

The value of dynamic contrast-enhanced MRI in the detection of recurrent prostate cancer after external beam radiotherapy: correlation with transrectal ultrasound and pathological findings

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PURPOSE

To assess the effectiveness of dynamic contrast-enhanced (DCE) T1- and T2-weighted magnetic resonance imaging (MRI) during the follow-up of patients with prostate cancer after undergoing external beam radiotherapy (EBRT) and to compare these imaging findings to pathological and transrectal ultrasound (TRUS) findings.

MATERIALS AND METHODS

In this retrospective study, the MRI findings of 20 patients who had prostate cancer and were treated with EBRT were evaluated to detect tumor recurrence. The MRI findings were compared to those that had been obtained by TRUS and pathological analysis.

RESULTS

The sensitivity and specificity of TRUS in the detection of tumor recurrence in patients who had undergone EBRT were 53.3% and 60%, respectively. In the same group of patients, the sensitivity and specificity of T2-weighted MRI were 86% and 100%, respectively. Strikingly, the sensitivity and specificity of DCE T1-weighted MRI in the diagnosis of recurrent prostate cancer were 93% and 100%, respectively. The accuracy of the DCE T1-weighted images in the detection of recurrence was significantly higher in comparison to that obtained using T2-weighted images.

CONCLUSION

During the follow-up of these patients, TRUS without the use of any other imaging or biochemical modality is not a sufficient method for the detection of prostate cancer recurrence. DCE T1-weighted MRI increases the sensitivity of MRI alone for the detection of recurrence during the follow-up of prostate cancer patients who have been treated with EBRT. Thus, DCE T1-weighted MRI must be used as part of the routine MRI analysis to check for tumor recurrence in patients with prostate cancer.

Key words: • radiotherapy • magnetic resonance imaging • prostatic neoplasms • transrectal ultrasonography

In patients with prostate cancer, magnetic resonance imaging (MRI) is primarily used to determine the stage of the disease. After the treatment of the cancer, serum prostate specific antigen (PSA) levels, transrectal ultrasonography (TRUS), computed tomography (CT), MRI, and the analyses of biopsies are used to check for recurrence during follow-up. Unfortunately, there is no entirely reliable imaging method that can be used to diagnose tumor recurrence during the follow-up of prostate cancer patients who have been treated with external beam radiotherapy (EBRT) (1).

An analysis of the effectiveness and accuracy of TRUS and MRI for detection of tumor recurrence is crucial to the adequate management of patients with prostate cancer and to the avoidance of the need for invasive procedures. Approximately 30% of patients with newly diagnosed prostate cancer undergo EBRT as their initial treatment (2, 3). After EBRT, a relapse in the increase of PSA levels within five years of treatment occurs in 15% and 67% of patients in the low- and high-risk groups, respectively (4).

The aim of this study was to assess the effectiveness of dynamic contrast-enhanced (DCE) T1- and T2-weighted MRI and TRUS in the follow-up of prostate cancer patients who had undergone EBRT and to correlate these radiological and pathological findings.

Material and methods

In this retrospective study, we evaluated 172 patients who were diagnosed with prostate cancer by biopsy analysis and treated with EBRT. Patients who were included in the study had to have completed their radiotherapy treatment [at least a 7368-cGy isocenter dose (ICRU) of EBRT] and had a control biopsy, control MRI, and TRUS 18 months after the EBRT therapy and within one month prior to participating in the study. Patients with prior prostate surgery and who had a prostate MRI study and biopsy more than one month apart and who had MRI studies without DCE imaging were excluded from the study. Of the 172 patients who we initially evaluated, 20 fulfilled the required criteria and were included in the study.

The patients underwent TRUS in a lateral decubitus position using a 6.5 MHz endocavitary transducer (Antares, Siemens, Erlangen, Germany). The procedure was performed by two senior radiologists with more than 10 years of experience in genitourinary radiology. All of the patients had previously undergone a TRUS scan shortly after being diagnosed with prostate cancer. All of the images that were taken before and after the patients underwent EBRT were recorded using the MagicView (Siemens) workstation.

