can be used to guide intracavitary planning. Appropriate training for brachytherapy personnel is necessary to ensure safe and optimum use. Guidelines for planning and reporting treatment are also necessary. Ultrasound can be used to improve the technical quality of implants. These improvements have the potential to improve local control and reduce toxicity in these patients.

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Editorial in regard to Chapter 4: Comparison of measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix cancer  
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**EDITOR'S SELECTION**

**Date:** April 2014  
**Editor or Editors:** ANTHONY H. RUSSELL, M.D., DAVID GAFFNEY M.D., Ph.D.  
**Topic | SubTopic:** Gynecological | Cervix  
**Article:** **Comparison of measurements of the uterus and cervix obtained ...**

**Comment By:** **DAVID GAFFNEY M.D., Ph.D.**

Mirror, mirror on the wall, what is the best imaging modality of them all?

For image-guided brachytherapy, MRI is the gold standard due to its soft-tissue discrimination. For evaluating implant placement dynamically, US is optimal. Additionally, CT has also been shown to be highly reproducible for gynecologic image-guided brachytherapy and to differ little from MRI. These experienced authors from Peter MacCallum Cancer Centre make the practical argument that one should use what is available.

This study evaluates ultrasound as a method to identify the brachytherapy target in 192 patients with cancer of the cervix. The authors indicate that MRI is expensive and difficult to access for many physicians. A particular strength of the study is that these authors perform both ultrasound and MRI. In only 2 of 192 patients could the cervix and uterus not be adequately imaged due to fibroids greater than 8 cm. There are attributes of US that make it highly desirable. First, US is widely available and not too expensive. The authors indicate that in high-resource settings, US can be used as an aid in conjunction with MRI or CT to verify applicator position. In limited-resource settings, US can be used as the primary imaging modality to provide accurate information for applicator insertion, to identify the target, and to plan image-guided treatment. Significant limitations, however, with US include 1) defining organs at risk; 2) defining the high-risk CTV as defined by the GEC-ESTRO guidelines; and 3) developing expertise in this operator-dependent modality. US is a powerful imaging tool that has proven use in the radiation oncology clinic. This is an important contribution to the literature and a valuable modality for use in brachytherapy.

<https://www.acrjournaladvisor.com/User/EditorsChoice?id=1&date=4/1/2014%2012:00:00%20AM#Comparison%20of%20measurements%20of%20the%20uterus%20and%20cervix%20obtained%20by%20magnetic%20resonance%20and%20transabdominal%20ultrasound%20imaging%20to%20identify%20the%20brachytherapy%20target%20in%20patients%20with%20cervix%20cancer>.

## Letter to Editor in regard to Chapter 4: Comparison of Measurements of the uterus and cervix obtained by magnetic resonance and transabdominal ultrasound imaging to identify the brachytherapy target in patients with cervix

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(RILA) and chronic toxicity in patients receiving radiation therapy (3, 4). Understanding the risks associated with radiation-induced toxicity is a challenge in radiation oncology. If we can differentiate between radiosensitive patients and those who are not, we may in some cases be able to increase the dose without increasing the risk of toxicity. This is especially important in prostate cancer as we know that increasing the dose improves outcomes. Based on previous publications studies by Ozsahin et al (5), we conducted a prospective study with a homogeneous group of patients diagnosed with prostate cancer that were candidates for radiation therapy. We found a significant relationship between RILA and chronic genitourinary toxicity (1). Patients with a percentage of RILA in T-lymphocytes below the mean had a higher risk of toxicity after radiation therapy, our results confirmed those obtained by Ozsahin et al (3), although these results should be confirmed using a larger series, as the study has recently begun (REQUIRE).

In addition, we observed in our study a significant relationship with the overall survival and RILA of CD8 T lymphocytes that the probability of death during follow-up was 2.7 times higher in patients when the percentage of RILA was below the mean value. The same conclusion was shown in a recent publication by Ordoñez et al (6). This showed that RILA of CD8 T lymphocytes was a predictive factor for survival in patients with cervical cancer. Patients who had a low percentage RILA of CD8 T lymphocytes had lower local disease-free survival, regional disease-free survival, disease-free survival, and cause-specific survival. In addition to being a predictor of toxicity, RILA could also be a predictive factor for response. However, the data should be confirmed by conducting additional studies with a larger series, which our group will continue to investigate in future studies.

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### Comparison of Measurements of the Uterus and Cervix Obtained by Magnetic Resonance and Transabdominal Ultrasound Imaging to Identify the Brachytherapy Target in Patients With Cervix Cancer

In Regard to van Dyk et al



*To the Editor:* We read with great interest the report by van Dyk et al (1) in which the authors compared magnetic resonance imaging (MRI) to transabdominal ultrasonography for use in identifying the brachytherapy target in patients with cervical cancer. In recent years, ultrasonography imaging has re-emerged in oncology and can now be considered, together with computed tomography and MRI, a reliable method for diagnosis, staging, treatment planning, and follow-up in several malignancies (2, 3).

We want to congratulate the authors for their large, well-designed study that included numerous measurement comparisons between the 2 imaging techniques. However, we would like to address 2 issues that caught our attention.

First, regarding the methodology of cervical tumor evaluation, given that the target volume for brachytherapy must include the initial tumor extension (ie, intermediate risk clinical target volume), we believe that it would have been useful if the authors had also provided the same comparison at the beginning of the treatment, before external beam radiation therapy (4).

Second, it is important to note that although transabdominal ultrasonography is a widely available imaging method, it has its limitations (as the authors acknowledged) in patients with pelvic pathologies or those with significant obesity. In such cases, transrectal ultrasonography (TRUS) is another, "older," imaging technique that has new applications, such as evaluation of uterine cervical tumors (5). In fact, recent studies have found that in early-stage cervical cancer, TRUS may even be more precise than MRI in evaluating the primary tumor and parametrial invasion (6). Of course, like transabdominal ultrasonography, the limitations and accuracy of TRUS are dependent on 3 variables: (1) the operator, who should have extensive experience with abnormal findings and complementary imaging methods; (2) the equipment (ie, sensitivity and type of endocavitary probe); and (3) the patient characteristics (eg, the presence of air in the bowel) (7). When a modern intrarectal probe, which

offers the possibility of sagittal scanning and a broad view of the anterior and posterior compartments of the pelvic floor, is used, the correlation between TRUS and MRI measurements in brachytherapy treatment planning is very high (8).

Finally, we fully agree with the authors' conclusion that in limited-resource settings, ultrasonography imaging is sufficiently accurate to replace more expensive methods such as MRI in diagnosis and treatment planning for uterine cervix tumors. The choice between transabdominal and transrectal ultrasonography should be made according to each center's local experience.

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## In Reply to Coza and Ordeanu



*To the Editor:* We appreciate Drs Coza and Ordeanu's interest in our report comparing magnetic resonance imaging (MRI) with transabdominal ultrasound for use in identifying the brachytherapy target in patients with cervix cancer (1, 2).

Two issues were raised, to which we would like to respond.

First, we do not agree that the brachytherapy target must include the initial tumor extension intermediate-risk clinical target volume (IRCTV). The concepts of both high-risk clinical target volume (HRCTV) and IRCTV were developed as reporting recommendations for practitioners embarking on 3-dimensional imaging protocols for cervix brachytherapy. As is want to happen, these reporting recommendations are being interpreted as practice guidelines. We have shown that treating the original primary disease and any extension in surrounding tissues to 40 to 45 Gy with an additional boost of 6 or 10 Gy to positron emission tomography/computed tomography—positive nodes, and thereafter treating cervix and any remaining disease with conformal brachytherapy is adequate for locoregional control (3, 4).

Second, we have not found significant limitations in our use of transabdominal ultrasound and did not report any limitations in regard to patient body habitus. Although all patients in our study underwent MRI, we do encounter patients that cannot. These morbidly obese patients are often unable to undergo MRI owing to limitations in bore size. Use of ultrasound is the only recourse for these patients.

Regarding the use of transrectal ultrasound (TRUS), the studies cited all looked at correlations between MRI and TRUS in early-stage cancers, assessing resectability for surgical treatment (5). The 1 small study looking at TRUS assessment of cervix cancer at the time of brachytherapy only included 3 patients with applicators in situ (6). The cervix width was compared, but measurement of cervix thickness was not able to be obtained with TRUS owing to applicator artifacts. This does not constitute a high correlation. To plan brachytherapy effectively, both the target tissue and the applicators must be visible. We did not encounter difficulties in measuring width, thickness, or height of the cervix using transabdominal ultrasound with the applicators in treatment position. We would find TRUS impractical to use during applicator insertion and inadequate to plan treatment.

