Early localization of recurrent prostate cancer after prostatectomy by endorectal coil magnetic resonance imaging

Brian J. Linder, MD,[1] Akira Kawashima, MD,[2] David A. Woodrum, MD,[2] Matthew K. Tollefson, MD,[1] R. Jeffrey Karnes, MD,[1] Brian J. Davis, MD,[3] Laureano J. Rangel, MS,[4] Bernard F. King, MD,[2] Lance A. Mynderse, MD[1]

[1]Department of Urology, Mayo Clinic, Rochester, Minnesota, USA
[2]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA
[3]Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota, USA
[4]Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

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Introduction: *To evaluate the ability of endorectal coil (e-coil) magnetic resonance imaging (MRI) to identify early prostatic fossa recurrence after radical prostatectomy.*

Materials and methods: *We identified 187 patients from 2005-2011 who underwent e-coil MRI with dynamic gadolinium-contrast enhancement followed by transrectal ultrasound (TRUS) guided prostatic fossa biopsy for possible local prostate cancer recurrence. For analysis, local recurrence was defined as a negative evaluation for distant metastatic disease with a positive prostatic fossa biopsy, decreased prostate-specific antigen (PSA) following salvage radiation therapy, or increased lesion size on serial imaging.*

Results: *Local recurrence was identified in 132 patients, with 124 (94%) detected on e-coil MRI. The median PSA was 0.59 ng/mL (range < 0.1-13.1), and median lesion size on MRI was 1 cm. The sensitivity of MRI was 91%, with a specificity of 45%. The positive predictive value was 85%, with a negative predictive value of 60%. For patients with a PSA < 0.4 ng/mL the sensitivity of e-coil MRI was 86%. When a lesion was identified on MRI, the positive biopsy rate was 65% and lesion size was a significant predictor of positive biopsies. The positive biopsy rates were 51%, 74%, and 88% when the lesion was < 1 cm, 1 cm-2 cm, or > 2 cm, respectively (p = 0.0006).*

Conclusions: *E-coil MRI has a high level of sensitivity in identifying local recurrence of prostate cancer following radical prostatectomy, even at low PSA levels. E-coil MRI should be considered as the first imaging evaluation for biochemical recurrence for identifying patients suitable for localized salvage therapy.*

Key Words: magnetic resonance imaging, prostate cancer, biopsy, recurrence

Introduction

It is estimated there will be 233,000 new cases of prostate cancer in the US in 2014,[1] with a substantial portion treated by radical prostatectomy (RP).[2] Despite the current stage migration in the landscape of prostate cancer, reports have shown that between 10%-53% of patients will have biochemical recurrence (BCR) following RP as determined by serum prostate-specific antigen (PSA) measurement.[3-6]

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Address correspondence to Dr. Lance A. Mynderse, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 USA

Since management strategies for BCR vary based on the likelihood of local versus distant recurrence, nomograms have been developed to predict the site of recurrence and likely response to localized therapy.[7,8] Characteristics to aid in determination of the location of recurrence such as time from surgery to BCR, PSA doubling time, Gleason score, surgical margin status and pathologic stage have been described.[7,9-11]

Given the potential side effects to which patients may be exposed with salvage therapies, such as radiation therapy (RT)[12] accurate prediction of the location of recurrence is important for selection of appropriate candidates and guidance of radiation therapy delivery. In addition, with continued development of focal

therapies,[13] in the setting of recurrent disease, accurate lesion localization is crucial. This study is intended to evaluate the ability of endorectal coil (e-coil) magnetic resonance imaging (MRI) to accurately detect local recurrences of prostate cancer following RP.