The MRI images were obtained using a 1.5 Tesla MRI scanner (Symphony, Siemens, Erlangen, Germany), which was equipped with pelvic

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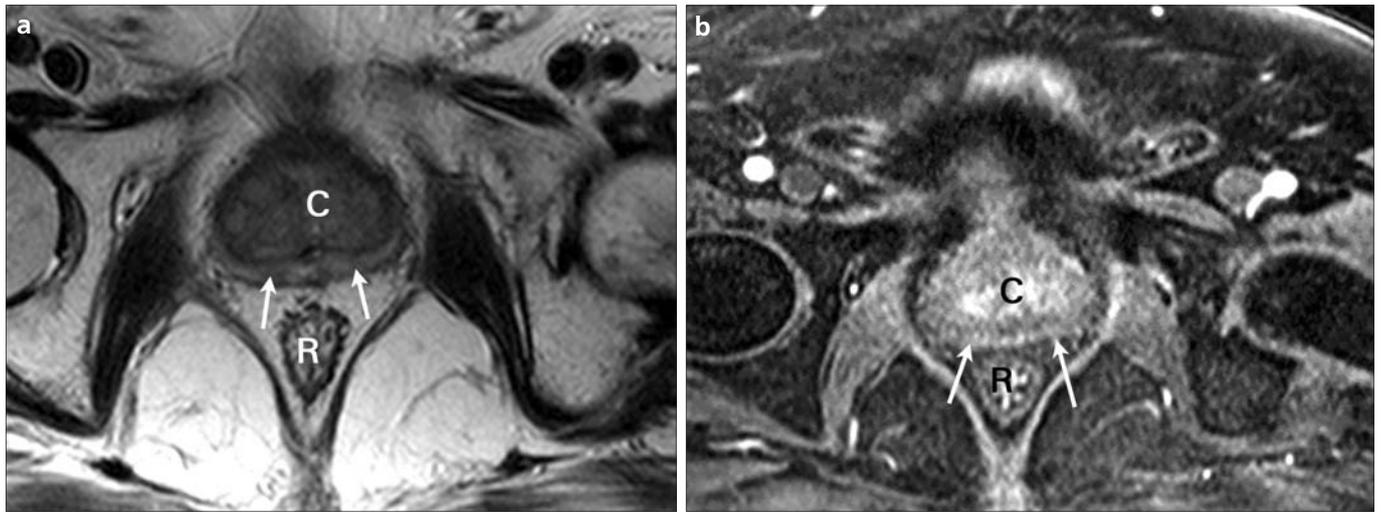


Figure 1. a, b. Prostate gland negative for tumor recurrence. The axial T2-weighted MR image (a) shows a heterogeneous peripheral zone (arrows) that is suspected to harbor a recurrent nodule. The dynamic contrast-enhanced T1-weighted MR image (b) shows no contrast enhancement in the arterial phase (arrows). The biopsy was negative for tumor recurrence. R, rectum; C, central zone.

phased-array coils. The parameters for the image acquisition were as follows: T2-weighted turbo spin echo (TSE) sagittal, transverse, and coronal images [repetition time (TR)/echo time (TE), 4110/99 ms; 4-mm slice thickness; 0.4-mm interslice gap; matrix, 392×512; field of view (FOV), 240×240]; T1-weighted transverse (TR/TE, 480/5.2 ms); and fat-suppressed T2-weighted. Four sets of consecutive DCE images (VIBE) were obtained after the intravenous administration of 20 mL of gadoterate meglumine (Dotarem, Guerbet, Roissy, France) at a rate of 2 mL/s (4-mm slice thickness; no interslice gap; TR/TE, 6.4/3.1 ms; 15 s duration per dynamic scan; matrix, 128×114; FOV, 180×180).

All of the MRI exams were reviewed by two radiologists, one of whom was a senior radiologist with 10 years of experience in genitourinary radiology, at a Centricity RA 600 independent workstation (GE Medical Systems, Milwaukee, Wisconsin, USA). The radiologists first evaluated the T2-weighted MR images that were obtained in the sagittal, coronal, and axial planes. To independently evaluate the contrast-enhanced study from the T2-weighted images, the DCE T1-weighted images were reviewed one week later.

