MRI scans significantly change target coverage decisions in radical radiotherapy for prostate cancer

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Abstract

Introduction: Conventional clinical staging for prostate cancer has many limitations. This study evaluates the impact of adding MRI scans to conventional clinical staging for guiding decisions about radiotherapy target coverage.

Methods: This was a retrospective review of 115 patients who were treated between February 2002 and September 2005 with radical radiotherapy for prostate cancer. All patients had MRI scans approximately two weeks before the initiation of radiotherapy. The T-stage was assessed by both conventional clinical methods (cT-stage) as well as by MRI (mT-stage). The radiotherapy target volumes were created firstly based on the cT-stage and then based on the addition of the mT-stage. The number of times extracapsular extension (ECE) or seminal vesicle invasion (SVI) was incorporated into target volumes was quantified based on both the cT-stage and the addition of the mT-stage.

Results: ECE was incorporated into target volumes significantly more with the addition of mT-staging (46 patients [40%]) compared to cT-staging alone (37 patients [32%]) ($p = 0.002$). SVI was incorporated into target volumes significantly more with the addition of mT-staging (21 patients [18%]) compared to using cT-staging alone (3 patients [3%]) ($p < 0.001$). A total of 23 patients (20%) had any changes to their target coverage based on the mT-stage.

Conclusions: MRI scans significantly change decisions about target coverage in radical radiotherapy for prostate cancer.

Keywords:
Prostate cancer

Magnetic resonance imaging

Radiotherapy

Target volume delineation

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Introduction

The clinical T-stage is one of the most important factors (along with initial PSA and Gleason score) for deciding on target coverage for radical radiotherapy for prostate cancer. As such, incorrect T-staging has potential consequences for patients who are selected for definitive radiotherapy. If a patient has extracapsular extension (ECE) or seminal vesicle invasion (SVI) that is not detected at staging, then standard radiotherapy target volumes may not adequately cover all of the disease, potentially leading to poorer outcomes.

Currently, the digital rectal examination (DRE) remains the gold-standard method for determining the clinical T-stage in prostate cancer in almost all guidelines and protocols.[1, 2] This is in spite of mounting evidence showing that the DRE has severe limitations - in terms of poor correlation with pathological T-stage in radical prostatectomy series[3] (with agreement in less than 50% of cases) and also poor interobserver variability.[4]

Several other methods have been used for clinical T-staging including transrectal ultrasound (TRUS), computed tomography (CT), and TRUS-guided biopsy. TRUS by itself has not been shown to be any better than DRE[2, 5], and computed tomography (CT) has virtually no role in T-staging because of its limited soft tissue definition.[6] TRUS-guided biopsy-based staging can improve on the DRE[7] however its accuracy is user-dependent.

MRI has been shown to have superior accuracy to both DRE and TRUS-guided biopsy for staging and localising prostate cancer.[8] This is due to its ability to allow visualisation of normal anatomy including prostate zonal anatomy, prostate capsule, seminal vesicles, and surrounding normal tissues, as well as pathological features such as ECE and SVI.[9] Studies comparing MRI with prostatectomy-based staging have generally shown high specificity for

detecting both ECE and SVI.[10, 11] The MRI-defined T-stage has also been shown to be more prognostically important than the DRE-defined T-stage, having a better correlation with biochemical control in a cohort undergoing radical radiotherapy for prostate cancer.[12] Therefore, using MRI scans to guide decisions about radiotherapy target coverage may be more accurate than conventional clinical staging using DRE and/or TRUS-guided biopsy.

Prostate staging MRI scans are already performed relatively commonly in the United Kingdom, where National Institute for Health and Clinical Excellence (NICE) guidelines[13] advocate their use in patients with high risk disease. This is not the case in Australia, where prostate cancer staging MRI scans are currently not funded and not routinely used in most centres.

This study evaluates the impact of adding MRI scans to conventional clinical staging for guiding decisions about radiotherapy target coverage.

Materials and Methods

This was a retrospective review of 115 consecutive patients treated with radical radiotherapy for prostate cancer between February 2002 and September 2005. The Austin Health Human Research Ethics Committee granted approval for this study. All patients in this study had TRUS-guided biopsy-proven adenocarcinoma of the prostate. Clinical T-staging was performed primarily using digital rectal examination (DRE), with an allowance for upstaging where the TRUS-guided biopsy detected ECE or SVI. Patients were then risk-stratified according to these initial characteristics using National Comprehensive Cancer Network (NCCN) criteria.[1] Patients who were classified as high to very high risk, or who had signs or symptoms of metastatic disease were further staged with CT scans and whole body

scintigraphic bone scans. Patients who were found to have nodal or distant metastatic disease were excluded from this study.

