2020

Development of a System for Comprehensive in-vivo validation of Transrectal ultrasound based high Dose rate prostate brachytherapy Treatments

Joel Poder

Follow this and additional works at: https://ro.uow.edu.au/theses1
DEVELOPMENT OF A SYSTEM FOR COMPREHENSIVE IN-VIVO VALIDATION OF TRANSRECTAL ULTRASOUND BASED HIGH DOSE RATE PROSTATE BRACHYTHERAPY TREATMENTS

A Thesis Submitted in Partial Fulfilment of the Requirements for the Award of the Degree of

Doctor of Philosophy

from

UNIVERSITY OF WOLLONGONG

by

Joel Poder
B Med. Rad. Phys. (Distinction), MSc. (Research)

School of Physics
Faculty of Engineering

2020
CERTIFICATION

I, Joel Poder, declare that this thesis, submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Physics, Faculty of Engineering, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

(Signature Required)

Joel Poder
29 January 2020
Table of Contents

| List of Tables | v |
| List of Figures/Illustrations | viii |
| ABSTRACT | 1 |
| Acknowledgements | 3 |
| List of Publications | 5 |

1 Introduction
1.1 Project Aim | 8 |

2 Literature Review | 9
2.1 The Prostate | 9
  2.1.1 Prostate Cancer | 10
2.2 Treatment of Prostate Cancer | 10
  2.2.1 High Dose Rate Brachytherapy | 11
2.3 Clinical Indications for HDR Prostate Brachytherapy | 11
2.4 The Ir-192 Source | 12
2.5 The TG-43 Dosimetry Protocol | 13
2.6 High Dose Rate Prostate Brachytherapy Planning and Treatment Process | 18
  2.6.1 Transrectal Ultrasound Based High Dose Rate Prostate Brachytherapy Planning | 20
2.7 High Dose Rate Brachytherapy Mistreatments and the Requirement for Quality Assurance | 20
2.8 Current Methods of High Dose Rate Brachytherapy In-vivo Dosimetry | 22
  2.8.1 Challenges associated with HDR Brachytherapy In-vivo Dosimetry | 23
  2.8.2 Thermoluminescent Dosimeters | 23
  2.8.3 Semiconductor Diodes | 24
  2.8.4 MOSFETs | 25
  2.8.5 Optically Stimulated Luminescent Dosimeters | 26
  2.8.6 Plastic Scintillation Dosimeters | 26
  2.8.7 Radiochromic Film | 27
2.9 Current Methods of High Dose Rate Brachytherapy In-vivo Source Tracking | 27
  2.9.1 Flat Panel Detectors | 27
# TABLE OF CONTENTS

2.9.2 Detector Arrays .................................................. 28
2.9.3 Point Detectors .................................................. 29
2.9.4 Pinhole Collimator Devices ................................. 30
2.9.5 Electromagnetic Tracking .................................... 30

3 The Geant4 Monte Carlo Toolkit ................................. 32
3.1 User Action Classes ............................................... 33
  3.1.1 G4UserDetectorConstruction .................................. 33
  3.1.2 G4UserPhysicsList ........................................... 34
  3.1.3 G4UserPrimaryGeneratorAction .............................. 35
  3.1.4 G4UserEventAction .......................................... 35
  3.1.5 G4UserRunAction ............................................ 35
  3.1.6 G4UserSteppingAction ....................................... 35
3.2 Interface Commands ............................................... 36
3.3 Visualisation ........................................................ 36
3.4 Geant4 in the Field of Brachytherapy ......................... 36

4 A Risk based Approach to Development of Ultrasound-guided High Dose Rate Prostate Brachytherapy Quality Management 39
4.1 Introduction .......................................................... 39
4.2 Materials & Methods ............................................... 41
  4.2.1 TRUS Based Real-Time HDR pBT Technique .............. 41
  4.2.2 Process Map .................................................. 43
  4.2.3 Failure Modes and Effects Analysis ...................... 43
4.3 Results ............................................................... 45
  4.3.1 Ultrasound based high dose rate prostate brachytherapy process map .................................................. 45
  4.3.2 Failure Modes and Effects Analysis based Quality Management 45
4.4 Discussion ............................................................. 53
4.5 Conclusion ............................................................ 54

5 In-vivo Source Tracking Error Thresholds for Ultrasound Based HDR Prostate Brachytherapy 56
5.1 Introduction .......................................................... 56
5.2 Materials & Methods ............................................... 57
  5.2.1 Patient and Treatment Characteristics .................... 57
  5.2.2 Simulated Treatment Planning Source Positioning Errors 58
  5.2.3 Plan Analysis .................................................. 60
5.3 Results ............................................................... 61
5.4 Discussion ............................................................. 68
5.5 Conclusion ............................................................ 73
6 Ir-192 Flexisource TG-43 Monte Carlo Simulations
   6.1 Introduction .................................................. 74
   6.2 Materials & Methods ........................................ 75
      6.2.1 Ir-192 Flexisource Model .............................. 75
      6.2.2 Phantom Geometry ......................................... 76
      6.2.3 Physics Modelling ......................................... 76
      6.2.4 Dose Scoring ............................................... 77
   6.3 Results .......................................................... 78
      6.3.1 Radial Dose Function ..................................... 78
      6.3.2 2D Anisotropy .............................................. 79
   6.4 Discussion ...................................................... 80
   6.5 Conclusion ..................................................... 82

7 HDR Prostate Brachytherapy In-vivo Source Tracking using the Magic Plate Diode Array: A Monte Carlo Study
   7.1 Introduction .................................................... 83
   7.2 Materials & Methods .......................................... 84
      7.2.1 Ir-192 Flexisource Model .............................. 84
      7.2.2 Magic Plate 121 Model .................................... 84
      7.2.3 Patient Geometry .......................................... 86
      7.2.4 Dwell Positions and Dose Scoring ..................... 86
      7.2.5 Source Tracking Algorithm ............................. 88
   7.3 Results .......................................................... 91
   7.4 Discussion ...................................................... 92
   7.5 Conclusion ..................................................... 96

8 Feasibility of Real-time In-vivo Source Tracking During Ultrasound Based HDR Prostate Brachytherapy
   8.1 Introduction .................................................... 97
   8.2 Materials & Methods .......................................... 98
      8.2.1 Ir-192 Flexisource Model .............................. 98
      8.2.2 Magic Plate 900 Model .................................... 98
      8.2.3 Patient Geometry .......................................... 99
      8.2.4 Trans-rectal Ultrasound Probe Model .................. 100
      8.2.5 Dwell Positions and Dose Scoring ..................... 101
      8.2.6 Source Tracking Algorithm ............................. 102
   8.3 Results .......................................................... 103
   8.4 Discussion ...................................................... 108
   8.5 Conclusion ..................................................... 114

9 Towards Real Time In-vivo Rectal Dosimetry During Trans-rectal Ultrasound Based High Dose Rate Prostate Brachytherapy Using MOSkin Dosimeters
   9.1 Introduction .................................................... 115
**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.2 Materials &amp; Methods</td>
<td>116</td>
</tr>
<tr>
<td>9.2.1 Treatment Technique &amp; Patient Characteristics</td>
<td>116</td>
</tr>
<tr>
<td>9.2.2 MOSkin Dosimeters and Calibration Technique</td>
<td>117</td>
</tr>
<tr>
<td>9.2.3 In-vivo Measurements and the Dual Purpose Probe</td>
<td>118</td>
</tr>
<tr>
<td>9.2.4 Measurement &amp; Uncertainty Analysis</td>
<td>120</td>
</tr>
<tr>
<td>9.3 Results</td>
<td>122</td>
</tr>
<tr>
<td>9.4 Discussion</td>
<td>126</td>
</tr>
<tr>
<td>9.5 Conclusion</td>
<td>131</td>
</tr>
<tr>
<td><strong>10 Conclusion</strong></td>
<td>132</td>
</tr>
<tr>
<td>10.1 Final Summary</td>
<td>132</td>
</tr>
<tr>
<td>10.2 Future Work</td>
<td>135</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>161</td>
</tr>
</tbody>
</table>
# List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Emission spectrum of the Ir-192 source, obtained from the NuDat database</td>
<td>14</td>
</tr>
<tr>
<td>4.1</td>
<td>DVH metric coverage planning goals used in our institution.</td>
<td>41</td>
</tr>
<tr>
<td>4.2</td>
<td>Time required for each step in the TRUS based real-time HDR pBT workflow</td>
<td>42</td>
</tr>
<tr>
<td>4.3</td>
<td>Scoring of occurrence (O), severity (S) and detectability (D) as per the</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>AAPM TG 100 formalism</td>
<td></td>
</tr>
<tr>
<td>4.4</td>
<td>Failure modes identified during FMEA process, ranked according to RPN.</td>
<td>46</td>
</tr>
<tr>
<td>4.5</td>
<td>QM checklist developed for TRUS based HDR pBT treatment planning and delivery</td>
<td>50</td>
</tr>
<tr>
<td>5.1</td>
<td>Characteristics of the patient plans considered in this study.</td>
<td>58</td>
</tr>
<tr>
<td>6.1</td>
<td>Uncertainty analysis for MC TG43 simulations used in this study.</td>
<td>81</td>
</tr>
<tr>
<td>7.1</td>
<td>Difference between MP predicted and actual source positions in mm (k=1).</td>
<td>91</td>
</tr>
<tr>
<td>7.2</td>
<td>Uncertainty analysis for source tracking MC simulations used in this study.</td>
<td>92</td>
</tr>
<tr>
<td>8.1</td>
<td>Characteristics of the three HDR pBT plans considered in the study.</td>
<td>101</td>
</tr>
<tr>
<td>8.2</td>
<td>Average difference between MP900 predicted and actual source positions in mm, without and with a TRUS probe (corrected with 70% threshold) with standard deviation (k=1) in the patients rectum.</td>
<td>106</td>
</tr>
<tr>
<td>9.1</td>
<td>Uncertainty analysis for MOSkin measurements performed in this study.</td>
<td>121</td>
</tr>
<tr>
<td>9.2</td>
<td>Uncertainty analysis for MOSkin measurements performed in this study.</td>
<td>125</td>
</tr>
</tbody>
</table>
List of Figures

2.1 Image of the Ir-192 Flexisource with ruler for scale. 13
2.2 TG43-U1 coordinate system used for brachytherapy dosimetry calculations [3]. 15
3.1 Schematic of Geant4 toolkit class hierarchy. 38
4.1 Major process map for ultrasound based HDR pBT planning and delivery. 45
5.1 Frequency of the position for the three most heavily weighted catheters across all of the patients considered in this study, superimposed with a typical prostate contour (red), urethra contour (yellow), and rectum contour (brown) at the mid-prostate slice. 60
5.2 a) Average change in DVH metrics ($\pm 2$ standard deviation (SD)) for the prostate contour as a function of source positioning errors in the cranial-caudal direction (all catheters), b) the anterior-posterior direction (3 most heavily weighted catheters), and c) the medial-lateral direction (3 most heavily weighted catheters). Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions. 62
5.3 Percentage of patients whose plans would fail according to the prostate V100\% DVH planning aim (V100\% $>95\%$) as a function of source positioning error for all three directions. Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions. 64
5.4 a) Average change in DVH metrics ($\pm 2$ SD) for the urethra and rectum contours as a function of source positioning errors in the cranial-caudal direction (all catheters), b) the anterior-posterior direction (3 most heavily weighted catheters), and c) the medial-lateral direction (3 most heavily weighted catheters). Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions. 65
5.5  a) Percentage of patients whose plans would fail according to the urethra D1cc DVH planning aim (D1cc <120%) as a function of source positioning error for all three directions, b) Percentage of patients whose plans would fail according to the rectum D2cc DVH planning aim (D2cc <70%) as a function of source positioning error for all three directions. Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions.

5.6  a) Average change in DVH metrics (2 SD) for the urethra and rectum contours as a function of source positioning errors towards the OAR, b) Percentage of patients whose plans would fail according to the urethra D1cc DVH planning aim (D1cc <120%) and the rectum D2cc DVH planning aim (D2cc <70%) as a function of source positioning error towards the OAR.

6.1  Geometric design of the Flexisource Ir-192 HDR source [4].

6.2  Top-down schematic view of the concentric spherical shells (in black) around the Ir-192 source (in red) used for dose scoring. Image is not to scale.

6.3  Comparison of calculated radial dose function with studies by Granero [4] and Taylor & Rogers [5].

6.4  a) Calculated 2D anisotropy function at a radial distance of 1 cm, and b) at 10 cm. As compared with studies by Granero [4] and Taylor & Rogers [5].

7.1  a) Schematic of the MP121 diode spacing, the origin of the coordinate system is defined as the bottom left corner diode of the MP121. (b) Close up of the diode design (distances in mm).

7.2  Partial axial view of voxelized patient geometry in Geant4 source position simulations. The carbon couch is shown below the patient geometry outlined in green, the Kapton substrate in blue and the diode array in pink.

7.3  a) Difference between MP predicted and actual source position for heterogeneous and water only simulations in X direction, b) Difference in Y direction, c) Difference in Z direction, d) 3D difference vector. Coordinate system orientation is shown in Figures 6.1 & 6.1.

8.1  Schematic of the MP900 and of the edgeless diode design used source tracking simulations. All dimensions are in millimetres, image is not to scale.
8.2 a) Distance calculation (mm) between the source and each diode in the MP900 from a source position in Patient 1 plan, affected by the presence of the TRUS probe. b) Distance calculation, without the TRUS probe present, c) Distance calculation with 70% threshold applied, and diodes with red colours not included in the reconstruction algorithm. 104

8.3 Effect of threshold level in the source tracking algorithm. The 3D error vector in the presence of the TRUS probe is shown in green (k=1). The 3D error vector without the TRUS probe is shown in red (k=1). The 3D error vector with different threshold levels applied is shown in blue, pink, and orange, for patients 1, 2 and 3, respectively (k=1). 105

8.4 Average 3D source tracking error in each catheter considered in the study for patient 1, 1 standard deviation. Red columns show the average error without the TRUS probe. Blue columns show the average error with the TRUS probe present and a 70% threshold level applied. 107

8.5 3D source tracking error in the form of a box-whisker plot for catheter 2 (C2) and catheter 8 (C8). TRUS probe present and TRUS probe corrected results are presented for each catheter. 108

8.6 a) Schematic of the setup with the source, TRUS probe and MP900 array. a is the distance between the centre of the TRUS probe and the array; b is the distance between the external surface of the TRUS probe and the source; h is the length of the array; d is the diameter of the probe. Image is not to scale, b) Minimum source-probe distance necessary to avoid the complete shielding of the primary radiation of the source that would be detected by the array, plotted at changing array-probe distance a, c) TRUS image of the prostate after needle implantation. The closest needle is 10.4 mm over the TRUS probe. 111

9.1 Top view schematic of the MOSkin dosimeter. 118

9.2 Side view schematic of the MOSkin dosimeter. 118

9.3 Placement of the MOSkin dosimeters on the TRUS probe, under the endorectal balloon to produce the DPP. 119

9.4 Creation of ROI's around MOSkin measurement points (red spheres), shown on sagittal view of an example plan with prostate contour (red), urethra (yellow), and dwell position within an example catheter (red dot in yellow cylinder). 122

9.5 Histogram of $\Delta_{DPP,BTPS}$ values for 63 MOSkin measurement points across 20 treatment fractions. 124

9.6 Histogram of $\Delta_{DPP,BTPS}$ values for 1071 MOSkin measurement points across 342 measured catheters. 126

9.7 BTPS predicted (blue) vs MOSkin measured (red) dose accumulated across catheters for one of the fractions included in this study. 128
High dose rate (HDR) brachytherapy is a treatment modality commonly used for the treatment of prostate cancer. In this technique, radiation is emitted from within the prostate, allowing for high doses to be delivered to the prostate whilst still sparing the surrounding organs at risk such as the urethra, bladder, and rectum. However, due to the close proximity of these organs at risk to the prostate, and therefore the radiation source, there is potential that small errors in placement of the source may lead to substantial changes in the delivered dose distribution. Consequently, these errors may lead to significant post-treatment gastrointestinal or genitourinary complications as well as suboptimal biochemical progression free survival.

Due to the risk of HDR prostate brachytherapy (pBT) mistreatment resulting in significant post-treatment complications, it is essential that all potential risks in the treatment planning and delivery process are identified, and that these risks are minimised. One method of minimising these risks is through the implementation of routine in-vivo treatment verification (IVTV), through either in-vivo dosimetry or in-vivo source tracking.

The aim of this thesis is to identify all types of potential treatment planning and
delivery errors for transrectal ultrasound (TRUS) based HDR pBT and to investigate the feasibility of reducing the impact of these errors through the introduction of routine IVTV. To achieve this, a novel two-dimensional diode array known as the Magic Plate will be considered for in-vivo source tracking, and novel MOSFET type dosimeter known as the MOSkin will be considered for in-vivo dosimetry of TRUS based HDR pBT.

**KEYWORDS:** prostate, brachytherapy, in-vivo source tracking, in-vivo dosimetry, Magic Plate, MOSkin
Acknowledgements

I would to acknowledge all those who have supported and assisted me during my research and helping me to complete this PhD.

Firstly, I would like to express my sincere appreciation and gratitude to my primary supervisor Distinguished Professor Anatoly Rosenfeld, Director of the Centre for Medical Radiation Physics at the University of Wollongong. Professor Rosenfeld has provided continual leadership and guidance throughout this entire project. Without Professor Rosenfeld, a lot of the work presented in this thesis would not be realised.

Secondly, I would like to acknowledge Dr. Dean Cutajar for all of his support given to me over the course of this project. His guidance, and almost constant availability for advice has allowed me to complete this project in the time frame that I have. Like Professor Rosenfeld, without Dr. Cutajar this project would not have reached it’s potential. It is important also to acknowledge Dr Cutajar’s work in maintaining the computer cluster used to perform many of the Monte Carlo simulations performed in this thesis. Most importantly however, Dean’s friendship has made completion of this project a very enjoyable experience.

I would also like to acknowledge other members of staff at the Centre for Medical Radiation Physics for their assistance in completing this project. Firstly Associate Professor Susanna Guatelli for her guidance on all things Geant4, Associate Professor Marco Petasecca for lending his knowledge on the details of the technical components
of the instrumentation, and last but not least Karen Ford, for always keeping things moving along.

Much of the work presented in this project was also performed at the St George Hospital Cancer Care Centre. I’d like to acknowledge the following members of staff for their contributions and support: Andrew Howie for always providing me with his expert clinical knowledge of prostate brachytherapy and going over all my writing with a fine toothed comb; Ryan Brown for allowing me to bounce ideas of him, and for assisting with experiments performed in the department; Dr. Joseph Bucci for his expert clinical knowledge, being principal investigator of the clinical trial, and his continued financial assistance.

I’d also like to take the opportunity to thank my two clinical director’s whom I have worked under throughout the duration of this thesis; Dr. Robin Hill, and Ms Anna Ralston. Both Robin and Anna have been nothing but enthusiastic and supportive of me and my desire to complete my PhD. Thank you Anna in particular for recognising the importance of this work to St George Cancer Care Centre and affording me all the relevant opportunities to both work on and present my work.

Thank you to Professor Mauro Carrara for his input into the design and presentation of much of the work presented in this thesis.

I would like to thank my friends and family, for keeping my sane over the last 5 years and providing me with some valuable time away from work and this project to refresh my mind. Last but not least, I’d like to thank my partner Carla, for her continual love and encouragement throughout the time it has taken me to complete this thesis.
List of Publications


Chapter 1

Introduction

In Australia, over 75 000 people with cancer will need radiation therapy in 2020 [6]. Despite improved screening, prostate cancer still remains one of the leading causes of death for Australian males, accounting for 3824 deaths in 2011. The projected number of deaths from prostate cancer is expected to increase to more than 3900 per year by 2020 [6]. It is also predicted that the incidence of prostate cancer will rise to 25 000 from 21 000 new cases per year during the same span [6]. Similar trends have been observed on a world scale, with 250 000 deaths per year due to prostate cancer, the burden of which is expected to rise to 499 000 new deaths [7].

High dose rate (HDR) brachytherapy is a form of radiation therapy that is commonly used for the treatment of prostate cancer. In this form of therapy, the radioactive source (typically Ir-192) is temporarily placed at multiple positions within the prostate for a prescribed amount of time. To achieve this, thin catheters are temporarily inserted into the trans-perineally under trans-rectal ultrasound (TRUS) guidance. The HDR source is then stepped through these catheters sequentially, driven by a device called a remote afterloader.

As in HDR pBT the radiation source is placed directly within the target in HDR prostate brachytherapy (pBT), ablative doses can be delivered to the prostate whilst
still sparing adjacent organs at risk (OARs), such as the urethra, rectum, and the bladder [8]. This is also made achievable due to the millimetre precision of the equipment and the steep dose gradients associated with Ir-192 source. These steep dose gradients however also necessitate strict quality assurance (QA), as small differences between planned and measured source positions within the target may result in a severe underdosage of the target and/or overdosage of OARs [9].

HDR pBT treatments are traditionally planned on computed tomography (CT) scans of the patient after implantation of the catheters. However, the use of TRUS for treatment planning has been increasing rapidly in recent years due to its excellent visibility of the prostate and surrounding OARs [10]. Modern TPSs are able to use the ultrasound (US) echoes of the implanted catheters for the definition of the catheter position within the patient, allowing for real-time HDR pBT treatment planning [11]. HDR pBT is both intensive and complex, and therefore robust methods of QA are required.

Traditional methods of QA for HDR pBT focus on minimising the risk of afterloader malfunction [9]. It is now beginning to be recognised however that the likelihood of afterloader malfunction is low, and that there are many other steps in the treatment planning and delivery process that may result in incorrect delivery of treatment [12]. This is true especially the complex process of TRUS based HDR pBT treatment delivery.

Consequently, an ultimate QA program for TRUS based HDR pBT should consider all potential errors in the treatment planning and delivery process. The potential incidence and severity of these errors may be reduced, and detectability increased through introduction of department specific procedures, protocols, and checklists. However, these checklists and procedures are not likely to catch errors, and they should be supplemented through some form of in-vivo treatment verification (IVTV) such as in-vivo
1.1. Project Aim

The aim of this project is to identify all types of potential treatment planning and delivery errors for TRUS based HDR pBT and reduce the impact of these errors through the introduction of IVTV. This aim is divided into the following objectives:

- Review the literature for current methods of IVTV in HDR pBT.
- Identify all potential risks associated with the TRUS based HDR pBT process.
- Assess the applicability of IVTV to detect and reduce the risk associated with these errors.
- Determine appropriate action thresholds for in-vivo source tracking in TRUS based HDR pBT.
- Evaluate the feasibility of using a two-dimensional (2D) diode array to perform in-vivo source tracking in HDR pBT.
- Benchmark a novel dosimeter against more established dosimeters in performing IVD during TRUS based HDR pBT.
- Perform a clinical trial in which the novel dosimeter is used for IVD during TRUS based HDR pBT treatments at a single institution.
Chapter 2

Literature Review

2.1 The Prostate

The prostate gland is part of the male reproductive system and is approximately the size and shape of a walnut. The gland is located immediately anterior to the rectum and inferior of the bladder, completely surrounding the urethra. The urethra is central to the prostate at its inferior aspect (apex) but located more anteriorly at the superior aspect (base). Its main function is to secrete fluids that protect and enrich sperm.

