Evaluating clinical dosimetry of modern techniques in brachytherapy for gynaecological cancers and the feasibility of using deformable image registration and knowledge-based planning for brachytherapy

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Declaration

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes. I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged. Information derived from the published and unpublished work of others has been acknowledged in the text with a list of references given at the end of each chapter. The four main chapters have been published (or submitted) in peer-reviewed journals, as per the publications section.

Emily Flower

23 January, 2023

Abstract

Aim: To evaluate dosimetric plan quality and clinical outcomes for advanced brachytherapy (BT) of gynaecological malignancies following implementation of evidence-based planning aims. For cervical cancer BT, to test the feasibility of deformable image registration (DIR) for organ at risk (OAR) dose accumulation, and of simple knowledge-based planning (KBP) for OAR dose prediction.

Method: Dosimetry and clinical outcomes for the above patient groups were comprehensively evaluated for a five-year period that included various changes. KBP models based on overlap volume histograms were developed to predict OAR $D2cm^3$ and were assessed on goodness of fit and of prediction and on dosimetric performance when used as planning optimisation criteria. DIR was applied to 39 cervical cancer patients and reproducibility was assessed for different implementation methods. Accumulated DVH parameters ($D2cm^3$ and $D0.1cm^3$) for bladder and rectum were compared with dose summation without DIR.

Results: 21 patients with vaginal malignancies were evaluated. Local control was achieved in 67%. Median CTV D90 was 78.3Gy. Median $D2cm^3$ to bladder and rectum was 64.8Gy and 62.9Gy respectively. 70 patients with locally advanced cervical cancer were evaluated. 100% had a CTV_HR dose > 85Gy and rectum $D2cm^3$ <75Gy and 88.6% a bladder $D2cm^3$ < 90Gy. Local control was achieved for 95.2% of patients. KBP-based optimization proved to be feasible and decreased mean OAR doses. Using DIR, summed $D2cm^3$ and $D0.1cm^3$ decreased within clinical uncertainties. Adding contour information improved reproducibility.

Conclusion: Implementation of evidence-based planning aims for advanced BT for vaginal malignancies and cervical cancer showed consistent plan quality considering the e-b recommendations, excellent local control and acceptable toxicity. The KBP planning method predicting $D2cm^3$ was able to automate optimization of BT plans for cervical cancer. DIR is not yet feasible for routine dose summation in BT.

Statement of Attribution

This thesis contains work that has been published and prepared for publication, where I was the first author. My contributions to the publications and manuscripts are outlined below:

Chapter three was published as Flower E, Zanjani S, Busuttil G, Sullivan E, Smith W, Tran K, Thwaites D, Chard J, Do V. A single-institution review of image-guided brachytherapy for vaginal malignancies using customized moulded applicators and interstitial needles. J Contemp Brachytherapy. 2021 Dec;13(6):663-669. Doi: 10.5114/jcb.2021.110347.

The original idea of this review was a combination of the primary author and the Director of Radiation Oncology. The primary author completed all the data collection and analysis and wrote the paper. The other authors critiqued the manuscript and were involved in the clinical provision of treatment.

Chapter four was submitted for publication as Flower E, Thiruthaneeswaran N, Busuttil G, Cosgriff E, Zanjani S, Sullivan E, Salkeld A, Sykes J, Thwaites D, Chard J. Implementation of evidence-based planning aims for image-based adaptive brachytherapy including a vaginal dose analysis using two different applicators. Submittted to JMIRO 19/01/2023. However, following peer-review, it was decided to publish the dosimetric, safety and toxicity aspects of this chapter, which was resubmitted to JMIRO. The resubmission in response to the reviewers is now titled “Plan quality, safety and toxicity evaluation for brachytherapy for cervical cancer in an

Australian setting following changes in prescription and applicator design" and was resubmitted 6 June 2023. A future paper will investigate local control and survival, but this is being held until the data mature further and the mean follow-up time allows direct comparison with other published papers.

The original idea of this study was a combination of the primary author and the second author. The primary author completed all the data collection and analysis and wrote the paper. The other authors critiqued the manuscript and were involved in the clinical provision of treatment.

Chapter five was published as Flower E, Sykes J, Sullivan E, Busuttil G, Thiruthaneeswaran N, Cosgriff E, Chard J, Salkeld A, Thwaites D. Improving plan quality in cervical brachytherapy using a simple knowledge-based prediction tool for OAR dose ($D2cm^3$). Brachytherapy, in press. https://doi.org/10.1016/j.brachy.2023.05.004

The original idea of this study was from the primary author. The primary author completed all the data collection and analysis and wrote the paper. The other authors critiqued the manuscript and were involved in the clinical provision of treatment.

Chapter six was published as Flower E, Do V, Sykes J, Dempsey C, Holloway L, Summerhayes K, Thwaites DI. Deformable image registration for cervical cancer brachytherapy dose accumulation: Organ at risk dose-volume histogram parameter reproducibility and anatomic position stability. Brachytherapy. 2017 Mar-Apr;16(2):387-392. Doi: 10.1016/j.brachy.2016.12.006.

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Emily Flower

23 January, 2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor David Thwaites

23 January, 2023

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I would firstly like to thank my supervision team, Professor David Thwaites, Dr Jonathan Sykes and Dr Niluja Thiruthaneeswaran. They have been very supportive throughout my candidature. We had regular meetings, often over zoom, across various time zones. My supervisors always provided valuable feedback, both as encouragement and constructive criticisms of my work. I thank them for their involvement. There were also many emails and casual conversations had with my supervision team, all feeding into a better thesis.

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I wish to acknowledge the support from my family while I completed this thesis. My father especially for encouraging me to enrol and complete this degree, and my mother for her practical assistance so I could complete this research. My family strongly value the pursuit of education and have supported my doctoral studies.

Whilst undertaking this degree, I was also fighting a losing battle to save my feet. This battle resulted in both my legs being amputated. In 2018, I also suffered from diabetic ketoacidosis, leaving me in a coma in ICU, followed by pneumonia. As well as my legs being amputated, I also had osseointegration, with the osseointegrated rod fracturing in the brachytherapy suite during preparation for a patient treatment. I have had eight operations whilst completing this degree. I thank my medical teams for supporting my ongoing studies, and the university for their understanding when I needed suspensions or delayed progress interviews etc. I am not sure I would have been able to complete this degree without the fantastic care provided by my orthopaedic surgeons Dr Tim O'Carrigan and Professor Munjed Al Muderis and their teams, and the enormous improvement in my quality of life that being a bilateral amputee with osseointegration has brought to my life.

Finally, I wish to acknowledge my church family at Revival Centres Church and faith in God for support during this degree. I was diagnosed with a learning disability and began school with this diagnosis, teacher's aides etc. My parents prayed and only told me in my senior high school years. God's healing power and the comfort and strength I receive from my faith, as a Spirit-filled Christian, contributed to my finishing this degree.

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List of Abbreviations

AAPM	American Association of Physicists in Medicine
ABS	American Society of Brachytherapy
ACROP	Advisory Committee for Radiation Oncology Practice
BT	Brachytherapy
CI	Conformity Index
CIPM	Comité International des Poids et Mesures
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
CTV_HR	High-Risk Clinical Target Volume
CTV_IR	Intermediate-Risk Clinical Target Volume
$D2cm^3$	Minimum dose to the most irradiated volume of $2cm^3$ in the specified organ.
$D0.1cm^3$	Minimum dose to the most irradiated volume of $0.1cm^3$ in the specified organ.
D90	Minimum dose to 90% of the volume
D98	Minimum dose to 98% of the volume
DHI	Dose Homogeneity Index
DIR	Deformable Image Registration
DSC	Dice similarity coefficient
DVH	Dose Volume Histogram
DTGR	Dwell Time Gradient Restriction
EBRT	External Beam Radiation Therapy

EMBRACE	An International Study on Magnetic Resonance Imaging (MRI)-Guided Brachytherapy in Locally Advanced Cervical Cancer
EQDx	Equi-effective Dose in xGy fractions
EQD2	Equi-effective Dose in 2Gy fractions
EUA	Examination Under Anaesthesia
FIGO	International Federation of Gynaecology and Obstetrics
FSD	Fletcher-Suite-Delclos
GEC-ESTRO	Groupe European de Curietherapie and European Society for Radiotherapy and Oncology
GTV	Gross Tumour Volume
GTV_res	Gross Tumour Volume residual at time of brachytherapy
HDR	High Dose Rate
HIPO	Hybrid Inverse Planning Optimisation
HPV	Human Pappilloma Virus
HU	Hounsfield Units
IC	Intra-Cavitary
ICRU	International Commission of Radiation Units and measurements
IMRT	Intensity Modulated Radiation Therapy
IS	Interstitial
MPPG	Medical Physics Practice Guideline
MRI	Magnetic Resonance Imaging
MSE	Mean Square Error
NTCP	Normal Tissue Complication Probability
OAR	Organ at Risk

OV2cc	Volume of the intersection between the expanded CTV_HR contour and the contour of the organ at risk was 2cm^3
OVH	Overlap Volume Histogram
PIBS	Posterior-Inferior Border of Symphysis
PQM	Plan Quality Metrics
retroEMBRACE	A Retrospective International Study on Magnetic Resonance Imaging (MRI)-Guided Brachytherapy in Locally Advanced Cervical Cancer
STAPLE	Simultaneous Truth And Performance Level Estimation
TCP	Tumour Control Probability
TPS	Treatment Planning System
TNM	Tumour, Nodes and Metastases
TRAK	Total Reference Air Kerma
VolD2cm^3	Overlap of the D2cm^3 isodose and the bladder or rectum
VolD0.1cm^3	Overlap of the D0.1cm^3 isodose and the bladder or rectum

Research publications and presentations related to this thesis work

Peer Review Publications

Flower E, Do V, Sykes J, Dempsey C, Holloway L, Summerhayes K, Thwaites DI. Deformable image registration for cervical cancer brachytherapy dose accumulation: Organ at risk dose-volume histogram parameter reproducibility and anatomic position stability. Brachytherapy. 2017 Mar-Apr;16(2):387-392. Doi: 10.1016/j.brachy.2016.12.006.

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local control and survival, but this is being held until the data mature further and the mean follow-up time allows direct comparison with other published papers.

Flower E, Sykes J, Sullivan E, Busuttil G, Thiruthaneeswaran N, Cosgriff E, Chard J, Salkeld A, Thwaites D. Improving plan quality in cervical brachytherapy using a simple knowledge-based prediction tool for OAR dose ($D2cm^3$). Brachytherapy, in press. https://doi.org/10.1016/j.brachy.2023.05.004

Oral Presentations

Plan planning aims, whilst changing brachytherapy systems: a retrospective dosimetric plan quality review.
Australasian Brachytherapy Group Annual Scientific Meeting, Melbourne, 2022

A Single Institution Review of Brachytherapy for Malignancies of the Vagina, Vulva and Urethra using Customised Mould Applicators and Interstitial Needles
Australasian Brachytherapy Group Annual Scientific Meeting, 2018

Deformable Image Registration (DIR) for Cervical Cancer Brachytherapy
EPSM 2016

Deformable Image Registration (DIR) For Cervical Cancer Brachytherapy: A Comparison of The Reproducibility Of Three Different Methods And The Effects Of DIR On The Anatomical Stability Of OAR DVH Parameters
Australasian Brachytherapy Group Annual Scientific Meeting, 2016

Poster Presentations

Implementation of IGABT evidence-based planning aims, whilst changing brachytherapy systems ESTRO 22

A single institution review of vaginal brachytherapy with customized moulds and interstitial needles World Congress of Brachytherapy, 2021

Deformable Image Registration (DIR) for Cervical Cancer Brachytherapy: A Comparison of the Reproducibility of Three Different Methods and the Effects of DIR on the Anatomical Stability of OAR DVH Parameters. World Congress of Brachytherapy, San Francisco 2016

Chapter One – Overview

1.1 Thesis aims and objectives

Gynaecological cancers affecting the vagina, vulva or cervix are diagnosed in approximately 1000 women a year in Australia. Of these, approximately 900 are cervix cancers [1] and 100 are primary vaginal malignancies [2]. Additional vaginal recurrences from cervix and endometrial cancers occur as well and are more common than primary vaginal cancers [2]. Gold standard care for both vaginal malignancies and locally advanced cervical cancer is chemoradiation with an image guided brachytherapy (BT) boost. [3-4]

Whilst increased cervical cancer screening and Human Papilloma Virus (HPV) prophylactic vaccinations are reducing the cervical cancer burden in Australia, the progress is slower taking a worldwide view, with cervical cancer still a global oncological problem [5]. Globally, cervical cancer is the fourth most common cancer among women [7]. In 2020, Sung et al [7] reported that there were an estimated 604 000 new cases and 342 000 deaths due to cervical cancer.Approximately 90% of the new cases and deaths from cervical cancer worldwide in 2020 occurred in low and middle-income countries.

Brachytherapy for gynaecological cancers is one of the oldest forms of radiation oncology, dating from soon after Marie Curie discovered and isolated radium 226. Brachytherapy for gynaecological cancers soon became common practice, and there have been many advances since, from the use of low dose rate remote afterloading with caesium 137 to modern techniques with cobalt 60 or Iridium 192 [8].

This thesis evaluates the dosimetric plan quality and clinical outcomes of current advanced brachytherapy treatments, including interstitial needles, for vaginal malignancies and cervical cancer. Having evaluated our current clinical and dosimetric practice, the secondary aim is to evaluate the feasibility of introducing and applying two modern methods of improving radiotherapy techniques into brachytherapy for gynaecological cancers. The two techniques evaluated are deformable image registration (DIR) and knowledge-based planning (KBP).

Deformable image registration allows for elastic registration of voxels from two different images, taken at two different time points. This technology allows for contour and dose distribution mapping. In cervical brachytherapy, an assumption is that the DVH parameter showing the least dose to the most irradiated $2cm^3$ ($D2cm^3$) of the organs at risk (OAR) occurs in the same topographical position at each fraction. This work tests if a commercially available deformable image registration package can produce accurate and reproducible results to test this assumption.

Knowledge-based planning uses models based on the geometric relationship between the target volume and organs at risk to predict DVH parameters. This work develops and applies a simplified dose prediction model to the $D2cm^3$ prediction, to evaluate plan quality and test if modelled predictions can be used to improve dose optimisation.

1.2 Thesis Structure

Chapter two gives an overall literature review and relevant background knowledge for material in the thesis. As each main chapter is in the form of a peer-reviewed publication, there are more focussed literature reviews in each chapter as well.

The next two chapters are devoted to reviewing, analysing and evaluating dosimetric and clinical practice (and change of practice) within the author's local institution, for both vaginal malignancies and locally advanced cervical cancer. Following the recommendations made in the tri-partite Radiation Oncology Standards in Australia [9], it is important to evaluate the technical quality of care and to benchmark to best practice.

Chapters three and four aim to assess the dosimetric quality along with the clinical outcomes of brachytherapy for these patient cohorts over time as technology and treatments have evolved. The overall objective is to assess the achievement of the recommended standard of care.

The research question for chapter three was how consistent with published literature and clinically acceptable is the quality of a single-institution's pattern of practice, dosimetry results, and clinical outcomes for patients with unresectable malignancies of vagina, vulva, or urethra, receiving brachytherapy using customised vaginal moulds with or without interstitial needles.

The research question for chapter four was how consistent plan quality is following the implementation of evidence-based planning goals as the clinical planning aims at the Crown Princess Mary Cancer Centre Westmead.

The next two chapters investigate new techniques and emerging technologies that can be applied to brachytherapy, including knowledge-based planning (KBP) and deformable image registration. The aim is to assess the feasibility of their use and their potential impact.

The research question for chapter five was whether a simple KBP relationship could be used to predict the $D2cm^3$ for organs at risk (OAR), and if this can be used to detect sub-optimal plans and improve plan quality?

The research question for chapter six was what is the effect of, and how reproducible are, different methods of deformable image registration (DIR) on cumulative organ at risk dose volume histogram (DVH) parameters summed over three brachytherapy fractions and can DIR be used to assess the stability of the anatomical position of the DVH parameters for the bladder and rectum?

1.3 References

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Chapter Two – Background and General Literature Review

2.1 Clinical Introduction

2.1.1 Vaginal Malignancies

Primary and recurrent malignancies of the vagina, vulva or urethral are rare diseases [1] with an estimated 123 women to be diagnosed during 2023 in Australia [2]. Primary vaginal cancer constitutes only 1%–2% of all female genital tract malignancies and only 10% of all vaginal malignant neoplasms [3]. Primary vaginal cancers accounted for an estimated 30 deaths in Australia last year [2]. Squamous cell carcinomas account for 85 – 90% of primary vaginal cancers, and 8 – 10% are adenocarcimonas [3]. The International Federation of Gynaecology and Obstetrics (FIGO) and/or TNM classification systems are used for staging purposes for primary vaginal cancers [4-5].

Surgical treatment with negative resection margins is difficult due to the proximity of organs at risk. The American Brachytherapy Society (ABS) have produced guidelines or consensus documents for treating primary vaginal disease [1] and salvage treatment for endometrial recurrences [6]. Brachytherapy has been shown to be beneficial for local control for both primary [1, 7-15] and recurrent [7-8, 10-12, 16-21] disease of the vagina, with acceptable toxicity risk.

External beam radiotherapy is recommended due to the risk of lymphatic involvement [20] although there are reports of a single modality being used [14, 18, 23-24]. Jhingran et al [18] reported that much higher doses were delivered with combined modalities. External beam radiotherapy also reduces the volume of the gross target prior to brachytherapy [6]. Jhingran et al [18] found that patients who received combined EBRT and BT had better overall survival. Local control has also been found to be

favourable with combined EBRT and BT [25-26]. Brachytherapy (alone or in combination with EBRT) was found to benefit overall survival compared with EBRT alone [27]. Median overall survival (OS) for patients receiving EBRT alone was 3.6 years versus 6.1 years for patients receiving EBRT and brachytherapy.

2.1.2 Locally Advanced Cervical Cancer

Cervical cancer develops within the cervix, the entrance to the uterus from the vagina. Cervical cancer is estimated to affect 942 women in Australia in 2022, representing 1.3% of all female cancer diagnoses, with an estimated 222 deaths (1% of all female cancer deaths). Based on data from 2014 – 2018, the five-year survival rate for cervical cancer in Australia is 74%. [28] Australia has a national cervical cancer screening program, available to all women aged from 25 to 74 years [29].

The most common cervical cancer type is squamous cell carcinoma (over 70% of cases). A further 25% of cases are adenocarcinomas. Persistent infection with the human papilloma virus is the most common cause of cervical cancer [30]. Gold standard treatment for locally advanced cervix cancer is chemoradiation with radio-sensitizing chemotherapy, external beam radiotherapy and an MRI-guided brachytherapy boost [31].

Cervical cancer is staged using the FIGO staging, which was revised in 2009 [32] and 2019 [33].

2.2 Introduction to Brachytherapy

2.2.1 High Dose Rate (HDR) Brachytherapy

HDR brachy allows delivery of radiation using solid radio-isotope sources placed internally within the body. The source may be placed either within the tumour or next/adjacent to it. The source is administered using an afterloader which, drives the source into shaped applicators or needles within the patient. HDR brachytherapy has a dose rate above 10Gy/hr and is most commonly delivered using an Iridium-192 source. The source is attached to a guide wire that is stepped into different positions, according to the treatment plan.

Iridium-192 decays into platinum-192 via β^- decay 95.1% of the time and the remaining 4.9% into osmium-192 by electron capture. This leads to a complex decay pattern resulting in 29 gamma emission peaks from 0.110 to 1.378MeV, with an average energy of 0.38MeV.

The Ir-192 sources used for this work were a VS2000 housed within a Varisource iX afterloader (Varian Medical Systems, USA) and a Flexisource (Elekta, Sweden), housed within an Elekta Flexitron afterloader. The active cylindrical core of the Flexisource is 3.5mm long (Fig 2.1), with a diameter of 0.6mm, encapsulated by stainless steel, leading to a total outer diameter of 0.85mm and 4.6mm total length [34]. The VS200 (Fig 2.2) is comprised of two cylindrical sources with a total length of 5mm and a diameter of 0.34mm, encapsulated in nitinol, leading to a total outer diameter of 0.59mm and a total length of 6mm [35].

A remote afterloader steps the source into a series of applicators or needles, which are previously inserted, usually with the patient under general anaesthesia. Fig 2.3 shows an Elekta Flexitron remote afterloader and a Varian Varisource iX remote afterloader.