Patients with intermediate, high and very high risk prostate cancer were given 3 months of neoadjuvant androgen deprivation therapy (ADT) in the form of goserelin or leuprorelin followed by concurrent and adjuvant ADT. The total period of ADT was 6 months for intermediate risk prostate cancer and 3 years for high and very high risk prostate cancer. All patients were planned for 7-field step-and-shoot IMRT. Low risk patients received 74 Gy in 37 fractions to the prostate alone. Intermediate and high risk patients received 56 Gy to the uninvolved seminal vesicles and 78 Gy to the prostate, ECE and SVI using a simultaneous integrated boost over 39 fractions.

Radiotherapy planning CT and MRI scans were done approximately 2 weeks before the initiation of radiotherapy. The planning CT scan was performed on a GE Lightspeed RT (General Electric, Fairfield, CT, USA) with 2.5 mm axial slice thickness with a matrix size of 512 x 512. The planning MRI scan was acquired on a GE Signa 1.5 Tesla with an external phased-array body coil. T1 and T2-weighted sequences were acquired in axial, sagittal and coronal planes, covering the prostate and seminal vesicles. The following parameters were used for T1-weighted sequences: repetition time / echo time (TR/TE) 600-640 ms / 8-16 ms, matrix size 512 x 512, with slice thickness 4.5 mm in axial plane and 3 mm in sagittal and coronal planes. The following parameters were used for T2-weighted sequences: TR/TE 4000-5260 ms / 65-67 ms, matrix size 512 x 512, with slice thickness 4.5 mm in axial plane and 3 mm in sagittal and coronal planes.

The axial T2-weighted planning MRIs were then fused with the planning CT scans using manual rigid co-registration in the radiotherapy treatment planning software. Bony anatomy was matched first, and then soft tissues (rectum, prostate, bladder, pelvic musculature) were matched in a second step if there was a shift in the prostate position due to organ

deformation. Using conventional clinical T-staging (cT-staging) information alone, contouring was performed, covering the prostate, seminal vesicles, ECE and SVI as necessitated clinically. Following that, all the MRIs were reviewed by a urological radiologist and radiation oncologist. According to the criteria listed in Table 1, the presence of visible tumour, ECE and SVI were recorded and a MRI T (mT) stage was assigned. Using the mT-stage information in addition to the cT-stage (using whichever method resulted in higher stage disease), contouring was performed, covering the prostate, seminal vesicles, ECE and SVI as necessitated clinically. The number of times that ECE and SVI were incorporated into target volumes was counted for both methods.

Where ECE was detected using either method, a further 3 mm margin[14, 15] was added to the involved region of the prostate capsule, and incorporated into the high dose (78 Gy) Clinical Target Volume (CTV) (Fig. 1). Where SVI was detected using either method, the SVI was also incorporated into the high dose CTV (Fig. 2). Planning Tumour Volumes (PTVs) were created by automatic expansions from the CTVs of 6 mm posteriorly and 10 mm in the other directions.

In a second analysis, Partin tables[16] were used to predict the risk of SVI. Where the risk was determined to be greater than 15%, the cT-stage and mT-stage were upgraded to have SVI included, and were then designated “Partin table-adjusted cT and mT-stages”.

The proportions of patients with different target coverage based on the various methods were compared using one-tailed McNemar’s tests. The discrepancies in staging and NCCN risk groupings between cT-staging and mT-staging were also quantified.

Results

The characteristics of the 115 patients are listed in Table 2. ECE was incorporated into target volumes in 37 patients (32%) using cT-staging and 46 patients (40%) with the addition of mT-staging. The difference between the discordant findings was statistically significant ($p = 0.002$). SVI was incorporated into target volumes in 3 patients (3%) using cT-staging and 21 patients (18%) with the addition of mT-staging. The difference between the discordant findings was also statistically significant ($p < 0.001$) (Table 3). Overall, a total of 23 patients (20%) had any changes to their target volumes due to the addition of mT-staging (where patients found to have both ECE and SVI on mT-staging were counted only once).

In the analysis of the addition of Partin table[16] information to staging, SVI would have been incorporated into target volumes in 60 patients with Partin table-adjusted cT-staging, and 68 patients with Partin table-adjusted mT-staging. The difference between the discordant findings was still statistically significant ($p = 0.004$). This means that using Partin table-adjusted cT-staging alone would still have missed 8 out of 23 patients found to have SVI on mT-staging. Using Partin table-adjusted cT-staging, 52% of patients would have required SV irradiation, whereas using mT-staging without Partin tables, only 18% of patients would have required SV irradiation.

mT-staging was higher than cT-staging in 33 patients (29%), the same in 36 patients (31%), and lower in 46 patients (40%) (Table 4). mT-staging was used only for upstaging, therefore resulted in upstaging in 33 patients (29%) and no change in 82 patients (71%). One patient with low risk disease and seven patients with intermediate risk disease (totalling eight patients (7%)) had their risk groups upgraded.

