Title
Correlation of Imaging and Pathology to Advance the Study of Prostate Cancer Focal Therapy

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Correlation of Imaging and Pathology to
Advance the Study of Prostate Cancer Focal Therapy

A dissertation submitted in partial satisfaction
of the requirements for the degree
Doctor of Philosophy in Biomedical Engineering

by

Alan Martin Priester

2017
ABSTRACT OF THE DISSERTATION

Correlation of Imaging and Pathology to Advance the Study of Prostate Cancer Focal Therapy

by

Alan Martin Priester

Doctor of Philosophy in Biomedical Engineering

University of California, Los Angeles, 2017

Professor Warren Grundfest, Chair

Prostate cancer, a disease diagnosed in approximately 220,000 men in the U.S. annually, has historically been treated through extirpation of the entire gland. Unfortunately, whole-gland interventions exact a heavy toll, often resulting in incontinence and impotence. One proposed alternative is focal therapy, wherein MR-visible tumor foci are treated locally while sparing the majority of healthy tissue. This approach has great potential to deliver curative treatment while reducing costs and risks. In order to demonstrate the safety, efficacy, and practicality of focal therapy, several key questions remain:

1. How reliably can tumor location be distinguished?
2. What treatment margins are necessary?
3. Can treatment be delivered safely in a clinic setting?

This thesis presents a concerted effort to answer these questions, guided by the central hypothesis that focal therapy can be made safe and effective by registering MRI with ultrasound, pathology, and thermal data. To this end, we characterized and clinically implemented a means of accurately correlating MRI with histopathology. We
discovered that many tumors extend far beyond the confines of MR-visibility, and the average tumor was three times its predicted volume. Isotropic margins in excess of 1 cm would have been necessary to treat the majority of focal therapy eligible men. However, by registering tracked biopsy data with MRI, we demonstrated that patient-specific treatment margins can greatly improve cancer prediction.

We performed clinical trials investigating the safety of focal laser ablation (FLA) of prostate cancer, a modality wherein an interstitial laser delivers thermal energy and induces coagulative necrosis. Through analysis of MRI thermometry data, we found that thermal damage could be predicted with less than 15% volumetric error (0.5 cc). In a second clinical trial, FLA was performed under the guidance of MRI-US fusion imaging. This trial demonstrated that focal therapy could be performed safely, in a clinic setting, and without risk of incontinence or impotence. Furthermore, clinically significant cancer was eliminated from 60% of men, demonstrating the potential efficacy of localized treatment.

Future work is necessary to refine all aspects of prostate focal therapy. However, this thesis lays a foundation for safe and effective treatment of localized prostate cancer.
The dissertation of Alan Martin Priester is approved.

Daniel Ennis
Leonard Marks
Shyam Natarajan
Dan Ruan
Jonathan Said

Warren Grundfest, Committee Chair

University of California, Los Angeles
2017
This thesis is dedicated to the millions of men whose quality of life suffered following prostate cancer treatment
# Table of Contents

List of Figures ........................................................................................................... xi
List of Tables .............................................................................................................. xiv
List of Abbreviations ............................................................................................... xv
Acknowledgements ...................................................................................................... xvii
Vita ............................................................................................................................... xviii

1. Introduction ............................................................................................................. 1

   1.1 Overview of the Chapters ................................................................................... 2

2. Overview of Localized Prostate Cancer Management ........................................ 10

   2.1 Prostate Cancer Imaging ...................................................................................... 10

   2.2 Prostate Biopsy .................................................................................................... 12

      2.2.1 Historical Biopsy Methods ........................................................................... 13

      2.2.2 Magnetic Resonance Imaging Guided Biopsy ............................................. 13

      2.2.3 Magnetic Resonance Imaging to Ultrasound Fusion Biopsy ...................... 14

   2.3 Prostate Pathology ............................................................................................... 16

   2.4 MRI-Pathology Correlation ............................................................................... 18

      2.4.1 Correlation Error Sources .......................................................................... 18

      2.4.2 Correlation Methodologies ......................................................................... 20

   2.5 Prostate Therapy .................................................................................................. 21

      2.5.1 Whole Gland Therapies .............................................................................. 22

      2.5.2 Active Surveillance ....................................................................................... 23

      2.5.3 Focal Therapy ............................................................................................... 26

      2.5.4 Focal Laser Ablation .................................................................................... 28
3. Development and Validation of a System for MRI-Pathology Correlation ................................................................. 30

3.1 Patient-Specific 3D-Printed Prostate Molds .......................................................... 31

3.1.1 Mold Design ........................................................................................................ 31

3.1.2 Mold Manufacture ............................................................................................ 33

3.2 In Vitro Characterization of Mold Slicing Accuracy ........................................... 34

3.2.1 In Vitro Study Materials and Methods ............................................................... 35

3.2.2 In Vitro Study Results ....................................................................................... 41

3.2.3 In Vitro Study Discussion .................................................................................. 44

3.3 Ex Vivo Characterization of 3D-Printed Mold Target Registration Error .......... 45

3.3.1 Ex Vivo Study Materials and Methods .............................................................. 46

3.3.2 Ex Vivo Study Results ...................................................................................... 51

3.3.3 Ex Vivo Study Discussion .................................................................................. 53

3.4 Conclusions ........................................................................................................... 55

4. Evaluation of the Predictive Accuracy of MRI Tumor Contours ........... 57

4.1 Materials and Methods ....................................................................................... 58

4.1.1 Patient Population ............................................................................................. 58

4.1.2 Imaging, Segmentation, and Pathology Processing ........................................... 59

4.1.3 MR-Pathology Registration .............................................................................. 61

4.2 Analysis ................................................................................................................ 62

4.2.1 Automated Matching ....................................................................................... 62

4.2.2 Tumor and ROI Characterization .................................................................. 63

4.2.3 Statistical Analysis ........................................................................................... 64

4.3 Results .................................................................................................................. 65
6.1 Materials and Methods ........................................................................................................... 102
   6.1.1 Procedure Planning ........................................................................................................... 103
   6.1.2 Treatment Protocol ........................................................................................................... 104
   6.1.3 Follow-Up ......................................................................................................................... 107

6.2 Analysis .................................................................................................................................. 107
   6.2.1 MR Thermometry Interpolation ....................................................................................... 108
   6.2.2 Arrhenius Analysis and Optimization .............................................................................. 110
   6.2.3 Interstitial Thermal Probe Measurements ........................................................................ 110

6.3 Results .................................................................................................................................. 111
   6.3.1 Patient Safety and CaP Treatment Efficacy ................................................................. 111
   6.3.2 Optimal Arrhenius Damage Estimation ......................................................................... 113
   6.3.3 Interstitial Probe Data .................................................................................................... 114

6.4 Discussion ............................................................................................................................. 116

6.5 Conclusions ........................................................................................................................... 118

7. MRI-Ultrasound Fusion Guided Focal Laser Ablation ......................................................... 119

7.1 Materials and Methods ........................................................................................................... 122
   7.1.1 Treatment Planning ........................................................................................................... 123
   7.1.2 Treatment Protocol ........................................................................................................... 126

7.2 Results .................................................................................................................................. 129
   7.2.1 Treatment Safety .............................................................................................................. 129
   7.2.2 Treatment Efficacy .......................................................................................................... 130
   7.2.3 Comparison with MR-Guided FLA ................................................................................. 133

7.3 Discussion ............................................................................................................................. 135

7.4 Conclusions ........................................................................................................................... 137

8. Conclusions and Future Directions ....................................................................................... 138
8.1 Improvements in MRI-Pathology Correlation .................................................. 139
8.2 Refinement of Margin Generation ................................................................. 141
8.3 Validation of Thermal Profile and Damage Estimation .............................. 143
8.4 Next Steps for US-Fusion Guided Focal Laser Ablation .......................... 144

APPENDIX A: FLA INCLUSION AND EXCLUSION CRITERIA .................................. 148

APPENDIX B: INTERNATIONAL PROSTATE SYMPTOM SCORE QUESTIONNAIRE .... 151

APPENDIX C: SEXUAL HEALTHY INVENTORY IN MEN QUESTIONNAIRE .......... 152

REFERENCES ............................................................................................................ 153
List of Figures

2.1 Exemplary image of multiparametric MRI .......................................................... 11
2.2 Artemis MRI-US fusion biopsy platform ............................................................. 15
2.3 Conventional process for production of whole mount slides at UCLA ............. 17
2.4 Angle mismatch between image and slicing planes ........................................... 19
3.1 Segmentation of prostate capsule and ROIs on T2 MRI ................................ 32
3.2 Generation of patient-specific prostate cavity from MR contours .................. 32
3.3 CAD model of a patient-specific prostate mold ............................................... 33
3.4 Design and manufacture of phantoms with inked fiducials ............................. 37
3.5 Fiducial pattern on sliced phantom and digital model ...................................... 39
3.6 Fiducial patterns for example depths and slice angles .................................... 40
3.7 Trends in angle and depth error vs. phantom slice location ............................ 43
3.8 CAD model of a mold and frame for ex vivo prostate scanning .................... 47
3.9 Preparation of a prostate for ex vivo scanning ............................................... 48
3.10 Anatomic landmarks on in vivo, ex vivo, and whole mount images ................ 49
3.11 Registration improvement from optimum rigid transform ............................. 54
4.1 Prostate gland within a patient-specific mold .................................................... 60
4.2 Annotated whole mount prostate slide ............................................................. 60
4.3 Digital 3D reconstruction of tumors and overlay on MRI ............................... 62
4.4 CaP detection relative to MR suspicion and Gleason score ............................. 65
4.5 Mean volume and longest axis of matched and missed tumors ........................ 67
4.6 Correlation between tumor and ROI size ....................................................... 68
4.7 Anisotropic proportions of prostate cancer underestimation ........................... 69
4.8 Percent of tumors encapsulated by ascending isotropic margins .................... 72
5.1 Definition of negative nodes within a biopsy needle’s throw ........................................ 85
5.2 Three feature distributions for CaP-positive and negative voxels ................................. 92
5.3 Per-voxel ROCs for optimized feature sets vs. isotropic margins ................................. 93
5.4 Per-patient ROCs for optimized feature sets vs. isotropic margins .............................. 93
5.5 Example cancer probability maps adjacent to a positive core ....................................... 93
5.6 Per-voxel ROC for support vector machine vs. isotropic margins ................................. 95
5.7 Per-patient ROCs for support vector machine vs. isotropic margins ............................. 95
5.8 Per-patient ROCs for two alternative machine learning algorithms ............................. 95
6.1 Patient-specific planning of margins and laser fiber locations ..................................... 102
6.2 Example treatment plan export ..................................................................................... 103
6.3 Planned interstitial thermal probe locations .................................................................... 105
6.4 T2 MR image showing interstitial laser fiber and thermal probes ................................. 106
6.5 MR thermometry readings during laser activation ......................................................... 106
6.6 Cylindrical interpolation of MR thermometry planes ..................................................... 109
6.7 Cumulative thermal damage estimate Vs. DCE segmentation ....................................... 109
6.8 Non-perfused zones following MR-guided focal laser ablation ................................. 112
6.9 12-month PSA following MR-guided focal laser ablation ........................................... 112
6.10 Arrhenius Damage estimates overlaid with non-perfused zones ................................. 114
6.11 Temperatures for an interstitial probe and adjacent thermometry voxel ................. 115
6.12 Exemplary case of temperature and probe positions during FLA ..................... 115
7.1 Key equipment necessary for MR-US fusion guided FLA ........................................... 123
7.2 Ellipsoidal damage volume expected for a 3-minute burn ........................................ 125
7.3 Planned catheter trajectories for both needle guide channels ................................. 125
7.4 Insertion and visualization of transperineal thermal probes ..................................... 127
7.5 Insertion and visualization of transrectal probes ......................................................... 127
7.6 Example interstitial probe temperatures during fusion-guided FLA .................. 131
7.7 Non-perfused zones following fusion-guided focal laser ablation ...................... 131
7.8 9-month PSA follow-up after fusion-guided focal laser ablation ....................... 132
7.9 Successful case of cancer extirpation via fusion-guided FLA ............................ 133
8.1 One embodiment of a multi-element thermal probe ........................................ 146
8.2 One embodiment of a dual-plane ultrasound probe ........................................... 147
List of Tables

3.1 Power analysis for detection of differences in mold vs. hand-sliced phantoms... 35
3.2 Randomized assignment of phantoms to pathology department subjects .......... 38
3.3 Slicing and reconstruction errors for mold vs. hand-sliced phantoms ............... 41
3.4 3D-printed mold registration errors based on anatomic landmarks.................. 52
3.5 3D-printed mold registration errors based on optimum rigid registration, and optimum rigid registration accuracy as assessed by high-intensity foci ............. 52
4.1 Demographics and clinical data for prostates sliced with 3D printed molds ...... 58
4.2 MR Sensitivity, MR specificity, and patients with tumor foci missed on MRI ....... 65
4.3 Proportions and sizes of missed and matched tumors and ROIs ...................... 66
4.4 Size, extent, position, and overlap of matched tumors and ROIs ..................... 67
4.5 Anisotropic tumor size estimation accuracy and correlation with MRI............. 69
4.6 Size and HDmax of tumors and ROIs stratified by Gleason and MR suspicion .... 71
5.1 Clinical and correlation data for cases with molds and targeted biopsy.......... 83
6.1 Volume errors of published and optimized Arrhenius constants .................... 113
7.1 Fusion-guided FLA patients, treatment parameters, and outcomes ................. 131
7.2 Comparison of outcomes and costs of fusion-guided vs. MR-guided FLA ....... 134
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>Two-Dimension(al)</td>
</tr>
<tr>
<td>3D</td>
<td>Three-Dimension(al)</td>
</tr>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AP</td>
<td>Anterior-Posterior (anatomic axis)</td>
</tr>
<tr>
<td>AS</td>
<td>Active Surveillance</td>
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<tr>
<td>CAD</td>
<td>Computer Aided Design</td>
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<tr>
<td>CaP</td>
<td>Cancer of the Prostate</td>
</tr>
<tr>
<td>cc</td>
<td>centimeters cubed</td>
</tr>
<tr>
<td>csCaP</td>
<td>clinically significant Cancer of the Prostate</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCE</td>
<td>Dynamic Contrast Enhanced</td>
</tr>
<tr>
<td>DLC</td>
<td>Dual-Lumen Catheter</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
</tr>
<tr>
<td>EBRT</td>
<td>External Beam Radiation Therapy</td>
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<tr>
<td>FLA</td>
<td>Focal Laser Ablation</td>
</tr>
<tr>
<td>FT</td>
<td>Focal Therapy</td>
</tr>
<tr>
<td>GS</td>
<td>Gleason Score</td>
</tr>
<tr>
<td>HDmax</td>
<td>Hausdorff maximum</td>
</tr>
<tr>
<td>IPSS</td>
<td>International Prostate Symptom Score</td>
</tr>
<tr>
<td>IS</td>
<td>Inferior-Superior (anatomic axis)</td>
</tr>
<tr>
<td>LITT</td>
<td>Laser Interstitial Thermal Therapy</td>
</tr>
<tr>
<td>LR</td>
<td>Left-Right (anatomic axis)</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>---------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>MI</td>
<td>Mutual Information</td>
</tr>
<tr>
<td>mpMRI</td>
<td>Multiparametric Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NPZ</td>
<td>Non-Perfused Zone</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operator Characteristic</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>RP</td>
<td>Radical Prostatectomy</td>
</tr>
<tr>
<td>SHIM</td>
<td>Sexual Healthy Inventory for Men</td>
</tr>
<tr>
<td>STdev</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SVM</td>
<td>Support Vector Machine</td>
</tr>
<tr>
<td>tBx</td>
<td>Targeted Biopsy</td>
</tr>
<tr>
<td>TPS</td>
<td>Thin Plate Spline</td>
</tr>
<tr>
<td>TRE</td>
<td>Target Registration Error</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal Ultrasound</td>
</tr>
<tr>
<td>TURP</td>
<td>Transurethral Resection of the Prostate</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
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</table>
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SELECTED JOURNAL PUBLICATIONS


**PATENT APPLICATIONS**


**SELECTED ABSTRACTS**


CHAPTER 1
Introduction

Prostate cancer (CaP) is the second most commonly diagnosed malignancy in United States males, with over 180,000 new cases and over 26,000 deaths estimated in 2016. Despite statistics on the meager benefits of treating low-grade CaP, the stigma of cancer compels most patients to seek radical treatment, wherein the entire prostate gland is irradiated or surgically removed. Radical prostatectomy and radiation therapy, in addition to their considerable direct costs, often severely impair the patient's quality of life, with high incidence of incontinence and impotence.

The disparity between the number of diagnoses and deaths is largely due to the indolent nature of many prostate tumors. A large proportion of CaP is essentially benign, with a 2-year doubling time that renders it unlikely to threaten the health of many patients. Screening techniques such as prostate specific antigen (PSA) have fairly low specificity for aggressive disease, leading to over-detection and over-treatment of CaP. Histological prostate cancer has been shown to be incidentally present in 50% of men in their 50's and over 75% of men over 85 years old, indicating that much of what we classify as disease is often insignificant and undetected.

The over-treatment of prostate cancer, and the acute side effects associated with treatment, are ongoing concerns in the urologic community. Many CaP tumors are dangerous and should be treated, but many are indolent, and thus the appropriate treatment strategy is often difficult to ascertain. Patients often demand aggressive treatment, and many physicians are understandably reluctant to eschew extirpation of what may develop into life-threatening disease. It would be ideal if a therapeutic
modality could be employed that resolved the patient's disease without inflicting high risks of incontinence and impotence.

One promising strategy for delivering the ‘trifecta’ of continence, potency, and CaP extirpation is known as partial gland ablation (PGA) or focal therapy (FT). Using this approach, only a portion of the prostate harboring disease is destroyed. If the remainder of tissue is left unharmed, damage to local anatomy such as the neurovascular bundles is hypothesized to be much less likely, thus reducing the incidence of long-term side effects. This approach has great potential, but several key research questions must be answered in order to demonstrate that focal therapy can be performed safely and effectively.

Firstly, focal therapy relies on image-guidance, and thus the reliability of CaP imaging must be thoroughly characterized. Next, after accounting for the accuracy of prostate cancer imaging, treatment margins beyond visible disease must be defined. Third, a means of delivering treatment and monitoring its progress must be employed and validated. Lastly, it should be clinically verified that prostate focal therapy can be performed safely and in a manner that may be disseminated to the urologic community.

The research presented herein describes a rigorous investigation of these topics. The central hypothesis for our research efforts was that focal therapy can be made safe and effective by registering MRI with ultrasound, pathology, and thermal data.

1.1 Overview of the Chapters

Chapter 2 presents an extensive overview of the radiologic, urologic, and histopathologic components of prostate cancer management. Chapter 3 presents a method for evaluating the predictive accuracy of prostate MRI, characterized with in vitro and ex
vivo validation studies. The accuracy of prostate MRI is then investigated in Chapter 4, the results of which inform an attempt to optimize treatment margins in Chapter 5. Lastly two clinical trials are presented: the first in Chapter 6 validates a means of monitoring CaP treatment, and the second in Chapter 7 establishes the safety of an ultrasound-fusion guided focal therapy procedure. A brief summary of the chapters can be found below.

Chapter Two: Overview of Localized Prostate Cancer Management

This chapter summarizes all major aspects of localized cancer management, including imaging, biopsy, therapy, and treatment outcomes. It begins with a description of multiparametric magnetic resonance imaging, including the sequences used, the contouring techniques, and historical rates of sensitivity (50% to 81%) and specificity (82% to 92%). Next prostate biopsy is discussed, beginning with historical methods that sampled the gland in a blind but systematic fashion. With the advent of multiparametric MRI, it was an intuitive step to biopsy regions of interest under direct MRI guidance, which yielded substantially improved (38% to 56%) cancer detection rates in biopsy-naive patients. However, some tumors remained MR-invisible, and detection rates are best if targeted and systematic cores are taken. Fusion biopsy systems were developed to enable the sampling of MRI targets under real-time US guidance, and UCLA has reported a substantial improvement in CaP detection relative to systematic biopsy alone.

Next prostate pathology is discussed, beginning with tumor staging and grading via the Gleason scoring system. Conventional whole-mount slide production is described, wherein the prostate gland is manually sliced posterior-side down prior to fixation. These whole mount slides are often used as the basis for MRI-pathology correlation, but this process is prone to registration errors due to differences in slice depth, slice angle,
and gland shape between \textit{in vivo} MRI and excised specimens. Many groups have published on their efforts to improve MR-pathology correlation, including registration software and mechanisms to regulate prostate slicing. The National Institute of Health first published on the use of 3D-printed patient-specific molds to ensure that prostate slices match MR image planes, a method that we adopted and expanded upon.

Next prostate therapies are discussed, beginning with a description of the irradiation and surgical options currently available for extirpation of the entire gland. Unfortunately, whole-gland therapy is associated with impotence rates between 50\% and 85\%, and incontinence rates between 4\% and 38\%. The high cost of treatment and severe toll on a patient's quality of life has motivated many institutions to maintain 'active surveillance' programs, wherein treatment is eschewed in favor of periodic imaging and biopsy. Between 14\% and 41\% of active surveillance patients go on to receive treatment, either because of disease progression or patient preference. Disease specific mortality is very low (0.2\%) for such programs, and studies indicate that there is no survival benefit to treatment vs. active surveillance in a low-risk population. However, patients on active surveillance are prone to anxiety, and the discomfort and costs associated with repeated biopsy.

Lastly focal therapy is discussed, wherein a portion of the prostate containing tumor is destroyed. Focal therapy is ideal for men with low to intermediate-risk disease, and many clinical trials employing half a dozen treatment modalities have been attempted. Side effect rates such as incontinence (0\% to 5\%) and impotence (0\% to 46\%) have been reported, and appear favorable relative to whole-gland therapies. However, residual cancer has been detected in 15\% to 37\% of patients for whom follow-up was performed. Focal laser ablation (FLA)—the treatment modality employed at UCLA—is particularly promising due to the small size of interstitial fiber optics, adjustable and well-confined.
treatment zone, and their intrinsic MRI compatibility. Most trials to date have been safety studies performed under direct MR guidance, and negligible side effect rates have been widely reported. However, the only intent-to-treat trial performed with rigorous follow-up reported a residual cancer rate of 37% 12 months' post-treatment.

Chapter Three: Development and Validation of a System for MRI-Pathology Correlation

This chapter introduces the UCLA system of 3D-printed, patient-specific molds for MRI-pathology correlation. These molds were designed to hold an excised prostate in the same position and orientation observed in vivo, and to guide slicing such that each whole-mount slide corresponds to a predetermined MR image. Molds were manufactured from plastic, at low cost, using a consumer-grade 3D printer.

In order to evaluate the benefit of the molds relative to handheld slicing, tissue-mimicking prostate phantoms were manufactured with inked fiducials that could be used to calculate what position and orientation a slice had been obtained from. Pathologists and pathology assistants then sliced the phantoms in matched pairs, one by hand and one guided by a mold. Slice locations were reconstructed in 3D, and relative to handheld slicing target registration errors using the mold were reduced by a factor of 2, from 4 mm to 2 mm. Rotational errors about the left-right anatomic axis were also reduced by a factor of 2, and volumes were reconstructed with greater fidelity.

In order to evaluate registration accuracy with human tissue, ex vivo scans of prostatectomy specimens were performed. Excised glands were placed within a 3D-printed mold, immersed in oil, and then imaged in high resolution. An evaluation of anatomic landmarks visible on the in vivo, ex vivo, and whole mount prostate images for 3 patients showed mean registration accuracy to be between 3.5 and 4 mm, and mean
through-plane alignment errors were 1.5 mm. A rigid intensity-based registration algorithm was also employed by maximizing mutual information, and using anatomic landmarks it was demonstrated that *in vivo* MR could be registered to *ex vivo* MR with a mean error of 1.4 mm.

**Chapter Four: Evaluation of the Predictive Accuracy of MRI**

This chapter presents data from the first 114 patient-specific molds that were used to process radical prostatectomy specimens beginning in August 2013. The molds were generated from MR prostate contours, and regions of interest suspicious for cancer were prospectively identified and segmented on high-resolution T2 sequences. After glands were sliced and whole-mount slides were annotated, prostate contours were non-rigidly registered with preoperative MRI and tumors were reconstructed in 3D. They were matched to corresponding ROIs using an algorithm validated through comparison with tumor board findings.

Through examination of the matched and missed tumors, it was shown that mpMRI had 53% sensitivity and 82% specificity. However, after stratifying according to clinical significance and index disease, mpMRI had 82% sensitivity for index tumors, and highly suspicious ROIs had a specificity approaching 90%. The vast majority of missed tumors were small-volume and low-grade, and thus clinically insignificant. However, among matched tumors, the average prostate cancer had three times greater volume and a longest dimension 11 mm longer than prospective MR contours. Tumor size and ROI size had a correlation coefficient on the order of 0.5.

The worst correlations and largest errors were observed along the inferior-superior (through-plane) axis, likely due to segmentation from an axial perspective and reduced through-plane MRI resolution. Tumor volume and the extent of underestimation tended
to increase with rising Gleason scores, and ROI size was shown to be predictive of Gleason score. Perhaps most significantly, the median Hausdorff maximum distance between tumors and matched ROIs in retrospectively focal therapy eligible men was 10.2 mm. This has critical implications for focal therapy treatment planning, since more than half of patients would have required an isotropic margin greater than 1 cm for complete tumor extirpation.

Chapter Five: Patient-Specific Treatment Margins

This chapter presents efforts to improve upon isotropic margins for focal therapy treatment planning through incorporation of targeted biopsy data. 21 patients were identified who had targeted biopsy data, prostatectomy specimens that were processed with a patient-specific molds, and retrospective focal therapy eligibility. Whole mount and biopsy information were registered to T2 MRI, and voxels were sampled in 1-mm increments throughout the MR volume. Each voxel was labeled positive or negative for prostate cancer, and various features were measured relating each voxel position to T2 intensity, anatomic position, positive and negative biopsy cores, and ROI surfaces.

38 features were identified with significantly different distributions for CaP-positive and CaP-negative voxels at a threshold of $p = 0.01$. By linearly combining these features in proportions optimized for CaP recognition specificity, 30% less healthy tissue would have been treated to achieve 99% CaP extirpation relative to isotropic margins. After one outlier was removed, between 1 and 4 more patients would have been completely CaP-free using the optimal feature combination, depending on volume of tissue treated. Machine learning algorithms trained using leave-one-out cross validation also improved upon isotropic margins, with 12% less healthy treated for 99% CaP extirpation and a median of 2 additional patients fully treated once the outlier case was excluded.
Incorporation of machine learning techniques and targeted biopsy data was thus shown to be a substantial improvement over isotropic treatment margins, which is the current norm for focal therapy planning.

Chapter Six: MRI-Guided Focal Laser Ablation
This chapter presents an 8-patient clinical trial of MR-guided focal laser ablation, and an analysis of the temperature data derived from MRI thermometry and interstitial probes. The laser fiber was introduced transrectally, and after 2-6 laser applications a mean of 4.1 cc had been treated according to measurements of non-perfused tissue on contrast enhanced MRI. After 12 months of follow-up no serious adverse events had been observed, with no significant decrease in urinary or sexual health. Enduring reductions in patient PSA were observed in 7/8 men, indicating that CaP had been successfully targeted. However, residual disease was detected on follow-up biopsy in 7/8 men, suggesting that targeting accuracy and/or treatment margins had been insufficient for complete CaP extirpation.