We agree that TRUS may be a credible alternative when assessing tumor extent and response. We also agree that departments need to be innovative with the resources available to them to improve the quality of care for their patients.

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## Chemoradiation of Hepatic Malignancies: Prospective, Phase 1 Study of Full-Dose Capecitabine With Escalating Doses of Yttrium-90 Radioembolization

### In Regard to Hickey et al



*To the Editor:* This was a very interesting and timely study (1) evaluating the use of a radiosensitizer with radioembolization; however, there are methods and findings which merit further explanation.

Why did the study design include a cycle of capecitabine alone prior to radioembolization? When using the drug as a sensitizing agent for chemoradiation, it needs to be given concurrently with radiation, according to National Comprehensive Cancer Network (NCCN) Guidelines (2). Given the rapid excretion of capecitabine, there was no therapeutic benefit, and it appears that this only added risk and cost. This added risk is supported by the fact that 9 of 16 patients required drug dose reductions based on drug toxicity.

Complication data and consensus statements addressing radioembolization (3, 4) support lobar or segmental radioembolization as a safer alternative to whole-liver treatments in the salvage setting. What was the rationale for whole-liver versus lobar or segmental treatments in these pretreated patients, especially in the patients with low tumor burden? Three of the patients in the study had tumor volumes of 5% or less. These patients certainly received a high radiation dose to normal liver tissue. In particular, the patient with cholangiocarcinoma and a 1% tumor burden who reportedly received 170 Gy to the whole liver would have received a nearly equal dose to normal liver tissue as tumor. An explanation of how the liver can tolerate these high

radiation doses from radioembolization, when comparable external beam radiation levels are sure to be profoundly hepatotoxic would be helpful.

Using the data reported in this study, independent calculations performed using the standard Therasphere (BTG, Canada) dose calculation formula from the TheraSphere package insert {activity required [GBq] = desired dose (Gy) × liver mass (kg)/50 × (1-lung shunt fraction)}, reveal that the patient with the largest liver in the study (4833 cc or 4.98 kg, and assuming lowest lung shunt of 2%) would require a whole-liver dose of 13.2 GBq to achieve the corresponding absorbed dose of 130 Gy, well above the highest reported administered activity of 4.98 GBq. In fact, performing this calculation for all patients in the study with reported liver volumes and activities reveals that at least 8 of the 16 patients would require more than 4.98 GBq to obtain reported absorbed doses. What is the explanation of these much lower-than-expected administered activities if indeed whole-liver volumes were treated?

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### In Reply to Putnam



*To the Editor:* We appreciate the commentary by Dr Putnam regarding our article and offer some responses (1, 2).

With regard to the assertion that capecitabine alone provided no therapeutic benefit, we remind the authors that the treatment paradigm for this study included capecitabine for 1 cycle (2 weeks on/1 week off); this permitted us to adjust capecitabine for patient tolerance (like all chemotherapeutics) before Yttrium-90 (Y90). This was followed by Y90 during the first week of cycle 2 at the tolerable



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## INTRODUCTION



We have had, as always, a large selection of abstracts submitted from which we have selected an exciting programme of high-quality proffered papers for the brachytherapy track of ESTRO 33. These reflect many aspects of modern image-guided brachytherapy covering some of the major sites: gynaecology and prostate, as well as a major physics contribution and less common clinical indications such as choroidal melanoma. We have 'donated' our best papers to the 'highlights' sessions to ensure that brachytherapy is seen by a wide audience as a major important modality in radiation oncology. In addition I have selected five of those chosen for presentation in the brachytherapy track which are shown here demonstrating the breadth and depth of the brachytherapy programme.

Image guided brachytherapy for cervical cancer is now generally accepted as the gold standard however many radiotherapy centres, particularly in less well developed health care environments struggle to apply the GEC-ESTRO guidelines which are based on MR imaging. The paper from Melbourne evaluating ultrasound as a means of imaging to define the target volume is therefore of great importance in developing the image-guided concept beyond MR. No clinically significant differences in measurement using MR or ultrasound in 141 patients was seen providing considerable reassurance for those who are able to access ultrasound but not MR or CT that this offers a viable and potentially equivalent approach which can be used to integrate the advantages of image-guided cervical brachytherapy into practice.

LDR brachytherapy is now well established as an effective treatment for early prostate cancer having a highly favourable toxicity profile. Considerable advances have been made in the technique based on real time implant dosimetry. These however depend upon accurate tracking of seed deposition at the time of implantation. The paper from Quebec is therefore of considerable interest in describing a novel approach using RF electromagnetic technology to accurately validate the seed drop position during a seed implant. Evaluation in a phantom using this EM hollow needle prototype has achieved a detection rate of 100% with a mean position error of only 1.5mm. Successful integration of this novel technology into brachytherapy systems for LDR prostate implantation will have a further impact on improving implant quality as we strive to optimise our techniques.

One of the major advantages of LDR brachytherapy over radical surgery is the different toxicity profile and in particular the chance for many men to retain potency. The series from Vienna featured here is therefore important in providing mature data on this effect after seed brachytherapy with either palladium or iodine. The strength of this study lies in the prospective evaluation of erectile function with patient-based questionnaires using the internationally recognised IIEF scale. Overall potency was maintained in 46% at two years and 51% over five years in a large cohort of 285 patients with no major effect seen in age up to 70 years, previous use of androgen deprivation therapy or external beam therapy. This series confirms therefore the very high potency rates to be expected after seed brachytherapy and gives us robust data with which to counsel patients considering this approach.

Local relapse of prostate cancer presents a difficult management problem with no clear preferred option, until recently re-irradiation has not been widely considered but the ability to deliver localised high doses to the prostate using brachytherapy is now being exploited by several groups in this setting. The contribution from the group in Gliwice describing their experience using high dose rate brachytherapy for recurrent prostate cancer in 61 men is therefore of great interest. Toxicity after reirradiation is always of concern and it is encouraging to note only one grade 3 acute urinary toxicity event and late toxicity limited to grade 2 or less in 55 patients. Three year disease-free survival was 69% with eight patients developing metastatic disease and an overall survival at three years of 98% falling to 83% at five years. Their conclusion that HDR brachytherapy is a good option in carefully selected patients is borne out by their data and should encourage other groups to explore this approach in well-designed prospective studies.

In addition don't miss out on reading the two abstracts which have received awards. The paper by V. Rudzianskas from Lithuania has been selected for the GEC-ESTRO Best Junior Presentation Award. This addresses the important area of reirradiation in head and neck cancer and reports on 64 cases treated in a prospective randomised study using salvage external beam or HDR brachytherapy. Superior local control rates were achieved with brachytherapy. The authors are to be congratulated for completing a prospective randomised study in this difficult area providing us with important data supporting HDR brachytherapy as the preferred salvage modality. The ESTRO-Nucletron brachytherapy award is presented to H. Westerveld for her paper on a novel dose reporting method for vaginal dose in gynaecological brachytherapy demonstrating the utility of the new reporting parameters in comparing vaginal dosimetry across centres in the EMBRACE study (European and International study on MRI-guided brachytherapy in locally advanced cervical cancer).

Peter Hoskins

Chair of the Scientific Advisory Group for Brachytherapy



1.

## USING MRI AND INTEGRATED ULTRASOUND TO GUIDE BRACHYTHERAPY FOR CERVIX CANCER

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### BACKGROUND

Incorporating MRI imaging into multi-fractionated gynaecological brachytherapy programmes is difficult. Alternative imaging modalities have to be sought which enable imaging to be used at all fractions and all stages of the procedure. Ultrasound is an accessible imaging modality that can be used to guide applicator insertion, position, identify the target volume and surrounding tissues, assess dosimetry, and verify treatment (Fig.1).

### OVERVIEW OF ABSTRACT

The purpose of this research was twofold:

1. To compare measurements of the cervix and uterus made with MRI and ultrasound to determine the level of agreement between the imaging modalities.
2. To evaluate changes in brachytherapy volume over the course of treatment with ultrasound.

### WHAT WERE THE THREE MAIN FINDINGS OF YOUR RESEARCH?

1. There was good agreement of measurements of the cervix and uterus on MRI and ultrasound. This means ultrasound can be used in conjunction with or as an alternative to MRI in limited resource settings.
2. Agreement was strongest at the posterior surface of the cervix and uterus. This is important as accurate identification of the posterior uterine wall ensures radiation can be conformed to the uterus and so avoid the surrounding rectum and bowel.
3. Changes in measurements to the posterior uterine wall over the course of brachytherapy were not statistically significant. This means a conformal plan devised at fraction one can be used over the course of treatment reducing the rate of replanning (Fig.2).

