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Endorectal MR imaging after radiation therapy: questioning the sextant analysis

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Abstract

Purpose—To evaluate whether the information gained by three co-registration systems (sextant, hemi-prostate and whole gland) differs significantly, suggesting that one approach should be routinely favored over the others. Despite its known limitations, sextant is the generally accepted standard for MR imaging and biopsy co-registration; nevertheless, depending on the magnitude of localization errors, other options may be adequate.

Materials and methods—Institutional review board approval was obtained and the study was HIPAA compliant. We identified 70 patients who underwent 1.5 Tesla endorectal MR imaging of the prostate between 1999 and 2008 after external beam radiotherapy for prostate cancer. A single reader reviewed all T2-weighted images for the presence or absence of tumor. The performance of each approach was quantified using receiver operating characteristic (ROC) curve analysis. Transrectal ultrasound-guided sextant biopsies were used as a standard of reference.

Results—The areas under the ROC curve indicating accuracy for each MR imaging approach were 0.63 (sextant), 0.68 (hemi-prostate), and 0.71 (whole gland). There was no statistically significant difference among these approaches.

Conclusion—As expected, the point estimate was higher for the whole-gland approach, but not significantly. Reliable assessment of locally recurrent prostate cancer after external beam radiotherapy by endorectal MR imaging may be made using a sextant, hemi-prostate, or whole gland approach. The option for one or other approach should not be solely based on estimations of imaging accuracy, but on the purpose of the procedure.

Keywords

prostate cancer; transrectal ultrasound-guided biopsy; T2-weighted MR imaging; localization; sextant

INTRODUCTION

External beam radiation therapy is one of the common, conventional definitive therapies for prostate cancer, and is the choice of about 25% of men with newly diagnosed disease (1).

After treatment, these men are followed with serial serum prostatic specific antigen (PSA). If a rising PSA is detected, transrectal ultrasound-guided sextant biopsy may be performed to evaluate possible local recurrence. Several recent studies have suggested that endorectal MR imaging may provide reasonable accuracy in the detection of locally recurrent prostate cancer after external beam radiotherapy (2–5). It may also guide subsequent biopsies or be a non-invasive alternative to transrectal ultrasound-guided sextant biopsy (6).

Ideally, the accuracy of MR imaging in the detection of locally recurrent tumor would be determined using radical prostatectomy specimens as the reference standard, but salvage radical prostatectomy is seldom performed in these patients. In practice, transrectal ultrasound-guided sextant biopsy is frequently the only histopathological reference standard available, despite its known limitations in prostate cancer localization. The estimated inherent error for ultrasound-guided biopsy in correctly localizing tumor by sextant ranges from 4% to 42% (7–9). These limitations are presumably due to sampling error and errors in needle localization by ultrasound (8,10,11). Such errors may be compounded in the irradiated gland because of radiation-induced shrinkage, distortion, and loss of zonal anatomic landmarks. When radical prostatectomy specimens are used as the reference standard for tumor localization prior to treatment, MR imaging performs better than transrectal ultrasound-guided biopsy (12).

These errors in transrectal ultrasound-guided sextant biopsy may lead to biased estimates of accuracy for the detection of locally recurrent disease by endorectal MR imaging. Indeed, this concern has been directly demonstrated in a study of prostate cancer localization by MR imaging and MR spectroscopic imaging using radical prostatectomy specimens as the standard of reference (13). The accuracy of imaging for biopsy sextant localization was only 67% to 74%, while that of tumor lateralization reached 75% to 88% (13).

Despite its known limitations, sextant is the generally accepted standard for MR imaging and biopsy co-registration; nevertheless, depending on the magnitude of localization errors, other options may be adequate. To assist clinicians and researchers in choosing which co-registration method to utilize, we evaluated whether the information gained by three co-registration systems (sextant, hemi-prostate and whole gland) differs significantly, suggesting that one approach should be routinely favored over the others.

MATERIALS AND METHODS

Study population

This retrospective single institution study was approved by the Institutional Review Board with a waiver of informed consent and was compliant with the Health Insurance Portability and Accountability Act. By a retrospective search of our computerized prostate cancer database, we identified all men with biopsy-proven prostate cancer who met the following three inclusion criteria:

1. Endorectal 1.5 Tesla MR imaging of the prostate performed between February 1999 and February 2008.
2. Definitive external beam radiotherapy for prostate cancer (with or without associated androgen deprivation therapy) administered prior to MR imaging.
3. Transrectal ultrasound-guided-biopsy of the prostate performed within 180 days of MR imaging.

