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Research Article

Discrimination of local recurrence after radical prostatectomy: value of diffusion-weighted magnetic resonance imaging

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ABSTRACT

Background: Multiparametric magnetic resonance is the most accurate imaging technique for prostate cancer detection, staging, localization, and aggressiveness evaluation. We assessed accuracy of diffusion-weighted imaging in local recurrence diagnosis after radical prostatectomy.
Materials and methods: A retrospective study was conducted in 118 patients with findings suggestive of local recurrence in dynamic contrast-enhanced-magnetic resonance imaging. Local recurrence was defined clinically as a rising prostate-specific antigen level (biochemical recurrence) without radiographic evidence of distant metastasis over 6 months after surgery. Eighty-four patients (71.2%) had local recurrence (group 1) and 34 (28.8%) showed no recurrence (group 2). The diagnostic accuracy of diffusion-weighted imaging was assessed, and factors associated with local recurrence were evaluated using multivariate logistic regression analysis. Additional accuracy analysis was carried out according to the size of the nodule.
Results: In post-operative findings, group 1 patients had significantly higher serum prostate-specific antigen ($P = 0.001$), larger enhancing nodules ($P = 0.005$), and more positive findings in diffusion-weighted imaging ($P = 0.001$) than group 2 patients. The sensitivity of diffusion-weighted imaging was significantly higher for nodules $\geq$1 cm than for all nodules (96.6 vs. 80.9%, $P = 0.001$), whereas the specificities were equivalent (100.0 vs. 97.1, $P = 0.529$). In multivariate analysis, a positive finding in diffusion-weighted imaging was the independent predictor of local recurrence ($P = 0.005$), along with pathologic T stage ($P = 0.018$).
Conclusions: Diffusion-weighted imaging is accurate in distinguishing recurrence from enhancing nodule on dynamic contrast-enhanced-magnetic resonance. Nodules showing decreased diffusion suggest local recurrence, especially if sized $\geq$1 cm.

1. Introduction

Currently, most patients with localized prostate cancer are treated with radical prostatectomy (RP).[1] This is due to the good functional results, satisfying the oncological radical criteria that can be achieved with modern surgical techniques. However, approximately 10–50% of patients experience a recurrence after RP.[2] Generally, prostate-specific antigen (PSA) is a nonspecific tumor marker but, after RP, the rise of PSA serum levels indicates the existence of PSA-producing tissue, suggesting the presence of persistent or recurrent disease in the pelvis or distant metastases.[3] According to the European Association of Urology and the American Urological Association, biochemical recurrence (BCR) after RP is defined as two consecutive rises in PSA > 0.2 ng/mL.[4,5]

The most important issue in the presence of a BCR after RP is to distinguish between a local and a distant recurrence, to guide the selection of the appropriate treatment: local recurrences undergo salvage radiation therapy, whereas for systemic recurrences the additional treatment is androgen-deprivation therapy (ADT).[6] Therefore, there is a strong need for imaging techniques that may be able to recognize small lesions and to identify their features (recurrent neoplastic tissue, postoperative change such as granulation tissue and fibrosis). However, the current diagnostic tests for

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distinguishing the type of recurrence, which include transrectal ultrasonography (TRUS)-guided biopsy and computed tomography, are not useful when PSA levels after RP are < 1 ng/mL. Moreover, the sensitivity and specificity of TRUS are not sufficient in detecting early recurrent cancer, and TRUS-guided biopsy is not recommended by European Association of Urology guidelines in patients with PSA serum level <1 ng/mL.[4,7]

Technological advances in recent years have made possible the development of multiparametric (mp) magnetic resonance imaging (MRI); dynamic contrast-enhanced (DCE) MRI is a useful method to identify local recurrence of prostate cancer in patients with BCR after RP.[8,9] However, enhancing in MRI is not specific for tumor recurrence and may result from postoperative changes.[9] Diffusion-weighted imaging (DWI) has emerged as an accurate tool for the identification of tumor recurrence. DWI is sensitive to the microscopic motion of water molecules and allows for noninvasive characterization of biologic tissues based on their water diffusion properties.[10] Therefore, DWI is a very useful technique to exclude the presence of pathological tissue in the postoperative bed. In our current study, we assessed the accuracy of DWI in the discrimination between local recurrence and postoperative change after RP.