### WHAT IMPACT COULD YOUR RESEARCH HAVE?

The implications of these findings are that it is possible to integrate an accessible imaging modality (ultrasound) into gynaecological brachytherapy programmes. Use of imaging at each insertion and at each stage of the procedure ensures greater technical accuracy of applicator placement and

greater precision of dose delivery. This has the potential to enable individualised conformal treatment to be planned and delivered. The impact of this is better targeted radiation with scope for dose escalation and reduced toxicity.

### IS THIS RESEARCH INDICATIVE OF A BIGGER TREND IN ONCOLOGY?

This research is indicative of trends in oncology that seek to offer individualised treatment to patients. Use of imaging to verify beam placement and target coverage prior to treating with external beam is becoming standard of care. This research highlights how this is possible in gynaecological brachytherapy.



Fig. 1. Ultrasound at each insertion and stage of the brachytherapy procedure.

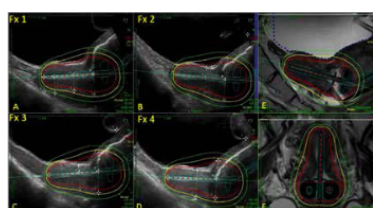


Fig. 2. Ultrasound used to guide applicator insertion, verify the brachytherapy volume, and assess dosimetry over the course of brachytherapy.

- A. Transabdominal ultrasound - longitudinal view of uterus with applicator in situ at fx 1 showing ultrasound based volume coverage.
- B. Transabdominal ultrasound - longitudinal view of uterus with applicator in situ at fx 2 showing same volume distribution as fx 1, then volume change in treatment volume or volume coverage.
- C. Transabdominal ultrasound - longitudinal view of uterus with applicator in situ at fx 3 showing same volume distribution as fx 1, then volume change in treatment volume or volume coverage.
- D. Transabdominal ultrasound - longitudinal view of uterus with applicator in situ at fx 4 showing same volume distribution as fx 1, then volume change in treatment volume or volume coverage.
- E. T2 sagittal MRI - view of uterus with applicator (taken at fx 4). Isodose coverage was derived on ultrasound and bulk projected onto MRI after treatment had been delivered.
- F. T2 coronal MRI - view of uterus with applicator (taken at fx 1). Isodose coverage was derived on ultrasound and bulk projected onto MRI after treatment had been delivered.

## Editorial in regard to Chapter 5: Assessing changes to the brachytherapy target for cervical cancer using a single MRI and serial ultrasound



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BRACHYTHERAPY

### Editorial

## High-tech image-guided therapy versus low-tech, simple, cheap gynecologic brachytherapy

There is overall agreement that major progress in radiation oncology has been achieved during the last decades through major progress in imaging, treatment planning, treatment delivery, and information technology (1). This not only applies for external beam radiotherapy (EBRT) but also for brachytherapy, in particular for prostate and cervix cancer. Clinical evidence for progress in outcome has been provided mainly from monocentre and multicenter patient cohorts, with more clinical evidence recently reported also from prospective clinical trials. “Image-guided brachytherapy,” therefore, remains one of the “hot topics,” both in regard to current challenges in clinical practice and to research and development activities (2).

In EBRT, “image guidance” is linked to the most sophisticated technology, for example in using functional MRI and positron emission tomography CT or positron emission tomography MRI for treatment planning or cone beam CT or the upcoming MRI linac technology for treatment verification. In brachytherapy, “image guidance” has become standard of care in prostate brachytherapy with volumetric ultrasound (US) imaging and is currently under increasing consideration for gynecologic brachytherapy, in particular for cervix cancer. Volumetric imaging-based brachytherapy, in particular using morphologic MRI, has provided excellent clinical outcome in regard to local control and survival (3, 4). However, in big contrast to the “world of EBRT” where new technologies are increasingly implemented—often without major clinical evidence—, there is still major discussion in the radiation oncology community, if volumetric imaging for gynecologic brachytherapy, in particular MRI, is really needed, or if maybe CT is sufficient, or if even more simple radiographic techniques might be appropriate. Although sophisticated US techniques providing three-dimensional (3D) scans or CT are without question becoming state of the art for prostate brachytherapy, for cervix cancer brachytherapy, there is still discussion if volumetric imaging should be integrated into daily clinical practice.

One major discussion for cervix cancer is to make treatment as simple and cheap as possible as this is a frequent disease worldwide (~500,000 new cases per year), predominantly occurring in countries with limited resources. There is no doubt that any treatment modality should be as effective as possible—both in terms of patients’ benefit but also

in terms of costs. Three-dimensional brachytherapy for cervical cancer has been recently shown to be cost-effective (5). Cost-effective image-guided brachytherapy is an essential topic for countries with limited resources and institutions with high patient numbers and many presenting at an advanced stage. However, much investment goes into new high-tech equipment for EBRT (including robotic radiosurgery, helical delivery, image-guided radiotherapy, and particle beam therapy) which is increasingly installed (6), whereas new modern brachytherapy equipment, for example for image-guided BT in cervix cancer, does not follow the same trend. We do not see any rationale why image-guided brachytherapy for cervix cancer should be mainly simple and cheap: It should be disseminated and implemented worldwide according to the technological and clinical evidence provided.

The use of US for image guidance in cervical cancer brachytherapy seems attractive for various reasons: A reasonable soft tissue contrast—also for tumors infiltrating into the parametria (7)—, the possibility for real-time imaging, an easy handling (after a learning phase), low costs, and a vast experience as diagnostic tool in the field of gynecology obviously qualify US for its application in cervical cancer brachytherapy.

The Peter MacCallum group was among the first to start such an ambitious project to investigate and clinically use transabdominal US in cervical cancer brachytherapy resulting in a large number of patients treated based on US and reflected in a considerable number of publications. Altogether, various steps for using US in the treatment chain of cervical cancer brachytherapy have been described so far by various groups in small patient cohorts, including intraoperative image guidance, target volume assessment, treatment planning, and treatment verification (8). Such steps were found to be clinically feasible and even comparable to MR image-guided adaptive brachytherapy (IGABT) in target assessment (9–11).

The advantages of US as intraoperative real-time image guidance to support tandem insertion and avoid uterine perforation are unquestionable (12). The use of abdominal US for target assessment and treatment planning is, however, controversially discussed (13, 14). Limitations in detecting parametrial invasion, absence of volumetric imaging, and significant interobserver variation seem to reduce the

applicability of transabdominal US for target volume assessment. The complex target assessment approach in the present study, which is based on the combination of transabdominal US, transvaginal US, and clinical examination, confirms these limitations (15).

Treatment planning as described in the current Peter MacCallum study is based on several reference points derived from single US snapshots. This represents a slightly advanced two-dimensional treatment plan and is definitely no 3D-volumetric treatment plan. Such a treatment planning approach may—as a next step to simple point-A-based approaches—work well for limited residual tumors at the time of brachytherapy confined to the cervix. However, in more advanced tumors with moderate-to-poor response to EBRT ± chemotherapy, in which the highest benefit in local tumor control is to be expected from MRI-based IGABT, the situation is different. The technique described here with serial US images is not able to account for extracervical disease extent at the time of brachytherapy. The relatively low number of advanced tumors in the published US series confirms these limitations for advanced parametrial disease.

What is currently missing is a comprehensive and fair comparison between optimal MRI-based IGABT including combined intracavitary and interstitial implants for advanced disease and optimal US-based IGABT in such patient cohorts. Furthermore, the US technique used in the Peter MacCallum study does not account for critical organ motion between the fractions which can affect treatment planning and risk of complications. In contrast to sophisticated methods used in prostate brachytherapy with transrectal US assessments, this simple US method is not containing 3D-volumetric data sets.

The Peter MacCallum group did a great job during the last decade in creating an affordable and pragmatic solution for US-based brachytherapy for cervical cancer. We see this solution somewhere between point-A-based brachytherapy and MRI-based IGABT, in regard to treatment conformity. This method may be useful, mainly in limited size and well-responding tumors, which are confined to the cervix at the time of BT. However, this clinical scenario does not represent most patients in advanced stage as seen in the countries with high patient numbers and limited resources. From this point of view, it seems to be simple and cheap but may be not as effective for bringing full benefit of image-guided brachytherapy to the patients.

Why not to exploit the full potential of US, also integrating transrectal US? Because of its technological properties, transrectal US enables depicting parametrial (residual) disease at the time of BT—Epstein *et al.* (7), for example, demonstrated in a prospective multicenter study that transrectal US was even superior to MRI for the detection of parametrial infiltration compared with histopathologic results. The successful development of US-guided prostate cancer brachytherapy during the last decades may serve as a model (16). Why not integrate the most modern US equipment and

methods into cervix cancer brachytherapy? US has obvious advantages (see previously mentioned advantages) which can clearly match and even complement MR- or CT-IGABT.