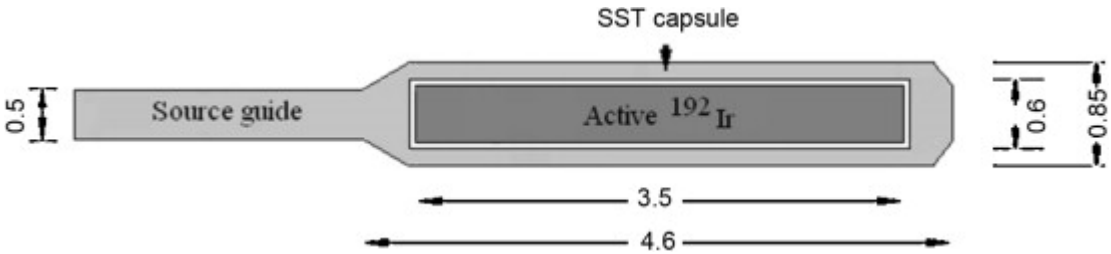

Fig 2.1 – Diagram of the Flexisource [34]

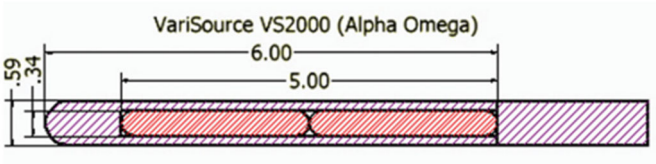

Fig 2.2 - Varian VS2000 source [35]

Fig 2.3 – a) Elekta Flexitron afterloader, which delivers HDR brachytherapy using the Flexisource and b) Varian Varisource iX afterloader, which delivers HDR

brachytherapy using the VS2000 source. The necessary source transfer tubes which link the afterloader to the applicators are not shown

2.2.2 HDR Brachytherapy Dose Calculation Algorithm

HDR brachytherapy doses are calculated using the AAPM TG43 update 1 (TG43U1) dose calculation algorithm, as shown in Eq 2.1, with the co-ordinate system geometry illustrated in figure 2.4 [36].

$$\dot{D}(r,\theta) = S_K \cdot \Lambda \cdot \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} \cdot g_L(r) \cdot F(r,\theta), \qquad \text{Eq 2.1}$$

where:

r denotes the distance (in centimetres) from the centre of the active source to the point of interest

r_0 denotes the reference distance which is specified to be 1cm

θ denotes the polar angle specifying the point of interest P(r, θ), relative to the source longitudinal axis.

The reference angle θ_0, defines the source transverse plane and is specified to be 90 degrees.

S_K is the source air kerma strength

Λ is the dose rate constant

$G_L(r, \theta)$ is the geometry function

$g_L(r)$ is the radial dose function

F(r, θ) is the anisotropy function

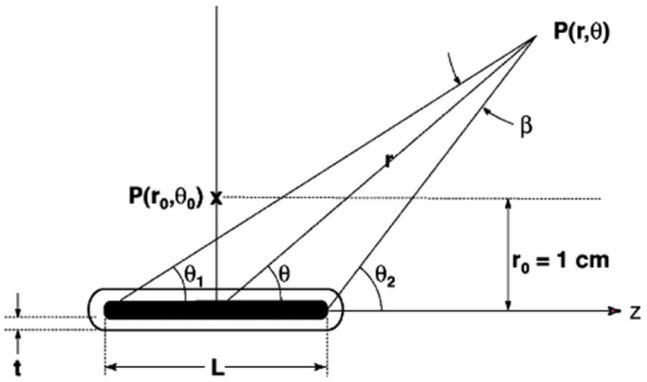

Fig 2.4 – Co-ordinate system for brachytherapy dose calculations.

2.3 Radiobiological Calculations

The University of Vienna [37] have developed a framework for combining EBRT and brachytherapy doses. The equi-effective absorbed dose (EQDx) concept uses the linear quadratic model and allows comparison of dose to the CTV and OAR when the dose is delivered in different fractionation schema, for example, external beam radiation therapy (EBRT) combined with brachytherapy [38-39]. Equi-effective absorbed doses are defined as doses, that when delivered under specified but different conditions, produce the same probability of a specific radiation effect or endpoint.

Because of the large body of clinical data collected with 2Gy fractions, it is most common to express EQDx as EQD2.

The biologically effective dose (BED) can be calculated as

$$BED = Nd\left[1 + \frac{d}{\alpha/\beta}\right] \qquad \text{eq 2.2}$$

where

N is the number of fractions

d is the dose per fraction

α/β is a parameter describing lethal/sublethal lesions

The conventional external beam equi-effective dose in 2Gy fractionation becomes

$$EQD_2 = \frac{BED}{1+2/\frac{\alpha}{\beta}} \qquad \text{eq 2.3}$$

2.4 Vaginal Brachytherapy

2.4.1 Vaginal Brachytherapy Delivery Systems

Depending on the depth of the lesion, brachytherapy can be delivered using either intracavitary (IC) or interstitial (IS) approaches. Recommendations are that for disease depth less than 0.5cm, intracavitary brachytherapy is suitable, with thicker lesions requiring interstitial brachytherapy [1].

Intracavitary brachytherapy can be delivered using either single or multi-channel applicators, however single channel applicator use is limited for vaginal cancers due

to the inability to effectively shape the dose [40]. Figure 2.5 shows examples of single channel and multi-channel vaginal cylinders commercially available from Varian Medical Systems (Palo Alto, California, USA).

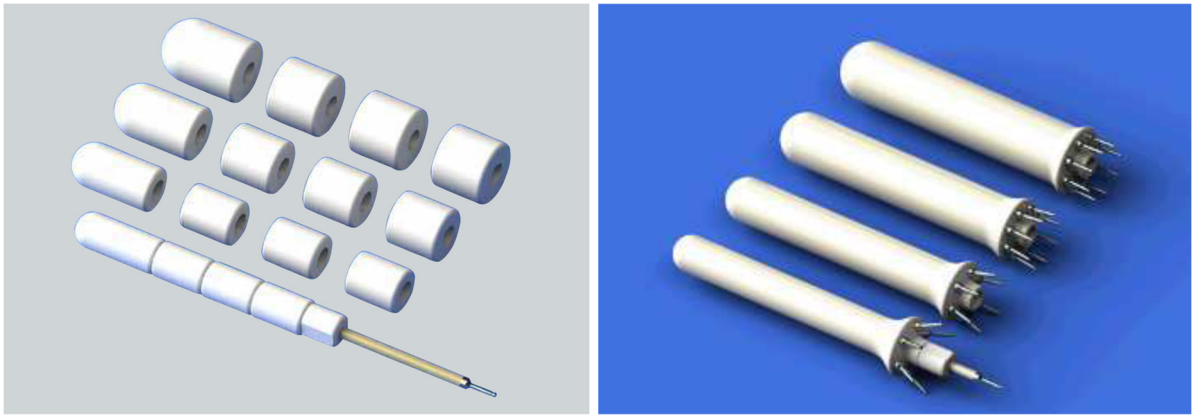

Fig 2.5 – a) Single channel vaginal cylinder and b) multi-channel vaginal cylinder.

Albano et al [41] describe a method for taking a mould of the vagina to manufacture a customised applicator for intracavitary brachytherapy, the technique used at the Institut Gustav-Roussy. They report this allows personalised, tailored irradiation, integrating tumour shape, size, extension and vaginal anatomy. The expansion of the vagina also reduces dose to the vaginal mucosa and organs at risk.

Interstitial brachytherapy can be delivered using either a free-hand or template technique [7, 18, 24]. Combined interstitial and intracavitary brachytherapy has also been used for vaginal cancers [42]. Mendez et al [43] performed a dosimetric comparison of interstitial and multichannel vaginal applicators, finding that interstitial brachytherapy gives lower doses to organs at risk but for circumferential disease multi-channel vaginal applicators give acceptable doses to organs at risk but a better dose to the vaginal mucosa.

3D printing has also been investigated and implemented for constructing customised applicators for delivering vaginal brachytherapy [44-48]. Zhao et al [49] report the ability to add interstitial needle guide holes into a 3D printed applicator for further customization of the dose distribution. Yan et al [50] reported that compared to multi-channel cylinders, 3D printed customised moulds allow a higher dose, larger treatment volume, more homogenous dose and greater CTV conformity.

2.4.2 Target doses and local control for Vaginal Malignancies

In 2020, Schmid et al [51] from the Groupe European de Curietherapie and European Society for Radiotherapy and Oncology gynaecology working party (GEC-ESTRO GYN) working group published consensus concepts and recommendations for target volume delineation for image guided adaptive brachytherapy for primary vaginal cancer. They defined target volumes at the time of brachytherapy as being the residual gross tumour volume (GTV_res), high-risk clinical target volume (CTV_HR) and intermediate risk clinical target volume (CTV_IR).

Prior to the GEC-ESTRO recommendations, different definitions of clinical target volume (CTV), CTV_HR and CTV_IR were reported, making dose reporting and comparisons more challenging. Published CTV doses have varied across different publications, but most authors report between 70Gy and 80Gy D90 total EQD2 [52 – 56]. Fokdal et al [9] aimed to deliver >80Gy to the CTV_HR and reported a median CTV_HR D90 of 82Gy.

2.5 Cervical Brachytherapy

2.5.1 MRI guidance for cervical brachytherapy

Dimopoulos et al [57] published the GEC-ESTRO recommendations for the basic principles and parameters for MR imaging in the frame of image based adaptive brachytherapy for locally advanced cervical cancer. The ABS [58] have also published consensus imaging guidelines for cervical brachytherapy. MRI gives superior soft tissue contrast, compared to other imaging modalities such as CT, which enables visualization of both the patho-anatomical structures (uterus, cervix, vagina and gross tumour volume) and organs at risk. MRI for cervical cancer brachytherapy planning requires T2 weighted para-axial, para-sagittal and para-coronal scans with fast spin echo sequences, obtained with pelvic surface coils. The surface coils increase the signal to noise ratio. It is important to administer an anti-spasmodic medication prior to imaging, to reduce artefacts caused by bowel motion. The scan should extend from above the uterine corpus to at least 3cm below the surface of the vaginal applicator (or the entire vagina if disease extends into the vagina) and to the pelvic side walls.

There are also GEC-ESTRO recommendations for applicator reconstruction [59], including for MR imaging, for commercially available MRI-compatible brachytherapy applicators. Applicators appear as black voids on MR images. Applicator models in the treatment planning system, or image registration with CT images can be used to relate the contours and the source dwell positions.

Historically, information from clinical examinations has been documented with clinical drawings. Target delineation should still include information from the clinical drawings taken during examination under anaesthesia (EUA) from the time of diagnosis and the time of brachytherapy [60]. These clinical drawings provide a semi-quantitative graphical assessment of the size and extension of disease across all directions at the time of examination, and quickly demonstrate the difference due to radiation response between the time of diagnosis and the time of brachytherapy.

2.5.2 Dose Reporting for Cervix cancer

Historically, brachytherapy for cervical cancer was reported using the ICRU38 recommendations [61]. These were point based, arising from 2D planning techniques. In 2005 the GEC-ESTRO group produced recommendations for new volumetric concepts for target definitions and dose volume histogram (DVH) parameter based reporting [62-63]. The ABS also produced similar volume-based guidelines in 2012 [64]. In 2016, the ICRU report 89 [38] superseded these local guidelines, producing international recommendations for the reporting of doses in radiation therapy for cervical cancer, including both the external beam and brachytherapy components.

The ICRU 89 report provides common concepts and terms for volumes, such as the initial and residual GTV, initial and adaptive CTV and OAR, dose volume parameters, radiobiological variations and three different levels of clinical practice.

At the time of brachytherapy, the high-risk CTV includes the residual GTV and the entire cervix for all cases, and any presumed tumour extension in adjacent tissues, as

defined by clinical assessment and “grey zones” on T2 weighted MRI, with no added safety margins. The intermediate risk CTV should include the entire GTV from the time of diagnosis and the entire high-risk CTV, with safety margins of 1 – 1.5cm cranially, 0.5cm antero-posteriorly and 0.5cm laterally. Other parameters are still required to be reported as well, such as the dose to the Manchester point A, bladder and rectum ICRU points and the Total Reference Air Kerma (TRAK; the sum of the product of the reference air kerma rate at one metre and the irradiation time for each source dwell position).

2.5.3 Target doses and local control for locally advanced Cervical Cancer

The GEC-ESTRO GYN network performed a retrospective study of 852 locally advanced cervix patients, retroEMBRACE [65] followed by the EMBRACE I study [66] across their network. EMBRACE I was a prospective, multi-centre, observational study including both external beam radiotherapy and a brachytherapy boost. It aimed to evaluate local tumour control and morbidity after chemoradiation with an MRI guided brachytherapy boost [66]. The study closed in 2015 with 1416 patients accrued. In 2016, the EMBRACE II trial was launched as a prospective interventional study [67], based on the results of retroEMBRACE [65, 68-71] and EMBRACE I [66, 72 – 97]. `

Mono-institutional studies, the retro-EMBRACE series and the EMBRACE I study have demonstrated that by following the GEC-ESTRO recommendations [62-63] for standardised reporting, target dose response curves for local control can be collated. Prior to the EMBRACE I study, there was insufficient evidence for planning aims in brachytherapy [98].

The gradient of the dose effect curves depends on disease stage and the volume of the CTV_HR, as well as disease histology (squamous cell carcinoma doing better than adenocarcinoma, all other parameters being equal). Other dose effect modulators include tumour hypoxia, radio-sensitivity and repopulation [98].

Evidence-based dose effects assume an overall treatment time of approximately 50 days. The linear quadratic model and EQD2 calculations used do not take tumour repopulation into account, hence the loss of treatment efficacy if overall treatment time is extended [39, 99 - 100]. It has been shown that an additional dose of 5Gy (EQD2) is required for every additional week of treatment beyond 50 days [101].

Escalating the CTV_HR D90 dose from 75Gy to 85Gy increased local control by 3% in tumour volumes of 20 – 30cm^3 and by 7% in larger tumours up to 70cm^3 [101]. A CTV_HR D90 dose ≥85Gy delivered in 50 days resulted in 3-year local control rates of >94% for limited size tumours (20cm^3) to >86% in larger tumours (70cm^3). CTV_IR and GTV D98 ≥60Gy and ≥95Gy respectively resulted in similar levels of local control [98]. Other studies have shown a similar dose response supporting a CTV_HR D90 of around 90Gy for high local control rates [22, 35, 66].

2.54 Toxicity from gynaecological brachytherapy

Cancer Toxicity can be reported using the USA National Cancer Institute's Common Terminology Criteria for Adverse Effects (CTCAE) [102]. A grading scale based on severity is described for each adverse outcome. Patient related factors such as smoking and co-morbidities can also affect treatment toxicity [98].

Two large mono-institutional studies [103-104] have correlated bladder toxicity with dose. Both used different endpoints for analysing genitourinary toxicity. Fokdal et al [105] reported the most common urinary bladder toxicities were frequency or urgency, incontinence and cystitis, with grade 2 – 4 toxicities reported in 4.3%, 5% and 1.7% of patients respectively. Grade 3-4 fistula, bleeding, spasms and cystitis were all reported in <1% of patients. No grade 5 toxicities were reported. Data from the EMBRACE studies provides high level evidence that the bladder D2cm^3 correlates with the risk of high-grade bleeding, cystitis and fistula [78].

Mazeron et al [106] and Nkiwane et al [107] investigated that the dose to different bladder locations correlate with different toxicities. The use of the ratio between the dose to the Bladder ICRU point and the bladder D2cm^3 has been used to quantify the relationship between the location of hotspot and the dose effect. Bladder incontinence has been found to correlate with hot spots in the bladder base [108]. Neither the bladder D2cm^3 nor ICRU point were found to be predictive of urinary frequency, which seems to be more linked to EBRT volumes and doses and patient risk factors [98].

Diarrhoea and flatulence were the most commonly reported bowel toxicity. At five years the actuarial incidence of grade 3-4 bowel toxicity was 5.9% and grade 4 stenosis, stricture or fistula was 2.6%. Grade 1- 2 morbidity was far more prevalent, with rates of 28-33% during follow up. [87]. The rectal D2cm^3 has been shown to correlate with the risk of high-grade rectal bleeding, fistula and proctitis [103, 109]. There is also evidence that the ICRU rectal point dose correlated with rectal bleeding and fistula [109].

Sigmoid D2cm^3 has not been found to correlate with bowel morbidity [87]. Data from EMBRACE shows the bowel D2cm^3 is also correlated with the increased risk of gastrointestinal toxicity [87].

The probability of grade 2 or higher vaginal stenosis has been found to increase with ICRU rectovaginal point doses >65Gy [93]. EMBRACE data has also found that higher doses to the posterior-inferior border of symphysis (PIBS) and PIBS+2 point correlate with increased risk of > grade 2 vaginal stenosis [73]. Murakami et al [110] found that the vaginal D2cm^3 correlated with the risk of vaginal ulceration.

Severe urethral toxicity has been correlated with the D0.1cm^3 [111]. Actuarial 3 and 5 year risk for ureteral stricture grade 3 to 4 was 1.7% and 2.1%, respectively, for all patients [85]. Fokdal et al [85] found the only risk factor for ureteral stricture was advanced disease with hydronephrosis at diagnosis. The EMBRACE study has not found the proximity of interstitial needles increases the risk for urethral stenosis [98].

2.5.5 The effect of applicator design on dose distribution for cervix cancer

Brachytherapy for locally advanced cervical cancer has been traditionally delivered using intracavitary techniques, with either a ring and tandem or tandem and ovoid configuration. In recent years, interstitial components have also been added. Figure 2.6 shows sample applicator designs.

Fig 2.6 - Applicators used for cervical cancer brachytherapy, including tandem and ovoid style, ring and tandem style and the Venezia advanced gynaecological applicator.

The use of the IC/IS technique in EMBRACE I showed improved target coverage and conformality as compared with IC alone [83]. Other studies have also shown an increased CTV_HR D90 with the application of an IS component, with similar OAR doses [71, 112 – 114].

Pre-planning plays an important role in applicator choice. Chakrebarti et al [115] found that lack of pre-planning was a contributing factor when there was imperfect applicator insertions. For ring and tandem applicators, the tandem angle affects the dose to the bladder, rectum and sigmoid. The ring diameter also affects OAR doses, such that the largest possible ring should be inserted [116].

2.6 Plan Quality Assurance in Brachytherapy

The AAPM Medical Physics Practice Guideline (MPPG) 11.a [117] includes recommendations for plan quality assurance in brachytherapy. Recommended checks include ensuring the plan meets the prescription, verifying the activity or air kerma strength based on a decay table, correct planning image used, along with any image

registration being checked, plan normalization, channel numbering, indexer length and offset, channel orientation, number of dwell positions and the position of the first dwell position of each channel, step size, applicator model name and size, catheter reconstruction, including with magnification and 3D views, appropriate plan optimization and dose distribution, calculation algorithm and secondary calculation. End of treatment checks are also recommended. Following the tri-partite Radiation Oncology Standards in Australia [118], it is important to evaluate the technical quality of care and to benchmark to best practice.

Different anatomy, target volumes, applicator styles and dimensions all affect the plan quality parameters achievable. Apart from an experienced planner trying to get the best plan possible from experience, using evidence-based planning aims, there is very little on offer to ensure brachytherapy plan optimization criteria and dose distribution is optimal for each individual patient [119].

This lack of quality assurance/consistency options could affect clinical trials using cervical brachytherapy, as well as the potential for individual patients to be treated with sub-optimal plans undetected by the standard plan checking process. Brachytherapy planning for cervix cancer is typically completed in a time-constrained environment, adding to the pressure to get a plan ready in a timely manner.

2.7 Uncertainties in gynaecological brachytherapy

The current standardised method for expressing and evaluating uncertainties comes from the Comité International des Poids et Mesures (CIPM) [120]. Brachytherapy can

be subject to uncertainties arising from source calibration, imaging, treatment planning, dose delivery and anatomical variations [121]. Uncertainties in brachytherapy can be either systematic (eg – source calibration) or random (eg anatomical variations). Dosimetric uncertainties can affect both the tumour control probability (TCP) and normal tissue complication probability (NTCP). Uncertainties arising from brachytherapy source calibration and dose calculation have been reviewed by DeWard et al [122]. Within the pelvis region, these uncertainties are expected to be below 3%. Additional uncertainties arise from the radiobiological effect calculations [123]

The precision of cervical brachytherapy has significantly improved with the use of MRI guided adaptive brachytherapy [124]. Petric et al [125] reviewed the target volume delineation uncertainties for cervical cancer brachytherapy. Using reference contours created by an expert group and by using an expectation maximization algorithm for simultaneous truth and performance level estimation (STAPLE) method and found the CTV_HR had less deviation between observers than the GTV or CTV_IR, but that uncertainties in target volume delineation may challenge the technical gains in treatment precision. This highlights the importance of high-quality imaging, adequate training and respecting the recommendations. Hellebust et al [126] found that the target uncertainties are 9% and the OAR uncertainties are 5% - 11%. Uncertainties from dose summation across fractions for cervical brachytherapy have been investigated [127-128], compared to the clinical implementation of using the worst-case scenario [63].

Nesvacil et al [129] found the dosimetric impact depends on the magnitude and distribution of the uncertainties, the fractionation protocol and the dose response curve. Brachytherapy target doses are typically high enough to be in the flat part of the

higher level of the tumour control probability curve. This makes the probability of tumour control robust against uncertainties. Normal tissue control probability can potentially be improved by reducing uncertainties.

2.8 21st Century Technology in Brachytherapy

Some of the assumptions and uncertainties in brachytherapy might be reduced with the additional of newer technology, as well as improving plan quality. Newer applicator designs and the implementation of volumetric imaging allow for increased use of optimization techniques, whereby an array of optimised dwell positions and dwell times are generated, replacing standard loading patterns. Deformable image registration and knowledge-based planning may also be able to be translated from EBRT to BT.

2.9 HIPO optimization

HIPO is a hybrid inverse planning optimization algorithm originally developed by pi-medical (Athens, Greece) before being implemented into the Oncentra treatment planning system. It is hybrid because it combines deterministic and stochastic optimization algorithms. It can optimise using multiple targets (CTV, GTV) and organs at risk. It uses objective functions that linearly penalise doses above or below the specified level [130].