Using MR thermometry data from this safety trial, the optimal method of predicting tissue damage using the Arrhenius integral was computed. After interpolating the temperature measurements into 3D and registering all laser applications, it was demonstrated that tissue damage could have been predicted with 0.5 cc (< 15%) volumetric error. Furthermore, interstitial thermal probes were proven to be far more precise than MR thermometry, with less than one tenth of the noise recorded in baseline signals. Through observation of probe temperatures during laser application, was hypothesized that treatment safety and efficacy could be ensured through judicious placement of interstitial probes in lieu of MR thermometry.
Chapter Seven: MRI-Ultrasound Fusion Guided Focal Laser Ablation

This chapter presents a technique for and results from MR-US fusion guided transrectal focal laser ablation, the first trial of this technique ever performed. 10 men with intermediate-risk prostate cancer were treated with fusion-guided FLA in the clinic and under local anesthesia. Treatment was monitored using interstitial thermal probes, with temperature at an 8-mm radius always exceeding 55°C and temperature at the rectum never exceeding 42°C. Fusion-guided focal laser therapy was safe in all men, with no serious adverse events or long term detriment to patient health.

For the first 4 patients treated, PSA decline was minimal and cancer bearing pattern 4 disease was detected on follow-up biopsy. However, after factors such as probe visualization had been improved, the next 6 patients had enduring PSA reduction after 9 months' follow-up. Of these men 3 had their tumor burden reduced below the threshold of significance, with only small volumes of Gleason 3+3 evident on biopsy. The other 3 had no evidence of CaP on follow-up biopsy. Thus fusion-guided FLA was shown to have potential for effective cancer control. Furthermore, fusion-guided FLA appeared to confer benefits in efficacy and cost relative to the MR-guided trial, though the studies were not statistically powered to test such improvements.
CHAPTER 2
Overview of Localized Prostate Cancer Management

In the modern clinic and hospital environment, prostate cancer management involves close collaboration between the departments of urology, radiology, pathology, and radiation oncology. Each stage in the process, from screening to diagnosis to treatment and follow-up, requires physicians to wield unique sets of tools which have been rapidly evolving in recent years. This chapter aims to provide an overview of various aspects of localized prostate cancer management, in order to give adequate background for an understanding of focal therapy. The rationale for prostate focal therapy, the resources available to focal therapy researchers, and the challenges faced by focal therapy practitioners are summarized below.

2.1 Prostate Cancer Imaging

Prostate cancer is unusual among solid malignancies in that it is a heterogeneous disease difficult to visualize with standard medical imaging technology. Unlike breast cancer, which is analogous in many respects, x-ray and computed tomography have virtually no utility for the detection or staging of CaP\(^6\). CaP foci are likewise not generally visible on medical ultrasound, though practitioners will occasionally observe exceptions to this rule\(^10,11\). Even for magnetic resonance imaging, T2-weighted sequences have limited sensitivity for visualization of CaP tumors\(^12\). Positron Emission Tomography (PET) has shown promise for the visualizing of lymph node\(^13\) and bone\(^14\) CaP metastases, but its utility for localized CaP has thus far been confined to metabolic modeling\(^15\).
Multiparametric Magnetic Resonance Imaging (mpMRI), which combines information from multiple MR sequences, has been shown to improve CaP characterization over T2 alone\textsuperscript{16}. This is typically performed in 1.5 or 3 T diagnostic scanners, with a combination of abdominal and/or transrectal receiver coils. Multiparametric MRI at UCLA includes the following sequences:

- High-resolution 3D T2-weighted imaging (Fig 2.1A), for which peripheral zone tumors appear as low-intensity foci. The sequence typically used for lesion contouring has a 170x170x90 mm field of view, interpolated resolution 0.66 x 0.66 x 1.5 mm, and 2 averages, requiring a 7-minute scan.

- Diffusion-Weighted Imaging (DWI) with apparent diffusion coefficient (Fig 2.1B), a measure associated with the restriction of water diffusion, wherein tumor foci are expected to show diminished signal\textsuperscript{17}.

- Dynamic Contrast-Enhanced (DCE) MRI (Fig 2.1C), a measure of blood perfusion and thereby microvessel density, wherein tumor foci are expected to show increased signal\textsuperscript{18}.

A radiologist reviewing the mpMRI identifies regions of interest (ROIs) that are suspicious for the presence of prostate cancer, due to signal contrast relative to surrounding tissue on one or more of the sequences. At UCLA a suspicion level between
1 and 5 is assigned according to a Likert-like scale\textsuperscript{19} similar to but predating PI-RADS Version 2\textsuperscript{20}, with 1 corresponding to negligible suspicion and 5 corresponding to very high suspicion of prostate cancer. The three scores assigned to the T2, DWI, and DCE sequences are combined in order to assign an overall level of suspicion to the ROI. High overall suspicion levels have been shown to correspond to heightened specificity for prostate cancer\textsuperscript{21}. The ROI shown in Figure 2 was assigned an overall suspicion of 5 due to hypointense T2 signal with irregular borders, low apparent diffusion coefficient, and early intense focal enhancement on DCE.

One meta-analysis of 7 studies including 526 patients indicated that mpMRI had a specificity of 88\% (95\% confidence interval of 82\% to 92\%) for CaP detection\textsuperscript{22}. CaP sensitivity was much lower on average, spanning a range of 66\% to 81\%. However, some studies comparing mpMRI to radical prostatectomy—considered the highest standard of evidence for radiology-pathology correlations—have quoted sensitivities on the order of 50\% for all CaP\textsuperscript{23} or transition zone CaP\textsuperscript{16}. Higher sensitivities have been reported (76\%\textsuperscript{24} to 80\%\textsuperscript{23}) for detection of the most advanced tumor foci, called the ‘index lesion,’ which has been hypothesized to drive clinical progression of CaP.

2.2 Prostate Biopsy

Although ROIs can be identified on MRI, CaP diagnosis must be confirmed via prostate biopsy. In the United States this is typically performed transrectally as opposed to transperineally, since CaP detection rates have been shown similar and procedures can be performed more quickly, without spinal anesthesia\textsuperscript{25}. A transrectal approach is also ideal since the rectum runs directly adjacent to the prostate’s posterior, and the majority of CaP foci—68\% according one study\textsuperscript{26} of 104 prostatectomy specimens—arise in the
peripheral zone. Transrectal biopsies are accompanied by a small risk of infection\textsuperscript{27} and frequent minor adverse events such as hematuria, but studies report no significant difference in complication rates relative to transperineal biopsy\textsuperscript{25,28}.

### 2.2.1 Historical Biopsy Methods

Prior to the adoption of transrectal ultrasound guidance, prostate biopsy was performed blindly, directly targeting palpable nodules through a needle guide\textsuperscript{29}. However, studies reported that 12\%-67\% of CaP tumors are not palpable\textsuperscript{30}, and it was concluded that CaP diagnostic sensitivity would benefit from a structured sampling of the gland. Systematic blind biopsy, wherein biopsy cores are sampled in a grid spanning both prostate hemispheres, was eventually introduced and proven superior to directed biopsy of hypoechoic artifacts\textsuperscript{31}. One systematic review of transrectal ultrasound (TRUS) guided biopsy, now the diagnostic standard, reported that 27\% of sextant biopsies resulted in CaP diagnosis, and use of a 12-cores scheme improved yield by 31\%\textsuperscript{32}.

Systematic TRUS-guided biopsy was a revolutionary leap relative to older methods, but tumors were still frequently missed as evidenced by the frequent detection of CaP in men with prior negative biopsies\textsuperscript{21,33,34}. By its nature transrectal biopsy has reduced sensitivity to anterior lesions, and even large posterior foci can be missed. Blind biopsy was the only option for decades, since the majority of tumors could not be directly visualized and targeted until the advent of mpMRI.

### 2.2.2 Magnetic Resonance Imaging Guided Biopsy

Multiparametric MRI enabled visualization of regions suspicious for cancer, and it was thus intuitive that such regions could be biopsied under direct MR guidance. This was
first performed transperineally at the Brigham and Women’s hospital, where 1.5 Tesla MRI was used to detect and guide biopsy of a single lesion. Since then commercial products for MR-guided biopsy have been developed and used at multiple institutions, including a transrectal biopsy system.

MRI-guided biopsy has been reported to confer needle placement accuracies on the order of 1-2 mm and yield CaP detection rates between 38% and 56%, a substantial improvement upon blind TRUS biopsy. However, widespread adoption of MRI-guided prostate biopsy has been limited by high costs, long procedure times, and an effective limitation on the number of cores acquired. Furthermore, recent studies have indicated that targeting only MR-visible foci is not sufficient, since many tumors are MR-invisible and thus require systematic biopsy.

### 2.2.3 Magnetic Resonance Imaging to Ultrasound Fusion Biopsy

Most limitations of MRI-guided biopsy can be addressed through application of MRI-ultrasound (US) fusion biopsy. For this approach, the patient receives a multiparametric MRI, with which ROIs and the prostate capsule are contoured. The contours are used to generate 3D surfaces that are imported to an MRI-US fusion biopsy platform. Such a device tracks motion of a TRUS probe to acquire a 3D ultrasound image volume, on which the prostate capsule is contoured. A registration between the prostate capsule on MRI and the prostate capsule on ultrasound is then performed, such that mpMRI-visible ROIs are superimposed on the US image volume. Biopsy cores can then be taken under real-time US guidance, both systematically and specifically targeting ROIs.

At least six MRI-US image fusion platforms have been developed and marketed for clinical use. The devices differ in many respects, including their method of tracking the TRUS probe’s position (electromagnetic vs. mechanical encoders), their registration.
algorithms (rigid vs. nonrigid), and their biopsy approach (transrectal vs. transperineal). The best technology and methodology has not been established, but studies report that MRI-US image fusion targeted biopsy (tBx) confers considerable advantages over conventional systematic biopsy. One study reported that fusion biopsy diagnosed 30% more high-risk CaP cases and 17% fewer low-risk CaP cases\textsuperscript{42}, while another 33% CaP detection with fusion relative to 7% CaP detection with systematic biopsy\textsuperscript{19}. Depending on the fusion platform and registration methodology, mean targeting error during clinical fusion biopsy has been reported on the order of 2 to 4 mm\textsuperscript{43-45}, a slight reduction from the accuracy of direct MRI guidance. However, more cores—including systematic cores—can be sampled using fusion biopsy, a critical factor for detection of many tumors\textsuperscript{39}.

The primary fusion platform used at UCLA is the Artemis (Eigen, Grass Valley CA), a commercial device developed through an NIH-funded academic-industrial partnership (Fig 2.2). The Artemis employs validated non-rigid registration algorithms and a

Figure 2.2: The Artemis MRI-US fusion biopsy platform, used at UCLA for targeted prostate biopsy
mechanical arm for TRUS position tracking\textsuperscript{46}. Peer-reviewed publications using the Artemis system have reported that tBx cores are 2 to 3 times more sensitive for CaP than systematic cores\textsuperscript{47}. Fusion biopsy has been employed in approximately 2500 targeted biopsy procedures at UCLA to date.

### 2.3 Prostate Pathology

After a biopsy or surgical specimen is formalin-fixed and paraffin-embedded, it is thinly sliced via microtome and evaluated microscopically for evidence of cancer. CaP is classified using the Gleason grading system, established in 1966 to describe the degree of tissue de-differentiation\textsuperscript{48}. Tumor foci are assigned a primary and secondary Gleason score (GS) or pattern between 1 and 5, with 1 corresponding to benign tissue and 5 corresponding to very highly undifferentiated CaP. A tumor's Gleason score is strongly correlated with pathologic stage and patient prognosis\textsuperscript{49,50}, and it remains one of the primary factors for determination of CaP management. Also critical is the stage of the disease, describing extent of CaP within the prostate as well as invasion of adjacent anatomy\textsuperscript{51}.

Surgically excised prostate specimens are often sliced and then quartered prior to fixation\textsuperscript{52}. However, at UCLA true whole-mount slides are prepared whenever possible, displaying entire slices at various depths of the excised prostate specimen in order to evaluate CaP stage and tumor morphology. The conventional procedure for whole-mount slide production at UCLA is summarized below:

1. After delivery of a prostate specimen (Fig 2.3A) to the surgical pathology laboratory, the specimen is inked to denote anatomic orientation, followed by shaving of the apex and base to evaluate surgical margins (Fig 2.3B).
2. The gland is then placed posterior-side-down and grossed in 3- to 5-mm increments along a cutting plane perpendicular to the base-apex axis (Fig 2.3C-D).

3. After each tissue specimen is formalin-fixed, embedded in paraffin, and microtomed, they are typically stained with hematoxylin and eosin (Fig 2.3E).

Pathologists often annotate these slides with prostate orientation. They also identify and contour tumor regions, determine if they belong to the same cancer focus observed on other levels, check for positive surgical margins, and evaluate tumor stage. The location, stage, Gleason grade, and geometry of each tumor are described in a surgical pathology report.
2.4 MRI-Pathology Correlation

Though multi-parametric MRI (mpMRI) has become a critical tool in the diagnosis and treatment of prostate cancer, the reported sensitivity of mpMRI remains fairly low, with many small and low-grade tumor regions escaping detection\textsuperscript{22,23}. Furthermore, although mpMRI can be used to identify the presence of most tumors, its utility in the prediction of a tumor’s true size and extent remains poorly characterized. It is critical that the sensitivity of mpMRI is improved, and the relationship between a lesion and its appearance on MRI is fully explored and understood. The most robust method of evaluating the accuracy of mpMRI is through correlation with whole-mount histopathology of surgically excised prostate glands.

2.4.1 Correlation Error Sources

Even whole-mount prostatectomy slides, which present the most geometrically coherent representation of CaP distribution, are subject to substantial error during correlation with imaging\textsuperscript{53-55}. During MR scanning, the patient lies in a prone position and images are typically acquired perpendicular to the axis of the magnet’s bore. As a result, prostate orientation during imaging can vary substantially, particularly due to rotations about the patient's left-right anatomic axis. When a prostatectomy specimen is sliced in the UCLA pathology laboratory, no attempt is usually made to match the slice plane with the MR image plane. Instead, a series of slices are acquired approximately parallel to one another and approximately perpendicular to the specimen’s posterior surface. Therefore, any difference in angle between the image axis and the prostate posterior surface results in rotation of the whole mount slides relative to \textit{in vivo} imaging. This rotation can be substantial, observed to approach 45 degrees in some cases (Fig 2.4).
MR image slices are acquired parallel to one another and evenly spaced, typically 1.5 mm apart for high-resolution T2 scans. However, manual slices from a prostatectomy specimen have variable slice width and orientation relative to one another. Thus, the true depth from which whole mount slides were sampled is unknown, and registration errors arise from the typical assumption that slices were evenly spaced. Furthermore, since manually acquired slices are not from parallel planes, attempts to estimate or reconstruct tumor volumes are prone to inaccuracy.

The prostate shape in vivo can differ greatly from the prostate ex vivo. If an endorectal receiver coil was used for MRI acquisition, the prostate often undergoes substantial deformation. The prostate itself can grow in the time period between imaging and prostatectomy, and extraprostatic tissue can be resected in addition to the gland. Vascular and urethral pressure collapse, tissue dehydration, and bladder neck dissection tend to deform prostate structure and reduce prostate volume by an average of 10%. The production of pathology slides subjects the specimen to additional stresses, including shrinkage during formalin fixation and tensile stresses during
slicing. As a result of the mismatch between the observed prostate shapes on MRI vs. whole mount pathology, correlations are further confounded.

The divergence in slice orientation, slice depth, and prostate shape between in vivo images and ex vivo slides has impeded attempts to perform quantitative MRI-pathology correlation. Ideally, all of these effects should be addressed in order to reliably register imaging with pathology and refine prostate cancer localization.

### 2.4.2 Correlation Methodologies

Some groups have attempted to register pathology slides to MRI purely through image analysis software. Manual annotation of landmarks such as the capsule, urethra, and prostatic nodules were often employed as a basis for non-rigid image registration. Voxel-based registrations using machine vision or mutual information were also commonly employed. Registration accuracy was typically assessed by comparing the location of anatomic landmarks or tumor extent, and mean errors were reported between 1.5 to 3 mm. However, most publications on this approach have been limited to relatively small sample sizes—between 3 and 36 patients for those studies referenced above. Also, in most cases critical assumptions were made regarding the spacing and orientation of slices. Because prostates were sectioned manually, these assumptions were likely incorrect, and consequently registration errors were underestimated.

Others attempted to regulate slice position through use of a guide or template, with evenly spaced slits designed to guide placement of the sectioning knife. This ensured that slices were evenly spaced and parallel to one another, allowing reasonably accurate estimation of tumor volume. However, such systems did not ensure that slides were acquired from the same depth or orientation as in vivo image planes. They also had
no way of compensating for differences between in vivo and ex vivo gland shape. Thus, many critical registration issues remained unresolved.

Some groups implemented ex vivo MRI scanning to aide in the registration process\textsuperscript{55,66-68}. Reynolds et al. immersed 6 prostate specimens in agarose gel, performed ex vivo mpMRI, and deformably registered the resulting image sets. Based on fiducials manually annotated by independent observers, their in vivo MR to ex vivo MR registration had 3.1 mm mean error and their in vivo MR to whole-mount registration had 3.3 mm mean error. Gibson et al. injected 9 prostatectomy specimens with gadolinium-soaked lamb kidney strand fiducials, which were visible on ex vivo MRI and whole mount slides. The fiducials served as the basis for an affine registration, and sub-mm mean errors were reported. Though these efforts appeared to produce highly accurate registrations, they were limited to small number of patients due in large part to the necessity for specialized pathology processing, ex vivo MRI, and long of processing times.

In order to assure accurate alignment of in vivo images with ex vivo specimen slices, the National Institute of Health first described the use of 3D-printed, patient specific molds\textsuperscript{69-71}. The molds contained a cavity exactly matching the in vivo prostate capsule segmentation and slits, spaced 6 mm apart, matching the position of MR image planes. Thus, theoretically the slice position, slice angle, and even prostate shape were matched to in vivo MRI. This method shows much promise, but sample sizes were modest and registration accuracy was not formally investigated.

\section*{2.5 Prostate Therapy}

The treatment of prostate cancer is a rapidly evolving field, and disease management is highly dependent on the grade and stage of a patient's disease. Mostly commonly,
newly diagnosed patients are managed through whole-gland extirpation such as radical prostatectomy, external beam radiation therapy, or brachytherapy. However, over the past decade the urologic community has begun to embrace active surveillance, or ‘watchful waiting,’ as an alternative to treatment for men with low-risk disease. A third paradigm, ‘focal therapy’, has gained traction in recent years and has the potential to deliver curative CaP treatment while minimizing side effects. An overview of whole gland therapies, the rationale for active surveillance, and a summary of the developing field of prostate focal therapy are included in the sub-sections below.

2.5.1 Whole Gland Therapies

The majority of patients diagnosed with localized prostate cancer are treated via radical prostatectomy (RP), wherein the entire prostate gland is surgically excised. Historically this was accomplished via open surgery, an invasive technique that necessitated several days of hospitalization post-procedure. However, radical prostatectomy gradually transitioned to a minimally invasive procedure, first via conventional laparoscopy and then with laparoscopic surgical robotics. Both techniques reduced invasiveness, blood loss, and the length of hospitalization, while robotic prostatectomy further improved blood loss, positive surgical margins, dexterity, ergonomics, and surgeon hand tremor. The dominant technology in robotic prostatectomy is the Da Vinci surgical robot (Intuitive Surgical, Sunnyvale CA), though competing devices are in development.

A common alternative to radical prostatectomy is radiation therapy. External beam radiation therapy (EBRT), the least invasive CaP treatment paradigm, has been practiced for over 5 decades. In its modern embodiment it involves focusing intense x-ray beams on the prostate while tracking patient position with periodic x-ray images. The prostate
is thus heavily irradiated while relatively low doses are delivered to surrounding tissue. Alternatively, brachytherapy involves implantation of a radiation source within the prostate, and has been frequently employed for treatment of CaP. Permanent seeds are implanted in a regular 3D distribution for low-dose-rate brachytherapy, whereas a highly radioactive isotope is temporarily passed through catheters for high-dose-rate brachytherapy\textsuperscript{78}. Combined regimens of EBRT and brachytherapy are frequently combined for CaP treatment\textsuperscript{79}.

Unfortunately, both prostatectomy and radiation therapy are prone to damaging sensitive local anatomy, particularly the neurovascular bundles posterior to the gland, the rectal wall, and the urethral sphincter near the prostate apex. This results in a high incidence of severe side effects, including incontinence and impotence. In one 704-patient, 5-year follow-up, prospective observational study of treatment outcomes in \textit{Radiotherapy and Oncology}, post-treatment impotence ranged from over 50% in brachytherapy patients to 85% in non-nerve sparing prostatectomy patients\textsuperscript{4}. Post-treatment incontinence ranged from 3-4% in radiation therapy patients to 38% in nerve sparing prostatectomy patients. Pain or burning during urination was also a frequent side effect, occurring most commonly (at \textasciitilde9\% in radiation therapy patients).

The high rates of incontinence and impotence are perhaps the most compelling argument against whole-gland therapy, as they constitute a severe impairment of quality of life. Material costs of prostate therapy are also very high, with mean open-market costs quoted at $34,720 ± $20,335 in 2013\textsuperscript{80}.

\subsection{2.5.2 Active Surveillance}

Overtreatment of prostate cancer has long been a concern in the medical community. Patients diagnosed with low-Gleason and low-stage disease have been shown to be
inherently low risk, with 8% CaP-specific mortality after 10 years and less than a 25% chance of upgrade following prostatectomy\textsuperscript{81,82}. One study cited incidental histologic rates of low-grade CaP in 30% of men in their 30’s, none of whom would have been symptomatic for decades and most of whom would likely never have even been diagnosed\textsuperscript{81}. It is evident that prostate cancer is a common phenomenon of the male aging process, and treatment should often be eschewed in low-risk patients.

Given the risks of prostate cancer therapy and the benign nature of low-risk disease, support has grown for active surveillance (AS), or ‘watchful waiting’, which serves as an alternative to curative therapy. Men enrolled in an active surveillance program typically harbor low- to intermediate-risk disease, and they undergo periodic imaging and biopsy in order to monitor for CaP progression. Theoretically, these patients only receive treatment if their disease advances to a more serious grade or stage. Thus, patients can avoid the costs and side effects of treatment while maintaining reasonable certainty that their disease remains in a manageable state.

Active surveillance programs have been highly successful nationwide. Ultimately many patients (14% to 41%) go on to receive whole gland therapy, but this is often attributable to patient preference rather than evidence of disease progression\textsuperscript{84}. The prognosis of such patients is generally no worse than if they had immediately sought curative therapy; one AS program reported no CaP deaths despite recruiting 769 patients over the course of 15 years, 33% of whom ultimately received curative treatment\textsuperscript{85}. It is very rare for a patient’s disease to progress to an unresectable state, since a prerequisite for most programs is relatively small, localized, and well-defined disease. In a review of 6 large AS programs reporting CaP-specific mortality, less than 0.2% of 3454 total patents died of prostate cancer\textsuperscript{86}.
Randomized, prospective studies have supported the preferential use of AS over whole gland therapy for low-risk patients. In the New England Journal of Medicine in 2012, a study of 731 men in the United States with minimum 8-year follow-up demonstrated no radical prostatectomy survival benefit for men with low-risk CaP; in fact, survival was worse for RP patients after 14-year follow-up\(^8\). A modest survival benefit was observed for men with intermediate-risk CaP, with more appreciable benefits for high-risk patients. However, even for high-risk men, a 10% improvement in disease-specific survival did not occur until after approximately 10 years of follow-up.

Results were similar for another New England Journal of Medicine study published in 2015, wherein 695 European men were followed for 13-14 years\(^8\). Regardless of treatment vs. observation, low-risk CaP patients had uniformly high survival rates (~95% at 12 years). Similarly, regardless of treatment strategy high-risk CaP patients had uniformly lower survival rates (~65% at 12 years). This implied that low-risk \textit{and} high-risk patients, at least in that population, did not benefit from treatment. Only intermediate-risk patients survived longer following radical prostatectomy, perhaps because, unlike high-risk patients, they had lower-stage disease that was still possible to fully resect.

The rationale for AS is clear, but there are drawbacks to this method of CaP management. Considerable anxiety is reported by men and their wives, stemming from the knowledge that they are living with cancer\(^9\). This fear is not entirely baseless since progression is possible, though extremely rare in a well-managed AS program. Furthermore prostate biopsy is uncomfortable for patients, it results in high rates of low-level adverse events such as hematuria, and each transrectal procedure carries an infection risk, with fever occurring in approximately 2% of patients\(^2\). Though much less expensive than whole-gland treatment, repeated biopsy sessions in AS programs cost
$1154-$1752 per year\textsuperscript{90}, and mpMRI charge estimates were $2000-$3000 in the United States\textsuperscript{91}. Active surveillance adoption rates remain fairly low, with approximately 10% of eligible men choosing it over treatment\textsuperscript{92}.

2.5.3 Focal Therapy

It is generally accepted that low-risk CaP is appropriate for AS programs, and high-risk CaP should be aggressively treated with whole-gland therapy. However, for intermediate-grade CaP, the ideal treatment strategy remains unclear. One recent study suggest that these men stand to receive the greatest survival benefit from treatment\textsuperscript{96}, perhaps because their tumors are more localized and thus more easily treatable than high risk disease. Since intermediate-risk patients harbor lower-stage disease, it is a logical supposition that instead of extirpating the entire prostate gland the tumors of some men might be focally treatable. Given proper image guidance, focal therapy has the potential to provide patients with curative treatment without compromising local anatomy such as the neurovascular bundles, thus avoiding the severe side effects of incontinence and impotence. Furthermore, focal therapy is likely to be performed in a minimally invasive manner, reducing morbidity and the length of hospitalization. As of 2012, 30 studies had been published on clinical trials of prostate focal therapy, 9 of which reported on primary FT with intent to treat\textsuperscript{8}.

The ideal standards for FT-eligibility have yet to be determined, but consensus panels have suggested that trials restrict themselves to low or intermediate risk patients with unilateral disease\textsuperscript{93}. Treatment is often preceded by transperineal template mapping biopsy, which was reported in one biopsy-and-resect study to detect 96% of significant tumors\textsuperscript{94}. However, other studies have reported significant CaP to be missed in 17% of men\textsuperscript{95} or misdiagnosed as clinically insignificant in 11% of men\textsuperscript{96}. Alternatively, mpMRI
often serves as the primary modality for patient selection and focal treatment planning, supplemented by biopsy information\cite{97-99}. The specificity of this approach is unknown, but a retrospective study of prostatectomy patients by our group suggests that 26.5% of FT candidates identified using fusion biopsy were not truly FT eligible. If correct, this result would likely warrant supplementation of the typical fusion biopsy schema with a higher density of targeted and/or systematic cores in preparation for focal therapy.