2. Materials and methods

2.1. Study participants

After institutional review board approval, we identified 827 consecutive patients who underwent additional MRI after RP between July 2007 and June 2014. The inclusion criterion was documented local recurrence diagnosed by DCE-MRI. The exclusion criteria included prior or current history of ADT, and the presence of metastatic disease in bones or lymph nodes on bone scan or computed tomography. Among these patients, 181 met the inclusion criteria. We excluded patients who received ADT ($n = 31$) and who had metastatic disease ($n = 32$). Finally, 118 patients were included in this study.

2.2. MRI technique and imaging interpretation

MRI was performed with a 3-T Achieva unit (Philips Medical Systems, Best, The Netherlands) and a 16- or 32-channel external phased array coil. Patients were imaged while supine. Transverse T1-weighted images, and transverse, coronal, and sagittal T2-weighted fast spin-echo images of the prostate and seminal vesicles were obtained. DCE imaging was performed after intravenous injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany). DWI was performed using a single spin-echo echoplanar imaging sequence at 3,400/117 with b values of 0 and 1,000 s/mm^2, as reported previously.[11]

The imaging results were interpreted by experienced radiologists in the genitourinary division of the radiology department of our institution. These reviewers, who were blind to the histological and clinical findings, analyzed the images independently. The readers first interpreted T2-weighted imaging alone (in the axial, sagittal, and coronal planes). In the same sitting, the readers then recorded DCE imaging (the DCE-MRI was performed in the axial plane only). Local recurrence was suspected if an area of slight hyperintensity relative to the surrounding muscles was seen on T2-weighted imaging, particularly if the area had a nodular appearance and if it showed greater enhancement than the surrounding muscles on DCE imaging. A DWI finding was considered positive when focal high intensities at b = 1,000 s/mm^2 of DWI were shown as low-signal focal lesions on apparent diffusion coefficient maps (Fig. 1).[10]

2.3. Standard of references

A patient was considered to have local recurrence if a rising PSA level, defined as BCR, was detected without radiographic evidence of distant metastasis more than 6 months after surgery. Of the 118 patients, 84 (71.2%) had local recurrence (Group 1) and 34 (28.8%) had undetectable level of PSA and had no other evidence of recurrence (Group 2; Fig. 2).

2.4. Statistical analysis

The clinicopathological features in the two groups were compared using Pearson's Chi-square test for categorical variables and Student t test for continuous variables. Quantitative data are expressed as mean ± standard deviation. The sensitivity and specificity of DWI were assessed and compared according to enhancing nodule size using the exact version of McNemar's test. Factors associated with local recurrence were evaluated using logistic regression analysis. For multivariate analysis, the multiple logistic regression model was fitted and then backward elimination of the least significant factor was conducted. All reported P values are two-sided, with P values < 0.05 considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics Version 21 (IBM Corporation, Somers, NY, USA).

3. Results

The descriptive characteristics of the 118 patients are presented in Table 1. The two groups differed significantly in terms of PSA and pathologic status. The median preoperative PSA of the whole cohort was 7.5 ng/mL (range, 1.0–22.8 ng/mL), whereas the median PSA of group 1 and 2 were 9.1 ng/mL (2.7–78.3 ng/mL) and 5.8 ng/mL (2.8–24.5 ng/mL), respectively ($P = 0.021$). Patients with local recurrence (group 1) were also significantly more likely to have higher biopsy Gleason score ($P = 0.001$), pathologic T stage ($P = 0.001$), and pathologic Gleason score ($P = 0.001$) than patients without local recurrence (group 2). However, there were no between-group differences in the positive surgical margin status. In postoperative findings, patients in group 1 were significantly more likely to have higher serum PSA level ($P = 0.001$), larger enhancing nodules ($P = 0.005$), and positive findings in DWI ($P = 0.001$) than patients in group 2.

Table 2 presents a comparison of the diagnostic accuracies of DWI according to the size of the enhancing nodules. Table 2 also lists sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. The sensitivity for nodules ≥1 cm was significantly superior to that for all nodules (96.6% vs. 80.9%, $P = 0.001$), whereas the specificities were equivalent (100.0% vs. 97.1, $P = 0.529$).

Univariate logistic regression analysis showed that preoperative PSA level ($P = 0.003$), pathologic T stage ($P = 0.001$), pathologic Gleason score ($P = 0.001$), size of enhancing nodule in DCE-MRI ($P = 0.006$), and positive finding in DWI ($P = 0.001$) were significantly associated with a local recurrence. Multivariate analysis showed that positive finding in DWI (odds ratio 86.12, $P = 0.005$) was the variable independently associated with local recurrence, along with pathologic T stage (odds ratio 7.70, $P = 0.018$; Table 3).

