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Correlation of Magnetic Resonance Imaging Tumor Volume with Histopathology

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Abstract

Purpose—The biology of prostate cancer may be influenced by the index lesion. The definition of index lesion volume is important for appropriate decision making, especially for image guided focal treatment. We determined the accuracy of magnetic resonance imaging for determining index tumor volume compared with volumes derived from histopathology.

Materials and Methods—We evaluated 135 patients (mean age 59.3 years) with a mean prostate specific antigen of 6.74 ng/dl who underwent multiparametric 3T endorectal coil magnetic resonance imaging of the prostate and subsequent radical prostatectomy. Index tumor volume was determined prospectively and independently by magnetic resonance imaging and histopathology. The ellipsoid formula was applied to determine histopathology tumor volume, whereas manual tumor segmentation was used to determine magnetic resonance tumor volume. Histopathology tumor volume was correlated with age and prostate specific antigen whereas magnetic resonance tumor volume involved Pearson correlation and linear regression methods. In addition, the predictive power of magnetic resonance tumor volume, prostate specific antigen and age for estimating histopathology tumor volume (greater than 0.5 cm³) was assessed by ROC analysis. The same analysis was also conducted for the 1.15 shrinkage factor corrected histopathology data set.

Results—There was a positive correlation between histopathology tumor volume and magnetic resonance tumor volume (Pearson coefficient 0.633, $p < 0.0001$), but a weak correlation between

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prostate specific antigen and histopathology tumor volume (Pearson coefficient 0.237, $p=0.003$). On linear regression analysis histopathology tumor volume and magnetic resonance tumor volume were correlated ($r^2=0.401$, $p<0.00001$). On ROC analysis AUC values for magnetic resonance tumor volume, prostate specific antigen and age in estimating tumors larger than 0.5 cm³ at histopathology were 0.949 ($p<0.0000001$), 0.685 ($p=0.001$) and 0.627 ($p=0.02$), respectively. Similar results were found in the analysis with shrinkage factor corrected tumor volumes at histopathology.

Conclusions—Magnetic resonance imaging can accurately estimate index tumor volume as determined by histology. Magnetic resonance imaging has better accuracy in predicting histopathology tumor volume in tumors larger than 0.5 cm³ than prostate specific antigen and age. Index tumor volume as determined by magnetic resonance imaging may be helpful in planning treatment, specifically in identifying tumor margins for image guided focal therapy and possibly selecting better active surveillance candidates.

Keywords

prostatic neoplasms; magnetic resonance imaging; tumor burden

Screening strategies such as serum PSA and digital rectal examination have led to the earlier diagnosis of prostate cancer. Tumors detected by screening are typically smaller and better localized than those detected clinically. Although whole gland therapies remain the standard of care, there is increasing interest in minimally invasive focal therapies, especially image guided ablation to avoid the well-known morbidities associated with whole gland therapy.^{1,2} Focal therapy involves selective ablation of an index prostate cancer including a margin of normal tissue, with preservation of the remainder of the prostate, urethra and neurovascular bundles, thereby reducing side effects.^{3,4} Some groups have defined focal therapy as a hemiablation or subtotal prostate ablation procedure.^{5,6} However, to perform index tumor based focal therapy, imaging must be able to accurately define margins of the tumor that would enable target localization, size estimation, real-time monitoring and followup. Among current imaging modalities MRI, with its morphological and functional pulse sequence capabilities, is the most promising method.^{7–13} Nevertheless, the ability of MRI to estimate PCa volume at 3 Tesla has not been extensively evaluated.^{14–16} We determined the accuracy of MRI in assessing ITV using whole mount histopathology for validation to determine the suitability of MRI for guiding focal therapy of PCa. In addition, we tested the ability of MRTV and some clinical variables (patient age, serum PSA) in estimating tumors larger than 0.5 cm³ at histopathology.