Given the propensity of CaP for multifocality and MR-invisible extensions, some physicians reported extirpation of three quarters\cite{100} or one hemisphere\cite{101,102} of the gland. Others attempted true focal therapy, wherein only the biopsy-proven tumor plus a surgical margin was treated\cite{103,104}. Regardless of treatment extent, focal therapy trials have reported favorable side effect rates relative to whole-gland therapy, with 54%-100% erectile function and 95%-100% continence\cite{8}. Unfortunately, residual CaP has also been reported in many cases, with post-treatment positive biopsy rates from 4% to 50% in the 9 intent-to-treat studies published before 2013\cite{8}. More recently published studies have reported residual CaP in 15% to 37% of patients, a noteworthy improvement over prior work\cite{105-110}. All reported no significant decrease in urinary health with one exception (8%\cite{108}), and sexual health decline was reported as insignificant with three exceptions (23%\cite{108}, 26%\cite{110} and 48%\cite{106}).

Various treatment modalities have been implemented in FT trials. High-intensity focused ultrasound is commonly adopted for true focal or hemi-abelations; one 42-patient trial conducted by the Ahmed et al. reported 77% successful CaP extirpation, 89% potency and 100% continence after 6 to 12 months of follow-up\cite{102}. Cryoablation is also frequently employed, though some trials have reported high impotence rates approaching that of whole-gland therapy\cite{106}. Focal brachytherapy, irreversible electroporation, and photodynamic therapy have also been reported, albeit less
Photothermal laser therapy, also called laser-interstitial thermal therapy (LITT) or focal laser therapy (FLA), is the primary modality employed in this work, and thus it is described in greater detail in the following subsection.

### 2.5.4 Focal Laser Ablation

Focal laser ablation is a treatment modality wherein a laser-coupled optical fiber is placed interstitially, within or adjacent to the tumor. Most commonly the fiber's distal end contains a diffuser, to help evenly distribute laser energy. Thus, when the laser is activated photons are absorbed by tissue around the fiber and temperature begins to rise. Irreversible thermal damage is achieved within a few seconds above 60° Celsius, after which the tissue subsequently undergoes coagulative necrosis. Interstitial laser manufacturers recommend maximum temperatures well below 100 degrees, to avoid vaporization and gas pocket formation.

There are a number of advantages to FLA relative to other treatment modalities. First, fiber optic probes are inherently flexible and can be manufactured with sub-mm core diameters, facilitating minimally invasive insertion. Second, laser power is easily adjusted and fiber optic tips are customizable, allowing treatment to be tailored to patient anatomy. Third, laser fibers are inherently MRI-compatible, facilitating direct implantation within MR-visible lesions and monitoring via MRI thermometry.

Two treat-and-resect studies, wherein FLA was followed by radical prostatectomy and whole-mount pathology, have verified that thermal damage was well-confined, margins between homogeneously treated and untreated tissue were narrow (sub-mm), and damaged volumes closely matched post-procedure contrast-enhanced MRI. Early FLA studies confined themselves to low-risk CaP patients, but recent efforts have included low to intermediate-grade disease. Three groups reported use of a
transrectal approach\textsuperscript{113,119,120} for laser fiber insertion, and three took the transperineal route\textsuperscript{105,115,121}. Most relied on direct MR guidance for fiber placement and temperature monitoring; only one group reported use of US fusion-guided FLA\textsuperscript{114,115}.

Hundreds of patients have been treated with FLA in a number of ongoing trials, but only a handful of publications are currently available. Every FLA publication, from single-patient case studies to phase II clinical trials, has reported excellent patient safety and impressive side effect profiles, with no significant change in urinary or erectile function in the largest trial to date (N = 27)\textsuperscript{105}. However, thus far only 2 trials have listed CaP control, not safety, as their primary endpoint. These intent-to-treat trials reported residual CaP at frequencies of 7\%\textsuperscript{105} and 37\%\textsuperscript{120}. This discrepancy in reported CaP recurrence is likely a consequence of variations in treatment and follow-up procedures; patients in the former trial only received biopsies from the treated zone, whereas the latter trial acquired targeted cores and 12 systematic cores. Despite the promise of these preliminary results, adoption of FLA has been slow, partly due to the costs, lack of reimbursement, and availability of interventional MRI.
CHAPTER 3
Development and Validation of a System for MRI-Pathology Correlation

In order to characterize the accuracy of MRI tumor segmentations, a reliable means of MRI-pathology correlation was necessary. Such a system needed to overcome the limitations of conventional grossing by regulating the depth and orientation of prostate slices. Each whole-mount slide was required to match the depth and orientation of a predetermined in vivo MR image. One promising method of ensuring such precise slice acquisition was via patient-specific 3D-printed molds, first reported by the National Institute of Health.

Based on the work of Trivedi et al., patient-specific 3D-printed molds were designed for MRI-pathology correlation at UCLA. In order to demonstrate that patient-specific molds ensured more accurate MRI-correlation than conventional grossing, we conducted a powered in vitro study using tissue-mimicking prostate phantoms. Then, in order to measure the accuracy of mold-based registrations, prostate specimens were placed within 3D-printed molds and scanned ex vivo. Together, the in vitro and ex vivo studies demonstrated the advantage of 3D printed molds and the mean error that could be expected from mold-based MRI-pathology correlations. Portions of the material in this chapter were presented at the American Urology Association annual meeting in 2014 and have been submitted to the International Society of Magnetic Resonance in Medicine.
3.1 Patient-Specific 3D-Printed Prostate Molds

Prostate molds were designed to hold an excised prostate in the same position and orientation with which it was imaged \textit{in vivo}. Furthermore, the mold was intended to guide slicing of the excised gland such that each whole mount section corresponded to a predetermined MR image. The mold was designed to facilitate registration of prostate specimens with high resolution T2 MRI, for which image slices were acquired in 1.5 mm increments. Since prostate geometry and MRI orientation varied widely from subject to subject, it was necessary to make each mold single-use and patient-specific.

3.1.1 Mold Design

The use of patient-specific molds was predicated on the assumption that the prostate capsule, as visualized on \textit{in vivo} T2 MRI, was a close approximation of the boundary with which the gland would be surgically excised. Consequently, the first stage of mold design was segmentation of the prostate capsule on T2 MRI. This was accomplished using ProFuse (Eigen, Grass Valley, CA), a semi-automated software package that required the user to segment the prostate capsule on one image from the sagittal, axial, and coronal perspective (Fig 3.1A-C). Profuse then interpolated these segmentations to produce a smoothed capsule contour, which could be fine-tuned with additional manual segmentations. Regions of interest were also contoured, and all segmentations were exported as triangulated 3D surfaces (Fig 3.1D).

The capsule surface was imported into Solidworks 2014 (Dassault Systèmes, Vélizy France), a computer aided design (CAD) software suite. After rotation such that MR image orientation was parallel to the mold's apical surface, the capsule segmentation was used to generate a corresponding cavity within a prostate mold template (Fig 3.2).
This cavity was intersected with slits in 4.5 mm intervals, sampling one in three images from the registered MRI sequence. Each slit corresponded precisely with the location and orientation of an image from \textit{in vivo} MRI.

Figure 3.1: Axial (A), sagittal (B), and coronal (C) views of a high-resolution T2 scan, with ROI contours in green and the prostate capsule in blue. Contours were used to generate 3D surfaces (D).

Figure 3.2: Prostate capsule contours (blue, left) were used to generate a corresponding cavity (right, red) within a prostate mold template (right, gray/blue).
Multiple versions of the template were designed in order to accommodate a range of prostate gland volumes up to 110 cc. Each template was also annotated with anatomic descriptors to ensure correct alignment of the prostate specimen, and letters aligned with each slit to facilitate record keeping within the surgical pathology report. A CAD image of a completed mold can be seen in Figure 3.3.

![Figure 3.3: Completed mold as viewed in computer aided design software.](image)

### 3.1.2 Mold Manufacture

After generation of a prostate capsule cavity within a mold template, the anterior and posterior halves of the mold were separately exported as triangulated 3D surfaces. These surfaces were then imported into Makerware 3D printing software (Makerbot Industries, Brooklyn NY). The mold was 3D printed from polylactic acid, a biocompatible plastic, with 0.2 mm resolution along the anterior-posterior axis and 0.1 mm along other
axes. Using a Makerbot Replicator 2, the average mold required 6 hours to print and consumed material costing approximately 4 US dollars. The anterior and posterior mold halves could then be fitted together using an aligned set of pegs and holes, encapsulating the prostate cavity within.

### 3.2 In Vitro Characterization of Mold Slicing Accuracy

An *in vitro* study was designed in order to quantify the benefit of patient-specific molds and justify their clinical deployment. This study involved the production of tissue-mimicking prostate phantoms, which were sliced with and without a 3D-printed mold. Data from a single pair of phantoms, sliced by a pathologist assistant, was used as the basis for a power estimation performed by the UCLA Department of Medicine Statistics Core. 1000 Simulations were conducted for various sample sizes assuming random normal distributions with the same mean and standard deviations as the preliminary data. Statistical tests for differences in handheld versus mold-sliced specimens were conducted using a mixed effects linear regression model with case random intercept, conducted with the “lme” command from the “nlme” package in R Version 3.2.1 (R Foundation for Statistical Computing). The simulation reported that differences in slice angle error and slice thickness would be detected with greater than 95% power for paired sample numbers of 20 or higher (Table 3.1). The *in vitro* study was ultimately conducted with a paired sample number of 28, evenly distributed across 7 subjects. This study was IRB-exempt, as it required no human tissue and imposed negligible risks to subjects (IRB#16-000021).
3.2.1 In Vitro Study Materials and Methods

In Vitro Mold Design

Six prostate molds were designed from the T2 prostate capsule segmentations of six radical prostatectomy patients. The patients were chosen to include a range of prostate morphologies, volumes (33-68 cc), and posterior capsule angles (1°-22°) relative to the MR image plane, which was hypothesized to be a major source of correlation error. In order to simulate imperfect fit of molds with prostatectomy specimens, the prostate cavity dimensions were enlarged by 5% relative to the phantom. The six molds were 3D-printed with the same settings described in section 3.1.2.

Phantom Design and Manufacture

Six prostate phantoms were designed, corresponding to each of the six prostate segmentations used to generate patient-specific molds. Each prostate model was placed inside a casting mold template, which also included an anterior aperture for casting, a divot to indicate location of the urethra, and trajectory guides for 12 fiducial vectors (fig 3.4A). These fiducials, used to track slice angle and location, were split into 3 equal groups and designed according to the following criteria:

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Power for X-Angle Error</th>
<th>Power for Y-Angle Error</th>
<th>Power for Total Angle Error</th>
<th>Power for Slice Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>96.4%</td>
<td>100%</td>
<td>100%</td>
<td>25.0%</td>
</tr>
<tr>
<td>3</td>
<td>99.6%</td>
<td>100%</td>
<td>100%</td>
<td>32.5%</td>
</tr>
<tr>
<td>4</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>41.8%</td>
</tr>
<tr>
<td>5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>48.1%</td>
</tr>
<tr>
<td>10</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>78.6%</td>
</tr>
<tr>
<td>15</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>91.1%</td>
</tr>
<tr>
<td>20</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>96.5%</td>
</tr>
</tbody>
</table>

Table 3.1: Power Analysis for detecting differences in mold vs hand slicing
**Fiducials 1-4 (inked blue):** These 4 trajectories ran parallel to the MR image axis, and were arranged to form the corners of a 15mm x 15mm square. The distance between these fiducials was sensitive to the angle with which a phantom was sliced.

**Fiducials 5-8 (inked red):** These 4 trajectories formed a pyramidal structure, largest near the prostate phantom apex and tapering as they approached the phantom’s base. Therefore, the distance between these fiducials was sensitive to the depth with which a phantom was sliced.

**Fiducials 9-12 (inked green):** These 4 trajectories were perturbed from the MR image axis using a random number generator, constrained to lie within 2 cm of it at the apex and base surface of the casting mold. Their position was further altered, as needed, to avoid intersection with fiducials 1 through 8. Each green-inked fiducial trajectory was intended to be uncorrelated with the other fiducials, and their positions should therefore have been sensitive to both slice depth and slice angle.

The casting molds were 3D-printed in anterior and posterior halves, with the same printer and settings used to produce patient-specific molds. Phantom manufacture proceeded according to the following steps:

1. The casting mold’s anterior and posterior halves were fitted together.
2. The superior, inferior, left, and right faces of the mold were sealed with Parafilm.
3. Luer lock needles were inserted along the 12 fiducial trajectory guides (fig 3.4B).
4. Agarose gel (3%) was poured into the casting molds from the anterior aperture.
5. The phantom was refrigerated for 3 hours and allowed to set.
6. As the 12 Luer lock needles were withdrawn, water-insoluble acrylic ink was injected along their former trajectories.
7. The phantom was removed from the casting mold (Fig 3.4C), and extra agar from the anterior aperture was cut off.
8. The apex and base urethra locations were marked with black and yellow acrylic, respectively. A yellow line connecting the two urethra apertures was traced along the anterior phantom surface. These were included as a reference for the phantom’s anatomic orientation, since real prostate specimens are labeled with analogous ink patterns.

9. The phantoms were placed in sealed containers and refrigerated until use.

![Figure 3.4: Phantom design with 12 color-coded fiducials (A) which were implanted along 3D-printed trajectories using Luer lock needles (b) in an agarose tissue-mimicking prostate phantom (C)](image)

**Phantom Slicing**

Seven subjects were recruited from the surgical pathology laboratory: 3 pathologists and 4 pathology assistants, all of whom were experienced in the grossing of prostate specimens. Each subject was randomly assigned 3 of the 6 prostate phantom models available (Table 3.2). Prior to data collection, each subject was equipped with a long-bladed sectioning knife, a short-bladed sectioning knife, forceps, a cutting board, and three prostate molds corresponding to the three phantoms they had been assigned. They were shown a sample prostate phantom, with an explanation of the correspondence between external ink patterns and the phantom’s anatomic orientation. Placement of a
phantom within the patient-specific mold, and mold-based slicing with the long-bladed sectioning knife, was also explained in full.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Prostate 1</th>
<th>Prostate 2</th>
<th>Prostate 3</th>
<th>REPEAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
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<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>6</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3.2: Randomized assignment of phantom models 1 through 6 to the 7 subjects. Each subject processed a repeat of their first phantom model before concluding the study.

The subjects were then given the first pair of (identical) prostate phantoms, based on the first of three prostate models. They were instructed to slice the first phantom by hand, exactly as they would in a real prostate specimen in clinical practice. They were then instructed to slice the second phantom with using its corresponding mold. The order of slicing was not randomized, since we did not want to bias handheld slice locations through observation of the mold-sliced specimens. The mold-slicing was effectively blinded, since the prostate could not be visualized once placed inside the mold. This process was repeated for each of the 3 phantom models assigned to each subject. Lastly, the subject sliced a fourth pair of prostate phantoms identical to the first, in order to assess intra-subject slice variability.

In total 56 prostate phantoms were sliced in this manner—28 by hand, and 28 with the mold. According to the power analysis, this sample size conferred over 97% likelihood of detecting differences in slice thickness and 100% likelihood of detecting differences in slice angle. Between 7 and 13 slices were acquired per phantom.
Slice Digitization and Annotation

For each of the 56 phantoms, the sliced specimens were laid out on a transparency and digitized with 600 dots per inch using a flatbed scanner (Fig 3.5A). The phantom images were adjusted using histogram equalization in order to maximize fiducial visibility. The images were then imported into adobe illustrator, where a template was used to annotate the fiducial positions with color-coded dots, each dot designating the intersection of a fiducial vector with the slice plane. The fiducial-intersection images for each phantom were then exported as a single image file.

Slice Reconstruction and Analysis

Each of the 6 digital phantom models (Fig 3.5B) was imported to MATLAB 2015a (Mathworks, Natick MA) along with its 3D fiducial trajectories. The phantom model was then digitally intersected with slice planes in 0.2 mm depth increments and one degree angle increments, rotated around the left-right (LR) and anterior-posterior (AP) anatomic axes. Between 275,000 and 350,000 unique slice plane combinations were sampled for each phantom model, depending on prostate size. The intersection of each slice plane with the 12 fiducial vectors (Fig 3.6) was calculated and transposed into 2 dimensional
(2D) coordinates. The library of fiducial-intersections corresponding with each slice plane was then recorded in matrix form.

For each of the 56 prostate phantoms, its fiducial-intersect image was imported into MATLAB. The fiducial locations for each slice were recorded, and an in-plane rotation was performed in order to match the orientation of the fiducial-intersection library. The observed fiducial locations were then compared against the library, and the closest match was chosen according to minimum mean error between observed and modelled fiducial coordinate sets. Thus, the depth and angle of each slice was determined based on the pattern of fiducials. The depths and angles were then each compared to the ‘ideal’

Figure 3.6: Example fiducial formations (right) expected for various planes of intersection with a prostate phantom (left). Fiducial formation changed uniquely with the depth and angle of the intersection plane.
slice planes that are typically assumed in MRI-pathology correlation, i.e. planes perpendicular to the imaging axis and evenly spaced throughout the prostate. The depth error, rotational error (LR and AP) and slice width were then recorded for each phantom slice.

Lastly, in order to investigate 3D reconstruction error, 30 ROIs suspicious for CaP were imported to MATLAB and registered with the prostate for each of the 6 phantom models. The intersections of these ROIs with the actual slice planes for all 56 phantoms were calculated. Each ROI was then reconstructed using the typical assumptions of MRI-pathology correlations, i.e. equal spacing of slice planes perpendicular to the imaging axis. The 2D contours of each ROI were transposed to its assumed slice plane, and then used to construct a 3D surface under the assumption that each 2D contour extended halfway to each neighboring slice plane. The volumetric error and overlap between each ROI and its reconstruction were then measured.

### 3.2.2 In Vitro Study Results

The study hypothesis (H1) was that registration errors would be lower for mold-processed phantoms, and the null hypothesis (H0) was that registration errors would be the same. Based on the tabulated study results (Table 3.3), the null hypothesis was firmly rejected. All reported P-values were calculated using a Wilcoxon signed-rank test.

For the 21 (non-repeat) matched pairs, the mean LR-axis rotational error in hand-sliced phantoms was about 2.4 times greater than in mold-sliced phantoms. Mean AP-axis rotation errors were nearly identical, at 3.9 and 3.7 degrees respectively. Depth error was 2.1 times greater in hand-sliced phantoms.

The mean 3D point-to-point reconstruction error, conventionally referred to as the target registration error (TRE), was 2.2 times greater in hand-sliced phantoms than mold-
sliced phantoms. The mean centroid of reconstructed ROIs was 1.6 times farther from
the true centroid in hand-sliced phantoms. The reconstructed volume error was 10%
lower in mold-sliced phantoms, and the mean reconstructed ROI overlapped with 58%
of the original ROI, whereas hand-sliced ROI reconstructions had only 43% overlap.

<table>
<thead>
<tr>
<th>Mean Inter-Phantom Error (N = 21)</th>
<th>Mold Sliced</th>
<th>Hand Sliced</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-Axis Angle Error ± SD (°)</td>
<td>4.5 ± 2.9</td>
<td>10.7 ± 6.7</td>
<td>0.001</td>
</tr>
<tr>
<td>AP-Axis Angle Error ± SD (°)</td>
<td>3.9 ± 3.6</td>
<td>3.7 ± 4.2</td>
<td>0.9 (NS)</td>
</tr>
<tr>
<td>Depth Error ± SD (mm)</td>
<td>1.0 ± 0.4</td>
<td>2.1 ± 1.4</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Reconstruction Accuracy (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recon. Point-to-Point Error ± SD (mm)</td>
</tr>
<tr>
<td>Recon. Centroid Error ± SD (mm)</td>
</tr>
<tr>
<td>Recon. Volume Overlap ± SD (%)</td>
</tr>
<tr>
<td>Recon. Volume Difference (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Intra-Phantom STD (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-Axis Angle (°)</td>
</tr>
<tr>
<td>AP-Axis Angle (°)</td>
</tr>
<tr>
<td>Slice Width (mm)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Mean Intra-Subject Errors (N = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR-Axis Angle Diff ± SD (°)</td>
</tr>
<tr>
<td>AP-Axis Angle Diff</td>
</tr>
<tr>
<td>Depth Diff ± SD (mm)</td>
</tr>
</tbody>
</table>

Table 3.3: Data summary for mold vs. hand-sliced prostate phantoms

Slice width and angle had less intra-phantom variation for mold-sliced specimens. In
other words, mold-sliced cutting planes tended to be clustered more tightly around that
phantom’s mean than hand-sliced cutting planes. This is evidenced by the significantly
higher intra-phantom standard deviation observed in the hand-sliced population.

Of the N=7 phantom pairs that were repeated, one was excluded as an extreme
outlier. Mold-sliced angle error was 20 times higher than hand-sliced angle error for this
case, whereas mold-sliced angle error was lower than hand-sliced angle error for all other
samples. As this was the last phantom experimented upon, but one of the first phantoms
manufactured, it is hypothesized that agar dehydration caused an uncharacteristically
poor fit within the mold. For the remaining N = 6 mold-sliced phantom pairs, the original specimen’s mean plane was 3.8° (LR-axis rotation) and 2.4° (AP-axis rotation) different the mean plane of the repeat specimen. However, when hand-sliced, the original specimen had a 12.3° (LR-axis rotation) and 5.5° (AP-axis rotation) difference in slice plane from the repeat specimen. Slice depth was also somewhat more consistent in the mold-sliced population. Due to the small intra-subject sample size, only LR-axis rotation errors were significantly different.

As slicing proceeded from apex to base, a few noteworthy trends were observed. AP-axis rotation in mold-sliced phantoms was seen be positive near the prostate apex, zero near the prostate center, and negative near the prostate base (Fig 3.7A, red). No such trend was observed for hand-sliced phantoms (Fig 3.7, yellow). Absolute depth error was lowest near the prostate center for mold-sliced phantoms, but highest near the prostate center for hand-sliced phantoms (Fig 3.7B).

Observation of data trends suggests that various error measures, especially reconstruction error, increase with prostate size. However, the sample size was not sufficient to test such correlations, since only 6 variations in phantom model were used.

![Figure 3.7: Trends in A) slicing angle and B) depth error relative to slice position from apex to base.](image-url)
3.2.3 *In Vitro* Study Discussion

The mold ensured that slices were significantly closer to their target depths than in phantoms processed manually. Mold slice planes were also significantly closer the MR image plane, at least with reference to LR-axis rotation. This was by far the larger of the rotational errors in the hand-sliced population, suggesting that, as hypothesized, differences between the MR image axis and posterior prostate surface are a major source of error in radiology-pathology correlations.

The fact that AP-axis rotation errors did not follow this trend and were nearly identical between the two populations helps highlight one potential weakness the 3D-printed mold. Unlike handheld tissue processing, where a sectioning knife cut down from the prostate’s anterior to posterior, within a mold the knife cut from the prostate’s right to left. The torque exerted on the prostate by the knife likely caused the specimen to rotate inside the mold. This hypothesis is supported by observation of the mean AP rotation angle vs. slice number for mold-sliced phantom, which was seen to be high near the apex, zero near the phantom center, and negative near the base. Likely as a result of this rotational error, the mean absolute depth error in the mold-sliced population was lowest in the phantom center (0.7 mm) and highest in the far apex and base (1.5 and 1.1 mm). This trend was not observed in the hand-sliced population, which had more uniform AP rotation error and high depth error (2.3 mm) near the prostate center.

Perhaps the most important metric measured in this study was the point-to-point reconstruction error. This represents the mean registration error during MRI-pathology correlation, and was improved from 4 mm in the manually sliced population to only 2 mm in the mold-sliced population. When ROIs were reconstruction volumetrically, they overlapped with the true MRI location more consistently when mold-sliced. This is
critical, since tumors will tend to span multiple slices they should therefore be reconstructed and compared volumetrically, not slice-by-slice, with MRI predictions.

The standard deviation of slice width and LR-axis rotation angle were also lower intra-phantom for mold-sliced cases. This indicates that slice position and LR-axis angle changed much more erratically in the hand-sliced populations. However, intra-mold standard deviation was significantly higher for AP-axis rotation, further supporting the hypothesis that torque from the sectioning was causing the prostate to gradually rotate relative to the AP axis.

The lower intra-subject LR rotational errors for mold-sliced phantoms that were repeated (3.8 vs. 12.3 degrees) indicate that handheld slicing delivers less consistent and predictable results, even when performed by the same operator. Other measures of error were also lower for the repeat measurements, but the study was not sufficiently powered to prove their significance.

Overall, the mold-sliced phantoms greatly improved registration accuracy, reducing mean 3D error from 4 to 2 mm. These results constitute strong evidence that 3D-printed molds should be used preferentially over conventional manual prostate slicing for any study where accurate MR-pathology registration is desirable.

3.3 Ex Vivo Characterization of 3D-Printed Mold Target

Registration Error

The in vitro phantom study previously described demonstrated the superior registration accuracy afforded by 3D-printed molds, but no phantom perfectly simulates human tissue. Human prostates differ from their phantom counterparts in their mechanics and their fit within the mold. Relative to MRI capsule contours, prostate specimens tend to
have extra tissue in the posterior missing around the bladder neck due to surgical dissection\textsuperscript{17}. In order to fully characterize mold registration accuracy, it was therefore necessary to perform MR imaging of \textit{ex vivo} prostate specimens.

3.3.1 \textbf{Ex Vivo Study Materials and Methods}

A variation of the previously described prostate mold template was designed for scanning and slicing \textit{ex vivo} specimens (Fig 3.8). First, instead of printing a mold with solid interfaces along all 6 sides, the posterior and anterior mold faces were a permeable mesh with 3-5 mm diameter channels running continuously parallel to the AP axis. Second, backup versions of each mold were designed and printed with isotropically expanded prostate cavities. These secondary molds were designed to accommodate a prostate with 15-20\% increased volume relative to MRI contours, and were only used if the original mold was of insufficient size to house the specimen. Third, an additional cavity was placed in the left side of the mold to house a ‘fiducial cartridge’ and facilitate \textit{in vivo} to \textit{ex vivo} registration.

The fiducial cartridge (Fig 3.9A) was designed with a channel running along its length. Evenly spaced along this channel were 4.5-mm lengths of solid plastic and 4.5-mm offshoot channels running perpendicular to its main axis. This channel was injected with 2\% liquid agarose, which filled all available space and was then allowed to set into solid agar. The result was a pattern of MR-visible agar striations, interspersed with MR-invisible plastic, in a pattern that repeated every 9 mm. The center of each agar and each plastic stratum corresponded with one of the mold slits. In order to indicate the prostate apex, an additional ‘L’-shaped channel was also included. After manufacture, the fiducial cartridges were sealed and refrigerated until use.
For a total of 7 patients, once the excised prostate was delivered to the surgical pathology laboratory, the specimen was considered a suitable fit within the 3D-printed mold and it was placed inside along with a fiducial cartridge (Fig 3.9B). The mold was then housed within a 3D-printed frame, designed to hold it rigidly near the center of a cylindrical container (Fig 3.9C). The frame was placed within the container and subsequently immersed in a perfluorocarbon solution (Fomblin, Solvay S.A., Belgium) to match the magnetic susceptibility of tissue while avoiding background signal (Fig 3.9D). The container was sealed and then transported to an experimental MR suite for scanning.