The objective functions for the low dose f_L and high dose f_H are [131]:

$$f_L(x) = \frac{1}{N}\sum_{i=1}^{N} \Theta\big(D_L - d_i(x)\big)\big(D_L - d_i(x)\big)^{\propto} \qquad \text{eq 2.4}$$

$$f_H(x) = \frac{1}{N}\sum_{i=1}^{N} \Theta(d_i(x) - D_H)(d_i(x) - D_H)^{\propto} \qquad \text{eq 2.5}$$

where:

N is the number of sampling points

D_L and D_H are the lower and high dose limits

d_i is the dose at the ith sampling point

$$\Theta(x) = \begin{cases} 1\ if\ x > 0 \\ 1/2\ if\ x = 0 \\ 0\ if\ x < 0 \end{cases} \quad \text{with } \alpha = 1$$

The following objectives are used in brachytherapy:

$$f_L^{PTV} = \frac{1}{N_{PTV}}\sum_{i=1}^{N_{PTV}} \Theta(D_L^V - d_i) \qquad \text{eq 2.6}$$

$$f_H^{PTV} = \frac{1}{N_{PTV}}\sum_{i=1}^{N_{PTV}} \Theta\,(d_i - D_H^V) \qquad \text{eq 2.7}$$

$$f_{OAR}^{j} = \frac{1}{N_{OAR}^{j}}\sum_{i=1}^{N_{OAR}^{j}} \Theta\left(d_i - D_{crit}^{j}\right) \qquad \text{eq 2.8}$$

$$f_{NT} = \frac{1}{N_{NT}}\sum_{i=1}^{N_{NT}} d_i^2 \qquad \text{eq 2.9}$$

where:

D_L^V is the prescription dose, or lower dose limit

D_H^V is the high dose limit within the PTV

f_L^{PTV} is the fraction of the PTV with a dose value $D < D_L^V$

f_H^{PTV} is the fraction of the PTV with a dose value $D > D_H^V$

f_{OAR}^j is the fraction of the j th OAR with a dose value $D > D_{crit}^j$

f_{NT} is the mean squared dose in the surrounding normal tissue.

Such that the complete optimization function is [130]:

$$f = w_1 f_L^{PTV} + w_2 f_H^{PTV} + w_3 f_{NT} + \sum_{j=1}^{OARs} w_{j+3}\, f_{OAR}^j \qquad \text{eq 2.10}$$

In 2009 Trnkova et al [132] demonstrated that HIPO can be used to generate clinically acceptable plans for cervical cancer. HIPO includes a dwell time gradient restriction (DTGR) option, which limits dwell time modulation between neighbouring dwell positions. The DTGR input can vary between 0 and 1, with 0 allowing large fluctuations between dwell positions.

2.10 Deformable Image Registration and OAR DVH parameter summation

THE GEC-ESTRO recommendations include linear summation of the OAR dose, which inherently includes a worst-case scenario assumption that the topographical location of each organ's D2cm^3 is in the exact same location each fraction [63].

Deformable image registration (DIR) algorithms have been introduced to map voxels between different image datasets, allowing for testing of the uncertainties associated with the worst-case scenario assumption of the D2cm^3 being in the same position each fraction. Several clinical software platforms allow for DIR in radiotherapy, including MIM Maestro, Varian Velocity, Mirada and RayStation.

DIR uses similarity metric, transformation, and optimization algorithms. The optimiser changes parameters until an optimal similarity metric is obtained. The American Association of Physicists in Medicine AAPM task group report 132 [133] provides guidance for the use of image registration and fusion algorithms and techniques in radiotherapy, which includes DIR. Barber et al [134] published guidelines for DIR in Australia. It is not yet recommended to use DIR for clinical brachytherapy, with further technical and clinical investigations required.

Several groups have investigated the use of DIR in the setting of brachytherapy dose summation, as summarised by Swamidas et al [135]. Theoretically, DIR could be used to add the dose distribution from each brachytherapy plan together with the EBRT plan. The dose contribution from EBRT to the locations of the BT D2cm³ hotspots should be uniform, as these organ subvolumes are part of the PTV at time of EBRT. However, insertion of brachytherapy applicators can cause large tissue deformations, along with vaginal packing and tumour shrinkage, adding to the uncertainties of the DIR.

Swamidas et al [136] investigated the uncertainties of deformable image registration in the setting of cervical cancer brachytherapy, finding large variations in the

differences DIR could make to dose accumulation, including implausible registrations, resulting in dose increases from the worst case scenario.

Swamidas et al [135] found that rigid registration is sufficient for contour mapping and applicator reconstruction during the brachytherapy planning process, current DIR algorithms are not yet robust enough for the complexities involved in the clinical application of DIR in brachytherapy for cervical cancer. Direct addition of DVH parameters provides a reasonable estimate for the target volumes, bladder and rectum. There are much greater uncertainties however if the EBRT plan has large dose gradients across the irradiated volume in brachytherapy, such as could occur with pelvic node boosts.

2.11 Knowledge-Based Planning

Knowledge-based planning uses machine learning models from a previous database of patient plans to predict achievable DVHs for an individual patient. It uses the geometric relationship between the target and organs at risk to predict the doses achievable for each organ at risk. It enables quality control of an individual plan, particularly that of organ sparing, which for techniques such as IMRT and brachytherapy would otherwise rely on subjective measures and the experience of the planner and clinician [119].

Wu et al [137] introduced the overlap volume histogram (OVH) concept to define the geometric relationship of each organ at risk to a target volume, for intensity modulated radiation therapy (IMRT).

The overlap volume histogram defines the fractional component of an organ at risk within a specified distance from a target. To establish a full overlap volume histogram, the target is uniformly contracted and expanded until there is no overlap, through to full overlap, of the organ at risk and the target volumes.

In a conformal external beam plan, the OVH and DVH curves for each organ are directly related [137]. These relationships have also been shown to be useful for IMRT and VMAT plans. Cornell et al [138] showed that across a range of disease sites, KBP was non-inferior (based on physician choice) to plans optimised by humans.

Cervical cancer radiation oncology inherently involves large anatomical variations between patients, presenting a challenge for KBP. Several groups [139- 143] have implemented a KBP model for intact cervical cancer in EBRT. Yusufaly et al [144] has reviewed the use of KBP in cervical cancer. Tao et al [142] also demonstrated that KBP can be used to calculate generalised uniform equivalent dose for cervical cancer EBRT.

Over time, models for knowledge-based planning can be improved. Li et al (139] describe methods for model training, refinement and validation for EBRT clinical trials for cervical cancer EBRT plans. They note the important difference between DVH parameters predicted by a model and generated by the routine of implementing the model. They used filtering to refine models based on better OAR sparing. Fogliata et al [145] explored the use of iterative training, re-applying the model to plans that were created with the model. Kang et al [141] specifically improved models for cervical and

endometrial cancers using a looping method, where only plans with good mean doses get looped back into the model.

Yusufaly et al [146] demonstrated that for cervical cancer brachytherapy a full DVH estimate for bladder, rectum and sigmoid could be derived for N sets of model training data, using a boundary function from the clinical target volume. Reijtenbagh et al [147] used machine learning based on overlap volume histograms to predict the $D2cm^3$ for cervical cancer brachytherapy plans from two different institutions. They used random forest networks to generate models that predicted the entire DVH. Li et al [148] implemented a DVH prediction workflow combining kernel density estimation and principal component analysis. Cortes et al [149] found that 3D knowledge-based dose predictions provide voxel-level and DVH metric estimates that could be used for plan generation and treatment plan quality control for bachytherapy with tandem and ovoids. All the models were able to predict the DVH and be implemented into clinical workflows for brachytherapy plans.

Given that Yusufaly [146] and Cortes [149] were able to produce KBP models that accurately predict DVHs for HDR brachytherapy for cervical cancer, Kallis et al [150] used knowledge base planning models to evaluate the dosimetric differences of tandem-and-ring and tandem-and-ovoids applicators.

There are also other more complicated decision-making implementations of machine learning in brachytherapy for cervical cancer. Stenhouse et al [151] trained a model using a range of data for optimal applicator selection. Abdalvand et al [152] used machine learning for modelling predicted outcome following brachytherapy for cervical

cancer. Fan et al [153] used deep learning inference modelling for independent plan verification. Shen et al [154] used deep reinforcement learning to automate the optimization process, including weighted priority tuning.

Knowledge-based planning could also be used to give clinicians confidence that they are achieving high quality dose distributions with their implants, by comparing with large multi-institutional datasets, as proposed by Yusufaly et al [146]. This could be used to reduce the decline in brachytherapy utilization and drive further improvements in brachytherapy technology.

2.12 Summary

The initial literature review of brachytherapy for gynaecological cancers, considering the state of the topic at the beginning of this research, and in the light of the then recent developments in local practice and the possible opportunities for further improvement, led to the aims, objectives and research questions discussed in Chapter 1, specifically the need to evaluate current local dosimetric and clinical practice to assess changes over the period of changes in technology and methods and to investigate the feasibility and usefulness of applying DIR and KBP in brachytherapy for cervical cancer. These issues are addressed in the following four chapters of this thesis.

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Chapter Three - A single-institution review of image-guided brachytherapy for vaginal malignancies using customised moulded applicators and interstitial needles

3.1 Preface

In this chapter a review was undertaken of image-guided brachytherapy for vaginal malignancies using customised moulded applicators and interstitial needles. Reviewing clinical practice forms an important part of quality management and optimization, especially for highly specialised techniques.

This review showed that this technique allows for acceptable doses to the CTV with local control achieved in 67% of patients and reasonable doses to the organs at risk and acceptable toxicity. This data enables the centre to continue to assess changes of practice to improve treatment for vaginal cancers.

Changes to international guidelines, such as the release of the GEC-ESTRO ACROP consensus guidelines for contouring primary and recurrent vaginal malignancies, the availability of new applicators, such as the Advanced Gynaecological Applicator (Venezia) and advanced medical imaging can all affect the way we treat vaginal malignancies, and continued reviews and quality management are imperative.

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3.2 Abstract

Purpose: To review a single-institution's pattern of practice, dosimetry results, and clinical outcomes for patients with unresectable malignancies of vagina, vulva, or urethra, receiving brachytherapy using customised vaginal moulds with or without interstitial needles.

Material and methods: Twenty-one consecutive patients were reviewed. Patients were treated using customised moulds with or without interstitial needles, implanted with a free-hand technique. Technical implementation, such as type of implant and imaging used were recorded. D90 and D98 of clinical target volume (CTV), D0.1cm^3 of urethra, and D2cm^3 and D0.1cm^3 of bladder and rectum were analyzed. Any adverse clinical outcomes were reported.

Results: Eleven patients experienced endometrial cancer recurrences, one a cervical cancer recurrence and nine vaginal or peri-urethral primary disease. After a median follow-up of 3.5 years, local control was achieved in 14 patients (67%). Median D98 and D90 to CTV was 73.7Gy and 78.3Gy, respectively. One patient died from disease progression, one developed distant metastasis, and seven failed locally. Median D2cm^3 to bladder was 64.8Gy, with low-grade toxicity reported. Median D2cm^3 to rectum was 62.9Gy, with low-grade toxicity and one case of rectal proctitis was observed. Median urethral D0.1cm^3 was 66.0Gy, with no toxicity reported. One patient suffered from a sacral insufficiency fracture. It was presumed that vaginal mucosa proximal to CTV received the total dose, with two patients developing vaginal ulcers, which both resolved; 10 patients reported mild telangiectasia, fibrosis, or stenosis.

Conclusions: A review of patients treated with a customised vaginal mould and interstitial needles showed acceptable doses to CTV, with local control achieved in 67% of patients, and reasonable doses to organs at risk (OARs) and acceptable toxicity.

3.3 Introduction

Primary and recurrent malignancies of the vagina, vulva or urethra are rare diseases [1] with approximately 70 women diagnosed per year in Australia [2]. Treatment with surgery is difficult due to the proximity of organs at risk. The American Brachytherapy Society have produced guidelines or consensus documents for treating primary vaginal disease [1] and salvage treatment for endometrial recurrences [3]. Brachytherapy (BT) has been shown to be beneficial for local control for both primary [1, 4-12] and recurrent [5-9, 13-19] disease of the vagina, with acceptable toxicity risk.

External beam radiotherapy (EBRT) with a brachytherapy boost is recommended due to the risk of lymphatic involvement [20], although there are reports of a single modality being used [11, 15, 21-22]. Higher EQD2 total doses were delivered with external beam radiotherapy followed by a brachytherapy boost [15]. External beam radiotherapy also reduces the volume of the gross target prior to brachytherapy. Patients who received combined EBRT and BT had better overall survival [3,15]. Local control was also found to be favourable with combined EBRT and BT [23-24]. Brachytherapy (alone or in combination with EBRT) was found to benefit overall survival compared with EBRT alone [25].

Recommendations from the published literature can be summarised as follows: 1) For disease depths less than 0.5cm, intracavitary brachytherapy is suitable and 2) thicker lesions require interstitial brachytherapy [4]. If an intracavitary approach is used, multiple channels work better than single channel vaginal cylinders [26] Intracavitary brachytherapy can be delivered using either single or multi-channel applicators,

however single channel applicator use is limited for vaginal cancers due to the inability to effectively shape the dose [27]. Albano et al [28] describe a method for taking a mould of the vagina to manufacture a customised applicator for intracavitary brachytherapy. Interstitial brachytherapy can be delivered using either a free-hand or template technique [1, 15, 22]. Combined interstitial and intracavitary brachytherapy has also been used for vaginal cancers.

Dosimetric comparisons of interstitial and multichannel vaginal applicators have found that interstitial brachytherapy gives lower doses to organs at risk but for circumferential disease multi-channel vaginal applicators give a better dose to the vaginal mucosa [30-31].

MRI and 3D planning are recommended for planning vaginal brachytherapy [27]. Organ at risk toxicity for gynaecological brachytherapy has been extensively studied in the setting of cervix cancer. Dose volume histogram parameters such as $D0.1cm^3$, $D1cm^3$ and $D2cm^3$ have been found to be predictive of toxicity, including correlation with the grade of toxicity [32-37]. Kasibhatla et al recommended limiting the rectal dose to less than 76Gy for interstitial brachytherapy for advanced gynaecological malignancies [38]. Severe urethral toxicity has been correlated with the $D0.1cm^3$ [39]. Sigmoid toxicity is usually not a concern with vaginal brachytherapy due to the distance between the recto-sigmoid junction and the vagina. Murakami et al found re-irradiation and vaginal $D2cm^3$ were significant predictors of vaginal ulcers in interstitial brachytherapy for gynaecological malignancies [40].

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This report presents a single institution's pattern of practice, dosimetry results and clinical outcomes for patients with unresectable malignancies of the vagina, vulva or urethra receiving brachytherapy delivered using customised vaginal moulds, with or without interstitial needles.

3.4 Material and Methods

Following an examination under anaesthesia and often an MRI, patients received pelvic external beam radiotherapy. During the initial examination under anaesthesia most patients received gold seeds to mark the size and location of the original tumour.

External beam radiotherapy was delivered using either a 4 field box conformal technique using 18MV or volumetric arc radiotherapy using either 6MV or 10MV. The prescriptions were 45 - 50.4Gy in 25 - 28 fractions.

Brachytherapy was performed as a boost following external beam radiotherapy. The patient was anaesthetised and an examination performed. A mould for the customised applicator was made using a similar technique as described by Albano et al [28]. Dental alginate was used to form an impression of the vaginal canal (see figure 3.1). This mould was then placed in quick setting gypsum plaster. The plaster mould was then used to create a thin acrylic applicator shell conformal to the vaginal canal. 4.7 French catheters were then inserted into the acrylic mould in such a way as to enable the dose distribution to be conformal to the clinical target volume. Wax filling was used to stabilise the catheters within the mould. Figure 3.2 shows

the mould construction process. Figure 3.3 shows the completed customised applicator.

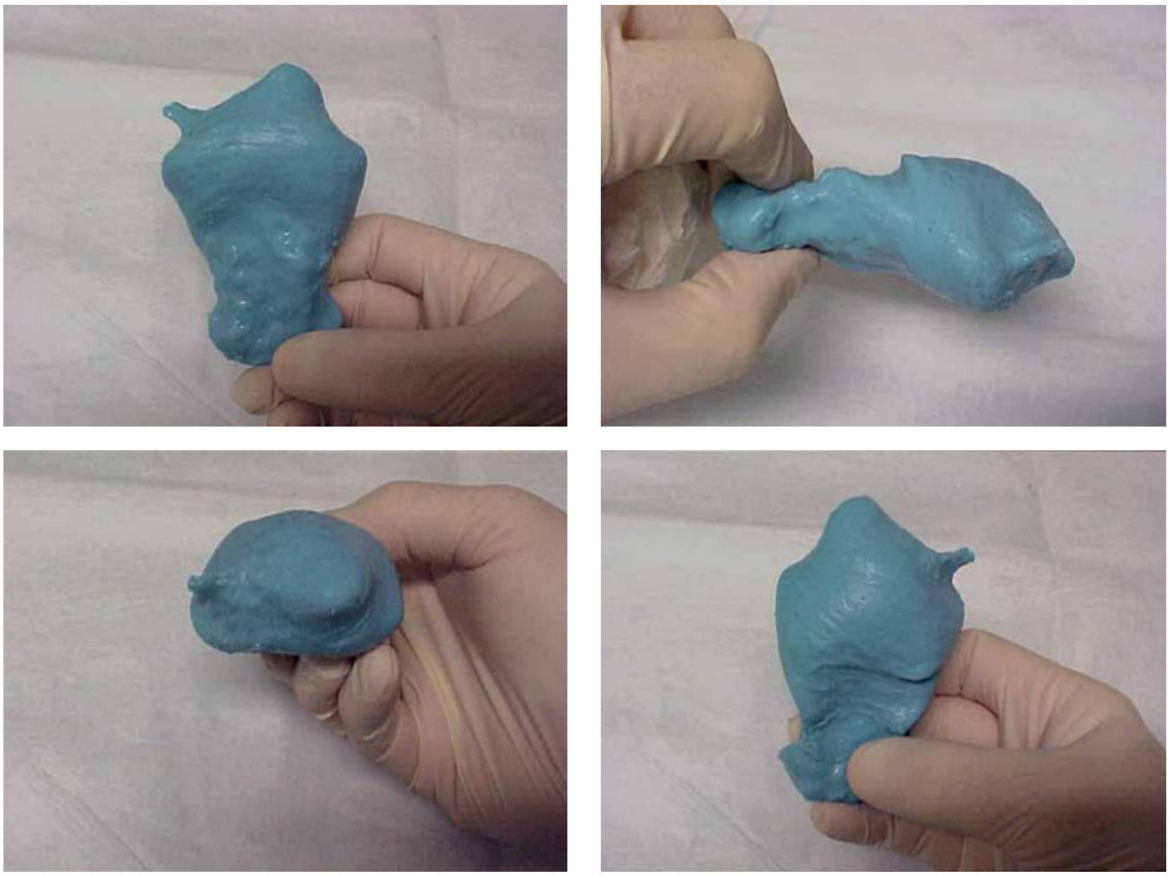

Fig 3.1 – Dental alginate mould of vaginal canal

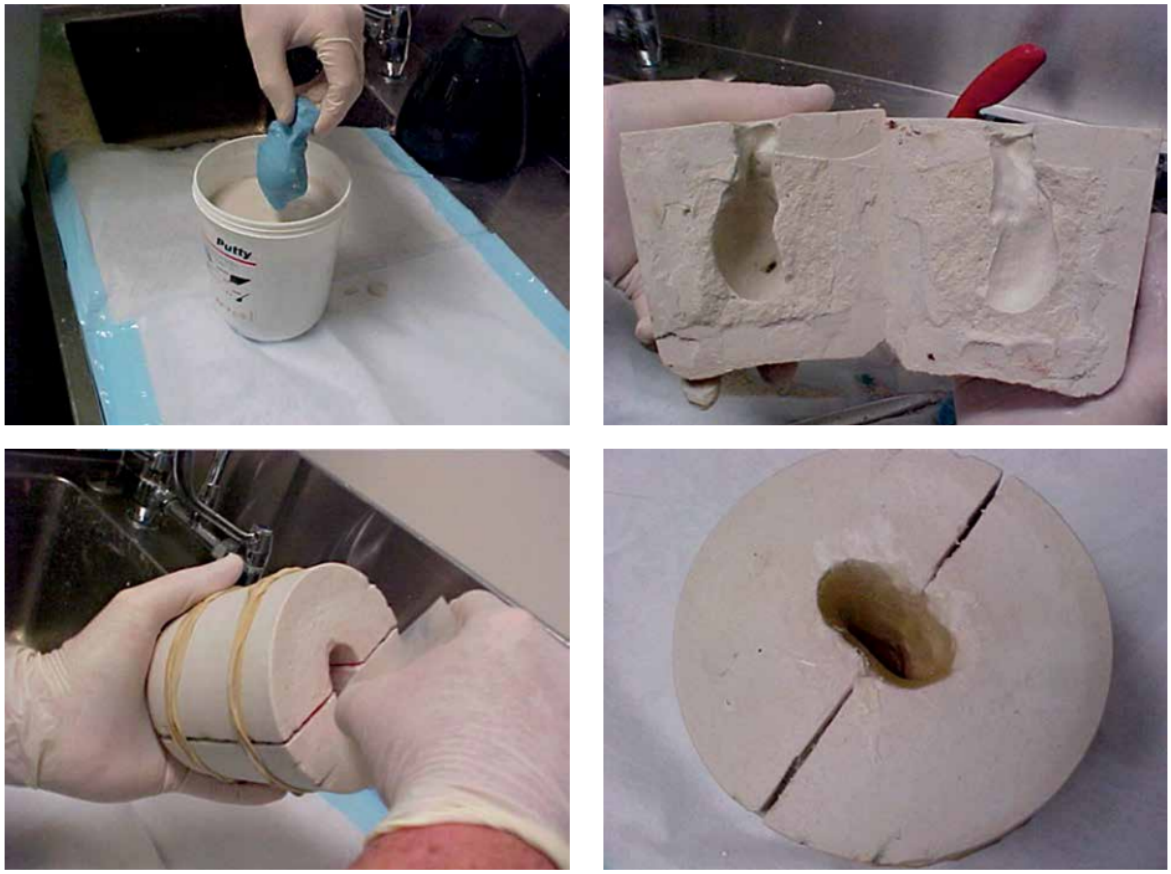

Fig 3.2 – Manufacture of acrylic shell

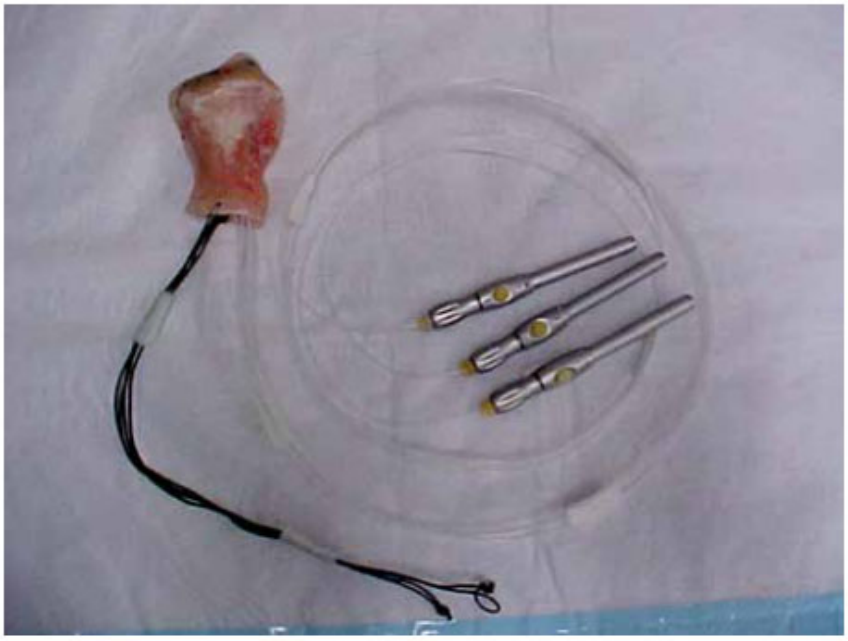

Fig 3.3 – Completed vaginal mould

If required, interstitial needles were placed along the lateral vaginal wall near the clinical target volume, using a free hand technique. Interstitial needles were inserted prior to the mould so the Oncologist could palpate the path of the needles from within the vaginal canal. The mould was inserted into the patient and surgically stitched into place.