In the era of diversification, sophistication, and individualization of (radiation) oncology, we should be careful with aiming at making brachytherapy mainly simple and cheap—this may lead to a further decline of brachytherapy. Recent epidemiologic studies from the United States show an increasing trend for using sophisticated intensity-modulated radiation therapy (IMRT)/stereotactic body radiation therapy (SBRT) boost replacing two-dimensional brachytherapy for cervical cancer during the last decade; its detrimental effect on survival is alarming (17–19).

Physical dose distribution of intracavitary and interstitial brachytherapy is optimal, appropriate imaging techniques are available and compatible with applicators (MRI, US, and CT)—they even visualize the delivery device together with anatomy—, treatment planning tools have been developed and clinically tested, and most accurate dose delivery verification systems are under development. Upcoming clinical evidence is encouraging, in particular for advanced disease. Therefore, the overall international road map must be to build a comprehensive system of image-guided gynecologic brachytherapy integrating all the various technological possibilities and making them available for the various clinical scenarios—comparable with EBRT—which then can lead to their worldwide dissemination and implementation. This is more than “simple and cheap” but will serve the needs of women in one world living in regions with varying resources.

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## Response to Editorial by Kirsits et al.



Brachytherapy 15 (2016) 205–206

BRACHYTHERAPY

Gynecologic Oncology

In response to Kirsits,  
Schmid, Beriwal, and PotterHigh-tech image-guided therapy vs. low-tech, simple,  
cheap gynecologic brachytherapy

We thank the authors for drawing attention to the disparities existing between external beam radiotherapy and brachytherapy, particularly in relation to the use and availability of advanced imaging and treatment technologies used to treat cervix cancer. We understand their desire for all patients to be treated equally and to make advances in treatment and care universally available. We were, however, dismayed to read that the authors think attempts to improve clinical outcomes for patients with cervix cancer using “low-tech” solutions are nothing but simple and cheap. The use of the word “cheap” is most unfortunate, while it means inexpensive or low cost it now usually suggests shoddiness or inferiority or unworthiness. We have never used the word cheap in our publications and have always listed the economic advantages of using ultrasound as inexpensive, low cost, and affordable. We would also like to address a number of points raised by the authors about the work we do in gynecologic brachytherapy at the Peter MacCallum Cancer Centre.

There was no controversy about the use of ultrasound in the cited publications (1, 2). Mirza posed four questions about the limitations of data coming from a single institution and its ability to be practice changing; the nature of the patterns of failure and what can be learned from them; the role of brachytherapy, radiotherapy, and systemic treatment on overall survival; and conclusions that can be drawn from uncontrolled data collection of a retrospective analysis. Similarly, Coza and Ordeanu raised two points: one being they believed it would have been useful to compare ultrasound and MRI measurements of the cervix and uterus pretreatment and two, the notion of using transrectal ultrasound to help overcome perceived limitations of transabdominal ultrasound. We responded to both these commentaries (3, 4).

We do not believe that the applicability of transabdominal ultrasound for target volume assessment is limited by the reasons stated by Kirsits *et al.* The article being discussed reports on sequential measurement of the uterus and cervix over the course of brachytherapy using transabdominal ultrasound (5). It is not an interobserver article, and there were no significant interobserver variations reported.

Our approach to target assessment is pragmatic, systematic, and no more complex than that recommended by GEC-ESTRO. It is based on years of thorough and continuous

study of cervix cancer through clinical assessment, MRI, and PET studies and treatment outcomes in terms of patterns of failure and treatment toxicity. We have studied clinical behavior of untreated cervix cancer on presentation; the local tumor growth in terms of tumor volume, type of tumor growth, and invasive characteristics within the cervix and uterus and in surrounding tissues; and the primary tumor's response to radiotherapy (6–8). These studies of prospectively collected clinical, radiologic, and pathologic data were started in 1996 and have culminated in a thorough understanding of locally advanced cervix cancer through the patterns of failure, survival, and toxicity reporting following both conventional brachytherapy and progressively over the years conformal brachytherapy (9–12). We use clinical, transvaginal ultrasound, transabdominal ultrasound, and MRI examinations to assess the brachytherapy target volume that we have defined through empirical evidence gleaned through our work over the years.

We are not limited in evaluating parametrial involvement at the time of brachytherapy as we use both clinical assessment and transvaginal ultrasound for all patients and include MRI assessment for most patients. (MRI is only excluded when contraindicated by the patient's condition.) All patients in the present study underwent MRI at the first brachytherapy insertion. Transvaginal ultrasound has been shown to be comparable to MRI when assessing parametrial invasion (13, 14). We realize we are not using 3D imaging and specifically point out that we cannot conduct volumetric analyses. This has not detracted from the technical quality of our implants or our clinical outcomes. We include the information from the clinical, transvaginal, and transabdominal examinations when determining the isodose coverage of the target volume. We undertake a thorough “volume” scan of the cervix, uterus, adnexa, and parametria with both transvaginal and transabdominal ultrasound. If parametrial disease is present, we identify it and take it into consideration when planning isocoverage.

We agree it would be ideal to have the resources, infrastructure, and quality control utilized in external beam treatment available to users of brachytherapy. Treatment verification for external beam radiotherapy now occurs in “real time,” especially when utilizing IMRT and VMAT. We achieve similar point of care verification in brachytherapy using ultrasound. We are one of the few centers that verifies the implant position minutes before treatment delivery, and this is only possible because we use ultrasound.

If we compare clinical outcomes from Vienna, Pittsburgh, and Melbourne, we can see that advanced stage of disease distribution was similar with 20%, 16%, and 16% of patients staged as FIGO IIIB, respectively. Local control

at 3 years was 95% for Vienna, 92% for Pittsburgh, and 87.5% at 5 years for Melbourne. Likewise, overall 3-year actuarial survival was 68% for Vienna, 76.6% for Pittsburgh, and 76.8% for Melbourne (10, 15, 16).

We have stated in our article that we cannot volumetrically assess organs at risk but can certainly see these organs around the cervix and uterus and shape isodoses accordingly. The low toxicity reported in a previous study bear out our capability to avoid critical structures (10).

The vast majority of patients with advanced disease as seen in countries with high patient numbers are currently being treated with x-ray point-based brachytherapy using standard applicators due to a lack of resources and poverty. The cost-effective analysis cited in this editorial is based on a US population and US Medicare reimbursements. Extrapolating findings from this study to different populations and regions is most assuredly not appropriate. Incorporating an accessible affordable soft tissue imaging modality like ultrasound into gynecologic brachytherapy protocols can only improve the technical quality of the implant even if it makes obvious the extent of disease and the inadequacy of Point A-based dosimetry. These patients cannot be denied incremental improvements to treatment just because the advances are not the same as those on offer in select centers in Europe and the United States.

As we have said in all our publications, practitioners must be innovative with the resources available to them. This is what we have done. We do not seek to deny the use of transrectal ultrasound and look forward to prospective clinical studies showing its benefit in brachytherapy for cervix cancer. Until then, we will continue to use MRI when possible, and transvaginal and transabdominal ultrasound always, as we have proven results with these modalities.

In an ideal world, every woman would have access to state-of-the-art imaging and treatment technology, but alas, this is not reality. We do not advocate “simple and cheap” and the unsavory connotations they conjure up. We do, however, advocate for innovative and safe practices that improve outcomes for all patients.

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## Kirisits et al. in response to van Dyk et al.



ELSEVIER

Brachytherapy 15 (2016) 207

Gynecologic Oncology

### In response to the letter to the editor from Sylvia van Dyk *et al.* regarding our editorial “High-tech image-guided therapy vs. low-tech, simple, cheap gynecologic brachytherapy”

Without doubt, our goal is to make the most effective brachytherapy treatment modality available for cervical cancer patients worldwide. Our clear vision is the use of three-dimensional (3D) imaging for treatment planning, which has already become state of the art for most external beam radiotherapy treatment approaches. The 3D planning in brachytherapy should, however, not be limited to the use of 3D reconstruction of points with orthogonal radiographs. Volumetric 3D imaging-based treatment planning which can be performed with CT, MRI, and/or ultrasound should become the state of the art for cervix cancer brachytherapy.