MATERIALS AND METHODS

Study Population

This institutional review board approved, HIPAA (Health Insurance Portability and Accountability Act) compliant retrospective study included 143 consecutive patients with PCa documented by biopsy (mean patient age 59.4 years, median 59, range 39 to 74) with a mean PSA of 6.6 ng/dl (median 4.7, range 0.9 to 48.9) who underwent multiparametric MRI of the prostate at 3T with subsequent RRP. There were 8 patients excluded from study with

MRI obscured by hemorrhage related to prior biopsy. The final study population consisted of 135 patients (mean age 59.3 years, median 59, range 39 to 74) with a mean serum PSA of 6.74 ng/dl (median 4.93, range 0.9 to 48.9).

MRI Data Acquisition

MRI was performed using a combination of an endorectal coil (BPX-30, Medrad, Pittsburgh, Pennsylvania) tuned to 127.8 MHz and a cardiac coil (6 or 16-channel) (SENSE, Philips Medical Systems, Best, The Netherlands) on a 3T magnet (Achieva, Philips Medical Systems). The endorectal coil was inserted using a semi-anesthetic gel (lidocaine, AstraZeneca USA) while the patient was in the left lateral decubitus position. The balloon surrounding the coil was distended with perfluorocarbon (3 mol/l Fluorinert™) to a volume of approximately 50 ml to reduce susceptibility artifacts induced by air in the coil's balloon. MRI protocol included triplanar T2W turbo spin echo, DW MRI, 3D MR spectroscopic imaging, axial precontrast T1-weighted MRI, axial 3D fast field echo DCE MRI sequences, and their detailed sequence parameters were defined in a prior study.¹¹

Histopathology Data Acquisition

All patients underwent RRP following MRI performed by a single surgeon (PAP). The mean interval between MRI and RRP was 60 days (range 3 to 180, median 48). In the first set of 62 patients the specimens were sectioned manually from apex to base at 4 mm intervals after RRP.¹¹ In the most recent 73 patients a customized MRI based specimen mold was used to process prostatectomy specimens. The specimen was fixed in formalin for 2 to 24 hours at room temperature, then placed in the customized 3D mold and sliced in axial 6 mm sections.¹⁷ In both techniques each slice was sequentially annotated by slice number and then kept in fixative for a further 24 to 48 hours, followed by paraffin embedding, cutting and mounting on a glass slide. Whole mount sections were 5 μ m in thickness.

Data Analysis

The index tumor was outlined in each prostatectomy specimen by 2 pathologists (HM and MJM) blinded to MRI. The criteria for the index lesion were that it be the largest and have the highest Gleason score of the entire prostatectomy specimen.^{3,18} The volume of each outlined tumor was measured using the ellipsoid formula ($\text{length} \times \text{width} \times \text{height} \times 0.52$) in cm^3 . For example, a tumor with greatest axial dimensions of 0.8×1 cm outlined on a single 6 mm section was measured as $0.8 \times 1 \times 0.6 \times 0.52 = 0.25 \text{ cm}^3$. The height used in the formula was 4 mm for the first set of 62 patients with manual sectioning vs 6 mm for the second set of 73 patients with sectioning using an MRI based patient specific mold. In addition, volumes measured at histopathology were corrected for tissue shrinkage with a factor of 1.15.¹⁹

For multiparametric MRI analysis, on T2W MR images and apparent diffusion coefficient maps of DW MRI, the criterion for a visible lesion was a well circumscribed, round-ellipsoid low signal intensity region within the prostate gland.¹¹ The 3D MR spectroscopy analysis evaluated choline-to-citrate ratios. Voxels were considered abnormal when the choline-to-citrate ratio was 3 or more SDs above the mean healthy choline-to-citrate ratio value (0.373 or greater), which was defined as 0.13 ± 0.081 based on prior results.¹¹ DCE