The container was placed inside a 15-channel knee coil within a whole-body 3T MRI scanner. A crosshair printed into the frame was aligned with the scanner laser for consistent positioning. The specimen was scanned for approximately one hour, including a T2-weighted high resolution sequence (2D Turbo Spin Echo, Field of View 75x75 mm, acquired in-plane resolution 0.29x0.29 mm, slice thickness 1.5 mm, 3 averages, 8 min) which would be used to evaluate registration accuracy. The specimen
was then returned to the surgical pathology laboratory, where a pathology assistant performed slicing without altering the prostate's position within the mold. Thus, the whole-mount slices were assumed represent a plane nearly identical to that visualized \textit{ex vivo} at the center of each stratum within the fiducial cartridge.

![Figure 3.9: Ex vivo prostate scanning setup including A) a fiducial cartridge with MR-visible striations, B) a permeable patient-specific mold, and C) a frame to hold the mold stably inside D) a container filled with MR-neutral fluid.](image)

Target registration error was evaluated using two methods. In the first method, a genitourinary radiologist manually annotated points within the prostate based on
anatomic landmarks that were visible on *in vivo*, *ex vivo*, and whole mount prostatectomy slides (Fig 3.10). For each specimen, 12 to 20 points were annotated in this manner, depending on the number of whole-mount slides available. The target registration error between *in vivo* and *ex vivo* scans was evaluated by measuring the distance between corresponding points after performing a rigid registration between the scans, according to the fiducial cartridge location. The target registration error between imaging and pathology was evaluated by first registering the pathology slides with the T2 scans (see section 4.1.4 for methodology) and then measuring the distance between corresponding points. The advantage of this approach is that all three image sets could be registered with one another. The disadvantages are that the identification of anatomic landmarks was somewhat subjective, rotational error could not easily be evaluated, and the process was very time-intensive; thus, only the first 3 cases were evaluated in this manner.

The second method of evaluation involved a rigid intensity-based registration, using custom MATLAB scripts and a robust methodology reported in prior publications\(^\text{124}\). Using this method, the *in vivo* and *ex vivo* DICOM sequences were resampled in order to have identical isotropic resolution (0.37 mm\(^3\)). Then, the intensities of voxels within the prostate were normalized. Lastly, the *ex vivo* scan, called the ‘floating’ volume, was
rotated and translated in 3D space until the intensity of voxels ideally matched those of
the *in vivo* scan, the ‘reference’ volume. Two similarity measures, the correlation
coefficient and mutual information (MI), were measured for voxels within the prostate
during each registration.

The formula for the correlation coefficient is given below:

\[
CC(R, F) = \frac{\sum (R(r) - \bar{R}(r))(F(f) - \bar{F}(f))}{\sqrt{\sum (R(r) - \bar{R}(r))^2 \sum (F(f) - \bar{F}(f))^2}}
\]

Eq 3.1

Where R and F are the lists of voxel intensities within the reference and floating
volumes respectively, and \( \bar{R} \) and \( \bar{F} \) are the mean voxel intensities respectively. The
correlation coefficient was used to measure similarity between the reference volume and
floating volume at lower resolutions, sampling around the default registration in 1.1 mm
and 2° increments. It was employed for the first-pass registration because prior studies
have shown the correlation coefficient to be less susceptible to local minima than MI
measures\(^{125}\).

The formula for measuring mutual information is given below:

\[
MI(R, F) = \sum_{r,f} p_{RF}(r, f) \log \frac{p_{RF}(r, f)}{p_R(r) \cdot p_F(f)}
\]

Eq 3.2

Where \( p_{RF} \) is the joint probability, \( p_R \) is the marginal probability of the reference
volume, and \( p_F \) is the marginal probability of the floating volume. These were estimated
from the normalized joint and marginal intensity histograms, respectively. Mutual
information was used to measure similarity between the reference and floating volume
at higher resolution, in 0.37 mm and 1 degree increments, once an initial registration
had been determined using the correlation coefficient. It was employed for the second-
pass registration because prior studies have shown MI measures to converge more sharply to the optimum registration than the correlation coefficient\textsuperscript{125}.

Once an optimum transform was determined, the mean difference between default floating-volume voxel positions and transformed floating-voxel positions was measured. The overlap between prostate capsule segmentations was also calculated. The advantages of the rigid registration method are that it does not rely on subjective landmarks, that it can be used to measure rotational errors, and that it can be fully automated. The disadvantages are that it cannot accurately register slides to MR volumes, nor could it register \textit{in vivo} to \textit{ex vivo} prostates with very different shapes. For this reason, 2 of the 7 patients were excluded from \textit{in vivo} to \textit{ex vivo} rigid registration, and only 5 cases were evaluated in this manner.

Both of the first and second method were designed to characterize the TRE achieved through patient-specific mold registration. Lastly, in order to evaluate the TRE of the rigid registration method itself, 5 high-intensity landmarks were identified on the registered sequences for each case, and their coordinates were annotated in 3D. The distance was then measured between them. This served as a means of quantifying the reliability of our rigid registration methodology, which has been previously reported to produce prostate registration errors on the order of 1.5 mm\textsuperscript{125}.

3.3.2 \textit{Ex Vivo} Study Results

Nine cases were scanned \textit{ex vivo}, of which one was an improper fit within the mold and one had highly unusual morphology. Therefore, 7 were considered appropriate candidates to evaluate mold registration accuracy. Target registration error was measured via anatomic landmark annotation for $N = 3$ patients and via intensity-based
rigid registration for $N = 5$ patients, the results of which are summarized in Table 3.4 and Table 3.5 respectively.

Using manually annotated anatomic landmarks, the mean target registration error was between 3.5 and 4.2 mm. Average overlap was between $in$ $vivo$ and $ex$ $vivo$ prostate capsule segmentations was 91%. Using the optimized intensity-based registration algorithm, mean target registration error was 4 mm and through-plane alignment error was 1.5 mm. Mean rotational errors were on the order of 10 degrees about the left-right axis and 5-6 degrees about the inferior-superior and anterior-posterior axes. The mean error of the rigid registration between $in$ $vivo$ and $ex$ $vivo$ sequences, as evaluated via high-intensity landmarks, was 1.4 mm.

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<tr>
<td>1</td>
<td>0.8</td>
<td>3.0</td>
<td>92%</td>
<td>0.0</td>
<td>2.6</td>
<td>1.0</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>4.6</td>
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<td>3.1</td>
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<td>4</td>
<td>2.3</td>
<td>4.9</td>
<td>92%</td>
<td>2.8</td>
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<tr>
<td>Mean</td>
<td>1.3</td>
<td>4.2</td>
<td>91%</td>
<td>1.4</td>
<td>3.6</td>
<td>0.9</td>
<td>3.5</td>
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</tbody>
</table>

Table 3.4: Evaluation of mold registration error using manually annotated anatomic landmarks. All measures are reported in mm.

<table>
<thead>
<tr>
<th></th>
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<td>1</td>
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<td>4</td>
<td>1.9</td>
<td>1.3</td>
<td>11.2</td>
<td>-5.3</td>
<td>4.6</td>
<td>4.1</td>
<td>1.1</td>
<td>1.3</td>
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<tr>
<td>6</td>
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<td>0.5</td>
<td>-2.1</td>
<td>-0.7</td>
<td>-6.7</td>
<td>2.4</td>
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<tr>
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<td>9.4</td>
<td>-8.5</td>
<td>4.1</td>
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<td>2.0</td>
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<tr>
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<td>2.3</td>
<td>2.3</td>
<td>-8.1</td>
<td>-2.5</td>
<td>2.1</td>
<td>3.3</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Mean (abs)</td>
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<td>1.6</td>
<td>10.1</td>
<td>5.4</td>
<td>5.8</td>
<td>4.0</td>
<td>1.1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Table 3.5: Evaluation of $in$ $vivo$ to $ex$ $vivo$ mold registration error by aligning volumes with an intensity-based rigid registration algorithm. Errors are reported in mm and rotations are reported in degrees. The first 6 columns report on the transform necessarily to optimally align $in$ $vivo$ with $ex$ $vivo$. The last two columns evaluate that transformation's accuracy by measuring distance between anatomic landmarks.
3.3.3  *Ex Vivo* Study Discussion

Using anatomic landmarks, the mean target registration between *in vivo* and *ex vivo* scans was 4.2 mm, indicating that significant discrepancies exist between the *in vivo* and *ex vivo* prostate. The mean through-plane alignment error of 1.3 mm was much lower, suggesting that the majority of TRE is from in-plane and rotational misalignment.

In-plane error can be corrected for using non-rigid prostate capsule registration, which was employed for registrations with the whole-mount prostatectomy slides. This may account for the observed reduction in mean TRE (3.5 and 3.6 mm) for MRI to whole mount registrations. The fact that errors remained fairly high despite more than 90% overlap of prostate capsule contours suggests that rotational misalignment, which are much more difficult to assess via anatomic landmarks, may be the dominant error source. This is supported by the fairly large rotations necessary to achieve optimum alignment using rigid registration. In addition, some error is certainly attributable to the subjective nature of landmark annotation (i.e. fiducial localization error), though its influence is difficult to assess without performing a study of inter-user variability.

Fiducial localization error was not a factor for the intensity-based rigid registration, which was also used to assess rotational misalignment between *in vivo* and *ex vivo* MRI. Rotation error along the left-right axis was 10 degrees on average, nearly double the mean rotation around the other anatomic axes. This is attributable to differences between the posterior prostate capsule segmentation *in vivo* and the surgical margins along the prostate posterior. It seems that, on average, additional tissue is present near the base of the prostate, perhaps due to seminal vesicle dissection. In the most extreme case, a 27-degree rotation was necessary to achieve correct prostate alignment, which resulted in a TRE of 6 mm.
On average, 3D TRE was 4 mm for the intensity-based registration. Rotational misalignment was confirmed to be the greatest contributor to this error, and through-plane misalignment error 1.5 mm on average, indicating that the prostate specimen was typically aligned with ± 1 image of the target MRI depth. Interestingly, TRE was slightly reduced relative to the manual landmark annotations, perhaps due to the absence of fiducial localization error. It was not possible to employ this method for registration with the whole-mount images, but the manual annotation results suggest that TRE would be somewhat reduced for these correlations.

A valid critique of rigid registrations is that they do not account for changes in the prostate gland shape; indeed, 2 of the 7 cases were disqualified from rigid registration analysis for this reason. However, for the remaining 5 cases, for which the excised specimen shape subjectively matched that observed inside the body, the rigid registration appeared to be quite accurate. Numerous landmarks were clearly visible in pairs of aligned images, and their position matched much more closely after optimum rigid registration (Fig 3.11). Measurements of their coordinates revealed a mean discrepancy of only 1.4 mm. This is slightly better than errors reported by other groups for this rigid registration technique\textsuperscript{125}, perhaps because our \textit{ex vivo} scans had very high resolution (0.29 mm).

![Figure 3.11: Example of a distinct anatomic landmark, within the red circle on the \textit{in vivo} image (left). Before optimum rigid registration, a large rotational error displaced the anatomic landmark (middle). After registration, the \textit{ex vivo} landmark’s position matched its counterpart \textit{in vivo} very closely (right).](image-url)
There are several limitations to the ex vivo study described herein. First, up to 5 months (mean 63 days) passed between in vivo scanning and radical prostatectomy, during which time prostate morphology could have changed. Second, though in-plane non-rigid registration could be used to compensate for differences in prostate shape, through-plane non-rigid registration was not possible for whole-mount prostatectomy slides due to sparse sampling. Third, the sample size was relatively small, though we will continue accruing patients as we work towards publication.

Through the use of 3D-printed, patient specific molds, correlations could be performed between imaging and pathology with approximately 3.5 mm 3D error. This number is expected to eventually improve with time and mold modification, since systematic errors such as rotation about the left-right anatomic axis can be compensated for by altering the mold design. For the subset of prostates with reasonably similar prostate shapes, comparisons between in vivo and ex vivo imaging could be performed with excellent accuracy, on the order of 1.5 mm. This registration technique may prove invaluable for future work, since experimental scans of excised specimens should be compared with high fidelity to clinical images of living tissue.

3.4 Conclusions

Based on work published by the National Institute of Health, patient-specific 3D printed molds were developed at UCLA in order to facilitate registration between imaging and pathology. We improved upon their methodology by slicing excised glands prior to formalin fixation and in higher resolution (4.5 mm 6 mm). In order to demonstrate the benefit of patient-specific molds over handheld slicing, matched pairs of tissue mimicking prostate phantoms were processed by pathology staff, and their slice planes
were digitally reconstructed. Registrations performed with the mold were 2.4 times as accurate as registrations performed based on handheld slicing. In order to measure registration accuracy in living human tissue, 7 prostates were scanned within patient specific molds after removal via radical prostatectomy. If an intensity-based rigid registration was performed, ex vivo MRI could be registered to in vivo MRI with 1.4 mm accuracy. If the mold alone was used, the ex vivo MRI indicated that mold slice planes were within ± 1 of the target in vivo MR image. However, due in large part to rotational misalignment, the mean 3D target registration error between in vivo MRI and whole mount prostatectomy slides was measured to be 3.5 mm. This is the registration accuracy that can be expected for MRI-pathology comparison with 3D-printed molds, and it should be considered for when drawing conclusions from such correlations.
CHAPTER 4
Evaluation of the Predictive Accuracy of MRI Tumor Contours

As the most reliable imaging modality for visualization of localized prostate cancer, mpMRI will play a central role in lesion characterization prior to and/or during focal therapy. Targeted treatment is necessarily image-guided, and MRI contours are essential for defining treatment zones regardless of therapeutic modality. Even for focal therapy variants such as hemi-ablation, accurate characterization of tumor geometry is crucial for determination of patient eligibility. The predictive accuracy of MRI must be characterized extensively, particularly regarding its ability to predict the size and extent of prostate cancer.

Patient-specific molds, the design and characterization of which was described in the previous chapter, were therefore deployed to perform MRI-pathology correlation in a large clinical population of radical prostatectomy patients. This required coordination between radiology, which analyzed the patient’s MR images, urology, which performed the radical prostatectomies, pathology, which processed and interpreted the surgical specimens, and bioengineering, which produced molds, performed registrations, and analyzed data. The results have important implications for the targeting and treatment of prostate cancer, and may guide improvements in prostate imaging to address its deficiencies. The majority of the work presented in this chapter has been presented at the American Urology Association annual meeting\textsuperscript{126} and published in the American Journal of Clinical and Experimental Urology\textsuperscript{122} and Journal of Urology\textsuperscript{127}.
4.1 Materials and Methods

Between August 2013 and November 2015, 114 patient-specific 3D molds were designed, manufactured, and used to process surgical specimens. The production of patient-specific 3D printed molds was described in the previous chapter; all other steps in the process will be detailed below.

4.1.1 Patient Population

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Median</th>
<th>IQR</th>
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<tbody>
<tr>
<td>Age</td>
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<td>56 – 67</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>6.5</td>
<td>4.6 – 8.7</td>
</tr>
<tr>
<td>Prostate Volume (CC)</td>
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<td>32 – 51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRI Characteristics</th>
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<td>Endorectal Coil Use</td>
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<td>47%</td>
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<tr>
<td>ROI Score ≤ 3</td>
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<td>39%</td>
</tr>
<tr>
<td>ROI Score = 4</td>
<td>51</td>
<td>34%</td>
</tr>
<tr>
<td>ROI Score = 5</td>
<td>39</td>
<td>26%</td>
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</table>

<table>
<thead>
<tr>
<th>Final Pathology</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason Grade ≤ 3+3</td>
<td>99</td>
<td>46%</td>
</tr>
<tr>
<td>Gleason Grade = 3+4</td>
<td>83</td>
<td>37%</td>
</tr>
<tr>
<td>Gleason Grade = 4+3</td>
<td>38</td>
<td>17%</td>
</tr>
<tr>
<td>Pathologic Stage &gt; pT3</td>
<td>46</td>
<td>40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>88</td>
<td>77%</td>
</tr>
<tr>
<td>African American</td>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 4.1: Demographics, Gleason grades, and MR suspicion levels for N = 114 whole mount patients whose prostatectomy specimens were processed with a 3D-printed patient-specific mold

All 114 specimens were collected over a period of 2 years and 3 months. Based upon a joint decision between physicians and patients, radical prostatectomy was performed in an attempt to eliminate non-metastasized prostate cancer. Specimens were eligible for
this study if the expected prostate volume was at most 110 cc, and if it had been imaged with multiparametric pelvic MRI at UCLA within 6 months of surgery. Some otherwise eligible specimens were excluded due to the availability of personnel, 3D-printing resources, and conflicting research projects that required whole prostate glands. A minority of specimens (<10%) did not fit properly within the mold, most commonly due to large surgical margins and the resulting unanticipated volume of extraprostatic tissue. The characteristics of the 114 patients and their excised prostates are summarized in Table 4.1.

4.1.2 Imaging, Segmentation, and Pathology Processing

All patients received a multiparametric pelvic MRI in a 3T Siemens scanner. Endorectal coils were used in 47% of patients at the discretion of the supervising radiologist. The scanning protocol included T1-weighted, high resolution T2-weighted, apparent diffusion coefficient, DWI, and DCE sequences. A radiologist with 10 years’ experience prospectively reviewed each mpMRI and identified any ROIs suspicious for cancer while blinded to biopsy results. As described in Chapters 2 and 3, the ROIs were assigned suspicion levels, the T2 sequence was used to generate ROI and prostate capsule contours on ProFuse, and patient-specific molds were manufactured according to the prostate segmentation.

A patient-specific mold was delivered to the surgical pathology grossing room the morning of each patient’s radical prostatectomy. The specimen arrived approximately an hour after excision, after which it was inked and the margins were shaved in accordance with standard procedure. The gland was oriented according to the anatomic labels, and then placed in the cavity between the mold’s anterior and posterior halves (Fig 4.1). Each mold slit was used to guide the sectioning knife, which sliced the prostate
in 4.5 mm intervals from base to apex. After sectioning, the specimen slices were removed from the mold, labeled, and sent for standard histopathology processing.

Two of the slices per case were reserved for genetics research, and slices of insufficient quality were discarded. All others were formalin-fixed, paraffin-embedded, stained with hematoxylin and eosin, and processed into slides. A urologic pathologist blinded to MRI findings examined each slide, annotated it, and drew contours around each distinct tumor region (Fig 3A). After the slides were digitized, the prostate and tumor contours were traced and color-coded (Fig 4.2) using Illustrator CS6 (Adobe Systems Incorporated, San Jose CA).

Figure 4.1: Excised, inked, and shaved prostate gland within a patient-specific mold prior to slicing

Figure 4.2: Example slide for which CaP locations (red) and the capsule (orange) were digitally annotated
4.1.3 MR-Pathology Registration

Our MR-pathology registration process has been described in a prior publication\textsuperscript{122}. Custom software was written in MATLAB 2015a (Mathworks, Natick MA) to register and reconstruct the tumor regions in 3D, according to the following steps:

1. Prostate and ROI 3D surfaces, prospectively contoured on MRI, were imported.
2. Pathology slide prostate and tumor contours were imported.
3. Pathology contours were transformed to be parallel to MR image plane.
4. Pathology contours were aligned according to the corresponding mold slot.
5. Pathology contour alignment was allowed to shift up to 4.5 mm in order to minimize mean squared difference in prostate capsule surface area relative to the MRI contours. This helped compensate for small misalignments on the superior-inferior axis due to shaving of apex and base, which was necessary to assess surgical margins.
6. A centroid-based rigid registration placed MRI and pathology contours in the same space.
7. Control points were assigned by evenly sampling 200 points along each 2D pathology capsule contour.
8. After measuring the pathology prostate capsule slope at each of the 200 points, a line orthogonal to that slope and intersecting the point was enlarged until it contacted the MR capsule contour. Each intersection was recorded, and became the MRI control points for that plane.
9. Thin plate spline (TPS) interpolation\textsuperscript{128} was performed, non-rigidly warping the \textit{ex vivo} tumor contours to match the prostate shape \textit{in vivo}.
10. Tumor contours that spanned multiple surfaces were knitted into 3D surfaces and overlaid with MRI (Fig 4.3).
4.2 Analysis

Once registration was complete, the ROI and tumor contours could be matched, characterized, and compared in 3D. Registration and 3D analysis was performed using MATLAB, and results were visualized using Adobe Illustrator and 3D Slicer\textsuperscript{129}.

4.2.1 Automated Matching

An algorithm was written to perform automated matching of ROIs and tumors, quantitatively determining if they corresponded to the same body of tissue. After observation of various examples of missed and matched tumors, it was hypothesized that the distance between the centroids and surfaces of the ROI and tumor 3D contours would be sufficient to predict matching. If the centroid-to-centroid distance plus the surface-to-surface distance between an ROI and tumor was less than 15 mm, they were called as a match. The only exception to this rule was if the centroid of one object was encapsulated by the other; in this case, they were considered matched regardless of

Figure 4.3: A) Digital reconstruction of prostate tumors spanning multiple slides, and B) tumor overlay on T2 MRI for comparison with prospectively contoured regions of interest, Visualized with 3D Slicer\textsuperscript{129}
centroid and surface distances. Multiple tumors and ROIs were allowed to match simultaneously, provided they all surpassed the 15 mm threshold.

For the first 48 patients, a panel of 3-4 physicians including a urologist, radiologist, and pathologist manually reviewed the slides and determined which tumors were matched to ROIs. Matching was also performed automatically for these cases, after which the panel's radiologist evaluated any discrepancies between the findings. Upon review of the MR volumes and 3D-reconstructed tumor regions, it was determined that the physician panel matched 95% (84/88) of tumors correctly, and the algorithm matched 94% (83/88) of tumors correctly. A chi-squared test assigned this distribution a p-value of 0.73, indicating that automated matching had effectively equivalent performance relative to that of a physician panel. Automated matching was performed exclusively in the remaining 66 cases.

4.2.2 Tumor and ROI Characterization

For all tumors and ROIs, the 3D object's volume and longest axes (3D, in-plane, and out-of-plane) were recorded. For matched tumors and ROIs, the minimum distance between each point on the ROI surface and the reconstructed tumor surface was measured. The maximum value among these minimum distances was the Hausdorff maximum distance (HDmax), which is equivalent to the distance an ROI would have to be expanded isotropically, i.e. uniformly, in order to encapsulate the tumor. The volume and percent overlap of matched ROIs and tumors was also recorded.

Various tumor and patient subpopulations were also analyzed. Clinically significant prostate cancer (csCaP) tumors, defined as those for which Gleason Grade exceeded 3+3 or volume exceeded 0.5 cc, were compared to clinically insignificant ones. Also considered was the subpopulation of index lesions, defined as the tumor with the
highest grade or else greatest volume. To retrospectively examine the utility of ROIs for guiding focal therapy in eligible men, a patient population was also examined who fit the following criteria:

1. All clinically significant tumors were matched to an ROI
2. All tumors had Gleason grade $\leq 4+3$
3. No clinically significant tumors were present in the prostate hemisphere contralateral to the index lesion
4. The disease stage on pathology was less than pT3b (i.e. no macroscopic invasion of the seminal vesicles, bladder neck, rectum, pelvic wall, or levator muscles).

### 4.2.3 Statistical Analysis

When analyzing numerical data, Wilcoxon signed-rank tests were used for paired samples and Mann-Whitney U-tests for unpaired samples. When analyzing categorical data, Pearson’s chi-squared tests were used. When comparing more than two groups, transformations were performed when necessary to achieve equal group variance, followed by Kruskal-Wallis one-way analysis of variance tests and Mann-Whitney post-hoc tests. When examining linear correlations, the Pearson product-moment coefficient was used. When examining trends between matched and unmatched populations, chi squared tests were used. Correlations were measured using Microsoft Excel, and all other tests were performed using MATLAB.
4.3 Results

In 114 patients, 148 ROIs and 222 tumors were identified. On average, there were 1.3 ROIs and 1.9 tumors per patient. 118 of the tumors were matched using the automated matching algorithm described in section 4.2.1.

4.3.1 MRI Sensitivity and Specificity

For the detection of all tumors in this population, MRI had a sensitivity of 55% and a specificity of 82%. The sensitivity and specificity of MRI for clinically significant lesions and index lesions are reported in Table 4.2. 55% of the 114 patients had at least one tumor region missed by MRI. 26% and 18% of patients had missed clinically significant lesions and index lesions, respectively.

![Figure 4.4: Trends in CaP detection relative to MR suspicion level and Gleason score](image-url)
The sensitivity of MRI was closely linked to tumor Gleason grade (Fig 4.4A). Only 23% of Gleason pattern 3+3 tumors were detected, whereas high grade tumors (GS ≥ 4+3) had an 82% detection rate. Similarly, the specificity of MRI was closely linked to the overall suspicion level assigned to each ROI (Fig 4.4B). As suspicion level rose from level 2 to level 5, matching rates increased from 25% to nearly 90%. Chi-squared tests revealed detection rates to differ significantly (p < 0.001) relative to Gleason grade and MR suspicion level (Fig 4.3A-B).

MRI suspicion level was also seen to correlate strongly with the Gleason grade of matched tumors (Fig 4.4C). Only 5% of low-suspicion ROIs corresponded to tumors with Gleason ≥ 4+3, and only 3% of high-suspicion ROIs corresponded to tumors of Gleason < 3+4. Both of these trends were statistically significant (p < 0.001). The sensitivity of mpMRI was 54% for peripheral tumors and 49% for transition zone tumors, an insignificant difference.

The mean values of various measures for missed and matched populations were computed (Table 4.3C), and a strong correlation was observed between tumor size and detection on MRI. Missed Tumors had an average volume of 0.34 cc, while matched tumors were 2.5 cc (Fig 4.5). Similarly, missed tumors had a longest axis of 16 mm, while matched tumors were 28 mm. Both of these differences were highly significant (p < 0.001). Prostate volume was significantly larger for missed tumors (p = 0.02).
Excised prostate glands had an average volume of 43 cc, 7% larger than the mean 40 cc predicted on T2-weighted MRI (p < 0.001). The longest prostate diameter was 50.2 mm, a measure slightly smaller but not significantly different than the 50.8 mm predicted by MRI. This is consistent with our observation that most excised specimens were a snug fit within the mold.
MRI was observed to systematically underestimate tumor size (Table 4.4, Fig 4.5). The volume of tumors was on average 3 times greater than matched ROIs, and the tumor longest axis was 11 mm greater. Both of these differences were highly significant, with p values less than $10^{-18}$. Furthermore, the longest ROI axis was misaligned from the longest tumor axis by a median 46 degrees. The correlation between ROI size and tumor size ($r = 0.5$, $p < 0.01$) was fairly weak (Fig 4.6A-B). These trends held for clinically significant and index tumor sub-populations.