According to the McNeal model, the prostate gland can be divided into zones [13]. The urethra runs through the centre of the prostate, with the fibromuscular stroma immediately anterior to the urethra and the glandular tissue immediately posterior. The glandular tissue can then be divided into three zones; the peripheral zone (PZ), the central zone (CZ) and the transition zone (TZ). The PZ comprises of approximately 70% of the glandular tissue, located primarily at the apex of the prostate. The CZ comprises 25% of the glandular tissue, and the TZ up to 10% and is separated into 2 equal sized portions lateral to the urethra and anterior to the peripheral zone in the mid-prostate [13].
2.1.1 Prostate Cancer

Prostate cancer is a disease that occurs when cells in the prostate gland become abnormal and grow uncontrollably to form tumours. Whilst cancerous cells in the prostate are generally not responsible for deaths on their own, they are capable of metastasising (spreading to other parts of the body) via the blood or lymphatic system and producing new tumours. Approximately 60% of prostate cancers are found in the PZ, 8% in the CZ and 24% in the TZ [13]. Prostate cancer exhibits few symptoms while the disease is confined within the gland [14]. Traditionally, patients were examined for prostate cancer using a digital rectal exam. The development of new techniques such as the measurement of prostate-specific antigen (PSA) levels and the use of TRUS guided biopsies has improved the screening for prostate cancer and decreased the mortality rate [15].

2.2 Treatment of Prostate Cancer

In non-metastatic prostate cancer patients, the most frequently used treatment modalities are radical prostatectomy (removal of the prostate), radiotherapy and active surveillance. Overall, approximately 50% of men with localized prostate cancer undergo radical prostatectomy and 25% receive radiotherapy (external beam radiotherapy and/or brachytherapy) [16]. The decision-making process regarding primary treatment often depends on many factors, including TNM classification and PSA. The potential side effects profile of surgery and radiotherapy vary enormously; prostatectomy has been shown to cause more urinary incontinence and erectile dysfunction [17] [18] whereas radiotherapy causes more urinary irritation and bowel/rectal symptoms [17] [19]. The severity of treatment side effects are also often key factors in the treatment decision.
2.2.1 High Dose Rate Brachytherapy

Brachytherapy is radiation therapy treatment modality where a radiation source is placed close to, or within the tumour to be treated. Radiation is emitted from the source randomly in all directions, the intensity of which decreases following the inverse square law. Adherence to the inverse square law results in steep dose gradients around the source, allowing for large doses to be delivered to the tumour whilst still sparing surrounding OARs.

Brachytherapy can be separated into two categories; removable, and permanent source implants. HDR brachytherapy, which is the type of brachytherapy that will be investigated in this thesis, makes use of removable implants. Characteristics of HDR brachytherapy sources include; high specific activity (341 TBq/g), high dose rate (>12 Gy/hour), medium energy (average energy of gamma emission being 0.38 MeV) photons delivered for a short period of time (5-20 minutes). HDR sources were traditionally implanted manually, but recent advances in technology have allowed for remote afterloading techniques, resulting in a reduction of radiation exposure to staff. Catheters are surgically inserted directly into the tumour, usually under the guidance of US or C-arm CT. Once all the catheters have been inserted, the patient is taken for imaging from which a treatment plan is created and delivered remotely by the afterloading machine. The most commonly used HDR brachytherapy source is Ir-192.

2.3 Clinical Indications for HDR Prostate Brachytherapy

The current standard of care for intermediate and high risk prostate cancer patients involves the use of a combination of external beam radiotherapy (EBRT) and HDR brachytherapy [20]. This typically involves a prescription of approximately 46 Gy...
(in 2 Gy per fraction) to the prostate and/or lymph nodes using EBRT and a conformal boost of 15 Gy (in 1 fraction) fraction using HDR brachytherapy. However, recent technological advances in EBRT such as intensity modulated radiation therapy (IMRT), volumetric modulated radiotherapy (VMAT) and image guided radiotherapy (IGRT) as well as the use of hypofractionated schedules \[21\] have resulted in improvements in dose conformity of EBRT, allowing larger biological doses to be prescribed whilst still decreasing normal tissue toxicities \[22\]. These advancements have caused some to question the need for HDR brachytherapy in this setting and it is currently a major subject of debate in the literature \[23\]. However, there have been a number of recent studies however showing improved quality of life outcome for combined EBRT and HDR brachytherapy compared with EBRT alone \[24, 8, 25\] and several studies have reported favourable results using HDR brachytherapy alone \[26, 27\].

2.4 The Ir-192 Source

One of the most commonly used sources in HDR brachytherapy is Ir-192 (Figure 2.1), due to a number of characteristics which make it attractive for its use with the remote afterloading technique. The source has a high specific activity (341 TBq/g), allowing for relatively large amounts of activity to be contained within a small source (approximately 5 mm length and 1 mm diameter) that can be inserted into the catheters used in remote afterloading. Radiation therapy departments typically receive a source of approximately 40 $\mu$Gym$^2$/hr and the half-life of the source is 73.83 days, therefore the source can be used for up to 3 months allowing for treatments of approximately 10-20 minutes.

Ir-192 is produced by neutron bombardment of the stable Ir-191 isotope and decays by $\beta$ emission to Pt-192 95.1% of the time and through electron capture to Os-192 4.9% of the time. There are approximately 2.21 photons emitted per decay of the
source in the energy range from 9.44 to 1378.5 keV with a weighted mean energy of 354 keV (for the stainless steel encapsulated source used clinically). The complex spectrum of photon energies emitted from the source is summarised in Table 2.1, obtained from the NuDat database [1].

2.5 The TG-43 Dosimetry Protocol

In 1995 the American Association of Physicists in Medicine (AAPM) Task Group 43 released a report entitled Dosimetry of Interstitial Brachytherapy Sources [9]. In this report the task group provided a dose calculation formalism for Ir-192, I-125 and
2.5. The TG-43 Dosimetry Protocol

Table 2.1: Emission spectrum of the Ir-192 source, obtained from the NuDat database [1].

<table>
<thead>
<tr>
<th>Photon</th>
<th>Energy (keV)</th>
<th>Intensity (gamma/100decay)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X L</td>
<td>9.44</td>
<td>3.9200</td>
</tr>
<tr>
<td>X Kα2</td>
<td>65.122</td>
<td>2.6200</td>
</tr>
<tr>
<td>X Kα1</td>
<td>66.831</td>
<td>4.4400</td>
</tr>
<tr>
<td>X Kβ3</td>
<td>75.368</td>
<td>0.5310</td>
</tr>
<tr>
<td>X Kβ2</td>
<td>75.749</td>
<td>1.0210</td>
</tr>
<tr>
<td>X Kβ1</td>
<td>77.831</td>
<td>0.3640</td>
</tr>
<tr>
<td>γ</td>
<td>136.39</td>
<td>0.1990</td>
</tr>
<tr>
<td>γ</td>
<td>176.98</td>
<td>0.0043</td>
</tr>
<tr>
<td>γ</td>
<td>280.27</td>
<td>0.0080</td>
</tr>
<tr>
<td>γ</td>
<td>295.957</td>
<td>28.7100</td>
</tr>
<tr>
<td>γ</td>
<td>308.455</td>
<td>29.7000</td>
</tr>
<tr>
<td>γ</td>
<td>316.506</td>
<td>82.8600</td>
</tr>
<tr>
<td>γ</td>
<td>416.468</td>
<td>0.6700</td>
</tr>
<tr>
<td>γ</td>
<td>468.068</td>
<td>47.8400</td>
</tr>
<tr>
<td>γ</td>
<td>485.301</td>
<td>0.0047</td>
</tr>
<tr>
<td>γ</td>
<td>588.581</td>
<td>4.5220</td>
</tr>
<tr>
<td>γ</td>
<td>593.63</td>
<td>0.0420</td>
</tr>
<tr>
<td>γ</td>
<td>599.41</td>
<td>0.0039</td>
</tr>
<tr>
<td>γ</td>
<td>604.411</td>
<td>8.2160</td>
</tr>
<tr>
<td>γ</td>
<td>612.462</td>
<td>5.3400</td>
</tr>
<tr>
<td>γ</td>
<td>765.8</td>
<td>0.0013</td>
</tr>
<tr>
<td>γ</td>
<td>884.537</td>
<td>0.2920</td>
</tr>
<tr>
<td>γ</td>
<td>1061.49</td>
<td>0.0531</td>
</tr>
<tr>
<td>γ</td>
<td>1089.96</td>
<td>0.0012</td>
</tr>
<tr>
<td>γ</td>
<td>1378.5</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

Pd-103 brachytherapy sources [3]. This report was updated in 2004 (TG43-U1) to; include new brachytherapy sources released since the publication of the first report, critically reassess published brachytherapy dosimetry data, and to eliminate minor inconsistencies from the original report. The following paragraphs summarise the TG43-U1 calculation formalism. The general 2D dose rate formalism can be expressed
using the following equation:

\[
\dot{D}_r(r, \theta) = S_K \Delta \frac{G_L(r, \theta)}{G_L(r_0, \theta_0)} g_L(r) F(r, \theta)
\] (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 1 cm in this protocol, and \( \theta \) denotes the polar angle specifying the point of interest \( P(r, \theta) \), relative to the source longitudinal axis. The reference angle \( \theta = 0 \) defines the source transverse plane, and is specified to be 90 or \( \pi/2 \) radians.

Figure 2.2: TG43-U1 coordinate system used for brachytherapy dosimetry calculations.

\( S_K \) is the air kerma strength, which has units of \( \mu \text{Gym}^2/\text{h} \) (U) and is numerically identical to the quantity Reference Air Kerma Rate recommended by ICRU 38 [28] and ICRU 60 [29]. Air kerma strength is the air kerma rate \( (K_\delta(d)) \) in vacuo and due to photons of energy greater than \( \delta \), at a distance \( d \), multiplied by the square of this
distance, \( d^2 \).

\[
S_K = \dot{K}_\delta(d)d^2
\]  

(2.2)

The quantity \( d \) is the distance from the source centre to the point of air kerma rate specification which should be located on the transverse plane of the source. The energy cutoff \( \delta \), is intended to exclude low-energy or contaminant photons (e.g. characteristic x-rays originating in the outer layers of steel or titanium source cladding) that increase the air kerma rate without contributing significantly to dose at distances greater than 0.1 cm in tissue. This value \( \delta \) is typically 5 keV for low-energy photon emitting brachytherapy sources.

The dose-rate constant in water, \( \Delta \), is the ratio of dose rate at the reference position \( P(r_0, \theta_0) \) and \( S_K \). \( \Delta \) has units of cGy/Uh. The dose-rate constant depends on both the radionuclide and source model, and is influenced by both the source internal design and the experimental methodology used by the primary standard to realise \( S_K \).

The purpose of the geometry function is to improve the accuracy with which dose rates can be estimated by interpolation from data tabulated at discrete points. Physically, the geometry function neglects scattering and attenuation, and provides an effective inverse square law correction based upon an approximate model of the spatial distribution of radioactivity from within the source. The TG43-U1 protocol recommends the use of point or line source models giving rise to the following geometry functions:

\[
G_p(r, \theta) = r^{-2} \text{ point source approximation} \tag{2.3}
\]

\[
G_L(r, \theta) = \frac{B}{L_{rsin}(\theta)} \text{ line source approximation if } \theta \neq 0 \tag{2.4}
\]

\[
G_L(r, \theta) = \left( r^2 - \frac{L^2}{4} \right)^{-1} \text{ line source approximation if } \theta = 0 \tag{2.5}
\]
Where $B$ is the angle, in radians, subtended by the tips of the hypothetical line source with respect to the calculation point, $P(r, \theta)$. The protocol recommends consistent use of the line-source geometry function for evaluation of 2D dose distributions [3].

The radial dose function, $g(r)$, accounts for dose fall-off on the transverse plane due to photon scattering and attenuation i.e., excluding dose fall-off included by the geometry function and is equal to unity at $r_0 = 1$ cm.

The 2D anisotropy function describes the variation in dose as a function of polar angle relative to the transverse plane. The value of $F(r, \theta)$ off the transverse plane typically decreases as $r$ decreases, as $\theta$ approaches 180, as encapsulation thickness increases, and as photon energy decreases. The active length, $L$, used to evaluate the geometry function, should be the same used to extract the radial dose and 2D anisotropy functions. Otherwise, significant errors in dosimetry at small distances may arise.

The uncertainty in the dose rate at any given depth is calculated by computing the sum of squares of the associated uncertainties of all the factors outlined above. One also must take into account the uncertainty associated with the specified source strength (the uncertainty in the source strength given on the calibration certificate of Ir-192 sources as 5%, however according to AAPM Task Group Report 138 [30] the source strength measurement in the clinic using an appropriately calibrated well chamber yields an uncertainty of 2k6%). Thus combining all of the uncertainties yields a total uncertainty in the dose rate of 8.5-11.7% at 1 cm and 9.2-12.2% at 0.1 cm. However, the uncertainty at 0.1 cm may be even higher in brachytherapy treatment planning systems (BTPS), due to insufficient published $F(r, \theta)$ data for small angles of $\theta$ [3].

The TG43-U1 protocol is currently the standard for BTPS dose calculation, sup-
implemented by the recommendations from the AAPM and European Society for Radiotherapy and Oncology (ESTRO) on dose calculations for high energy (> 50 keV) photon emitting brachytherapy sources published in 2012 [31]. However, this type of dose calculation model is only strictly valid for calculations in homogeneous water phantoms, of the same size and shape used to obtain the model parameters [3]. This presents a severe limitation of the algorithm in regions of heterogeneous densities (metal applicators, prostate calcifications) [32], near air interfaces (breast, rectum, small bowel) [33] and for low energy brachytherapy sources (I-125) [34]. This has led to the development of model based dose-calculation algorithms (MBDCAs) where radiation transport is modelled in non-water mediums, resulting in more accurate determination of dose delivered to the patient in BTPS. A description of the guidelines for MBDCAs was developed by the AAPM Task Group 186 [35].

2.6 High Dose Rate Prostate Brachytherapy Planning and Treatment Process

The traditional CT based HDR brachytherapy process begins with the patient being placed under anaesthetic and their legs moved to the lithotomy position. TRUS is then used to determine the shape and size of the prostate and guide the insertion of catheters into the prostate [36]. The catheters enter the body via the perineum, over which a template is placed that aids in the identification of the catheters during planning and treatment. Once the required number of catheters have been inserted the patient is transferred to a CT scanner for imaging, during which a helical scan is obtained with 1 mm slice spacing [36].

The CT scan is then used for treatment planning, beginning with the contouring of the prostate, rectum, urethra and bladder by the radiation oncologist (RO) on the
2.6. High Dose Rate Prostate Brachytherapy Planning and Treatment Process

BTPS. Digital reconstruction of the catheters is then performed by the brachytherapy team, followed by the selection of the type of optimisation to be used in creating the treatment plan. Plan optimisation can be performed via a number of methods, the most common of which usually involves a method of inverse planning. Inverse Planning is the process through which the TPS determines the dwell positions and times of the HDR source within the catheters in order to best shape the dose distribution around the PTV and minimize the dose to the OARs [37].

Once the plan has been approved by the RO the plan is transferred to the treatment console system (TCS) and some treatment plan checks are performed by the brachytherapy team. The patient is then transferred to the brachytherapy treatment bunker and catheters connected to the HDR remote brachytherapy afterloader. The afterloader receives treatment plan data from the TCS and controls the placement of the Ir-192 source through each catheter [38]. The Ir-192 source is welded to a steel cable that is wound around a drum inside of the afterloader device, positioning of the source is achieved through rotation of the drum using stepper motors varying the source position through the desired catheter for a time specified by the TCS [38].

One example of a HDR brachytherapy remote afterloader is the Flexitron HDR afterloader produced by Elekta (Elekta Brachytherapy, Veendendaal, The Netherlands). The afterloader is able to support up to 40 catheters and a minimum step size of 1 mm. The Ir-192 source positioning accuracy has been shown to be better than ± 0.5 mm and a dwell time resolution 0.1 seconds has been proven [39]. The Flexitron HDR afterloader will be investigated in this thesis.
2.7 High Dose Rate Brachytherapy Mistreatments and the Requirement for Quality Assurance

2.6.1 Transrectal Ultrasound Based High Dose Rate Prostate Brachytherapy Planning

The use of TRUS for treatment planning has been increasing rapidly in recent years due to its excellent visibility of the prostate and surrounding OARs \[10\]. Modern TPSs are able to use the US echoes of the implanted catheters for the definition of the catheter position within the patient, allowing for real-time HDR pBT treatment planning \[11\]. This technique results in a dramatic decrease in the time required for the HDR pBT planning and treatment process, from 4-6 hours down to approximately 2 hours \[40\]. The major advantage of this is the removal of the requirement to correct for catheter displacements relative to the prostate in the time between imaging and treatment, which has been shown to be strongly correlated with time \[41\]. The definition of the catheter position however strongly affects the dose distribution in brachytherapy, and as this is a new technique there is a need for more comprehensive pre-treatment or in-vivo QA \[10\]. A more detailed description of the real-time TRUS based HDR pBT workflow will be given in future chapters of this thesis.

2.7 High Dose Rate Brachytherapy Mistreatments and the Requirement for Quality Assurance

There are a number of published documents by the International Commission on Radiological Protection (ICRP) \[42, 43\] as well as the International Atomic Energy Association (IAEA) \[44\] that describe errors that have occurred in HDR brachytherapy. Many of these errors are related to human miscalculations, less often they are due to machine or computational malfunction. Some examples of human errors include incorrect source strength entered into the planning system, patient misidentification, incorrect site of treatment, incorrect prescription, incorrect catheter connection or incorrect
applicator placement. Other errors that may occur include; mistakes or uncertainties in identification of applicator length on 3D imaging, incorrect import/export of treatment plan from planning system and organ/applicator movement between imaging and treatment [44]. The likelihood of remote afterloader malfunction is generally considered as extremely low, however small deviations from the plan in source dwell position and time can result in significant errors in the dose delivered to the patient [45].

A successful HDR brachytherapy treatment is one where the source is driven to the planned position, in the planned catheter, for the desired amount of time. Successful execution of these three parameters will ensure that the delivered dose distribution matches the one calculated by the brachytherapy TPS. With the introduction of inverse planning optimisation techniques, the complexity of HDR brachytherapy treatment planning has increased significantly. Therefore, it is essential that QA techniques continue to evolve at the same rate. The AAPM Radiation Therapy Task Group No.59 recommends that institutions employ a QA program that exploits redundancy, and review the entire treatment planning and delivery process to isolate any actions susceptible to errors. The report suggests that incidence of these errors may be reduced by the introduction of pre-treatment QA in the time between treatment planning and delivery [38]. Further to this, another AAPM Report from the Radiation Therapy Task Group 56 recommends that the source position, source dwell time and transit time be quantified by the medical physicist on a regular basis [36]. A combination of these regular and pre-treatment QA checks, along with a well-documented treatment planning and delivery protocol will go a long way to ensuring safe and successful delivery of HDR brachytherapy treatment plans.

However, this type of QA program will not safeguard the HDR brachytherapy delivery from all types of errors. More recently, the AAPM published the Task Group
100 report, which describes a risk based approach to the development of quality management (QM) [2]. It has been shown in some publications that this type of approach to QM may result in an improved QA program when compared to more traditional methods of QM [46].

Therefore, an ideal QM program for HDR pBT should be one that considers all potential errors in the treatment planning and delivery process, and may be supplemented by a system that provides real-time identification of the dwell positions, measure the dwell and transit times, and compare these parameters with the prescribed treatment plan both before and during treatment [47].

2.8 Current Methods of High Dose Rate Brachytherapy In-vivo Dosimetry

One method of performing IVTV for HDR brachytherapy is through the use of IVD. IVD for HDR brachytherapy has been referenced in international recommendations as far back as 1985 by the International Commission on Radiation Units and Measurements (ICRU) [48]. Since this time, the complexity of brachytherapy has increased exponentially due to the introduction of remote afterloading devices, three-dimensional (3D) imaging and inverse planning. However, despite this increase in complexity, systematic patient specific QA of dose delivery is still not performed. Additionally, the large dose per fraction (>5 Gy) delivered during brachytherapy treatments means that the consequence of an error in the dose delivery process may be substantial compared to EBRT [44]. Therefore, IVD in HDR brachytherapy should be considered an essential part of the treatment QA process. Unfortunately, performing accurate and precise IVD in brachytherapy is extremely difficult due to the challenges of precise detector positioning and the high dose gradient fields.
2.8. Current Methods of High Dose Rate Brachytherapy In-vivo Dosimetry

There are a number of published documents by the ICRP [43, 42] as well as the IAEA [44] that describe errors that have occurred in HDR brachytherapy. A number of these errors can be identified by a rigorous brachytherapy QA schedule and manual safety checks prior to treatment. However, not all of these errors can be covered by such checks. In these cases, routine IVD can be a useful tool to complement QA and manual checks prior to treatment for HDR brachytherapy.

2.8.1 Challenges associated with HDR Brachytherapy In-vivo Dosimetry

Brachytherapy dose distributions, especially at close distances to the source, are characterized by steep gradients (e.g. 50%/mm at 4 mm distance and 6%/mm at 20 mm distance). Because of this, accurate detector positioning is crucial in IVD and small uncertainties in positioning can lead to unacceptably large deviations in measured dose [49].

Another major challenge for IVD in HDR brachytherapy is the energy dependence of the detectors used in energy range of Ir-192. The energy dependence of the detector is defined as the dependence of the detector reading as a function of the absorbed dose in water on the photon or electron energy spectrum. This has implications both for calibration of the dosimeter and for conversion of detector reading into measured dose during patient measurements, as the energy spectrum measured by the dosimeter changes significantly with distance from the source [49].

2.8.2 Thermoluminscent Dosimeters

Thermoluminescent dosimeters (TLDs) have historically been used for IVD in HDR brachytherapy [50]. Lithium Fluoride (LiF) TLD rods have been the most widely used due to their ability to fit into catheters. However, TLDs require special handling
procedures, individual calibration and a long annealing process which does not allow them to give an instantaneous read-out. When considering these limitations, it can be established that there are other dosimeters that are more suitable for IVD in HDR brachytherapy.