Materials and methods

Following approval by our Institutional Review Board we retrospectively identified 187 patients at a large academic institution from 2005-2011 that underwent e-coil MRI with dynamic gadolinium-contrast enhancement followed by transrectal ultrasound (TRUS) guided biopsy of the prostatic fossa for evaluation of possible local prostate cancer recurrence. The study cohort included patients that were treated with salvage therapies including androgen deprivation (22 patients), radiation therapy (25 patients) or both (19 patients) prior to e-coil MRI. E-coil MRIs were ordered according to individual practitioner preference within our institution in the setting of rising PSA after RP. Prostatic fossa biopsies were performed by one surgeon following review of the e-coil MRI. TRUS guided prostatic fossa biopsies were performed with a side-fire bi-planar ultrasound transducer (8808 or 8818, BK Medical, Peabody, MA, USA) in the right lateral decubitus position, with directed biopsies of known MRI detected lesions. In addition, random sampling of the prostatic fossa was performed, including the full circumference of the vesico-urethral anastomosis using cognitive or mental fusion with real time B- mode imaging.

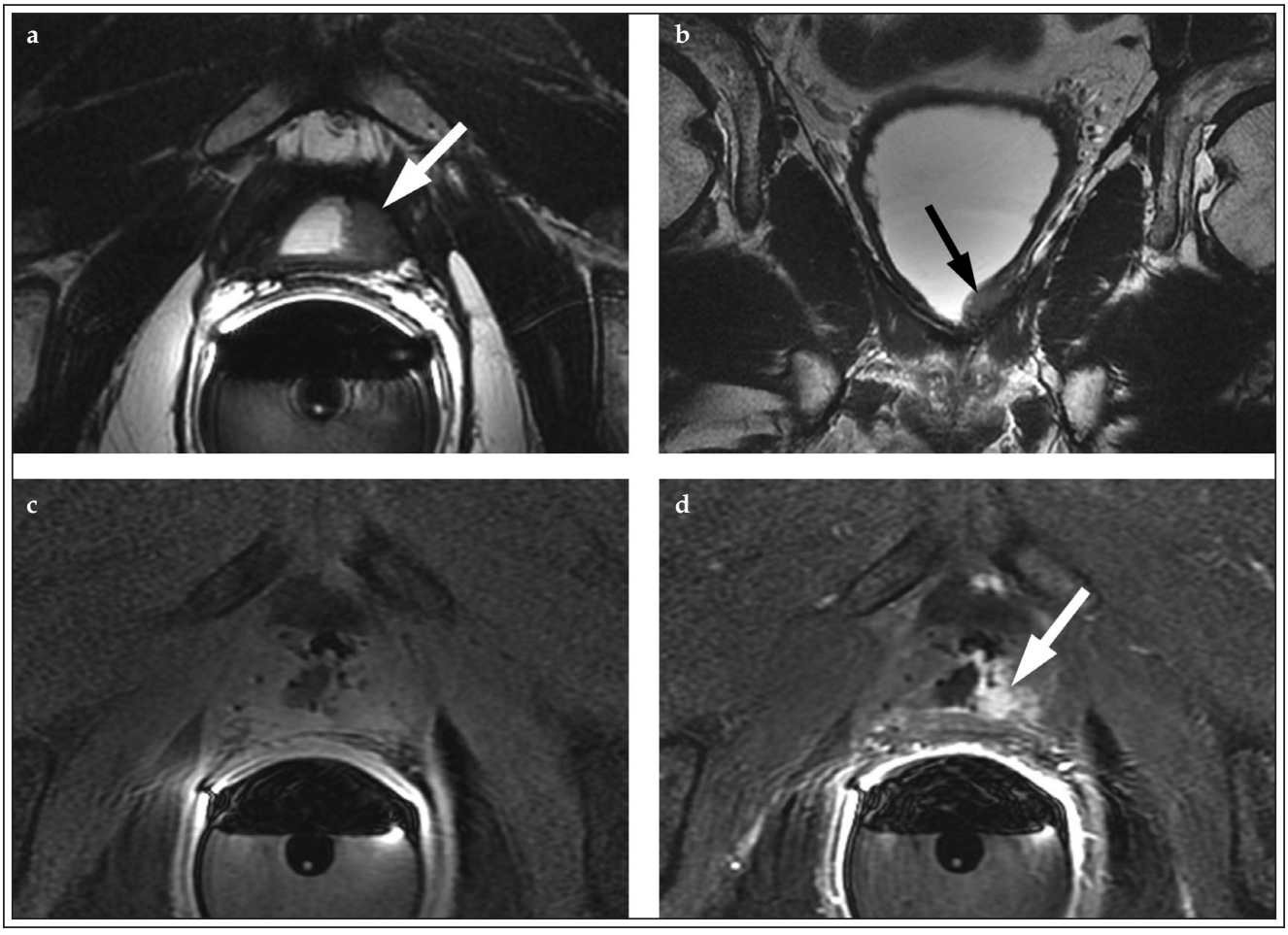

Figure 1. A 70-year-old man with history of rising PSA values to 1.14 ng/mL, who underwent radical prostatectomy for pT3b prostate carcinoma with negative surgical margin 24 months earlier.
a and b) Axial **(a)** and coronal **(b)** T2-weighted images of the prostatic fossa at 3 Tesla demonstrate nodular thickening of the bladder neck on the left (arrow). **c and d)** Axial unenhanced **(c)** and dynamic gadolinium contrast enhanced **(d)** T1-weighted fast spoiled gradient echo images with fat suppression reveal markedly increased enhancement (arrow).

Data analysis

An e-coil MRI was deemed positive for local recurrence based on depiction of a lesion in the prostatic fossa that was iso-intense on T1 weighted imaging, intermediate to hyper-intense on T2 imaging and had increased contrast enhancement after IV administration of gadolinium contrast agents, Figure 1. Gadolium based MR contrast agent was administered in all e-coil MRI exams except one due to renal insufficiency. Diffusion-weighted imaging (DWI) of the prostate was obtained in 36 of 187 patients (19%) in this study. All images were reviewed by radiologists in our radiology department with expertise in genitourinary MRI. The standard of reference was based on previous reports in the literature as well as our clinical practice.[14,15] This included the following criteria: a positive TRUS guided prostatic fossa biopsy, reduction in PSA following external beam radiation therapy, or increased prostatic fossa lesion size (greater than 50% increase) on serial e-coil MRI. Patients were determined to be negative for local recurrence if: they had a negative TRUS biopsy of the prostatic fossa and/or the PSA remained stable for 1 year with or without administration of pelvic radiation. Based on these standards the e-coil MRI result was classified as a true positive, false positive, true negative or false negative.