All of the images were evaluated according to the conspicuity of the lesion and were classified as follows: positive, if the radiologist was highly confident that there was a nodular lesion present; suspiciously positive, if a lesion could not be definitely distinguished from

changes in the surrounding tissue due to secondary radiotherapy; and negative, if no lesion was observed. For purposes of the statistical analysis, the findings were classified as either positive or negative, and suspiciously positive findings were also classified as negative. In addition, the MRI findings were compared to those obtained by TRUS and by pathological analysis.

Results

The mean age of the patients was 65.3 (48–78) years. The lesion detection capacities of the T2-weighted and DCE T1-weighted images are shown in Table 1. The biopsies were positive for nodular lesions in 13 patients and negative in four patients. The biopsy was negative in one patient who had a suspiciously positive T2-weighted image (Fig. 1). The biopsy analysis confirmed the presence of a tumor in two

cases that were classified as suspiciously positive according to the T2-weighted images. Based on the DCE T1-weighted images in the axial plane, we classified 14 out of 20 patients as positive for the presence of a tumor, one as suspiciously positive, and five as negative (Fig. 2). The biopsy analysis confirmed the presence of a tumor in the 14 patients who had been classified as tumor-positive according to the DCE T1-weighted images. The five patients who were classified as negative by DCE T1-weighted MRI were also found to be negative by pathological examination. One patient, who was classified as suspiciously positive by DCE T1-weighted MRI, was found to be positive by biopsy analysis. The accuracy of the DCE T1-weighted images in the detection of recurrence was significantly higher in comparison to that achieved using T2-weighted images (chi-square, $P = 0.002$).

Table 1. A comparison of the efficacies of T2-weighted MRI, dynamic contrast-enhanced (DCE) T1-weighted MRI, and biopsy analysis in the detection of recurrent tumors

T2-weighted MRI	Positive biopsy	Negative biopsy
Positive	13	0
Suspiciously positive	2	1
Negative	0	4
DCE T1-weighted MRI		
Positive	14	0
Suspiciously positive	1	0
Negative	0	5