### 2.8.3 Semiconductor Diodes

Conversely, semiconductor diodes to have the advantage of providing the user with an instantaneous read-out. They also have the desirable dosimetric characteristics of high sensitivity (approximately 18,000 times higher than an ionisation chamber of the same volume), mechanical stability and small physical dimensions (typically of the order of 1 mm). However, they also have the undesirable dosimetric characteristics of energy and directional dependence, temperature dependence and changes in radiation sensitivity due to radiation damage. Although, these undesirable characteristics can be measured and accounted for using phantom measurements prior to clinical application. Two studies exist in which a diode array manufactured by PTW was used for IVD for patients undergoing HDR brachytherapy treatments [51, 52]. Seymour et al. [51] performed IVD inside the rectum for prostate HDR brachytherapy patients. When comparing against the TPS, measured values ranged from -42% to +35%. Waldhaeusl et al. [52] used the same rectal probe and a bladder probe consisting of a single diode for IVD of cervix HDR brachytherapy treatments. Their measured values, when compared against the BTPS ranged from -31% to +90% for the rectum and -27% to +26% for the bladder. These results re-enforce the notion that performing accurate and precise IVD in brachytherapy is extremely difficult due to the challenges of precise detector positioning and the high dose gradient fields.
2.8.4 MOSFETs

MOSFET detectors have similar advantages and disadvantages to diodes in their application to IVD of HDR brachytherapy. Although unlike diodes, their temperature dependence can be overcome by using specially designed dual-MOSFT-dual bias detectors [53]. They can also be produced in smaller size compared to diodes (typically by an order of magnitude), allowing them to be placed inside intraluminal catheters and even needles. One example of their application in HDR brachytherapy is their characterization of Leipzig surface dose applicators, which were found to agree with Monte Carlo simulations to within 3% [54].

Mason et al. performed IVD for HDR pBT by placing a single MOSFET into an additional needle [55]. An expanded measurement uncertainty was calculated to be 31.9% and 12.3% per needle and per plan, respectively (k=2). The largest contributor to measurement uncertainty was attributed to the positional uncertainty of the MOSFET relative to the source (13.0% and 4.1% per needle and per plan, respectively). An error detector threshold of this magnitude is unacceptably large and could result in errors going undetected by the system.

Carrara et al. have demonstrated an improved measurement uncertainty using MOSFET dosimeters (namely MOSkin dosimeters), through coupling of the dosimeters to the TRUS probe during HDR pBT [56, 57]. By coupling the MOSkin dosimeters to the TRUS probe, the uncertainty of relating the position of the dosimeters relative to the source was reduced significantly. Consequently, in-vivo measurements over 18 treatment fractions yielded an agreement with treatment planning predicted doses to within 3.6% ± 1.9% [57]. It is this type of approach that will be reproduced in this thesis.
2.8. Current Methods of High Dose Rate Brachytherapy In-vivo Dosimetry

2.8.5 Optically Stimulated Luminescent Dosimeters

Recent advances in optically stimulated luminescence dosimeters (OSLDs) have proven their ability to operate in a mode that allows real-time information about the dose rate during irradiation. These systems are not yet commercially available, however a prototype developed by Anderson et al. [58] was examined in order to determine its ability to identify dose delivery errors in HDR brachytherapy. The system was capable of measuring absorbed dose rate directly inside the tumour using small OSL dosimeters fit inside standard needles, with a time resolution of 0.1 seconds. The combined estimated uncertainty of the system was calculated to be 8% (standard deviation).

2.8.6 Plastic Scintillation Dosimeters

Plastic scintillation dosimeters (PSDs) have also been considered for IVD of HDR brachytherapy. They have the added advantage of relative energy independence and water equivalence when compared with many other dosimeters considered for this application. Lambert et al. compared PSDs to MOSFET, diamond and TLD detectors in a phantom study [50]. The study concluded that based on size, accuracy and real-time possibilities, PSDs showed the best combination of characteristics to perform IVD in HDR brachytherapy. Cerenkov light production however has also been identified in the optical guide used in PSD systems [59] [60]. This component, often referred to as stem effect, is produced in the fibre when struck by electron radiation over a certain energy threshold, and needs to be removed in order to perform accurate dosimetry. A number of different methods have been proposed to account for this effect [61] [62].
2.8.7 Radiochromic Film

Radiochromic films have not traditionally been considered for IVD of HDR brachytherapy treatments. The advantage of radiochromic films over other dosimeters is their spatial resolution, which is unmatched, as well as the lack of directional dependence. However, these films require special handling procedures, and a significant amount of processing before they are able to be analysed. Furthermore, they are unable to be cut into small pieces (which would allow the films to fit into catheters), as the accuracy of the measured dose in regions close to the edge of the film is suboptimal [63]. Consequently, there is only a small amount of published literature on the topic of IVD for HDR brachytherapy using radiochromic films [64, 65], most of which are related to skin dose measurements [66, 67].

2.9 Current Methods of High Dose Rate Brachytherapy In-vivo Source Tracking

Another, more recently developed method, of performing IVTV in HDR brachytherapy is in-vivo source tracking. Unlike IVD, where the dose delivered to a detector is placed within the patient is verified, in-vivo source tracking attempts to track the position of the HDR brachytherapy source in three-dimensions as it steps through the patient delivering the treatment. An ideal solution for this method is able to track the source in real time, verifying both the dwell positions and dwell times, whilst having the ability to interrupt the treatment if any deviation is found.

2.9.1 Flat Panel Detectors

Smith et al. [68] present the characterization of the response of an a-Si electronic portal imaging device (EPID) embedded in a customized carbon fibre couch top to an
Ir-192 HDR brachytherapy source, demonstrating its use as a QA tool and assessing its potential for use as a HDR brachytherapy source tracking system. Source position measurements were validated using contact films placed against the catheter during measurements. All source x and y coordinates were measured to be within 0.5 mm of the programmed source positions. The mean error across all measurements was 0.01 mm. Smith et al. [69] also directly compared a delivered treatment using the measured EPID signal against the treatment plan in a phantom study. The EPID measured dwell positions were directly compared against those predicted by the TPS. Average dwell position variation was found to be 0.6 mm (S.D. = 0.3 mm and max = 1.4 mm). Fonseca et al. have replicated the work by Smith et al. on a separate EPID device, achieving similar results [70].

In a further study, Smith et al. retrospectively compared the planned versus measured source positions using an EPID embedded into the couch for 8 treatment fractions, and the mean linear distance between the planned and measured dwell positions was found to be 1.8 mm (range 0.7 to 3.9 mm) [71].

### 2.9.2 Detector Arrays

HDR brachytherapy source tracking has also been demonstrated using 2D diode arrays [39, 47, 72, 73]. Manikandan et al. first used a commercial 2-D array of ionisation chambers known as the IMatriXX (IBA, GmBH) and found that with brachytherapy catheters placed directly over the array the dwell positions of the Ir-192 source could be identified to within 1.18 mm [73]. Espinoza et al. further developed this concept through the use of an 11 x 11 2D diode array (Magic Plate 121, MP121) packaged in a specially designed Magic Phantom for pre-treatment checks of remote HDR brachytherapy treatment plan [39].

Espinoza et al. performed a further study, testing the source triangulation algo-
Current Methods of High Dose Rate Brachytherapy In-vivo Source Tracking

2.9. Current Methods of High Dose Rate Brachytherapy In-vivo Source Tracking

Algorithm in combination with the MP121 for 20 catheter treatment plans created by the Oncentra (Elekta Brachytherapy, Veenendaal, The Netherlands) BTPS [47]. Using the algorithm, the MP121 was able to accurately track the source position, with 75% of the measurements falling within 0.5 mm. Dwell times, as well as source transit times were also determined.

Finally, the MP121 has also been shown to be able to reconstruct source positions to within 1 mm even when the source is placed approximately 12 & 15 cm away from the detector plane in a solid water phantom, easily resolving the 2 mm step size of the source as it moves through the phantom [74]. This final study demonstrates the potential of the MP121 for in-vivo source tracking in HDR pBT, as this is the approximate distance the MP121 would be placed away from the source during in-vivo studies.

2.9.3 Point Detectors

In-vivo source tracking during HDR pBT with point dosimeters has also been exhibited in the literature through several publications [75, 76, 77]. Johansen et al. demonstrated this approach through implementation of a single radioluminescent crystal placed into a dedicated needle during HDR pBT [75]. In this scenario, only radial and longitudinal shifts of the source relative to planned positions were detected, due to only a single point detector being used. Rosales et al. also performed source tracking inside a dedicated needle, this time with a multi-point plastic scintillator dosimeter [77]. For these experiments three dosimeters were placed inside the dedicated needle for source tracking of a HDR brachytherapy treatment and achieved a source tracking accuracy of approximately 1.8 1.6 mm, and a dwell time verification accuracy of less than 0.1 seconds.
2.9. Current Methods of High Dose Rate Brachytherapy In-vivo Source Tracking

2.9.4 Pinhole Collimator Devices

Pinhole collimator devices have also been used in for source tracking, with several publications in the literature illustrating this [78] [79] [80]. Safavi-Naeini et al. used a prototype high resolution pixelated silicon detector array, coupled with a multi-pinhole tungsten collimator (known as the BrachyView) to track a HDR source in phantom [78]. The study demonstrated an ability of the BrachyView to track the source to within 1.3 mm. Alnaghy et al. used the same BrachyView system, this time coupled with a TRUS probe, to perform HDR source source with simultaneous TRUS image fusion [79]. In this study, it was shown that the BrachyView was able to resolve dwell times down to 0.3 seconds, and measure dwell positions to within 1 mm for 78% of the planned dwell positions in a prostate gel phantom. More importantly however, coupling of the BrachyView to the TRUS probe also results in a smaller combined uncertainty when transforming coordinate systems between the BrachyView and the TRUS probe, which is the imaging device used for treatment planning in real-time HDR pBT [80].

2.9.5 Electromagnetic Tracking

Electromagnetic tracking (EMT) systems have also shown promise in the field of IVTV of HDR pBT [81] [82] [83]. Poulin et al. have shown that EMT systems have sufficient accuracy and precision in brachytherapy theatre environments [82] and Damato et al. have demonstrated that EMT systems can also detect some common brachytherapy treatment errors including catheter swaps and reconstruction errors [81]. The EMT systems have also been incorporated into BTPS for TRUS based HDR pBT and used for accurate and efficient reconstruction of catheters [83]. Finally, prototype HDR brachytherapy afterloaders are being produced with EMT systems in-built for the purpose of catheter reconstruction and transfer tube connection QA [84]. Whilst
these EMT systems show promise for HDR brachytherapy IVTV, there are limitations of the approach. For example, the source being used to treat the patient is not being tracked in this approach, and therefore the EMT systems may not be able to detect all types of errors that may occur in the HDR brachytherapy planning and treatment process, such as incorrect reference length being used in the BTPS, as well as all dwell time errors.
Chapter 3

The Geant4 Monte Carlo Toolkit

The Geant4 toolkit is a general purpose C++ based code that was developed by CERN for high energy particle physics applications. Geant4 is able to simulate the transport of many types of particles, including the interactions of low energy particles which have been added in recent years. The toolkit also provides basic functionality of simulation as to describe detector geometry and materials, to transport particles and to describe the detector response. This makes Geant4 an attractive tool for the simulation of a variety of applications in radiotherapy physics, including brachytherapy [85].

Geant4 electromagnetic physics manages the electromagnetic interactions of photons, electrons, protons and ions over an energy range from 1 eV up to 1000 PeV. The physics processes that can be modelled in Geant4 include: multiple scattering, ionization, bremsstrahlung, positron annihilation, photoelectric effect, Compton and Rayleigh scattering, pair production, synchrotron and transition radiation [85]. There are two main packages within Geant4 that handle alternative approaches to model the electromagnetic interaction of particles with matter; the Standard, and Low Energy Package [86].

The Low Energy Package used in this thesis is able to handle ionization by primary particles. It handles the interactions of electrons, positrons, photons, charged hadrons
3.1. User Action Classes

and ions, offering different sets of models for each of the physics processes involved
[86]. Below 1 keV the interactions are described by the free electron gas model, in the
intermediate energy range (between 1 keV and 2 MeV) parameterized models based on
experimental data from the ICRU are used and above 2 MeV the Bethe-Bloch formula
is applied [85].

The Geant4 MC toolkit requires the user to write his or her own C++ program
using classes which inherent behaviour from kernel Geant4 classes [85]. The kernel
Geant4 classes are grouped in independent categories, with defined roles, as shown
in Figure 3.1. The classes which need to be implemented in developing a Geant4
application are described in the following sections.

3.1 User Action Classes

These are virtual classes whose methods control the geometry of the simulation, the
definition of particles, their physics processes, and the generation of primary particles
[86]. They also control the flow of the simulation and allow the retrieval of useful
information concerning track structure, interactions, energy depositions, etc. in the
simulation of the experimental set-up.

3.1.1 G4UserDetectorConstruction

This base class controls the definition of the experimental setup, in terms of geometrical
components and material composition. A geometrical component is defined in terms
of shape, material, positions and rotation in the experimental setup. Visualisation
attributes can be defined at this level, to allow the visualisation of the experimental
setup [86]. In a Geant4 simulation the detector is just a component of the experimental
setup, declared sensitive, where the user can retrieve information about the hits. A
hit is a snapshot of the physical interactions of a track in the sensitive region of the
detector. The concept of a track represents the physics information (position, energy deposition, mass, spin, etc.) of the particle under propagation [87].

### 3.1.2 G4VUserPhysicsList

There are three methods of this class which must be implemented.

The ConstructParticle method defines all particles involved in the experimental setup. Geant4 provides the implementation of all of the particles defined in the Particle Data Group Book [86], however the particles involved in the experimental setup of the simulation must be explicitly invoked in this method [87].

The ConstructProcess method determines the models of interaction for these particles. All interaction processes are treated in the same manner from the tracking point of view, this enables the user to create a process and assign it to a particular particle type. This transparency allows the customization of physics processes by individual users [87].

The final method is SetCuts which determines the threshold of production of secondary particles, expressed in range. If a secondary particle is generated with a residual range in the material less than this value, the particle will not be generated and tracked, but its energy will be considered locally deposited in the medium. Otherwise, if the secondary particle energy is greater than the range cut the secondary particle will be generated and tracked [87].

To support the users, the Geant4 collaboration provides examples of Physics Lists realised within the toolkit every six months, to be activated directly in the specific Geant4 application.
3.1.3 G4VUserPrimaryGeneratorAction

This class allows modelling of the radiation field in the experimental setup of the simulation, in terms of the type of particle, polarisation, position, direction, energy and time. The number of primary particles to be generated in one event must also be defined. An event consists of a collection of primary particles to be tracked [86].

3.1.4 G4VUserEventAction

An event in Geant4 begins with the initiation of tracking one or more primary particles and finishes with the completion of tracking all secondaries [87]. The G4BUserEventAction class possesses two virtual methods which are invoked at the beginning and at the end of each event, the BeginOfEventAction and the EndOfEventAction, respectively.

3.1.5 G4UserRunAction

The concept of a run in Geant4 is to keep a set of events to be simulated using the same detector geometry, the same event generator and the same physics processes [87]. The G4UserRunAction class has several methods. One method that is commonly used is the BeginOfRunAction method which is invoked before entering the simulation event loop. The second is EndOfRunAction which is invoked at the very end of the event processing.

3.1.6 G4UserSteppingAction

The concept of a run in Geant4 is to keep a set of events to be simulated using the same detector geometry. The tracking category manages the propagation of a particle through the detector taking into account its physics interaction with matter. The concept of a step in Geant4 describes the transport of a particle between two points
3.2 Interface Commands

Geant4 has various built-in user interface commands. These commands can be used interactively via a user interface (GUI), or in batch mode in a macro file. User defined commands can be implemented in user defined classes, inheriting behaviour from the G4UIMessenger base class, which represents a messenger that delivers these commands to a class object. These commands are particularly useful when the geometry, primary beam, or physics parameters need to be altered between simulations. In this way, one may execute several simulations using a macro file, containing a number of suitable commands, to change the experimental setup ad-hoc.

3.3 Visualisation

Geant4 has the ability to visualise particle trajectories, detector components and interactions of particles within these detector components. Despite the fact that there are many methods available for visualisation, the one employed in the simulations described in this thesis is the OpenGL driver. The OpenGL driver is the most useful for visualising and debugging the detector components as well as the locations of particle interactions occurring within the geometry.

3.4 Geant4 in the Field of Brachytherapy

Geant4 has been proven to be a trusted tool in the field of brachytherapy in a significant number of publications over the past decade. Firstly, Geant4 has been used to
contribute towards the consensus TG43 dosimetry parameters used in the brachytherapy dose calculation formalism \cite{4}. Geant4 has also been used to estimate dose to organs at risk in specific brachytherapy applications such as breast brachytherapy \cite{88} and eye plaque brachytherapy \cite{89}. Finally, the Geant4 toolkit has also been used as the dose calculation engine for a clinical brachytherapy treatment planning system \cite{90}. These are just some of the examples in the literature that demonstrate Geant4 as a proven toolkit for the use of accurate brachytherapy dose calculations.
3.4. Geant4 in the Field of Brachytherapy

Figure 3.1: Schematic of Geant4 toolkit class hierarchy
Chapter 4

A Risk based Approach to Development of Ultrasound-guided High Dose Rate Prostate Brachytherapy Quality Management

4.1 Introduction

With the introduction of complex processes, such as TRUS based HDR pBT planning and delivery, a more intensive and robust QA system is needed. Prescriptive approaches to HDR brachytherapy QA are provided in the AAPM Task Group Reports 56 [36] and 59 [38]. Williamson [91] reviewed published brachytherapy misadministrations in 2008 and found that almost 40% of these were related to: image

---

misinterpretation, implanting the wrong organ due to poor image quality, and failure to verify the needle position. It is therefore beginning to be acknowledged in the brachytherapy community that prescriptive methods of QM may not be sufficient in HDR brachytherapy to prevent serious errors in the treatment planning and delivery process.

Despite its long standing use in industry, the use of failure modes and effects analysis (FMEA) in radiation oncology has been comparatively recent \[2\]. Over the past several years, the number of publications applying FMEA to radiation oncology has increased dramatically. For EBRT, FMEA has been successfully applied to IMRT \[2\], intraoperative radiation therapy \[92\], stereotactic body radiotherapy \[93\], amongst many others.

FMEA has also been shown to be effective for HDR brachytherapy. Swamidas et al. \[94\] identified 20 failure modes specific to intracavitary HDR brachytherapy, including aspects of treatment planning, source strength measurement and applicator QA. Mayadev et al. \[12\] also performed FMEA on intracavitary HDR brachytherapy and found 170 failure modes, the highest ranking of which were applicator instability and communication failures after patient simulation. Wadi-Ramadi et al. \[95\] examined potential failure modes during HDR brachytherapy leading to the incorrect treatment volume.

The aim of the work presented in this chapter is to apply a risk based approach to the development of a QM program for TRUS based HDR pBT treatment planning and delivery using Oncentra Prostate BTPS (Elekta Brachytherapy, Veenendaal, Netherlands) \[10\] \[82\]. To achieve this aim, an FMEA approach was considered. Detection of high-risk failure modes in the TRUS based HDR pBT treatment planning and delivery process allows a tailored approach to the development of QM and identifies whether there is a need for IVTV through either IVD or source tracking.
4.2 Materials & Methods

4.2.1 TRUS Based Real-Time HDR pBT Technique

At St George Hospital Cancer Care Centre (STGCC), TRUS based HDR pBT is planned using the Oncentra Prostate BTPS (Elekta Brachytherapy, Veenendaal, Netherlands). After patient sedation and preparation, the patient is placed in the dorsal lithotomy position and the TRUS probe (covered by an endorectal balloon) is inserted by the RO. A 3D US image is then acquired through sagittal rotation of the probe and the RO contours the prostate, urethra and rectum on the 3D US image. A 6-mm Foley catheter inserted during patient preparation is visualized on the US images and used to aid contouring of the urethra. The STGCC protocol defines the contours for the rectum and the urethra to extend 10 mm caudally from the apex and 10 mm cranially from the base. The urethra contour also includes the bladder neck, based on the US visible filled part of the bladder.

Following this, the RO inserts Proguide plastic catheters (Elekta Brachytherapy, Veenendaal, Netherlands) guided by the live US images, and a physicist simultaneously identifies only 1 or 2 points of the catheters on the BTPS. A urologist is present to assist with insertion of the plastic catheters if required.

Table 4.1: DVH metric coverage planning goals used in our institution.

<table>
<thead>
<tr>
<th>DVH Parameter (%)</th>
<th>Planning Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate (V100%)</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Prostate (V150%)</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Prostate (V200%)</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>Urethra (D1cc)</td>
<td>&lt;120%</td>
</tr>
<tr>
<td>Rectum (D2cc)</td>
<td>&lt;70%</td>
</tr>
</tbody>
</table>

A second 3D US image set is then acquired, and the prostate, urethra and rectum volumes adjusted accordingly. Final reconstruction of the catheters is performed by the physicist and RO on the second image set. After reconstruction, the catheter
4.2. Materials & Methods

tips are adjusted using a manual measurement of the free length of catheter extending beyond the template [40]. This measurement is checked against the catheter tips in the BTPS and independently verified using a fluoroscopic image by the radiation therapist. DVH based inverse optimization is then performed to determine source dwell positions and times. Dwell positions are activated every 3 mm within the prostate volume. The DVH based planning aims are shown in Table 4.1. Immediately following planning, QA checks are performed by the physicist and radiation therapist [40]. The treatment is delivered with the patient still in the dorsal lithotomy position and TRUS probe in place. Typical times required for each step in the workflow are given in Table 4.2.

Table 4.2: Time required for each step in the TRUS based real-time HDR pBT workflow

<table>
<thead>
<tr>
<th>Action</th>
<th>Typical Time Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquisition of pre-implant 3D TRUS images</td>
<td>5 min.</td>
</tr>
<tr>
<td>Contouring of prostate and OARs</td>
<td>10 min.</td>
</tr>
<tr>
<td>Implant &amp; identification of all catheters</td>
<td>20 min.</td>
</tr>
<tr>
<td>Acquisition of post-implant 3D TRUS images</td>
<td>5 min.</td>
</tr>
<tr>
<td>Adaptation of contours onto post-implant image</td>
<td>5 min.</td>
</tr>
<tr>
<td>Reconstruction of all catheters</td>
<td>30 min.</td>
</tr>
<tr>
<td>Dose prescription &amp; optimization</td>
<td>10 min.</td>
</tr>
<tr>
<td>Plan review &amp; approval</td>
<td>5 min.</td>
</tr>
<tr>
<td>Quality assurance checks</td>
<td>10 min.</td>
</tr>
<tr>
<td>Plan transfer &amp; delivery</td>
<td>10 min.</td>
</tr>
<tr>
<td>Total</td>
<td>110 min.</td>
</tr>
</tbody>
</table>

3D = three-dimensional

TRUS = trans-rectal ultrasound

OAR = organ at risk
4.2. Materials & Methods

4.2.2 Process Map

A process map of the TRUS based HDR pBT planning and delivery process was developed initially by three physicists, one radiation therapist and two RO’s familiar with the treatment. Each team member firstly developed their own process map and identified failure modes at each step in the process. Individual process maps and failure modes were then discussed and amalgamated at a multi-disciplinary team meeting. In this analysis, all potential failure modes were considered, regardless of the current QA program.