As van Dyk *et al.* state in their letter, treatment verification is based on sophisticated three-dimensional (3D) methods in external beam radiotherapy. However, it remains unclear, how their approach can achieve a similar level of verification for brachytherapy using their ultrasound method. It is evident that their proposed method with ultrasound only is based on two-dimensional images as illustrated in their publications (1, 2). No direct 3D volumetric image-based treatment planning and verification is performed, but distances are used based on ultrasound assessment of thickness and width of uterine cervix and corpus. However, the authors also state that 3D volumetric MR imaging is standard part of their treatment approach for first fraction. This fact causes some contradictions with their main argument. On the one hand, the method should be made available to every patient, even in very limited infrastructure. On the other hand, their 3D planning is based on MRI imaging, which is certainly not available in all radiotherapy centers worldwide. The probability of having access to CT scan in radiotherapy departments, even with limited resources, is for sure higher. In addition for

organ at risk dose assessment, the role of two-dimensional ultrasound imaging seems unclear. Fact is that major interfraction variations do not occur for the target, but for the organs at risk (3). Therefore, we favor 3D volumetric imaging for each implantation (at least with CT) although we agree that the approach as highlighted by van Dyk *et al.* using abdominal ultrasound is certainly one of the options as long we understand the limitations. Overall, the main goal is to develop gynecological brachytherapy practice from old standards to new standards which are based on a sophisticated, effective, and state of the art treatment showing its great potential within the radiotherapy and oncology community.

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Letter in response to Editorial by Swamidas and Kirisits in Journal of Medical Physics  
2015 40(1) pp. 1-5

Letters to Editor

## In response to Swamidas and Kirisits

Sir,

On the editorial 'IMRT, IGRT, and other high technology becomes standard in external beam radiotherapy: However, is image-guided brachytherapy for cervical cancer too expensive?' by Swamidas and Kirisits, J Med Phys 2015;40:1-4.

We were dismayed to read the short and unsatisfactory paragraph discussing the use of transabdominal ultrasound to guide brachytherapy for cervix cancer in an editorial from a country burdened with one-fifth of all new cases of cervix cancer. We expected a more pragmatic approach from this region given the recognition of the disparity in resource and technology utilization between external beam treatment and brachytherapy in your environment. To say that ultrasound "will certainly play an important role in the future" implies ultrasound has no role in the present, this is both erroneous and mendacious reporting. Two clinical outcome studies using transabdominal ultrasound have been reported in the literature, neither of which were discussed in the editorial.<sup>[1,2]</sup> These reports have both shown how the use of low cost accessible transabdominal ultrasound can incorporate soft tissue imaging into a brachytherapy program and achieve similar survival rates and late effects as magnetic resonance imaging-based three-dimensional planning. It is possible to see the width, height, and thickness of the cervix using transabdominal ultrasound. One just has to turn the transducer through 90°. To caution against the use of ultrasound because technology is not as advanced as desired is extremely self-limiting. It is not necessary to track the applicator in relation to the ultrasound scan set as the applicator itself acts as a fiducial and calibration device within the image. Transrectal ultrasound (TRUS) is limited by the short focal length (60 mm) and small field of view and while it may be a useful tool to assess cervix tumor width, there are no reports of its use in measuring cervix tumor height in locally advanced cancers. Tumor width, height, and thickness have not been measured with the applicator *in situ* with TRUS, nor has brachytherapy been planned using these images. At present, two-dimensional transabdominal ultrasound images, which depict the applicator and anatomy, are

used to verify applicator position by many departments around the world and used to guide planning in the two departments mentioned. These two departments have shown that use of transabdominal ultrasound significantly improved the dose distribution for target and OAR in comparison with conventional point X-ray based planning. In a region where X-ray based planning is the norm, resources are limited and patients are poor, it behooves us to explore accessible time and cost-effective solutions and make image-guided conformal brachytherapy possible for all.

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## Appendix D: Miscellaneous

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## Appendix D: Miscellaneous

Journal of the ICRU Vol 13 No 1-2 (2013) Report 89  
Oxford University Press

### ICRU report 89

#### 13. Summary of the recommendations

Level 1: *Minimum standard for reporting* Page 161

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##### Level 1: *Minimum standard for reporting*

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Volumetric imaging approximation based on:

- Comprehensive clinical gynecologic examination
- Volumetric imaging (MR, CT, US, PET-CT) at the time of diagnosis and brachytherapy

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions (width, thickness, height) and volumes for:

- GTV<sub>init</sub> (the GTVat diagnosis)
- GTV<sub>res</sub> (the GTVat brachytherapy)
- CTV<sub>HR</sub> [the GTV<sub>res</sub> (if present) plus residual pathologic tissue (if present) plus whole cervix]
- (CTV<sub>IR</sub>: area of GTV<sub>init</sub> and/or CTV<sub>HR</sub> plus safety margin if used for prescription)

Dose reporting:

- TRAK
- Point A dose
- Recto-vaginal reference point dose
- $D_{0.1cm^3}$  and  $D_{2cm^3}$  for the bladder and rectum

Dose delivery pattern:

- Absorbed dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

- Radionuclide and source model
- Source strength
- Dose calculation algorithm

Radiographic approximation based on:

- Comprehensive clinical gynecologic examination
- Radiographic imaging (plus additional volumetric 3D imaging if available)

FIGO/TNM stage

Baseline morbidity and QoL assessment

Schematic 3D documentation on a clinical diagram indicating dimensions (width, thickness, (height)) and volumes for:

- GTV<sub>init</sub> (the GTVat diagnosis)
- GTV<sub>res</sub> (the GTVat brachytherapy)
- CTV<sub>HR</sub> [the GTV<sub>res</sub> (if present) plus residual pathologic tissue (if present) plus whole cervix]
- (CTV<sub>IR</sub>: area of GTV<sub>init</sub> and/or CTV<sub>HR</sub> plus safety margin if used for prescription)

Dose reporting:

- TRAK
- Point A dose
- Recto-vaginal reference point dose
- Bladder reference point dose

Dose delivery pattern:

- Absorbed dose rate/dose per fraction
- Number of fractions
- Time between fractions
- (Pulse number, size, time, if PDR)
- Overall treatment time
- Total EQD2 dose

Source and dose calculation:

- Radionuclide and source model
  - Source strength
  - Dose calculation algorithm
-

## ICRU report 89

### 13. Summary of the recommendations

#### Level 2: *Advanced standard for reporting* Page 178

Level 2: *Advanced standard for reporting*  
All that is reported in Level 1 plus:

<p>Volumetric imaging approximation based on:</p> <p>3D delineation of volumes (on volumetric images with applicator):</p> <ul style="list-style-type: none"> <li>• <math>GTV_{res}</math></li> <li>• <math>CTV_{HR}</math></li> <li>• (<math>CTV_{IR}</math> if used for prescription)</li> <li>• With maximum width, height, thickness, and with volume</li> </ul> <p>Dose reporting for defined volumes:</p> <ul style="list-style-type: none"> <li>• <math>D_{95\%}</math>, <math>D_{90\%}</math>, <math>D_{50\%}</math> for the <math>CTV_{HR}</math></li> <li>• (<math>D_{95\%}</math>, <math>D_{90\%}</math> for the <math>CTV_{IR}</math> if used for prescription)</li> <li>• <math>D_{95\%}</math> for <math>GTV_{res}</math></li> <li>• <math>D_{95\%}</math> for pathological lymph nodes</li> </ul> <p>Dose reporting OARs:</p> <ul style="list-style-type: none"> <li>• Bladder reference point dose</li> <li>• <math>D_{0.1cm^3}</math>, <math>D_{2cm^3}</math> for sigmoid <sup>a</sup></li> <li>• <math>D_{2cm^3}</math> bowel</li> <li>• Intermediate and low dose parameters in bladder, rectum, sigmoid, bowel (e.g., <math>V_{15Gy}</math>, <math>V_{25Gy}</math>, <math>V_{35Gy}</math>, <math>V_{45Gy}</math> or <math>D_{95\%}</math>, <math>D_{60\%}</math>, <math>D_2</math> %) <sup>a</sup></li> <li>• Vaginal point doses at level of sources (lateral at 5 mm)</li> <li>• Lower and mid-vaginal doses (PIBS, PIBS + 2 cm) <sup>a</sup></li> </ul>	<p>Radiographic approximation based on:</p> <p>Topography for volumes (on isodose plan with applicator/on radiographs with applicator)</p> <ul style="list-style-type: none"> <li>• <math>GTV_{res}</math></li> <li>• <math>CTV_{HR}</math></li> <li>• <math>CTV_{IR}</math> (if used for prescription)</li> <li>• With maximum width, thickness, standard height, and with volume</li> </ul> <p>Dose reporting for defined volumes:</p> <ul style="list-style-type: none"> <li>• Estimated dose to <math>CTV_{HR}</math></li> <li>• (according to estimated maximum width and thickness)</li> <li>• Pelvic wall point (optional)</li> <li>• Lymphatic trapezoid (optional)</li> </ul> <p>Dose reporting OARs:</p> <ul style="list-style-type: none"> <li>• Vaginal point doses at level of sources (lateral at 5 mm)</li> <li>• Lower and mid-vaginal doses (PIBS, PIBS + 2 cm)</li> </ul>
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<sup>a</sup>Surrogate points for volumetric vaginal dose assessment.