For patients with at least 1 year of follow up, the ability of e-coil MRI to evaluate local recurrences was determined by calculation of the sensitivity, specificity, positive predictive value and negative predict value. In addition, at the outset of the study it was determined we would examine a PSA cutoff of 0.4 ng/mL for establishing the ability of e-coil MRI to evaluate local recurrences at low PSA values.[14] Evaluation of the relationship between maximum lesion size and positive biopsy rate was performed with a chi-square analysis.

MRI technique

Two different models of MRI scanner were utilized, with 136 (73%) performed using a 1.5 Tesla scanner (Signa, GE Healthcare, Waukeshau, WI, USA), and 51 (27%) with a 3 Tesla scanner (Discovery MR750, GE Healthcare, Waukeshau, WI, USA). An integrated torso-phased array and endorectal coil (Medrad, Indianola, PA, USA) was used. Two dimensional, T2-weighted, fast relaxation fast spin echo images centered at the prostatic fossa were obtained in axial, coronal and sagittal planes employing the following parameters (1.5T and 3T): repetition time/echo time (TR/TE) = 3,000 to 7,000/100 to 120 msec, slice thickness = 2.5 mm to 3 mm, field of view (FOV) = 14 cm to 18 cm, and matrix size = 256 to 320 x 256. With introduction of 3T MRI for prostate imaging, the spatial and temporal resolution have improved. For example, slice thickness of 2.5/0.5 mm and 320 x 256 were used for T2WI at 3T while slice thickness/gap of 3/0 mm and matrix size of 256 x 256 were used for T2WI at 1.5 T. Similarly, parameters of fast 3D T1weighted spoiled gradient echo sequence for dynamic gadolinium contrast enhanced imaging at 3T included slice thickness/gap of 2.6/0 mm, matrix of 320 x 192 while those at 1.5 T included slice thickness/gap of 3/0 mm, matrix size of 256 x 192. A dynamic contrast enhanced (DCE) sequence was obtained using a 3 dimensional T1-weighted fast spoiled gradient echo sequence with fat suppression in an axial plane before and after intravenous injection of 0.1 mmol/kg gadodiamide (Omniscan; GE Healthcare, Waukesha, WI, USA) or gadobenate dimeglumine (MultiHance; Bracco, Princeton, NJ, USA) using an automated injector (Spectris Solaris, Medrad, Indianola, PA, USA), followed by a saline chaser of 20 mL. The parameters for DCE (1.5T and 3T) were flip angle of 12 to 15 degrees, slice thickness of 2.6 to 3 mm, FOV of 14 cm to 18 cm, and matrix of 256 to 320 x 192. The temporal resolution of DCE-MRI sequences was approximately 40-50 sec for 1.5 Tesla and 30-40 sec for 3 Tesla.