The mean volume of transition zone tumors was significantly greater than peripheral zone tumors ($3.6 \pm 0.7$ vs $1.8 \pm 0.2$ cc, $p = 0.01$). ROIs also underestimated the volume of transition zone tumors by a greater amount than peripheral zone tumors ($2.5 \pm 0.7$ vs $1.5 \pm 0.5$ cc, $p = 0.01$).
cc vs. 1.0 ± 0.3 cc, p < 0.05). However, the longest diameter and HDmax values did not significantly differ between transition and peripheral zone tumors.

The degree of size underestimation and the strength of MRI-pathology correlation were slightly greater for csCaP and index tumors, which differed from one another only slightly.

### 4.3.3 Anisotropic Tumor Characterization Accuracy

It is noteworthy that the in-plane resolution of both MRI and pathology images is greater than the out-of-plane resolution. Also, the influence of prostate zonal anatomy could cause tumor underestimation that varies with direction, particularly apex vs. base and anterior vs. posterior. Therefore, tumor length and extent beyond the ROI was recorded when projected on the inferior-superior (IS), anterior-posterior (AP), and left-right (LR) axes (Table 4.5).

<table>
<thead>
<tr>
<th></th>
<th>Length diff. (mm)</th>
<th>Length Upgrade (%)</th>
<th>Length Correlation (r)</th>
<th>HDmax (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior-Superior Axis</td>
<td>10.0 ± 0.9</td>
<td>97%</td>
<td>0.22</td>
<td>9.4 ± 0.6</td>
</tr>
<tr>
<td>Anterior-Posterior Axis</td>
<td>7.1 ± 0.9</td>
<td>56%</td>
<td>0.43</td>
<td>7.2 ± 0.6</td>
</tr>
<tr>
<td>Left-Right Axis</td>
<td>8.2 ± 1.1</td>
<td>58%</td>
<td>0.58</td>
<td>7.4 ± 0.6</td>
</tr>
</tbody>
</table>

Table 4.5 (left) Mean CaP-ROI length difference, HDmax, and Pearson’s R coefficients for projections onto the 3 anatomic axes. Figure 4.7 (right): Proportional graphic displaying relative directional CaP length underestimation.

The tumor IS length projection was on average 10 mm smaller than MR, a significantly larger underestimation (p < 0.01) than both the AP and LR length projections, with respective values of 7.1 and 8.2 mm. HDmax projections were also largest in the IS direction, with a mean ROI surface to tumor surface distance of 9.4 mm.
This was significantly greater than projections along the AP and LR directions \((p < 0.001)\), with respective values of 7.2 and 7.4 mm. When measured as a percentage of ROI length the anisotropy was even more pronounced, with 97\% underestimation along the IS axis and 56\% to 58\% underestimation along the other two axes (Fig 4.7). ROI to tumor size correlations in-plane \((r = 0.43\) for AP; \(r = 0.58\) for LR) were also far better than correlations out-of-plane \((r = 0.22)\).

There is greater alignment uncertainty out-of-plane, since 3 to 5 mm of tissue was shaved from the prostate's apex and base prior to placement in the mold. In order to verify that out-of-plane misalignment was not the cause of anisotropic tumor characterization error, the same registration process was performed after realigning slide depth such that tumor centroids were as close as possible to matched ROI centroids. This only resulted in a minor improvement to HDmax (mean 0.7 mm reduction).

### 4.3.4. Size Underestimation Stratified by Gleason and ROI

**Suspicion**

Tumor size, ROI size, volumetric error, and HDmax were stratified by both MRI suspicion level and Gleason score (Table 4.6). The mean tumor volume and ROI volume rose with both MR suspicion and Gleason score, with significant differences observed for most of the stratified comparisons. The volumetric error and HDmax was not significantly correlated with MR suspicion, but did depend strongly upon Gleason score.

Tumors were significantly larger than ROIs for all Gleason scores \((p < 0.001)\). GS 3+3 tumors were smaller than GS 3+4 or greater tumors \((p < 0.001)\), with lower HDmax values and less volume error \((each \ p < 0.01)\). No difference in tumor volume, diameter or
HDmax was seen between GS 3+4 tumors and higher grade tumors. However, tumor volume was significantly different intermediate and high suspicion level ROIs.

ROI diameter was directly proportional to the diameter of GS 4+3 or greater (\(r = 0.67\)) and GS 3+4 tumors (\(r = 0.46\), both \(p < 0.01\)). However, no significant correlation was found between the diameters of GS 3+3 tumors and matched ROIs. Volume correlations followed a similar trend, with weak coefficients for low Gleason disease.

<table>
<thead>
<tr>
<th></th>
<th>CaP Volume (CC)</th>
<th>ROI Volume (CC)</th>
<th>Volume Error (CC)</th>
<th>HDmax (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gleason = 3+3 (N = 22)</strong></td>
<td>1.1 ± 0.5</td>
<td>0.31 ± 0.07</td>
<td>1.0 ± 0.4</td>
<td>10.9 ± 1.5</td>
</tr>
<tr>
<td><strong>Gleason = 3+4 (N = 61)</strong></td>
<td>2.6 ± 0.3</td>
<td>0.7 ± 0.1</td>
<td>1.9 ± 0.3</td>
<td>16.3 ± 0.9</td>
</tr>
<tr>
<td><strong>Gleason ≥ 4+3 (N = 32)</strong></td>
<td>3.2 ± 0.5</td>
<td>1.2 ± 0.2</td>
<td>2.1 ± 0.5</td>
<td>15.2 ± 1.0</td>
</tr>
<tr>
<td>P (Kruskal Wallace)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.003</td>
<td>0.007</td>
</tr>
<tr>
<td>P (Mann-Whitney)</td>
<td>&lt; 0.001; 0.57; &lt; 0.001</td>
<td>0.023; 0.011; &lt; 0.001</td>
<td>&lt; 0.001; 0.82; 0.008</td>
<td>0.002; 0.54; 0.015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CaP Volume (CC)</th>
<th>ROI Volume (CC)</th>
<th>Volume Error (CC)</th>
<th>HDmax (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MR Score ≤ 3 (N = 37)</strong></td>
<td>1.9 ± 0.4</td>
<td>0.29 ± 0.05</td>
<td>1.6 ± 0.4</td>
<td>15.0 ± 1.3</td>
</tr>
<tr>
<td><strong>MR Score = 4 (N = 44)</strong></td>
<td>2.5 ± 0.4</td>
<td>0.7 ± 0.2</td>
<td>1.8 ± 0.4</td>
<td>14.4 ± 1.1</td>
</tr>
<tr>
<td><strong>MR Score = 5 (N = 34)</strong></td>
<td>3.1 ± 0.5</td>
<td>1.4 ± 0.2</td>
<td>1.9 ± 0.4</td>
<td>15.6 ± 1.2</td>
</tr>
<tr>
<td>P (Kruskal Wallace)</td>
<td>0.0125</td>
<td>&lt; 0.001</td>
<td>0.51</td>
<td>0.75</td>
</tr>
<tr>
<td>P (Mann-Whitney)</td>
<td>0.20; 0.07; 0.003</td>
<td>.005; &lt; 0.001; &lt; 0.001</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 4.6: Volume and HDmax of matched tumors and ROIs stratified by Gleason score and MRI suspicion level. The three values quoted for the Mann-Whitney U test (performed only if the Kruskal-Wallace test was passed) apply to the 1\(^{st}\) vs. 2\(^{nd}\) group, then the 2\(^{nd}\) vs. 3\(^{rd}\), then the 1\(^{st}\) vs. 3\(^{rd}\).

### 4.3.5 Isotropic Treatment Margins

The median Hausdorff maximum distance between ROIs and matched tumor surfaces was 13.5 mm. By its definition, the Hausdorff maximum is equivalent to the isotropic margin that would have been necessary for focal treatment success. An isotropic margin of 13.5 mm would have resulted in a mean treated volume of 12 ± 10 cc. Figure 4.8 shows the percent of tumors encompassed by isotropic margins of ascending size, and indicates that a margin of more than 20 mm would be necessary to
successfully treat 80% of tumors. Focal therapy eligible patients (N = 35) would have required somewhat reduced margins, with a median HDmax of 10.2 mm.

![MRI Underestimation of Tumor Extent](image)

Figure 4.8: Percent of patients (y-axis) at or below ascending Hausdorff maximum values (x-axis) for all and focal therapy eligible patients. The Hausdorff maximum is equivalent to the minimum isotropic margin around the ROI that would have encapsulated the tumor.

### 4.4 Discussion

The results indicate that, though most significant tumors were prospectively identified on multiparametric MRI, T2-weighted MRI contours underestimated the volume, longest axis and extent of pathological tumors in nearly every case. Underestimation occurred for all Gleason scores and for all mpMRI suspicion levels.

#### 4.4.1 Sensitivity and Specificity of MRI

While the specificity of MRI for prostate cancer detection was high, its sensitivity was fairly poor. Nearly half of prostate cancers were missed on MRI, the vast majority being
small volume and low-grade disease. It stands to reason that lower-grade tumors should have reduced MRI visibility, especially on DCE and DWI sequences that have limited resolution. The average missed tumor was only 0.34 cc, which (assuming spherical geometry) corresponds to a radius of 4.3 mm. Even on high-resolution T2-weighted imaging, lesions of this size would have a maximum length of 13 voxels, occupying less than 5% of an average prostate’s area within a 2D image. Small tumor foci were typically low-grade, and would be considered ‘clinically insignificant’ even by conservative standards. Since they will likely have no impact on the patient’s prognosis or disease progression, it may not even be desirable to visualize them on MRI. Prospective identification of these clinically insignificant tumors could lead to unnecessary biopsies, diagnoses, and treatments.

However, 26% of patients had at least one clinically significant lesion missed on MRI, which highlights the continued importance of alternative detection methods such as systematic prostate biopsy. Interestingly, 7% of patients had no clinically significant disease evident on pathology, though it is possible for foci to be missed due to sparse sampling. For these men, it is likely that treatment was not strictly necessary, and they would have been better served in an active surveillance program.

The strong correlation between MR suspicion level and Gleason grade is encouraging, since this can be used for risk stratification even before the acquisition of biopsy data. For ROIs of the highest suspicion level, nearly all exhibited Gleason pattern 4, which is clinically significant by most standards. This trend may even serve as a justification to re-biopsy the location of highly suspicious ROIs, if at first only low-grade disease is evidenced.
4.4.2 Underestimation of Tumor Geometry

The systematic underestimation of tumor size has important ramifications for targeted interventions. The average ROI had a maximum dimension that was 11 mm smaller than the corresponding tumor's longest axis. Even if the ROI and tumor axes had been perfectly aligned, the average margin necessary for treatment success would therefore have been over 5 mm. Furthermore, ROI positioning was far from ideal, with a mean centroid offset of 6.7 mm and a mean longest-axis misalignment of 46 degrees. As a result, the median HDmax was greater than 13 mm.

The systematic underestimation of tumor extent suggests that a large margin would be required if MRI alone serves as the basis for targeted therapy. If the median Hausdorff maximum had been used as the cutoff for isotropic margins, the mean treated volume would have been 12 ± 10 cc. Five times more healthy tissue than tumor would be treated with these margins, yet they would have been insufficient for half of men. In order to assure treatment success, far larger margins would be necessary, which are impractical for many focal therapy modalities such as laser interstitial laser thermal therapy. Theoretically, less tissue could be extirpated if it were only necessary to destroy Gleason pattern 4 or 5 disease; this remains a promising avenue for future research. However, if complete CaP extirpation is the goal of focal therapy, it is clear that isotropic treatment margins around T2-visible lesion contours are insufficient.

The significant correlations between Gleason grade, MR suspicion level, and tumor size suggest that focal treatment margins could be adjusted in a patient-specific manner. Intermediate to high Gleason grades and MR suspicion levels correlated with larger tumors and greater segmentation errors, necessitating treatment margins of 14+ mm. However, MR-visible Gleason 3+3 tumors and focal therapy eligible-patients required median 10-mm margins, far more feasible for focal treatment.
Interestingly, intermediate-grade tumors extended farthest from the ROI surface and thus would have necessitated the largest treatment margins. Though the post-hoc test did not reach the threshold of significance, this trend suggests that Gleason 3+4 tumors may be more difficult to accurately contour than lower or higher grade disease. Since MR visibility improves with Gleason grade, and since Gleason 3+4 tumors have components of both Gleason pattern 3 and 4 disease, it is plausible that one portion of the tumor may be more highly MR-visible than the other. This may result in physicians limiting their contours to the high-grade tumor focus, neglecting Gleason pattern 3 regions and necessitating greater treatment margins. This is another promising hypothesis for future investigation.

Though Gleason 3+3 tumors were smaller than others, no significant difference in size was found between Gleason 3+4 and Gleason 4+3 or greater tumors. For example, average tumor diameter was 30 mm for GS=3+4 and 31.9 mm for GS ≥4+3. However, ROI diameter was 16.5 for GS=3+4 and 20.5 mm for GS ≥4+3, respectively. This illustrates an interesting phenomenon: even for tumors of equivalent size, the corresponding ROI tended to be larger and more accurate for the high GS tumor than for lower grade tumors. This suggests that, in addition to suspicion score, ROI size may be a useful metric for evaluating disease severity. This also implies that higher-grade disease has enhanced MR visibility irrespective of tumor size, perhaps due to the absence of Gleason 3 components.

4.4.3 Comparison with Recent MRI-Pathology Correlation Work

The correlation between MRI and whole mount pathology is highly dependent on the imaging and contouring procedure. Early studies often reported that mpMRI overestimated tumor volume\textsuperscript{130,131}, but these were based on older technologies and did
not employ software registration. More recent publications reported that mpMRI underestimates tumor size, though to a lesser degree than measured in our study. Turkbey et al. calculated a mean volume underestimation of 0.16 cc (7%)\textsuperscript{11}, but they used 3D-molds only for a subset of their patients. Furthermore, lesion volume was calculated using an ellipsoid formula, which does not account for actual tumor shape. Specimens were also processed after formalin fixation, forcing Turkey et al. to assume a fixed volumetric percent of tissue shrinkage.

Le Nobin et al. reported tumor volumes 1.5 times greater than ROIs, compared to a factor of 3 in our study\textsuperscript{132,133}. Furthermore, they measured no HDmax greater than 9 mm, whereas our median HDmax was 13.5 mm and maximum HDmax was over 3 cm. This disparity can be partly attributed to differences in mean tumor volume, which was 2.5 cc for our patients and 1.38 cc for the Le Nobin study. Additionally, their work was restricted to small sample sizes (n = 33 and n = 37) that were retrospectively selected for mpMRI-tumor visibility, and radiologists were informed of tumor location prior to ROI delineation. This constitutes a critical bias, for contouring can be performed much more aggressively for regions that have been retrospectively identified as cancer-positive. A prospective study such as that performed at UCLA is a far better representation of MR contouring accuracy.

Perhaps most importantly, the Le Nobin study relied exclusively on in-plane measurements between mpMRI and pathology, whereas we observed the largest errors to be out-of-plane. 2D measures of contouring accuracy are insufficient to capture the true HDmax, and their reported correlation results are likely to be an underestimation of true MRI error. The present work addresses many of the limitations of prior studies, and thus appears to more accurately reflect the utility of prostate mpMRI for prediction of tumor geometry.
4.4.4 Anisotropic Tumor Characterization Accuracy

MRI tended to underestimated tumor extent, but it did not do so isotropically. The maximum distance from ROI to tumor was 14.5 mm on average, but along the three anatomic axes mean tumor-to-ROI distance varied from 7.2 to 9.4 mm. This highlights the potential for a non-isotropic margin based on MR accuracy relative to the image plane and prostate anatomy.

Tumor underestimation appeared to be largest along the inferior-superior axis. This is very likely a consequence of non-uniform MRI resolution, which is several times greater in-plane than out-of-plane. Furthermore, the contours were drawn from a transverse perspective, and thus it is likely that the operator was better able to discriminate tumor boundaries in-plane than out-of-plane. As a result, tumor extent was most commonly underestimated along the IS axis. There are several potential methods of addressing this trend; first, operators could be required to contour tumors while referencing multiple anatomic perspectives, i.e. axial and coronal, to better distinguish patterns in image contrast. Second, an MR sequence with isotropic resolution could be used. Third, treatment margins along the IS axis could be increased asymmetrically in order to counteract reduced out-of-plane accuracy.

4.4.5 Improvement of MRI contours

Due to the heterogeneous nature of CaP and its tendency to blend with healthy tissue, MRI characterization of tumor geometry will always have a degree of uncertainty. In order to improve the predictive capacity of MRI, several steps can be taken. First and foremost, MR-visible tumors should be contoured more aggressively, utilizing
information from multiple image planes and mpMRI sequences. Second, high-level image processing and analysis can be used to inform physicians which regions are most likely to harbor cancer\textsuperscript{135,136}, and contours can be modified accordingly. Last, targeted biopsy systems are already able to confirm, via gold-standard histopathology, whether cancer is present along multiple vectors within the prostate gland. Registration of tracked biopsy cores with MRI, and adjustment of tumor contours in response, have been shown to improve the characterization of cancer geometry\textsuperscript{137}.

### 4.4.6 Study limitations

There are several notable limitations to this study. Firstly, \textit{ex vivo} MRI data suggested that 3D target registration error was 3-4 mm (Chapter 3), and \textit{in vitro} phantom-based simulations indicated that volumetric reconstruction error was 34%. These are the errors that could be expected even if MR was perfectly predictive of CaP size and shape. Therefore, in the worst-case registration scenario, the true median HDmax could be on the order 6 mm (down from 10 mm), and the true mean volume could be 194\% (down from 294\%). This represents the lower bound for tumor size, for which ROIs would still have been a substantial underestimation. Therefore, the key findings of this study—namely that MR contours dramatically underestimate tumor size and extent—remain valid even considering registration uncertainty. Furthermore, it is highly unlikely for average tumor size to occupy this lower bound, since random reconstruction errors would have \textit{decreased} volume and HDmax values for many cases.

The non-rigid registration methodology was intended to help compensate for in-plane errors, but through-plane misalignment was difficult to detect and compensate for. In order to establish the lower limit on correlation error, a ‘best-possible’ through-plane alignment performed, in which tumor-bearing slides were artificially shifted in
order to best match ROI location along the IS axis. Even with this best-possible alignment, Hausdorff maximum distances were reduced by only 1 mm. This strongly implies that the majority of error observed was truly due to the inaccuracy of MRI contours, and was not an artifact of slice misalignment.

Another limitation is that our study was comprised of radical prostatectomy patients, which is not necessarily representative of other populations. The average patient who is newly diagnosed, on active surveillance, or eligible for focal treatment will likely have smaller, lower stage, and lower grade disease. In an attempt to investigate patients more representative of these lower-risk populations, stratification by Gleason score and retrospective focal therapy eligibility was performed. Based on observed trends in Hausdorff maximum distances, treatment margins would likely be reduced for populations with lower-risk disease. However, treatment margins remained high for intermediate grade CaP, which is unfortunately the ideal population for focal therapy.

The contouring procedures for both ROIs and tumors are potential points of weakness. ROI contours were drawn using criteria optimized for targeted biopsy, where sampling of the tumor center is paramount and characterization of tumor extent is secondary. Furthermore, only the high-resolution T2 scan was used to draw contours, since geometric distortion and patient movement make registration of the other sequences difficult. If the ROI contours on multiple sequences were registered and combined into a single 3D object, as previous groups have reported\textsuperscript{130,132,138}, it is possible they would match the tumor more closely. Furthermore, on pathology slides tumors were contoured according to a binary distinction of CaP vs. healthy tissue, without distinguishing between areas of different Gleason pattern or CaP density. It is likely that ROIs are a better estimate of high-Gleason and high density CaP than low-Gleason and low density CaP, but such an analysis has not yet been performed.
Fit within the mold was not always ideal. Bladder neck dissection often disrupted tissue at the prostate base, changing it dramatically from the shape observed \textit{in vivo}. Surgical margins were variable, and excess tissue sometimes made the prostate difficult to fit within the mold’s cavity. Also, shaving of the prostate apex and base was a source of alignment uncertainty, though for future research cavity design could be altered in anticipation of this missing tissue. However, patient-specific mold size was sufficiently precise for use in processing approximately 90% of attempted cases.

### 4.5 Conclusions

The aim of this chapter was to investigate the predictive utility of MRI for prostate cancer geometry. Unlike most other studies of this topic, we rigorously registered pathology to preoperative MRI, using custom software and patient-specific 3D-printed molds in a large population. Given the increasing availability of 3D-design and printing resources, other institutions could adopt this approach and expect a substantial improvement in registration accuracy relative to manual slicing techniques. Indeed, adoption by other research groups is highly desirable, since different contouring techniques and patient populations are likely to have a strong influence on correlation results. Patient-specific molds could even be generalized for use with other organs such as the kidney, liver, and brain.

The results of our MR-pathology correlation study indicate that while mpMRI is fairly specific for CaP, its sensitivity is low due to the common occurrence of low-volume, low-Gleason tumors. However, mpMRI sensitivity for index tumors and clinically significant tumors are reasonably high at 82% and 76% respectively. The likelihood of tumor detection, and the degree of tumor size underestimation, was seen to strongly correlate
with MR suspicion level and Gleason score. Most Gleason 3+3 tumors were missed on MRI, whereas a strong majority of high-risk cancer (Gleason 4+3 and above) were detected.

ROIs systematically underestimated the volume, longest axis, and extent of matched tumors, a trend that would have persisted even in the worst-case registration scenario. The degree of tumor underestimation was correlated with Gleason grade, and seen to be greatest out-of-plane. The substantial tumor size underestimation would have necessitated very large margins for any attempt at prostate focal therapy unless patient-specific margins had been implemented.

Prostate cancer imaging has never been more accurate, and our ability to predict and characterize prostate tumors will improve as MRI technology advances. Despite recent developments, prostate MRI still has significant shortcomings, and it is important that the radiology, urology, and pathology community recognizes both its strengths and its weaknesses. Knowing the predictive accuracy of MRI—for the presence of cancer, the geometric features of tumors, and focal therapy eligibility—is critical for the management of CaP. With this information in mind, physicians will be able to review MRI tumor contours and make the best-possible treatment decisions.
As demonstrated in Chapter 4, isotropic treatment margins around MR-visible tumors are not feasible in many cases. Among patients retrospectively determined to have been focal therapy eligible, a median margin of 10.2 mm around the ROI would have been required to encapsulate the associated tumor. In order to have been successful in 90% of cases, 2 cm margin would have been required, which encapsulates a large volume of healthy tissue unlikely to be safe and feasible in most patients. Therefore, alternative methods to generate treatment margins in an anisotropic, patient-specific fashion were investigated.

5.1 Materials and Methods

UCLA maintains a large targeted biopsy database, tracking the location and pathologic data associated with prostate biopsy cores. It was hypothesized that incorporation of this tBx data could improve margin generation relative to an isotropic expansion of MR-visible lesions. Early efforts by our group took a geometric approach, depressing an isotropic margin's surface in the region of negative biopsy cores and inflating it in the region of CaP-positive cores. However, optimizing the parameters for such a method was difficult, and computation time was a severe limiting factor. We instead opted for a ‘voxel-based approach’, wherein each 1-mm³ voxel was labeled with various features derived from MRI, biopsy, and whole-mount data.
5.1.1 Patient Population

As described in Chapter 4, 3D tumor surfaces had been reconstructed for 114 patients using patient-specific mold-based registration. Of these 114 patients, 41 had also received at least one targeted prostate biopsy with the Artemis system. The minimum requirement for image-guided therapy was prospective identification of an ROI corresponding to the index lesion, and subsequently biopsy confirmation with at least one targeted core. 35 of the 41 patients fit these specifications. Patients who would have been focal therapy eligible were then retrospectively identified according to the following criteria:

1. Clinically significant index lesion (i.e. GS > 3+3 or volume ≥ 0.5 cc)
2. Maximum Gleason Score ≤ 4+3
3. Stage < PT3b
4. No clinically significant bilateral disease present

21 of the 35 patients were considered focal therapy eligible according to these requirements. The bulk of analysis was performed on this subset of the population, for which median Gleason Score was GS = 3+4. Mean statistics and standard deviations for all (N = 35) and focal-therapy-eligible (N = 21) patients can be found in Table 5.1.

<table>
<thead>
<tr>
<th></th>
<th>Prostate Vol (cc)</th>
<th>Baseline PSA (ng/mL)</th>
<th>MR Grade</th>
<th>Index Tumor Vol (cc)</th>
<th>HDmax (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (All Patients)</td>
<td>36.3</td>
<td>7.2</td>
<td>3.9</td>
<td>3.1</td>
<td>15.2</td>
</tr>
<tr>
<td>STD (All Patients)</td>
<td>11.1</td>
<td>4.9</td>
<td>0.7</td>
<td>3.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Mean (FT Eligible Patients)</td>
<td>35.6</td>
<td>8.3</td>
<td>3.8</td>
<td>1.7</td>
<td>12.3</td>
</tr>
<tr>
<td>STD (FT Eligible Patients)</td>
<td>10.0</td>
<td>5.1</td>
<td>0.8</td>
<td>1.3</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Table 5.1: Statistics for cases that had both targeted biopsy and whole mount data furnished by patient-specific molds. The retrospectively focal therapy eligible sub-population statistics are also listed.
5.1.2 Feature Measurement

For each patient, data from various sources was imported and registered to high-resolution T2 MRI. The prostate capsule and ROI volumes were derived from the radiologist's prospective segmentations, and their centroids were calculated. The tumor surfaces were reconstructed from whole mount slides according to patient-specific mold alignment, as described in Chapter 4. The biopsy coordinates were imported from the Artemis targeted biopsy database. Lastly, the biopsy histopathology results were transcribed from the integrated radiology/pathology report, including Gleason score, cancer length, and total tissue length per core.

The throw of the biopsy needles was 19 mm, and the trajectory of each throw was recorded by the tBx system. Since the number of and length of core samples was highly variable, it was considered prudent to identify the regions along each throw most likely to harbor the histopathologic sample. For cores containing only CaP-negative tissue, ‘negative nodes’ were defined as regions for which CaP was known to not present, regardless of the tissue position within the biopsy needle’s throw (Fig 5.1). Given a list of tissue lengths, an algorithm computed via ‘brute force’ all possible configurations within the biopsy needle's throw in 0.5 mm resolution. Regions that definitely contained CaP-negative tissue were labeled as ‘negative nodes’, and all other regions within a negative core, which may or may not have harbored CaP-negative tissue, were recorded separately and labeled ‘negative-minor’. Similarly, regions within CaP-positive cores most likely to harbor CaP were labeled ‘positive nodes.’ This was defined as the vector along the needle’s throw closest to the ROI and equal in size to the CaP length measured on histopathology. All other regions within a positive core, which could have harbored the CaP-positive tissue but were deemed less likely to do so, were recorded separately and labeled ‘positive-minor’.
A custom MATLAB script evenly sampled voxels throughout each patient's prostate in 1 mm intervals. The only regions excluded were those at the far apex and base that surpassed the extent of whole-mount prostatectomy slides, since CaP presence there was unknown. Each voxel was labeled as negative for CaP, or positive for CaP if it lay inside the volume of a 3D-reconstructed tumor. Various features, hypothesized to be correlated with the presence of CaP, were then automatically generated for each voxel. All distances and angles were measured from the ‘perspective’ of the voxel in question, i.e. considering that voxel's location to be the origin [0,0,0]. The 67 numeric features and 20 categorical features are briefly summarized below:

1. T2 ROI Features (N = 17): Position and angle of the T2 ROI surface and centroid relative to each voxel, including distance measures transposed onto the three anatomic axes.

