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Are magnetic resonance imaging undetectable prostate tumours clinically significant? Results of histopathological analyses



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ABBREVIATIONS

AS, active surveillance;
ASA, American
Society of Anesthesiologists;
BMI, body mass index;
RALP, robot-assisted

Abstract Objective: To investigate whether tumours at threshold values for detection on magnetic resonance imaging (MRI) represent clinically significant tumours or not, and therefore the utility of MRI in active surveillance (AS) protocols.

Patients and methods: A retrospective analysis of a single institution database was performed after Institutional Review Board approval. Between 2010 and 2013, 1633 patients underwent robot-assisted laparoscopic prostatectomy (RALP) at a single institution by a single surgeon. Of these, 1361 had complete clinical data and were included in analysis. Multivariate logistic regression was used to assess histopathological grade compared to tumour size whilst controlling for biopsy Gleason score, prostate-specific antigen level, body mass index, race, and age.

Results: Of 120 tumours < 5 mm in size, four were Gleason score 4 + 3. Of 276 tumours of 5–10 mm, 22 (8.1%) were Gleason score 4 + 3 and one (0.2%) was Gleason score 8. On multivariate regression analyses, tumours of < 5 mm were much less likely to be high grade (Gleason score > 3 + 4) at RALP compared to larger tumours (3.3% vs 25.1%, $P < 0.001$), or Gleason score ≥ 8 (0.0% vs 7.6%,

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laparoscopic
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$P < 0.001$). Size was further shown to significantly correlate with grade on multivariate regression ($P < 0.001$).

Conclusions: Prostate tumours below the detection threshold for MRI (5 mm) most probably represent clinically insignificant tumours, which alone would not necessitate leaving AS in favour of more aggressive therapy. These findings point to a possible role of MRI in modern AS protocols.

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Introduction

Prostate cancer is the most common cancer in men worldwide. As detection technologies have improved in recent decades, more patients are diagnosed at early stages of the disease. Prostate cancer has a slow progression course over time, which makes active surveillance (AS) a treatment option for an increasing proportion of patients. AS has been increasingly accepted and adopted in the management of low-risk prostate cancer [1]. With AS cohorts growing rapidly and evidence of excellent outcomes mounting, use of this management option will probably increase greatly in the coming years. Whilst proponents of AS laud the delay to definitive treatment and consequent postponement of treatment-related adverse effects [2], critics of AS aptly acknowledge its reliance on serum biological markers, with confirmation of disease state only through requisite repeated prostate biopsy, with their own comorbid burdens [3]. Further, the relative inaccuracy of prostate biopsy, carrying a reported reclassification risk as high as 38%, with ~27% of patients reportedly upstaged [4,5], strengthens the call for better diagnostic tests to assess and confirm disease state, especially in younger men on AS protocols.

In the absence of a reliable non-invasive test, many clinicians have investigated endorectal MRI as an adjunct to confirmatory prostate biopsy as a means of better staging of prostate cancer [6–8]. Once the diagnosis of prostate cancer is confirmed and a patient is placed on AS, MRI, if accurate, would carry the advantage of being less invasive than repeating prostate biopsy, and be associated with a much lower complication rate, whilst still providing valuable staging information about tumour size, growth, and extension [9,10].

MRI has shown varying accuracy in classifying tumour characteristics; there have been consistent questions about limitations on the resolution of the imaging technique. Some studies conservatively suggest that tumours of < 10 mm are unable to be accurately characterised by MRI, and others support a resolution limit of 5 mm [11–13]. MRI, whilst potentially useful in prostate cancer as it has been for other cancers, has a significantly lower sensitivity for small tumours, which is of

significant concern for the presumably low-volume disease that should represent the bulk of patients eligible for AS. In this vein, we sought to explore the pathological characteristics of prostate cancers that would be unreliably characterised by MRI based on their small size, and determine how many, if any, of the tumours below these resolution thresholds represent clinically significant disease.

Patients and methods

Under Institutional Review Board approval, data were extracted on eligible patients from a prospectively maintained database that was analysed retrospectively. In all, 1633 patients diagnosed with prostate cancer underwent robot-assisted laparoscopic prostatectomy (RALP) at a single institution by a single surgeon (DBS) from January 2010 to April 2013. Relevant information about clinical characteristics, histopathology, medication use, comorbidities, and demographics were registered at enrolment.

All RALP specimens were examined and tumour diameters measured by genitourinary pathologists at our institution. Preoperative specimens were re-evaluated by the pathology department for preoperative Gleason score reports. Patients without reports of tumour diameter or preoperative Gleason score were excluded from our study to avoid convolution by different methods of tumour size estimation and Gleason scoring.