Results

The median time from prostatectomy to prostatic fossa biopsy was 5 years (range 0-18). In addition, patients typically had risk factors for cancer recurrence based on the initial prostatectomy findings: 68% had a Gleason grade ≥ 7, 41% had positive surgical margins and 40% had pT3 disease. The median maximum lesion size was 1 cm (range 0.3 cm-4.4 cm) and the median pre-biopsy PSA was 0.59 ng/mL (range < 0.1 to 13.1). The clinicopathologic characteristics of the cohort are displayed in Table 1.

Using the standards of reference previously described, local recurrence was identified in 136 of the 187 (73%) patients, with 124 (91%) of these detected on e-coil MRI. Local recurrence was determined by a positive biopsy in 114 of the 131 patients (87%), response to RT in 19 patients (14%) and an increase in lesion size on serial e-coil MRI in 1 patient (1%). For the 176 patients with at least 1 year of follow up, a high level of sensitivity in lesion detection was found for the entire cohort (91%), with a positive predictive value of 85%. In addition, 53 of the 187 (28%) patients had a PSA < 0.4 ng/mL with at least 1 year of follow up, and in this subgroup, e-coil MRI had a sensitivity of 86%, with a positive predictive value of 86%, Table 2. Furthermore, after excluding the 43 patients treated with androgen deprivation therapy, 135 of the

TABLE 1. **Clinicopathologic characteristics of patients undergoing endorectal coil MRI and TRUS biopsy of the vesicourethral anastomosis**

	No. patients (%) (n = 187)
Median age (years)	68
Pathologic Gleason grade (n = 179)	
6	56 (31.3%)
7	95 (53.1%)
8-10	28 (15.0%)
Pathologic tumor stage (n = 176)	
pT2	106 (60.2%)
pT3	70 (39.8%)
Positive surgical margins at RP	71 (40.8%)
Adjuvant or salvage therapy prior to MRI	
Radiation therapy	25
Androgen deprivation	21
Combined therapy	22
Median time to biopsy (years)	5 (0-18)
Median PSA at biopsy (ng/mL)	0.59 (0-13.1)
MRI type	
1.5 Tesla	136 (72%)
3 Tesla	51 (27%)
Median time of biopsy from MRI (days) (IQR)	15 (6, 29)
Median maximum lesion size on MRI (cm) (n = 121)	1 (0.3-4.4)

MRI = magnetic resonance imaging; TRUS = transrectal ultrasound; RP = radical prostatectomy; PSA = prostate-specific antigen

remaining patients had at least 1 year of follow up. In these patients the sensitivity was found to be 90%, with a specificity of 38%, a positive predictive value of 81% and a negative predictive value of 56%. The median PSA in this cohort was largely unchanged compared to the entire cohort at 0.6 ng/mL, with a median lesion size of 1 cm.