4. Discussion

Up to 40% of patients who undergo RP for localized prostate cancer eventually develop BCR. Treatment of prostate cancer recurrence after RP remains a controversial area and different therapeutic options are available. In the absence of systemic metastases an increase in serum PSA level is assumed to be due to a

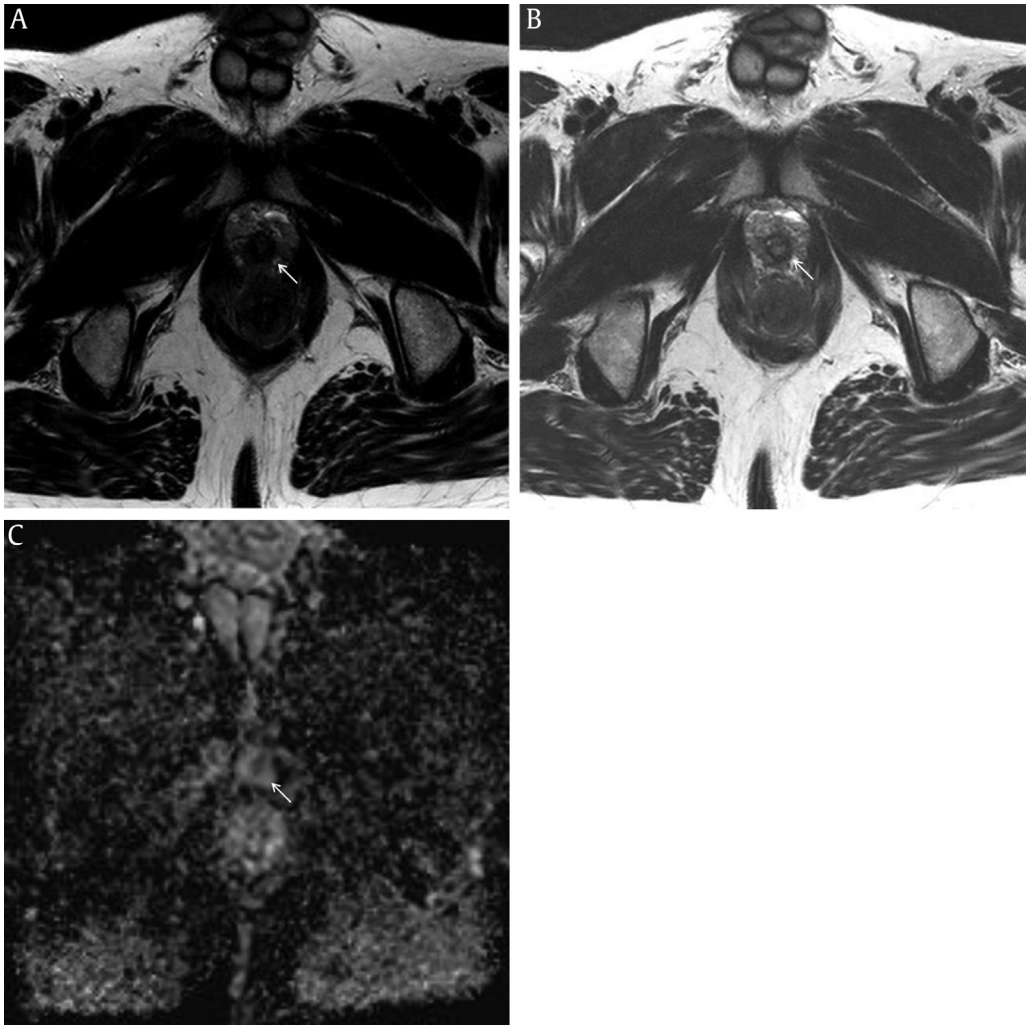

Fig. 1. Multiparametric-magnetic resonance images of a 56-year-old man with prostate-specific antigen progression (prostate-specific antigen serum level 0.25 ng/mL) after radical retropubic prostatectomy, with suspected local recurrence. (A) Axial T2-weighted image shows a soft tissue nodule of 1.1 cm in size on perianastomotic site (white arrow). (B) Nodular enhancement than the surrounding muscles is shown on dynamic contrast-enhanced imaging (white arrow). (C) Axial apparent diffusion coefficient map reconstructed from images obtained at b values of 1,000 s/mm^2 showing marked restricted diffusion (white arrow).