After recovering from the anaesthetic, the patient had a CT scan at which radio-opaque CT marker wires were inserted into all channels within the mould and the needles. If MRI was required (and not contra-indicated) the markers were removed prior to imaging). MRI was not performed if there was a lack of residual tumour evident during the examination under anaesthesia, or if MRI was contra-indicated for the patient. T2 fast spin echo sequences were performed with axial, sagittal and coronal planes.

The CT and MR images (if applicable) were fused, using rigid image registration, matching the mould applicator, needles and gold seeds. Organs at risk and clinical target volumes were delineated on the MRI (if available, otherwise CT), whilst the CT was used for applicator reconstruction.

Using BrachyVision (Varian Medical Systems, Palo Alto, USA) a plan was generated to deliver the prescription dose to the CTV D90% ≥ 75Gy total dose EQD2, while maximizing conformity and limiting the dose to the organs at risk, with dose constraints to D0.1cm^3 and D2cm^3 of the bladder, rectum and sigmoid-colon and D0.1cm^3 to the urethra. Dwell time optimization was performed using a combination of volumetric

and/or graphical optimization techniques. The dose formalism described by the American Association of Physicists in Medicine Task Group 43 was used for dose calculations [29]. The total EQD2 bladder and rectum planning objectives were D2cm^3 ≤ 90Gy and D2cm^3 ≤ 75Gy respectively.

After a quality review the plan was approved by the Radiation Oncologist and treatment delivered using a Varisource iX (Varian Medical Systems, Palo Alto, USA). The patient usually remained in hospital overnight and two additional fractions were given the following day (if four fractions the patient stayed two nights), allowing a minimum of six hours between fractions. A combination of verification measurements including: 1) protruding needle length 2) a verification CT scan and 3) fluoroscopic imaging were performed prior to each additional fraction as appropriate for each case.

For this audit, patient medical records were accessed for determining treatment response, disease recurrence (local or distant) and toxicity as well as dosimetric data such as CTV D90 and D98, Bladder and rectum D2cm^3 and D0.1cm^3 and urethral D0.1cm^3. For comparison to other literature, the dose homogeneity within the CTV and the dose conformity were evaluated. The dose homogeneity was calculated using the brachytherapy-specific dose homogeneity index (DHI, eq 3.1) [41], which has been widely applied for interstitial-only HDR and by some authors for intracavitary HDR [42-45]. Dose conformity was calculated using the simplified conformity index (CI, eq 3.2) [46]

$$DHI = 1 - \frac{V_{CTV,150}}{V_{CTV,100}} \qquad \text{eq 3.1}$$

$$CI = \frac{V_{CTV,100}}{V_{CTV}} \times \frac{V_{CTV,100}}{V_{REF}} \qquad \text{eq 3.2}$$

Where: DHI = dose homogeneity index

$V_{CTV,150}$ = Volume of the CTV that receives 150% of the prescribed dose

$V_{CTV,\ 100}$ = Volume of the CTV that receives 100% of the prescribed dose

CI =conformity index

V_{CTV} = Volume of the CTV

V_{ref} = Volume of the 100% isodose

3.5 Results

21 consecutively treated patients were reviewed following treatment between 2010 and 2018. Table 3.1 shows details of the diagnoses for the patient cohort for this study. The mean follow-up was 4.0 years (range 1.6 to 9.2 years). The mean age was 70 years (range 54 - 88 years).

Number of patients	Diagnosis
11	Endometrial recurrence
7	Vaginal primary
1	Cervix recurrence
1	Urethral primary
1	Vulva primary

Table 3.1 – Diagnosis of patients treated with customised moulds and/or needles.

Ten patients were treated using only channels within the customised mould. For eleven patients, free hand interstitial needles were used in addition to the channels within the mould. For one patient all the dwell positions were in the interstitial needles, with the customised mould only being used to stabilise the vaginal anatomy. The average number of channels per patient was 5, with a range of 2 - 12 (including interstitial needles). When interstitial needles were required, either 2 or 3 needles were inserted. Six patients were planned using only CT imaging. All other patients had CT and MR imaging for planning. CT enabled catheter reconstruction within the mould.

The EQD2 values were calculated assuming an α/β ratio of 10Gy for target volumes and 3Gy for late responding normal tissue *[43].* Sixteen patients were treated over three fractions and five patients received four fractions. The average CTV volume was 14.3cm^3 (1.5cm^3 to 47.3cm^3**).** CTV and organ at risk plan quality metrics (PQM) and toxicity are recorded in table 2. Figure 3.4 shows an example of an MR image showing the customised applicator, CTV and isodoses.

	Structure/organ	Plan Quality Metric (PQM)	Median	Toxicity
Target	CTV	D98 (Gy, EQD_2)	73.7	
		D90 (Gy, EQD_2)	78.3	
		DHI	0.5	
		CI	0.4	
Organs at risk	Bladder	D2cm^3 (Gy, EQD_2)	64.8	Low grade toxicity
		D0.1cm^3 (Gy, EQD_2)	81.2	
	Rectum	D2cm^3 (Gy, EQD_2)	62.9	Low grade toxicity; one patient developed radiation proctitis,
		D0.1cm^3 (Gy, EQD_2)	80.3	
	Urethra	D0.1cm^3 (Gy, EQD_2)	66.0	None recorded
	Sacrum			One patient had an insufficiency fracture

Table 3.2 – plan quality metrics and toxicity

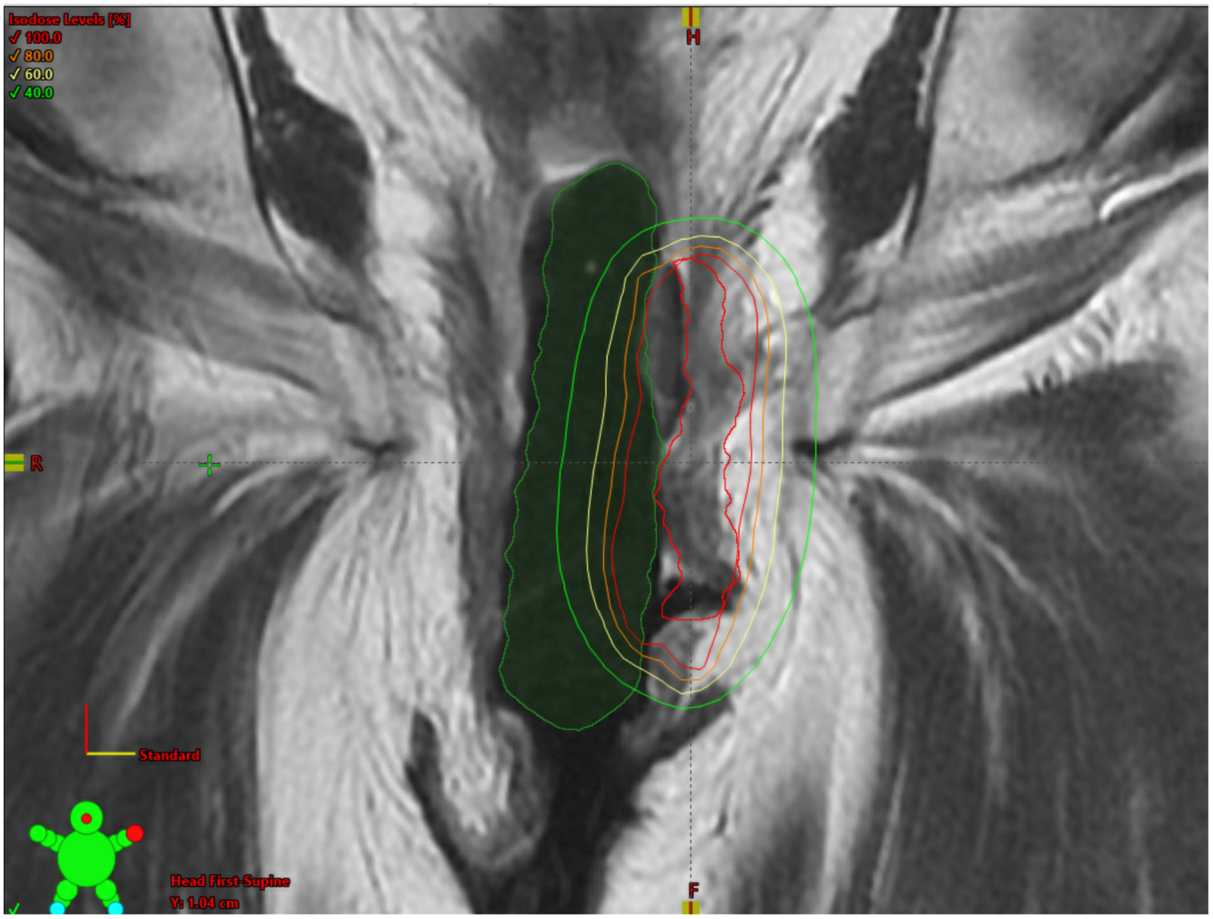

Fig 3.4 – A coronal view of an MR image with customised applicator in situ. Clinical target volume (CTV) is displayed with red colour, customised mould in green and isodoses are also shown.

Local disease control was achieved for 67% of patients. Disease related adverse outcomes included two incomplete responses, leaving residual vaginal tumour and local recurrences in five patients, and one out of field recurrence in the groin. One of the local progression cases died 28 months after brachytherapy. One patient with a recurrence had a vaginal resection and continues to remain disease free at 31 months.

It can be assumed the vaginal mucosa proximal to the CTV received the prescribed dose. Two patients developed vaginal ulcers, one responded to hyperbaric oxygen therapy, and one resolved with time, and 10 patients reported mild vaginal telangiectasia, fibrosis, or stenosis.

Two patients had previously received radiation treatment to the pelvis. One patient received EBRT for rectal carcinoma 22 months prior to her vaginal cancer and received a CTV D90 of 29.1Gy EQD_2 from the customised mould treatment. The other patient had received 21Gy in 3 fractions at 5mm depth 5.5 years previously as a vaginal vault treatment with a cylinder. We delivered an additional CTV D90 of 26.1Gy EQD_2 as the boost for the recurrence. Doses for these patients are reported as the sum of both treatments. The CTV doses for these two patients (CTV D90 79.2Gy and 73.2Gy) in a similar range to the other patients, not significantly skewing the results.

3.6 Discussion

Using a combination of customised moulded applicators and free-hand interstitial needles acceptable doses to both the target and organs at risk were achievable. Given the challenging anatomical positions of some of these tumours, combined with limitations of curvature in the source path, there were often very limited dwell positions that could be used to deliver the dose, which affected the conformity of the doses around the small volumes.

Ideally, a direct dosimetric comparison of a multi-channel applicator plan with the mould technique would be performed as a planning study to determine which of the

two gives the highest plan quality. However, this is not achievable with the data available, as the shape of the vagina is different between the two types of insertions.

There are many uncertainties related to brachytherapy for vaginal malignancies. Given the rarity of these tumours, most data is from small single institution studies. This leads to a lack of consensus for prescription doses and fractionation and contouring uncertainties. A range of practice has been reported related to contouring clinical target volumes for recurrent endometrial treatment, including variation in reporting and prescription to CTVs and variation with different imaging techniques (CT and MRI). [3]

Two patients in this series had a history of previous pelvic radiotherapy. Sadozye et al [47] reviewed re-irradiation in the setting of recurrent gynaecological cancers and concluded there were significant uncertainties regarding treatment modality and doses in this setting. Kamrava et al [3] suggest that there are greater uncertainties in the retreatment setting as well as higher risk of toxicity and overall worse outcomes [3]. Yoshida et al [48] reported higher vaginal mucosa reactions for re-irradiation. A single institution audit of re-irradiated gynaecological malignancies found that it gave a reasonable chance of long-term local control and acceptable organ at risk toxicity [14]. Whilst not statistically significant, the two patients in this series who developed vaginal necrosis were the two who had previous radiotherapy to the pelvis. Ling et al [49] concluded that if OAR doses were limited, successful salvage could be achieved for 40% of patients with recurrent vaginal disease, similar to the results reported in this series. Raziee et al [50] found that re-irradiation provided a safe and effective salvage option for over a quarter of patients.

The most significant prognostic factor was reported to be the FIGO tumour stage with other prognostic factors being the size and location of tumour [11]. Higher doses have been shown to improve local control for recurrent endometrial cancer [51-54]. 3D image guidance also seems to be assisting in local control outcomes [13, 55-57].

Chronic side effects from radiotherapy for vaginal cancers are relatively rare. Grade 1 - 4 side effects have been reported for the bladder and rectum at ≤2% and up to 6% for vaginal side effects [11]. Dilator use has been shown to decrease vaginal stenosis [58-59].

There are also different methods reported to produce customised moulds. Nilsson et al used a two part putty [60]. Further work is warranted investigating the use of 3D printing in the treatment of vaginal malignancies [61-62].

3.7 Conclusion

A review of patients treated with a customised vaginal mould and interstitial needles showed that this technique allows for acceptable doses to the CTV with local control achieved in 67% of patients and reasonable doses to the organs at risk and acceptable toxicity.

3.8 References

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Chapter Four - Implementation of evidence-based planning aims for image-based adaptive brachytherapy including a vaginal dose analysis using two different applicators.

4.1 Preface

In a similar manner to chapter three, in chapter four the evaluation moves to a review of cervix cancer brachytherapy, with a retrospective clinical review and plan quality analysis following implementation of evidence-based planning aims for image-based adaptive brachytherapy including a vaginal dose analysis using two different applicators.

This adds to knowledge about the dosimetry of cervix cancer, especially vaginal dose de-escalation, as well as being the first Australian review following implementation of modern evidence based planning aims.

This then enables a baseline for changes of practice in the future, and leads into advanced methods of brachytherapy quality assurance, such as knowledge-based planning methods for individual plan quality review (refer to chapter seven).

Chapter four was submitted for publication as Flower E, Thiruthaneeswaran N, Busuttil G, Cosgriff E, Zanjani S, Sullivan E, Salkeld A, Sykes J, Thwaites D, Chard J. Implementation of evidence-based planning aims for image-based adaptive brachytherapy including a vaginal dose analysis using two different applicators. Submittted to JMIRO 19/01/2023. However, following peer-review, it was decided to

publish the dosimetric, safety and toxicity aspects of this chapter, which was resubmitted to JMIRO. The resubmission in response to the reviewers is now titled “Plan quality, safety and toxicity evaluation for brachytherapy for cervical cancer in an Australian setting following changes in prescription and applicator design” and was resubmitted 6 June 2023. A future paper will investigate local control and survival, but this is being held until the data mature further and the mean follow-up time allows direct comparison with other published papers.

4.2 Abstract

Purpose

Radiochemotherapy with MRI guided brachytherapy boosts are gold standard care for locally advanced cervical cancer. Recent data from the RetroEMBRACE and EMBRACE I trials provide dose response curves for both target volumes and organs at risk. In this study we evaluate plan quality following implementation of evidence-based planning goals from clinical protocols as our planning aims.

Methods

A retrospective dosimetric plan quality review was undertaken for consecutively treated locally advanced cervical cancer brachytherapy boosts between 2017 and 2022, using two different brachytherapy systems and two different applicator designs. Doses to the target volumes and OAR were reported, as well as the relationships between implant TRAK and CTV_HR volume and vaginal TRAK and vaginal dose. A clinical review investigated control control, overall survival and grade 3 or higher toxicity.

Results

70 patients were identified. 100% of patients had a CTV_HR dose > 85Gy, 88.6% had a bladder $D2cm^3$ < 90Gy and 100% had a rectum $D2cm^3$ < 75Gy. For the intracavitary-only patients, the mean point A dose was 68.6Gy. Needles were used in 48.6% of

patients. When needles were used, the mean percentage needle TRAK was 38.2%. Increasing the %needle TRAK decreased the vaginal TRAK. Local control was achieved for 95.2% of patients, overall survival was 77.8%, grade 3 or higher toxicity was seen in 4.8% and 1.6% for the vagina and genitourinary respectively.

Conclusion

Evidence-based planning aims were successfully adopted into an Australian practice, meeting the benchmark published recommendations for dose planning aims and interstitial needle use. Excellent local control rates were achieved with acceptable toxicity rates.

4.3 Purpose

Cervical cancer was diagnosed in approximately 933 women in Australia in 2021 [1]. The standard of care for locally advanced cervical cancer is pelvic +/- para-aortic radiation therapy with radio-sensitizing chemotherapy, followed by a brachytherapy boost. Since 2005, image-guided brachytherapy using magnetic resonance imaging (MRI) has been the gold standard of care [2,3]. In 2013, the ICRU released a new report in collaboration with GEC-ESTRO, updating the reporting of cervical cancer radiation therapy in the era of volumetric planning [4], superseding the previous GEC-ESTRO group recommendations.

The GEC-ESTRO GYN network led the EMBRACE I (External beam radiotherapy MRI based adaptive brachytherapy in locally advanced cervical cancer) prospective observational study, including both external beam radiotherapy and a brachytherapy boost, to evaluate local tumour control and morbidity following chemoradiotherapy and MRI-guided adaptive brachytherapy [5]. The study closed in 2015 with 1416 patients accrued. Prior to EMBRACE I, a retrospective study of 852 locally advanced cervical cancer patients (retroEMBRACE) was completed [6]. In 2016, the EMBRACE II trial [7] was launched as a prospective interventional study based on the results of retroEMBRACE and EMBRACE I.

Dose-effect relationships have been established for local control at three years based on the high-risk clinical target volume (CTV_HR) dose to 90% (D90) for International Federation of Gynecology and Obstetrics (FIGO) stage II and stage III + IV tumours [8]. CTV_HR D90 was a significant predictor for improved local control, whilst

increasing CTV_HR volume and overall treatment time were associated with decreasing local control. The linear quadratic model and equivalent dose in 2Gy fractions (EQD2) calculations do not take tumour repopulation into account, hence the loss of treatment efficacy if overall treatment time is extended.

Data from retroEMBRACE and EMBRACE I has been used to establish dose-effect curves for organ at risk (OAR) toxicity. The probability of bladder and rectum grade >2 morbidity is based on the dose to 2 cc ($D2cm^3$) [9–11]; however, the sigmoid $D2cm^3$ has not been found to correlate with bowel toxicity [12]. The probability of vaginal stenosis grade >2 is based on the ICRU recto-vaginal point dose [13]. High bladder $D2cm^3$ doses have also been found to be a risk factor for bladder fistula and bleeding [11], and bladder incontinence is correlated with hot spots in the bladder base [14]. Grades of morbidity refer to the Common Terminology Criteria for Adverse Events (CTCAE) with scoring from grade (G) 1 to 5 [15].

In addition to establishing dose-effect relationships, the EMBRACE studies have also investigated other measures of plan quality within the study cohort. Serban et al. [16] investigated the change in target coverage and conformity when an interstitial component is used, and OAR sparing when using tandem and ovoid or tandem and ring style applicators, as well as the difference from adding an interstitial component.

This study aims to report and evaluate the dosimetry parameters from a single institution cohort of 70 patients, following the implementation of EMBRACE II evidence-based planning aims in an Australian setting, using two different brachytherapy systems and applicator designs. Clinical outcomes are also reported.