4.2.3 Failure Modes and Effects Analysis

Individual team members scored each of the failure modes identified in the process map according to likelihood of occurrence (O), severity (S) and detectability (D). Each parameter (O, S, D) was given a score from 1 (less likely to occur, less severe, easy to detect) to 10 (more likely to occur, more severe, hard to detect) using the AAPM TG 100 formalism [2], as shown in Table 4.3. Scoring for severity was determined using the descriptions in Table II of the AAPM TG 100 report [2]. Scores for O, S and D for each failure mode were then multiplied together to give an risk priority number (RPN) ranking. Finally, RPN rankings for each failure mode were then averaged amongst the team members.

From the RPN rankings, the multidisciplinary team determined a QM schedule to minimise risk at each stage of the TRUS based HDR pBT planning and delivery process and determine the necessity for IVD/source tracking.
4.2. Materials & Methods

Table 4.3: Scoring of occurrence (O), severity (S) and detectability (D) as per the AAPM TG 100 formalism [2].

<table>
<thead>
<tr>
<th>Rank</th>
<th>Occurrence (O)</th>
<th>Severity (S)</th>
<th>Detectability (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Qualitative</td>
<td>Frequency(%)</td>
<td>Qualitative</td>
</tr>
<tr>
<td>1</td>
<td>Failure unlikely</td>
<td>0.01</td>
<td>No effect</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.02</td>
<td>Inconvenience</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.05</td>
<td>Inconvenience</td>
</tr>
<tr>
<td>4</td>
<td>Relative few failures</td>
<td>0.1</td>
<td>Minor dosimetric error</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>&lt;0.2</td>
<td>Limited toxicity or tumour underdose</td>
</tr>
<tr>
<td>6</td>
<td>Occasional failures</td>
<td>&lt;0.5</td>
<td>Wrong dose, dose distribution, location, or volume</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>&lt;1</td>
<td>Potentially serious toxicity or tumour underdose</td>
</tr>
<tr>
<td>8</td>
<td>Repeated failures</td>
<td>&lt;2</td>
<td>Possible very serious toxicity or tumour underdose</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>&lt;5</td>
<td>Very wrong dose, dose distribution, location or volume</td>
</tr>
<tr>
<td>10</td>
<td>Failures inevitable</td>
<td>&gt;5</td>
<td>Catastrophic</td>
</tr>
</tbody>
</table>
4.3 Results

4.3.1 Ultrasound based high dose rate prostate brachytherapy process map

During process mapping, 7 major processes in the TRUS based HDR pBT planning and delivery process were identified, as shown in Figure 4.1. This major process map was then used to identify minor processes, from which an FMEA was performed to identify potential failure modes during each minor process.

1. Patient & Equipment Setup
2. Catheter Insertion
3. Imaging & Structure Definition
4. Catheter Reconstruction
5. Dose Optimisation & Prescription
6. Plan Evaluation
7. Plan Transfer & Delivery

Figure 4.1: Major process map for ultrasound based HDR pBT planning and delivery.

4.3.2 Failure Modes and Effects Analysis based Quality Management

From the FMEA, the authors identified 35 potential failure modes within the 7 major processes shown in Figure 4.1. A full list of potential failure modes sorted according to
rank are presented in Table 4.4. The failure mode with the highest RPN was identified to be mislabelling of catheters/incorrect transfer tube connected. The failure mode with the highest occurrence (O = 8) was the US grid settings being changed. This failure mode was ranked 13th overall though according to RPN due to its relatively high detectability. The failure mode with the highest severity (S = 9) was the incorrect source details being entered into the BTPS/afterloader. This failure mode ranked 2nd overall according to RPN. Finally, the failure mode with the lowest detectability (D = 8) was the error in drive cable positioning during patient treatment. This failure mode was ranked 3rd overall according to RPN. Only 2 potential failure modes (5.4%) had an average RPN greater than 200, 21 (55.3%) had an average RPN between 100-200 and 15 (39.0 %) had an average RPN between 0-99. Potential failure modes with the highest RPN were observed to have high severity (S >7) and low detectability (D >6), but low occurrence (O >6).

Table 4.4 also summarises which failure modes would potentially be detectable by IVTV. As can be seen from Table 4.4, IVTV is able to detect 25/35 (71%) of identified failure modes, including 9/10 (90%) of the 10 highest ranked failure modes.

Table 4.4: Failure modes identified during FMEA process, ranked according to RPN.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Failure Mode</th>
<th>O</th>
<th>S</th>
<th>D</th>
<th>RPN</th>
<th>Detectable by IVTV?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mislabelling of catheters/incorrect transfer tube connection</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>245</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Incorrect sources details in BTPS/afterloader</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>216</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### 4.3. Results

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Error in drive cable positioning during patient treatment</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>192</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Incorrect reconstruction of catheter points due to imaging artefacts</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>180</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Incorrect OAR contour</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>180</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Error in TRUS stepper distance encoder calibration</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>175</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Error in TRUS stepper rotation encoder calibration</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>168</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Incorrect catheter free length used in BTPS</td>
<td>3</td>
<td>8</td>
<td>7</td>
<td>168</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Incorrect distance from template to TRUS transducer entered into BTPS</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>168</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>TRUS grid not locked after insertion of catheters</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>168</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Incorrect target contour</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>150</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>Entire prostate not in final volume acquisition</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>150</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>TRUS grid settings changed</td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>144</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>Coordinate system origin not set/set incorrectly in BTPS</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>140</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### 4.3. Results

<table>
<thead>
<tr>
<th>No.</th>
<th>Error Description</th>
<th>Count 1</th>
<th>Count 2</th>
<th>Count 3</th>
<th>Count 4</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Catheters shifted in time between volume scan and treatment</td>
<td>4</td>
<td>7</td>
<td>5</td>
<td>140</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>Perforation of urethra/rectum during catheter insertion</td>
<td>4</td>
<td>7</td>
<td>5</td>
<td>140</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>Incorrect reference length entered into BTPS</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>140</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>Incorrect prescription dose entered into BTPS</td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>135</td>
<td>No</td>
</tr>
<tr>
<td>19</td>
<td>DVH grid used for plan assessment too coarse</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>126</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>Incorrect grid position selected during catheter reconstruction</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>125</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
<td>TRUS probe removed before treatment</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>120</td>
<td>Yes</td>
</tr>
<tr>
<td>22</td>
<td>Catheter tips not visible in final volume acquisition</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>100</td>
<td>Yes</td>
</tr>
<tr>
<td>23</td>
<td>Incorrect reconstruction due to complex catheter placement</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>96</td>
<td>Yes</td>
</tr>
<tr>
<td>24</td>
<td>Inability to detect catheter during reconstruction due to shadowing</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>90</td>
<td>Yes</td>
</tr>
<tr>
<td>No.</td>
<td>Issue Description</td>
<td>Count</td>
<td>Level 1</td>
<td>Level 2</td>
<td>Level 3</td>
<td>Resolution</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------------------------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>25</td>
<td>TRUS image settings changed</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>84</td>
<td>Yes</td>
</tr>
<tr>
<td>26</td>
<td>Suboptimal optimisation due to not applying changed after manual optimisation</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>72</td>
<td>No</td>
</tr>
<tr>
<td>27</td>
<td>Poor image quality due to poor contact between TRUS and rectal wall</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>50</td>
<td>Yes</td>
</tr>
<tr>
<td>28</td>
<td>Plan/DVH assessment settings changed in BTPS</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>42</td>
<td>No</td>
</tr>
<tr>
<td>29</td>
<td>Poor connection between transfer tube and catheter</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>42</td>
<td>Yes</td>
</tr>
<tr>
<td>30</td>
<td>Incorrect date/time in BTPS</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>40</td>
<td>Yes</td>
</tr>
<tr>
<td>31</td>
<td>Incorrect optimisation parameters used in BTPS</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>40</td>
<td>No</td>
</tr>
<tr>
<td>32</td>
<td>Incorrect normalisation mode</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>33</td>
<td>Manual dwell activation causes change in normalisation</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>30</td>
<td>Yes</td>
</tr>
<tr>
<td>34</td>
<td>Faulty cables/connectors</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>30</td>
<td>Yes</td>
</tr>
<tr>
<td>35</td>
<td>TRUS/stepper cradle lost/broken</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>20</td>
<td>Yes</td>
</tr>
</tbody>
</table>
4.3. Results

O = occurrence
S = severity
D = detectability
RPN = risk priority number
IVTV = in-vivo treatment verification
BTPS = brachytherapy treatment planning system
OAR = organ at risk
TRUS = transrectal ultrasound probe
DVH = dose volume histogram

Based on the FMEA a QM checklist (Table 4.5) was developed with the aim to reduce the occurrence and increase the detectability of the failure modes presented in Table 4.4. The QM checklist was also developed to ensure that the efficient nature of the TRUS based HDR pBT planning and treatment process is maintained, due to the time pressures associated with performing the procedure whilst the patient is anesthetised. The used of this QM checklist in combination with some form of IVTV will result in a significant reduction of risk of mistreatment during TRUS based HDR pBT.

Table 4.5: QM checklist developed for TRUS based HDR pBT treatment planning and delivery.

<table>
<thead>
<tr>
<th>Pre-Treatment QA</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Afterloader daily QA completed</td>
</tr>
<tr>
<td>□ TRUS stepper rotation and distance encoder calibration checked</td>
</tr>
<tr>
<td>□ TRUS and BTPS grid settings checked</td>
</tr>
<tr>
<td>□ Source strength details entered into BTPS and cross-checked</td>
</tr>
<tr>
<td>□ Patient details entered into BTPS and cross-checked</td>
</tr>
<tr>
<td>4.3. Results</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>□ Patient consent completed</td>
</tr>
<tr>
<td>□ Patient time out completed</td>
</tr>
<tr>
<td><strong>Pre-Implant 3D Image Acquisition</strong></td>
</tr>
<tr>
<td>□ All stepper motions and track are locked</td>
</tr>
<tr>
<td>□ TRUS grid covers entire expected implant geometry</td>
</tr>
<tr>
<td>□ Prostate base plane and origin set correctly</td>
</tr>
<tr>
<td>□ Image quality and volume coverage acceptable in sagittal view</td>
</tr>
<tr>
<td><strong>Contouring</strong></td>
</tr>
<tr>
<td>□ Prostate and OAR contours delineated accurately</td>
</tr>
<tr>
<td>□ Base, reference, and apex planes set according to prostate contour</td>
</tr>
<tr>
<td><strong>Prescription</strong></td>
</tr>
<tr>
<td>□ Check and apply correct prescription</td>
</tr>
<tr>
<td>□ Ensure correct source selected</td>
</tr>
<tr>
<td><strong>Catheter Insertion</strong></td>
</tr>
<tr>
<td>□ All catheters inserted by radiation oncologist, catheter positions correctly identified in BTPS</td>
</tr>
<tr>
<td>□ All catheters reconstructed on live TRUS images</td>
</tr>
<tr>
<td>□ All catheters pushed to appropriate depth (tips visible on sagittal image)</td>
</tr>
<tr>
<td>□ Obturators removed, template locked</td>
</tr>
<tr>
<td>□ Fluoroscopic image taken with CT markers, measure catheter tip distance beyond base fiducial</td>
</tr>
<tr>
<td><strong>Post-Implant 3D Image Acquisition</strong></td>
</tr>
<tr>
<td>□ Prostate base plan and origin set correctly</td>
</tr>
<tr>
<td>□ Image quality and prostate volume/catheter tip coverage acceptable in sagittal view</td>
</tr>
<tr>
<td><strong>Contouring</strong></td>
</tr>
</tbody>
</table>
4.3. Results

- All pre-implant contours imported
- All contours modified on post-implant acquisition if required

**Catheter Reconstruction**
- Catheters reconstructed accurately in all three views (sagittal, axial, coronal)
- Catheters free lengths measured, cross-checked and entered into BTPS
- Catheter tip QA performed

**Dose Optimisation**
- Inverse optimisation performed
- Graphical optimisation performed if necessary

**Plan Evaluation**
- Isodose and DVH reviewed by radiation oncologist
- Plan approved

**Independent Plan Check**
- Point doses checked in independent plan check software
- Contours are acceptable
- Catheters reconstructed accurately
- Catheter orientation is correct
- Catheter reference length is correct
- Activated dwell positions are within prostate volume + margin
- Correct source details are selected
- Treatment plan date/time is correct
- Prescription as per protocol
- Prostate coverage as per protocol
- Prostate high dose regions as per protocol
- Organ at risk doses as per protocol
Plan Transfer & Delivery

- Transfer tubes connected to corresponding numbered catheters and connections cross-checked
- Plan exported to afterloader
- Source details correct in afterloader
- Cross-check of dwell times and positions between BTPS and afterloader
- Shielding in place next to afterloader
- All staff out of theatre, treatment initiated

QA = quality assurance TRUS = transrectal ultrasound probe
BTPS = brachytherapy treatment planning system
3D = three dimensional OAR = organ at risk

4.4 Discussion

From the analyses, 7 potential risks/failure modes were found to be related to the catheter reconstruction major process. Furthermore, the catheter reconstruction major process was also found to have the highest average ranked potential failure modes according to RPN. This is largely due to the difficulty in visualising the catheters on the US images, especially towards the catheter tips. To minimise the potential for error in catheter tip identification, a catheter tip check was incorporated into the QM checklist shown in Table 4.5 similar that developed by Zheng & Todor [96].

The FMEA identified a number of potential risks that would not have been considered if following prescriptive QA recommendations in consensus guidelines [36, 38, 97]. For example, risks/failure modes related to catheter tip location and catheter recon-
4.5 Conclusion

FMEA was shown to be a valuable tool in developing a QM program for TRUS based HDR pBT treatments. Many potential failure modes were identified that were not previously considered when following international consensus QA recommendations for HDR pBT. Furthermore, a considerable number of the potential failure modes identified were related to human or procedural errors, highlighting the importance of checklists and IVTV in delivering a safe and effective TRUS based HDR pBT treatment. Future chapters of this thesis will further examine the feasibility of performing
IVTV during TRUS based HDR pBT to supplement the QM checklist developed in this chapter.
Chapter 5

In-vivo Source Tracking Error Thresholds for Ultrasound Based HDR Prostate Brachytherapy

5.1 Introduction

Due to the increased awareness of risks associated with brachytherapy treatments like those described in the previous chapter, there has been an increased focus amongst the brachytherapy community in recent years towards more in-vivo treatment validation (IVTV). One aspect of this focus has been on the use of several detector types for IVD in HDR brachytherapy [56, 98, 75]. Another form of IVTV has been real-time in-vivo source tracking, through the use of either 2D detector arrays [99, 100, 70, 101], or single point detectors [75, 102, 103]. In-vivo source tracking techniques using 2D arrays have been shown to have the ability to track the brachytherapy source to within 1.9 mm.

Part of this chapter has been published in the Brachytherapy journal: Poder, J, Carrara, M, Howie, A, Cutajar, D, Bucci, J & Rosenfeld, A 2019, Derivation of invivo source tracking error thresholds for TRUS based HDR pBT through simulation of source positioning errors, Brachytherapy, vol. 18, no. 5, pp. 711-9.
relative to the patient anatomy [99, 100, 70, 101], whilst point detectors placed within
a catheter have measured shifts in dwell positions (relative to the detector) on the
order of 0.5 mm [75]. There has, however, been no published studies demonstrating
the minimum source positioning error that must be resolved by source tracking devices
in order to detect potentially clinically significant changes in dose distributions around
the target and surrounding OARs.

The purpose of this chapter is to simulate source positioning errors in TRUS based
real-time HDR pBT and determine appropriate in-vivo source tracking action thresh-
olds so that clinically significant changes in the delivered dose distributions might be
prevented. Error thresholds calculated in this chapter will serve as a benchmark to
determine the feasibility of performing in-vivo source tracking during TRUS based
real-time HDR pBT using a the Magic Plate (MP) diode array in future chapters of
this thesis.

5.2 Materials & Methods

5.2.1 Patient and Treatment Characteristics

Twenty patients who have previously been treated with a HDR pBT boost in the period
of 2016-2018, in combination with EBRT were randomly selected for this study. The
HDR pBT boost was delivered as 2 fractions of 9 Gy delivered 1 week apart, with the
aim to deliver 18 Gy to the target volume using an Ir-192 source. The HDR pBT boost
was delivered prior to the EBRT component of the treatment, which aimed to treat
the whole pelvis with a prescription of 46 Gy in 23fractions. The TRUS based HDR
pBT technique used to treat the patients is described in section 5.2.1 of this thesis.
Characteristics of the patients prostate volumes, and treatment plans are shown in
Table 5.1.
Table 5.1: Characteristics of the patient plans considered in this study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Average (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate volume (cc)</td>
<td>39.9 (23.2 68.7)</td>
</tr>
<tr>
<td>Number of catheters</td>
<td>19 (17 25)</td>
</tr>
<tr>
<td>TRAK (Gy.m^2)</td>
<td>3.4 (2.6 4.7)</td>
</tr>
<tr>
<td>Percentage weight of 3 most heavily weighted catheters (%)</td>
<td>30.9 (23.3 37.8)</td>
</tr>
<tr>
<td>Prostate (D90%)</td>
<td>106.5 (104.0 109.1)</td>
</tr>
<tr>
<td>Prostate (V100%)</td>
<td>97.6 (96.4 98.6)</td>
</tr>
<tr>
<td>Prostate (V150%)</td>
<td>20.1 (15.8 24.0)</td>
</tr>
<tr>
<td>Prostate (V200%)</td>
<td>4.1 (1.8 6.9)</td>
</tr>
<tr>
<td>Urethra (D1cc)</td>
<td>116.3 (111.9 119.3)</td>
</tr>
<tr>
<td>Rectum (D2cc)</td>
<td>63.4 (57.9 69.0)</td>
</tr>
</tbody>
</table>

5.2.2 Simulated Treatment Planning Source Positioning Errors

Treatment planning source positioning errors were simulated in the BTPS by manually adjusting the dwell position coordinates within the selected catheters without plan re-optimization. A previous study by the STGCCC team identified high risk failure modes in the TRUS based HDR pBT process, which can result in two distinct types of treatment planning source positioning error [40].

The first type of treatment planning source positioning error results in the actual source dwell positions being shifted in the cranial or caudal direction relative to the planned source dwell position. Examples of the causes of these errors include: incorrect catheter indexer length used in BTPS, incorrect catheter free length entered into BTPS, and BTPS coordinate system origin not set correctly. Source positioning errors of this type were simulated in this study from -6 mm (caudal) to +6 mm (cranial) in 1 mm increments.

The second type of treatment planning source positioning error considered in this study results in source dwell positions being shifted in the anterior/posterior or me-
dial/lateral directions relative to planned source dwell positions. Examples of the causes of these errors include: incorrect reconstruction of catheter points due to imaging artefacts, incorrect grid position selected for catheter reconstruction, and inability to detect catheter during reconstruction due to shadowing. Source positioning errors of this type were simulated in this study from -6 mm (posterior/medial) to +6 mm (anterior/lateral) in 1 mm increments. A previous study by Rylander, et al. identified that a median of 3 catheters per plan require correction, with catheter reconstructions errors in the range from 0 to 9.6 mm [104].

In this study two types of anterior/posterior or medial/lateral treatment planning source positioning error scenarios were assumed. The first scenario assumed source positioning errors from the 3 most heavily weighted catheters in the plan were all in the same direction, e.g. all 3 catheter source positioning errors simulated in the posterior direction. Figure 5.1 shows the frequency of the position for the three most heavily weighted catheters across all of the patients considered in this study, superimposed with a typical prostate contour (red), urethra contour (yellow), and rectum contour (brown) at the mid-prostate slice. The second scenario assumed treatment planning source positioning errors from the 3 catheters closest to the urethra and the rectum in the direction towards the OAR, e.g. source positioning errors for the 3 catheters closest to the urethra, moving towards the urethra.
5.2.3 Plan Analysis

All patient plans were assessed by evaluating the DVH indices outlined in Table 5.1. The change in the DVH indices was then calculated as a function of the magnitude of source positioning errors outlined above. The change in these indices with increasing magnitude of source positioning error gives an indication of the suitable in-vivo source tracking action thresholds that should be applied to prevent clinically significant changes in DVH indices.
5.3 Results

The change in DVH indices for the prostate volume as a function of treatment planning source positioning errors are shown in Figure 5.2. For the cranial/caudal direction (Figure 5.2a) all prostate DVH indices were found to be more sensitive to source positioning errors in the cranial direction than the caudal direction. Each of the prostate DVH indices showed little variation with increasing magnitude of source positioning errors in the anterior-posterior direction (Figure 5.2b). However, for the medial-lateral direction (Figure 5.2c) the prostate DVH indices were found to be more sensitive to source positioning errors in the lateral direction, relative to the medial direction. For each direction, the prostate V100% and D90% were more sensitive than the V150% and V200%.
5.3. Results

Figure 5.2: a) Average change in DVH metrics (± 2 standard deviation (SD)) for the prostate contour as a function of source positioning errors in the cranial-caudal direction (all catheters), b) the anterior-posterior direction (3 most heavily weighted catheters), and c) the medial-lateral direction (3 most heavily weighted catheters). Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions.

Figure 5.3 shows the percentage of patients considered in this study that fail the prostate V100% DVH planning aim (V100% > 95%) as a function of source positioning error for all three directions. The results support the data presented in Figures 5.2 a) - c) where the source positioning errors in the cranial-caudal direction are more sensitive than those in the anterior-posterior and medial-lateral directions. For the cranial and caudal directions, 75% and 50% of the patients in this study fail the prostate V100%
planning aim for a 3 mm shift respectively, whilst 0%/5% fail for a 3 mm shift in the posterior/anterior directions and 35%/10% fail for a 3 mm shift in the medial/lateral directions.

The percentage of patients failing the prostate V100% DVH planning aim increases significantly when the source positioning error becomes greater than 2 mm in the cranial/caudal direction. This is likely due to the 3 mm step size used in treatment planning. As source positioning errors reach 3 mm in the cranial/caudal direction, dwell positions begin to move outside of the prostate volume, having a more significant effect on the prostate V100% DVH metric.