locoregional recurrence, and salvage radiation treatment could theoretically be the first line therapy. However, if metastatic disease is diagnosed, radiation therapy on the prostatectomy bed would be unnecessary, with a high risk of morbidity, and the proper treatment is hormone-deprivation therapy.[12] Therefore, localization of recurrent prostate cancer is important for appropriate patient management, and mpMRI is gaining acceptance as the most accurate imaging method for identifying sites of local recurrence after RP.[8,9,13] Previous studies on the detection of postoperative local recurrence showed that the addition of DCE-MRI to T2-weighted imaging significantly increased sensitivities (from 48–61% to 84–88%) and specificities (from 52–82% to 89–100%).[8,9] However, enhancing in the MRI is not specific for tumor recurrence and may result from postoperative changes.[9] In our current study, although 118 patients had documented local recurrence in DCE-MRI, only 84 turned out to develop local recurrences. Conversely, our study showed that DWI had incremental value for detection of local recurrence after radical prostatectomy. Moreover, the specificity of DWI in enhancing nodules $\geq$1 cm was 100% (16/16). In univariate analysis for detection of local recurrence, the size of the enhancing nodule in DCE-imaging and a positive finding in DWI were significant prognostic factors. Positive finding in DWI was also a significant predictor for detection of local recurrence in multivariable analysis.

Currently, TRUS has neither good sensitivity nor good specificity in detecting early recurrent cancer, and TRUS-guided biopsy of the postprostatectomy bed is not recommended by European Association of Urology guidelines in patients with PSA serum level <1 ng/mL.[4,7] Moreover, Scattoni et al[14] showed that TRUS-guided biopsy to detect local recurrence after RP has a limited sensitivity (25–54%) when the PSA serum value is < 1.0 ng/mL. In addition, TRUS-guided biopsy has limitations, such as high false-negative rates, the inability to diagnose small lesions, and the risk of bleeding and complications. In addition, benign findings in biopsy specimens cannot rule out the presence of malignancy in the rest of the lesion. Moreover, small lesions are difficult to identify in biopsies. Therefore, mpMRI including DWI has emerged as an accurate and safe tool for the detection of local recurrence after RP.

Pathologic stage is an important predictor of local recurrence in our study. Moreover, patients with recurrence had a higher Gleason score at the time of RP than patients without recurrence. It is well known that recurrence is associated with adverse pathologic findings at the time of RP.[15] The results presented here indicate that mpMRI is a useful diagnostic imaging method to determine local

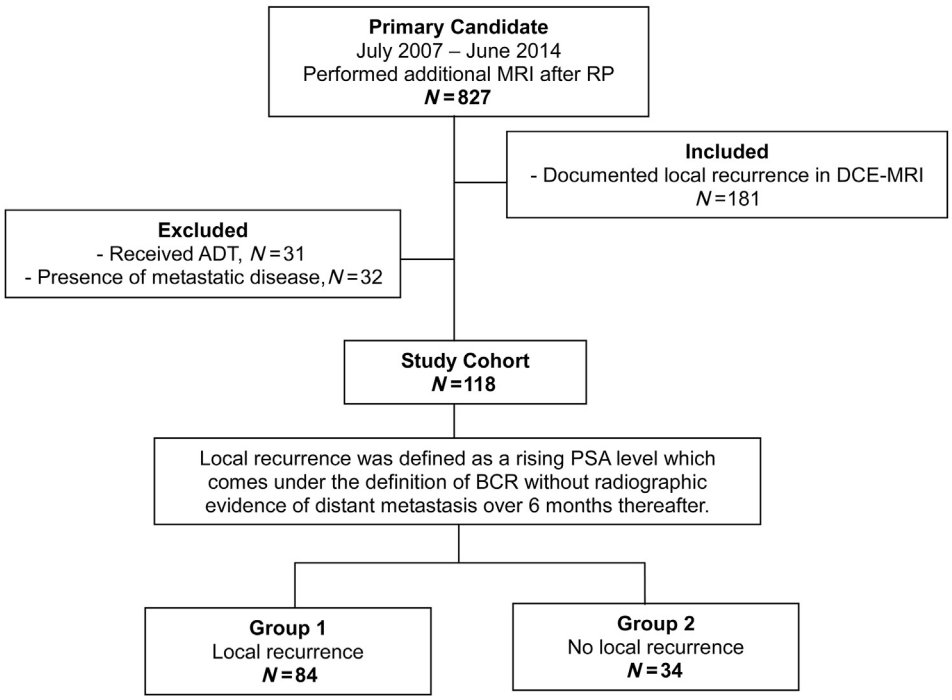

Fig. 2. Patient selection and grouping flow diagram. ADT = androgen-deprivation therapy; BCR = biochemical recurrence; DCE = dynamic contrast-enhanced; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; RP = radical prostatectomy.