The maximum lesion size on MRI and the type of MRI modality utilized were significant predictors for a positive biopsy. The positive biopsy rates were 50.7%, 74% and 88% when the lesion was < 1 cm, 1 cm-2 cm, or > 2 cm, respectively (p = 0.0006; Table 3). Patients that underwent MRI with a 3T scanner had a significantly higher rate of positive biopsy, 70.6% versus 52.2%

TABLE 2. **Sensitivity, specificity, positive predictive value and negative predictive value of MRI in general and stratified by PSA at the time of TRUS-guided biopsy of the prostatic fossa**

True positives	**True negatives**	**False positives**	**False negatives**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
124	18	22	12	0.91	0.45	0.85	0.60
PSA at biopsy < 0.4 ng/mL							
36	5	6	6	0.86	0.45	0.86	0.45
PSA at biopsy ≥ 0.4 ng/mL							
88	13	16	6	0.94	0.45	0.85	0.68

MRI = magnetic resonance imaging; PSA = prostate-specific antigen; TRUS = transrectal ultrasound

TABLE 3. **Impact of maximum lesion size on MRI on biopsy results**

	Positive biopsy rate (positive/total)	Positive (n = 99)	Negative (n = 53)	Total (n = 152)	p value
Length of MRI lesion					0.0006
< 1 cm	50.7% (34/67)	34 (34.3%)	33 (62.3%)	67 (44.1%)	
1 cm-2 cm	73.9% (51/69)	51 (51.5%)	18 (34.0%)	69 (45.4%)	
> 2 cm	87.5% (14/16)	14 (14.1%)	2 (3.8%)	16 (10.5%)	

MRI = magnetic resonance imaging

(p = 0.024) compared to those imaged with a 1.5T scanner. No difference in median maximum lesion size (p = 0.19), time from biopsy to scan (p = 0.17), surgical margin status (p = 0.12), Gleason grade (p = 0.58) or age (p = 0.9) was seen between the cohorts when based on scanner type.

Discussion

Our study demonstrates the ability of e-coil MRI to accurately detect local recurrences of prostate cancer following RP, even at low PSA levels and small lesion sizes. MRI with e-coil has been increasingly used to detect prostate cancer in intact prostate and following RP. Multiparametric MRI imaging, and TRUS biopsy aided by MRI/US fusion imaging for biopsy has also been described for whole glands.[14-17] Our series is the largest sampling reported using e-coil MRI in the evaluation of recurrent prostate cancer following RP.

Previous reports using e-coil MRI in the setting of suspected local prostate cancer recurrence have demonstrated favorable results.[14,18-21] Sella et al reported a series in which e-coil MRI at 1.5 T utilizing T2-weighted imaging was able to detect recurrence in 39 of 41 (95%) patients with a sensitivity of 95%, and a specificity of 100%. In comparison to our study, a higher proportion of their cohort (41/48, 85%) had local recurrence. In addition, there was a mean PSA of 2.18 ng/mL (range 0-10) and a mean diameter of lesions of 1.4 cm (range 0.8-4.5).[14] Similarly, a study by Cirillo et al evaluated 72 patients at risk for local recurrence after prostatectomy by 1.5 Tesla e-coil MRI. Using dynamic contrast enhanced imaging 37 of 44 events (84%) of local recurrence were detected.[18] The sensitivity of contrast enhanced e-coil MRI was 84%. The mean lesion size in the study was 1.7 cm (range 0.8-3.5), and the median PSA was 0.84 (0.2-8.8).[18] Our results demonstrate a similar high level of sensitivity of e-coil MRI, though with lower PSA values (median 0.59 ng/mL) and lesion sizes (median 1 cm). This is notable as our results indicate that positive biopsy rate is predicted by increasing lesion size. Additionally, a recent study validated the use of MRI in detecting small volume prostate cancer recurrences (4 mm to 8 mm). In a study of 126 patients with small lesion Panebianco et al found a 98% sensitivity, 94% specificity and 93% accuracy of combined T2 weighted and dynamic contrast MRI.[21] Notably, differences in the prevalence of local recurrence between study populations may account for some variation in results.