4.4 Material and Methods

The EMBRACE II evidence-based planning aims were implemented at the beginning of 2017 at our institution [7]. Staging imaging included a PET/CT for all patients, and an MRI if a decision is required to determine between stages 1B2 and 1B3, and an examination under anaesthesia (EUA) at the time of diagnosis. Locally advanced cervical cancer patients receiving concurrent chemoradiation initially receive external beam radiation (EBRT) delivered using volumetric modulated arc therapy or intensity modulated radiation therapy with doses in the range of 45Gy to 50.4Gy to the primary target volume and simultaneous integrated boosts to nodal volumes up to 55Gy if required. All patients from the beginning of 2017 were included in this study.

Cervical cancer brachytherapy boosts in our centre are delivered over three fractions following two or three applicator insertions. The overall treatment time is aimed to be under 51 days. Patients receive an MRI scan in the last week of the EBRT, which is used to develop a pre-plan for the first brachytherapy insertion. Decisions regarding applicator configuration, including interstitial needles, were made based off the pre-planning study. The pre-plan can be adapted based on clinical findings during the EUA before the applicators are inserted. All patients are instructed to use vaginal dilators following brachytherapy.

Applicators are inserted with trans-abdominal ultrasound guidance, and needles are added with transvaginal application if required. One patient also received freehand trans-perineal needles. Between 2017 and 2018, the Fletcher-Suit-Delclos (FSD)

applicator (Varian, USA) was used, with the interstitial needle kit as an available option if required. From 2019 onwards, the Venezia advanced gynecological applicator (Elekta, Sweden) was used, with an intrauterine tube, lunar ovoids and the option of vaginal caps when required for extensive vaginal disease.

Following anaesthetic recovery, T2-weighted spin echo sequence para-axial, para-sagittal, and para-coronal MRI scans of the treatment area are obtained. Computed tomography (CT) scanning was also used to assist with accurate needle definition. Between 2017 and 2018, treatment planning was completed using the Brachyvision treatment planning system (Varian, USA) and from 2019 onwards with the Oncentra treatment planning system (Elekta, Sweden). Target volumes and OARs are contoured, points of interest are defined, the applicator is delineated (using applicator modelling in Oncentra), and any needles are delineated. No standard loading patterns are used; the optimiser has access to all activated dwell points. The tandem was only loaded as high as the CTV_HR coverage required. Graphical optimization is used to adjust the dose distribution as required. Once the plan has been optimised, it is checked and then approved by the radiation oncologist. Treatment was performed with a Varisource iX afterloader (2017–2018, Varian, USA) or a Flexitron afterloader (2019 onwards, Elekta, Sweden).

The brachytherapy plans were retrospectively reviewed, and doses to the target volumes and OARs were reported as well as the relationships between the implant Total Reference Air Kerma (TRAK; the sum of the product of the reference air kerma rate at 1 metre and the irradiation time for each source dwell position), CTV_HR volume, percentage TRAK from ovoids and needles and vaginal dose. If more than

one fraction was delivered following one insertion, the patient received a CT scan immediately prior to the subsequent fraction, to ensure the plan was still clinically acceptable.

A clinical review based on medical imaging, pathology and clinician correspondence was undertaken. Using CTCAE terminology [15], any grade 3 or 4 toxicity was reported, along with any local disease recurrence, metastatic disease, or death. Ethics approval was obtained, as a quality assurance project, from our institution.

4.5 Results

A total of 70 patients consecutively treated from January 2017 to February 2022 were included. Table 4.1 shows the patient FIGO staging in this cohort, staged using the 2018 FIGO system, as well as the presence of vaginal involvement at diagnosis and the histopathology. Table 4.2 shows the dose volume histogram (DVH) parameters and points linked with evidence-based planning aims, the mean value for each parameter, and the percentage of plans that were compliant with the planning aim or limit. Whilst the mean point A doses increased for the Venezia applicator, the mean CTV_IR coverage was lower for the Venezia applicator, possibly due to the unavailable space at the end of the intrauterine tube.

FIGO Stage		Number of patients
1B		10
2		17
3		43
Vaginal involvement at diagnosis		36
Histopathology	Squamous cell carcinoma	54
	Adenocarcinoma	7
	Adenosquamous carcinoma	3
	Signet ring cell	1
	Neuroendocrine	5

Table 4.1 – Patient Characteristics in this cohort

Interstitial needles were used in 48.6% of patients, above the 20% lower benchmark from the EMBRACE II trial protocol [7]. Out of all the needles inserted, only 7.7% were not activated in the final plan. Figure 4.1 shows the number of needles used for different CTV_HR volumes. Needle use can vary based on clinical requirements (some patients were medically unfit for interstitial needles), or on CTV_HR volume and shape (a smaller volume offset to one side could require needles more than a centrally located CTV_HR of the same volume and topographical shape). Hence there are some quite small volumes that required needles to optimise the plan, and some larger volumes that did not. Some smaller volumes were treated with interstitial needles as the same applicator and needle configuration was used for both the second and third fraction, with sometimes significant tumour regression between brachytherapy

insertions. Figure 4.2 shows that even for small CTV_HR volumes (<30 cc), the use of interstitial needles can assist in reducing bladder, rectum, and sigmoid D2cm^3 doses and vaginal point doses.

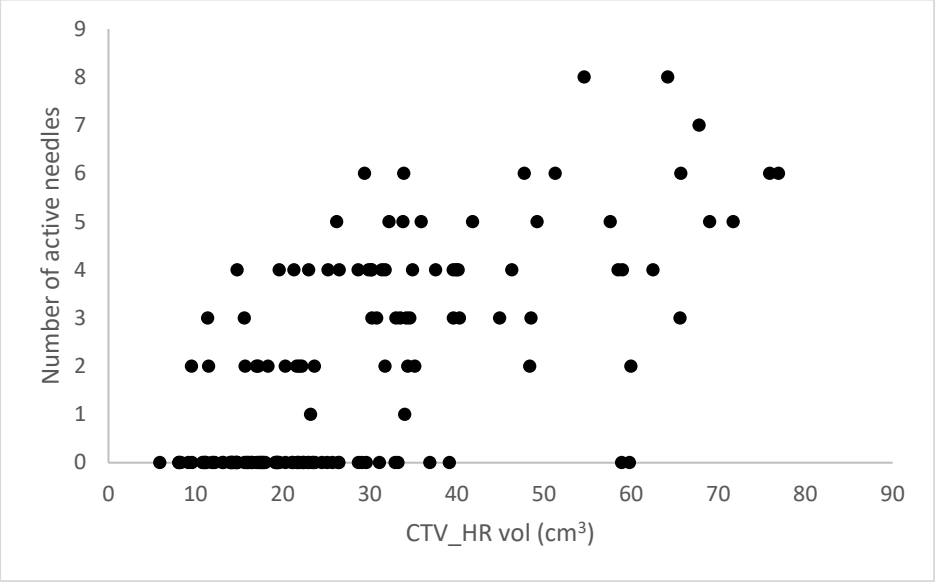

Fig. 4.1 - Relationship between needle use and CTV_HR volume for the treatments in this study.

DVH Parameter	Planning aim or limit	Mean (Gy)				Compliant (%)			
		T&O	Ven.	T&O + IS	Ven. + IS	T&O	Ven.	T&O + IS	Ven. + IS
GTV D98	Limit > 90 Gy	101.4	109.1	89.9	104.6	71.4	86.7	42.9	75.0
	Aim > 95Gy					25.0	62.5	33.3	60.0
CTV_HR									
D98	Aim > 75Gy	80.6	82.1	81.0	80.2	100	100	100	93.3
D90	Limit > 85Gy	92.4	93.0	91.6	91.7	100	100	100	100
D90	Aim > 90Gy					75.0	93.8	91.7	66.7
D90	Aim < 95Gy					91.7	87.5	91.7	90.0
CTV_IR D98	Aim > 60Gy	63.2	59.0	66.2	59.1	83.3	31.3	100	30.0
Point A	Aim > 65Gy	66.7	68.6	—	—	58.3	75.0	—	—
Bladder $D2cm^3$	Aim < 80Gy	72.3	71.7	84.9	76.0	75.0	87.5	25.0	53.3
	Limit < 90Gy					91.7	93.8	58.3	96.7

Rectum D2cm^3	Aim < 65Gy	57.5	59.0	64.3	60.7	83.3	87.5	58.3	63.3
	Limit < 75Gy					100	100	100	100
Sigmoid D2cm^3	Aim < 70Gy	55.5	55.9	65.1	60.6	100	100	66.7	80.0
	Limit < 75Gy					100	100	100	96.7
Bowel D2cm^3	Aim < 70Gy	60.7	56.1	61.9	61.9	91.7	100	83.3	76.7
	Limit < 75Gy					91.7	100	91.7	93.3
RV point	Aim < 65Gy	69.8	64.6	74.6	63.4	33.3	56.3	25.0	63.3
	Limit < 75Gy					83.3	93.8	66.7	93.3

T&O: Tandem and Ovoids; Ven.: Venezia; IS: Interstitial; GTV: Gross target volume; CTV_HR: High-risk clinical target volume; CTV_IR: Intermediate-risk clinical target volume; RV point: Rectovaginal point.

Table 4.2 - Results for DVH parameters and point doses based on evidence-based planning aims and limits: mean doses and compliance with the EMBRACE II protocol [7].

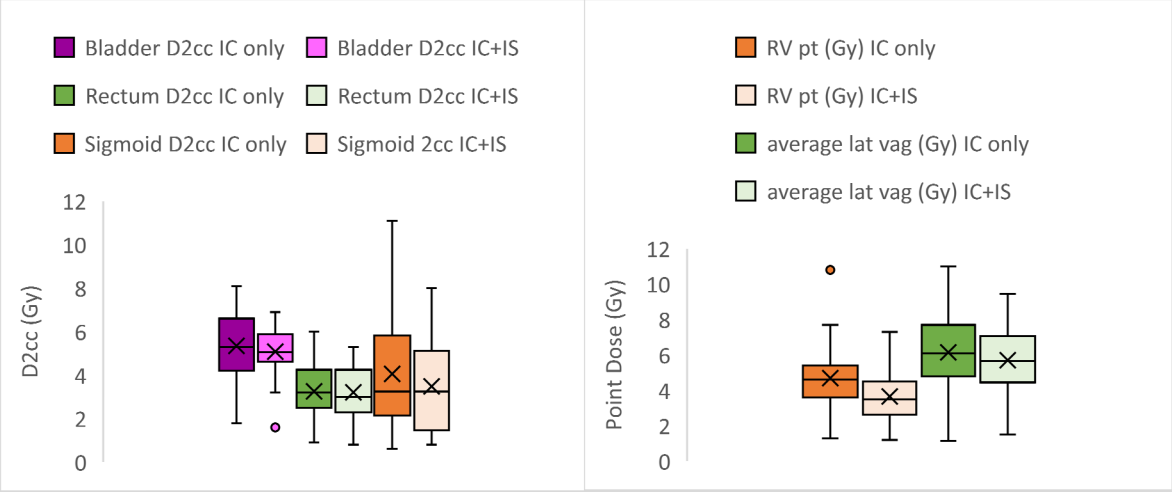

Fig. 4.2 - The effect of needles on a) OAR and b) vaginal doses for small volume (<30cm^3) CTV_HR.

When needles were used, the mean percentage needle TRAK was 38.2%. The mean vaginal TRAK was 32.4%. Increasing the percentage needle TRAK decreased the ovoid TRAK, as can be seen in Figure 4.3. Figure 4.4 shows how the total TRAK, ovoid TRAK, and needle TRAK vary with CTV_HR volume. The mean vaginal TRAK was 32.6% of the overall TRAK, within the 30 to 40% range recommended [14]. Delivering a larger proportion of the dose through the needles reduces the vaginal TRAK, resulting in vaginal dose de-escalation. However, needle TRAK is almost independent of the CTV_HR volume.

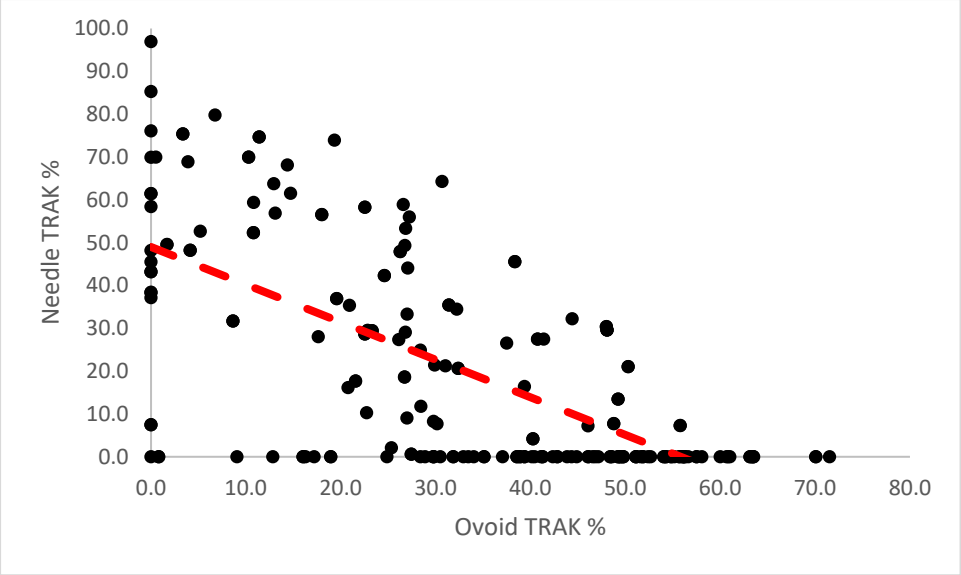

Fig. 4.3 - Relationship between ovoid TRAK and needle TRAK (as a percentage of the overall treatment TRAK) with a best linear fit shown as the dashed line.

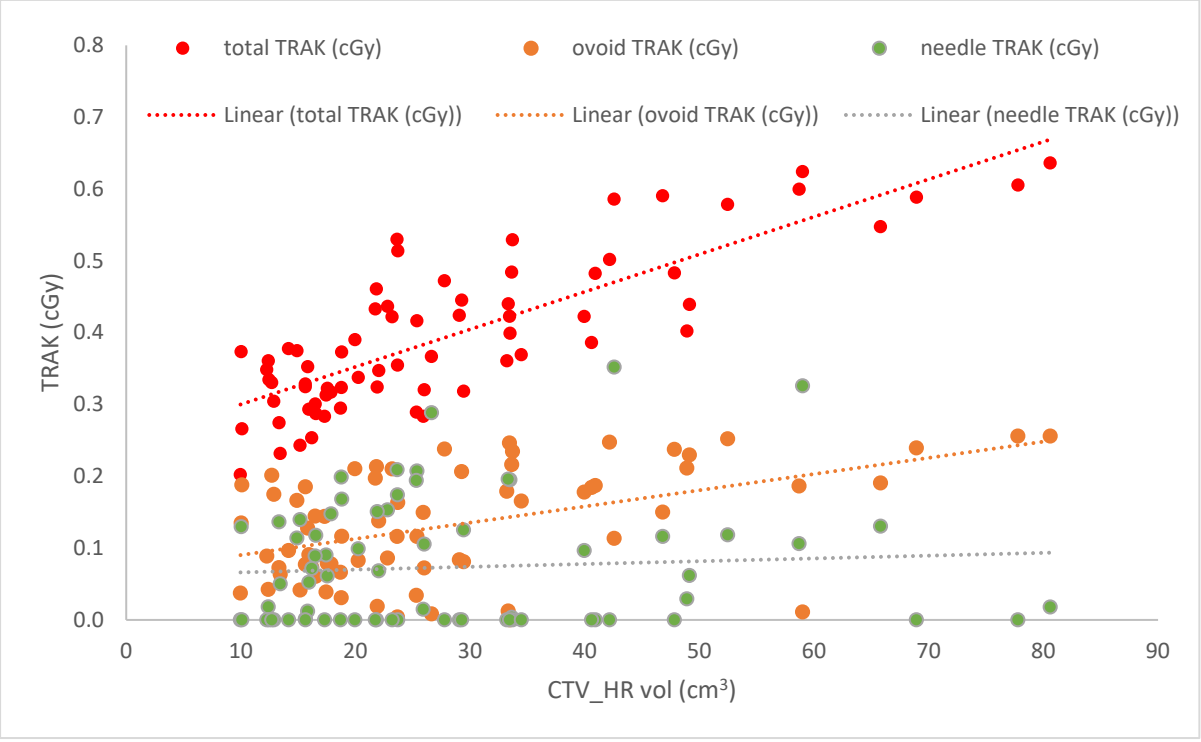

Fig. 4.4 Relationship between the total TRAK, ovoid TRAK, needle TRAK, and CTV_HR volume for the entire treatment with best linear fits shown as dashed lines.

Figure 4.5 shows the mean lateral vaginal doses and recto-vaginal doses against the vaginal TRAK for both the tandem and ovoid style FSD applicator and the lunar ovoid Venezia applicator. For intracavitary only applicators, the mean recto-vaginal point was higher for the tandem and ovoid applicator than the Venezia applicator, whereas for the lateral vaginal points, the reverse was true, with a bigger difference, especially for higher vaginal TRAK. Adding interstitial needles changes this such that there is very little difference between applicator design, with both lateral vaginal and recto-vaginal doses with an interstitial component higher for tandem and ovoid applicators for any given vaginal TRAK.

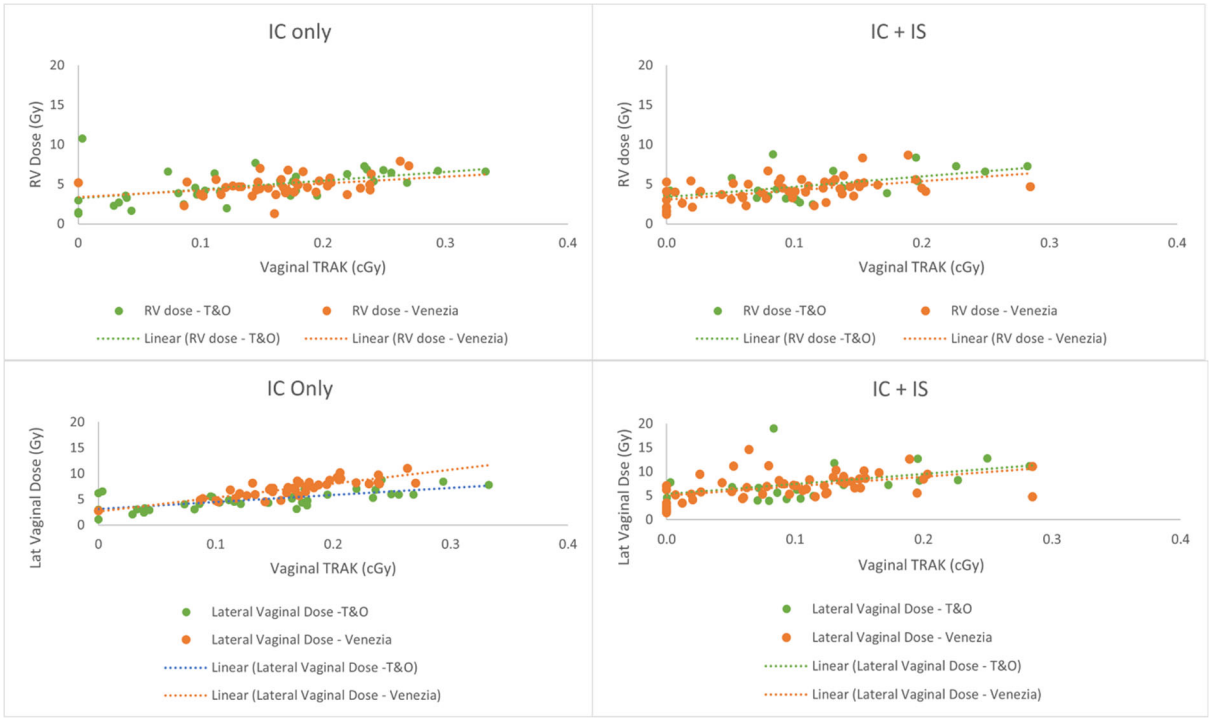

Fig. 4.5 Vaginal doses and ovoid TRAK. a) IC only recto-vaginal dose, b) IC + IS recto-vaginal dose, c) IC only lateral vaginal dose, and d) IC + IS lateral vaginal dose.

From this cohort of patients, 63 patients have 12 months or more follow-up, with a median time of 25 months. Local control within the follow-up time was achieved in

95.2% of patients. A total of fourteen patients developed metastatic disease, with an average time from treatment completion to metastatic disease diagnosis being 11 months. Nine patients have died from disease progression, with the average time from completion of treatment to death being 12 months. One patient died from non-oncological disease. Of the 14 patients who developed metastatic disease, initial staging varied from 2 patients with 1B disease, through to 5 that had 3C2 disease. Of these patients, 1 had the signet ring cell histopathology, 1 had an adenocarcinoma, two had small cell neuroendocrine cancer type and the remaining patients had squamous cell carcinomas.

Two patients had recto-vaginal fistulas and one patient had vaginal ulceration that resolved. The patients who developed recto-vaginal fistulas and vaginal ulceration had vaginal extension at diagnosis, with involvement still at the time of brachytherapy. One patient developed a ureteric stricture requiring surgery. One had vaginal stenosis that made physical examination challenging and had not had vaginal involvement. One patient developed a sacral insufficiency fracture. Together with the grade 3 or higher toxicities, there were also grade 1 and 2 toxicities, including bladder urgency, frequency, nocturia and dysuria, bowel urgency or frequency, and vaginal telangiectasia and stenosis.