Tumours were stratified to diameters above and below both 5 and 10 mm. These threshold sizes are commonly cited as the resolution limits for MRI [11–13]. No preoperative MRI was performed as standard protocol in this study. Univariate variables were compared using chi-squared for categorical and *t*-test or ANOVA for continuous variables, where appropriate. A multivariate logistic regression model was created to assess histopathological grade compared to tumour size, whilst controlling for Gleason score at biopsy, race, body mass index (BMI), PSA level, and age at RALP. All analyses were performed using SPSS version 19 (SPSS IBM, Armonk, NY, USA).

Results

Of 1633 patients accrued during the study period, 1361 had data including histopathological evaluation of tumour volume, grade, and preclinical parameters and were included in the analyses. The demographics, preoperative and postoperative characteristics of our cohort are presented in Table 1. The mean (SD) age of the patients in ≤ 5 and 5–10 mm groups was similar [58.2 (6.8) vs 59.5 (7.4) years, $P = 0.11$] and younger than patients with tumours of > 10 mm, with a mean (SD) age of 60.0 (7.1) years ($P = 0.03$). There was no difference in racial distribution of patients. The PSA level in the ≤ 5 and 5–10 mm groups was similar, at a mean (SD) of 4.8 (2.6) and 4.8 (2.3) ng/mL, respectively ($P = 0.79$). However, patients with tumours of > 10 mm had higher PSA levels, at a mean (SD) of 6.8 (5.1) ng/mL ($P < 0.001$).

Of the 120 tumours sized ≤ 5 mm, there were four (3.3%) with pathological Gleason scores of 4 + 3 and no tumour had a higher Gleason score. Of the 276 tumours sized 5–10 mm, there were 22 (8.1%) with pathological Gleason scores of 4 + 3 and only one (0.36%) with a higher Gleason score, an 8-mm tumour with a Gleason score of 8. Tumours of ≤ 5 mm were much less likely to be high grade (Gleason score $> 3 + 4$) at RALP compared to those of 5–10 mm (3.3% vs 8.1%, $P < 0.001$), and > 10 mm (3.3% vs 20.4%, $P < 0.001$). No tumours sized ≤ 5 mm were Gleason score ≥ 8 (0.0% vs 7.7%, $P = 0.002$). Tumours of 5–10 mm had higher grades than those of ≤ 5 mm ($P < 0.001$). Similarly, tumours of > 10 mm had higher grades than those of 5–10 mm. In assessing the extracapsular involvement of tumours, only one patient with a tumour of ≤ 5 mm had pT3b and three patients with tumours of 5–10 mm had pT3a stage. Tumours of

Table 1 Demographics and histopathological data of the patients in the study.

| | | Tumour ≤ 5 mm | Tumour 5–10 mm | <i>P</i> | Tumour > 10 mm | <i>P</i> |
|--|--------------|--------------------|---------------------|-----------|---------------------|-----------|
| Number of patients | | 120 | 276 | | 965 | |
| Age at RALP, years, mean (SD, range) | | 58.2 (6.8, 41–72) | 59.5 (7.4, 40–78) | 0.11 | 60.0 (7.1, 38–79) | 0.03 |
| Race [§] , <i>n</i> (%) | White | 101 (89.3) | 235 (86.0) | 0.38 | 788 (83.4) | 0.25 |
| | Black | 4 (3.5) | 22 (8.1) | | 107 (11.3) | |
| | Other | 8 (7.2) | 16 (5.9) | | 49 (5.3) | |
| PSA level, ng/mL, mean (SD, range) | | 4.8 (2.6, 0.1–16) | 4.8 (2.3, 1.0–16.8) | 0.79 | 6.8 (5.1, 1.1–47.0) | < 0.001 |
| ASA classification [¶] , <i>n</i> (%) | I | 9 (7.8) | 15 (5.5) | 0.48 | 59 (6.2) | 0.37 |
| | II | 74 (63.8) | 205 (74.3) | | 648 (67.2) | |
| | III | 33 (28.4) | 55 (19.8) | | 249 (25.9) | |
| | IV | 0 (0) | 1 (0.4) | | 7 (0.7) | |
| D'Amico risk [‡] , <i>n</i> (%) | Low | 96 (82.8) | 177 (64.1) | < 0.01 | 363 (37.6) | < 0.001 |
| | Intermediate | 19 (16.4) | 86 (31.3) | | 463 (48.0) | |
| | High | 1 (0.8) | 12 (4.6) | | 139 (14.4) | |
| Clinical stage [†] , <i>n</i> (%) | \leq T1c | 101 (91.9) | 241 (86.1) | 0.31 | 692 (78.7) | 0.01 |
| | \geq T2a | 9 (8.1) | 39 (13.9) | | 189 (21.3) | |
| Biopsy Gleason score, <i>n</i> (%) | ≤ 6 | 104 (86.2) | 186 (67.5) | < 0.01 | 380 (39.4) | < 0.001 |
| | 3 + 4 | 12 (9.9) | 56 (20.3) | | 333 (34.5) | |
| | 4 + 3 | 3 (3.0) | 21 (7.6) | | 118 (12.3) | |
| | ≥ 8 | 1 (0.9) | 13 (4.6) | | 134 (13.8) | |
| Pathological stage, <i>n</i> (%) | pT2 | 119 (99.2) | 273 (98.3) | 0.18 | 636 (66.0) | < 0.001 |
| | pT3 | 1 (0.8) | 3 (1.7) | | 328 (33.9) | |
| | pT4 | 0 | 0 | | 1 (0.1) | |
| Pathological Gleason score, <i>n</i> (%) | ≤ 6 | 89 (74.2) | 75 (27.0) | < 0.001 | 41 (4.2) | < 0.001 |
| | 3 + 4 | 27 (22.5) | 177 (64.1) | | 635 (65.8) | |
| | 4 + 3 | 4 (3.3) | 22 (8.1) | | 196 (20.4) | |
| | ≥ 8 | 0 (0) | 2 (0.8) | | 93 (9.6) | |