Table 1
Comparison of the clinicopathological features of the study participants.

	Overall	Group 1 (recur)	Group 2 (no recur)	*P*
No	118	84	34	
Pre-plus perioperative				
Mean age ± SD, (y) (median, range)	64.6 ± 7.8 (69, 42–84)	65.7 ± 7.7 (65, 42–76)	63.4 ± 8.1 (71, 56–84)	0.311
Mean body mass index ± SD, kg/m^2 (median, range)	24.4 ± 2.4 (24.4, 18.5–32.4)	24.5 ± 2.3 (24.1, 20.8–28.3)	24.3 ± 2.7 (24.4, 18.5–32.4)	0.804
Medical history				
No. of patients on medication for DM (%)	18 (15.3)	14 (16.7)	4 (11.8)	0.584
No. of patients on medication for HTN (%)	53 (44.9)	39 (46.4)	14 (41.2)	0.378
No. of patients on alcohol consumption (%) (at least one alcoholic beverage weekly)	40 (33.9)	31 (36.9)	9 (26.5)	0.261
Smoking status				
Current smokers (%)	14 (11.9)	11 (13.1)	3 (8.8)	0.728
Mean PSA ± SD, ng/mL (median, range)	12.8 ± 19.4 (7.5, 2.7–78.3)	15.3 ± 22.4 (9.1, 2.7–78.3)	6.4 ± 3.8 (5.8, 2.8 –24.5)	0.021
Mean prostate volume on MRI ± SD, mL (median, range)	34.2 ± 12.3 (32.0, 17.0–80.0)	33.4 ± 9.7 (32.0, 17.0–59.0)	36.1 ± 19.9 (34.0, 17.0–80.0)	0.598
Stage on MRI				0.081
≤ T2	81 (68.6)	54 (64.3)	27 (79.4)	
≥ T3	37 (31.4)	30 (35.7)	7 (20.6)	
Biopsy Gleason score				0.001
≤6	31 (26.3)	14 (16.7)	17 (50.0)	
7	38 (33.2)	28 (33.3)	10 (29.4)	
≥8	49 (41.5)	42 (50.0)	7 (20.6)	
Pathologic T stage				0.001
≤ T2	54 (45.8)	28 (33.3)	26 (76.5)	
T3	64 (54.2)	56 (66.7)	8 (23.5)	
Pathologic Gleason score				
≤ 6	18 (15.3)	8 (9.5)	10 (29.4)	0.001
7	62 (52.5)	40 (47.6)	22 (64.7)	
≥ 8	38 (32.2)	36 (42.9)	2 (5.9)	
Positive surgical margin, n (%)	62 (52.5)	45 (53.6)	17 (50.0)	0.839
Mean prostate volume on pathology ± SD, mL (median, range)	35.6 ± 16.4 (34.0, 17.0–86.0)	35.5 ± 9.7 (34.5, 17.0–59.0)	36.1 ± 18.1 (35.0, 17.0–86.0)	0.898
Postoperative (at the time of MRI performed)				
Duration from prostatectomy ± SD, (mo) (median, range)	27.9 ± 16.2 (24.6, 3.3–69.2)	26.9 ± 15.9	30.5 ± 16.9	0.287
Mean PSA ± SD, ng/mL (median, range)	0.87 ± 2.66 (0.24, 0.04–25.10)	1.20 ± 3.09 (0.39, 0.20–25.10)	0.04 ± 0.00 (0.04, 0.04–0.04)	0.001
The size of enhancing nodule, cm (median, range)	1.0 ± 0.5 (1.0, 0.3–3.6)	1.1 ± 0.5 (1.0, 0.3–3.6)	0.8 ± 0.4 (0.8,0.3–2.6)	0.005
Positive finding in DWI	69 (58.5)	68 (81.0)	1 (2.9)	0.001

DM = diabetes mellitus; DWI = diffusion-weighted imaging; HTN = hypertension; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; recur = recurrence; SD = standard deviation.

Table 2
Diagnostic accuracies of DWI according to size of enhancing nodule.