2. Negative Biopsy Features (N = 15): The distance and angle of negative and negative-minor nodes relative to each voxel

3. Positive Biopsy Features (N = 12): The distance and angle of positive and positive-minor nodes relative to each voxel, as well as the core’s Gleason Score

4. ROI/Biopsy Hybrid Features (N = 12): Measures of the position of each voxel relative to the ROI and nearest biopsy node

Figure 5.1: Examples of negative nodes and negative-minor nodes generated for one (A) and two (B) pieces of CaP-negative biopsy tissue whose total length was less than that of the biopsy needle’s throw.
5. Prostate Anatomy (N = 6): Prostate zone of each voxel, as well as voxel distance from the capsule, from apex to base, from central to lateral, and from posterior to anterior

6. T2 Intensity (N = 4): Normalized T2 intensity of each voxel and the region surrounding it relative to norms for that prostatic zone

7. Minimum and Maximum Volumes (N = 6): Distance and angle between each voxel and regions defined as:
   a. The minimum convex volume encapsulating positive biopsy nodes
   b. The maximum volume after excluding negative biopsy nodes

8. Patient-Level Data (N = 15): Features that did not change voxel-to-voxel within a patient, such as PSA, maximum Gleason, and ROI suspicion level. Since the sample size was low, these features were excluded from most analyses.

Voxel features measured within a patient were not independent, so statistical analysis was performed on an inter-patient basis. CaP-positive and CaP-negative voxel group means were calculated for each patient. Then, differences in patient means between the CaP-positive and CaP-negative voxels were evaluated using Wilcoxon signed-rank tests, and differences in the distribution of means were evaluated using Kolmogorov-Smirnov tests, a nonparametric test of equality of probability distributions. Given that 67 numeric features were tested in this manner, 3-4 of them could be expected to appear falsely significant at a threshold of alpha = 0.05. Significance was therefore tested at both a alpha = 0.05 and a alpha = 0.01 level.

5.1.3 Composite Feature Generation

For every feature, the probability of a voxel containing CaP was recorded at various thresholds in high-resolution. The units of each feature were then normalized, with 0 as
the lower bound and 1 as the upper bound for feature magnitude. For example, considering the feature ‘voxel distance from the ROI surface,’ voxels 0.1% or less from the min to max might be 80% CaP-positive, whereas voxels 0.2% or less from the min to max might be 80.2% CaP-positive, etc. Similarly, considering the ‘distance from the prostate centroid’ feature, voxels 0.1% or less from the min to max might be 5% CaP-positive, whereas voxels 0.2% or less from the min to max might be 5.1% CaP-positive, etc.

An optimized ‘composite feature’ was constructed by assigning variable weights to its component features and then linearly combining them. For example, the ‘voxel distance from the ROI surface’ feature was assigned a weight of 1 relative to the ‘distance from the prostate centroid’ feature, which was assigned a weight of 0.615. For every voxel, the CaP probabilities of the two feature were added in order to yield a composite feature value at that voxel, combining influence from its components according to their assigned weights. The composite feature was normalized, and again CaP probability was measured in high resolution. For example, voxels 0.1% or less from the min to max might be 85% CaP-positive, whereas voxels 0.2% or less from the min to max might be 85.3% CaP-positive, etc. The strength of the composite feature was tested according to its receive operator characteristic (ROC), with the goal of minimizing false positives in the 95%-99% false negative range.

The ‘voxel distance from the ROI surface’ feature is equivalent to application of an isotropic margin, and was used as the first component of the composite feature. Each of the other 66 numeric features was iteratively tested for inclusion as a component of the composite feature according to the following algorithm:

1. The test feature was assigned various test weights in 10 percent increments.
2. The test feature was linearly combined with the composite feature at each of the test weights.

3. The composite feature thresholds necessary to encompass 95%-99% of CaP-positive voxels was determined, and the proportion of CaP-negative voxels encompassed at these thresholds was calculated.

4. The feature weight conferring the greatest specificity (lowest proportion of CaP-negative voxels) for 95%-99% sensitivity was determined.

5. New weights were assigned in 2 percent increments around the optimum test feature weight from step 4, and steps 2-5 were repeated.

6. If the optimally weighted test feature improved specificity of the composite feature, the test feature and composite feature were linearly combined.

Steps 1 through 7 were repeated until the composite feature specificity ceased to improve in the desired range. The composite feature was then compared against the performance of isotropic margins on a per-voxel and per-patient basis.

5.1.4 Machine Learning

Machine learning classifiers using the MATLAB machine learning toolbox were trained in an attempt to distinguish CaP-positive vs. CaP-negative voxels using the features generated in 5.1.2. In order to determine the optimum feature set for machine learning, 400 CaP-positive and 400 CaP-negative voxels were randomly sampled from each of the 21 focal therapy eligible patients, for a total sample size of 16,800. This number was chosen in order to facilitate reasonable runtimes. Each of the 70 voxel-level features was then assessed for inclusion in the optimally predictive feature set according to the following algorithm:
1. A N\times16800 matrix was constructed, where N was the number of features in the optimum set plus 1 (for the feature being tested for inclusion).

2. A classifier was trained using the matrix from step 1 in order to predict the presence of CaP. A linear support vector machine with kernel scale 1 was used.

3. The classifier was applied to the entire N\times590705 dataset.

4. The classifier’s true positive rate was measured for various false-positive values ranging from 30% to 50%.

The feature imparting the best sensitivity over the given range was then selected for inclusion in the optimum feature set. Steps 1 through 4 were repeated until the classifier’s performance ceased to appreciably improve. The optimum set consisted of the following features, from most predictive of CaP to least predictive of CaP:

- Distance in 3D from the ROI surface
- Position along the left-right anatomic axis relative to the ROI and prostate centroid
- Local density, then length, then distance to negative biopsy cores
- Presence of positive biopsy cores farther from the ROI, and CaP length within it
- Angular proximity of negative cores between the ROI and voxel
- Position along the inferior-superior anatomic axis relative to the ROI

In order to estimate the clinical efficacy of machine learning for CaP prediction with the optimized feature set, it was tested using leave-one-out cross validation in the 21 focal therapy eligible patients. Again, the dataset was sub-sampled to facilitate runtime, randomly sampling 1000 CaP-positive and 1000 CaP-negative voxels from each patient. Various classifier algorithms were investigated, including a linear, quadratic, and Gaussian support vector machine (SVM), and a boosted decision tree. The following algorithm was then performed for each patient, denoted the ‘Nth’ patient:
1. A Nx40000 matrix was constructed, using data from all patients except for the Nth
2. A classifier was trained using the matrix from step 1
3. The classifier of step 2 was applied to the full dataset (18500 to 40900 voxels) from the Nth patient
4. The classifier ROC was constructed, both on a voxel-level and patient-level

The classifier results were then compared to the ROC of isotropic margins applied to the same dataset.

5.2 Results

Many features had radically different distributions for CaP-positive vs. CaP-negative voxels. Of 67 numeric features, the inter-patient means were significantly different for 46 features at a p = 0.05 threshold and 38 features at a p = 0.01 threshold. The distribution of patient means was significantly different for 45 features at a p = 0.05 threshold and 34 patients at a p = 0.01 threshold. The most significant features, attaining the lowest observed p-value for both Wilcoxon signed-rank and Kolmogorov-Smirnoff tests, were:

- Distance to nearest ‘positive node’ of a CaP-positive biopsy core
- Distance to the minimum convex volume constructed of CaP-positive cores
- Distance from the ROI surface, transposed onto the left-right anatomic axis
- Distance from a voxel to the line between the nearest negative node and ROI centroid

Normalized histograms of the CaP-positive and CaP-negative voxel distributions were plotted for the significantly different features. Histograms for the ‘distance to ROI
surface,’ ‘Angle between voxel, ROI centroid, and nearest negative node,’ and ‘Distance to nearest positive core’ features are shown in figure 5.2. All three of these feature means had inter-patient signed-rank p-values below 0.001, and thus were significantly different.

5.2.1 Composite Feature Performance

13 features were linearly combined using the algorithm of section 5.1.3. Of these, 6 were derived from voxel position relative to the ROI, 3 were derived from voxel position relative to negative biopsy cores, 2 were derived from voxel position relative to positive biopsy cores, and 2 were derived from the voxel's anatomic location within the prostate.

When the composite feature ROC curve was plotted alongside that of isotropic treatment margins (Fig 5.3A), it was clear that the composite feature improved specificity at all sensitivity levels. However, the specificity benefit was fairly modest, at or below 7%, for true positive levels below 90%. It was only at higher true positive thresholds that the composite feature dramatically outperformed isotropic margins; for true a true positive rate of 99%, the composite feature false positive rate was 32% relative to 62% for isotropic margins.

Distance to the ROI surface was easily the strongest indicator of CaP presence, and close to the ROI the composite feature behaved similarly to isotropic margins. However, farther from the ROI surface, other features gained influence. For example, as seen in Figure 5.5, a positive core far outside the ROI surface radically altered the CaP probability map relative to isotropic margins. The true CaP location, seen in red, was much more closely approximated using the composite feature.
Figure 5.2: Example normalized features with strongly differentiated distributions for CaP-positive (red) vs. CaP-negative (blue) subpopulations.
Figure 5.3: Per-Voxel Receiver-operator characteristic (ROC) of the optimized feature set for detection of cancer in all 21 FT-eligible patients (A) and after excluding a single outlier (B)

Figure 5.4: Per-patient treatment success vs. healthy tissue treated for the optimized feature set in all 21 FT-eligible patients (A) and after excluding a single outlier (B)

Figure 5.5: Case study in which presence of a positive biopsy core caused the optimized feature (B) to dramatically outperform isotropic margins (A) for approximation of true cancer contours (C)
Upon closer analysis, the majority of the composite feature’s performance benefit was due to outlier cases, which would have required unusually large isotropic treatment margins. This is evident from observation of the per-patient ROC (Fig 5.4A), where an outlier was case was given disproportionate weight. Upon exclusion of the most severe outlier, the composite feature was still favorable, though its per-voxel performance was reduced relative to isotropic margins (Fig 5.3B). Per-patient performance was marginally improved after removal of the outlier, with 1-4 (median 1) additional patients successfully treated at a given false positive level.

5.2.2 Machine Learning Algorithm Performance

Similarly, a linear SVM trained using leave-one-out cross validation an ROC visibly superior to isotropic margins (Fig 5.6A). Like the composite feature of section 5.2.3, the benefits of machine learning were modest until the 90-99% true positive range, for which false positives were 19%-48% relative to 23.5%-60% for isotropic margins. Upon exclusion of the most severe outlier, the linear SVM produced per-voxel results superior to isotropic margins, but its advantage was less pronounced (Fig 5.6B). However, on a per-patient basis, exclusion of the outlier improved algorithm performance. For intermediate to high sensitivities the linear SVM would have enabled 1 to 4 t successfully treated patients (median 2, 10% of the population) who would have been incompletely treated using isotropic margins (Fig 5.7B).

The quadratic SVM produced good voxel-level curves but inferior patient-level curves (Fig 5.8A). Conversely, the boosted decision tree had good patient-level performance (Fig 5.8B) but voxel-level curves that were nearly indistinguishable from isotropic margins.
Figure 5.6: Per-Voxel receiver-operator characteristic (ROC) of a cross-validated linear SVM for detection of cancer in all 21 FT-eligible patients (A) and after excluding a single outlier (B)

Figure 5.7: Per-patient treatment success vs. healthy tissue treated for a cross-validated linear SVM in all 21 FT-eligible patients (A) and after excluding a single outlier (B)

Figure 5.8: Per-patient treatment success vs. healthy tissue treated for a quadratic SVM (A) and a boosted decision tree (B) in all 21 FT-eligible patients
The Gaussian support vector machine was markedly worse than all others, including curves derived from isotropic margins, most likely due to over-fitting.

5.3 Discussion

With both machine learning and composite feature generation, the algorithms identified lateral distance from the ROI as the most influential feature aside from 3D distance to the ROI surface. Specifically, voxels lateral to the ROI were more likely to harbor CaP, whereas voxels proximal to the ROI were more likely to harbor healthy tissue. This stands to reason, since a prerequisite for focal therapy is unilateral CaP, so tumors that extended beyond the prostate centroid were likely to have been excluded from the study population. However, it may also be a representation of prostate cancer's noted tendency to expand adjacent to the capsule. CaP probability was also asymmetric along the inferior-superior (through-plane) axis, as noted in chapter 4.

Negative core density was also highly weighted using both algorithms. It appeared more significant than most other negative biopsy measures, most likely because the presence registration error and tissue fragmentation rendered biopsy information imperfect. In other words, a negative biopsy core reduced the likelihood of adjacent CaP, but it did not eliminate it; multiple negative cores within a region were a stronger predictor of healthy tissue. The length of the nearest negative core, and the correspondingly large angle relative to nearby voxels, was also a stronger predictor of CaP than distance to negative cores. This also stands to reason, since larger and less-fragmented cores had much less uncertainty regarding tissue location within a biopsy needle's throw. The presence of negative cores between a voxel and the ROI was a
particularly predictive feature, as only a highly tortuous (and highly unlikely) tumor could have occupied its volume.

Distance to positive cores was not as strongly weighted as might be expected, most likely because the majority of the CaP-positive cores were targeted sampled from within the ROI. Though they were significant predictors of CaP, they were therefore not often independent predictors, since distance to the ROI surface was usually very small. The strongest positive-core feature for machine learning was the boolean “is there a positive core farther from the ROI than this voxel,” which conferred a specificity improvement of less than 0.5%. For composite feature generation, the strongest positive-core features were related to CaP length, perhaps because this indicated a larger tumor.

On a voxel-level, both the composite feature and the machine learning algorithms were improvements over isotropic margins, especially for high CaP sensitivities. This is partly because feature selection was optimized for prediction of CaP at high percentiles, since cases with incompletely treated CaP are highly undesirable. However, a byproduct of this approach was heavily weighted outlier cases, particularly 1 of the 21 patients whose CaP far exceeded the ROI boundaries. Removal of this case noticeably altered the voxel-level ROC curves, somewhat reducing their performance relative to isotropic margins. However, removal of the outlier also improved the patient-level ROC. Over the 50-95% true positive range, relative to isotropic margins a median of 1 additional patient would have been successfully treated using the composite feature, whereas a median of 2 additional patients would have been successfully treated using the linear SVM.

Interestingly, on a voxel level the machine learning algorithms all slightly underperformed relative to the composite feature, perhaps because the latter lacked cross-validation. The patient-level performance for most machine learning algorithms was better, and this is the more robust indicator of the approach’s efficacy.
The work done to date has been subject to a number of limitations. First, the sample size was fairly small, necessitating leave-one-out cross validation instead of more traditional training and validation schema. Second, registration error was certainly a factor in both biopsy and whole-mount data, introducing positional uncertainties on the order of 3-4 mm. Third, all patients received radical prostatectomy, making this experimental population not necessarily representative of typical focal therapy candidates. Fourth, both patient-specific margin generation schemes were highly dependent on the ROI contours, and thus the results may not be applicable to institutions with different segmentation procedures. Lastly, multiparametric MR features, which would likely improve machine learning performance, were not yet included due to registration difficulties. It is likely that CaP prediction could also benefit from fine tuning of machine learning parameters and feature selection, for which work remains in progress.

5.4 Conclusions

The results of this Chapter demonstrate that isotropic margins around MR-visible lesions can be improved through inclusion of targeted biopsy and anatomic data. Using machine learning techniques, patient-specific margins outperformed isotropic margins on a voxel- and patient-level. However, the scope of these improvements is relatively modest, and (depending on desired specificity) approximately 2 of 21 tumors (9.5%) were fully encapsulated that would have been incompletely treated using isotropic margins. Though the approach shows promise, the algorithms generated herein may not necessarily be applicable to institutions with different patient populations or MRI contouring procedures. In order to disseminate these results the conditions of imaging
and biopsy would have to be approximately matched to those at UCLA, or else the analysis should be repeated using data from the new population.

Additional work is needed to improve the sensitivity and specify of these patient-specific margins. It is likely that, in order to optimize the utility of biopsy information, ‘focal therapy planning biopsies’ should be performed in and around the ROI with a higher core density. Performance could be further enhanced through inclusion of additional MR sequences and characteristics. Acquisition of a larger sample size would also enable patient-level statistics such as Gleason score and MR suspicion to be leveraged, which were shown in Chapter 4 to be predictive of CaP.
CHAPTER 6
MRI-Guided Focal Laser Ablation

With a few exceptions\textsuperscript{114,115}, published focal laser ablation studies to date have been performed under MRI guidance. This allows the laser fiber and MRI-visible tumor to be directly visualized, ensuring accurate probe placement. Furthermore, MR thermometry can be performed in pseudo-real time (typically 1 image plane updated once every 3 seconds), allowing physicians to track thermal distributions and monitor treatment progress.

The temperature-time history of each voxel on MR thermometry can be used to estimate tissue damage, most commonly with the Arrhenius integral\textsuperscript{140}. In theory, the Arrhenius integral approximates the probability of thermal protein denaturation that leads to coagulative necrosis, and can be expressed via the equation:

$$\Omega = \int_0^t A e^{\frac{-E_a}{RT(\tau)}} d\tau$$

(Eq 6.1)

where $R$ is universal gas constant (J · mol$^{-1}$ · K$^{-1}$), $T$ is temperature (°K), $A$ is the frequency factor (s$^{-1}$), $E_a$ is the activation energy barrier (J · mol$^{-1}$), and $\Omega$ quantifies damage sustained by tissue. The variable $\Omega$ represents $\ln(C_0/C_\tau)$, or the natural log of the proportion of undamaged tissue at time $= 0$ relative to damage tissue at time $= \tau$. The damaged tissue proportion corresponding to coagulative necrosis is most commonly considered to occur when $\Omega = 1$, i.e. 63% tissue damage. The precise value of omega is irrelevant, since the constants $A$ and $E_a$ are empirically derived to match observed irreversible thermal damage in living tissue. Due to differences in biochemical
composition, the empirical constants $A$ and $E_a$ are tissue-dependent, and they must be derived through observation of thermal damage in living specimens.

Several studies have been published proposing Arrhenius constants for prostate thermal therapy, but all of them relied on *in vivo* animal tissue, *ex vivo* human tissue, and/or computer modelling$^{141-146}$. To date the Arrhenius constants for prostate have never been derived using *in vivo* human data, and thus all current models fail to account for properties such as blood flow and inflammatory/immune system responses. Consequently the optimal constants are not known, and one recent treat-and-resect FLA study employing unvalidated constants$^{141}$ derived for skin reported Arrhenius integral overestimation of tissue damage between 2 and 20 times$^{113}$. Fortunately they and others$^{112}$ have reported a strong correlation between irreversible damage seen on pathology and the non-perfused zone observed on post-treatment contrast-enhanced MRI. Thus the need for further treat-and-resect experimentation is obviated, and researchers can instead use MRI as ground-truth.

Any thermal therapy of prostate cancer, including focal laser ablation, requires a reliable method of monitoring treatment progress. Since a means of thermal damage estimation had never been validated *in vivo*, we initiated a phase I clinical trial of prostate FLA with the following goals:

- Through follow-up imaging and questionnaires, ensure that focal prostate FLA can be performed safely and without long-term side effects.
- Using *in vivo* thermal measures, compare the non-perfused zone with Arrhenius damage estimations computed using published constants, and determine the optimal values.
- Investigate an alternative to MR thermometry as a means of temperature measurement.
Trial results after 6 months of follow-up were published in the Journal of Urology\textsuperscript{119}.

### 6.1 Materials and Methods

8 men were recruited after receiving mpMRI and targeted biopsy at UCLA. All had MR-visible, unilateral, clinically significant CaP. Median age was 63 years (range 54-72), PSA was 7.54 (4.8-20.3), and prostate volume was 35.5 (29-66). 7 patients had biopsy-proven Gleason 3+4 CaP, and one had a clinically significant volume of Gleason 3+3. Additional patient characteristics can be found in the publication of our clinical results\textsuperscript{127}, and a full list of inclusion/exclusion criteria are listed in appendix A.

![Figure 6.1: A) Patient-specific planning wherein margins were expanded for positive biopsy cores and contracted for negative cores, and B) focal laser damage estimation and fiber placement planning, visualized with 3D Slicer\textsuperscript{129}](image_url)
6.1.1 Procedure Planning

Tumor-bearing regions were contoured on T2 MRI, and biopsy information as described in section 5.1.2 was imported. Using an algorithm written in MATLAB, a 15-mm isotropic margin was traced around the ROI. Afterwards, the margin was shrunk back to exclude regions bearing negative biopsy cores, and expanded if necessary to encompass regions bearing CaP-positive biopsy cores (Fig 6.1A). The anisotropic margins were then reviewed with a physician, and further altered according to their discretion in order to ensure procedure safety and feasibility using a small number of laser applications. The margins served as a general guideline for treatment, though they could not be directly imported.

Figure 6.2: Treatment planning images recorded for reference during focal laser therapy in the A) transverse, B) sagittal, and C) sagittal 3D view. Planned probe positions (blue, teal) are shown relative to the prostate capsule (green) and region of interest (red). The expected damage, not accounting for capsular cooling, is seen in pink.
Laser fiber target positions were specified by overlaying the treatment margin with ellipsoidal volumes of 8-mm radius and 17-mm length, i.e. the mean damage volume reported for a 12.5 W 90 second laser application in animal studies\textsuperscript{147}. This was considered a conservative estimate, since the laser could be applied for up to 3 minutes, for which collaborators at Desert Medical Imaging reported burn radii on the order of 1cm. These ellipsoidal volumes were overlapped within the desired treatment margins in order to compensate for placement error (Fig 6.1B) and variability in patient response to treatment. Target fiber optic trajectories were then recorded, corresponding to the center of each ellipsoidal volume. These trajectories were overlaid with MRI, and images were recorded for reference during the procedure (Fig 6.2).

6.1.2 Treatment Protocol

Prior to admission to the interventional MRI suite, a periprostatic block was administered with 1% lidocaine and 0.5% bupivacaine. Between 2 and 3 brachytherapy-style 15-Ga catheters were then inserted transperineally under US guidance. Inside the catheters were FDA-approved, fiber-coupled, fluoroptic temperature probes (LumaSense, Santa Clara CA), pre-calibrated for sub-degree accuracy in the expected range. They were positioned in pre-planned locations adjacent to the planned treatment zone, in order to collect additional temperature data (Fig 6.3) and assure safety. At least one probe was always located between the treatment zone and the rectum, in order to preclude formation of a rectal fistula.
The patient was then fitted with a transabdominal coil and placed in the bore of a 1.5T MR scanner (Avanto, Siemens). A transrectal needle guide (DynaTRIM, InVivo Corp, Gainsville FL) designed for prostate biopsy was inserted, and a baseline scan was performed. After segmentation of the prostate within the initial T2 scan, TPS nonrigid registration was performed with the treatment plan. The target fiber locations could then be displayed relative to the interventional MR coordinate system. However, due to vendor-locked software, the target fiber positions could not be directly imported, and the radiologist had to approximate them through visual inspection.

The transrectal guide was adjusted to align with a target fiber trajectory, and a 13 Ga titanium catheter was inserted to the target depth. After another T2 scan confirming catheter locations (Fig 6.4), the trocar was removed and replaced with a dual-lumen catheter (DLC). The DLC housed a 600µm-core laser fiber and was connected to both a 980nm 15 W laser and peristaltic pump, all of which comprised the Visualase thermal therapy system (Biotex/Medtronic, Houston TX). The purpose of the DLC was to channel water over the laser fiber's diffusing tip, imposing a more uniform temperature distribution and helping to prevent char.

Figure 6.3: Thermal probe planning images recorded for reference during focal laser therapy in the A) transverse 2D and B) transverse 3D view. The planned probe positions (red on left, blue on right) are shown relative to the prostate capsule (green) and region of interest (red), visualized with 3D Slicer.
After DLC insertion, MR thermometry was initiated according to the Visualase system's specifications. Thermometry was acquired from two orthogonal images, one approximately sagittal and the other between the transverse and coronal planes (Fig 6.5). Temperature measurements were updated every 6 seconds in 0.86 mm increments within these planes.

Once the cooling pump was engaged, the laser was briefly activated at 6-8 W and the heat center was confirmed to be in the planned location. Then, under the radiologist's guidance, the laser was activated at 11-14 Watts for 1-3 minutes. MR thermometry and

Figure 6.4: A) Unedited sagittal T2 MR scan after insertion of the dual lumen catheter during FLA, and B) the same image annotated with transrectal probe, interstitial probe, and prostate locations

Figure 6.5: MR thermometry overlay during focal laser therapy, with two image planes—one axial (A) and one sagittal (B)—updated every 6 seconds.
interstitial probe readings were monitored continuously, and laser power was disengaged if temperature was deemed unsafe. The laser was also deactivated if, in the radiologist's judgement, sufficient temperatures had been induced to ensure treatment at that location. The fiber was then repositioned and the imaging/treatment process was repeated for each burn location.

6.1.3. Follow-Up

Immediately post-treatment the patient received a bolus of gadolinium contrast in order to visualize the non-perfused zone (NPZ). They were then monitored in a recovery room and discharged after voiding. At 1 week, 1 month, 3 months, 6 months, 9 months, and 12 months post-treatment, patients were examined via prostate specific antigen, urinalysis, International Prostate Symptom Score (IPSS, Appendix B) and Sexual Health Inventory for Men (SHIM, Appendix C) questionnaires. After 6 and 12 months, patients received mpMRI scans which were evaluated for treatment effect and evidence of residual disease. They then received MR-US fusion targeted prostate biopsy, wherein cores were taken from in and around the treatment zone, as well as systematically from the prostate hemisphere that had received treatment.

6.2 Analysis

Temperature readings from MRI thermometry, MR localization images, and interstitial probes were time stamped using synchronized clocks, so all datasets were temporally concordant. However, patient movement between scans and prostate swelling necessitated spatial coregistration of the MRI datasets. This was accomplished through manual segmentation of the prostate gland, laser fiber position, and interstitial
probe positions using the localization scan performed prior to each laser application. A TPS nonrigid registration was then performed\textsuperscript{128}, registering 2 to 6 pelvic volumes per patient with the baseline scan. The same algorithm was used to register baseline T2 with the post-treatment contrast-enhanced sequence, on which the NPZ was visible. Once all datasets were spatially and temporally registered, analysis could proceed.

### 6.2.1. MR Thermometry Interpolation

In order to compare the NPZ with a volume of estimated tissue damage, the temperature-time history of every voxel in the prostate had to be tracked in three dimensions. Since MR thermometry had only been recorded on two orthogonal planes, this necessitated interpolation. Each laser fiber trajectory was segmented on the saved localizer images, and it was used as the center of rotation to interpolate voxels cylindrically (Fig 6.6) with temperatures weighted according to the arc distance from each thermometry plane. For example, if the laser fiber were located on the intersection of the two planes, a voxel 30 degrees from the sagittal plane and 60 degrees from axial plane would be assigned a temperature equal to \(0.6T_s + 0.3T_a\), where \(T_s\) and \(T_a\) are temperatures on the sagittal plane and axial plane, respectively. \(T_s\) and \(T_a\) were not equivalent to a single thermometry voxel, but were instead bilinear interpolations of voxels around the intersection of the thermometry plane and an arc with the laser fiber at its center.