For the medial/lateral and posterior/anterior source positioning errors the shape of the curves in Figures 5.2 and 5.3 are governed by the position of the 3 most heavily weighted catheters within the plan, relative to the anatomy. As can be seen in Figure 5.1, the 3 most heavily weighted catheters often occur in the central region of the prostate (rows 2-3 and columns C-E). Movement of these catheters laterally, results in cold spots in the central region of the prostate. The effect of moving these catheters either anteriorly or posteriorly however is minimal.
5.3. Results

Figure 5.3: Percentage of patients whose plans would fail according to the prostate V100% DVH planning aim (V100% >95%) as a function of source positioning error for all three directions. Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions.

The change in DVH indices for the OARs as a function of treatment planning source positioning errors are shown in Figure 5.4. The urethra D1cc was observed to be more sensitive than the rectum V70% for source positioning errors in the caudal, anterior, and medial directions. The sensitivity of the urethra D1cc was similar to the rectum V70% in the cranial, posterior, and lateral directions. The urethra D1cc was more sensitive to source positioning errors in the cranial direction than the caudal direction (Figure 5.4a). Conversely, the rectum V70% has the same sensitivity to source positioning errors in both the cranial and caudal directions. As expected, the
rectum V70% was most sensitive to source positioning errors in the posterior direction relative to the anterior direction (Figure 5.4b) and the urethra D1cc was most sensitive to source positioning errors in the medial direction relative to the lateral direction (Figure 5.4c). The sensitivity of the urethra D1cc to source positioning errors in all directions was again observed to have a significant amount of variation amongst the cohort of patients in the study.

Figure 5.4: a) Average change in DVH metrics (±2 SD) for the urethra and rectum contours as a function of source positioning errors in the cranial-caudal direction (all catheters), b) the anterior-posterior direction (3 most heavily weighted catheters), and c) the medial-lateral direction (3 most heavily weighted catheters). Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions.
Figures 5.5a and 5.5b show the percentage of patients whose plans would fail according to the urethra D1cc DVH planning aim (D1cc <120%) and the rectum D2cc DVH planning aim (D2cc <70%) as a function of source positioning error for all three directions. The urethra again was found to be most sensitive to source positioning errors in the medial, anterior and posterior directions, with a 2 mm source positioning error resulting in a violation of the urethra D1cc planning aim for more than 50% of patients. The rectum was again observed to be less sensitive to source positioning errors, with only a 5 mm error in the posterior direction resulting in a violation of the rectum D2cc planning aim for more than 50% of the patients.

The percentage of patients failing the urethra D1cc DVH planning aim increases significantly when the source positioning error reaches 1 mm in the medial, anterior, and posterior directions. This can be attributed to the proximity of the 3 most heavily weighted catheters in the plan to the urethra (Figure 5.1). In contrast, the 3 most heavily weighted catheters are a significant distance from the rectum, and source positioning errors within these catheters has minimal effect on the rectum D2cc DVH metric.
5.3. Results

Figure 5.5: a) Percentage of patients whose plans would fail according to the urethra D1cc DVH planning aim (D1cc <120%) as a function of source positioning error for all three directions, b) Percentage of patients whose plans would fail according to the rectum D2cc DVH planning aim (D2cc <70%) as a function of source positioning error for all three directions. Negative values in source positioning error correspond to the caudal, posterior and medial directions. Positive values correspond to the cranial, anterior and lateral directions.

Figure 5.6 presents the second anterior/posterior or medial/lateral source positioning error scenario where source positioning errors from the 3 catheters closest to the urethra and the rectum in the direction towards the OAR. As was the case for the first scenario, where source positioning errors in the 3 most heavily weighted catheters were assumed, the urethra was again more sensitive to source positioning errors than the rectum. As can be seen in Figure 5.2b, only a 2 mm source positioning error is required before more than 50% of the patients result in a failure of the urethra D1cc planning aim, whilst a 4 mm source positioning error is required for the rectum.

This difference can be attributed to the catheters located close to the urethra being more heavily weighted than those close to the rectum, as can be seen in Figure 5.1. Additionally, from the OAR to the 3 closest catheters is less for the urethra than for the rectum. Therefore, the proximity, as well as the weight of the catheters closest to the urethra result in a higher sensitivity to source positioning errors relative to the rectum.
5.4 Discussion

Whilst the sensitivity of the DVH parameters to source positioning errors has been derived in this study, the question still remains as to what level the action threshold should be set for in-vivo source tracking devices to prevent clinically significant changes in the delivered dose distributions. According to Hoskin, et al. [105] both the prostate D90% and V100% are significant predictors for biochemical relapse in intermediate and high risk patients treated with HDR pBT boost. The study demonstrates that a 5% decrease in either the prostate D90% or V100% corresponds to a 10% increase in the risk of biochemical relapse. Considering source positioning errors in the cranial/caudal direction, from Figure 5.2a, this 5% change is represented by the red dashed lines. It can be seen from the figure that a 5% change in the prostate D90% and V100% occurs with source positioning errors of approximately 3 mm. Additionally, from Figure 5.3, the percentage of patients failing the prostate V100% DVH planning aim increases significantly when the source positioning error reaches 2 mm in the cranial/caudal
Consequently, a 2 mm source positioning error in the cranial/caudal direction may be an appropriate action level for in-vivo source tracking during HDR pBT to decrease the risk of potential biochemical relapse.

Again, considering source positioning errors in the cranial/caudal direction, from Figure 5.2b it can be seen that the urethra D1cc is more sensitive than the rectum D2cc to source positioning errors of this type. This is supported by the clinical evidence, where acute urinary symptoms and erectile dysfunction are more commonly reported than rectal complications in patients treated with HDR pBT in combination with EBRT. Given the extreme heterogeneity in dose fractionation schedules published in the literature with excellent results, there has been no established dose-volume relationship between risk of normal tissue complication and DVH indices for the urethra and rectum in HDR pBT. Therefore, for the purpose of this study a 5% change in the urethra D1cc was considered as a clinically relevant change in the delivered dose distribution. Applying this threshold in Figure 5.2b, a 5% change in D1cc for the urethra occurs for source positioning errors of 3-4 mm. From Figure 5.5a, a source positioning error of 3 mm results in 35% of patients considered in this study failing their urethra D1cc DVH planning aim. Therefore, an action threshold of a 3 mm source positioning error in the cranial/caudal direction should be applied when performing in-vivo source tracking in HDR pBT to prevent normal tissue complications.

For the prostate DVH metrics, treatment planning errors of the 3 most heavily weighted catheters in the medial/lateral direction were found to have similar sensitivity to those for all catheters cranial/caudal direction, with an in-vivo source tracking error threshold of 3 mm appearing to be appropriate. The sensitivity of the DVH metrics to source positioning errors of the 3 most heavily weighted catheters in the anterior/posterior direction however was observed to be weaker than the other directions, where for almost all patients in the study errors of up to 6 mm still resulted in
less than 5% change in prostate V100% and D90%.

Treatment planning source positioning errors for 3 the most heavily weighted catheters in the anterior/posterior and medial/lateral directions as related to the OARs are more complex for all catheters in the cranial/caudal direction. Due to the nature of the catheter implant pattern around the urethra and anterior to the rectum, the effect of the treatment planning source positioning errors in these directions on the dose to the OARs is highly patient dependent. For example, one patient from this study had a 31% increase in the urethra D1cc for the 3 most heavily weighted catheters moving 4 mm in the medial direction, whereas another patient only had an increase of 5%. The relationship between the change in the OAR DVH and the magnitude of source positioning error is therefore considerably complex, dependent on the proximity of the catheter to the OAR, along with the weighting of the catheter within the plan.

This study assumes two scenarios: 3 most heavily weighted catheters having source positioning errors in the same direction, and 3 catheters closest to the OAR (urethra/rectum) having a source positioning error towards the OAR. Consequently, the magnitude of the change in delivered dose distributions reported in this study due to source positioning errors may be considered clinically relevant and may even be biased towards a conservative estimate. However, it is difficult to draw any definitive conclusions on appropriate treatment planning source positioning error thresholds in the anterior/posterior and medial/lateral directions for in-vivo source tracking to prevent clinically significant changes in dose distributions to OARs. However, one conclusion that may be interpreted from the OAR results is that the urethra is much more sensitive to source positioning errors than the rectum, due to the increased weighting and the proximity of the catheters around the urethra in the treatment plans considered in this study. It may therefore be prudent to limit the weighting of individual catheters during the optimization process to improve the robustness of HDR pBT treatment
5.4. Discussion

plans to source positioning errors, subsequently easing the burden on in-vivo source tracking devices.

In this study, the sensitivity of DVH indices to treatment planning source positioning errors was observed to be directionally dependent. Consequently, when performing in-vivo source tracking during HDR pBT, action thresholds for source positioning errors may potentially be set independently for each direction. This is a significant finding in the context of in-vivo source tracking where it has been shown previously that source tracking accuracy using 2D arrays in the anterior-posterior direction is sub-optimal relative to the cranial/caudal and medial/lateral directions [99, 100, 101, 69]. If a larger action threshold can be set in the anterior-posterior direction, the sensitivity and specificity of the source tracking device can be improved.

Previous studies investigating the robustness of HDR pBT plans to catheter misplacements have also suggested tolerances of 2-3 mm as an error threshold for the difference between planned and delivered dwell positions [107, 108].

One limitation of this study is that only treatment planning source positioning errors are considered. However this is not the only error type that may occur in TRUS based real-time HDR pBT. For example, there have been several publications in the literature demonstrating the systematic migration of the catheter implant relative to the anatomy, in the time between imaging and treatment [56, 57, 109, 110]. This type of error is especially relevant when attempting in-vivo source tracking with point detectors placed within catheters [75, 103, 102], as the migration of catheter in which the detector is placed, relative to the other catheter from the implant will negatively affect the source tracking accuracy of the device. Reported catheter migration for stainless steel catheters (1 mm) [109] is less than that reported for plastic catheters (up to 8 mm) [57]. Consequently, the use of stainless steel catheters may not only aid in minimization of reconstruction errors, but also minimization of catheter migration.
in the time between imaging and treatment.

Additionally, as reported by Milickovic et al. [109], there is also potential for not only the catheters to migrate in the time between imaging and treatment, but also the patient anatomy (e.g. due to prostate oedema). In some instances, movement of the anatomy may occur in the same direction and with the same magnitude as the catheters, and the DVH indices will not be effected by the catheter migration [109]. This presents a unique problem with respect to in-vivo source tracking, as a treatment error may be identified by the source tracking system due to catheter migration away from the planned positions, when in fact no clinically significant change to the dose delivered to the prostate and OARs will have occurred. Therefore, it is necessary to confirm the position of both the patient anatomy and catheters within the BTPS coordinate system immediately prior to treatment. Previous studies utilising EMT systems for catheter reconstruction have exhibited an increase in both accuracy and efficiency of catheter reconstruction, confirming its potential for both direct catheter reconstruction in the BTPS as well as for confirmation of catheter position immediately prior to treatment [83, 82, 81]. Combining the EMT system for catheter reconstruction & confirmation of catheter position prior to treatment with a source tracking device such as the MP may allow for the realisation of a comprehensive in-vivo QA system for real-time TRUS based HDR pBT capable of detecting almost all error types.

Finally, the question of at which point should a treatment be interrupted using a real-time in-vivo source tracking device? also remains unanswered. For example, if three successive dwell positions were found to have a source positioning error of greater than 3 mm, should the treatment be interrupted? The answer is that it is dependent on the weight of the dwell position, its proximity to an OAR, as well as multiple other factors related to the plan and patient anatomy. Therefore, in order to implement appropriate real-time in-vivo source tracking error thresholds, some prior information
about the context of the dwell positons within the treatment plan may be required. This issue may be superseded however, through the use of the source tracking device to interface with both the BTPS and the brachytherapy afterloader to perform online adaptive HDR brachytherapy treatments.

5.5 Conclusion

In this chapter, in-vivo source tracking error thresholds for TRUS based real-time HDR pBT are investigated via the simulation of treatment planning source positioning errors and were found to be directionally dependent. Error thresholds in the anterior/posterior and medial/lateral directions for the prevention of normal tissue complications were found to be complex and patient dependent, requiring further investigation beyond the scope of this study. Finally, it should be noted that the proposed in-vivo source tracking error thresholds in the order of 2-3 mm proposed in this study are an estimate, and that there is still the potential for larger changes in DVH indices to occur for catheter shifts smaller than the proposed threshold levels. Future chapters of this thesis will aim to determine whether in-vivo source tracking using the MP 2D diode array will have sufficient accuracy to detect the clinically relevant source positioning errors identified in this chapter.
Chapter 6

Ir-192 Flexisource TG-43 Monte Carlo Simulations

6.1 Introduction

Future chapters of this thesis will present Monte Carlo (MC) simulations of HDR pBT, including the response of the MP) 2D diode array embedded into the patient couch.

Before using a MC model of an Ir-192 source in the simulation of HDR brachytherapy treatments, the Ir-192 source model must first be validated against benchmark data. The purpose of this chapter is to perform MC simulations of the AAPM TG43 parameters \([9, 3, 31]\) of the Ir-192 source used in the Flexitron afterloading system (Flexisource, Elekta Brachytherapy, Veenendaal, The Netherlands). The two specific TG43 parameters that will be studied are the radial dose function and the 2D anisotropy of the source. MC simulations used in the chapter will be performed using

---


---

74
the Geant4 simulation toolkit (v4.10.01) [86, 111], as described in Chapter 3.

6.2 Materials & Methods

6.2.1 Ir-192 Flexisource Model

The geometric design of the Flexisource model was obtained from the study performed by Granero et al. [4] and is shown in Figure 6.1. The Ir-192 core is modelled as a pure Iridium cylinder of length 3.5 mm and diameter 0.6 mm. It has a physical density of 22.42 g/cm$^3$ and is placed at the geometric centre of the simulation volume.

Figure 6.1: Geometric design of the Flexisource Ir-192 HDR source [4].

The active Ir-192 core is surrounded by a stainless steel shell of length 4.6 mm, 0.85 mm outer diameter and inner diameter of 0.67 mm. This results in a shell thickness of 0.09 mm. The composition by weight of the stainless steel shell is modelled as follows: Fe 67.92%, Cr 19%, Ni 10%, Mn 2%, Si 1% and C 0.08% and the physical density is 7.999 g/cm$^3$. The non-cable end weld of the stainless steel shell is modelled as a cylinder of length 0.65 mm and diameter 0.85 mm. The cable end weld of the stainless steel shell is modelled as a partial cone of maximum diameter 0.85 mm, minimum diameter of 0.5 mm and length 0.4 mm. Finally, the stainless steel cable is modelled as a cylinder of 5 mm length and 0.5 mm diameter, as recommended by Granero et
6.2. Materials & Methods

al. [4]. The space between the outer stainless steel shell and the inner Iridium core was modelled as dry air with a physical density of 1.20 mg/cm$^3$.

The spectrum of gamma energies emitted from the Ir-192 source was obtained from the NuDat database [1]. The $\beta$ spectrum was not considered in the study since its contribution to the dose delivered beyond the stainless steel shell is negligible [4].

6.2.2 Phantom Geometry

The AAPM TG43-U1 report [3] recommends that MC simulations used to obtain TG43 parameters be performed with the source placed in the centre of a spherical 80 cm diameter water phantom, so as to simulate an unbounded phantom [112]. The phantom geometry used in this simulation is an 80 cm length square box phantom made from liquid water with physical density 0.998 g/cm$^3$. The density of 0.998g/cm$^3$ was chosen so as to simulate the density of liquid water at 22°C as is recommended in TG43-U1 [3].

6.2.3 Physics Modelling

The interaction processes for photons (the photoelectric effect, Compton scattering and Rayleigh scattering) are modelled using the Geant4 Livermore low energy package. The interactions cross-sections tabulation is taken from the EPDL97 database [113]. In order to improve the efficiency of the simulations, the linear track-length kerma estimator [114] was utilised with a photon cut-off energy of 250 eV. Secondary particles with range less than 0.1 mm are assumed to deposit the dose locally in the interaction voxel.
6.2.4 Dose Scoring

To obtain the dose rate in polar coordinates and calculate the TG43 parameters, the dose is scored in concentric spherical sections with thickness of 0.5 mm (from 0 to 20 cm) and angular resolution of 1° (from 0° to 180°), as shown in Figure 6.2. The thickness and resolution of the voxels were chosen so as to ensure the effect of volume averaging is less than 0.1% for distances greater than 5 mm from the source [115]. In order to calculate the absorbed dose in each of the spherical sections the total energy deposited in each section is obtained and divided by the total mass of the section.

Figure 6.2: Top-down schematic view of the concentric spherical shells (in black) around the Ir-192 source (in red) used for dose scoring. Image is not to scale.

The longitudinal axis of the source is located along the z axis of the coordinate
system with the centre of the Ir-192 source placed the geometric centre of the calculation volume. To calculate the radial dose function, the absorbed dose along the x axis (perpendicular the longitudinal axis of the source) is normalised to the absorbed dose at a distance of 10 mm from the centre of the source along the x axis and divided by the normalised (at r = 10 mm) geometry function, as shown in Equation 6 of the AAPM TG43 U1 report [3]. To calculate the 2D anisotropy function, for a given radial distance from the centre of the source (r) the absorbed dose is plotted as a function of the angle from the longitudinal axis (θ), normalised to θ = 90° and then divided by the normalised (again at θ = 90°) geometry function, as shown in Equation 8 of the AAPM TG43 U1 report [3].

6.3 Results

6.3.1 Radial Dose Function

The radial dose function calculated in this study compared to Granero et al. [4] and Taylor & Rogers [5] is shown in Figure 6.3. An active length of $G_L(r, \theta) = 3.5$ mm was used to calculate the radial dose function from the calculated dose. Agreement to within 1% for radial distances up to 15 cm was found when compared to both studies. The increased discrepancy in the radial dose function at larger distances (r > 15 cm) may be due to the different size of water phantom used in the simulation. For example, an 80 cm square cube was used in this study and in the study by Taylor & Rogers [5], whereas an 80 cm diameter sphere was used in Granero et al. [4]. However, Prez-Calatayud, et al. [112] have previously shown that for Ir-192 source a spherical phantom of 40 cm radius effectively acts as an unbound phantom for distances up to 20 cm from the source. Therefore, the increased statistical uncertainty at larger distances due to the decrease in magnitude of the dose scored in these voxels may also
be contributing to the larger discrepancy.

Figure 6.3: Comparison of calculated radial dose function with studies by Granero [4] and Taylor & Rogers [5].

6.3.2 2D Anisotropy

The calculated anisotropy function, using an active length of $G_L(r,\theta) = 3.5$ mm, is shown for a distance of 1 cm and 10 cm, in Figure 6.4a and Figure 6.4b respectively. As shown in both figures, the calculated anisotropy data agrees with both benchmark cases within the calculated expanded uncertainty. Larger discrepancies can be observed at polar angles between 0°-15° and 165°-180° due to the minor variations in source capsule
modelling between the studies. In this study, the non-cable end weld of the stainless steel shell is modelled as a cylinder of length 0.65 mm and diameter 0.85 mm whereas in the studies by Graneo et al. [4] and Taylor & Rogers [5] the end weld is modelled as a 0.108 mm thick conical section with a half angle of 23.6° and the radius of the face being 0.17 mm. This conical section was then attached to a 0.49 mm long solid cylindrical section to complete the end weld. This minor difference in the end weld modelling was not observed to have a significant effect on the calculated anisotropy. There is also a substantial decrease in magnitude of the dose scored in these voxels due to the significant attenuation through the end welds. This leads to an increased statistical uncertainty and may also contribute to the larger discrepancies in calculated anisotropy between the studies.

Figure 6.4: a) Calculated 2D anisotropy function at a radial distance of 1 cm, and b) at 10 cm. As compared with studies by Granero [4] and Taylor & Rogers [5].

6.4 Discussion

The calculated radial dose function from this study is shown to agree with both the Granero [4] and Taylor & Rogers [5] benchmark datasets within the calculated uncertainty in the radial distance range of 1–200 mm. The 2D anisotropy was also
found to agree with the two benchmark datasets across most of the investigated range.

Table 6.1: Uncertainty analysis for MC TG43 simulations used in this study.

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical variation in absorbed dose determination from repeated MC simulation runs.</td>
<td>1%</td>
</tr>
<tr>
<td>Variations of the source geometry from one source to another in manufacturing process [4].</td>
<td>0.5%</td>
</tr>
<tr>
<td>Uncertainty in cross section library data for Ir-192 [116].</td>
<td>0.5%</td>
</tr>
<tr>
<td>Effect of volume averaging on absorbed dose calculation in sensitive volumes [117].</td>
<td>0.1%</td>
</tr>
<tr>
<td>Combined TG-43 simulation uncertainty</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

The uncertainties quoted in the results section have been evaluated using the combination of both type A and type B uncertainties combined in quadrature (Table 6.1), as recommended in TG43-U1 [3]. Type A, or statistical uncertainties are inherent to the MC technique. In this study $10^9$ primary photons are generated, resulting in a statistical uncertainty in the absorbed dose of less than 1% ($1\sigma$). Type B uncertainties arise in this study due to uncertainties in the cross section data and variations of the source geometry from one source to another in manufacturing process [4]. Ballester et al. [116] determined the uncertainty in the cross section library to be 0.5% and Granero et al. [4] estimated the uncertainty arising due to variations in manufacturing of the source to be less than 0.5%. Additionally, as mentioned previously, the thickness and resolution of the voxels were chosen so as to ensure the effects of volume averaging are less than 0.1%. This results in a combined type B uncertainty of 0.7% and a corresponding total combined uncertainty in the absorbed dose as 1.2% ($1\sigma$).
6.5 Conclusion

In this chapter the TG43 parameters for the Flexisource are calculated using the Geant4 MC simulation toolkit. The results obtained for both the radial dose function and 2D anisotropy agree with two benchmark datasets within the calculated expanded uncertainty. Therefore, this model of the Flexitron Ir-192 HDR brachytherapy source can be considered acceptable for use in further dosimetric studies. As mentioned above, these dosimetric studies will be discussed in future chapters of this thesis, including simulation of the response of the MP 2D diode array embedded into the patient couch, in order to study the feasibility of using the MP for in-vivo source tracking and identification of potential errors in HDR pBT treatments.
Chapter 7

HDR Prostate Brachytherapy

In-vivo Source Tracking using the Magic Plate Diode Array: A Monte Carlo Study

7.1 Introduction

This work in this chapter aims to investigate the feasibility of using the MP diode array for in-vivo source tracking of a HDR pBT treatment. Previous studies performed with the MP in homogeneous phantom media and have reported source localization accuracy of less than 1 mm \[17, 72, 39\] and temporal resolution of 1 ms \[72\], making it an ideal device for real-time source tracking. It is hypothesised that the introduction of heterogeneous media associated with the patient geometry may compromise the

---

accuracy of source localization using this device.