Discussion

This study shows that MRI scans have a significant impact on the radiotherapeutic management of prostate cancer in terms of decisions about target coverage. These findings are consistent with previous studies which have shown that MRIs have a significant impact on the surgical management of prostate cancer.[17, 18]

Previous studies have examined the impact of MRI on radiotherapy target volume definition in terms of changes to the anatomical contouring of the prostate.[19, 20] Contouring on MRI allows significantly smaller CTVs than contouring on CT due to less normal tissue being incorporated.[19, 20] Additionally, contouring on MRI has been found to allow lower inter- and intraobserver variability in target volume delineation, especially at the prostate apex.[20, 21] Our study shows that in addition to allowing better anatomical contouring of the prostate, it also allows better pathological feature contouring of the prostate, specifically for ECE and SVI.

ECE is not routinely accounted for in radiotherapy target volumes in many radiotherapy protocols where it is not detected on initial staging.[22] In such cases, the CTV encompasses the prostate only to the edge of the prostate capsule. However, pathological series[14, 15] have reported that where ECE is present, the average radial spread is 2-3 mm beyond the prostate capsule in the involved areas. This should be incorporated into the CTV in accordance with the ICRU 50 guidelines.[23] Our study shows that 9 patients (8%) would have had this microscopic disease extension missed if they did not have an MRI.

Additionally, SVI may not be accounted for correctly if it is not detected on initial staging. Without evidence of SVI on initial staging, some investigators advocate the coverage of only the proximal 1 – 2.5 cm of the SVs into the CTV, taking the SVs to a lower dose, or using predictive tools to identify patients at higher risk of SVI.[22, 24-26] A recent study on MRIs in patients undergoing radiotherapy has shown that in patients with SVI identified on MRIs, >90% had SVI longer than 1 cm and approximately 40% had SVI longer than 2.5 cm.[19] Our study shows that 18 patients (16%) would not have received an adequate dose to the full

extent of the SVI using cT-staging alone. If Partin tables were used to modify cT-staging, this would have resulted in a significantly greater number of patients requiring SV irradiation, however would have still missed eight patients out of 23 found to have SVI on mT-staging. Partin tables, which were based on a surgical cohort of lower risk patients, may not be the best method to determine whether or not to irradiate the seminal vesicles.

Target volume definition is the most important step in the radiotherapy planning pathway, as inaccurate definition can lead to a geographical miss of tumour and systematic underdosing of the target.[27] Poor radiotherapy planning including inaccurate target volume delineation has been associated with substantially poorer locoregional control and overall survival in other cancer sites.[28] Geographical misses of extracapsular disease extension and gross seminal vesicle invasion most likely would have similar impacts on outcomes. As the precision of radiotherapy increases with newer technologies such as image-guided radiotherapy (which allows tighter PTV margins), errors in target volume definition are likely to have an even greater impact on outcomes.

The upstaging effect of MRI found here is consistent with previous studies. When MRI is used for initial staging before any therapy, Jackson *et al.* reported that 55% of their prostate cancer cases did not correlate with DRE.[12] In this study of 199 patients, 52% were upstaged by MRI, 3% downstaged, and only 45% were concordant with DRE. In our study, if we had used the initial DRE-based T-staging for radiotherapy planning, we would have understaged 29% of cases, and potentially under-dosed or geographically missed the target in 20% of cases.

Another advantage of accurate staging is that patients may be more appropriately selected for different ADT schedules. In patients with high risk prostate cancer, there is evidence for better survival with longer courses of ADT.[1, 29] In our study, 7% of patients had an upgrade in their risk groups due to having an MRI, therefore would be more appropriately selected for longer ADT schedules.