Size category	All nodules		Nodules ≥1 cm		*P*
	No. nodules/total No.	DWI (95% CI)	No. nodules/total No.	DWI (95% CI)	
% Sensitivity	68/84	80.9 (72.5–89.3)	57/59	96.6 (91.9–99.8)	0.001
% Specificity	33/34	97.1 (91.4–99.8)	16/16	100.0 (100.0–100.0)	0.529
% Pos predictive value	68/69	98.5 (95.7–99.9)	57/57	100.0 (100.0–100.0)	
% Neg predictive value	33/49	67.3 (54.2–80.5)	16/18	88.9 (78.9–93.4)	
Pos likelihood ratio[a)]		27.5 (3.98–190.33)		—	
Neg likelihood ratio[b)]		0.19 (0.13–0.31)		0.03 (0.01–0.14)	

CI = confidence interval; DWI = diffusion-weighted imaging; Neg = negative; Pos = positive.
[a)] Sensitivity/1 − specificity.
[b)] 1 − sensitivity/specificity.

Table 3
Univariate and multivariable logistic regression models used to predict recurrence

Variables	Univariate		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (continuous)	1.03 (0.98–1.08)	0.310		
Body mass index (continuous)	1.02 (0.865–1.21)	0.802		
Diabetes mellitus (Yes)	1.50 (0.46–4.93)	0.504		
Hypertension (Yes)	1.24 (0.55–2.77)	0.604		
Alcohol consumption (Yes)	0.842 (0.47–1.49)	0.556		
Smoking status (Yes)	1.21 (0.67–2.18)	0.522		
Preoperative PSA (continuous)	1.19 (1.06–1.34)	0.003	1.08 (0.71–1.27)	0.374
Pathologic T stage (T3)	6.50 (2.61–16.19)	0.001	7.70 (1.41–41.97)	0.018
Pathologic Gleason score				
≤ 6	Reference		Reference	
7	2.27 (0.78–6.59)	0.131	0.94 (0.12–6.95)	0.953
≥ 8	22.50 (4.11–123.23)	0.001	3.60 (0.24–53.67)	0.352
Positive resection margin	1.15 (0.52–2.56)	0.725		
Pathologic prostate volume	0.99 (0.97–1.03)	0.896		
The size of enhancing nodule (continuous)	5.14 (1.61–16.44)	0.006	0.61 (0.11–3.42)	0.572
Positive finding in DWI	70.15 (17.82–250.29)	0.001	86.12 (21.10–283.94)	0.005

CI = confidence interval; DWI = diffusion-weighted imaging; OR = odds ratio; PSA = prostate-specific antigen.

recurrence after RP. Although the current National Comprehensive Cancer Network guidelines do not recommend MRI as a modality of detection for recurrence, it is necessary to perform mpMRI in suspected cases of local recurrence, especially if they have adverse pathologic status.

In our study, in all but one of the 83 patients, the local recurrence was in the perianastomotic site (98.8%). In previous studies, the most common location of local recurrence was the perianastomotic site, and 45–52% of recurrent lesions were perianastomotic.[8,9,16] However, the positive surgical margin rate was 52.5%, which is likely to be the overriding cause of this result. Moreover, most of the patients had a positive resection margin in the apex (75%). Unfortunately, by retrospective design, uncontrolled confounding and selection bias are particular methodological limitations in our study. Additional MRI after RP is not performed routinely in daily practice. Pathologic status such as positive surgical margin is one of the most important reasons to doubt local recurrence and perform additional MRI after RP.

There were additional limitations to this study. Its retrospective nature, the relatively small patient cohort limited our ability to draw definitive conclusions about the significant differences in certain variables between patient groups. Most importantly, there is no gold standard for validating MRI results. TRUS- or MRI-guided biopsies were not carried out in the prostate bed because they are not performed routinely owing to their cost, the mortality associated with the procedures, and doubts about their clinical benefits, as already mentioned. Therefore, the presence of local recurrence was not confirmed by biopsy but was suggested by the clinical course. However, we think that additional research is necessary to confirm this result. Nevertheless, the clinical results obtained from this study lay the foundation for future studies that may better guide the treatment of recurrent prostate cancer.

In conclusion, DWI is an accurate method to identify local recurrence of prostate cancer after RP. DWI has incremental benefits in distinguishing recurrence from enhancing nodule on DCE-MRI. Nodules showing decreased diffusion on DWI may suggest local recurrence, especially those of a large size (≥1 cm). However, because our current study cohort was relatively small, further research is needed to determine the clinical validity of this result.

Conflicts of interest

The authors have no conflicts of interest or financial disclosures to declare.

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