4.6 Discussion

In this work target coverage and OAR doses were reviewed for 70 consecutively treated patients, using either a tandem and ovoid or Venezia style applicator, with or without interstitial needles. CTV_HR coverage and OAR doses tended to be more

compliant with evidence-based planning aims using interstitial needles, regardless of the intracavitary component, and the Venezia tended to perform better for most parameters (including the recto-vaginal point dose) than the tandem and ovoid style applicator. The compliance for the CTV_HR D90 was the lowest with the Venezia with interstitial needles, due to the larger volumes we attempted to treat. Increasing CTV_HR volume was associated with increased needle use; however, the use of needles for some smaller volume CTV_HR cases resulted in decreased OAR doses. There were 63 patients who had 12 months or more available follow-up data and who were assessed for overall survival, local control, and grade 3 or higher toxicities.

According to EMBRACE II, the percentage of patients fulfilling dose limits should be 80–90% [7]. These results show we meet the evidence-based planning aims in an acceptable way. There were some patients in our series where all the EMBRACE II planning aims could not be met. For example, achieving the planning aim of point A > 65Gy or CTV_IR D98 > 60Gy would have violated the D90 < 95Gy constraint for the CTV_HR. Tanderup et al. [17] published planning aims that include planning aim priorities for when such conflicts arise. It is also likely that as evidence continues to be reported, evidence-based planning aims may also change. For example, the bladder limit in Tanderup et al. [17] is lower than the EMBRACE II planning aims.

The NSW Cancer Institute consensus guidelines for a definitive brachytherapy boost for cervical cancer recommends a total dose of 80–90Gy (ideally >85Gy) EQD2 to the CTV_HR and >60Gy to the CTV_IR [18]. A 2017 survey [19] found that 79% of institutions in Australia used CT guidance, and 50% reported they used MRI for planning. A CTV_HR volume was only used by 43% of centres. The mean EQD2

prescribed dose was 81.6Gy (range 73.2–85.6Gy). Planning constraints for the bladder D2cm^3 varied from 68Gy to 90Gy. Whilst centres may have developed their practice, it shows that a significant number of Australian centres were cautious regarding full implementation of evidence-based brachytherapy for cervical cancer, such as in the EMBRACE II protocol. An updated survey of practice may be warranted.

Hellebust et al. [20] found an interobserver uncertainty of ± 6Gy (EQD2) for target volumes and ±2–3Gy for OARs. Cannon et al. [21] investigated the UK experience of implementing evidence-based planning aims by performing a contouring and dose optimization survey on the datasets for two patients. They found that regardless of the uncertainty from contouring and differing prescription and dose optimization techniques, the EMBRACE II dose constraints for the CTV_HR could be met for both patients. Several studies show that following standardised training and consensus guidelines reduces contouring uncertainties [22–25].

Chimeno et al. [26] conducted an evaluation of the EMBRACE II protocol on centres in Spain. They showed that as centres implemented the evidence-based planning aims from the EMBRACE II protocol there was a statistically significant increase in the CTV_HR D90 or decrease in OAR D2cm^3.

Serban et al. [16] have previously reported from the EMBRACE I series that using a ring style applicator causes a small increase in the recto-vaginal point dose compared with a tandem and ovoid style applicator, but the lateral vaginal doses decrease significantly. The work presented in our study has shown that these differences are observed between the lunar ovoids of the Venezia and the FSD ovoids. Both the recto-

vaginal and vaginal lateral point doses increase with increasing vaginal TRAK as previously reported [27]. However, this work extends this to show that increasing needle TRAK decreases vaginal TRAK, meaning that additional loading in the needles provides a method for vaginal dose de-escalation. Mohamed et al [28] have previously shown that reducing ovoid loading by not using standard loading patterns reduces vaginal dose for intracavitary only implants [28]. In this study we achieved low vaginal doses (when the vagina was not involved) by not using standard loading patterns and adding interstitial needles, maximizing vaginal dose de-escalation as possible.

In this cohort, the mean vaginal TRAK was 32.4%. Mohamed et al. [28] showed that by using a planning technique to reduce the mean vaginal TRAK, vaginal dose de-escalation could be achieved. They reported a reduction in the mean vaginal TRAK from 51% to 33% using this technique. As we do not use a standard loading template but optimise prioritizing conformal coverage, our vaginal TRAK fits with this lower range.

Several studies have shown that adding an interstitial component allows for improved target coverage of the CTV_HR whilst respecting or even decreasing OAR doses [17, 25–27]. In our results we found that increasing the percentage TRAK in interstitial needles reduced the percentage TRAK in the ovoids. Mohamed et al have previously shown that reducing ovoid loading reduces vaginal dose [28]. It is therefore imperative to add an interstitial component to intracavitary implants with larger (>30cm^3) CTV_HR volumes.

The clinical review in this work shows favourable local control and toxicity compared with similar national and international studies. Van Dyk et al. [29] conducted a mono-institutional review in Australia of an ultrasound and MRI planned regimen for cervical brachytherapy, with larger patient numbers and a longer follow-up than in this study. Our local control rates were higher with similar toxicity. We also achieved comparable results with the EMBRACE I series [5].

Plan quality can be assessed using knowledge-based algorithms, including differences due to applicator design [30]. However, it remains difficult in the clinical setting to evaluate if a particular plan is clinically optimal. Work such as this allows for quality analysis of a cohort of patients, but further work is required to allow for widespread clinical use of efficient plan quality analysis on individual treatment plans.

4.7 Conclusion

Evidence-based planning aims were successfully adopted into an Australian practice. The benchmark published recommendations for dose planning aims and interstitial needle use were met and vaginal dose de-escalation techniques were demonstrated.

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Chapter Five – Improving plan quality in cervical brachytherapy using a simple knowledge-based prediction tool for OAR dose ($D2cm^3$).

5.1 Preface

Whilst the previous chapters have evaluated current practice, in chapter five I assess the feasibility of a knowledge-based organ at risk $D2cm^3$ prediction tool based on overlap volume histograms.

The $D2cm^3$ prediction tool was able to predict the dose for an individual patient's anatomy, and could be used to automate optimization of brachytherapy plans for locally advanced cervical cancer and to improve plan quality.

I will implement this work into clinical practice, and continue to monitor plan quality and refine the models. This work could also be used in clinical trials to assess plan quality, As changes in practice get implemented, this tool can easily assess the effects on plan quality. Unlike complex machine learning algorithms, this method is easily accessible to most clinics, with no machine learning software or expertise.

Chapter five has been published as Flower E, Sykes J, Sullivan E, Busuttil G, Thiruthaneeswaran N, Cosgriff E, Chard J, Salkeld A, Thwaites D. Improving plan quality in cervical brachytherapy using a simple knowledge-based prediction tool for OAR dose ($D2cm^3$). Brachytherapy, in press.
https://doi.org/10.1016/j.brachy.2023.05.004

5.2 Abstract

Aim: Toxicity from cervical brachytherapy has been demonstrated to correlate with the D2cm^3 of the bladder, rectum and bowel. This suggests a simplified version of knowledge-based planning investigating the relationship of the overlap distance for 2cm^3 and the D2cm^3 from planning may be possible. This work demonstrates the feasibility of simple knowledge-based planning to predict the D2cm^3, detect sub-optimal plans, and improve plan quality.

Methods: The overlap volume histogram (OVH) method was used to determine the distance for 2cm^3 of overlap between the OAR and CTV_HR. Linear plots modelled the OAR D2cm^3 and 2cm^3 overlap distance. Two datasets of 20 patients (plans from 43 insertions in each dataset) were used to create 2 independent models, and the performance of each model was compared using cross-validation. Doses were scaled to ensure consistent CTV_HR D90 values. The predicted D2cm^3 is entered as the maximum constraint in the inverse planning algorithm.

Results: Mean bladder D2cm^3 decreased by 2.9% for the models from each dataset, mean rectal D2cm^3 decreased 14.9% for the model from dataset 1 and 6.0% for the model from dataset 2, mean sigmoid D2cm^3 decreased 10.7% for the model from dataset 1 and 6.1% for the model from dataset 2, mean bowel D2cm^3 decreased 4.1% for the model from dataset 1 but no statistically significant difference was observed for the model from dataset 2.

Conclusion: A simplified knowledge-based planning method was used to predict D2cm^3 and was able to automate optimization of brachytherapy plans for locally advanced cervical cancer.

5.3 Introduction

Cervical cancer was diagnosed in 942 women in Australia in 2021, making it one of the most common cancers of the female reproductive system [1]. Radiation therapy with concurrent chemotherapy, incorporating an MRI-guided adaptive brachytherapy boost is gold standard treatment for local advanced cervical cancer [2]. As for all radiotherapy, independent plan checks, including plan optimization, are recommended in brachytherapy quality assurance [3]. However, there are few tools available specifically for testing that brachytherapy plan optimization criteria and dose distribution are optimal for each individual patient. Thus, a plan might meet planning goals, but still not be optimal [4].

Computerised knowledge-based planning (KBP) methods in EBRT have been in development since the late 1980s [5-6]. KBP uses machine learning models to predict either the achievable dose volume histograms (DVH) or 3D dose distribution for an individual patient. The geometric relationship between the target and OAR is used to predict the doses achievable for each OAR. The use of KBP in EBRT for cervical cancer is well established [7-10].

Wu et al [11] introduced the overlap volume histogram (OVH) concept to define the geometric relationship of each OAR to a target, where the OVH is a boundary function that defines the fractional component of an OAR within a specified distance from a target. In conformal external beam plans, the OVH and dose volume histogram (DVH) curves for each organ at risk (OAR) are correlated [10]. The relationship between OVH and DVH parameters has also been established for brachytherapy, using machine

learning methods [12, 13].

Toxicity from brachytherapy for the bladder, rectum and bowel has been demonstrated to have a high positive correlation with the DVH parameter D2cm^3 [14], where D2cm^3 is defined as the lowest dose to the most irradiated 2cm^3 in a volume. Therefore, a simplified version of KBP may be possible, through only investigating the relationship of the expansion distance required to give an overlap volume of 2cm^3 and the D2cm^3 from planning, without the need for complex machine learning algorithms. This paper investigates how such a simple relationship can be used to predict the D2cm^3, and how this can be used to detect sub-optimal plans and improve plan quality.

5.4 Material and Methods

Clinical cervical brachytherapy plans were generated using standard departmental clinical protocols, including MRI pre-planning, ultrasound guidance during insertion and MRI-based planning. The applicator used was the Advanced Gynaecological Applicator (Elekta, Sweden) with or without interstitial needles. Plans were generated using the Oncentra treatment planning system (Elekta, Sweden). Planners could use the hybrid inverse planning optimization algorithm (HIPO) and/or graphical optimization for planning. Planning aims were taken from Tanderup et al [14].

Two retrospective patient datasets were used for model training and validation. For each dataset, 20 consecutively treated patients were selected, giving 43 unique plans in each dataset. The model that used patient dataset 1 for training was validated using patient dataset 2 and vice versa.

To establish a full overlap volume histogram, the target is uniformly expanded by increasing increments from the point of no overlap to the point of full overlap with the organ at risk. In this work, for each plan the high-risk clinical target volume (CTV_HR) contour had a uniform expansion margin added, by distance T as measured from point P closest to the relevant OAR (as shown in Figure 1 for the bladder) until the volume of the intersection between the expanded CTV_HR contour and the OAR contour was $2cm^3$ (OV_{2cc}).

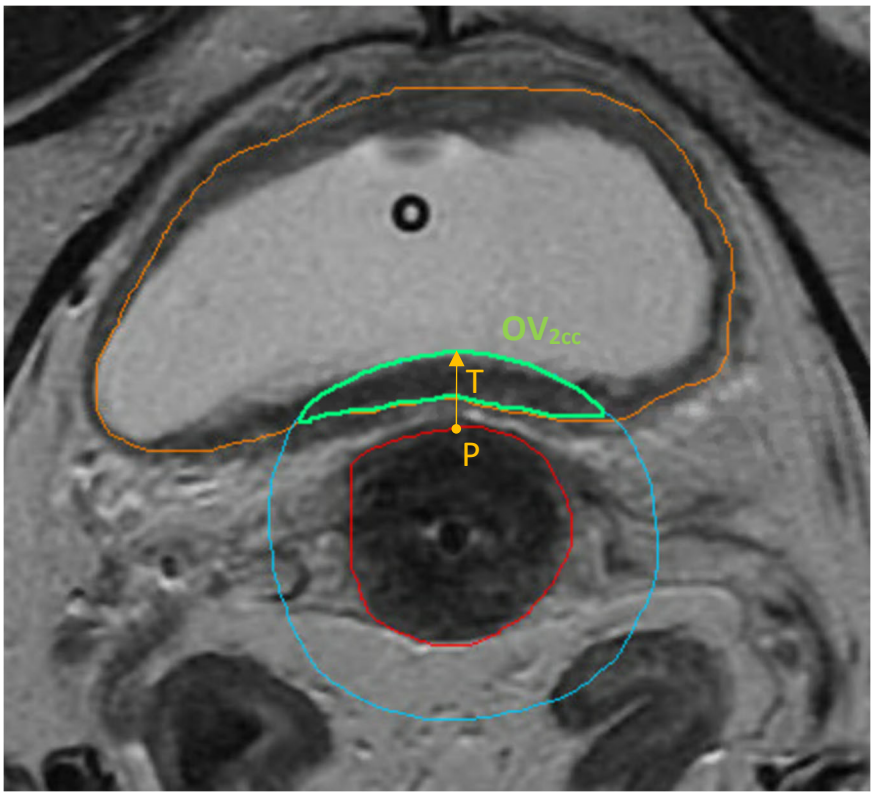

Fig 5.1 – An axial slice showing the CTV_HR (red) expanded from point P by distance T, with the cyan line representing the CTV-HR contour expanded by distance T, until an overlap volume of $2cm^3$ (OV_{2cc}, green) was achieved with the bladder (orange contour).

For each plan in dataset 1, the value of T and the planned D2cm^3 for each OAR were plotted and used to build a linear regression model to determine the D2cm^3 (predicted) for each OAR specific distance T. This created model 1, from dataset 1. This model development process was repeated with patient information from dataset 2 to generate model 2. The goodness of fit (R^2) and goodness of prediction (mean square error) were calculated.

The KBP performance of model 1 and model 2 for predicting D2cm^3 for optimal planning was assessed. Model 1 was applied to patient dataset 2. Likewise model 2 was applied to patient dataset 1, using the D2cm^3(predicted) for each OAR as the optimization criteria for that OAR within the HIPO algorithm [15]. The dose was then scaled to achieve the same CTV_HR D90 dose as the clinical plan and the weightings of different OAR criteria were modified to achieve a better plan as required. A dwell time gradient ratio of 0.2 was applied to the HIPO optimization, to limit fluctuations between adjacent dwell positions. A paired t-test was completed for the comparison between DVH parameters from the plans using the model-determined objectives and the clinically accepted plan to assess statistical significance (p-value < 0.05) of the knowledge-based planning optimization process.

Using the best performing model from the cross-validation method, box and whisker plots were generated to graphically show the differences in the DVH parameters between the human-driven optimization from the clinically approved plans and the model for each organ at risk.

5.5 Results

There were 20 plans with an interstitial component in dataset 1 and 17 in dataset 2. The linear regression models created for each OAR are shown in figure 2. Model 1 used the data from patient dataset 1 and model 2 used the data from patient dataset 2. The coefficient of determination (R^2) is also shown for each model, indicating the goodness of fit. Table 1 shows the mean square error (MSE) for each model.

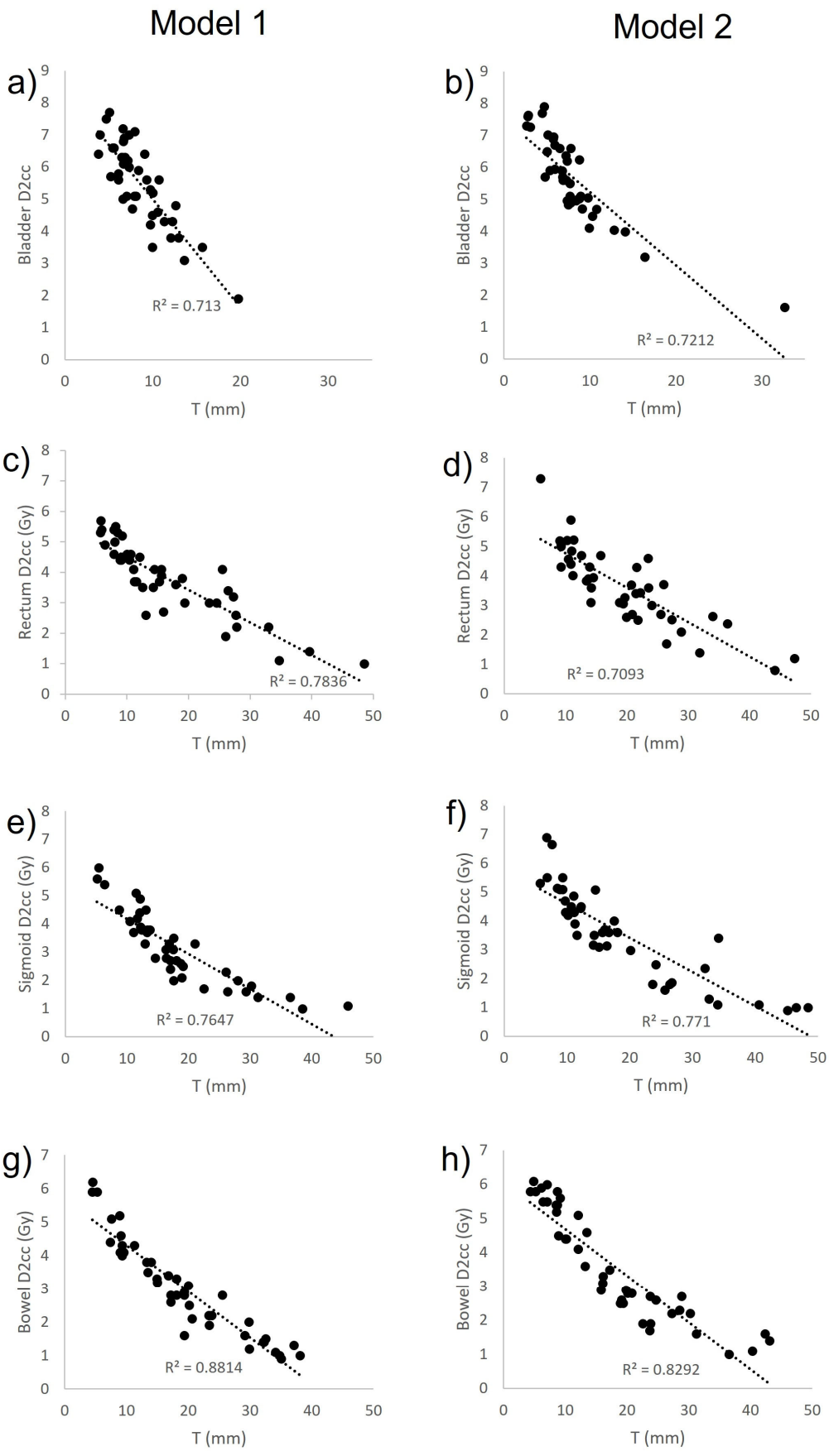
Model 1
Model 2
a)
b)
c)
d)
e)
f)
g)
h)
Bladder D2cc
Rectum D2cc (Gy)
Sigmoid D2cc (Gy)
Bowel D2cc (Gy)
T (mm)
R² = 0.713
R² = 0.7212
R² = 0.7836
R² = 0.7093
R² = 0.7647
R² = 0.771
R² = 0.8814
R² = 0.8292

Fig 5.2 - Model generation, showing linear regression models for a) and b) the bladder, c) and d) the rectum, e) and f) the sigmoid, and g) and h) the bowel, with model 1 (left column) being based on plan data from patient dataset 1 and model 2 (right column) being based on plan data from patient dataset 2.

OAR	Model 1 MSE (Gy)	Model 2 MSE (Gy)
Bladder	0.47	0.45
Rectum	0.31	0.49
Sigmoid	0.36	0.55
Bowel	0.24	0.43

Table 5.1 – The mean square error for each model, demonstrating the goodness of prediction.

Each model was cross validated on the other patient data set, to assess the dosimetric accuracy of using the models to generate maximum constraints for HIPO. Table 2 shows the percentage difference between the clinical plan and the plan created using HIPO-based optimization with model-generated dose constraints.

Based on the dosimetric performance comparison, model 1 performed better than model 2, indicating that the plans in dataset 1 were of higher quality than those in dataset 2. This is supported by table 1, which shows the model based on patient dataset 1 has a lower MSE, demonstrating that model 1 also has better goodness of prediction, as well as goodness of fit.

	Model 1 % diff from clinical plans (p value)	Model 2 % diff from clinical plans (p value)
Bladder	-2.9 (0.025)	-2.9 (0.030)
Rectum	-14.9 (<0.001)	-6.0 (0.001)
Sigmoid	-10.7 (<0.001)	-6.1 (0.043)
Bowel	-4.1 (0.002)	5.1 (0.204)
Recto-vaginal point	-19.9 (<0.001)	-6.2 (0.005)
Average vaginal points	-9.2 (0.012)	-6.4 (0.003)

Table 5.2 Assessment of the dosimetric performance based on the difference and statistical significance when the model generated from one dataset is applied to the other patient dataset.

To further test the difference between the clinical plans and model-based plans for model 1, figure 3 presents box and whisker plots showing the differences between the approved clinical plans and the plans optimised using KBP, using the model from dataset 1. In table 2 the bladder doses remained the same for both models during cross-validation. In figure 3 there is less variation in bladder doses than the other organs at risk, suggesting there is less potential for improvements in bladder doses from the different planning methods.