To assess the feasibility of source localization using the MP in the presence of patient related heterogeneities, MC simulations were performed using the Geant4 toolkit (v4.10.01) [86, 111]. During the HDR pBT treatment simulations, the Flexisource Ir-192 source (Elekta Brachytherapy, Veenendaal, The Netherlands) was simulated inside a voxelized patient geometry, and the dose deposited within the sensitive volume of each detector in the couch embedded 11x11 diode array was evaluated. The simulated detector dose was then used to determine the distance of all detectors in the array to each of the simulated source positions. Finally, the source position was determined using an iterative procedure where the source position is first estimated, and then repeatedly refined based upon the agreement of the predicted geometric distance from the source to the detectors against those determined by the detectors in the array.

7.2 Materials & Methods

7.2.1 Ir-192 Flexisource Model

The same geometrical Ir-192 Flexisource model as described in the Chapter 5 was used in the simulations, along with the same gamma spectrum and interaction processes previously described.

7.2.2 Magic Plate 121 Model

The MP121 is a 2D silicon diode array originally developed at the Centre for Medical Radiation Physics (CMRP), University of Wollongong, Australia for the purpose of IMRT QA [118]. The MP121 consists of an 11x11 array of epitaxial diodes mounted on a 0.6 mm Kapton substrate using the drop-in technique. The epitaxial layer of the MP121 diode is 50 µm thick p-Si grown on top of a 375 µm thick, low resistivity p+
substrate. The sensitive volume of the individual element defined by the n+ region is 0.6 x 0.6 x 0.05 mm$^3$, while the size of the die is 1.5 x 1.5 mm$^2$, the detector pitch is 10 mm [118]. The drop in mounting of the epitaxial diode attempts to minimize the energy dependence and improve the angular response of the diodes by avoiding the use of high Z metal contacts above the sensitive area. This is accomplished instead by using thin Aluminium contacts on the periphery of the 0.6 x 0.6 mm$^2$ n+ ion implanted regions, the lead of the diode is then fully embedded in the Kapton substrate and the diodes face is aligned with the Kapton substrates front surface [118]. The MP121 geometry was created in the simulations used in this study based on the description by Wong, et al. [118] and is shown in Figures 7.1a and 7.1b). In the simulations, the MP121 was embedded inside a 120 mm thick carbon couch, offset 5 mm from its anterior surface.

Figure 7.1: a) Schematic of the MP121 diode spacing, the origin of the coordinate system is defined as the bottom left corner diode of the MP121. (b) Close up of the diode design (distances in mm).
7.2.3 Patient Geometry

The patient model was created by converting a DICOM CT studyset from a prostate HDR brachytherapy treatment into a voxelized model that can be used in Geant4, as shown in Figure 7.2. This was achieved by first converting the Hounsfield unit (HU) numbers to a mass density value using a CT-density curve, and then converting from mass density to a material using a look up table [119, 120, 121]. Once imported into the simulation, a geometrical phantom is created, within which is an array of voxels containing the materials (and their compositions) determined from the HU numbers [121]. The compositions and the densities of materials used in the simulations were obtained from the AAPM TG 186 Report [35]. The voxel size was set to 3x3x3 mm$^3$ for the patient geometry in this study. This voxel size was chosen to model an accurate geometrical definition of patient related inhomogeneities and prevent prohibitively long simulation times. It is acknowledged that this voxel size is larger than that used clinically, but is less important in the context of this current study as dose deposition is not of concern within the patient volume, only the transport of the radiation. To prevent overlapping volumes, which causes tracking errors in simulations, a parallel geometry was used to place the source within the patient geometrical phantom at the planned dwell positions [122].

7.2.4 Dwell Positions and Dose Scoring

A selection of 12 source positions from a HDR pBT treatment plan created in the Oncentra BTPS (Elekta Brachytherapy, Veenendaal, The Netherlands) were used in the simulations. The source position coordinates were selected as three consecutive source positions from four catheters. The catheters were selected such that they spanned the extent of the prostate (left-right and anterior-posterior), to determine if consecutive source positions along a catheter could be localized by the MP at the maximum and
Figure 7.2: Partial axial view of voxelized patient geometry in Geant4 source position simulations. The carbon couch is shown below the patient geometry outlined in green, the Kapton substrate in blue and the diode array in pink.

minimum distances expected in a clinical HDR pBT treatment. The step size of the source used in the BTPS was 3 mm.

To calculate the absorbed dose in each of the sensitive silicon volumes, the total energy deposited in each volume was obtained and divided by the total mass of the volume. Each source position was simulated with $10^9$ primary photons for each simulation run. A total of 20 simulation runs were performed for each source position;
results from each run were averaged and the standard deviation (k=1) was less than 1%.

Each of the source localization simulations were then repeated with each voxel in the patient geometry overridden to the density of water, to compare the source localization accuracy of the MP with and without the presence of patient related inhomogeneities.

7.2.5 Source Tracking Algorithm

To determine the distance of each of the 12 source positions to all detectors in the array ($\alpha_i$), a separate group of simulations were first performed to determine the dose deposited in a single detector placed at 10 mm from the source ($D_{10}$), along the z axis (perpendicular to the longitudinal axis of the source) in a water phantom. A total of 10 simulations of $10^9$ primary photons were performed for this configuration, and the dose deposited in the single detector averaged across the 10 simulations. This average dose was then used to normalize the dose from each detector in the patient geometry simulations ($D_i$), before converting the relative dose to radial distance. No corrections are required for the response of the MP121 (and therefore the dose calculated) at the distances from the source considered in these simulations, as shown by Espinoza et. al. \[74\].

$$\alpha_i = \frac{D_i}{D_{10}}. \quad (7.1)$$

The radial distance from each detector to each source position can then be determined by converting the relative diode dose to distance via a fit of the TG43 parameters calculated in Chapter 6. Based on the derived distances ($r_i$) of each diode (i) in the array to the source, the estimated source position, $S_{es}(a,b,c)$ can be calculated. The geometrical distance, $d_i$, between $S_{es}$ and the coordinate of the i-th detector
7.2. Materials & Methods

\( D_i(x_i, y_i, z_i) \) is calculated by

\[
d_i(a, b, c) = \sqrt{(a - x_i)^2 + (b - x_i)^2 + (c - z_i)^2}
\] (7.2)

To determine the true source position, the geometrical distance, \( d_i \), is fitted to the derived distance, \( r_i \), by adjusting the estimated source position, employing a non-linear least squares fit method to determine the estimated source position. In least squares fitting, the estimate of error assessment can be expressed as the sum of squares of the relative error, \( \chi^2 \)

\[
\chi^2(a, b, c) = \sum_{i=1}^{n} \left( \frac{d_i(a_n, b_n, c_n; x_i, y_i, z_i) - r_i}{r_i} \right)^2
\] (7.3)

and assumes that the derived distance, \( r_i \), is correct. As there is an uncertainty associated with deriving \( r_i \), if the estimated source position were equal to the true source position, then calculating the square of the sums of the percentage difference of the value \( d_i \) and \( r_i \) would result in a minimum value.

To determine a source position that gives the minimal value to the estimate \( \chi^2 \) a multi-variable Newtons method approach is adopted. Newtons method is used in this case to determine the roots of a function by finding successively better approximations. In this analysis, it is necessary to determine the minimum values of \( \chi^2 \) for all three dimensions of the estimated source position, and can be expressed as

\[
\frac{\delta \chi^2(a, b, c)}{\delta a} = \frac{\delta \chi^2(a, b, c)}{\delta b} = \frac{\delta \chi^2(a, b, c)}{\delta c} = 0
\] (7.4)

Newtons method for the three source coordinates can be expressed for the k-th iteration
7.2. Materials & Methods

as

\[ a^k = a^{k-1} - \delta a^{k-1} \]

\[ b^k = b^{k-1} - \delta b^{k-1} \] (7.5)

\[ c^k = c^{k-1} - \delta c^{k-1} \]

where \( \delta a \), \( \delta b \) and \( \delta c \) are the changes made to the source position to produce the improved approximation. These changes can be determined by solving a set of linear equations, expressed in matrix form

\[
\begin{bmatrix}
\frac{\partial^2 \chi^2}{\partial a^2} & \frac{\partial^2 \chi^2}{\partial a \partial b} & \frac{\partial^2 \chi^2}{\partial a \partial c} \\
\frac{\partial^2 \chi^2}{\partial b \partial a} & \frac{\partial^2 \chi^2}{\partial b^2} & \frac{\partial^2 \chi^2}{\partial b \partial c} \\
\frac{\partial^2 \chi^2}{\partial c \partial a} & \frac{\partial^2 \chi^2}{\partial c \partial b} & \frac{\partial^2 \chi^2}{\partial c^2}
\end{bmatrix}
\begin{bmatrix}
\delta a \\
\delta b \\
\delta c
\end{bmatrix} =
\begin{bmatrix}
\frac{\partial \chi}{\partial a} \\
\frac{\partial \chi}{\partial b} \\
\frac{\partial \chi}{\partial c}
\end{bmatrix}
\] (7.6)

This process is repeated until all \( \delta s \) are sufficiently small, or until further estimations of the source coordinates fail to reduce \( \chi^2 \). This approach can converge rapidly to a minimum when close, as all three source coordinates are modified in a single iteration. The initial guess is determined by the coordinates of the detector with the highest response, \( D_{\text{max}}(x_{\text{max}}, y_{\text{max}}, z = 0) \), as the source is assumed to be closest to this position. The sum of the squares is calculated using the first estimation of the source position,

\[ S_{es}^0 = (a^0, b^0, c^0) = S_{es}(x_{\text{max}}, y_{\text{max}}, r_{\text{max}}) \] (7.7)

This approach assumes that the diodes are present within a homogeneous water phantom, when in fact the diode dose was calculated within the heterogeneous patient voxelized phantom. Once an initial estimation of the source position is found, a correction factor is then applied to the response of each of the MP detectors to take into account the angular dependence of the detectors. The source position is then re-estimated using the above method but uses the initial estimated source position of the previous calculation. Finally, the calculated source position is compared to known
source positions obtained from the Oncentra BTPS.

### 7.3 Results

The average difference between MP predicted and actual source positions was found to be $2.1 \pm 0.8 \text{ mm (} k = 1 \text{)}$ when all detectors in the array were used in the localization algorithm. Table 7.1 summarizes the localization results in three dimensions, along with the calculated 3D difference vector, for different number of detectors used in the source localization algorithm. When not all detectors in the array were used in the source tracking algorithm, the detectors with the highest deposited dose were chosen.

Table 7.1: Difference between MP predicted and actual source positions in mm ($k=1$).

<table>
<thead>
<tr>
<th>Number of detectors used</th>
<th>9</th>
<th>25</th>
<th>49</th>
<th>81</th>
<th>121</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>$0.5 \pm 1.0$</td>
<td>$0.2 \pm 0.4$</td>
<td>$0.0 \pm 0.2$</td>
<td>$0.0 \pm 0.2$</td>
<td>$0.2 \pm 0.2$</td>
</tr>
<tr>
<td>Y</td>
<td>$0.5 \pm 1.1$</td>
<td>$0.0 \pm 0.5$</td>
<td>$0.0 \pm 0.3$</td>
<td>$0.2 \pm 0.3$</td>
<td>$0.5 \pm 0.5$</td>
</tr>
<tr>
<td>Z</td>
<td>$1.8 \pm 0.5$</td>
<td>$1.8 \pm 0.5$</td>
<td>$1.9 \pm 0.5$</td>
<td>$2.0 \pm 0.5$</td>
<td>$2.0 \pm 0.5$</td>
</tr>
<tr>
<td>3D</td>
<td>$2.4 \pm 1.0$</td>
<td>$1.9 \pm 0.5$</td>
<td>$1.9 \pm 0.5$</td>
<td>$2.0 \pm 0.5$</td>
<td>$2.1 \pm 0.6$</td>
</tr>
</tbody>
</table>

As can be seen from Table 7.1, the MP could localize the source to within 1 mm in the X & Y directions (left/right and superior/inferior directions, respectively). However, it consistently overestimated the distance in the Z direction (anterior/posterior direction), with an average error of 1.9 mm.

The source tracking simulations were then repeated using the exact same methods, but with each voxel in the patient geometry assigned a density of water (Figure 7.3). The heterogeneous and water only results were compared by means of a students t test ($p < 0.05$) in each of the X, Y and Z directions. Only the Z direction differences
were found to be statistically significant ($p < 0.001$).

The heterogeneous results were used for a one-way ANOVA [123] analysis ($p < 0.05$) to determine if there was a statistically significant difference in the localization accuracy depending on the number of detectors used. The only significant difference was found for the 3D vector ($p < 0.001$). Subsequent Students t tests were performed to compare the datasets for the 3D vector. From this, it was found that only the dataset with 9 detectors had statistically significant differences to the other groups.

### 7.4 Discussion

The uncertainties quoted in this study have been evaluated using the combination of both type A and type B uncertainties combined in quadrature, as recommended in AAPM TG43-U1 [3] and AAPM TG138 [30]. A summary of the uncertainty budget for the source tracking simulations is presented in Table 7.2. Note that the uncertainties related to the response of the MP121 and its associated correction factors are not included in this table.

Table 7.2: Uncertainty analysis for source tracking MC simulations used in this study.

<table>
<thead>
<tr>
<th>Source of Uncertainty</th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical variation in absorbed dose determination from repeated MC simulation runs</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Variations of the source geometry from one source to another in manufacturing process</td>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>Uncertainty in cross section library data for Ir-192 [116].</td>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td>Effect of volume averaging on absorbed dose calculation in sensitive volumes [117].</td>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Uncertainty in composition of tissues used during source tracking simulations[124].</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Combined source tracking simulation uncertainty</td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>
7.4. Discussion

Figure 7.3: a) Difference between MP predicted and actual source position for heterogeneous and water only simulations in X direction, b) Difference in Y direction, c) Difference in Z direction, d) 3D difference vector. Coordinate system orientation is shown in Figures 6.1 & 6.1.
In a water only geometry, the MP121 was able to localize the source to within 1 mm. The source localization accuracy however was found to decrease with the introduction of inhomogeneities. This decrease in accuracy of source position localization due to the presence of inhomogeneities was found to be primarily in the direction perpendicular to the diode array (Z direction). This is due to the source localization algorithm Z direction estimate being more sensitive to the changing ratio of primary to secondary photons due to the presence of inhomogeneities and increased source to detector distance.

The distance estimate in the Z direction is depends directly on the absolute dose deposited in the detector array, whereas source localization in the X and Y directions depends only on the relative difference between the distance estimate for each detector and therefore is less sensitive to inhomogeneities. Small inhomogeneities however can affect the X and Y estimate if a smaller number of detectors are used in the localization algorithm.

This indicates that to track the Ir-192 source with the desired accuracy during HDR pBT treatments a correction may be required, based on density information obtained from the patient CT scan performed prior to treatment. This information could be used, along with a MBDCA built into the localization algorithm to more accurately predict the source to detector distances.

Moreover, it was found that source localization accuracy can be improved with an increased number of detectors used in the localization algorithm. By increasing the number of detectors used in the localization algorithm, a redundancy is built in to reduce the uncertainty introduced due to small heterogeneous media in the patient geometry. The increased number of detectors is also beneficial due to the relatively isotropic dose profile at large source to detector distances.

Previous studies have shown that source tracking using EPIDs is achievable. How-
ever, these studies have also shown that source tracking using EPIDs is restricted by the limited frame rate and read-out electronics of the devices and can result in a significant number of dwell positions not being captured by the EPID when performing source tracking \cite{126}. Source tracking using EPIDs also requires large and expensive systems that have limited availability. This study has shown that similar source tracking accuracy to EPIDs \cite{126, 71, 70} may be achieved with the MP system. Furthermore, the MP system has been shown to have a superior timing resolution of less than 1 ms \cite{72}. As such, the MP delivers a dedicated, inexpensive HDR brachytherapy in-vivo source tracking system with superior timing resolution that can easily be mass produced and is practical for routine clinical use.

The results of this study, along with previously published experimental results \cite{17, 74}, indicate that the MP will have sufficient sensitivity to detect errors in the order of 1-2 mm during the delivery of HDR pBT treatments when embedded in a carbon fibre couch beneath the patient. Such errors may be due to incorrect catheter connection or catheter reconstruction error. In Chapter 5 it was found that in-vivo source tracking error thresholds to prevent clinically significant changes in dose distributions were directionally dependent, as well as dependent on the end-point. In the cranio-caudal direction a 2-3 mm error threshold was found to be appropriate. In this Chapter the MP121 was able to track the source to within 0.5 mm in this direction. In the medial-lateral direction, a 1-2 mm error threshold should be applied according to the results in Chapter 5. Again, from the results in this chapter the MP121 could track the source to within 0.5 mm in this direction. However, for the anterior-posterior direction in Chapter 5, a 1-2 mm error threshold was deemed to be appropriate to prevent clinically significant changes in delivered dose distributions. But, in this chapter the MP121 was able to track the source to within 2 mm (assuming perfect co-registration of the MP121 to the BTPS coordinate system and negligible corrections required for
the MP121 response). Therefore in the case of the anterior-posterior direction, the error appropriate threshold is approximately equal to the accuracy of source tracking using this device, which may result in a suboptimal sensitivity and/or specificity when performing source tracking of these TRUS based HDR pBT treatments using the MP121.

### 7.5 Conclusion

Source localization using the MP121 during a HDR pBT treatment was examined using MC simulations. In a homogeneous geometry, the MP121 was able to localize the source to within 1 mm. The effect of tissue inhomogeneities in the patient geometry on source localization accuracy was also examined and was found to increase the difference between MP121 predicted and known source positions from the BTPS to $2.1 \pm 0.81$ mm ($k = 1$). However, this accuracy can be improved using density information obtained from CT with the MP accurately registered to the patient geometry, making the proposed tool attractive for use as a real time in-vivo source tracking device in HDR brachytherapy for prostate cancer. With the global trend being towards real-time pBT treatment planning based on TRUS imaging, future chapters will aim to examine the effect of the TRUS probe on source localization accuracy.
Chapter 8

Feasibility of Real-time In-vivo Source Tracking During Ultrasound Based HDR Prostate Brachytherapy

8.1 Introduction

This chapter presents the study performed to examine the feasibility of performing real-time in-vivo source tracking during TRUS based HDR pBT treatments.

HDR pBT treatment plans are traditionally performed with the use of a post-operative CT scan. The major drawback of this technique is that it necessitates movement of the patient off the operating table and out of the dorsal lithotomy position. Multiple studies have reported that movement of the patient in this manner...
may increase the risk of catheter displacement in the inferior direction, relative to the prostate, in the time between CT scanning and treatment \[127, 107\]. The use of TRUS for treatment planning \[128\] has been shown to reduce the magnitude of these shifts, as well as improve visibility of the prostate and OARs \[128\]. Modern BTPS are able to use the US echoes of the implanted catheters for the definition of the catheter position within the patient, allowing for real-time HDR pBT treatment planning \[128\]. Correct identification of catheter positions on these images however can be difficult, and there remains a need for comprehensive pre-treatment and/or in-vivo QA \[104, 56, 55\].

The aim of this study is therefore to determine the feasibility of using a 2D diode array for in-vivo source tracking during TRUS based HDR pBT using Monte Carlo simulations in the Geant4 toolkit (v4.10.01) \[86, 111\]. The presence of the TRUS probe was simulated inside the patient to evaluate its effect to the source position detection, and methods are evaluated for overcoming the presence of the probe.

### 8.2 Materials & Methods

#### 8.2.1 Ir-192 Flexisource Model

The same geometrical Ir-192 Flexisource model as described in the Chapter 6 was used in the simulations, along with the same gamma spectrum and interaction processes previously described.

#### 8.2.2 Magic Plate 900 Model

The Magic Plate 900 (MP900) contains diodes mounted on a 0.6 mm Kapton substrate using the edgeless-drop-in technique (Figure 8.1), as described in a study by Petasecca et al. \[129\]. These diodes have an improved angular dependence (less than 2%) compared to those used in the previous design of this system, thereby simplifying the
source reconstruction algorithm and improving source tracking accuracy. Furthermore, the diodes have a larger sensitive volume (higher sensitivity) to allow for enhanced signal to noise ratio at larger source-to-detector distance. The diodes are arranged in the Kapton carrier with a 7 mm pitch, resulting in a total array size of 21 cm x 21 cm. The materials and geometry of the MP900 were constructed within the simulations according to the description of the device above, embedded inside a 120 mm thick carbon fibre couch, offset 5 mm from its anterior surface.

![Schematic of the MP900 and of the edgeless diode design used source tracking simulations. All dimensions are in millimetres, image is not to scale.](image)

### 8.2.3 Patient Geometry

The model of the patient anatomy in the simulations was created by converting three DICOM CT studysets from HDR pBT treatments. As in Chapter 7, this was accomplished by initially converting the Hounsfield unit (HU) to a mass density values using a CT-density curve, and then converting from mass density to a material using a look up table \[119, 120, 121\]. The patient geometry in Geant4 is then created as a geometrical phantom consisting of an array of voxels containing the materials (and their compositions) determined from the HU \[121\]. The compositions and the densities of
materials used in the simulations were obtained from the AAPM TG 186 Report [35]. The voxel size was set to 3x3x3 mm in this study.

8.2.4 Trans-rectal Ultrasound Probe Model

A TRUS probe was modelled inside the rectum of the voxelized patient geometries by utilizing a parallel geometry [122] to prevent overlapping volumes in the simulation, e.g. patient rectum and TRUS probe. These overlapping volumes cause errors in the tracking geometry of Geant4 simulations, leading to erroneous results. The TRUS probe was constructed based on the Endocavity Biplane Transducer Type 8848 produced by BK Medical. The model of the probe consisted of a 110x15x3 mm bar of brass (70% Copper, 30% Zinc, effective atomic number of 29.5), embedded inside a cylindrical Silicon casing (length 200 mm, diameter 22 mm).

It should be noted that this model may not be representative of the true construction of the model 8848 probe, as details of the internal construction of the probe were unable to be obtained from the manufacturer. Therefore, a model was used that was intended to match the internal construction of the probe to the best of our knowledge and mimicked the construction of a probe analogue previously used in experiments by our institution [74]. Due to the presence of the high atomic number materials inside the TRUS probe, it was expected that the TRUS probe would attenuate the signal collected by the MP900 significantly, negatively affecting the source tracking accuracy. Nevertheless, its important to note that the TRUS probe must remain in the rectum during patient irradiation in order to not modify the patients anatomy acquired for treatment planning [56].
8.2.5 Dwell Positions and Dose Scoring

Three complete HDR pBT treatments were simulated, consisting of three unique voxelized patient geometries. The source position locations from the treatment plans were re-created in the simulation geometry by using the 3D source position locations obtained from the DICOM RTPlan files in the BTPS. As the patient geometry is also re-created in the simulations directly from the DICOM files, the position of the dwell locations relative to the patient anatomy in the simulations matches the BTPS. The characteristics of the three HDR pBT plans included in the study are outlined in Table 8.1. The Flexisource model used in the simulations is described in Chapter 6.

Table 8.1: Characteristics of the three HDR pBT plans considered in the study.