There were no exclusion criteria.

Seventy patients with a mean age at diagnosis of 68.5 years (range; 52 to 81) fulfilled the criteria. Sixty-four of these men were included in a prior study investigating the accuracy of T2-weighted MR imaging and MR spectroscopic imaging for the detection of recurrent prostate cancer after external beam radiation therapy (Radiology, in press). The baseline and post-treatment characteristics of the population are described in Table 1. All patients received a full course of external beam radiation therapy, but the exact delivered dose was available only for the 51 patients who received treatment at our institution (mean dose = 74 Gy; range: 65–82). Thirty-nine men (56%) were also treated with androgen deprivation hormonal therapy (neoadjuvant and/or adjuvant). The median interval from the end of external beam radiotherapy to MR imaging was 44.9 months (range, 17 to 140). The median interval between MR imaging and biopsy was 58 days (range, 0 to 175). All patients had biochemical failure, defined as three consecutive increases in PSA values (14), and both MR imaging and biopsy were performed for suspected local recurrence.

Transrectal ultrasound-guided biopsy

Transrectal ultrasound-guided biopsy was performed both at our hospital (n=63) and outside institutions (n=7) (15); a histopathological report was issued by one of the staff pathologists in our institution for all procedures and all samples were localized to prostate sextants, i.e., apex, midgland, and base of the right or left hemi-prostate. The reports of all cases were reviewed for this study. Identification of any amount of disease in a core biopsy specimen was sufficient to consider it positive for local recurrence. Histopathological evidence of post-treatment effect only, however, was considered a negative result (16).

Imaging technique

MR imaging studies were performed on a 1.5-Tesla whole body MR scanner (Signa; GE Medical Systems, Milwaukee, WI). Patients were scanned in a supine position using the body coil for excitation and a pelvic phased array coil (GE Medical Systems, Milwaukee, WI) in combination with a commercially available balloon-covered expandable endorectal coil (Medrad, Pittsburgh, PA) for signal reception. Following a localizer sequence, T1-weighted spin-echo MR images of the pelvis were obtained (TR/TE 766/8, slice thickness = 5 mm, interslice gap = 1.5 mm, field of view = 24 cm, matrix 256 x 192, anteroposterior frequency encoding, and 1 excitation). The MR sequences acquired also included thin-section high nominal spatial resolution axial and coronal T2-weighted fast spin-echo images of the prostate and seminal vesicles with the following parameters: TR/effective TE 5000/96 ms, echo train length = 16, slice thickness = 3 mm, interslice gap = 0 mm, field of view = 14 cm, matrix 256 x 192, anteroposterior frequency encoding, and 3 excitations.

Imaging interpretation

A single radiologist with 13 years of experience in prostate MR imaging reviewed all MR images on a picture archiving and communication system workstation (Impax; Agfa, Mortsel, Belgium) and recorded the presence or absence of recurrent prostate cancer in each sextant. The reader knew that patients had received prior external beam radiotherapy for prostate cancer and were suspected of having local recurrence, but was unaware of any other clinical or histological information. A study was considered positive if a mass-like nodule or crescentic subcapsular focus of low T2 signal intensity was identified in the peripheral zone, or if an ill-defined mass-like area of low T2 signal intensity was seen in the central gland (Figure 1) (17).

Statistical analysis

Agreement between MR imaging and biopsy results was determined according to three different anatomic units of analysis:

1. *Sextant approach*: exact match required between MR imaging and biopsy on a sextant-by-sextant basis to establish concordance.
2. *Hemi-prostate approach*: exact match required between MR imaging and biopsy on a side-by-side basis to establish concordance.
3. *Whole gland approach*: match required between MR imaging and biopsy on a per patient basis to establish concordance.

The analysis of agreement between biopsy and MR imaging was calculated using generalized estimation equations (to accommodate repeated measures for the sextant and hemi-prostate approaches) and a logistic regression model. This was used to estimate the predicted probabilities of a match for each patient under each approach. The performance of each approach was quantified using receiver operating characteristic (ROC) curve analysis. We used cluster resampled bootstrapping to compare the differences of the areas under the ROC curves (A_Z) for each approach, and constructed 95% confidence intervals. For all statistical analyses, a probability value of less than 0.05 was considered to indicate significance. Statistical analyses were performed with Stata 11 (College Station, TX).