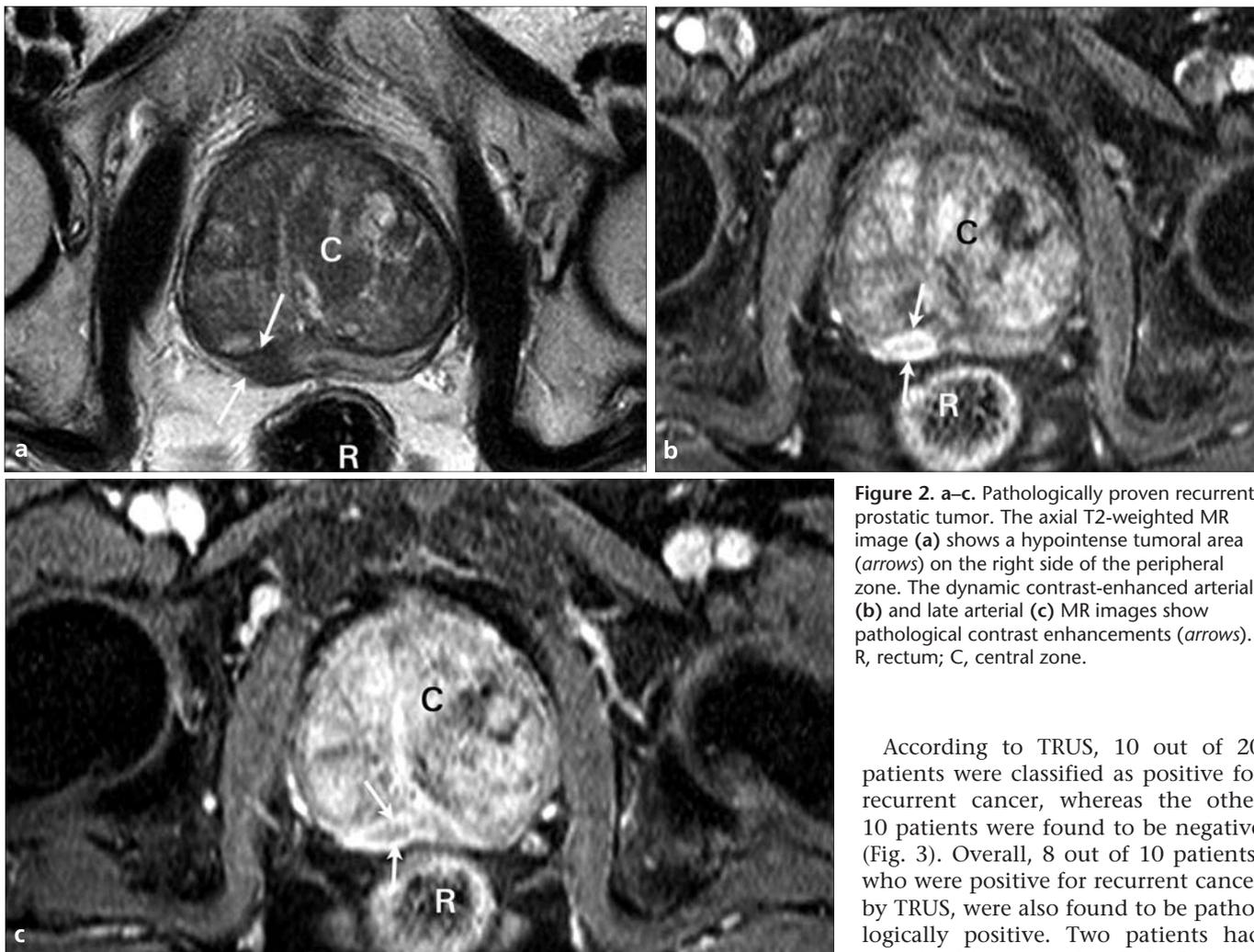


Figure 2. a–c. Pathologically proven recurrent prostatic tumor. The axial T2-weighted MR image (a) shows a hypointense tumoral area (arrows) on the right side of the peripheral zone. The dynamic contrast-enhanced arterial (b) and late arterial (c) MR images show pathological contrast enhancements (arrows). R, rectum; C, central zone.

According to TRUS, 10 out of 20 patients were classified as positive for recurrent cancer, whereas the other 10 patients were found to be negative (Fig. 3). Overall, 8 out of 10 patients, who were positive for recurrent cancer by TRUS, were also found to be pathologically positive. Two patients had negative biopsy results. Only 3 out of 10 patients with negative TRUS findings were confirmed to be pathologically negative (Table 2). The sensitivity, specificity, predictive values, and accuracy of TRUS and T2-weighted and DCE T1-weighted MRI are detailed in Table 3.

Discussion

In our study, TRUS detected tumor recurrence in only 8 out of 15 patients who were shown to have pathologically confirmed tumors. With a sensitivity of 53.3%, a specificity of 60%, and an accuracy rate of 55%, TRUS is limited in the detection of tumor recurrence during the follow-up of prostate cancer patients who have undergone EBRT. Beyersdorff et al. have compared digital examination, TRUS, and MRI, and they have found that the sensitivity of MRI (83%) in the detection of prostate cancer is higher than that of digital examination (67%) and TRUS (57%) (5). Hricak et al. have reported that MRI is more sensitive

Table 2. A comparison of transrectal ultrasound (TRUS) and pathological analysis in the detection of recurrent tumors

	Positive biopsy	Negative biopsy
Positive TRUS	8	2
Negative TRUS	7	3

Table 3. The sensitivity, specificity, predictive value, and accuracy of transrectal ultrasound (TRUS), T2-weighted MRI, and dynamic contrast-enhanced (DCE) T1-weighted MRI

	TRUS	T2-weighted MRI	DCE T1-weighted MRI
Sensitivity	53.3%	86.7%	93.3%
Specificity	60%	100%	100%
Positive predictive value	80%	100%	100%
Negative predictive value	30%	71%	83.3%
Accuracy	55%	90%	95%