## Appendix D: Miscellaneous

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### ICRU report 89

#### 13. Summary of the recommendations

##### Level 3: *Research oriented reporting* page 162

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###### Level 3: *Research-oriented reporting*

All that is reported in Level 1 and 2 plus:

Volumetric imaging approximation based on:

Tumor-related volumes:

- (1) GTV, CTV<sub>IR</sub> sub-volumes based on functional imaging (diagnosis, during treatment, and at brachytherapy)
- (2) PTV

Isodose surface volumes:

For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

Dose reporting for tumor:

- (1)  $D_{98\%}$  and  $D_{90\%}$  for the CTV<sub>IR</sub> even if not used for prescription
- (2)  $D_{90\%}$  for the GTV<sub>res</sub>
- (3) DVH parameters for the PTV
- (4)  $D_{50\%}$  for pathological lymph nodes
- (5) DVH parameters for non-involved nodes (ext/int iliac, common iliac)

OAR volumes and points:

- (1) Additional bladder and rectum reference points
- (2) OAR sub-volumes (*e.g.*, trigonum or bladder neck, sphincter muscles)
- (3) Vagina (upper, middle, lower)
- (4) Anal canal (sphincter)
- (5) Vulva (labia, clitoris)
- (6) Other volumes/sub-volumes of interest (*e.g.*, ureter)

Dose-volume reporting for OAR:

- (1) Dose-volume and dose-surface histogram parameters for additional OARs and sub-volumes
- (2) Vaginal dose profiles, dose-volume, and dose-surface histograms
- (3) Length of treated vagina

Radiographic approximation based on:

Isodose surface volumes: For example

- 85 Gy EQD2 volume
- 60 Gy EQD2 volume

OAR volumes, points:

- (1) Additional bladder and rectum points
- (2) Sigmoid point
- (3) Anal canal point (*e.g.*, low vagina point)
- (4) Vulva point (*e.g.*, low vagina point)
- (5) Other points of interest

OAR dose reporting:

- Length of treated vagina
-

## Appendix D: Miscellaneous

### Modified RTOG/WHO late toxicity criteria

LATE TOXICITIES AND FOLLOW UP							2008
Other UR. Number							
Surname							
Date of Birth							
Follow up Date							
<b>No recurrence</b>				<b>No toxicity</b>			
Next Review Months		Dictation		yes	no		
For recurrent disease or toxicities > grade 1, please dictate a note for a letter & patient's medical record							
Place of follow up	PMCI	MMC	Mercy	RWH	LMO	Other	
Smoker @ diagnosis	Non- Smoker			Ex-smoker >3 years			
Toxicity see below	Using cylinder	yes	no	Ovestin	yes	no	
Bladder	Small/Large bowel			Vagina			
Skin/Perineum	Lymphoedema			Symptoms			
Date relapse documented							
Relapse at Primary	yes	no	Tumour at Inguinal Node			yes	no
Pelvic relapse	yes	no	Abdominal relapse			yes	no
Supraclavicular	yes	no	Distant relapse			yes	no
Relapse treated	yes	no	RT	Chemo	Palliative		
Notes							
BLADDER	0=None 1=Symptomatic not requiring medication 2=Symptomatic requiring medication 3=Severe frequency and dysuria, severe generalised telangiectasia 4=Necrosis, contracted bladder (capacity <100cc), severe haemorrh. cystitis						
SMALL/LARGE BOWEL	0=None 1=Symptomatic not requiring medication 2=Symptomatic requiring medication 3=Obstruction or bleeding requiring surgery 4=Necrosis, perforation, fistula						
VAGINA (Mucous Membrane)	0=None 1= Slight atrophy, dryness minor adhesions. 2=Upper 2/3 vagina fused 3=Entire vagina fused 4=Chronic Ulceration						
SKIN/PERINEUM	0=None 1=Slight atrophy, pigmentation change, some hair loss 2=Patchy atrophy, moderate telangiectasia, total hair loss 3=Marked atrophy, gross telangiectasia 4=Ulceration						
Other	0=None 1=Mild 2=Moderate 3=Severe 4=Very severe, loss of organ or life threatening						
NB. Record worst grade for each late effect at time of assessment. Based on modified RTOG/WHO Toxicity criteria							

# Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

## Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

## Components and Organization

### CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

### Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

### Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

### Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms,

or diagnosis. A supra-ordinate term is followed by the word 'Select' and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

### REMARK

A 'REMARK' is a clarification of an AE.

### ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

### NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

### Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening or disabling AE
- Grade 5 Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

### Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – Select' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

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GASTROINTESTINAL						
Page 1 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
NAVIGATION NOTE: Abdominal pain or cramping is graded as Pain – <i>Select</i> in the PAIN CATEGORY.						
Anorexia	Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences	Death
Also CONSIDER: Weight loss.						
Ascites (non-malignant)	Ascites	Asymptomatic	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	Death
REMARK: Ascites (non-malignant) refers to documented non-malignant ascites or unknown etiology, but unlikely malignant, and includes chylous ascites.						
Colitis	Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)	Death
Also CONSIDER: Hemorrhage, GI – <i>Select</i> .						
Constipation	Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
Also CONSIDER: Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – <i>Select</i> .						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Also CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dental: dentures or prosthesis	Dentures	Minimal discomfort, no restriction in activities	Discomfort preventing use in some activities (e.g., eating), but not others (e.g., speaking)	Unable to use dentures or prosthesis at any time	—	—

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 2 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Dental: periodontal disease	Periodontal	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	—	—
REMARK: Severe periodontal disease leading to osteonecrosis is graded as Osteonecrosis (avascular necrosis) in the MUSCULOSKELETAL CATEGORY.						
Dental: teeth	Teeth	Surface stains; dental caries; restorable, without extractions	Less than full mouth extractions; tooth fracture or crown amputation or repair indicated	Full mouth extractions indicated	—	—
Dental: teeth development	Teeth development	Hypoplasia of tooth or enamel not interfering with function	Functional impairment correctable with oral surgery	Maldevelopment with functional impairment not surgically correctable	—	—
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea.						
ALSO CONSIDER: Dehydration; Hypotension.						
Distension/bloating, abdominal	Distension	Asymptomatic	Symptomatic, but not interfering with GI function	Symptomatic, interfering with GI function	—	—
ALSO CONSIDER: Ascites (non-malignant); Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation); Obstruction, GI – <i>Select</i> .						

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 3 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Dry mouth/salivary gland (xerostomia)	Dry mouth	Symptomatic (dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated; unstimulated saliva <0.1 ml/min	—	—
<p>REMARK: Dry mouth/salivary gland (xerostomia) includes descriptions of grade using both subjective and objective assessment parameters. Record this event consistently throughout a patient's participation on study. If salivary flow measurements are used for initial assessment, subsequent assessments must use salivary flow.</p> <p>ALSO CONSIDER: Salivary gland changes/saliva.</p>						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic; able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
<p>REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – Select.</p> <p>ALSO CONSIDER: Dehydration; Esophagitis.</p>						
Enteritis (inflammation of the small bowel)	Enteritis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
<p>ALSO CONSIDER: Hemorrhage, GI – Select; Typhlitis (cecal inflammation).</p>						
Esophagitis	Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
<p>REMARK: Esophagitis includes reflux esophagitis.</p> <p>ALSO CONSIDER: Dysphagia (difficulty swallowing).</p>						

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 4 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Fistula, GI – Select – Abdomen NOS – Anus – Biliary tree – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Oral cavity – Pancreas – Pharynx – Rectum – Salivary gland – Small bowel NOS – Stomach	Fistula, GI – Select	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated. For example, a tracheo-esophageal fistula arising in the context of a resected or irradiated esophageal cancer is graded as Fistula, GI – esophagus.						
Flatulence	Flatulence	Mild	Moderate	—	—	—
Gastritis (including bile reflux gastritis)	Gastritis	Asymptomatic radiographic or endoscopic findings only	Symptomatic; altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids indicated <24 hrs	Symptomatic and severely altered gastric function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., gastrectomy)	Death
Also Consider: Hemorrhage, GI – Select; Ulcer, GI – Select.						
NAVIGATION NOTE: Head and neck soft tissue necrosis is graded as Soft tissue necrosis – Select in the MUSCULOSKELETAL/SOFT TISSUE CATEGORY.						
Heartburn/dyspepsia	Heartburn	Mild	Moderate	Severe	—	—
Hemorrhoids	Hemorrhoids	Asymptomatic	Symptomatic; banding or medical intervention indicated	Interfering with ADL; interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences	Death