MR images were evaluated by direct visual interpretation of raw dynamic enhanced T1-weighted images. The diagnostic criteria for prostate cancer included a focus of asymmetric, early and intense enhancement with rapid washout compared to the background.¹¹ The multiparametric MRI score assigned to each lesion was based on the number of positive sequences (eg positive T2W, diffusion weighted, MR spectroscopy and DCE MRI were indicative of a high score). In this nonweighted scoring system, lesion scores were categorized as low (2 or fewer positive sequences), moderate (3 positive sequences) and high (4 positive sequences). The criteria for determining the index lesion on MRI were that the lesion be the largest and have the highest multiparametric MRI score. A radiologist (BT) manually segmented the index tumor on a picture archiving and communication (PACS) workstation blinded to the histopathology data. The tumor volume was obtained from PACS software after contouring lesions on MRI. For segmenting tumors on MRI, T2W MRI, apparent diffusion coefficient maps of DW MRI and DCE MRI sequences were used in conjunction, although final regions of interest were drawn on T2W MRI.

Statistical Analysis

The relationship between ITV at histopathology (HTV), index tumor volume at MRI (MRTV), patient age and serum PSA was analyzed using the Pearson correlation coefficient and linear regression analysis. Data were expressed as mean $\pm$ SE. ANOVA with Bonferroni post hoc correction for multiple comparisons was used to analyze differences in tumor volume at MRI and histopathology among the 3 Gleason score groups of low—Gleason 3 + 3, moderate—Gleason 3 + 4 and 4 + 3, and high—Gleason 4 + 4 or greater. ROC curve analysis was generated by plotting sensitivity vs 1-specificity to assess the diagnostic utility of estimating the HTV from MRTV, patient age and serum PSA. Likewise, AUC and significance were calculated for each variable. All significance tests were 2-tailed with significance considered as $p < 0.05$. The same statistical analysis was conducted for shrinkage factor corrected and noncorrected histopathology data sets. All statistical calculations were performed using a commercially available computer software package (SPSS® version 18).

RESULTS

A total of 135 index tumors were identified histologically from the radical prostatectomy specimens of 135 patients. Mean HTV of the index tumor lesion at histopathology was 1.89 cm³ (median 1.01, range 0.004 to 21.51) whereas mean HTV after shrinkage correction was 2.18 cm³ (median 1.17, range 0.0046 to 24.75). The Gleason score distribution of the lesions was Gleason 3 + 3 in 16, Gleason 3 + 4 in 72, Gleason 4 + 3 in 7, Gleason 4 + 4 in 17, Gleason 4 + 5 in 21 and Gleason 5 + 4 in 2.

In the 135 patients evaluated with MRI 127 (94%) index tumors were identified. No tumor was visualized in 8 patients because the cancer previously detected by biopsy was microscopic. Mean MRTV was 2.02 cm³ (median 0.98, range 0 to 21). In the 8 patients in whom no index tumor was visualized mean HTV was 0.17 cm³ (median 0.097, range 0.004 to 0.51), whereas mean HTV after shrinkage correction was 0.19 cm³ (median 0.11, range 0.0046 to 0.58).

Pearson correlation analysis revealed a positive correlation between HTV and MRTV (Pearson coefficient 0.633, $p < 0.0001$) but revealed a weaker correlation between serum PSA and HTV (Pearson coefficient 0.237, $p = 0.003$). A similar positive correlation was depicted between HTV with shrinkage factor correction and MRTV (see table, fig. 1). Linear regression analysis revealed a positive correlation between shrinkage corrected and noncorrected HTV and MRTV ($r^2 = 0.401$, $p < 0.00001$, fig. 2). HTV and MRTV volumes for low, moderate and high Gleason score tumors were measured as (mean $\pm$ SEM) 0.23 ± 0.06 and 0.28 ± 0.08 , 1.43 ± 0.17 and 1.69 ± 0.21 , and 3.46 ± 0.62 and 3.36 ± 0.66 , respectively. ANOVA analysis for the differences in MRTV and shrinkage corrected and noncorrected HTV among the 3 Gleason score groups revealed a significantly higher volume of tumor with higher Gleason scores compared to the volume of tumor at low and moderate Gleason scores ($p < 0.05$, fig. 3). ROC analysis revealed that the AUC for estimating the presence of index tumors with a volume greater than 0.5 cm^3 for MRTV, serum PSA and patient age was 0.949 ($p < 0.00001$), 0.685 ($p = 0.001$) and 0.627 ($p = 0.02$), respectively. The AUC for estimating the presence of index tumors larger than 0.5 cm^3 after shrinkage correction for MRTV, serum PSA and patient age was 0.963 ($p < 0.00001$), 0.650 ($p = 0.009$) and 0.653 ($p = 0.007$), respectively (fig. 4).