<table>
<thead>
<tr>
<th></th>
<th>Number of Catheters</th>
<th>Number of Source Positions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>19</td>
<td>154</td>
</tr>
<tr>
<td>Patient 2</td>
<td>22</td>
<td>165</td>
</tr>
<tr>
<td>Patient 3</td>
<td>18</td>
<td>153</td>
</tr>
</tbody>
</table>

The total energy deposited in the sensitive volume of each diode in the array was tallied during each simulation, which consisted of a total of $10^9$ primary photons. The total energy deposited in the sensitive region of each diode was then divided by the mass of the sensitive volume to calculate the dose deposited. The source positions were then determined using the average diode dose as input into an source tracking algorithm [99, 72, 125].

Finally, the MP900 determined source positions were compared to known source positions input into the simulations, which were obtained from the Oncentra Prostate (v4.2.3 Elekta Brachytherapy, Veenendaal, The Netherlands) BTPS. Source positions obtained from the BTPS coordinate system were converted to that of the MP900 coordinate system, as the position of the MP900 relative to the patient geometry is a known, fixed distance (the MP900 is rigidly embedded into the carbon fibre couch below the patient) within the simulation geometry. The simulations were repeated
with the TRUS probe replaced by tissue equivalent material in the patient geometry to examine the effect of the TRUS probe on the source tracking accuracy.

### 8.2.6 Source Tracking Algorithm

The same source tracking algorithm as described in Chapter 7 was utilized in this study with some modifications. Firstly, the algorithm was adapted to be used with the new version of the MP900 array with the increased number of detectors. Secondly, the correction factor for the angular dependence of the diodes was removed.

Lastly, to determine if the same accuracy of source tracking can be achieved both with and without the TRUS probe present, a thresholding technique was applied to the source tracking algorithm. Using the data from the simulations with the TRUS probe present, the maximum dose deposited in any single diode was found for each source position. Then, for each source position in the three patient plans a threshold was applied, ranging from 50% - 90% of the maximum dose deposited in the array in 10% increments. Any diode with dose deposited below this threshold is ignored in the algorithm, and the optimal threshold level found that gave the best results as input into the source tracking algorithm when all source positions from the three treatment plans were considered.

The average and maximum differences between MP900 predicted and actual source positions obtained with the TRUS probe, without the TRUS probe, and TRUS probe corrected (i.e. applying the optimal threshold), were computed and compared across all three patient volumes. Results without the TRUS probe and TRUS probe corrected were also compared by means of a Wilcoxonian matched pair test. A p-value of <0.05 was considered significant. The test was performed using the R software (v3.5.1, The R Foundation for Statistical Computing, Vienna, Austria).
8.3 Results

The average 3D error vector of source tracking in the presence of the TRUS probe is shown in Table 8.2 for each direction within the three patient volumes, including: the patient left-right direction (X), superior-inferior direction (Y), and anterior-posterior direction (Z). The average 3D error vector for all source positions in the three treatment plans was found to be $11.9 \pm 2.4$ mm ($k = 1$). Figure 8.2a presents the distance calculation between each diode in the MP900 array from a source position in patient 1s plan with the TRUS probe present. The colour scale represents the MP900 calculated distance (in mm) from each diode to the source. The effect of the TRUS probe can clearly be seen in the figure, resulting in an incorrect distance calculation for the diodes shadowed by the probe.

The simulations were then repeated without the TRUS probe present in the patient geometry examine the effect of the TRUS probe on the source tracking accuracy. Figure 8.2b presents the distance calculation between each diode in the MP900 array from a source position in patient 1s plan without the TRUS probe present. The average 3D error vector for all source positions in the three treatment plans without the TRUS probe was $1.5 \pm 0.3$ mm ($k = 1$).
8.3. Results

Figure 8.2: a) Distance calculation (mm) between the source and each diode in the MP900 from a source position in Patient 1 plan, affected by the presence of the TRUS probe. b) Distance calculation, without the TRUS probe present, c) Distance calculation with 70% threshold applied, and diodes with red colours not included in the reconstruction algorithm.

A thresholding technique was applied to the verification algorithm with the TRUS probe present. Figure 8.2c presents the distance calculation between each diode in the MP900 array from a source position in patient 1s plan with the TRUS probe present and a 70% threshold applied. As can be seen from the figure, the threshold is able to eliminate the diodes shadowed by the TRUS probe as input into the tracking algorithm. The effect of the application of different threshold levels in the source tracking algorithm is shown in Figure 8.3. The optimal threshold level, averaged over all source positions in the three treatment plans was found to be 70%. By disregarding
the signal of all diodes below 70% of the maximum signal of any diode in the array, an average source tracking accuracy of $1.8 \pm 0.4$ mm ($k = 1$) can be achieved in the clinically relevant condition of the presence of the TRUS probe inside the rectum.

As can be seen in Table 8.2, the variation in the 3D source tracking accuracy across the three patient volumes is less than 0.5 mm. This result highlights the excellent reproducibility of the MP900 system and associated source tracking algorithm,
8.3. Results

Table 8.2: Average difference between MP900 predicted and actual source positions in mm, without and with a TRUS probe (corrected with 70% threshold) with standard deviation (k=1) in the patients rectum.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>0.4±0.4</td>
<td>0.6±0.5</td>
<td>0.4±0.4</td>
<td>0.7±0.6</td>
<td>0.5±0.4</td>
<td>0.7±0.8</td>
</tr>
<tr>
<td>Y</td>
<td>0.4±0.2</td>
<td>0.6±0.5</td>
<td>0.4±0.2</td>
<td>0.6±0.4</td>
<td>0.5±0.3</td>
<td>0.7±0.7</td>
</tr>
<tr>
<td>Z</td>
<td>1.3±0.2</td>
<td>1.6±0.4</td>
<td>1.3±0.2</td>
<td>1.4±0.4</td>
<td>1.5±0.5</td>
<td>1.5±0.8</td>
</tr>
<tr>
<td>3D</td>
<td>1.4±0.3</td>
<td>1.8±0.6</td>
<td>1.4±0.3</td>
<td>1.7±0.6</td>
<td>1.7±0.4</td>
<td>1.8±0.7</td>
</tr>
</tbody>
</table>

regardless of variations in patient related tissue inhomogeneities. The maximum difference between MP900 predicted and actual source position was 15.4 mm, 2.2 mm, and 3.0 mm, with the TRUS probe, without the TRUS probe, and TRUS probe corrected (70% threshold), respectively across all three patient volumes. The difference between the latter two datasets was found to be statistically significant, with p <0.001.

The results were broken down further to show the average 3D error achieved per catheter (Figure 8.4) for patient 1 only, both without the TRUS probe and with the 70% threshold level applied. The catheter numbers increase in the posterior to anterior direction; therefore, the increasing catheter number represents an increasing distance between the source and the MP900 array. Typical average distances between the source positions in each catheter and the MP900 array ranged from 95 mm to 145 mm. A trend is observed showing an increased 3D error with increasing average distance between the source and the array.
Figure 8.4: Average 3D source tracking error in each catheter considered in the study for patient 1, 1 standard deviation. Red columns show the average error without the TRUS probe. Blue columns show the average error with the TRUS probe present and a 70% threshold level applied.

Figure 8.5 presents a box-whisker plot focusing on catheter 2 and catheter 8 from the patient 1 plan. Catheter 2 is an example of a catheter which is not shadowed by the TRUS probe as viewed from the MP900 array. Catheter 8 is an example where the TRUS probe shadows the primary radiation from the Ir-192 source from most detectors in the MP900 array.
8.4 Discussion

The uncertainties quoted in this study have been evaluated using the combination of both type A and type B uncertainties combined in quadrature, as recommended in AAPM TG43-U1 \[3\] and AAPM TG138 \[30\]. A summary of the uncertainty budget for the source tracking simulations is the same as presented in Chapter 7.

The presence of the TRUS probe was found to significantly affect the accuracy of source tracking in all three dimensions. Source tracking accuracy without the TRUS probe using the MP900 was found to be similar, but improved by approximately 0.5 mm, to that found previously using the MP121 device in Chapter 7. The major

Figure 8.5: 3D source tracking error in the form of a box-whisker plot for catheter 2 (C2) and catheter 8 (C8). TRUS probe present and TRUS probe corrected results are presented for each catheter.
discrepancy remains in the z direction (patient anterior-posterior direction). The discrepancy in the z direction has been shown in Chapter 7 to be due to the non-water equivalence of patient tissue related inhomogeneities between the source and the diode array. This was shown by repeating the simulations with each voxel in the geometry assigned a density of water, resulting in a significant improvement in source tracking accuracy. This effect is highlighted even more so in Figure 6.4 where an increased 3D error vector is observed with increasing distance between source position and the array, due to the increasing likelihood of the material composition between the source and the array being different to that of water.

The effect of the TRUS probe on source tracking accuracy can be overcome using a thresholding technique. An optimal threshold level of 70% of the maximum diode signal was found for all source positions in three complete HDR pBT treatment plans. With this threshold of 70%, approximately 60% of the detectors in the MP900 are not being used for source position verification for the reported example case (patient 1). However, the total number of detectors used in the verification algorithm under these conditions is on average equal to 315. This is approximately 2.5 times the total number of detectors in the previous version of the device (MP121 array) and justifies the need for the MP900 for this purpose. As shown in Figure 8.3 the 70% threshold level was found to be optimal for all three patient geometries, and there was remarkably little variation in source tracking accuracy between the three patient geometries. The optimal threshold level may depend more on the TRUS probe design and composition, rather than the patient geometry. The effect of the TRUS probe type and design on the optimal threshold level will be investigated further in future experimental studies with the MP900.

Figure 8.5 shows on patient 1 an example of a catheter (catheter 2) which is not shadowed by the TRUS probe as viewed from the MP900 array and of a catheter
(catheter 8) where the TRUS probe shadows the primary radiation from the Ir-192 source from most detectors in the MP900 array. Even for catheter 8, which is positioned directly anterior to the TRUS probe, the modified source tracking algorithm results in a similar source tracking accuracy to when no probe is present. However, when compared to catheter 2, the modified source tracking algorithm applied to catheter 8 results in larger discrepancies relative to when there is no probe present. As shown in Table 8.2, there is a higher standard deviation of the 3D error results in the TRUS probe corrected group (0.6 mm) compared to the results without the TRUS probe (0.3 mm). This is due to the larger uncertainty in correcting for the presence of the TRUS probe for catheters that are located directly above the probe where less detectors in the MP900 array can be used for input into the verification algorithm. In general, 3D errors resulted significantly higher \( p < 0.001 \) in the TRUS probe corrected group than in the group without TRUS probe. Nevertheless, an average source tracking accuracy lower than 2 mm (i.e., \( 1.8 \pm 0.4 \) mm) can be achieved in the clinically relevant condition of the presence of the TRUS probe inside the rectum, after application of the TRUS probe correction method.

Source position detection is in principle impossible, even applying a threshold technique, if the source is so close to the probe that its primary radiation oriented towards the array is shielded by the probe. Defining \( a \) the distance between the centre of the TRUS probe and the array, \( b \) the distance between the upper surface of the TRUS probe and the source, \( h \) the length of the array (i.e. 100 mm for the MP121 and 210 mm for the MP900) and \( d \) the diameter of the probe (i.e. 22 mm for the Endocavity Biplane Transducer Type 8848 produced by BK Medical) (Figure 8.6a), the following equation \( (a+b+d/2)/h=(b+d/2)/d \) is valid when the shadow of the source matches the lateral edges of the array. In Figure 8.6b, this equation was used to simulate \( b \) depending on both \( a \) and the diode array dimensions. According to the plot, the use
of MP900 allows the reconstruction of the source position even if it is over the TRUS probe and close to it, covering all the possible clinical situations. This wouldn't be possible with the MP121, in particular at increasing distances between TRUS probe and detector array. A typical clinical example is shown in Figure 8.6c, with a needle 10.4 mm over the TRUS surface.

Figure 8.6: a) Schematic of the setup with the source, TRUS probe and MP900 array. \(a\) is the distance between the centre of the TRUS probe and the array; \(b\) is the distance between the external surface of the TRUS probe and the source; \(h\) is the length of the array; \(d\) is the diameter of the probe. Image is not to scale, b) Minimum source-probe distance \(b\) necessary to avoid the complete shielding of the primary radiation of the source that would be detected by the array, plotted at changing array-probe distance \(a\), c) TRUS image of the prostate after needle implantation. The closest needle is 10.4 mm over the TRUS probe.
The results from this study indicate that the MP900 will have sufficient sensitivity to detect errors of approximately 2 mm in the delivery of TRUS based HDR pBT treatments. Such errors may include incorrect catheter connection, incorrect source strength, or incorrect reference length entered into the BTPS. Errors of this magnitude may also be due to uncertainties in reconstruction of catheters on US images, for example Rylander et al. [103] have shown that errors in catheter reconstruction on TRUS images relative to MRI may be up to 9.6 mm. Furthermore, possible needle displacements occurring during the treatment planning phase (i.e., post-imaging intra-fraction modifications), which might result in changes in the dosimetry of the prostate and OARs [56, 109], could also be detected by the use of MP900. Similarly to the results discussed in Chapter 7, the results in this chapter show that the MP121 has a source tracking accuracy of approximately 0.5 mm in the cranio-caudal and medial-lateral directions, this is smaller than the derived error thresholds in these directions found in Chapter 5 (2-3 mm, and 1-2 mm, respectively). Again, similarly to the MP121 in Chapter 7, the source tracking accuracy of the MP900 in the anterior-posterior directions was 2 mm, which is approximately equal to the derived error threshold of 1-2 mm. These results indicate that the MP900 should have significant sensitivity to detect clinically relevant source positioning errors in the superior/inferior and medial/lateral directions, however clinically relevant source positioning errors in the anterior/posterior direction may not be captured by the MP900.

There still remains, however, a number of significant challenges that must be overcome before translating these source tracking simulation studies to routine in-vivo source tracking in clinical practice. One example is the registration of the MP900 to the BTPS coordinate system. The accuracy of source tracking can only be as good as the registration between these coordinate systems, and any error in this registration carries through as a systematic error in the comparison between planned and measured
dwell positions. This may potentially result in an additional 1-2 mm of systematic error in the source tracking process, leading to a decrease in sensitivity/specificity when using the device. Previous publications have incorporated stereoscopic imaging [101], or EMT [83] in attempts to perform this registration. This issue remains one of the most significant challenges for accurate localisation of the source position and will also be a focus in future experimental studies using the MP900 system in combination EMT systems with gel phantoms.

Another challenge that still must be overcome is the poor signal to noise ratio experienced by the detector system at such large source to detector distances, when the detector system is placed beneath the patient during HDR pBT. This poor signal to noise ratio necessitates the use of longer integration times in the detector system and may therefore preclude the system from performing real-time source tracking analysis. This issue has been discussed in previous publications on the use of EPID devices for source tracking [68, 71, 69, 126, 70]. The MP system, however, is capable of operating with variable integration times between 14 to 9900 µs, with a stable sampling frequency between 0.1 to 10 kHz. Previous publications on the application of the MP system to HDR brachytherapy source tracking have demonstrated that real-time analysis is possible [47, 72]. Optimisation of detector integration times and sampling frequencies when performing source tracking in-vivo will be a focus of future studies.

Future studies will investigate the challenges of registering the MP900 to the BTPS coordinate system, as well as optimisation of the MP900 readout and electronics for in-vivo source tracking at large source to detector distances. It is acknowledged that through this investigation that it will be demonstrated that the sensitivity of the MP900 in detecting source positioning errors will be larger than the 2 mm value found in this study through the Monte Carlo simulations. This will be validated further through a thorough sensitivity-specificity analysis by performing phantom measure-
8.5 Conclusion

This chapter presents a novel methodology for performing source tracking during real-time TRUS based HDR pBT. Inclusion of the TRUS probe inside the patient was shown to negatively affect source tracking accuracy. However, modification of the source tracking algorithm using thresholding techniques was shown to improve source tracking in the presence of the TRUS probe. An optimal threshold level of 70% of the maximum diode signal at each source position was determined for all source positions in three complete HDR pBT treatment plans, with minor variation observed across the three patient volumes. Using this thresholding technique, similar accuracy can be achieved as to when the TRUS probe is not present inside the patient volume, highlighting the robustness of the proposed solution.
Chapter 9

Towards Real Time In-vivo Rectal Dosimetry During Trans-rectal Ultrasound Based High Dose Rate Prostate Brachytherapy Using MOSkin Dosimeters

9.1 Introduction

Previous chapters of this thesis have focused on examining the feasibility of in-vivo source tracking to detect clinically relevant source positioning errors during TRUS based real-time HDR pBT. As discussed in Chapter 2, an alternative means of performing IVTV during TRUS based HDR pBT is IVD. In-vivo dosimetry may provide independent verification of dose delivered to OARs, as well as verification of treatment delivery accuracy.
Performing accurate and precise IVD in brachytherapy is extremely difficult due to the challenges of precise detector positioning and the high dose gradient fields associated with HDR pBT treatments. Carrara et al. have demonstrated an improved measurement uncertainty using MOSkin dosimeters (Centre for Medical Radiation Physics, University of Wollongong, Australia) through coupling of the dosimeters to the TRUS probe during HDR pBT [56, 57]. By coupling the MOSkin dosimeters to the TRUS probe, the uncertainty of relating the position of the dosimeters relative to the source was reduced significantly. Consequently, in-vivo measurements over 18 treatment fractions yielded an agreement with treatment planning predicted doses to within 3.6% ± 1.9% [57]. This system was labelled as the dual purpose probe (DPP), a device which is suitable for both imaging and IVD during TRUS based HDR pBT.

The first aim of the work presented in this chapter was to reinforce the findings presented by Carrara et al. at a second institution with a unique clinical workflow. The second aim was to examine the feasibility of performing catheter-by-catheter analysis of in-vivo rectal dosimetry during TRUS based HDR pBT. The catheter-by-catheter analysis will be performed with the aim to verify the dose delivered to the rectum in real-time as well as to verify the accuracy of treatment delivery.

9.2 Materials & Methods

9.2.1 Treatment Technique & Patient Characteristics

Thirteen patients treated with a HDR pBT boost in the period of 2017-2019, were enrolled in this study. The HDR pBT boost was delivered as 2 fractions of 9 Gy delivered 1 week apart, with the aim to deliver 18 Gy to the target volume using an Ir-192 source. The HDR pBT boost was delivered prior to the EBRT component of the treatment, which aimed to whole pelvis with a prescription of 46 Gy in 23
fractions. Seven patients received in-vivo rectal dose monitoring for both fractions of their treatment, whilst 6 patients received in-vivo rectal dose monitoring for only 1 of their 2 boost fractions. Therefore, a total of 20 treatment fractions were included for analysis in this study. All patients included in the study were treated using the TRUS based real-time HDR pBT technique as described in Chapter 4.

9.2.2 MOSkin Dosimeters and Calibration Technique

MOSkin dosimeters are uniquely designed MOSFET dosimeters developed at the Centre for Medical Radiation Physics, University of Wollongong, Australia. The MOSkin design utilises a thin layer above the sensor, that replaces the dome style epoxy resin used for build-up on traditional MOSFET dosimeters used for IVD [130]. This unique design allows for a water equivalent measurement depth of 0.07 mm from the surface of the dosimeter. Furthermore, the MOSkins are produced through a patented drop-in techniques that allows the MOSFET die to be embedded in a Kapton carrier and to provide an electrical connection without the presence of high Z materials. This, along with the small sensitive volume (4.8 x 10^-6 mm^3), makes the MOSkin an ideal dosimeter for brachytherapy IVD where dose distributions are characterised by steep dose gradients and relatively low energies. Additionally, the physical size of the MOSkin (0.45 mm thick x 1.8 mm wide x 330 mm length), as shown in Figures 9.1 and 9.2, allows for placement of the dosimeter onto the TRUS probe during TRUS based HDR pBT without perturbing the geometry of the patient or the dose distribution.
The MOSkin dosimeters used in this study were calibrated using an Ir-192 source (Flexisource, Elekta Brachytherapy, Veenendaal, The Netherlands) in a specially designed calibration phantom at a distance of $10 \pm 0.1 \text{ mm}$ [130]. Five irradiations were performed for each MOSkin device. For each MOSkin a calibration factor $N$ was determined as $N = \frac{D_{\text{cal}}}{V_{\text{mean}}}$, where $D_{\text{cal}}$ is the dose delivered to the MOSkin as determined by the treatment planning system on the day of calibration, and $V_{\text{mean}}$ is the average MOSkin threshold shift across the 5 irradiations.

### 9.2.3 In-vivo Measurements and the Dual Purpose Probe

Immediately prior to commencing the TRUS based HDR pBT treatment four sterilised MOSkin dosimeters were placed onto the TRUS probe (Type 8848, BK Medical Systems, Herlev, Denmark) and secured with Kapton tape. The dosimeters were placed...
with 1.5 cm spacing, with the most superiorly placed MOSkin 1 cm inferior to the plane of the transverse transducer (Figure 9.3). So that the MOSkin dosimeters did not perturb the transverse or sagittal images produced by the TRUS probe, they were placed at an angle of 90° from the transducers on the surface of the probe. As per the standard treatment protocol the TRUS probe was covered by an endorectal balloon to aid in acquisition of high quality TRUS images. To provide an additional safeguard against the risk of infection or breakage of the balloon, a condom was then placed over the balloon before the procedure was commenced.

Figure 9.3: Placement of the MOSkin dosimeters on the TRUS probe, under the endorectal balloon to produce the DPP.

Directly after treatment planning, and preceding delivery of the treatment, the DPP was rotated by 90° such that the MOSkin dosimeters were oriented towards the anterior rectal wall of the patient. The DPP was then stepped superiorly through the patient so that the transverse transducer was located 1 cm superior to the base plane
of the prostate. The position of the MOSkin dosimeters could now be located within the reference frame of the BTPS to within 1 mm (k=2).

During treatment delivery the MOSkin dosimeters response was recorded using the OneTouch readout system [131], allowing for wireless readout of the MOSkin dosimeters via Bluetooth to a computer running the dedicated MOSkin OneTouch software in the treatment console. An additional advantage of the OneTouch system is online compensation for temperature dependence of the MOSkin dosimeters during irradiation [131].

9.2.4 Measurement & Uncertainty Analysis

Upon completion of treatment rectal IVD measurements using the MOSkin dosimeters were compared to doses predicted at the known points of interest (POIs) in the BTPS (Figure 9.4). The MOSkin measured (DPP) and BTPS predicted (DBTPS) doses were first compared via relative differences, i.e. $\Delta_{DPPvsBTPS} = (DPP-DBTPS) / DPP$.