RESULTS

Locally recurrent prostate cancer was identified in 88 of 420 sextants with transrectal ultrasound-guided biopsy, and in 37 of 420 sextants with endorectal MR imaging (Figure 2). Overall, 42 of the 70 patients had locally recurrent disease at biopsy, including 10 patients with bilateral recurrence. The areas under the ROC curves for MR imaging detection of local recurrence (Figure 3) were 0.63 for sextant analysis (95% CI: 0.58 to 0.68), 0.68 for hemi-prostate analysis (95% CI: 0.61 to 0.76), and 0.71 for whole gland analysis (95% CI: 0.60 to 0.81). No significant differences were found when comparing these approaches (Table 2).

DISCUSSION

Depending on sextant biopsy for tumor localization is problematic, given the inherent localization error and the lack of zonal landmarks in the irradiated prostate. Even when step-section radical prostatectomy specimens are available, tumor localization and definition of a true positive versus a false positive result is not straightforward (18). Our study helps clinicians to choose the correct unit of anatomic analysis in this setting. We found no statistically significant difference in the correctness of detection of tumor recurrence using the sextant, hemi-prostate, or whole-gland analyses.

Our results suggest that one co-registration approach should not be routinely favored over the others; and that perhaps the choice for one or other method should be driven by the reasons the correlation between imaging and biopsy results is needed. For instance, one may argue in favor of a sextant analysis if the goal is to use imaging to identify and target disease for focal therapy. Alternatively, another clinician may be interested in identification of tumor anywhere in the prostate, if the intention is to use one of the most common salvage therapies in which the entire gland becomes the focus of treatment once recurrence is detected (usually salvage brachytherapy or salvage radical prostatectomy). Finally, MR imaging may provide sufficient evidence of recurrent disease to allow for targeted hemi-prostate biopsy instead of more extensive protocols. In summary, the increased labor of performing sextant analysis does not lead to a significant gain and may not be necessary in all situations. We hope the results of our study will provide a measure of security to clinicians and researchers who opt for these alternative approaches.

At some institutions the need for salvage therapy is not determined by imaging, but simply by rising PSA and a positive biopsy; and patients are treated with local salvage therapy or systemic agents when there is evidence of metastatic disease on bone scan or cross-sectional imaging. A rising PSA, however, is not synonymous of local recurrence. Patients may present with benign PSA bounces (19) and a transrectal ultrasound-guided biopsy may be unnecessary. Imaging results may help clinicians and patients to decide on subsequent evaluation. When confirming disease is required, positive findings may allow for a limited and targeted biopsy protocol. It is also possible that a patient with clearly positive multiparametric imaging could skip biopsy and proceed to treatment. Alternatively, negative results may provide enough security to allow for continuous PSA follow-up.

The goal of this study was not to determine the accuracy of T2-weighted MR imaging, but to compare different units of analysis or methods of dividing the prostate gland to localize disease. Yet, our results agree with prior studies in that T2-weighted MR imaging has at best moderate accuracy in detecting locally recurrent prostate cancer after radiation therapy, irrespective of the approach used (2–5). It is important to note that we do not suggest using T2-weighted MR imaging to detect local recurrence. Prior studies have shown that combining T2-weighted MR imaging with other MR modalities improve detection of local recurrence (2,3,6,20–22).

The greatest improvement in accuracy over T2-weighted MR imaging seems to come from the addition of diffusion-weighted MR imaging. Kim et al. have shown that the technique is significantly better than T2-weighted MR imaging alone to discriminate patients with or without local recurrence (area under the ROC curve 88% versus 61%) (21). MR spectroscopic imaging has also shown to be promising in this clinical setting. The results of the studies suggest that the area under the ROC curve for detection of recurrent cancer after external beam radiation therapy is around 80% (2,22). The studies that investigated dynamic contrast enhanced MR imaging have conflicting results. Haider et al. showed that it is more sensitive than T2-weighted MR imaging (72% versus 38%) and also that it is a very specific technique (85%) with a high negative predictive value (95%) (20). The positive predictive value however, was only 46%. The results of Yakar et al., on the contrary, suggest that DCE-guided biopsies had a positive predictive value of about 68% to 75% (6).