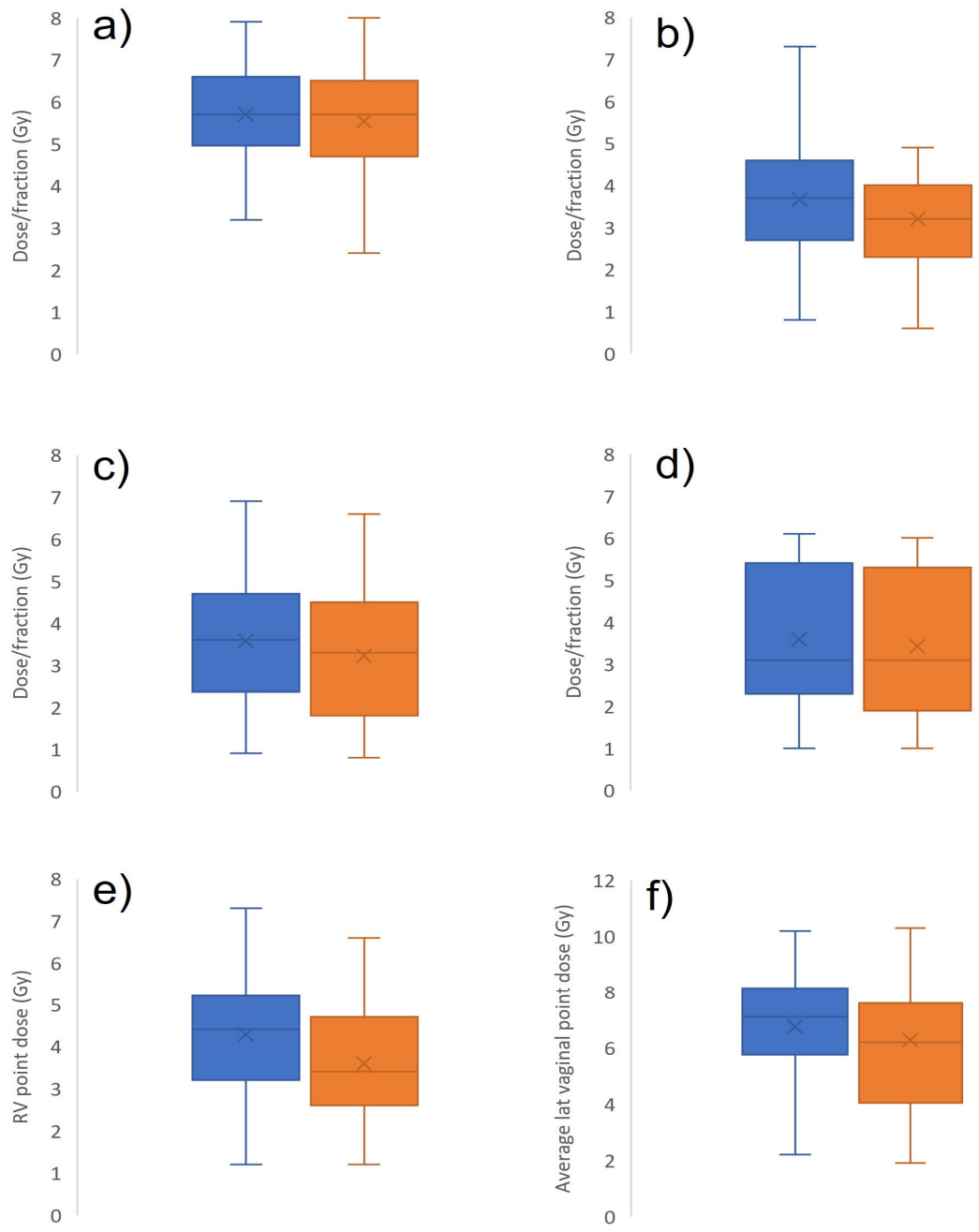

Fig 5.3 – Box and whisker plots showing the differences in DVH parameters and point doses between the approved clinical plan in patient dataset 2 (blue) and the quality assurance plans developed by using D2cm^3 values from the prediction model (Model 1) as maximum dose optimization constraints (orange) for a) the bladder, b) the rectum, c) the sigmoid, d) the bowel, e) the recto-vaginal point, and f) the average of the lateral vaginal points.

5.6 Discussion

Linear regression models were created for different geometric relationships between the CTV_HR and the OAR D2cm^3 parameter. The R^2 values for the models were comparable with other published data from KBP [16-17]. The predicted D2cm^3 from these models were used to create patient-specific optimization criteria for the maximum constraints in the HIPO algorithm within the commercially available Oncentra treatment planning system. This enables objective plan quality assurance for each individual patient's anatomy and CTV, as a manually optimised plan can be compared to a KBP optimised plan. The criteria are also a good starting point for manually driven optimization.

Plans created with a model should still be assessed by experienced planners and improvement attempted, by both changing priorities and weightings within HIPO through to graphical optimization, in conjunction with the radiation oncologist, to ensure that the plan is optimal for each individual patient, taking into account clinical judgements. The difference between the models made with the two datasets shows the importance of good quality plan input. Further model refinement can be undertaken.

The relationship between the OVH and the DVH has also been established for brachytherapy, using machine learning approaches. Yusufaly et al [12] demonstrated that a full DVH estimate for the bladder, rectum and sigmoid could be derived for N sets of model training data, using a boundary based function from the clinical target volume (CTV). Reijtenbagh et al [13] used OVHs to predict the D2cm^3 in cervical

cancer brachytherapy plans from two different institutions, using the random forest network method to generate models that predicted the entire DVH. However, the simplified D2cm^3-based prediction method presented here is more conceptually and economically accessible than a full machine learning DVH prediction for two main reasons. Firstly, it focusses only on the D2cm^3, which has been demonstrated to correlate with toxicity [14]. Secondly, it can be implemented using commercially available software, already in most clinics, including the automation of finding the expansion distance T required to obtain an overlap volume of 2cm^2.

There are also other complicated decision-making implementations of machine learning in brachytherapy for cervical cancer. Stenhouse et al [18] trained a model using a range of data for optimal applicator selection. Abdalvand et al [19] used machine learning for modelling predicted outcome following brachytherapy for cervical cancer. Fan et al [20] used deep learning inference modelling for independent plan verification. Shen et al [21] used deep reinforcement learning to automate the optimization process, including weighted priority tuning. Cortes et al [22] used a convolution neural network to predict doses with tandem and ovoid brachytherapy. All these require complex machine learning knowledge and applications.

KBP could also be used to give clinicians confidence that they are achieving high quality dose distributions with their implants, by comparing with large multi-institutional datasets, as proposed by Yusufaly et al [12]. This could be harnessed to reduce the decline in brachytherapy utilization and drive further improvements in brachytherapy technology.

Further testing can also be undertaken to assess if these models can be applied across different institutions and applicator types, as found by Reijtenbagh et al [13]. If the models work for different institutions and applicator configurations, then KBP could be a suitable quality assurance and credentialling tool for clinical trials incorporating a brachytherapy boost for locally advanced cervical cancer, such as described very recently by Reijtenbagh et al [23]. It would also be useful for assessing changes of practice and their effect on plan quality.

A limitation of this simple method is that it only predicts the D2cm^3. If, in the future, toxicity evidence is established with other DVH parameters, this method will not be able to optimise plans for these additional parameters. However, the HIPO algorithm only allows one data entry point, so having only one DVH parameter allows it to link with HIPO, which is approved for clinical use. Plans can also be improved for subsequent fractions by changing the implant design, for example adding interstitial needles or changing the tandem angle. In addition, KBP methods based on the OVH technique can be used to assist with comparing dose distributions from tandem and ovoid versus tandem and ring applicators and informing decisions regarding the use of interstitial needles [24-25]. These models are also based on applications with and without interstitial needles, and only one applicator type. Further work could determine if different models for intracavitary only or intracavitary and interstitial needles give better results.

5.7 Conclusion

A linear regression model can be created and used as a simplified KBP technique to predict D2cm^3 for OAR in cervical cancer brachytherapy. It is feasible to then use these predicted D2cm^3 parameters to drive commercial optimization algorithms to ensure individualised plan quality assurance is achieved.

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Chapter Six - Deformable image registration for cervical cancer brachytherapy dose accumulation: Organ at risk dose volume histogram parameter reproducibility and anatomic position stability

6.1 Preface

In chapter six I assess how robust and consistent deformable image registration is in the setting of dose accumulation across fractions of cervical brachytherapy. Deformable image registration (DIR) algorithms have been introduced in order to map voxels between different image datasets. The same deformation map can then be applied to the dose distribution.

DIR in cervical cancer brachytherapy leads to lower average OAR DVH parameters, and indicates that the worst case scenario assumption of complete overlap of the DVH parameter hot spots may not be ideal. However, DIR is not yet robust enough, even with additional contour information, for clinical use in a cervical cancer brachytherapy setting.

DIR algorithms require further work to become more robust, and the clinical implications of the application of DIR for dose accumulation in cervical cancer brachytherapy require further investigation.

Chapter six was published as Flower E, Do V, Sykes J, Dempsey C, Holloway L, Summerhayes K, Thwaites DI. Deformable image registration for cervical cancer brachytherapy dose accumulation: Organ at risk dose-volume histogram parameter

reproducibility and anatomic position stability. Brachytherapy. 2017 Mar-Apr;16(2):387-392. Doi: 10.1016/j.brachy.2016.12.006.

6.2 Abstract

Purpose: The purpose of this study was to determine the effect and reproducibility of different methods of deformable image registration (DIR) on cumulative organ at risk dose volume histogram (DVH) parameters summed over three brachytherapy fractions. DIR was used to assess the stability of the anatomical position of the DVH parameters for the bladder and rectum.

Materials and methods: DIR was completed for 39 consecutive cervical cancer brachytherapy patient's planning CTs. Reproducibility of DIR results was assessed for different methods of implementation based on adding contour biases added to the DIR algorithm. Accumulated DVH parameters ($D2cm^3$ and $D0.1cm^3$) for bladder and rectum were compared with dose summation without DIR. Structures $VolD2cm^3$ and $VolD0.1cm^3$ were created from the overlap of the $D2cm^3$ and $D0.1cm^3$ isodoses and the bladder or rectum. The overlap of $VolD2cm^3$ and $VolD0.1cm^3$ structures was calculated using the Dice similarity coefficient (DSC).

Results: DIR summed $D2cm^3$ and $D0.1cm^3$ decreased 2.9% and 4.2% for bladder and 5.08% and 2.8% for rectum compared with no DIR. The standard deviation of the bladder $D2cm^3$ and $D0.1cm^3$ for each fraction as the primary, averaged across all patients, decreased with addition of bladder contour biases to the DIR algorithm for the bladder. The average DSC was 0.78 and 0.61 for the bladder $D2cm^3$ and $D0.1cm^3$, and 0.83 and 0.62 for rectal $D2cm^3$ and $D0.1cm^3$.

Conclusions: Dose decreases were observed for summed DVH parameters using DIR. Adding contour-based biases to the algorithm increases the reproducibility of $D2cm^3$ and $D0.1cm^3$ accumulation. The anatomical positions of the $VolD2cm^3$ and $VolD0.1cm^3$ were not stable.

6.3 Introduction

A brachytherapy boost is a standard part of treatment for locally advanced cervix cancer. The Groupe European de Curietherapie, European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) working group and the American Brachytherapy Society (ABS) have produced a series of recommendations for dose reporting and prescribing in volume-based image guided brachytherapy for locally advanced cervix cancer, based on 3D image guided treatment planning [1-4]. Doses to organs at risk (OAR) are reported using dose volume histogram (DVH) parameters, such as the requirement to report the minimum dose in the most irradiated tissue volume 2cm^3 (D2cm^3) and 0.1cm^3 (D0.1cm^3). Studies have found that higher DVH parameter values (D2cm^3, D1cm^3 and D0.1cm^3) for the bladder and rectum correlated with grade 2 or higher late side effects [5, 6].

Currently, OAR DVH parameters for high dose rate (HDR) brachytherapy are accumulated assuming 100% of the prescribed dose from external beam radiotherapy (EBRT) is received by the entire organ. All doses are converted to the equivalent dose in 2Gy fractions (EQD2) during accumulation. When adding HDR brachytherapy DVH parameters, a worst case scenario assumption is made that the hot spots occur in the same anatomical position each fraction [2]. This assumption may be affected by organ deformation and movement. A study of the dosimetric effects of anatomical structure variations, relative to the fixed applicator geometry found that the bladder had the lowest dose uncertainty of all structures studied [7]. This is in line with the basic anatomy of pelvic organ mobility, with the posterior inferior bladder wall being relatively fixed in relation to the applicator. Another study found the topographical position of the

bladder D2cm^3 volume to remain stable [8]. Kim et al analyzed the location of the D2cm^3 hot spots relative to the applicator, finding it was positioned anterior and superior to the cervix, near the plane perpendicular to the tandem containing point A. Factors that affected the anatomical position of the D2cm^3 hot spots for standard loading plans included uterine wall thickness, uterine tandem position, fibroids, bladder filling, bowel gas and vaginal packing [9].

Deformable image registration (DIR) algorithms have been introduced in order to map voxels between different image datasets. The same deformation map can then be applied to the dose distribution. Despite the potential uncertainties related to DIR based on image intensity algorithms, previous studies have successfully used these algorithms for gynecological brachytherapy dose summation, although no validation method currently exists and DIR based dose accumulation should not be used clinically yet [10-14]. Constraints can be added to DIR algorithms based on selected contours. Additionally, selected contours can be masked to a higher Hounsfield Units (HU) and DIR performed. This gives higher biases in the image registration algorithm to that structure [13].

This work used MIM Maestro (version 6, MIM Software, Inc., Cleveland, OH)) for DIR, which uses an image intensity free form algorithm for DIR. In this study the cumulative DVH brachytherapy organ at risk parameters were used to assess the reproducibility of the DIR algorithm as additional biases were added based on the bladder contour. To assess the anatomical stability of the DVH parameter hot spots, structures were created from the overlap of the D2cm^3 and D0.1cm^3 isodoses and the bladder or

rectum. The overlap of the structures was calculated using the Dice similarity coefficient (DSC).

6.4 Material and Methods

Thirty-nine consecutive patients between 2009 and 2013 (FIGO stage IB to IV), who had received external beam radiotherapy prior to a brachytherapy boost, were retrospectively selected for this study. EBRT was delivered using a conformal 4-field box technique using 18MV photon beams. Thirty-two patients received 45Gy in 25 fractions, one 50Gy in 25 fractions, two 50.4Gy in 28 fractions and four 54Gy in 30 fractions, varying according to boost requirements to different volumes of primary and nodal disease. Following international recommendations it was assumed the OAR volumes being investigated received 100% of the prescribed dose from the EBRT treatment [1-4].

A HDR brachytherapy boost was delivered in 3 fractions, with a planning aim dose of 87Gy total EQD2 to the high risk clinical target volume (CTV_HR), limited by OAR $D2cm^3$ and $D0.1cm^3$ constraints doses of 90Gy to the bladder and 70Gy to the rectum.. Brachyvision (version 11, Varian Medical Systems, USA) was used as the brachytherapy treatment planning system (TPS). Treatment was delivered using a Varisource iX afterloader with an Ir-192 source and a titanium Fletcher-Suite-Delclos tandem and ovoid style applicator with flexible geometry. No interstitial needles were used for patients in this study. The applicators were inserted under ultrasound guidance.

Following recovery from the applicator insertion procedure, CT (GE Lightspeed) images of slice thickness 1.25mm were taken for treatment planning purposes. Some The most recent 28 patients also had a 1.5T MRI scan (Signa HDx, GE Medical Systems, Milwaukee, USA) for the first fraction only, to define the CTV_HR, but the OAR were defined on the CT. A foley catheter was inserted into the bladder prior to applicator insertion. The bladder was empty for 3D imaging and treatment. The MR and CT were fused using rigid registration (based on the applicators). All plans were performed on the CT, with the MR only used for CTV_HR definition. OAR and applicators were delineated on the CT whilst the patient was having their MRI scan to reduce planning time and maintain consistency across all fractions.

Patient images were imported into the TPS where the OAR and CTV volumes were delineated, the applicators reconstructed, and a treatment plan calculated in the treatment planning system. Standard plans were optimised using both inverse planning volume and graphical optimization to conform the prescribed dose to the CTV_HR. The bladder $D2cm^3$ and $D0.1cm^3$ were calculated and converted to EQD2 and OAR dose tolerances (incorporating the external beam dose) were not exceeded, and CTV doses were also within acceptable limits.

For this study the planning CT images, structure sets, RT plan and RT dose DICOM files were exported from the treatment planning system into the DIR software package, MIM Maestro (version 6, MIM Software, Inc., Cleveland, OH). Prior to DIR, the target and source CT images from two different brachytherapy fractions were automatically rigidly registered, with 6 degrees of freedom (translations along the x, y and z axis and rotations, pitch, yaw and roll). This rigid registration was visually assessed (using the

applicators as a reference) and corrected manually if required. The DIR was then based on this initial rigid-body image registration. Deformed images were visually assessed. For a deformed image to be acceptable, the bladder and rectum needed to be identifiable, especially the edges adjacent to the CTV_HR. The applicators also needed to appear un-deformed.

The CT scans from brachytherapy fractions two and three were deformably registered to the primary target CT image (fraction one). Using the resulting deformation maps for each of the deformable registrations, the dose distributions were then deformed and accumulated onto the geometry and anatomy of fraction one. The process was repeated with both fraction two and three also being the primary target image set, to assess the reproducibility of the DIR.

Three different DIR techniques were used. For technique one, DIRimage, the entire image set was deformed using a free form deformable image registration algorithm with a normalised intensity similarity metric [15]. For the second technique, DIRcbd, the bladder contour was given a higher bias for the DIR with locally locked adjustments (Reg Refine) as required. The third technique, DIRmasked, masked the bladder contour to a value of 1000 HU and then the entire image was deformed, with locally locked adjustments as required [13]. For locally locked adjustments, small volumes of the image including sections of the pelvic bones and ovoids were manually aligned and then the alignment of the centroid point of each volume locked before re-running the DIR algorithm.

The anatomical location of the D2cm^3 and D0.1cm^3 hotspots for the bladder and rectum were determined for both the un-deformed and deformed image sets. This was completed by determining the intersection of the organ D2cm^3 or D0.1cm^3 isodose with the respective organ volume (see Figure 6.1). This newly defined structure is referred to as the VolD2cm^3 or VolD0.1cm^3, respectively. The overlap of the structures VolD2cm^3 or VolD0.1c were calculated from 1) the original un-deformed final fraction and 2) the accumulated deformed doses (using the masking method) was evaluated using the DSC.

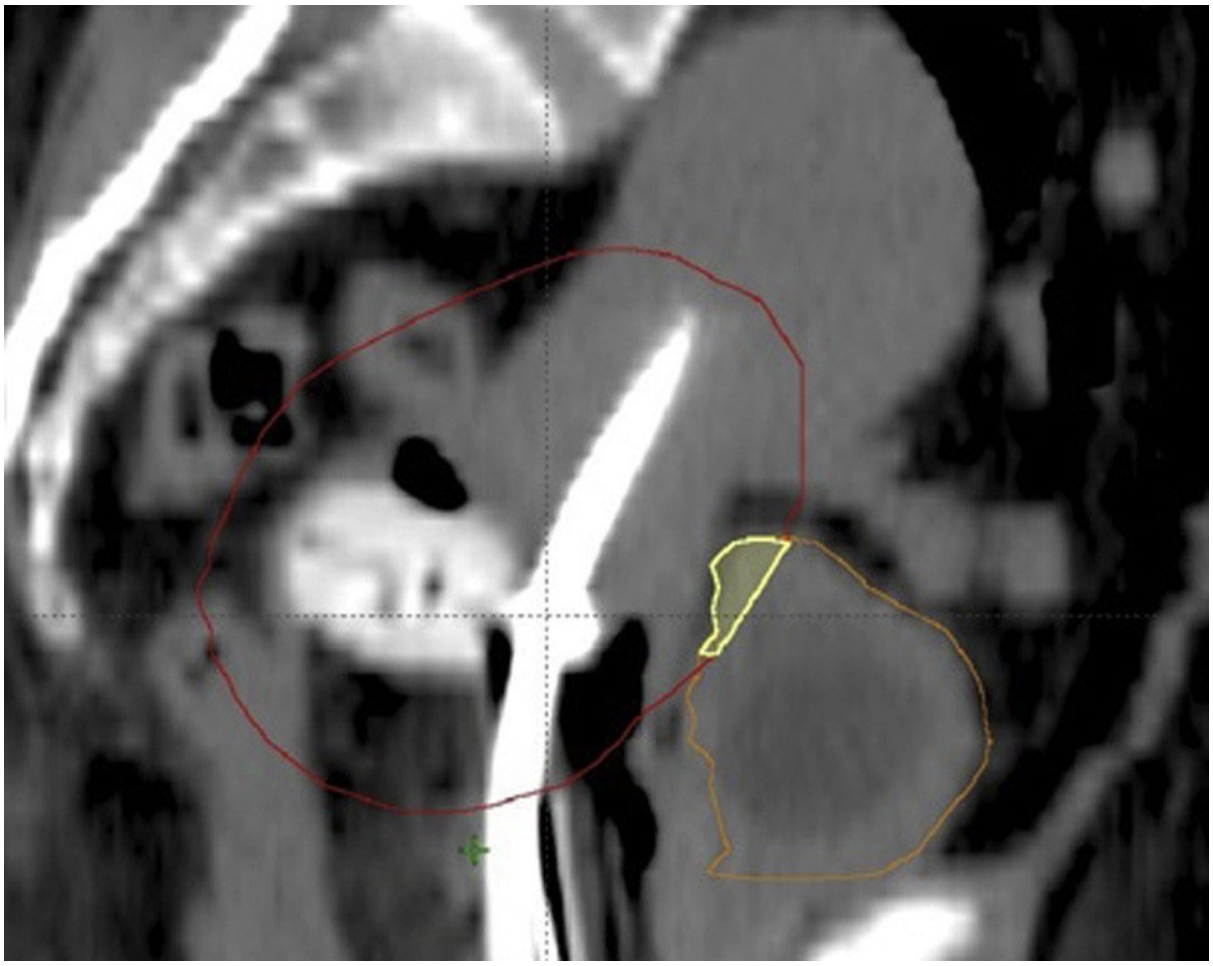

Fig 6.1 – The intersection between the bladder D2cm^3 isodose and the bladder contour, forming a structure representing the D2cm^3 for the bladder (VolD2cm^3).