DISCUSSION

Accurate detection of index PCa volume is critical for guiding focal therapy as it enables complete treatments to be planned, executed and followed up. In addition, this may have a role in appropriately selecting patients for AS.^{20,21} Among the imaging modalities to detect PCa, MRI has the greatest potential to depict the actual tumor margins and, thus, volumes in clinically relevant lesions.⁷⁻¹³ For instance, multiparametric MRI was demonstrated to be an accurate method for localizing prostate compared to carefully performed whole mount step section histopathology, especially for lesions larger than 0.5 cm^3 .²² Thus, MRI is the most likely modality to be used in conjunction with focal therapy, especially if urologists consider image guided index tumor based treatment. Planning considerations include size and location, especially with regard to critical adjacent structures. Moreover successful results depend on ablating the entire lesion, including a margin of normal tissue.²³

We found a positive correlation between ITV measured by MRI and histopathology. However, the MRTV tended to overestimate (by a mean of 7%) the HTV without a shrinkage factor correction. This finding is consistent with the results of Jager et al, who reported a similar discrepancy between MRI and pathology tumor volumes in 34 patients who had T2W MRI at 1.5T.²⁴ MRI volumes of PCa overestimated the histological tumor volume by more than 25% in 19 patients, which can be explained by inaccuracies of imaging as well as shrinkage of the histopathological specimen due to fixation and mounting. MRI underestimated the HTV with a mean of 7% after the shrinkage factor correction was applied as expected. However, in both analyses MRTV had a reasonable correlation with tumor volume at histopathology.

Several investigators have used multiparametric approaches to improve PCa volume estimations. Coakley et al investigated tumor volume using T2W MRI and MR spectroscopy at 1.5T in a cohort of 37 patients with 51 tumor lesions with a mean volume of 0.79 cm^3 .¹⁴

They reported a positive correlation between MRI and histology with coefficients of 0.49, 0.59 and 0.55 for T2W MRI alone, MR spectroscopy alone and T2W MRI-MR spectroscopy combination evaluations, respectively. Advances in the last decade may account for the better correlation in our study. Nakashima et al assessed the value of T2W MRI and DCE MRI at 1.5T in estimating tumor size in 95 patients with 186 tumor foci at histopathology by measuring the greatest axial tumor diameter.¹⁵ They showed a strong correlation between diameters measured at MRI and histopathology with a coefficient of 0.84. Mazaheri et al retrospectively evaluated 42 patients to determine the accuracy of T2W MRI and DW MRI at 1.5T in estimating the tumor volume at histopathology.¹⁶ They reported a correlation coefficient of 0.36 and 0.6 for T2W MRI alone and T2W MRI-DW MRI combined evaluations, respectively. To our knowledge this is the first volumetric MR study performed with an endorectal coil at 3T using all 4 sequences as well as accounting for and discounting shrinkage factor correction.

Determining the index tumor volume may have implications for disease management. PCa is a multifocal disease typically involving a larger index tumor and smaller satellite lesions. Some studies report that the index lesion is the biological driver of prostate malignancy in a given patient.²⁵⁻²⁷ If this hypothesis is correct, imaging to identify these lesions is crucial for focal therapy and AS. We observed that MRTV had a stronger predictive power for estimating HTV than clinical variables such as serum PSA and patient age. MRTV correlated with HTV in most cases but tended to overestimate the HTV by an average of 7%. This information can potentially be used to plan the ablation of the index tumor with a safe and reasonable margin. Of course, in some patients MRI could not visualize an index tumor and these tumors proved to be microscopic at histopathology with mean and median volumes of 0.17 and 0.097 cm³, respectively. Patients with such small tumors may be better candidates for AS instead of active therapy.