Figure 3. a–c. Follow-up transrectal ultrasonography (TRUS) (a) and MR images (b, c) of a patient 18 months after radiotherapy for prostate cancer. Axial TRUS image (a) cannot differentiate the peripheral and central zones of the prostate gland (arrows). The axial T2-weighted MR image (b) shows that the entire peripheral zone is hypointense (arrows), which is not suspicious for recurrence, but diffuse tumor infiltration cannot be excluded. The dynamic contrast-enhanced T1-weighted MR image (c) shows no contrast enhancement in the peripheral zone (arrows). The biopsy was negative for tumor recurrence. R, rectum; C, central zone.

than TRUS in the detection of prostate cancer but is less specific than TRUS (6). Although these studies were not conducted with patients who were not treated with EBRT, several studies have also reported and shown that TRUS is unreliable for the detection of cancer recurrence after EBRT (7–9). Therefore, in the absence of other imaging or biochemical analysis modalities, TRUS is not a reliable method for the detection of recurrent tumors in prostate cancer patients (7).

In this study, we used a pelvic phased-array coil during the MRI examinations. Previous reports have shown that the use of endorectal-pelvic phased-array coils during MRI significantly improves the visualization of anatomical details, extracapsular extension accuracy, and specificity of the images in prostate cancer patients (10). Although endorectal coils increase the signals and reduce the noise in the obtained images, they

are expensive and uncomfortable for the patients. In addition, due to the complications that prostate cancer patients have with EBRT, such as rectitis, fistulas, and fibrosis, the use of endorectal coil causes more discomfort in this group of patients.

Prostate cancer is observed as isointense or hypointense lesions on T1-weighted images and as hypointense lesions on T2-weighted images. Alternatively, prostate cancer can be observed as single, multiple, or diffuse hypointense lesions in the peripheral zone in T2-weighted images (11); however, the hypointense lesions in the peripheral zone that are observed in the T2-weighted images can be the result of cancer or hemorrhage, hyperplastic nodules, inflammation, or post-radiation changes (12). Thus, a hypointense appearance is not specific for prostate cancer.

T2-weighted MRI appears to have a low accuracy for the detection of recurrent cancer in patients who have un-

dergone EBRT (13, 14). Post-radiation changes, such as prostatic atrophy, the development of diffuse and low T2 signal intensity (Figs. 4 and 5), and indistinctness of the normal zonal anatomy, can adversely impact the accuracy of T2-weighted MRI (15). In a study by Coakley et al., which analyzed 35 patients with prostate cancer who underwent radiotherapy, the zonal anatomy was reported to be indistinct due to a decrease in the T2- signal intensity of the prostate, in all but one patient (16).

We found that the accuracy of DCE T1-weighted MRI in the detection of recurrence was significantly higher than that of T2-weighted MRI (chi-square, $P = 0.002$). Fütterer et al. have compared T2-weighted to DCE T1-weighted MRI for the diagnosis of prostate cancer and have found that the sensitivity and specificity of DCE T1-weighted MRI were 69% and 97%, respectively (17), whereas the sensitivity and specificity of T2-weighted MRI were 60% and 97%, respectively. Interestingly, the differences between DCE T1-weighted and T2-weighted MRI were not statis-