As per the second aim of this study, the MOSkin measured vs BTPS predicted doses were also analysed on a per catheter basis. Due to the continuous readout of the OneTouch system, the dose deposited to each MOSkin on the DPP by each catheter in the treatment plan could be determined in a straightforward manner due to the gap in time between transit of the source through each catheter. Analysis of a dose per dwell position was not attempted due to the low dose deposited at the position of the MOSkin detectors on the TRUS probe from dwell positions in the anterior portion of the prostate. The predicted dose to each of the MOSkins on the DPP was determined using the Radcalc independent verification software (v6.4, Lifeline, Melbourne, Florida) after DICOM transfer of the RTPlan file of the BTPS, due to the Oncentra Prostate BTPS not providing the dose to each POI on a per catheter basis.

The total combined uncertainty of the MOSkin measurements was estimated to be
11.5% (Table 9.1). The contribution towards the combined uncertainty from calibration of the dosimeters was approximately 1.8%, with 1.5% contribution from uncertainty in the source air kerma strength \( S_K \) and a further 1.0% from the phantom assembly (source to detector distance), and dose calculation algorithm uncertainty \[56\].

The change in response of the MOSkin dosimeters linearity during measurement contributes an uncertainty of 1% \[132\], and the combined uncertainty of the reproducibility and the precision of the system was approximately 1.5% \[131\]. Dependence of the MOSkin readout on temperature was removed through the use of automatic temperature compensation as discussed by Peters et al.\[131\]. The effect of energy (distance) dependence of the MOSkins resulted in an uncertainty of 3.5% \[133\], and angular dependence resulted in an uncertainty of 2% and 3% in the transverse and longitudinal directions, respectively \[132\].

Table 9.1: Uncertainty analysis for MOSkin measurements performed in this study.

<table>
<thead>
<tr>
<th>Contribution to uncertainty from MOSkin calibration</th>
<th>Uncertainty(%) (k=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source air kerma strength definition</td>
<td>±1.5</td>
</tr>
<tr>
<td>Phantom assembly, dose calculation algorithm</td>
<td>±1.0</td>
</tr>
<tr>
<td>Contribution to uncertainty from patient measurements</td>
<td></td>
</tr>
<tr>
<td>Linearity</td>
<td>±1.0</td>
</tr>
<tr>
<td>Reproducibility and precision</td>
<td>±1.5</td>
</tr>
<tr>
<td>Energy dependence</td>
<td>±3.5</td>
</tr>
<tr>
<td>Angular dependence (transverse)</td>
<td>±2.0</td>
</tr>
<tr>
<td>Angular dependence (longitudinal)</td>
<td>±3.0</td>
</tr>
<tr>
<td>Localisation of measurement point within BTPS coordinate system</td>
<td>±9.8</td>
</tr>
<tr>
<td>Total combined measurement uncertainty</td>
<td>±11.5</td>
</tr>
</tbody>
</table>

The dominant contributor towards the total combined uncertainty of the MOSkin measurements was the uncertainty in localizing the MOSkin dosimeters in the BTPS coordinate system. Due to the steep dose gradients in the area of the anterior rectal wall, small geometric errors in placement of the MOSkin dosimeter may result in sub-
9.3. Results

Substantial dose errors. Therefore, this uncertainty was quantified by creating a region of interest (ROI) with radius of 1 mm (approximately equal to the accuracy of placement of the MOSkin on the DPP), centered on each POI within the BTPS, as shown in Figure 9.4. The maximum and minimum dose to these ROIs was then determined in the BTPS, the difference between these maximum and minimum doses was then expressed as a percentage of the expected MOSkin dose at the POI and averaged across all measurement points in the study. This resulted in an expected 9.8% contribution towards MOSkin measurement uncertainty as shown in Table 9.1.

![Figure 9.4: Creation of ROI’s around MOSkin measurement points (red shperes), shown on sagittal view of an example plan with prostate contour (red), urethra (yellow), and dwell position within an example catheter (red dot in yellow cylinder).](image)

9.3 Results

Of the 80 dosimeter measurements across the 20 measured fractions, 17 measurements (21%) were excluded from the analysis due to dosimeter malfunction (loss of
signal). The rate of occurrence of dosimeter malfunction decreased across the length of the study due to an improved method of securing the MOSkins to the TRUS probe, whereby a layer of Kapton tape was placed over the dosimeters before covering with the endorectal balloon. The average number of MOSkin measurement points per fraction was 3.

Sixty-three measurements were therefore included for analysis in this study. The average dose measured by the MOSkins was 414 cGy ± 93 cGy (k=1). The range of measured MOSkin doses was from 219 cGy to 575 cGy. The average $\Delta_{DPP_{vs}BTPS}$ was -1.6% ± 11.1% (k=1), with a maximum of 25.7% and a minimum of -29.2%. Fourty-three measurements (68%) had a $\Delta_{DPP_{vs}BTPS}$ less than ±11.5% (the total combined uncertainty estimate) relative to the BTPS predicted dose. No fractions included in this study had greater than 50% of the MOSkin measurements with $\Delta_{DPP_{vs}BTPS}$ outside of the ±11.5% combined measurement uncertainty. A histogram of the $\Delta_{DPP_{vs}BTPS}$ across the 20 measured fractions is shown in Figure 9.5.
9.3. Results

Figure 9.5: Histogram of $\Delta_{DPPvsBTPS}$ values for 63 MOSkin measurement points across 20 treatment fractions.

The average number of catheters in the 20 MOSkin measured fractions was 17 (range 15-20), and the total number of catheters measured across the 20 fractions was 342. When analysing on a per catheter basis the total number of MOSkin measured points was 1071. The average MOSkin measured dose per catheter was 24.4 cGy ± 23.6 cGy (k=1) with a range of 0.7 cGy to 138.3 cGy.

The results of the per catheter analysis of $\Delta_{DPPvsBTPS}$ are summarized in Table 9.2 along with the differences between MOSkin measured and BTPS predicted doses in absolute terms. The average $\Delta_{DPPvsBTPS}$ per catheter was 2.5% ± 16.9% (k=1). Sixty-four percent of the per catheter MOSkin measurements (n=685) had a
Δ$_{DPP_{vsBTPS}}$ less than ±11.5% (the total combined uncertainty estimate) relative to the BTPS predicted dose. A histogram of the Δ$_{DPP_{vsBTPS}}$ across the 342 measured catheters is shown in Figure 9.6.

Table 9.2: Uncertainty analysis for MOSkin measurements performed in this study.

<table>
<thead>
<tr>
<th></th>
<th>Δ$<em>{DPP</em>{vsBTPS}}$ (%)</th>
<th>Dose Difference (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>2.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>16.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>-57.9</td>
<td>-35.8</td>
</tr>
<tr>
<td>Maximum</td>
<td>71.4</td>
<td>24.7</td>
</tr>
</tbody>
</table>

Of the 1071 available data points for the per catheter analysis, 25% of the MOSkin measurements had a BTPS predicted dose per catheter less than 10 cGy. Removal of these points from the Δ$_{DPP_{vsBTPS}}$ analysis due to their clinical insignificance (low contribution to total rectal dose) resulted in an improved average per catheter of Δ$_{DPP_{vsBTPS}}$ = 1.0% and an average absolute dose difference of 0.0 cGy.
9.4 Discussion

The average $\Delta_{DPPvsBTPS}$ per fraction found in the 20 fractions included this study was $-1.6\% \pm 11.1\%$ (k=1). This result compares favourably with the previous results presented by Carrara et al. [57] where DPP measurements over 18 TRUS based HDR pBT fractions yielded an agreement with treatment planning predicted doses to within $-2.1\% \pm 8.3\%$ (k=1). Carrara et al. performed a subsequent comparison of the DPP measurements with a treatment plan reconstructed on post-treatment
images and found an improved agreement of \(-0.6\% \pm 4.1\%\) (k=1). This difference was attributed to a systematic shift of the plastic catheters towards the rectum in the time between imaging and treatment [57]. The excellent agreement between the results of this study and those described by Carrara et al. reinforce the applicability of the MOSkin dosimeters (and their use as part of a DPP) for in-vivo rectal dosimetry during TRUS based HDR pBT irrespective of the nuances involved in individual departments clinical workflows.

The average $\Delta_{DPP_{vsBTPS}}$ per catheter found in this study was $2.5\% \pm 16.9\%$ (k=1). When catheters with small contributions ($<10$ cGy) to the MOSkin measurement were excluded from the analysis, the average $\Delta_{DPP_{vsBTPS}}$ per catheter improved to $1.0\% \pm 15.7\%$ (k=1). Modern HDR pBT treatment regimens often deliver the full brachytherapy prescription dose in a single fraction [134, 135], and it is therefore necessary for devices performing IVD to report dose to OARs prior to the end of the treatment fraction. The results presented in this study show that this may indeed be feasible using MOSkin dosimeters as part of a DPP. Even after excluding MOSkin measurements from analysis due to the small ($<10$ cGy), contribution to the total rectal dose, a minimum of 2 MOSkin dosimeters were available for analysis across all catheters measured in this study.

However, analysis of the per catheter results in the context of treatment verification is difficult. This is exemplified in Figure 9.7 where catheter 5 in the treatment plan has a $\Delta_{DPP_{vsBTPS}}$ of -19.1%, but the total treatment fraction $\Delta_{DPP_{vsBTPS}}$ is only +0.2%. This raises the question of whether or not it would be appropriate to interrupt the treatment after catheter 5 to investigate a potential error, and whether or not the per catheter differences between MOSkin measured and BTPS predicted doses are indicative of those accumulated across a total treatment fraction. The answer to this question likely depends on the aim of the measurement.
9.4. Discussion

Figure 9.7: BTPS predicted (blue) vs MOSkin measured (red) dose accumulated across catheters for one of the fractions included in this study.

If the aim of the measurement is to verify the dose delivered to the rectum it may not be feasible to rely on the per catheter results to predict the total dose to the rectum from the entire treatment fraction (as shown in Figure 9.7). This finding is further highlighted through additional analysis of the per catheter data. For example, for MOSkin measurement points that had a total treatment fraction $\Delta_{DPPvsBTPS}$ of less than 11.5% ($n = 43$), all but 5 measurements consisted of at least 1 catheter with a $\Delta_{DPPvsBTPS}$ of greater than 11.5%. Nevertheless, even though it was not exemplified in this study, a consistent $\Delta_{DPPvsBTPS}$ of greater than 11.5% for multiple catheters in sequence may indicate a potential overdose to the rectum for the entire treatment
fraction and could be cause to interrupt the treatment to investigate the source of the error.

If the aim of the measurement however is to verify correct delivery of the TRUS based HDR pBT treatment, the per catheter results may be of more relevance. For the example case shown in Figure 9.7 even though the total dose to the rectum for the entire fraction is within tolerance, the -19.1\% error for catheter 5 may indicate a potential error in the delivery of this catheter. If the error for this catheter was related to an incorrect catheter reconstruction in the BTPS, it may have resulted in an overdose to the urethra or significant loss in target coverage. Analysis of the 2 other MOSkin measurement points available for this catheter showed a $\Delta D_{PP,\text{vsBTPS}}$ of -6.5\%, and -1.2\%. Therefore, it is unlikely that there was a treatment delivery error related to this catheter in this example. Anderson et al. were able to overcome the issue of low signal at the position of the detector by placing an optically stimulated luminescence detector within a brachytherapy needle during a gynaecological brachytherapy treatment [136]. When the detector is placed within a brachytherapy needle, it is closer to the Ir-192 source and thus collects a sufficient signal to determine the dose per dwell position for every needle. It should be noted however that gynaecological brachytherapy treatments often consist of less needles than prostate brachytherapy treatments and often have larger dwell times, which would allow the detector to collect a larger signal per dwell position.

Despite 25\% of MOSkin measurements being excluded from the per catheter analysis due to low signal, there was still a minimum 2 MOSkin dosimeters available per catheter during each fraction being considered. Inclusion of multiple dosimeters in the per catheter analysis results in an improved redundancy to potential dosimeter errors and an increased ability to detect potential treatment delivery errors. For example, it may be appropriate to investigate a potential treatment delivery error if more than
50% of MOSkin dosimeters are showing a $\Delta_{DPPvsBTPS}$ of greater than 11.5% on a per catheter basis. No catheters analysed in this study were found to have >50% of measurement points with a $\Delta_{DPPvsBTPS} > 11.5%$.

One limitation of this study is that the total combined uncertainty of the measurement (11.5%, k=1) may be so large that treatment delivery errors or incorrectly predicted doses to the rectum may go undetected. From Table 9.1, it can be seen the dominant contributor towards this measurement uncertainty is the localisation of the MOSkin measurement point within the coordinate system of the BTPS. Improvement of this localisation to within 0.5 mm would reduce the total combined uncertainty to approximately 7% and will result in an improved sensitivity and specificity of the DPP. This could be achieved through fabrication of TRUS probes with well-defined recesses for placement of MOSkin dosimeters into the housing of the probe. Future studies are planned to validate further the MOSkin sensitivity-specificity by performing phantom measurements.

Another limitation of this study in the context of treatment delivery verification is that the measured MOSkin dose from anterior catheters in the plan is quite small. For example, the average MOSkin measured dose for catheters 1-10 (the most posterior catheters in our workflow) in this study was 33.5 cGy, as compared to 13.0 cGy for catheter numbers >10 (the most anterior catheters in our clinical workflow). This may result in a decreased sensitivity and specificity when attempting to catch treatment delivery errors for anterior catheters due to either: a) the catheters being excluded from analysis (catheter dose at MOSkin level <10 cGy), or b) small deviations between planned and delivered dwell positions not resulting in a significant difference in dose measured at the DPP. These small deviations may still result in a significantly increased dose to the urethra or a loss of target coverage, as shown in Chapter 5. Therefore, analysis of MOSkin measurements per catheter basis may not be sensitive
enough to detect all types of potential errors in the HDR pBT treatment planning and delivery process (such as those identified in Chapter 4 of this thesis). To quantify the likelihood of this occurring, future studies are planned to examine the effect of treatment delivery errors MOSkin measured doses through simulation of these delivery errors in gel phantom measurements involving the DPP.

9.5 Conclusion

This chapter presents a method for in-vivo rectal dosimetry during TRUS based HDR pBT using MOSkin dosimeters coupled to a TRUS probe. The results of the study were found to agree well with previously published data, despite differences in clinical workflows. Analysis of MOSkin measured doses as compared to BTPS predicted doses on a per catheter basis was found to be feasible. The use of MOSkin dosimeters as part of a DPP for in-vivo rectal dosimetry is suitable for detecting clinically relevant errors in the TRUS based HDR pBT treatment planning and delivery process that affect the dose delivered to the rectum. More studies are required however before real time error thresholds can be confidently applied to catch potential errors in treatment delivery prior to the end of treatment using this methodology. The results presented in this chapter resulted in an increased confidence of the dose delivery accuracy of the TRUS based HDT pBT at St George Hospital and contributed in the move towards a delivery of the HDR pBT treatment as a single fraction dose.
Chapter 10

Conclusion

The aim of this thesis was to identify potential treatment planning and delivery errors during TRUS based HDR pBT and investigate the feasibility of eliminating these errors through the introduction of routine IVTV. This aim was achieved through firstly performing a risk-based analysis to develop a QM program for TRUS based HDR pBT. It was acknowledged through this risk based analysis that IVTV would be able to identify a significant number of the identified failure modes in the TRUS based HDR pBT treatment planning and delivery process. Subsequent chapters of this thesis then showed that in-vivo source tracking using the MP is capable of capturing clinically relevant source positioning errors and that real-time IVD using MOSkins is achievable.

10.1 Final Summary

In Chapter 4 of this thesis FMEA was shown to be a valuable tool in developing a QM program for TRUS based HDR pBT treatments. In performing this analysis, several potential errors were identified that were not previously considered when following traditional QA methods. It was also identified in this chapter that a large number
of these errors were related to human and procedural faults. This finding emphasised the importance of performing IVTV as an additional safeguard against planning and delivery errors during TRUS based HDR pBT.

Clinically relevant in-vivo source tracking error thresholds were derived in Chapter 5 of this thesis through simulation of source positioning errors in the BTPS. Derivation of in-vivo source tracking error thresholds showed that the error thresholds were dependent on: the direction of the error, the patient geometry, and the endpoint. To prevent delivering too high dose to OARs error thresholds in the anterior/posterior and medial/lateral directions were found to be smaller than those in the cranial/caudal direction, and the urethra D1cc was found to be a more sensitive endpoint in deriving error thresholds than the rectum D2cc. In terms of target coverage, smaller error thresholds in the cranial/caudal direction were derived compared to the anterior/posterior and medial/lateral directions.

In Chapter 6 of this thesis TG43 parameters for the Ir-192 Flexisource were calculated using the Geant4 MC simulation toolkit. Both the radial dose and 2D anisotropy functions were calculated and compared to previously published benchmark data that is used in the BTPS. Both the radial dose and 2D anisotropy functions calculated in Chapter 6 were found to agree with the previously published benchmark data to within an expanded uncertainty of 1.2%. The work presented in Chapter 6 was essential in validating the Ir-192 Flexisource MC model prior to performing investigations in subsequent chapters.

The MC model of the Ir-192 Flexisource developed in Chapter 6 was used in Chapter 7 when simulating the source inside the patient and examining the feasibility of using the MP121 for in-vivo source tracking in heterogeneous media. It was determined that the MP121 could localise the Ir-192 source to within $2.1 \pm 0.8 \text{ mm} \ (k=1)$ inside a patient geometry, relative to the known source positions from the BTPS. If
the entire patient geometry was assigned a uniform density of 1 g/cm$^2$ and a material of water, this source tracking accuracy improved to less than 1 mm. Therefore, unless prior knowledge of the 3D patient geometry, including size and position of heterogeneities exists, 2 mm may be the upper bound of source tracking accuracy using the MP121 placed beneath the patient inside the carbon fibre couch.

In Chapter 8, the work presented in Chapter 7 was extended so that the patient geometry now also included a TRUS probe within the rectum, as would be the case when performing in-vivo source tracking during TRUS based HDR pBT. In the presence of the TRUS probe, the average 3D error for source tracking using the MP900 across three complete patient treatments (in three different patient geometries) was 11.9 ± 2.4 mm (k=1). Without the TRUS probe present, the MP900 source tracking accuracy improved to 1.5 ± 0.3 mm (k=1). A modification of the source tracking algorithm was implemented which applied a threshold that ignored the detectors in the MP900 array that were shadowed by the TRUS probe. Implementation of this modified source tracking algorithm improved the MP900 source tracking accuracy in the presence of the probe to 1.8 ± 0.4 mm (k=1). Therefore, through implementation of the modified source tracking algorithm, an equivalent source tracking accuracy in the presence of the TRUS probe can be achieved to in-vivo source tracking accuracy without a TRUS probe present.

Finally, in Chapter 9 MOSkin dosimeter in-vivo rectal dosimetry measurements were performed as part of a clinical study across 20 treatment fractions. The MOSkin dosimeters were coupled to the TRUS probe used for imaging and treatment planning to form a dual purpose probe (DPP). The average relative difference between MOSkin measured and BTPS predicted doses was -1.6% ± 11.1% (k=1), with a maximum of 25.7% and a minimum of -29.2%. When analysing on a per catheter basis, the average relative percent difference per catheter was 2.5% ± 16.9% (k=1). Per catheter analysis
of the MOSkin measurements was found not to predict the total treatment fraction dose to the rectum for all patients in the study. Additionally, it was determined that analysis on a per catheter basis may not be sensitive enough to detect all types of potential errors in the HDR pBT treatment planning and delivery process.

## 10.2 Future Work

Risk-based analysis of the TRUS based HDR pBT planning and treatment process identified a number of potential errors. These errors were simulated in the BTPS, so as to derive clinically significant error thresholds for in-vivo source tracking and MC simulations used to determine the feasibility of using the MP to capture source positioning errors of this magnitude. Finally, IVD using MOSkin detectors was performed during 19 patient treatment fractions to validate the dose to the rectum during these treatments and to examine the feasibility of performing real time analysis of this metric. Despite the successfulness of these investigations, there are a number of studies that may still be performed to further improve these two IVTV techniques.

Firstly, the in-vivo source positioning error thresholds derived in Chapter 5 are specific to the catheter implant patterns, and plan optimisation techniques used at STGCC. In this chapter it was also observed that there was significant variation in the proposed source tracking error threshold from patient to patient. This is likely due to the differences in proximity of the catheters to OARs such as the rectum and urethra. Subsequently, it is hypothesised that appropriate in-vivo source tracking error thresholds are also likely to depend on the catheter implant pattern rules and plan optimisation techniques used at different departments. Future studies will examine this by requesting individual departments to create a treatment plan on a single TRUS dataset. Source positioning errors will then be simulated on these plans as was performed in Chapter 5, and the spread in appropriate in-vivo source tracking error
thresholds across departments will be examined.

Secondly, as mentioned in Chapter 7 and Chapter 8, the accuracy of in-vivo source tracking using the MP as determined through MC simulations in these chapters likely presents the upper bound of their limit. This is because the MC simulations assume a perfect registration between the MP and the BTPS coordinate systems. In reality, this will not be the case, and any uncertainty in registration between these coordinate systems will carry through as a systematic error in source tracking accuracy using the MP. Additionally, the ability of the MP121 and MP900 to detect dwell position errors will also be affected by any dependence of the signal collected by the device on the distance between the source and the detector array (e.g. due to the low signal collected at extended distances, any dose rate dependence, and any energy dependence). Therefore the 2 mm source tracking accuracy calculated in Chapter 7 and Chapter 8 will likely not be achievable in a clinical environment.

To overcome these challenges, and to validate the MC results experimentally, future studies will investigate combining the MP with an EMT system to localise the MP position in world coordinates, relative to the TRUS probe (which controls the origin of the BTPS coordinate system relative to the MP). These experiments will be performed in gel phantoms so that end-to-end validation of the TRUS based HDR pBT technique can be performed, and the upper bound of source tracking accuracy using the MP can be determined experimentally. To address any dose rate and energy dependence identified, the detector array may be calibrated at the source to detector distances expected during in-vivo source tracking (e.g. 15-20 cm). Furthermore, errors identified in Chapter 4 of this thesis can be simulated to determine the sensitivity and specificity of the MP in catching these errors.

Finally, the study outlined in Chapter 9 shows that it is feasible to use MOSkin dosimeters coupled to a TRUS probe to confirm the dose delivered to the rectum
during TRUS based HDR pBT. It is not clear however whether the methodology is
sensitive enough to detect potential high risk errors in the TRUS based HDR pBT
treatment planning and delivery identified in Chapter 4 of this thesis. Future studies
are planned, also utilising gel phantoms, where these errors will be simulated and
MOSkin measurements performed as part of a DPP to determine the sensitivity and
specificity of the IVD technique. Comparisons with in-vivo source tracking using
the MP can then be performed. Furthermore, the ability of the MOSkin dosimeters
to perform both IVD and in-vivo source tracking will be investigated, as shown by
Linares-Rosales, et al.\cite{137}
References


References


References


References