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 5 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Ileus	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying).						
ALSO CONSIDER: Constipation; Nausea; Obstruction, GI – Select; Vomiting.						
Incontinence, anal	Incontinence, anal	Occasional use of pads required	Daily use of pads required	Interfering with ADL; operative intervention indicated	Permanent bowel diversion indicated	Death
REMARK: Incontinence, anal is to be used for loss of sphincter control as sequelae of operative or therapeutic intervention.						
Leak (including anastomotic), GI – Select – Biliary tree – Esophagus – Large bowel – Leak NOS – Pancreas – Pharynx – Rectum – Small bowel – Stoma – Stomach	Leak, GI – Select	Asymptomatic radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interfering with GI function; invasive or endoscopic intervention indicated	Life-threatening consequences	Death
REMARK: Leak (including anastomotic), GI – Select is to be used for clinical signs/symptoms or radiographic confirmation of anastomotic or conduit leak (e.g., biliary, esophageal, intestinal, pancreatic, pharyngeal, rectal), but without development of fistula.						
Malabsorption	Malabsorption	—	Altered diet; oral therapies indicated (e.g., enzymes, medications, dietary supplements)	Inability to aliment adequately via GI tract (i.e., TPN indicated)	Life-threatening consequences	Death



## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 6 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Mucositis/stomatitis (clinical exam) – Select: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (clinical exam) – Select	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
REMARK: Mucositis/stomatitis (functional/symptomatic) may be used for mucositis of the upper aero-digestive tract caused by radiation, agents, or GVHD.						
Mucositis/stomatitis (functional/symptomatic) – Select: – Anus – Esophagus – Large bowel – Larynx – Oral cavity – Pharynx – Rectum – Small bowel – Stomach – Trachea	Mucositis (functional/symptomatic) – Select	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function  Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL  Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL  Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Anorexia; Vomiting.						

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 7 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Necrosis, GI – Select: – Anus – Colon/cecum/appendix – Duodenum – Esophagus – Gallbladder – Hepatic – Ileum – Jejunum – Oral – Pancreas – Peritoneal cavity – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Necrosis, GI – Select	—	—	Inability to aliment adequately by GI tract (e.g., requiring enteral or parenteral nutrition); interventional radiology, endoscopic, or operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Also CONSIDER: Visceral arterial ischemia (non-myocardial).						
Obstruction, GI – Select: – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Obstruction, GI – Select	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, vomiting, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – Select Organ or Structure in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
NAVIGATION NOTE: Pelvic pain is graded as Pain – Select in the PAIN CATEGORY.						

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 8 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Perforation, GI – Select – Appendix – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Gallbladder – Ileum – Jejunum – Rectum – Small bowel NOS – Stomach	Perforation, GI – Select	Asymptomatic radiographic findings only	Medical intervention indicated; IV fluids indicated <24 hrs	IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences	Death
Proctitis	Proctitis	Rectal discomfort, intervention not indicated	Symptoms not interfering with ADL; medical intervention indicated	Stool incontinence or other symptoms interfering with ADL; operative intervention indicated	Life-threatening consequences (e.g., perforation)	Death
Prolapse of stoma, GI	Prolapse of stoma, GI	Asymptomatic	Extraordinary local care or maintenance; minor revision indicated	Dysfunctional stoma; major revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GI – Select; Leak (including anastomotic), GI – Select; Obstruction, GI – Select; Perforation, GI – Select; Stricture/stenosis (including anastomotic), GI – Select.						
NAVIGATION NOTE: Rectal or perirectal pain (proctalgia) is graded as Pain – Select in the PAIN CATEGORY.						
Salivary gland changes/saliva	Salivary gland changes	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion- induced symptoms not interfering with ADL	Acute salivary gland necrosis; severe secretion-induced symptoms interfering with ADL	Disabling	—
ALSO CONSIDER: Dry mouth/salivary gland (xerostomia); Mucositis/stomatitis (clinical exam) – Select; Mucositis/stomatitis (functional/symptomatic) – Select; Taste alteration (dysgeusia).						
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						

## Appendix D: Miscellaneous

GASTROINTESTINAL						
Page 9 of 10						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Stricture/stenosis (including anastomotic), GI – Select: – Anus – Biliary tree – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Pancreas/pancreatic duct – Pharynx – Rectum – Small bowel NOS – Stoma – Stomach	Stricture, GI – Select	Asymptomatic radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, bleeding, diarrhea); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., altered dietary habits, diarrhea, or GI fluid loss); IV fluids, tube feedings, or TPN indicated ≥24 hrs; operative intervention indicated	Life-threatening consequences; operative intervention requiring complete organ resection (e.g., total colectomy)	Death
Taste alteration (dysgeusia)	Taste alteration	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	—	—	—
Typhlitis (cecal inflammation)	Typhlitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis); operative intervention indicated	Death

Also CONSIDER: Colitis; Hemorrhage, GI – Select ; Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation).

## Appendix D: Miscellaneous

GASTROINTESTINAL						
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		Grade				
Adverse Event	Short Name	1	2	3	4	5
Ulcer, GI – Select: – Anus – Cecum – Colon – Duodenum – Esophagus – Ileum – Jejunum – Rectum – Small bowel NOS – Stoma – Stomach	Ulcer, GI – <i>Select</i>	Asymptomatic, radiographic or endoscopic findings only	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Hemorrhage, GI – <i>Select</i> .						
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
ALSO CONSIDER: Dehydration.						
Gastrointestinal – Other (Specify, __)	GI – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

## Appendix D: Miscellaneous

LYMPHATICS						
Page 1 of 2						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Chyle or lymph leakage	Chyle or lymph leakage	Asymptomatic, clinical or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening complications	Death
Also CONSIDER: Chylothorax.						
Dermal change lymphedema, phlebolymphe <sup>1</sup> dema	Dermal change	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation	—	—	—
REMARK: Dermal change lymphedema, phlebolymphe <sup>1</sup> dema refers to changes due to venous stasis.						
Also CONSIDER: Ulceration.						
Edema: head and neck	Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared to baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	Edema: limb	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death
Edema: viscera	Edema: viscera	Asymptomatic; clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and unable to aliment adequately orally; interventional radiology or operative intervention indicated	Life-threatening consequences	Death

## Appendix D: Miscellaneous

LYMPHATICS						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Lymphedema-related fibrosis	Lymphedema-related fibrosis	Minimal to moderate redundant soft tissue, unresponsive to elevation or compression, with moderately firm texture or spongy feel	Marked increase in density and firmness, with or without tethering	Very marked density and firmness with tethering affecting $\geq 40\%$ of the edematous area	—	—
Lymphocele	Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	—	—
Phlebolympathic cording	Phlebolympathic cording	Asymptomatic, clinical findings only	Symptomatic; medical intervention indicated	Symptomatic and leading to contracture or reduced range of motion	—	—
Lymphatics – Other (Specify, __)	Lymphatics – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

## Appendix D: Miscellaneous

PAIN							Page 1 of 1
		Grade					
Adverse Event	Short Name	1	2	3	4	5	
Pain – Select  'Select' AEs appear at the end of the CATEGORY.	Pain – Select	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—	
Pain – Other (Specify, __)	Pain – Other (Specify)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	—	
PAIN – SELECT							
AUDITORY/EAR – External ear – Middle ear		HEPATOBILIARY/PANCREAS – Gallbladder – Liver		PULMONARY/UPPER RESPIRATORY ( <i>continued</i> ) – Larynx – Pleura – Sinus – Throat/pharynx/larynx			
CARDIOVASCULAR – Cardiac/heart – Pericardium		LYMPHATIC – Lymph node		RENAL/GENITOURINARY – Bladder – Kidney			
DERMATOLOGY/SKIN – Face – Lip – Oral-gums – Scalp – Skin		MUSCULOSKELETAL – Back – Bone – Buttock – Extremity-limb – Intestine – Joint – Muscle – Neck – Phantom (pain associated with missing limb)		SEXUAL/REPRODUCTIVE FUNCTION – Breast – Ovulatory – Pelvis – Penis – Perineum – Prostate – Scrotum – Testicle – Urethra – Uterus – Vagina			
GASTROINTESTINAL – Abdomen NOS – Anus – Dental/teeth/peridontal – Esophagus – Oral cavity – Peritoneum – Rectum – Stomach		NEUROLOGY – Head/headache – Neuralgia/peripheral nerve					
GENERAL – Pain NOS – Tumor pain		OCULAR – Eye					
		PULMONARY/UPPER RESPIRATORY – Chest wall – Chest/thorax NOS					