Our study has several limitations. The customized shrinkage of the prostatectomy specimen could not be taken into account since it was not possible to determine it for each case. Instead we used a well established shrinkage correction factor of 1.15 based on previous studies,¹⁹ and presented noncorrected and corrected results for our cohort. In a few patients MRI tended to overestimate tumor volume, which would result in overtreatment in a possible image guided focal therapy approach. However, this may account for the safety margin around the treated area. In addition, an endorectal coil was used during MR scans, potentially deforming the posterior prostate gland as well as the tumors. Finally, we did not evaluate each MRI sequence separately for its ability to predict tumor size since the T2W image provided the highest spatial resolution among the MR parametric images. Therefore, we evaluated all MRI sequences collectively to define tumor margins.

CONCLUSIONS

Based on a comparison of image derived and histology confirmed tumor volumes, MRI accurately estimates the index tumor volume independent of Gleason score. MRI has a better accuracy than clinical variables (serum PSA, patient age) in the distinction of tumors larger than 0.5 cm³. The future of image guided index lesion based focal therapy in PCa relies on the accurate depiction by MRI of index lesions which can be used to guide focal treatment

by identifying tumor margins. As the field of urology continues to define the role of AS and minimally invasive treatments such as image guided focal therapy, prostate MRI may be necessary to accurately define the index tumor lesion.

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Abbreviations and Acronyms

3D	3-dimensional
AS	active surveillance
DCE	dynamic contrast enhanced
DW	diffusion weighted
HTV	histopathology tumor volume
ITV	index tumor volume
MR	magnetic resonance
MRI	magnetic resonance imaging
MRTV	magnetic resonance tumor volume
PCa	prostate cancer
PSA	prostate specific antigen
RRP	robotic radical prostatectomy
T2W	T2-weighted

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Figure 1. Imaging of 53-year-old man with serum PSA of 23.7 ng/dl. Axial T2W MRI demonstrates midline peripheral zone lesion (asterisk) with calculated MRI volume of 1.43 cc (A), and corresponding histopathology map confirms presence of Gleason 4 + 4 tumor (inked in black) in midline peripheral zone with volume of 1.48 cc (B).

Figure 2.

Linear regression plots of ITV (cm³) at pathology (with and without tissue shrinkage factor correction) and at MRI in 135 patients (for both analyses $r^2=0.401$, $p < 0.00001$). Discrete line represents 95% CI.

Figure 3.

Box plots demonstrating changes in shrinkage factor noncorrected (*A*) and corrected (*B*) ITV (cm³) at pathology, and at MRI in 3 different Gleason score groups (low—Gleason score 3 + 3, moderate—Gleason score 3 + 4 and 4 + 3, high — Gleason score 4 + 4 and higher). High Gleason group was significantly different from low and moderate groups ($p < 0.05$) at MRI and both pathology analysis groups.

Figure 4.

ROC curve estimating shrinkage noncorrected (*A*) and shrinkage corrected (*B*) pathology volumes using cutoff of 0.5 cm^3 from MRTV, age and serum PSA. Using threshold pathological tumor volume (without shrinkage factor correction) of 0.5 cm^3 , MRTV predicted HTV with sensitivity of 88% and specificity of 90% (*A*), whereas sensitivity and specificity were 88% and 95% for predicting HTV after shrinkage factor correction was applied (*B*).

Table

Pearson correlation matrix for ITV

	MRI Vol	Pathology Vol	Age	Serum PSA
MRI vol	–	–	–	–
Pathology vol (p value)	0.633(<0.0001)*	–	–	–
Age(p value)	0.135(0.59)	0.185(0.16)†	–	–
Serum PSA (p value)	0.441(0.0001)	0.237(0.003)‡	0.024(0.393)	–

Pearson correlation coefficient value between pathology volume after shrinkage correction, and MRI volume, age, serum PSA was 0.633(<0.0001), * 0.185 (p=0.32), † 0.24 (p=0.006), ‡ respectively.