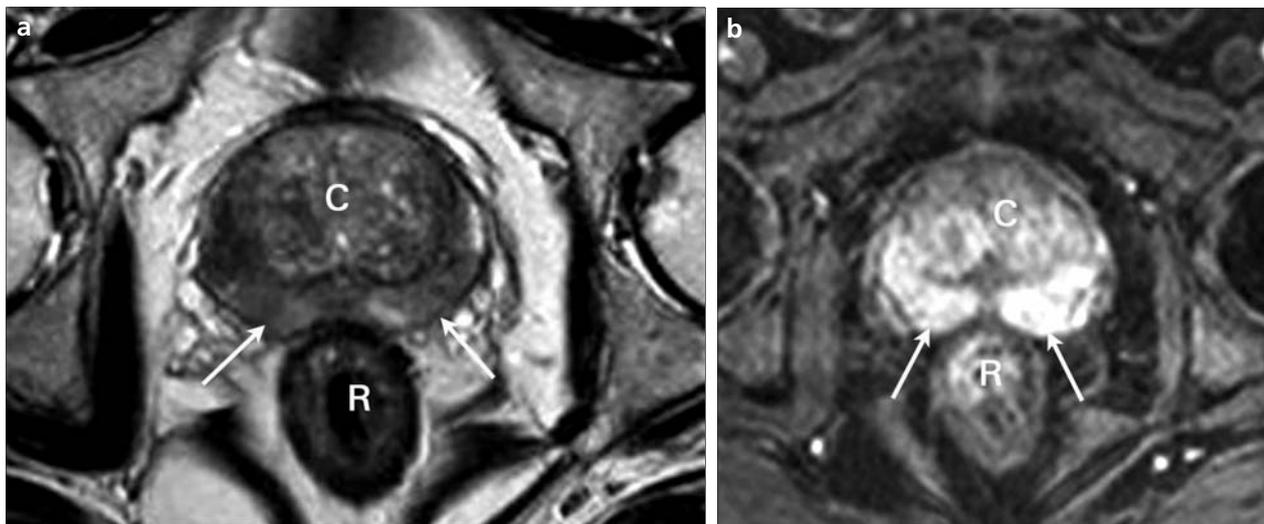


Figure 4. a, b. Pathologically proven prostatic tumor. The axial T2-weighted MR image (a) shows peripheral zone that is diffusely hypointense (arrows) due to radiotherapy; however, diffuse tumor infiltration cannot be excluded. On dynamic contrast-enhanced T1-weighted MR image (b), pathological contrast enhancement in the arterial phase at the peripheral zone (arrows) consistent with diffuse tumoral infiltration is seen. R, rectum; C, central zone.

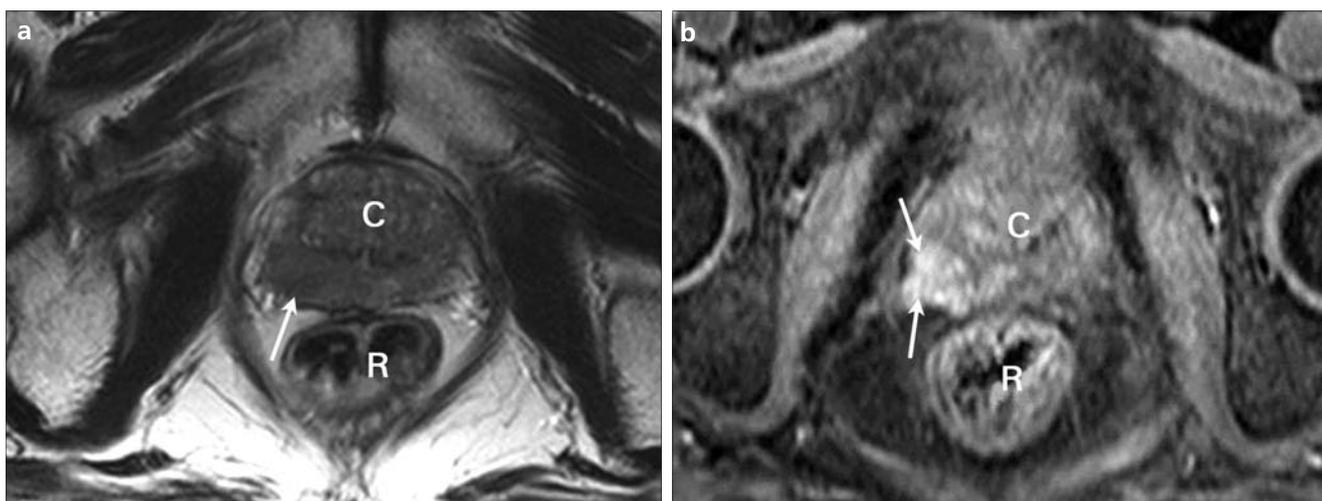


Figure 5. a, b. Pathologically proven prostatic tumor. The axial T2-weighted MR image (a) shows a hypointense area (arrow) that is suspected to be due to radiation or cancer recurrence. On dynamic contrast-enhanced T1-weighted MR image (b), pathological contrast enhancement in the arterial phase at the right peripheral zone and capsular invasion are observed (arrows). R, rectum; C, central zone.