## Appendix D: Miscellaneous

RENAL/GENITOURINARY						
Page 1 of 3						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Bladder spasms	Bladder spasms	Symptomatic, intervention not indicated	Symptomatic, antispasmodics indicated	Narcotics indicated	Major surgical intervention indicated (e.g., cystectomy)	—
Cystitis	Cystitis	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated	Death
ALSO CONSIDER: Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10 <sup>9</sup> /L) – Select; Infection with normal ANC or Grade 1 or 2 neutrophils – Select; Infection with unknown ANC – Select; Pain – Select.						
Fistula, GU – Select – Bladder – Genital tract-female – Kidney – Ureter – Urethra – Uterus – Vagina	Fistula, GU – Select	Asymptomatic, radiographic findings only	Symptomatic; noninvasive intervention indicated	Symptomatic interfering with ADL; invasive intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion	Death
REMARK: A fistula is defined as an abnormal communication between two body cavities, potential spaces, and/or the skin. The site indicated for a fistula should be the site from which the abnormal process is believed to have originated.						
Incontinence, urinary	Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous, pads indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)	—
Leak (including anastomotic), GU – Select – Bladder – Fallopian tube – Kidney – Spermatic cord – Stoma – Ureter – Urethra – Uterus – Vagina – Vas deferens	Leak, GU – Select	Asymptomatic, radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic, interfering with GU function; invasive or endoscopic intervention indicated	Life-threatening	Death
REMARK: Leak (including anastomotic), GU – Select refers to clinical signs and symptoms or radiographic confirmation of anastomotic leak but without development of fistula.						

## Appendix D: Miscellaneous

RENAL/GENITOURINARY						
Page 2 of 3						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Obstruction, GU – Select – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Obstruction, GU – Select	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Death
NAVIGATION NOTE: Operative injury is graded as Intra-operative injury – Select Organ or Structure in the SURGERY/INTRA-OPERATIVE INJURY CATEGORY.						
Perforation, GU – Select – Bladder – Fallopian tube – Kidney – Ovary – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Perforation, GU – Select	Asymptomatic radiographic findings only	Symptomatic, associated with altered renal/GU function	Symptomatic, operative intervention indicated	Life-threatening consequences or organ failure; operative intervention requiring organ resection indicated	Death
Prolapse of stoma, GU	Prolapse stoma, GU	Asymptomatic; special intervention, extraordinary care not indicated	Extraordinary local care or maintenance; minor revision under local anesthesia indicated	Dysfunctional stoma; operative intervention or major stomal revision indicated	Life-threatening consequences	Death
REMARK: Other stoma complications may be graded as Fistula, GU – Select; Leak (including anastomotic), GU – Select; Obstruction, GU – Select; Perforation, GU – Select; Stricture/stenosis (including anastomotic), GU – Select.						
Renal failure	Renal failure	—	—	Chronic dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
ALSO CONSIDER: Glomerular filtration rate.						

## Appendix D: Miscellaneous

RENAL/GENITOURINARY						
Page 3 of 3						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Stricture/stenosis (including anastomotic), GU – <i>Select</i> : – Bladder – Fallopian tube – Prostate – Spermatic cord – Stoma – Testes – Ureter – Urethra – Uterus – Vagina – Vas deferens	Stricture, anastomotic, GU – <i>Select</i>	Asymptomatic, radiographic or endoscopic findings only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Life-threatening consequences; organ failure or operative intervention requiring organ resection indicated	Death
Also CONSIDER: Obstruction, GU – <i>Select</i> .						
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	Urinary electrolyte wasting	Asymptomatic, intervention not indicated	Mild, reversible and manageable with replacement	Irreversible, requiring continued replacement	—	—
Also CONSIDER: Acidosis (metabolic or respiratory); Bicarbonate, serum-low; Calcium, serum-low (hypocalcemia); Phosphate, serum-low (hypophosphatemia).						
Urinary frequency/urgency	Urinary frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	—	—
Urinary retention (including neurogenic bladder)	Urinary retention	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for <6 weeks	More than daily catheterization indicated; urological intervention indicated (e.g., TURP, suprapubic tube, urethrotomy)	Life-threatening consequences; organ failure (e.g., bladder rupture); operative intervention requiring organ resection indicated	Death
REMARK: The etiology of retention (if known) is graded as Obstruction, GU – <i>Select</i> ; Stricture/stenosis (including anastomotic), GU – <i>Select</i> . Also CONSIDER: Obstruction, GU – <i>Select</i> ; Stricture/stenosis (including anastomotic), GU – <i>Select</i> .						
Urine color change	Urine color change	Present	—	—	—	—
REMARK: Urine color refers to change that is not related to other dietary or physiologic cause (e.g., bilirubin, concentrated urine, and hematuria).						
Renal/Genitourinary – Other (Specify, __)	Renal – Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

## Appendix D: Miscellaneous

SEXUAL/REPRODUCTIVE FUNCTION						
Page 1 of 2						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Breast function/lactation	Breast function	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—	—
Breast nipple/areolar deformity	Nipple/areolar	Limited areolar asymmetry with no change in nipple/areolar projection	Asymmetry of nipple areolar complex with slight deviation in nipple projection	Marked deviation of nipple projection	—	—
Breast volume/hypoplasia	Breast	Minimal asymmetry; minimal hypoplasia	Asymmetry exists, $\leq 1/3$ of the breast volume; moderate hypoplasia	Asymmetry exists, $>1/3$ of the breast volume; severe hypoplasia	—	—
REMARK: Breast volume is referenced with both arms straight overhead.						
NAVIGATION NOTE: Dysmenorrhea is graded as Pain – Select in the PAIN CATEGORY.						
NAVIGATION NOTE: Dyspareunia is graded as Pain – Select in the PAIN CATEGORY.						
NAVIGATION NOTE: Dysuria (painful urination) is graded as Pain – Select in the PAIN CATEGORY.						
Erectile dysfunction	Erectile dysfunction	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency/rigidity of erections), erectile aids indicated	Decrease in erectile function (frequency/rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	—	—
Ejaculatory dysfunction	Ejaculatory dysfunction	Diminished ejaculation	Anejaculation or retrograde ejaculation	—	—	—
NAVIGATION NOTE: Feminization of male is graded in the ENDOCRINE CATEGORY.						
Gynecomastia	Gynecomastia	—	Asymptomatic breast enlargement	Symptomatic breast enlargement; intervention indicated	—	—
ALSO CONSIDER: Pain – Select.						
Infertility/sterility	Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/ovulation	Male: sterile/azoospermia Female: infertile/anovulatory	—	—
Irregular menses (change from baseline)	Irregular menses	1 – 3 months without menses	$>3$ – 6 months without menses but continuing menstrual cycles	Persistent amenorrhea for $>6$ months	—	—

## Appendix D: Miscellaneous

SEXUAL/REPRODUCTIVE FUNCTION						
Page 2 of 2						
		Grade				
Adverse Event	Short Name	1	2	3	4	5
Libido	Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	—	—	—
NAVIGATION NOTE: Masculinization of female is graded in the ENDOCRINE CATEGORY.						
Orgasmic dysfunction	Orgasmic function	Transient decrease	Decrease in orgasmic response requiring intervention	Complete inability of orgasmic response; not responding to intervention	—	—
NAVIGATION NOTE: Pelvic pain is graded as Pain – Select in the PAIN CATEGORY.						
NAVIGATION NOTE: Ulcers of the labia or perineum are graded as Ulceration in DERMATOLOGY/SKIN CATEGORY.						
Vaginal discharge (non-infectious)	Vaginal discharge	Mild	Moderate to heavy; pad use indicated	—	—	—
Vaginal dryness	Vaginal dryness	Mild	Interfering with sexual function; dyspareunia; intervention indicated	—	—	—
ALSO CONSIDER: Pain – Select.						
Vaginal mucositis	Vaginal mucositis	Erythema of the mucosa; minimal symptoms	Patchy ulcerations; moderate symptoms or dyspareunia	Confluent ulcerations; bleeding with trauma; unable to tolerate vaginal exam, sexual intercourse or tampon placement	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	—
Vaginal stenosis/length	Vaginal stenosis	Vaginal narrowing and/or shortening not interfering with function	Vaginal narrowing and/or shortening interfering with function	Complete obliteration; not surgically correctable	—	—
Vaginitis (not due to infection)	Vaginitis	Mild, intervention not indicated	Moderate, intervention indicated	Severe, not relieved with treatment; ulceration, but operative intervention not indicated	Ulceration and operative intervention indicated	—
Sexual/Reproductive Function – Other (Specify, __)	Sexual – Other (Specify)	Mild	Moderate	Severe	Disabling	Death

## Appendix D: Miscellaneous