A full multiparametric approach—i.e. an MR protocol that includes T2-weighted MR imaging, dynamic contrast enhanced MR imaging, diffusion-weighted MR imaging, and MR spectroscopic imaging—after radiation therapy has not yet been investigated, but one would expect that this would result in improved detection of recurrent disease. Because the amount of data available from such imaging protocol can be overwhelming, future research should focus not only in determining if additional sequences increase the diagnostic accuracy of MR imaging, but also on determining that best way of interpreting various sequences in combination.

Our study has limitations. First, this was a retrospective, single institution study; therefore our results may not be generalizable, as expertise and imaging acquisition vary among institutions. Also, it is unclear if our conclusion can be extrapolated to other MR imaging modalities, e.g. diffusion-weighted MR imaging or dynamically contrast-enhanced MR imaging. Second, because only one radiologist reviewed the MR images, we cannot assess reproducibility of our findings, i.e. interobserver agreement. Also, if the results of a second reader were comparable, our conclusions would be more robust. Third, the time interval between imaging and biopsy is a potential limitation of our study. Although 75% of patients had biopsy performed within 82 days of imaging, some patients had an interval approaching 180 days. Another potential criticism is the small number of patients in our study, leading to relatively wide 95% confidence intervals. Again, our goal was not to determine the accuracy

of each modality, but rather to assess how they compare. As with any analysis, with a large enough sample size, and therefore narrower 95% confidence intervals, we would find statistically significant differences in the area under the ROC curve when comparing the various interpretative approaches. A statistically significant result, however, is not synonymous of a clinically relevant result, as small differences may not be important. Last, some may view as a limitation the fact we did not include in our analysis a “cranial-caudal approach,” i.e., localizing abnormalities to the apex, midgland, and base of the prostate, irrespective of the side of the gland. Our decision to discard this option was based on the results of a study by De Laet et al. (7) which demonstrated that a positive transrectal ultrasound-guided biopsy corresponds to tumor in the same region, rather than in the exact same location in prostatectomy specimens. The latter also found that the greatest variability in agreement occurred within sextants of one or the other side of the gland (i.e., right apex, right midgland, and right base), rather than within adjacent sextants located on different sides of the prostate (i.e., right midgland and left midgland).

As expected, the point estimate was higher for the whole-gland approach, but not significantly. Reliable assessment of locally recurrent prostate cancer after external beam radiotherapy by endorectal MR imaging may be made using a sextant, hemi-prostate, or whole gland approach. The option for one or other approach should not be based solely on estimations of imaging accuracy, but on the purpose of the procedure.

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Figure 1. 77 year-old man with locally recurrent prostate cancer. T2-weighted MR image shows findings consistent with disease in the right midgland (arrow). Biopsy results, however, were positive at the right apex, which on T2-weighted MR imaging demonstrated only post-radiation changes (not shown).

Figure 2. Schematic diagram showing the numerical distribution of 88 tumor-containing sextants based on transrectal ultrasound-guided biopsy and 37 tumor-containing sextants based on endorectal MR imaging in the 70 patients with suspected local recurrence of prostate cancer after external beam radiotherapy.

Figure 3.

Receiver operating characteristic curves of the diagnostic performance of each approach for detection of locally recurrent disease after external beam radiation therapy with T2-weighted MR imaging using biopsy results as the standard of reference - dotted line (whole-gland approach), solid line (hemi-prostate approach), dashed line (sextant approach).

Table 1

population baseline and post-treatment characteristics

Baseline PSA - ng/ml *	9.3 (3.5–93.0)
Baseline Gleason score **	7 (5–10)
Gleason categories †	
2 to 5	5
6 or 7	53
8 to 10	12
PSA nadir - ng/ml ††	0.31 (0.01–3.3)
Biochemical failure PSA - ng/ml ‡	2.55 (0.7–23.3)

* Median (range) of PSA serum level at the time of initial prostate cancer diagnosis.

** Gleason score at the time of initial diagnosis.

† Number of patients within each stratum.

†† Median (range) of lowest PSA serum level following treatment.

‡ Median (range) of PSA level serum at the time of diagnosis of biochemical failure.

Table 2

Summary of the results of comparisons between each ROC curves

<u>Compared approaches</u>	<u>Difference in Az</u> *	<u>95% confidence interval</u>	<u>p-value</u>
hemi-prostate vs. whole-gland	– 0.03	– 0.10 to 0.04	0.45
sextant vs. whole-gland	–0.08	–0.17 to 0.02	0.12
sextant vs. hemi-prostate	–0.05	–0.16 to 0.04	0.32

* Az = area under the ROC curve