ASA, American Society of Anesthesiologists.

[§] Data for 31 patients were missed.

[¶] Data for 6 patients were missed and not reported.

[‡] Data for 5 patients were missed and not reported.

[†] Data for 1271 patients are reported.

≤5 mm had similar pathological stage to tumours of 5–10 mm. However, tumours of >10 mm had higher pathological stages than both tumours of ≤5 and 5–10 mm. In D'Amico risk classification, tumours of ≤5 mm were more likely to be classified as low risk compared to tumours of 5–10 mm ($P < 0.01$) and tumours >10 mm ($P < 0.001$).

On multivariate regression, size was further shown to significantly predict grade whilst controlling for age at RALP, BMI, preoperative PSA level, race, and American Society of Anesthesiologists (ASA) comorbidity classification ($P < 0.001$). Using thresholds of 5 and 10 mm as binary classes in a multivariate model showed both to be significant predictors of high-grade disease (Table 2).

Discussion

If MRI is to be relied upon for risk classification of tumours, then the risk of significant disease in these smaller tumours must be quantified and understood. If MRI could be used to improve diagnostic accuracy and risk stratification at initial diagnosis, or to replace any number of surveillance biopsies on AS protocols, the burden of comorbidities accompanying AS could be greatly reduced. However, the limitations of a new technology must be explored and understood before it can be reliably applied clinically. The present study was designed to assess the clinical significance of tumours at detection threshold values of MRI.

AS is a validated strategy for managing low-risk prostate cancer, but it is limited by its reliance on sometimes misleading serum biomarkers and repeat prostate biopsy to assess disease progression and patient classification [14]. A reduction in the morbidity associated with repeat biopsies would vastly improve the appeal of the

option, as would a method to better assess, three dimensionally, disease growth and extension. Previous studies have shown that MRI can be reliably used to diagnose prostate tumours of >5 mm. Body coil MRI can detect up to 82% of tumours >5 mm [11] and endorectal MRI has been reported to have a sensitivity, accuracy and positive predictive value of 85%, 80% and 93% in tumours of >10 mm [13]. MRI has been shown to have a 89% detection rate for tumours of >10 mm but only a 5% detection rate in tumour foci of <5 mm [12]. Recently, Almeida et al. [15] reported that multiparametric MRI with Prostate Imaging Reporting and Data System criteria has a sensitivity of 92% and negative predictive value of 96% in upstaging of visible tumours of >10 mm. The results of the present study show that prostate tumours measuring <5 mm are less likely to be clinically significant, as only three of the tumours had Gleason score 4 + 3 and only one tumour showed signs of extracapsular involvement. Except for a single 8-mm tumour (0.36%) and four tumours that were T3 stage (1.0%), tumours of <10 mm had features of insignificant prostate cancer, further supporting MRI as a reliable technique in patients undergoing AS.