Two of the largest studies regarding use of TRUS alone for evaluation of the prostate fossa have shown it to be less sensitive and have a lower positive biopsy rate than that reported for e-coil MRI.[15,22] Leventis et al reported detection of local recurrence in 41 of the 99 (41%) patients evaluated, with a sensitivity of 76% and specificity of 67% for imaging and TRUS biopsy alone. The positive biopsy rate was 41%, including patients that underwent repeat biopsies. A higher positive biopsy rate was noted with increasing PSA, with a median of 2.4 ng/mL in those with a positive biopsy and 1.4 ng/mL in those with a negative biopsy (p = 0.034).[15] Similar results have since been reported in a series of 119 patients by Scattoni et al.[22] In their report, local recurrence was diagnosed in 60 patients (50%), with a sensitivity of 75% and a positive biopsy rate of 51%. TRUS biopsy had a 100% negative predictive value when the PSA was ≥ 2 ng/mL. However, 34% of local recurrences were not visible on TRU.[22] While TRUS may have some effectiveness in the evaluation of local recurrences, it is less sensitive than e-coil MRI and may require a greater PSA for detection. PSA level at detection is an important consideration as early initiation of salvage radiation may be more effective; particularly when implemented at PSA levels below 0.5 nl/mL.[23]

Interestingly, in our cohort e-coil MRI had a similar level of sensitivity in patients with a PSA < 0.4. Previous reports regarding cut off levels for BCR after prostatectomy have shown continued PSA progression in 49%, 62% and 72% of patients found to have a PSA of 0.2, 0.3 and 0.4, respectively.[24] In our patient cohort 76% of patients with a PSA ≥ 0.4 had evidence of local recurrence, compared to 79% in those with a PSA < 0.4.

This prevalence of local recurrence in those with low PSA values may contribute to the high sensitivity level seen. The prevalence rate may also be influenced by the inclusion of patients treated with hormonal deprivation prior to biopsy as well as the high risk features present in the majority of patients included in this study. Additionally, the referral nature of our tertiary care practice may influence the prevalence rate of this cohort.

It has previously been reported that biopsy of the prostatic fossa with ultrasound guidance prior to radiation therapy is not necessary as it may be non-diagnostic and does not predict survival following RT.[11,25] Of note, these reports are based on TRUS guided biopsy without prior MRI imaging, with a positive biopsy rate of 41%. Our results indicate that e-coil MRI has a high level of sensitivity, making this imaging modality useful in the evaluation of patients with evidence of BCR and selecting candidates likely to respond to local salvage therapy and guiding salvage radiation therapy delivery. Of note, the positive MR findings are not specific for recurrent tumor. On occasion, benign lesions such as prostatic remnants after RP could have similar MR findings. If histologic documentation is deemed to be necessary, e-coil MRI should be performed to help guide needle biopsy in the prostatic fossa in order to improve the yield. In some instances a negative e-coil MRI may allow patients to be continued on observation and avoid the potential side effects of salvage therapies. A similar approach has been reported regarding the use of MRI in the evaluation of prostate cancer patients undergoing active surveillance.[26] In addition, as focal ablative therapies for prostate cancer and prostate cancer recurrence continue to emerge, e-coil MRI may play a role in localizing lesions and helping to guide treatment.[27]

Limitations of our study, including the retrospective nature of data collection should be noted. In addition, the selection of patients for evaluation with e-coil MRI may be skewed given there was not a uniform algorithm within our institution to perform this imaging. Furthermore, since biopsies were performed with TRUS guidance and not direct MRI guidance, we could not directly correlate the biopsy results with e-coil MRI detection. Recently, there have been reports regarding fused MRI and TRUS imaging to guide biopsies.[16] This approach may increase the diagnostic yield of the biopsy. No calculation of the ability of TRUS to detect local recurrence was made in our study due to the inherent bias of the surgeon having reviewed the e-coil MRI and conducting cognitive fusion with real time TRUS prior to biopsy. Furthermore, a large proportion of patients in our study (77%) were found to have local recurrence. This may be secondary to the referral pattern at our center and has the potential to skew our results. Lastly, inter-observer variability in interpretation of e-coil MRI would also potentially impact interpretation of our results.

Conclusion

Our study demonstrates that e-coil MRI has a high level of sensitivity in identifying local recurrence of prostate cancer, even at low PSA levels and small lesion sizes. Thus, e-coil MRI should be considered early in the evaluation of biochemical recurrence following RP to better identify patients suitable for localized salvage therapy and possibly to help guide management strategies including active surveillance, ablative technologies and other focal therapies. Further studies, ideally in a prospective multi-institutional fashion, could be performed. □

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