This study does have a number of limitations. Firstly, because this was not a surgical study, false positive findings on the MRI scans could not be quantified, and therefore this study may slightly overestimate the benefits. However, previous studies investigating the correlation of MRI with pathology have generally shown high specificity, meaning that the false positive rate should be low. Nakashima *et al.*[10] performed a correlation study on 95 patients who had MRIs before radical prostatectomy and found a sensitivity and specificity of 57.1% and 82.1%, respectively for ECE and 62.1% and 81.8%, respectively for overall staging. Using MRIs with 3T field strength (higher than that used in this study), specificity values of 97-100% have been reported.[11] Given its relatively high specificity, it would be sensible to incorporate visualised ECE and SVI features into the high dose radiotherapy volumes. Secondly, the radiotherapy planning MRIs in this study were performed after 2.5-3 months of neoadjuvant ADT therefore are not true initial staging scans. Pre-ADT staging scans could not be obtained because of the logistical problems of organising an immediate MRI scan in a busy radiology department. Sanghani *et al.*[30] showed that following two months of ADT, prostate volumes and primary tumour volumes decreased by a median of 28% and 64%, respectively. As a result of this, a significant proportion of patients in our study may be downstaged on the MRI due to shrinkage of the tumour due to ADT. Therefore the impact of MRI in this study is most likely an underestimate compared with if one was to perform the MRI prior to ADT. We attempted to account for this by changing the management only in cases of upstaging, and not changing the management in cases of downstaging (in case the downstaging effect was due to ADT). Thirdly, endorectal coils were not used with the MRIs. Endorectal coils have been shown in some studies to improve image quality[11], however they have also been shown to deform the prostate, and therefore impair registration with radiotherapy planning CT scans.[31] Due to the problem of deformation, we chose not to use endorectal coils at our centre. Fourthly, MRI technology and protocols have improved substantially since the time this study was carried out. All of the patients in this study were scanned on a 1.5T MRI at 4.5 mm slice thickness, whereas

3T MRIs with 1 mm slice thickness are now readily available. Furthermore, functional and molecular imaging was not employed in any of the patients in this study. Functional and molecular imaging modalities such as diffusion-weighted MRI[32], dynamic contrast enhanced MRI[32], magnetic resonance spectroscopy[32], and ^{11}C-choline PET scans[33, 34] have been shown to be very promising for improving the accuracy of staging, however were not employed in the study period. Diffusion-weighted MRIs are now part of the routine protocol for prostate staging MRIs at our centre. With the improved sensitivity and specificity of newer technologies, it is likely that MRI would have an even greater impact on radiotherapy target coverage decisions than what is reported here.

The main implication of this study is that MRI can potentially have a significant impact on the radiotherapeutic management of patients with prostate cancer, and should therefore be further investigated in a prospective clinical trial.

Conflict of Interest Statement

All authors have indicated that they do not have any conflicts of interest in relation to this work.

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Table 1. MRI Prostate Cancer Summary Guidelines[35]

1. Tumour is defined by low signal lesion most often in the high signal peripheral zones on T2 MRI
2. ECE is defined by:
    a. Direct extracapsular extension of tumour into periprostatic fat
    b. Broad tumour contact with the capsule of greater than 1cm with smooth capsular bulge
    c. Obliteration of the rectoprostatic angle
    d. Asymmetry or involvement of the neurovascular bundles
3. SVI results in low signal intensity within the lumen of the SV, loss of normal fat plane between SV and prostate base or tubular wall thickening in continuity with prostate tumor on MRI T2 weighting. Correlation is made with T1 weighted sequences to exclude haemorrhage (bright on T1).

Table 2. Patient characteristics

Characteristic	Value
Age (years)	
Median (range)	69 (47 – 80)
Gleason sum	
2-6	36
7	56
8-10	23
PSA (µg/L)	
Median (range)	14.0 (1.8 – 194)
Initial clinical T stage	
T1a-T2a	45
T2b-T2c	30
T3a	37
T3b	3

Table 3. Number of patients with ECE or SVI incorporated into target volumes

	ECE		SVI	
Initial risk group	cT-staging	Addition of mT-staging	cT-staging	Addition of mT-staging
Low (n=7)	0 (0%)	1 (14%)	0 (0%)	0 (0%)
Intermediate (n=31)	0 (0%)	4 (13%)	0 (0%)	5 (16%)
High / Very High (n=77)	37 (48%)	41 (53%)	3 (4%)	16 (21%)
Total (n=115)	37 (32%)	46 (40%)	3 (3%)	21 (18%)

Table 4. Changes in staging due to MRI

	cT1	cT2	cT3a	cT3b	TOTAL
mT1	9	22	13	0	44
mT2	10†	20	10	0	40
mT3a	2†	3†	5	1	11
mT3b	3†	6†	9†	2	20
TOTAL	24	51	37	3	115

† where the initial clinical T-staging (cT staging) was upstaged by the subsequent MRI staging (mT staging).

Fig. 1. A CT scan (a) and a MRI scan (b) of a patient with ECE on the right posterior surface of the prostate. The prostate capsule as defined on CT scan is outlined in the solid white line. The MRI shows ECE bulging through the capsule into periprostatic fat. The dotted white line represents a 3 mm margin on the involved part of the capsule. ECE was not detected on either clinical examination or CT scan, and only found on MRI.

Fig 2. A CT scan (a) and a MRI scan (b) of a patient with SVI. The prostate is outlined in the solid white line and gross SVI (identifiable on the MRI as low signal intensity in the left seminal vesicle) in the dotted white line. The SVI was not detected on either clinical examination or CT scan, and only found on MRI.