There has been discussion and investigation into the accuracy of staging of MRI, the correlation of size between MRI estimates and pathological specimens, and the potential use of MRI as a protocol in AS of prostate cancer [14]. The maximum diameter of tumour has been shown as a simple clinical tool for assessment of the grade of prostate tumours [13]. Diameter of the tumour regardless of the size, is well correlated with the size determination in the MRI images [13]. However, in the current era of management for prostate cancer and AS the question of exact correlation in tumour volume and precise risk is not as important as the root question: should this patient remain on AS, or is active

Table 2 Multivariate regression of factors associated with high-grade (Gleason score >3 + 4) tumours using 10 and 5 mm tumour size thresholds.

| | | | β | Standard error | P |
|-------------------------|------------------------|-------|-------------|----------------|--------|
| Threshold size at 10 mm | Race | White | (Reference) | | |
| | | Black | -0.43 | 0.45 | 0.34 |
| | | Other | -0.01 | 0.44 | 0.97 |
| | Age at RALP | | 0.07 | 0.01 | <0.001 |
| | BMI | | 0.02 | 0.01 | <0.001 |
| | Preoperative PSA level | | 0.09 | 0.01 | <0.001 |
| | Tumour < 10 mm | | -3.36 | 1.01 | 0.001 |
| Threshold size at 5 mm | Race | White | (Reference) | | |
| | | Black | 0.94 | 0.44 | 0.03 |
| | | Other | -0.35 | 0.32 | 0.27 |
| | Age at RALP | | 0.03 | 0.01 | 0.008 |
| | BMI | | 0.02 | 0.02 | 0.25 |
| | Preoperative PSA level | | 0.16 | 0.04 | <0.001 |
| | Tumour < 5 mm | | -3.24 | 0.24 | <0.001 |

treatment warranted? Determining exactly how big a tumour is should take a back seat to the question of whether a tumour is aggressive and requires active treatment. In this sense, our question on the resolution of MRI and ability to detect small volume tumours is not exactly how big they are or even if we can see them, but instead: if a tumour is undetectable by MRI, is that tumour significant?

In the present study, we show that prostate cancers below the resolution limit of modern MRI techniques nearly always represent insignificant disease. In our present cohort, four patients with a tumour of ≤ 5 mm (resolution limit of MRI) had a pathological Gleason score $> 3 + 4$, and only one patient of 396 with a tumour of ≤ 10 mm had a Gleason score 8. Lee et al. [16] reported that tumours of > 10 mm in MRI assessments have a higher chance of being clinically significant. These findings suggest that tumours at threshold values for MRI assessment most likely do not represent high-risk tumours, and thus would not trigger a treatment recommendation to patients on AS protocols.

Whilst it is intuitive that larger tumours may be more aggressive and represent higher risk disease, it is possible that a small focus of cancer may also harbour high-grade disease. However, these high-grade tumours, representing tissue more distinct from normal prostate tissue than the generally benign Gleason $3 + 3$ or $3 + 4$ tumours, have been shown to be easier to detect by conventional MRI methods [17]. Further, if patients are maintained on an AS protocol, they will have a repeat MRI every 12–24 months. As prostate cancer is a slow growing disease, the delay to risk reclassification in these patients most probably does not represent a significant increase in risk of dangerous disease. It is unlikely that high-grade disease could escape detection after consistent monitoring using MRI.

In our present cohort of 1361 men treated for prostate cancer, we found that no patients with a tumour size below the current MRI resolution limit of 5 mm had high-grade disease, and that only one patient with a tumour size < 10 mm had high-grade disease. These findings suggest that the cited limitation of MRI as an adjunct to modern AS protocols, the limitation in resolving small size tumours, is not a significant limitation, as these tumours do not represent significant disease. As such, MRI should be investigated further for use in AS protocols in order to reduce the morbidities associated with such protocols.

As a retrospective single-surgeon cohort, there are inherent limitations and confounders. Our present patients were all treated with RALP at a tertiary centre; they likely represent a group with higher socioeconomic status than the general population, which may influence the rate at which these patients seek treatment. Some patients in the present study might qualify for AS as elderly population. However, there was a decent distri-

bution of tumour volume and cancer characteristics sufficient to support the current conclusions. Furthermore, although there is a treatment selection bias to a degree, these patients also represent individuals who would be deciding on treatment strategies, and for many of whom AS, with or without MRI, would be a suitable option. Although there are newer classifications to prostate cancer grading [18], the available data were not sufficient in the present study to apply the newer classification system.

It would also be preferable to assess size as detected by MRI before prostatectomy in this cohort in lieu of post-prostatectomy pathology tumour size assessment; however, as the purpose of our present study was to describe presumably MRI undetectable cancers and previous data suggest good correlation between pathological size and MRI measurements, MRI before RALP was not performed.

Conclusions

Prostate tumours below the detection threshold for MRI of 5 mm most probably represent clinically insignificant tumours, which alone would not necessitate leaving AS in favour of more aggressive therapy. Tumours of 5–10 mm require additional studies and closer follow-up. These findings point to a possible role of MRI in modern AS protocols.

Conflict of interest

Authors state that there is no conflict of interest to declare.

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