6.5 Results

	DIR_{image}	DIR_{cbd}	DIR_{masked}
Percent difference in D2cm^3 (accumulated over three fractions) with and without DIR (range). †	-3.7	-0.8	-2.9
Percent difference in D0.1cm^3 (accumulated over three fractions) with and without DIR. †	-6.5	-7.4	-4.2
$\frac{1}{n}\sum_{pt_1}^{pt_n} SD\left(D2cm^3_{fr1pri}, D2cm^3_{fr2pri}, D2cm^3_{fr3pri}\right)$	2.2	1.4	0.7
$\frac{1}{n}\sum_{pt_1}^{pt_n} SD\left(D0.1cm^3_{fr1pri}, D0.1cm^3_{fr2pri}, D0.1cm^3_{fr3pri}\right)$	3.4	1.5	1.5

Table 6.1 – The difference between deformed and undeformed brachytherapy dose summation for different DIR methods for the bladder († averaged for D2cm^3 and D0.1cm^3 calculated with each fraction as a primary image) and the reproducibility (measured by the standard deviation of the D2cm^3 or D0.1cm^3 for each fraction as the primary, averaged across all patients) of adding different biases to the DIR algorithm for the bladder.

Across all patients, the average undeformed accumulated bladder D2cm^3 was 19.2Gy. Using DIRmasked, the percentage difference of the D2cm^3 with and without DIR,

averaged with each fraction as the primary image, was -2.9%. The average undeformed accumulated bladder D0.1cm^3 was 26.5Gy. The average D0.1cm^3 decreased by -4.2%. For the rectum, the average undeformed D2cm^3 was 13.4Gy and the average D0.1cm^3 was 18.6. The average D2cm^3 decreased by 5.1% and the average D0.1cm^3 decreased -2.8%. The dose differences were not statistically significant but may have been clinically significant for some patients.

The average standard deviation of the accumulated D2cm^3 and D0.1cm^3 across all patients for each fraction as the primary obtained by DIRimage was 2.2Gy and 3.4Gy respectively. Adding contour based bias on the DIR algorithm, DIRcbd, for the bladder reduced the standard deviation (table 1). The overall reproducibility was further increased by DIRmasked [13]. The reproducibility results showed highest significance comparing DIRimage and DIRmasked ($p < 0.005$). Thus the remainder of this study masked the organ at risk before DIR (DIRmasked). Visually acceptable results were obtained for 21 patients when masking the bladder and 20 patients when masking the rectum. Eleven patients obtained visually acceptable results for both the bladder and rectum. This is similar to results from other authors [9, 21] who also had to exclude patients due to visually unacceptable results. There is no quantitative method to assess this, or reason why some images produce visually unacceptable results.

For all patients with visually acceptable registration results, the DSC was used to calculate the overlap of the VolD2cm^3 and VolD0.1cm^3 for the bladder and rectum. The primary was the undeformed dose from fraction three. The secondary was the deformed dose from fraction one and two was accumulated with fraction 3. The D2cm^3

and D0.1cm^3 were then calculated for the bladder and rectum and the VolD2cm^3 and VolD0.1cm^3 structures were determined, as per fig 1.

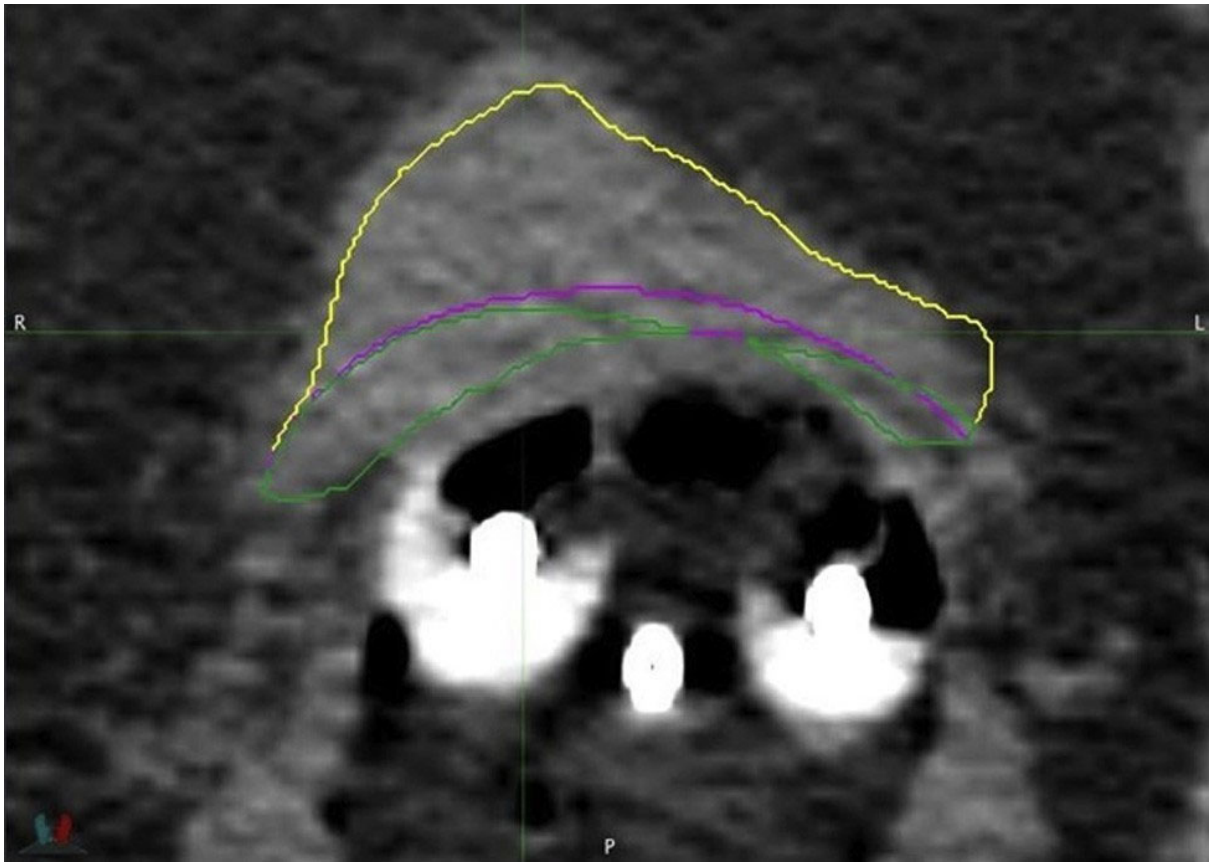

Fig 6.2 – The overlap of the VolD2cm^3 structures for the primary and secondary for the bladder. The average DSC for the bladder VolD2cm^3 was 0.78 (SD = 0.14, range 0.54 to 0.94). For the bladder VolD0.1cm^3 average DSC was 0.61 (SD = 0.31, range 0 to 0.94). For the rectum the average DSC was 0.83 and 0.62 for the VolD2cm^3 and the VolD0.1cm^3 respectively.

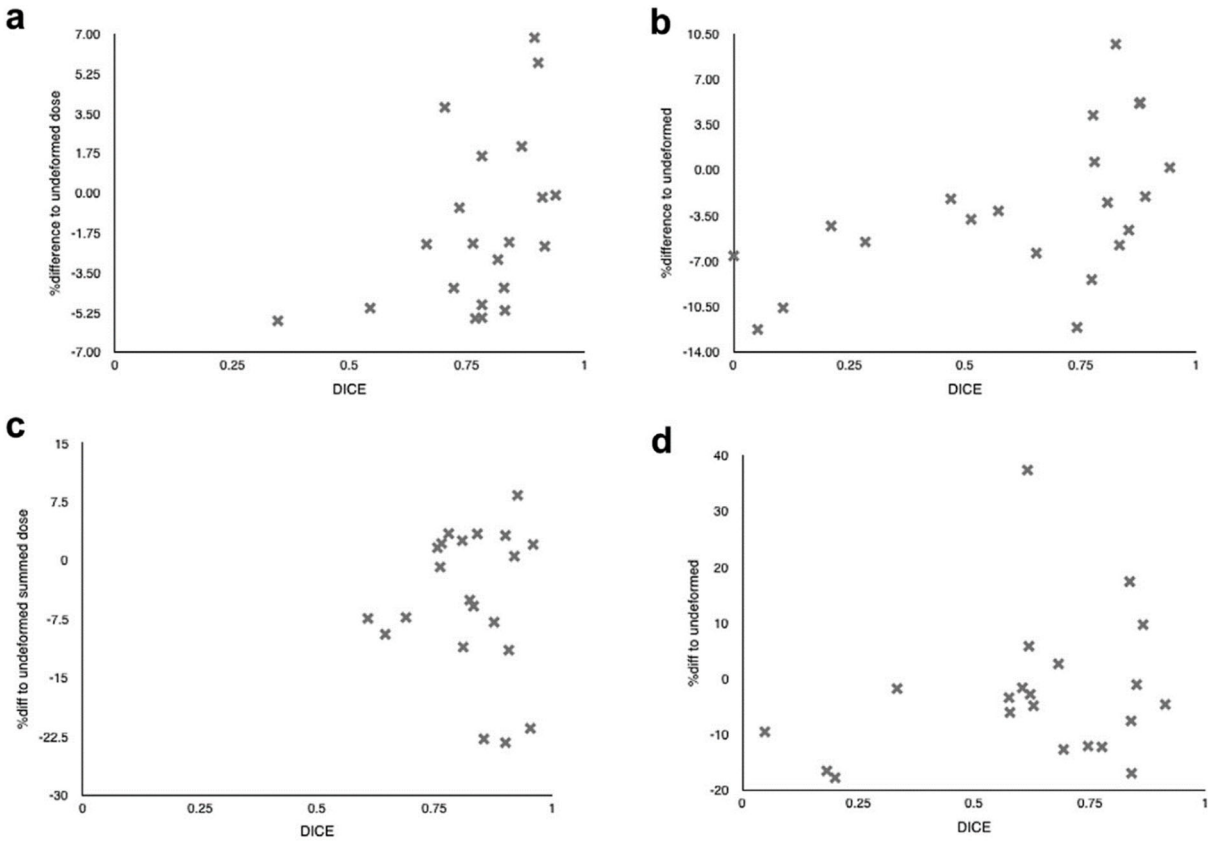

Fig 6.3 – Plots the percentage difference between summed doses (linear and deformed) against the DSC for a) bladder VolD2cm^3, b) bladder VolD0.1cm^3, c) rectal VolD2cm^3 and d) rectal VolD0.1cm^3 for fraction 3 as the primary reference image.

6.6 Discussion

There are many inherent uncertainties in brachytherapy treatments. These include source strength, treatment planning algorithm uncertainties, applicator definition, positional accuracy, and dose summation between brachytherapy fractions and with external beam, due to both anatomical topography and the relationship between the anatomy and applicators [16].

Another source of uncertainty in brachytherapy is contouring uncertainties. Due to the high dose gradients seen in brachytherapy, contouring uncertainties can cause uncertainties in DVH parameters [17]. Duane et al studied the effects of inter-observer contouring uncertainties on OAR DVH parameter uncertainties by using 8 patient CT scans. They found the effect of inter-observer variability to be 13.2% and 9% for the bladder and rectum $D2cm^3$ respectively [18]. Saarnak et al had three independent observers contour the bladder and rectum for 10 patient CT scans. The inter-observer variability for the $D2cm^3$ was 10% and 11% in the bladder and rectum respectively [19]. Hellebust et al used MR images from 6 patients and found the inter-observer variability was 5-8% for bladder and rectum $D2cm^3$ [20]. The differences between deformed and undeformed dose summation of $D2cm^3$ and $D0.1cm^3$ are less than inter-observer variability in OAR contouring but may be clinically significant. Additionally, uncertainties arising from contouring of the CTV also impact the OAR DVH parameters.

DIR in the pelvis has increased uncertainties due to the effects of gas, low image contrast and large deformations. There is no “gold standard” to analyze the accuracy of DIR for gynecological brachytherapy. This work showed that image pre-processing steps increase the reproducibility of DIR results. This process involves giving the organ of concern a higher bias in the DIR optimization algorithm (contour based deformation, masking the organ at risk) [13]. Other groups have used biomechanical contour based models for DIR [21]. Further work on DIR algorithms is required so that DIR can perform acceptably and consistently for more patients.

Wachter-Gerstner et al that found any DVH parameter below D5cm^3 for the bladder and rectum would be located within the bladder wall [22]. Nevascil et al found no significant correlation between bladder 2cm^3 and bladder filling [23]. Comparing the overlap of the OAR VolD2cm^3 and VolD0.1cm^3 between accumulated fractions and individual insertions is a novel approach, rather than comparing the overlap of the entire organ. Abe et al looked at the DICE coefficients for the entire bladder and rectum [12]. The DICE of VolD2cm^3 results of this study were comparable with the DICE coefficients for the entire organ.

Andersen et al found that the deformed D2cm^3 varied less than the D0.1cm^3, in agreement with the current study results [21]. The decrease in bladder and rectum D2cm^3 also agrees with results seen by Swamidas et al [14]. When plotting the percentage dose difference against the DSC, it was expected that the smaller the overlap, the higher the reduction in the D2cm^3 and D0.1cm^3. However, in some cases the dose increased, possibly due to uncertainties in deformation, or deforming into higher dose regions in different fractions [16]. There wasn't a strong correlation between the amount of DVH parameter hot spot overlap and the percentage dose difference.

Previous studies have found that the position of the bladder D2cm^3, as well as the magnitude, may correlate with the severity of morbidity [24, 25]. It should be noted that the clinical correlation between organ at risk toxicity and DVH parameters has been based on plain summation of the DVH parameters. This study shows the application of DIR may be beneficial in further correlating the accumulated overall dosimetric value and position of the hot spots, as long as careful consideration is given

to the method of DIR. Further study would need to be undertaken with a larger patient cohort to determine whether the deformed accumulated DVH parameters ($D2cm^3$ and $D0.1cm^3$) would be better predictors of toxicity than the current, undeformed summation of $D2cm^3$ and $D0.1cm^3$.

6.7 Conclusion

DIR in cervical cancer brachytherapy leads to lower average OAR DVH parameters, and indicates that the worst case scenario assumption of complete overlap of the DVH parameter hot spots may not be ideal. The use of masking the bladder followed by performing DIR with locally locked adjustments gives more reproducible results than deforming the entire image or using contour based DIR. The clinical implications of the application of DIR for dose accumulation in cervical cancer brachytherapy require further investigation.

6.8 References

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Chapter Seven – Conclusions

7.1 Summary of significant findings and impact of the work

As brachytherapy for gynaecological cancers moves towards increased personalisation of treatment, and the body of evidence grows, it is critical to continue to evaluate practice. Likewise, as new technologies are developed, such as deformable image registration and machine learning, it is critical that these technologies are assessed for feasibility in the brachytherapy for cervical cancer setting. In this summary, outcomes of the studies are linked back to aims and research questions, future directions are outlined, and final concluding remarks are made.

Chapter Three: The research question for chapter three was how consistent with published literature and clinically acceptable is the quality of a single-institution's pattern of practice, dosimetry results, and clinical outcomes for patients with unresectable malignancies of vagina, vulva, or urethra, receiving brachytherapy using customised vaginal moulds with or without interstitial needles. Evaluation and analysis found that brachytherapy with a customised vaginal mould and interstitial needles showed acceptable doses to CTV, with local control achieved in 67% of patients, and reasonable doses to OARs and acceptable toxicity.

Chapter three demonstrated that customised moulds and free-hand needles provide an acceptable method for treating vaginal malignancies in the Australian setting. This evaluation process provides a benchmark for continued assessment of changes in practice to improve treatment for vaginal cancers. Vaginal malignancies are often in

difficult anatomical places and often require salvage after previous treatment. Treating with freehand needles and a customised mould is less invasive than other treatment modalities such as pelvic exenteration.

Chapter Four: The research question for chapter four was how consistent plan quality is following the implementation of evidence-based planning goals using clinical protocols as our planning aims for the treatment of cervical cancer. The evaluation and analysis showed that the evidence-based planning aims were successfully adopted into an Australian practice. The benchmark published recommendations for dose planning aims and interstitial needle use were met, and vaginal dose de-escalation techniques were demonstrated. The clinical results were at least comparable with other national and international results.

Chapter four demonstrates that evidence-based planning aims can be implemented into practice in Australian settings, with acceptable dosimetric and clinical outcomes. This work demonstrates that increasing needle TRAK decreases vaginal TRAK, meaning that adding interstitial needles and additional loading in the needles provides a method for vaginal dose de-escalation. Together with previously published [1] planning techniques (for intracavitary only implants) that involve non-standard loading patterns, the technique described in chapter four allows for vaginal dose de-escalation, when the vagina is not involved at the time of brachytherapy.

The next two chapters investigate new techniques and emerging technologies that can be applied to brachytherapy for cervical cancer, including knowledge-based

planning (KBP) and deformable image registration. The aim is to assess the feasibility of their use and their potential impact for optimising clinical practice.

Chapter Five: The research question for chapter five was whether a simple KBP relationship could be used to predict the D2cm^3 for organs at risk (OAR), and if this can be used to detect sub-optimal plans and improve plan quality? The work showed that a linear regression model can be created and used as a simplified knowledge-based planning technique to predict D2cm^3 for organs at risk. It is feasible to then use these predicted D2cm^3 parameters to drive commercial optimization algorithms to ensure individualised plan quality assurance is achieved.

Chapter five demonstrates that a simplified KBP algorithm is feasible and can predict the D2cm^3 of OAR during brachytherapy for cervical cancer. This work will allow for faster planning, and the quality of plans to be objectively evaluated.

Chapter Six: The research question for chapter six was what is the effect of, and how reproducible are, different methods of deformable image registration (DIR) on cumulative organ at risk dose volume histogram (DVH) parameters summed over three brachytherapy fractions and can DIR be used to assess the stability of the anatomical position of the DVH parameters for the bladder and rectum? Dose decreases were observed for summed DVH parameters using DIR. Adding contour-based biases to the algorithm increases the reproducibility of D2cm^3 and D0.1cm^3 accumulation. The anatomical positions of the volumes of the D2cm^3 and D0.1cm^3 were not stable.

Chapter six demonstrates that whilst DIR is not yet feasible for clinical use, this work has been cited 19 times, adding to the body of knowledge regarding DIR in brachytherapy, and that linear summation of the DVH parameters continues to be optimal for clinical dose summation.

7.2 Future work

Following the publication of chapter three, Schmid et al [2] from the Groupe European de Curietherapie and European Society for Radiotherapy and Oncology gynaecology working party (GEC-ESTRO GYN) working group published consensus concepts and recommendations for target volume delineation for image guided adaptive brachytherapy for primary vaginal cancer. New applicators have also become available to treat vaginal malignancies. A new case series following the implementation of the new guidelines and applicators should be studied, to ensure standards are maintained or improved, compared with national and international benchmarks, and to actively look for practice and quality improvement.

Continued review and analysis of cervical cancer brachytherapy dosimetry and clinical outcomes will lead to continued improvements in patient outcomes. The benefits of vaginal dose de-escalation and analysis of functional imaging and other radiobiology markers are likely to lead to these types of improvements.

KBP algorithms will be implemented into clinical workflows, and models should continue to be refined. KBP will also be used to assess plan quality and across patient cohorts, and as practice changes occur.

DIR in brachytherapy needs more development to be robust enough for clinical implementation. In this work, DIR results were presented in physical dose (Gy). Future work looking at the differences in EQD_2 and clinical significance may be warranted. Given the uncertainties in cases where there are dose gradients in the external beam dose distribution within the brachytherapy volume [3], it is likely that a robust DIR algorithm could help assess dosimetry for some patients, and work should continue to develop this.

7.3 Final conclusions

Quality management plays an important role in brachytherapy. Evaluating technical implementation, plan dosimetry and clinical outcomes at an institutional level is an important step in fulfilling the Australian Radiation Oncology Practice standard for quality in Radiation Oncology and ensuring high standards of care in the Australian context [4]. Advanced brachytherapy for vaginal malignancies and cervical cancer following implementation of evidence-based planning aims showed acceptable doses to target volumes and organs at risk, excellent local control, and acceptable toxicity.

From reviewing the clinical data against evidence-based guidelines the next level is to also examine whether a plan is the best plan for an individual patient and to be able to optimise this in the future. Using overlap volume histograms to retrieve a geometric relationship between the target and the $D2cm^3$ for an OAR, modelling can be used to assess and even assist robust consistent planning to ensure an optimal plan is developed for each patient, and then across patient cohorts.

DIR dose summation saw decreases in the $D2cm^3$ and $D0.1cm^3$, but within the range of clinical uncertainties. Adding contour-based information improved the registration reproducibility. Developing methods like deformable image registration holds the potential of removing assumptions in dose reporting, but the technology is not yet mature enough for robust and consistent clinical implementation in brachytherapy.

7.4 References

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