This scheme was used to assign every voxel inside the prostate, sampled in 1-mm increments, to points from the thermometry planes in conjunction with appropriate weights. Thus, temperature at every voxel in the prostate was estimated for every MR thermometry time frame. 3D temperature reconstructions could be viewed (Fig 6.7) over the course of multiple fiber positions and laser activations.
Figure 6.6: A) Voxel coordinates in 3 space from the 2 thermometry planes, including axial (blue) and sagittal (green) voxels sampled from within the prostate. The laser fiber trajectory is plotted in black, and the yellow arrows indicate that it is the center of interpolation. B) An illustration of cylindrical interpolation for two orthogonal thermometry planes with a laser fiber at their intersection.

Figure 6.7: A) Cumulative Arrhenius damage (red) estimate, made by tracking all voxel temperatures throughout a procedure as the laser fiber (black line) was moved to multiple locations within the prostate (blue). B) The non-perfused zone (green) contoured on post-treatment contrast-enhanced MRI. C) the final 3D damage estimate overlaid with the non-perfused zone.
6.2.2. Arrhenius Analysis and Optimization

For every voxel, the Arrhenius integral was used to estimate tissue damage using 5 sets of constants proposed in the literature\textsuperscript{141-143,145,146}. After the final laser application, all voxels that exceeded the damage threshold were exported to a binary matrix. In an effort to reduce the effect of noise, the binary matrix was filtered by filling holes, then with a single erosion followed by dilation using a 3x3 kernel. In order to assess the best set of constants, the difference between each estimated damage volume and the ground-truth NPZ was calculated.

The optimal Arrhenius integral was also computed, in order to determine the closest-possible fit to our data. This was accomplished by sampling values in the range bounded by published constants, computing the combination of constants with lowest volumetric error, and then repeating with higher resolution about the global minimum. This process was repeated for 5 iterations, at which point both constants had been computed with 3 significant figures.

6.2.3. Interstitial Thermal Probe Measurements

Interstitial probe location was tracked wherever possible, but the probe-bearing catheter was not always visible in the localization sequences. Furthermore, most probes registered little or no temperature rise. Those that did detect increases in temperature were compared to the MR thermometry values of adjacent voxels.

In order to assess the impact of noise on interstitial probe measurements vs. thermometry, baseline noise was measured before laser activation. At these time points temperature should have been static, and a measure of standard deviation was considered an adequate representation of noise.
6.3 Results

All 8 patients were treated without incident, and were discharged within 6 hours. The patients received 11-14 Watt laser applications in 2 to 6 (mean 3) distinct fiber locations. Mean procedure time was 292 minutes, and mean time in-bore was 223 minutes.

6.3.1 Patient Safety and CaP Treatment Efficacy

Over 9 months of follow-up, 20 grade 1 and 7 grade 2 spontaneously resolving adverse events were recorded. No grade 3 or higher adverse events occurred. Median SHIM increased slightly after 6 months of follow-up, from 19.5 to 20. Median IPSS decreased slightly, from 4 to 3.5. Neither change was statistically significant, and no urinary incontinence or erectile dysfunction were reported.

All 8 patients had distinct non-perfused zones visible on post-treatment MRI (Fig 6.8), though most treatment zones were resorbed and minimally visible after 6 months. The mean NPZ was 4.1 cc (11% of the mean prostate volume), and after 6 months the prostate volumes as contoured on T2 MRI had decreased by a mean of 4.5 cc. All non-perfused zones overlapped at least partly with the MR-visible tumor and did not overlap the rectum, urethra, or bladder. However, quantitative assessment of overlap with the MR-visible lesion was confounded by tissue swelling.

A Wilcoxon signed-rank test showed median patient PSA to decrease significantly at 1, 3, 6, and 9 months (p < 0.01). After 12 months the decrease was no longer significant, as 2 of the 8 patients had experienced PSA increases beyond their baseline level (fig 6.9). Furthermore, 6/8 patients had experienced small PSA increases between 6 and 12
months’ post-treatment, a worrying though not yet significant \((p = 0.15)\) trend. Median PSA was 7.25 ng/mL pre-treatment and 5.25 ng/mL 12 months’ post-treatment.

Figure 6.8: The non-perfused zones from all 8 patients treated with FLA in bore.\(^{119}\)

Figure 6.9: Prostate-specific antigen measures of 8 FLA patients treated under direct MR guidance before and up to 12 months post-treatment.
Upon review of the combined results from 6-month and 12-month follow-up biopsy, 
CaP was detected within the treated region in 3 patients, and adjacent to the treated 
region in 6 patients. Another patient had a small length of Gleason 3+4 elsewhere in the 
gland, and thus only one of 8 patients was CaP-free 12 months’ post-treatment.

6.3.2 Optimal Arrhenius Damage Estimation

Representative results for four sets of Arrhenius constants from 3 patients can be 
found in Figure 6.10, and quantitative results can be found in Table 6.1. Two published 
constants\textsuperscript{141,146} were shown to overestimate the NPZ, and two others tended to 
underestimate it\textsuperscript{143,145}. The constants published by Jacques et al\textsuperscript{142}. performed nearly 
identically to the optimal constants for our dataset, with less than 15% (0.55 cc) mean 
volumetric error. Using a Wilcoxon signed-rank test, the Jacques constants produced 
significantly more accurate damage estimates than all other published values (p < 0.01) 
except those of Skinner et al (p = 0.15).

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<td>178</td>
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<td>A (1/s)</td>
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<td>3.80E+57</td>
<td>5.48E+25</td>
<td>1.03E+38</td>
<td>3.10E+98</td>
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<td>10.39</td>
<td>3.95</td>
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<tr>
<td>Mean Error (CC)</td>
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<td>1.48</td>
<td>2.25</td>
<td>4.52</td>
<td>6.41</td>
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Table 6.1: Mean volume estimates and volumetric errors associated with 5 published sets of 
Arrhenius constants and one set optimized for volumetric accuracy using our data.
Qualitatively, interstitial probe data appeared to have far greater precision than MR thermometry, as could be clearly observed from cases where probes were adjacent to the laser fiber (Fig 6.11). Probes that were close (approximately 1 cm) from the laser fiber tip reported temperatures in excess of 55°C, whereas probes that were remote from the treatment center reported modest temperatures, usually below 40°C (Fig 6.11). The probes adjacent to the rectum all remained below 42°C.

Figure 6.10: Arrhenius damage estimates (yellow) overlaid in 3D with non-perfused zones (blue), with overlap seen as green. The empirical constants from Henriques et al. resulted in damage overestimates, while those of Skinner et al. resulted in damage underestimates. The constants from Jacques et al. produced damage estimates that were nearly indistinguishable from the best-possible values derived for our dataset.

6.3.3 Interstitial Probe Data
Standard deviation (STdev) was measured in the baseline signal of interstitial 13 thermal probes in 6 patients, and in neighboring voxels on MR thermometry. Before laser application, the interstitial probes reported temperatures with a mean STdev of 0.2 degrees C. However, MR thermometry voxels adjacent to the probes reported temperatures with a mean STdev of 2.4 degrees. The average degree of signal variance was thus 12 times lower for interstitial probes (p < 0.01, Wilcoxon Signed Rank). After laser activation this measure was no longer appropriate to assess precision, though the trend appeared unchanged.
6.4 Discussion

Despite treating more than 10% of prostate tissue on average, the procedure’s safety was unequivocal. No serious adverse events occurred, all minor post-treatment symptoms resolved spontaneously, and sexual/urinary health did not change significantly. The effect of treatment was always well confined in the intended zone, and it never overlapped adjacent critical structures such as the bladder, rectum, neurovascular bundles, or urethra. It is clear that treatment was safe, which was the primary outcome of this trial.

Treatment efficacy was less clear-cut. The location of post-treatment NPZs and the dramatic short-term PSA decreases indicate that portions of CaP foci were treated in all patients. However, it is also evident that complete tumor extirpation was not achieved in 6/8 patients, as residual CaP was detected on follow-up biopsy. The 3/8 patients for whom CaP was detected in the treatment zone are particularly troubling, as this may have implications regarding the ability of FLA to induce irreversible damage. However, changes in prostate morphology and resorption of dead tissue made it difficult to assess treatment location 6 months after treatment. It is likely that treatment zones were inaccurately segmented and/or that registration error contributed to this trend. Also, since part of the 19-mm biopsy needle throw often lay outside the treatment zone, CaP-positive tissue from targeted cores could actually have been sampled proximal or distal to the former NPZ.

Though PSA remained below baseline for 6 patients 12 months after treatment, a gradual rising trend was apparent in the majority of men. This is likely an indicator that the residual tumors had recovered from treatment and were gradually growing once again. It is clear that targeting accuracy must be improved and/or treatment margins must be increased to achieve greater levels of CaP extirpation. This would likely require
additional laser applications, potentially increasing treatment times and the risk of adverse events.

Most Arrhenius constants derived in the absence of in vivo human data were proven to produce damage estimates that differed dramatically from the NPZs measured on post-treatment MRI. However, the constants proposed by Jacques et al. were an excellent, nearly optimal fit for our data. The 15% mean volumetric error observed for the Jacques constants is likely the result of variation in patient physiology, spatial registration error between the laser applications, and the noisy nature of MR thermometry. Thus, damage estimation accuracy could likely be further improved if temperature measures were more accurate and fiber localization was more robust. Even in its current state, the strong performance of the Jacques constants suggests that they should be used preferentially for prostate damage estimation. Since they are based only on measurements of temperature-time history, these results have the potential to be modality-agnostic and applicable to any form of prostate thermal therapy.

It was difficult to assess NPZ overlap with damage estimates due to tissue swelling, DCE contouring, and patient movement post-treatment. Thus only volumetric comparisons were performed, since the registration between laser applications was fairly reliable. Qualitatively, the shape between damage estimates and the NPZ matched closely for many cases, as is evident in figures 6.6 and 6.11. The broad range of Arrhenius constants quoted in the literature is somewhat troubling, and serves to emphasize that they are empirically derived, and will always be an imperfect model for prediction of irreversible thermal damage.

It was clear through assessment of baseline signal levels that interstitial probe temperature readings were far more reliable than MR thermometry. It was also clear, through review of the NPZs and probe locations, that low probe temperature precluded
tissue damage. This suggests that they could serve as a means of monitoring critical structures and ensuring patient safety, even in the absence of MR thermometry. Furthermore, interstitial probes close to the laser fiber detected temperatures of up to 55°C. This suggests that treatment efficacy could be monitored with interstitial probes as well. However, this is predicated on the assumption that the position of probes relative to the laser fiber and prostate anatomy is accurately known. Further analysis and experimentation is necessary in order to quantify how accurately temperature profiles can be reconstructed given a set of point measurements and 3D locations.

6.5 Conclusions

MR-guided FLA was demonstrated to be safe in all patients, though CaP was incompletely treated for most men. Furthermore, given temperature measures over the course of laser application, the Arrhenius damage integral could have been employed to predict tissue death with 15% volumetric accuracy. Interstitial thermal probes reported temperature with high precision, indicating a potential to monitor treatment safety and efficacy. Many aspects of the procedure require improvement, but FLA remains a promising modality for focal treatment of prostate cancer.
CHAPTER 7
MRI-Ultrasound Fusion Guided Focal Laser Ablation

MRI thermometry was critical for evaluation of FLA in living human tissue, but direct MRI guidance limits focal therapy in a number of respects. First and foremost, MR-guided procedures by their nature are highly cumbersome and time consuming. The mean procedure time for the in-bore trial described in Chapter 6 was over 4 hours, largely due to the necessity for maneuvering the patient in and out of the magnet and re-scanning them prior to each fiber insertion. This drove up procedure cost, and necessitated the use of conscious sedation drugs midazolam and fentanyl. Even under conscious sedation, patient discomfort during within the confines of a scanning magnet was substantial during such a lengthy procedure.

The technology available for probe placement was also quite restrictive. It did not allow for the importation of treatment plans, so the desired margins and laser fiber trajectories could not be accessed directly. Instead, fiber placement had to be visually assessed by comparing real-time images with preoperative plans, a lengthy and error-prone process. Furthermore, once the fiber was inserted and treatment was initiated, slight patient motions resulted in dramatic thermometry errors. Even under ideal circumstances thermometry was observed to be extremely noisy, and outlier temperatures were erroneously reported between negative 20 and 150 degrees Celsius.

MR-guided FLA as performed at UCLA also required a minimum of 6 personnel: One urologist to insert the interstitial probes, one radiologist to monitor imaging and laser application, one technician to operate the treatment monitoring software, one technician
to perform MR scanning, one nurse certified to administer intravenous drug doses, and one biomedical engineer to register treatment plans and monitor thermal probe data. This further drove up procedure cost, and reduced the likelihood of dissemination to institutions that lacked the requisite personnel or resources.

It was hypothesized that many of these limitations could be addressed by translating FLA from direct MR guidance to MR-US fusion guidance. The extensive UCLA experience with fusion biopsy has resulted in a robust procedure capable of applicator placement with approximately 3 mm accuracy. It was a reasonable supposition that instead of inserting a biopsy needle to test for CaP in an ROI, a laser fiber could be inserted for treatment of biopsy-proven cancer.

Since fusion biopsy procedures require less than 30 minutes, we hypothesized that fusion-guided FLA would dramatically reduce procedure time from over four hours to under two hours. This reduction in treatment time would justify reduction of sedatives, relying primarily on a peri-prostatic block. Perhaps most importantly, fusion guided FLA could be performed in a clinic exam room instead of a hospital suite, substantially reducing costs and improving the possibility of dissemination. In addition to the substantially lower hourly rate of an exam room relative to an interventional MR suite, three of the six personnel would be unnecessary for a clinic-based procedure: a radiologist, a MR technologist, and the laser system operator.

Various technical aspects of the procedure stand to be improved through translation to US-fusion guidance. By its nature fusion platforms can register arbitrary contours from MRI space with real time ultrasound, facilitating visualization of treatment margins and planned laser fiber trajectories. Treatment would be monitored with interstitial thermal probes, which are not susceptible to patient motion and provide high-fidelity temperature readings. Visualization of the laser fiber, which was often difficult on MRI
after perfusion with fluid, could conceivably be improved under US visualization. Lastly, custom needle guides could be designed, allowing simultaneous introduction of multiple probes.

With so many potential advantages relative to MR-guided FLA, we proceeded to design an US-fusion guided FLA safety trial. The only prior publication on US-guided prostate FLA was Lindner et al., who treated 12 patients with low-grade CaP in 2009\textsuperscript{115}. The authors had introduced their interstitial laser transperineally and verified treatment extent using microbubble contrast, and on 6-month biopsy they reported successful extirpation of disease in 50% of patients. Our trial differed from theirs in three major respects:

- We aimed to treat men with intermediate-grade CaP, since low-grade CaP patients have been proven to not significantly benefit from treatment
- We introduced our laser fiber transrectally, allowing for registration and targeting using a fusion biopsy platform
- We monitored treatment efficacy using an interstitial thermal probe, and did not employ microbubble contrast

Our trial thus constituted a novel variation of prostate FLA, never before attempted or reported in the literature. We therefore sought and received an Investigational Device Exemption from the United States FDA, and initiated an in-house clinical trial in October 2015. The trial goals were first and foremost to maintain patient safety while delivering US-guided FLA, and second to evaluate treatment efficacy relative to the MR-guided FLA trial of Chapter 6. Our efforts required specialized equipment, patient-specific planning, and a carefully designed protocol, all of which are described below.
7.1 Materials and Methods

Ultrasound fusion-guided FLA obviated the need for an interventional MR scanner and MR-compatible equipment, but an alternate means of lesion targeting and treatment monitoring was critical. The key pieces of equipment necessary for US-fusion guided FLA are listed and briefly described below:

- **Ultrasound system** (Noblus, Hitachi): a high definition ultrasound system, required for real-time prostate and applicator visualization (Fig 7.1B)

- **Transrectal ultrasound probe** (C41V, Hitachi): a convex, 200-degree field of view transducer specifically designed for prostate biopsy

- **MRI-ultrasound fusion platform** (Artemis, Eigen): a fusion system capable of nonrigid registration with MRI, importing arbitrary contours from MR space, overlaying prior targeted biopsy results, and supporting extended insertion of a laser fiber with its rigid stabilization arm (Fig 7.1C)

- **Laser** (Biotex): a 15W, 980nm, fiber-coupled laser for inducing thermal therapy (Fig 7.1A)

- **Pump** (K-Pump, Kolster Methods): a peristaltic pump that coupled with the dual lumen catheter (DLC) to actively cool the laser fiber tip (Fig 7.1A)

- **Interstitial temperature monitor** (FOT Lab Kit, Lumasense): an FDA-approved temperature sensing system, capable of measuring temperature with sub-degree accuracy from up to 4 interstitial fiber optic probes, updating once per second (Fig 7.1D)

- **Dual-channel needle guide**: a custom needle guide with one central 13Ga channel for the DLC and a second 15Ga channel, parallel to the first and 8 mm away, for an interstitial probe (Fig 7.1E)
• **FLA disposables**: one single-use set consisted of a 13Ga brachytherapy catheter (Best Medical International) which housed a 15Ga DLC which housed a 600 µm core laser fiber (both Visualase, Metronic)

• **Thermometry disposables**: 2-3 single-use 15Ga brachytherapy catheters (Best Medical International) which housed sterilizable, ten-use, 0.5 mm diameter fluoroptic probes (STB, Lumasense) which were secured with Tuohy-Borst Luer lock valves

![Figure 7.1: Key hardware for US-fusion FLA, including A) the laser and pump, B) high-resolution US, C) the fusion platform, D) an interstitial temperature tracker, and E) a custom dual channel needle guide](image)

### 7.1.1 Treatment Planning

The first phase of procedure planning, during which a treatment margin was defined using custom MATLAB scripts and physician input, was described in Chapter 6 section 6.1.1. The process of overlaying burn volumes and computing fiber trajectories was similar to the MRI-guided trial, with three minor differences:

First, instead of using treatment volume estimates from literature, we planned for a treated volume based on the in-house non-perfused zones resulting from a single laser 3-minute laser application. The result was an ellipsoidal volume 17 mm in diameter and
24 mm in length (Fig 7.2). These volumes were overlaid on the ROI and target margin, overlapping slightly in order to account for registration error. For some cases encapsulation of the entire margin was not possible with 2-3 laser applications, so regions less likely to harbor CaP were excluded at the physician’s discretion.

Second, in addition to computing the laser fiber trajectory necessary to induce the desired treatment volume, an orientation range was computed for which the parallel-channel thermal probe would be correctly placed, within the prostate but far from the urethra (Fig 7.3A). When possible it was also positioned relatively close to the capsule, to record the effect of capsular cooling from adjacent blood vessels. An L-shaped 3D object, or ‘L-bar,’ was exported such that that the L-bar's arm would only be visible on fusion overlay if the ultrasound probe was within the prescribed orientation limits (Fig 7.3B).

Third, the target margins, treatment volume, and probe positions were planned in ultrasound space, based on the prostate segmentation from the patient’s most recent fusion biopsy. This was done to account for prostate deformations from end-fire transrectal probe contact, which can substantially alter gland shape. If planning had been done in in MR space, US-fusion following prostate deformation would have resulted in curved fiber trajectories impossible to achieve, and planned treatment volumes that no longer matched the expected NPZ from a laser application. We hypothesized that these confounding factors could be avoided by planning in US space, so long as the prostate shape during treatment was similar to the most recent fusion biopsy.
Target interstitial thermal probe locations were also specified during planning. Like the in-bore trial, one probe was always positioned between the treatment zone and the rectum in order to preclude a rectal fistula. Another probe was typically placed adjacent to the lateral capsule, to ensure that capsular cooling did not prevent adequate thermal dosage. The third probe was placed at the physician's discretion, typically adjacent to the urethra, in the far anterior, between the treatment zone and urethral sphincter, or adjacent to the bladder. The fourth probe was always placed in the secondary channel.
of the dual-channel needle guide, to ensure that temperature did not approach boiling and that treatment of the planned 8.5-mm radius was achieved.

Screenshots were taken of the treatment plan and printed for reference during the procedure (Fig 7.3A). Lastly the ROI, prostate capsule, L-bars indicating laser fiber trajectory and probe orientation, and intended treatment margins were exported for fusion with real-time ultrasound during the procedure.

7.1.2 Treatment Protocol

Patients were eligible for the trial if they had 1) an MR-visible lesion that had been biopsy confirmed via 2) at least one targeted Artemis biopsy procedure, revealing 3) unilateral organ-confined prostate cancer of Gleason grade 3+4 or large-volume 3+3. Patients were considered only if they desired focal therapy and declined conventional treatment.

For pain management, the patient was administered intravenous midazolam, followed by a peri-prostatic nerve block in lateral decubitus position. The patient was then transitioned to dorsal lithotomy, and 2 to 3 15Ga brachytherapy catheters bearing thermal probes were inserted transperineally (Fig 7.4A). Probe positioning was guided by a side-firing TRUS probe, which verified that they were at approximately the intended axial position and depth (Fig 7.6B-C). The patient was then placed back into lateral decubitus, where they remained for the procedure's duration.

A 3D ultrasound scan was performed using the end-fire TRUS probe and Artemis fusion platform. The prostate capsule was semi-automatically contoured as per a typical targeted biopsy procedure. The treatment plan was then imported via nonrigid registration, overlaying all elements on a 3D prostate model which was synced with real-time US.
The TRUS probe was navigated to the planned trajectory of a laser fiber, indicated by the primary axis of a L-bar. The TRUS probe was then oriented such that the L-bar's arm was visibly overlaid on the US image. An open-ended 13 Ga catheter was inserted in the central channel of the dual-channel guide, with a biopsy needle serving as a trocar. Once needle depth was verified with real-time US, the biopsy needle was withdrawn and the DLC was inserted in its place. Ultrasound visualization of the DLC was poor, so the catheter was externally labeled in order to ensure that it occupied the correct depth. A thermal probe was then inserted in the secondary channel via a 15Ga catheter (Fig 7.5), which was externally labeled in order to ensure its depth matched the DLC tip. The planned thermal probe location was chosen to match the depth where temperature was highest, at a radial distance (8 mm) which matched the planned extent of tissue damage.

The peristaltic pump immersed the laser fiber tip in continuous flow of room-temperature saline, and the laser was activated. If the thermal probe monitoring rectal temperatures rose sharply, or exceeded 42° C at any time, the laser was immediately deactivated and the laser fiber's position adjusted. Otherwise, laser power was held at 13.75 Watts for up to 3 minutes, or until the parallel-channel probe approached 70°C. After laser deactivation, cooling was monitored and probes were only withdrawn once all probe temperatures had fallen below 42° C, the threshold for tissue damage.

Following treatment patients received a multiparametric MRI, including a contrast-enhanced sequence to visualize the non-perfused zone. Patients were then followed closely with PSA tests and questionnaires evaluating their sexual (SHIM) and urinary (IPPSS) health in 3-month intervals. After 6 and 12 months, patients received mpMRI scans, with which a radiologist contoured regions indicative of treatment and residual tumor. Targeted biopsy was performed following mpMRI, wherein a minimum of 12 cores were taken: 3 from the treatment zone, 3 adjacent to the treatment zone, 6
systematically from the treated hemisphere, and additional cores sampled from any observed ROIs.

It is important to note that the treatment protocol evolved over time. Catheter visualization was very difficult for the first 3-4 patients, so laser fiber depth could diverge substantially from the intended position. This limitation was eventually addressed through introduction of biopsy needles with enhanced ultrasound visibility, which could be placed with much greater certainty. Likewise, the system for controlling
probe depth and locking them in place was developed gradually, and had not been refined for the first several patients.

7.2 Results

A total of 11 men aged 53 to 75 were recruited. One man was not ultimately treated due to a prior transurethral resection of the prostate (TURP), rendering his gland insufficient to mechanically stabilize the laser fiber. Treatment proceeded as planned with the remaining 10 patients from September 2015 to January 2016. The treated patients had a baseline median prostate volume of 38.5 cc (range 21 to 68 cc) and a median PSA of 6.3 ng/mL (range 0.9 to 22.3). 6 of the treated patients had ROIs primarily in the transition zone, and 4 had ROIs primarily in the peripheral zone. Total procedure time was 93 minutes on average (range 71 to 105 minutes).

7.2.1 Treatment Safety

For all 10 patients, FLA was well tolerated under local anesthesia supplemented by midazolam. Temperature near the rectum, as reported by an interstitial thermal probe, never exceeded 42 degrees Celsius. Upon review of the post-procedure MRI, a radiologist determined that the treated region did not contact the transurethral sphincter, bladder, or rectum in any case, though they abutted the posterior prostate capsule for several patients. The NPZ overlapped the mid-gland urethra for one patient, and evidence of thermal damage was observed on subsequent transurethral imaging.

Despite 2 to 3 prolonged burns per patient, no significant adverse events (AEs) of grade 3 or higher or decline in sexual/urinary function occurred. On average 3.4 adverse events were reported per patient, and the most common were hematuria (6 patients),
weak urine stream (5 patients), bloody stool (4 patients), dysuria, hematospermia, and nocturia (3 patients each). A mild decrease in sexual function and urinary frequency/urgency were observed in two patients each. Uncommon AEs reported by only one patient each were tenesmus, perineal pain, dilute ejaculate, constipation, and lethargy. Most adverse events were short-lived and self-resolving.

As the procedure improved, the frequency of adverse events diminished. A mean of 4.5 AEs was recorded for the first 4 patients, whereas the next 6 had an AE mean of 2.5.

### 7.2.2 Treatment Efficacy

A summary of baseline, post-treatment, and safety statistics for the 10 patients can be found in Table 7.1. Each patient received 2-3 laser applications at 13.75 Watts, most commonly applied for 3 minutes each. During treatment, temperature was successful recorded by 3 to 4 interstitial thermal probes. A representative example of thermal probe positions and reported temperatures can be seen in Figure 7.6. Temperature at the closest thermal probe, positioned a radial distance of 8-mm from the laser fiber tip, exceeded 55°Celsius for every case and 60°Celsius for the majority of cases. The former threshold corresponded to a damage radius slightly below 8-mm and the latter corresponded to a damage radius of approximately 8 mm; exact values depended on the temperature-time history rather than the maximum temperature achieved. The maximum recorded temperature was below 75 degrees for all laser applications.

Upon review of post-treatment MRI, all 10 prostates had distinct non-perfused zones that overlapped with the intended treatment volume (Fig 7.7). The precise degree of overlap was difficult to assess due to tissue swelling post-treatment, though targeting accuracy appeared to improve for the latter half of patients. The mean treated volume
Table 7.1: Summary of clinical trial patient characteristics, treatment parameters, safety and efficacy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Prostate Vol. (cc)</th>
<th>Treated Vol. (DCE, cc)</th>
<th>Procedure Time (min)</th>
<th>Burns ≥ 90s</th>
<th>Adverse Events</th>
<th>Residual Gleason ≥ 7</th>
<th>Residual Gleason 6</th>
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<td>20.6</td>
<td>5.7</td>
<td>100</td>
<td>3</td>
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<td>51.1</td>
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<td>26.8</td>
<td>6.0</td>
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<td>4.8</td>
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<td>58</td>
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<td>4.5</td>
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<td>68</td>
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</tr>
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<td>11</td>
<td>60</td>
<td>26.1</td>
<td>3.4</td>
<td>105</td>
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<td>1</td>
<td>NO</td>
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</tr>
</tbody>
</table>

Figure 7.6: Interstitial thermal probe locations and corresponding temperature data for a representative fusion-guided FLA case

Figure 7.7: Contrast enhanced MRI showing distinct non-perfused zones for all 10 patients post-treatment
of the contoured NPZ was 4.5 cc (range 2.8 to 6.0 cc), 14% of the mean prostate volume. With one notable exception, treated volumes were less distinct on mpMRI during 6-month follow-up, most having shrunk to a fraction of their previous size. For one patient, a large fluid-filled cyst had formed in the treated region, which laboratory analysis showed to be benign. A second patient had a much smaller fluid-filled cyst, but this anomaly was absent from all others.

![PSA Follow-Up for Ultrasound Fusion-Guided Focal Laser Ablation in 10 men](image)

Figure 7.8: PSA test results from US fusion-guided FLA measured in 3-month intervals. The first 4 men treated (red) had worse biochemical outcomes than the next 6 (blue).

Though this study was not statistically powered for secondary analyses, treatment efficacy was observed to markedly improve over time. Of the first 4 patients, 2 experienced no decrease in PSA, and 2 had transient PSA drops at 3 months but PSA began to rise after 6 months (Fig 7.8). However, of the next 6 patients all experienced a decrease in PSA that was persistent after 9 months, a significant trend (Wilcoxon signed-rank test, p = 0.03). A similar trend was observed at the 6-month follow-up biopsy, which revealed residual Gleason 3+4 disease adjacent to the treatment zone in the first 4 patients. However, Gleason pattern 4 disease was absent from the next 6 patients. Three had residual Gleason 3+3 CaP, with tissue lengths that fell below the threshold for
evidence of a clinically significant tumor volume. Three had no evidence of CaP on biopsy, despite at least 12 cores sampled in and around the formerly CaP-positive zone; one of these successful cases is displayed before and after treatment in figure 7.9.

![Figure 7.9: Case study of one patient who had an MR-visible tumor (top left) biopsy-confirmed to harbor Gleason 3+4 (top right) disease with 4 cores positive for CaP (top middle). After fusion-guided FLA there were no suspicious regions on MRI (bottom left), and despite over a dozen cores sampled (bottom middle) all samples were negative for CaP, and those in the treatment zone showed evidence coagulative necrosis (bottom right).](image)

### 7.2.3 Comparison with MR-Guided FLA

Direct MR guidance is the current standard for prostate FLA. Although the trial was not statistically powered to detect differences given the modest sample sizes, even anecdotal equivalence to MR-guided procedure outcomes could help justify further research efforts for US-fusion FLA. Key statistics for the two trials were therefore compiled and compared (Table 7.2). Despite mean treatment times that were less than a third of the MR-guided trial (1.5 vs. 4.9 hours), US-fusion FLA burn volumes were slightly larger on average (4.7 vs. 4.1 cc). Relative to the MR-guided FLA trial, the mean number
of AEs decreased slightly for the US-guided trial as a whole (0.2 fewer), and decreased appreciatively for the last 6 patients with (1.1 fewer). Mean PSA after 9 months had decreased by 4.3 ng/mL in the MR-guided trial, 1.8 ng/mL in the fusion-guided trial, and 4.3 ng/mL in the last 6 fusion guided patients.

<table>
<thead>
<tr>
<th></th>
<th>MR-Guided</th>
<th>US-Guided (All)</th>
<th>US-Guided (Last 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Burn (cc)</td>
<td>4.1</td>
<td>4.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Mean Time (hours)</td>
<td>4.9</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Mean Adverse Event Count</td>
<td>3.6</td>
<td>3.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Mean 9-Month ΔPSA (ng/mL)</td>
<td>-4.2</td>
<td>-1.8</td>
<td>-4.3</td>
</tr>
<tr>
<td>Residual Gleason 3 CaP</td>
<td>7 of 8 (88%)</td>
<td>7 of 10 (70%)</td>
<td>3 of 6 (50%)</td>
</tr>
<tr>
<td>Residual Gleason 4 CaP</td>
<td>5 of 8 (63%)</td>
<td>4 of 10 (40%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Critical Personnel</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Facilities</td>
<td>Interventional MR Suite</td>
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</tr>
<tr>
<td>Plan Registration</td>
<td>Cognitive</td>
<td>Fusion</td>
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</tr>
</tbody>
</table>

Table 7.2: Qualitative and quantitative comparison (unpowered) of effects, outcomes, and costs between UCLA’s MR-guided FLA trial and US-fusion guided FLA trial.

For the fusion-guided trial residual Gleason pattern 3 CaP and pattern 4 disease was detected in fewer patients (70% vs. 80%, 40% vs. 63% respectively). Residual CaP in the last 6 men was even less frequent, with 50% of men harboring pattern 3 and 0% of men harboring pattern 4 disease. For fusion-guided FLA the number of critical personnel, facilities costs, and degree of anesthesia were substantially reduced. The registration methodology was also more robust in the fusion-guided trial, with treatment plans imported via surface-based nonrigid transformation instead of cognitively.
7.3 Discussion

Demonstration of procedure safety was the primary outcome for this trial, and the safety data is unequivocal. No grade 3 or higher adverse events occurred, and though grade 1 and grade 2 adverse events were fairly common they tended to be transient and spontaneously resolving. Patients did not experience any long-term reduction in health or quality of life, including incontinence and impotence. The noteworthy reduction of adverse events in the last 6 patients is likely the result of improved fiber placement accuracy, which decreased the number of unnecessary re-insertions. Eliminating the transperineal temperature probes would potentially help to further reduce adverse events, since probe positions were frequently adjusted and they contributed substantially to tissue trauma.

Lesion targeting accuracy was insufficient in the first four patients, as was evidenced by the lackluster PSA response and residual Gleason 4 disease. However, it is very encouraging that, after the problems of catheter visualization and positioning were addressed, procedure efficacy was observed to improve dramatically. Complete CaP extirpation appears to have been achieved for 3 patients, demonstrating strong potential for fusion-guided FLA to deliver curative treatment without risk of incontinence or impotence. The other three, who all had significant CaP at baseline, had only insignificant tumor foci detected on follow-up biopsy. Even though they had residual cancer, reduction of Gleason grade could be considered a lesser form of treatment success, and considering the slow doubling time of CaP it could be many years before the tumors return to their former volume. However, it is a noteworthy possibility that pattern 4 CaP was present in some or all of the last 6 patients treated, and it simply was not detected on biopsy.
The interstitial thermal probe data was sufficient to ensure safety of the procedure, as evidenced by the absence of serious adverse events and long-term side effects. However, the probe parallel to the laser fiber, which was intended to monitor tissue damage and treatment efficacy, reported a worrying degree of temperature variation. Maximum reported temperatures fell between 55°C and nearly 70°C, despite our intention to always place the thermal probe 8 mm from the DLC’s tip. Though variability in patient response to the laser certainly contributed to the probe's temperature disparities, incorrect thermal probe positioning likely accounted for most of the observed differences. Probe deflection was certainly a factor, since some catheters were visibly warped upon post-procedure examination. Probe depth was also imperfectly matched to the DLC, since tissue turgor frequently displaced one relative to the other. Their position was checked and adjusted if necessary prior to laser activation, but small deviations in depth (1-2mm) occasionally went uncorrected. In order to reliably monitor spreading temperature and tissue damage during treatment, the spatial relationship between laser fiber and thermal probe must be more rigidly controlled or more accurately assessed and accounted for.

Even including the first four patients, fusion-guided FLA compared favorably with the outcomes of the MR guided procedure. Nearly all aspects of the procedure, from adverse event frequency positive biopsy rates to procedure time and cost, appeared to improve under fusion guidance, though the sample sizes were too small to draw statistically valid conclusions. Inclusion criteria between the two trials were nearly identical, though baseline characteristics of the two patient groups did vary and thus some of the differences observed may have been artifacts of the study populations. The advantages of fusion-guided FLA were more pronounced in the sub-population comprised of the last 6 men treated. While population sizes were not sufficient to prove
the benefits of fusion-guidance, the results are suggestive and certainly warrant future research efforts in this field.

### 7.4 Conclusions

Ultrasound fusion-guided focal laser ablation was safe in all men, with no long-term impact on sexual, urinary, or general patient health. The procedure was ineffective extirpating CaP in the first four men treated (40%), but of the next 6 three (30%) had their tumors reduced below the threshold of clinical significance, and three (30%) had no evidence of CaP. Furthermore, fusion-guided FLA compared favorably to our institution's prior MR-guided trial for most cost and outcome measures. The results suggest that, although direct MR-guidance is the current standard of care, ultrasound fusion guidance may be a valid alternative.
CHAPTER 8
Conclusions and Future Directions

In men with localized prostate cancer, focal therapy has the potential to impart curative treatment without risk of incontinence and impotence. My central hypothesis was that focal therapy, still considered a controversial and experimental approach, could be made feasible though registration of MRI with ultrasound, pathology, and thermal data. Over the course of this dissertation I have sought to investigate a number of key questions that are critical for the development of focal therapy:

1. Since focal therapy is necessarily image-guided, how reliably can tumor location be distinguished on medical imaging?
2. Given the reliability of prostate cancer imaging, what margins are necessary for treatment success?
3. Can focal treatment be effectively monitored and safely delivered in a clinic setting?

Much work remains to be done, but substantial progress has been made on all three topics and the outlook for focal therapy remains promising. Though my research demonstrated that T2 MR contours underestimated the extent of cancer, I also showed that treatment margins could be improved through incorporation of biopsy data. I demonstrated that tissue damage could be estimated from real time thermal data, enabling physicians to ensure completion of a treatment plan without undue harm to local anatomy. Lastly, our research showed focal laser ablation to be safe in all 18 men treated, and the feasibility of MR-US fusion to guide effective focal therapy was demonstrated.
These results have important implications for the development of prostate imaging and focal therapy. The methodology for MR tumor segmentation needs to be radically altered, employing multiple sequences, multiple anatomic perspectives, and new contouring guidelines to compensate for the dramatic CaP underestimation of current T2 ROIs. The optimal thermal damage equation discussed herein should be employed for future thermal therapy studies, as it considerably outperforms other proposed Arrhenius constants. Perhaps most importantly, focal therapy should be performed with large patient-specific margins to avoid the incomplete extirpation of CaP observed in the majority of our subjects. Fusion guided FLA, as opposed to the current standard of MRI-guidance, should also be strongly considered since it appears to deliver comparable results in less time with fewer direct costs.

The conclusions of all major phases of my research, and future directions that research might now take, are summarized below.

### 8.1 Improvements in Radiology-Pathology Correlation

Patient-specific 3D-printed molds for MRI-pathology correlation were developed and rigorously characterized. Phantom experiments demonstrated that the use of patient-specific molds reduced mean registration errors by a factor of 2, from 4 mm to 2 mm. Furthermore, *ex vivo* scans of prostatectomy specimens showed that patient-specific molds aligned excised glands to *in vivo* MRI with mean through-plane error of 1.5 mm, equal to the spacing between an adjacent pair of MR image slices. Mean 3D registration error was approximately 4 mm. Characterization of these errors was critical, as they would affect the results of subsequent MRI-pathology correlations using molds.
Starting in August 2013, patient specific molds were used for 114 radical prostatectomy specimens, whose tumors were then registered with preoperative MRI and reconstructed in 3D. It was shown that mpMRI had 82% sensitivity for index disease, and highly suspicious ROIs had a specificity approaching 90%. However, the average tumor had three times greater volume and a longest dimension 11 mm longer than prospective MR contours. Furthermore, tumor size and ROI size were weakly correlated, with the worst correlation and largest errors observed along the inferior-superior (through-plane) axis. The median Hausdorff maximum distance between tumors and matched ROIs in retrospectively focal therapy eligible men was 10.2 mm. This has critical implications for focal therapy treatment planning, since more than half of patients would have required an isotropic margin greater than 1 cm for complete tumor extirpation. MRI alone was deemed inadequate for the guidance of focal therapy, since additional tumor characterization data would be necessary to ensure treatment success in the majority of eligible patients.

Several steps can be taken to further improve radiology-pathology correlation. As we continue to accrue ex vivo prostate MRI data, we will be able to measure trends and track systematic registration errors. Once these errors are fully characterized, the mold design can be altered to compensate for them. For example, over a large number of cases, we may note a systematic rotation error around the left-right anatomic axis. If this is the case, the prostate cavity can be adjusted for all future patient-specific molds in order to optimally counteract this effect. Furthermore, registration techniques described in Chapter 3 succeeded in registering in vivo to ex vivo MRI with 1.4 mm mean error, far more accurate than the default mold-based registration. MRI-pathology correlation can therefore be performed on these cases with far greater fidelity. Experimental scanning
sequences and segmentation techniques can be tested using the *ex vivo* MR specimens, improving CaP imaging in ways that may eventually be translated to patients.

The MR-pathology correlation results can also be used to guide improvements in contouring procedure. Though T2 MRI segmentations underestimate tumor volume, incorporation of contours from additional sequences has been reported to yield strong size correlations\(^\text{130,132,138}\), and UCLA has already begun to implement this practice. Further improvements could be made by scanning with higher through-plane accuracy and contouring from coronal and/or sagittal anatomic perspectives, since the greatest correlation errors were observed along the inferior-superior axis. More aggressive pre-treatment contouring protocols can also be formulated that are distinct from the conservative procedure intended to guide targeted biopsy.

Lastly, more efforts must be made to understand why some tumor regions are MRI-invisible. For tumors matched to MRI, pathology slides regions that overlapped the ROI should be re-examined separately from regions that did not. The relative importance of Gleason score, cell density, and blending with healthy tissue can then be evaluated, and differences can be measured between the MR-visible and MR-invisible tumor regions.

### 8.2 Refinement of Margin Generation

Efforts were made to improve upon isotropic margins for focal therapy treatment planning through incorporation of tBx data. Through an analysis of voxels with and without CaP after whole-mount registration, it was determined that features relating the geometries of ROIs, positive biopsy cores, and negative biopsy cores were highly predictive of cancer. Through optimal combination of these features with validated machine learning techniques, between 1 and 4 (5%-20% of patients sampled) more
patients could have been successfully treated relative isotropic margins. In order to identify 99% of CaP-bearing voxels, false positives were reduced from 60% for isotropic margins to 48% with machine learning.

While this was a marked improvement upon the isotropic margins, the current standard for treatment planning, additional data and validation steps would be necessary in order to deploy it clinically. First more data should be accrued, since the N=21 prostates examined herein are likely insufficient to capture the considerable heterogeneity of CaP. Secondly, additional features should be measured to fully leverage the information available in multiparametric MRI. Once more sequences are registered to high-resolution T2, ROIs and voxel intensities from diffusion- and perfusion-weighted imaging can be incorporated into our analysis. More advanced techniques in feature selection and machine learning, such as deep learning or neural networks, may further improve the classifier performance.

Once a robust algorithm for patient-specific treatment margins is optimized, the final step will be to test it with clinical data. Firstly, UCLA’s targeted biopsy database can be utilized retrospectively, since hundreds of patients have undergone serial biopsy with the Artemis system. For these men, the first biopsy session can serve as input (along with MRI) to the machine learning algorithm, and the second biopsy can test its reliability. Positive cores outside the predicted CaP volume will be indicative of false-negative voxels, and constitute strong evidence that focal therapy would have failed in that patient. Negative cores inside the optimal treatment zone will constitute false-positives, and be evidence of unnecessarily treated tissue.

Ultimately, of course, patient-specific margins can only be fully tested through a prospective clinical trial of focal therapy. If the recommended margins are achieved, their efficacy can be measured through long-term biopsy and biochemical follow-up.
8.3 Validation of Thermal Profile and Damage Estimation

Focal laser ablation was performed under directly MR guidance in 8 men, with 4.1 cc of tissue non-perfused after treatment and enduring reductions in patient PSA. Though the procedure was safe in all men, with no long-term impact on urinary or sexual health, 7 of 8 men had residual disease on follow-up biopsy. It was therefore evident that treatment of the MR-visible lesion was insufficient, and better margins would have been necessary for complete tumor extirpation.

Using MR thermometry data from this safety trial, the optimal method of predicting tissue damage using the Arrhenius integral was computed. It was demonstrated that tissue damage could be predicted with 0.5 cc (< 15%) volumetric error based on measurements of temperature over time. Furthermore, interstitial thermal probes were proven to be far more precise than MR thermometry, with less than one tenth the noise in baseline signals. It was hypothesized that treatment safety and efficacy could be ensured by thermal profile estimation from judiciously placed interstitial probes.

Though the Arrhenius constants published by Jacques et al.¹⁴² fit our *in vivo* data quite well, further work is necessary to verify that results are applicable in other populations and institutions. To that end, we intend to collaborate with other centers currently performing MRI-guided focal laser ablation. After 3D interpolation of their MR thermometry data and comparison with their non-perfused zones, the same Arrhenius constants will be tested for damage prediction fidelity. If the Jacques constants are not optimal for the expanded test population, it may be necessary to derive new constants.

Though interstitial probe data was far more reliable than MR thermometry for prediction of damage at one point in space, interstitial probes directly record
temperature in far fewer voxels. It therefore should be formally investigated how accurately a thermal profile can be reconstructed given this diminished dataset, and what the optimal probe placements should be. An algorithm will therefore be written to iteratively analyze the MR thermometry data, sampling randomly selected points around the laser fiber and using them to estimate temperatures elsewhere. The best possible point set will be computed, and the location of those points relative to the laser fiber will be used to inform probe location for future studies. Furthermore, thermal profile estimation errors will be used to define the upper and lower temperature limits to ensure treatment safety and efficacy, respectively. This will inform safety cutoffs for probes near sensitive anatomy. It will also dictate the time necessary to ensure full treatment of the target zone, accounting for error in temperature and damage estimation.

8.4 Next Steps for Fusion Guided Focal Laser Ablation

Focal laser ablation was performed under MR-US fusion guidance in 10 men, the first time such a procedure has ever been attempted using a transrectal approach. Treatment was monitored using interstitial thermal probes, with temperature in an 8-mm radius always exceeding 55°C and temperature at the rectum never exceeding 42°C. Fusion-guided focal laser therapy was safe in all men, with no serious adverse events or long-term detriment to patient health. For the first 4 patients treated, little PSA change was observed and residual pattern 4 CaP was found on follow-up biopsy. However, after limitations in probe visualization and positioning had been addressed, the next 6 patients experienced enduring PSA reduction. All 6 had significant CaP before treatment, but afterwards 3 men had their tumor burden reduced below the threshold of significance and 3 had no evidence of CaP on follow-up biopsy. Thus fusion-guided FLA
was shown to have potential for effective cancer control, and compared favorably relative to the MR-guided trial.

Much work remains to translate fusion-guided FLA from an experimental trial to a clinical technique eligible for dissemination and reproduction. First, it will be necessary to develop hardware for improving accuracy and procedure time. The most critical update is regarding a multi-element interstitial thermal probe (Fig 8.1), which will serve as a replacement to the four single-element probes previously employed. The multi-element probe will be inserted along the second channel of the dual-channel guide, recording multiple temperatures along that vector and thus sampling points throughout the treated region. This should enable much more accurate thermal profile estimation while also ensuring that temperature at the rectum remains within a safe range. Furthermore, without the necessity to insert transperineal probes, the procedure time is expected to decrease by approximately 30 minutes.

A bi-planar ultrasound probe (Fig 8.2) would also greatly improve the reliability of interstitial probe placement, since only the primary channel of the dual-channel needle guide is visualized using a conventional probe. Though the insertion depth of the secondary-channel interstitial probe could be mechanically matched to the first, it was not possible to verify its position directly. This was a major source of uncertainty in the procedure, since deflection or slippage of either channel’s interstitial probe could alter their relative locations and reduce the accuracy of thermal profile estimation. A transrectal ultrasound probe capable of directly visualizing both channels could be used to measure the distance between them and adjust our damage model appropriately.

In the long term, development and approval of treatment planning and guidance software will be critical. Ideally this would incorporate the key results of our research regarding CaP imaging uncertainty, tissue damage estimation, and interstitial probe
placement. It would import a patient's MRI and biopsy history, and export a recommended treatment margin with the probe trajectories necessary to achieve it. During treatment, given the position of the laser fiber and interstitial thermal probe within the prostate, a 3D damage estimate would be updated in real time. Laser power would be automatically reduced if temperatures approached unsafe thresholds.

Perhaps most importantly, studies performed to date at UCLA were safety trials for which treatment was planned and performed conservatively. However, in order to prove equivalent cancer control rates with competing technologies, a phase 2 ‘intent-to-treat’ trial must be performed with imaging and biopsy follow-up. Once we demonstrate that our procedure is capable of extirpating CaP in a large number of patients, we can move forward with deployment of the system at other institutions to test it in additional patient populations.

Figure 8.1: Diagram of a multi-element interstitial probe sampling temperatures from a thermal profile around a laser fiber (left). The recorded temperatures could then be used to reconstruct the thermal profile (right) and track the procedure’s progress.
Extirpation of prostate cancer quickly, inexpensively, and in a clinic setting was unthinkable only a few short years ago. However, thanks to research efforts by our group and others, such an approach has become feasible. The efficacy of this treatment strategy is only expected to improve along with the rapidly changing fields of prostate imaging and energy-tissue interactions. Though important questions remain unanswered and years of development remain, focal therapy research is poised to revolutionize the perception and management of prostate cancer.
The following inclusion and exclusion criteria were imposed for the clinical trial of MRI-guided focal laser therapy at UCLA. Any exceptions to these criteria required prospective IRB exemption, and were determined on a case-by-case basis. Additional information is available at ClinicalTrials.gov under the trial identifier NCT02224911.

**Inclusion Criteria:**

- Subjects with initial presentation of organ confined prostate cancer (clinical stage ≤ T2b)
  - Negative metastatic workup with bone scan and CT abdomen/pelvis, within 6 months of study treatment, if indicated by PSA >10
  - Age 40 years to 85 years of age
  - Multi-parametric MRI at UCLA within 6 months of study treatment, demonstrating a
    - Region of interest (ROI) of MRI suspicion level 3 or higher
    - ROI located proximal to the external sphincter by a margin of at least 2 cm
  - Transrectal ultrasound-guided biopsy with ≥ 10 systematic biopsy cores and ≥ 2 MRI-ultrasound fusion targeted biopsy cores from above MRI-derived ROI
    - Histologically-confirmed adenocarcinoma from tBx cores (≥ 2 cores)
    - Overall Gleason score not to exceed 3+4
  - Subjects desire focal therapy and declined conventional treatment (active surveillance, radical prostatectomy, radiation therapy, cryosurgery and hormone therapy)
Signed informed consent for the LITT treatment through the 12 month follow-up visit

**Exclusion Criteria:**

- Any significant cancer outside of MRI target (ROI) area, defined as Gleason score > 3+4
- < 10 years life expectancy
- American Society of Anesthesiologists (ASA) criteria of IV or higher
- Unfit for conscious sedation anesthesia
- Active bleeding disorder as determined by abnormal prothrombin time, partial thromboplastin time, INR or platelet count (as determined by institutional lab parameters) at the time of screening
- Use of coumadin or any other anticoagulant, unless anticoagulation can be temporarily reversed or stopped for a window of at least 7 days peri-procedure
- Active urinary tract infection
- Prostate abscess, chronic or acute prostatitis, or neurogenic bladder
- Any prior treatment for prostate cancer
  - Radical prostatectomy
  - Radiation therapy (external beam or brachytherapy)
  - Cryotherapy
  - High intensity focused ultrasound treatment
  - Photodynamic therapy
  - Androgen deprivation therapy
• Prior prostate, bladder neck, or urethral stricture surgery
  o Any prostate debulking procedure, including: transurethral resection of prostate, photovaporization, or electrovaporization
  o Transurethral incision of bladder neck
  o Urethral stricture dilation or reconstruction
• Any current 5-alpha reductase inhibitors (history of use ≥ 6 months prior to MRI is acceptable)
• Prior significant rectal surgery (hemorrhoidectomy is acceptable)
• Rectal fissure, fibrosis, stenosis, or other anatomic abnormality precluding insertion of transrectal device
• History of inflammatory bowel disease
• Urinary tract or rectal fistula
• Any contraindication to MRI (contrast allergy severe claustrophobia, MRI-incompatible prosthesis)
Appendix B

International Prostate Symptom Score (IPSS) Questionnaire
Developed and Made Publicly Accessible by the American Urological Association (1992)

<table>
<thead>
<tr>
<th>In the past month:</th>
<th>Not at All</th>
<th>Less than 1 in 5 Times</th>
<th>Less than Half the Time</th>
<th>About Half the Time</th>
<th>More than Half the Time</th>
<th>Almost Always</th>
<th>Your score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incomplete Emptying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>How often have you had the sensation of not emptying your bladder?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. Frequency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>How often have you had to urinate less than every two hours?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3. Intermittency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>How often have you found you stopped and started again several times when you urinated?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Urgency</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>How often have you found it difficult to postpone urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5. Weak Stream</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>How often have you had a weak urinary stream?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6. Straining</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>How often have you had to strain to start urination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7. Nocturia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>How many times did you typically get up at night to urinate?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total I-PSS Score</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Score: 1-7: Mild  8-19: Moderate  20-35: Severe

<table>
<thead>
<tr>
<th>Quality of Life Due to Urinary Symptoms</th>
<th>Delighted</th>
<th>Pleased</th>
<th>Mostly Satisfied</th>
<th>Mixed</th>
<th>Mostly Dissatisfied</th>
<th>Unhappy</th>
<th>Terrible</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Appendix C

Sexual Health Inventory for Men (SHIM)\textsuperscript{149}

In the past 6 months:

1. How do you rate your confidence that you could get and keep an erection?
   1. Very low  
   2. Low  
   3. Moderate  
   4. High  
   5. Very high  

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
   1. Very low  
   2. Low  
   3. Moderate  
   4. High  
   5. Very high  

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   1. Very low  
   2. Low  
   3. Moderate  
   4. High  
   5. Very high  

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
   1. Very low  
   2. Low  
   3. Moderate  
   4. High  
   5. Very high  

5. When you attempted sexual intercourse, how often was it satisfactory for you?
   1. Very low  
   2. Low  
   3. Moderate  
   4. High  
   5. Very high  

Scoring instructions

Add the numbers corresponding to the answers for questions 1 through 5. If the patient’s score is 21 or less, erectile dysfunction (ED) should be addressed. The SHIM score characterizes the severity of the patient’s ED in the following manner:

- 22-25 No ED
- 17-21 Mild ED
- 12-16 Mild-to-moderate ED 8-11 Moderate ED  
- 5-7 Severe ED
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