tically significant; however, there was a statistically significant difference with respect to the ability of DCE T1-weighted MRI to increase the sensitivity of tumor detection for a less-experienced radiologist. Rouvière et al. have also evaluated the value of DCE T1-weighted MRI for the detection of recurrent tumors in 22 patients with prostate cancer who underwent EBRT (18). They found that DCE T1-weighted MRI is more sensitive than T2-weighted MRI, but both methods have a similar rate of specificity; however, while the differences between DCE T1-weighted and T2-weighted MRI with respect to sensitivity were statistically significant, the differences with respect to specifi-

city were not. Our findings support previous findings demonstrating that DCE T1-weighted MRI is useful for the detection of prostate cancer recurrence in patients who have undergone EBRT. Nonetheless, our findings must be confirmed by additional studies that involve a larger number of patients.

To improve the diagnostic performance of MRI for the evaluation of prostate cancer patients, various other techniques have been applied. These include diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS). Because an irradiated prostate gland usually appears small and diffusely hypointense in T2-weighted images, MRS, which detects

abnormal metabolism rather than abnormal anatomy, has been shown to be a better technique for the detection of local tumor recurrence and complete metabolic atrophy (1). In addition, MRS allows tumors to be distinguished from normal glandular tissue on the basis of an increased choline plus creatine to citrate ratio (19). In studies analyzing the correlation between whole-mount histopathology and MRS, the sensitivity and specificity of MRS range between 29–89% and 62–95%, respectively (20); however, the sensitivity of MRS depends on the Gleason score. For example, the overall sensitivity of MRS is 56% for tumor detection and increases from 44% in

lesions with a Gleason score of 6 to 89% in lesions with a Gleason score of greater than or equal to 8 (21). In our group of patients, citrate and choline are often undetectable after radiation therapy, which limits the use of this ratio for MRS analysis (1). In addition, a decrease in the levels of citrate and/or an increase in choline levels are a common response to various forms of stress in the prostate (e.g., cancer, inflammation, androgen deprivation, and radiation) (19). In patients who undergo radiation therapy, the spectral peaks of citrate decrease rapidly and progressively over time, which does not occur in the untreated prostate gland. Thus, measuring the levels of citrate in these patients is of limited use for the identification of cancer recurrence (22). These metabolic alterations after EBRT limit the use of MRS for the detection of cancer recurrence.

DWI is a promising method, which has received increased attention, for the imaging of prostate cancer. In patients with prostate cancer, the normal glandular architecture is disrupted and replaced by aggregated cancer cells and fibrotic stroma. These changes inhibit the movement of water macromolecules, resulting in restricted diffusion and a reduction in apparent diffusion coefficient (ADC) values in cancerous tissue. Owing to their larger extracellular space and interstitial fluid, tumors of the prostate have lower ADC values than a normal prostate (23), which is a property that can be used to detect prostate cancer. Despite the significant difference in the mean ADC values between cancerous and normal tissues, individual variability may decrease the diagnostic accuracy of the ADC measurement for the detection and localization of prostate cancer (23, 24). In DWI, the diffusion sensitivity can be varied to control the contrast of the image; however, there is no consensus regarding the optimal b-value for the detection of prostate cancer. Higher b-values can increase the sensitivity of diffusion by diminishing the hyperintensity of the tissues with long T2 relaxation times (i.e., T2 shine-through); however, high b-values can decrease the absolute differences in signal intensity between cancerous and normal tissues. Importantly, DWI is not yet routinely used in the clinic, but it is expected to become an important adjunct to endorectal MRI in the future (25).

In conclusion, TRUS without the use of other imaging or biochemical analysis modalities is not a useful method for detecting cancer recurrence during the follow-up of prostate cancer patients who have undergone EBRT. In contrast, T2-weighted and DCE T1-weighted MRI are useful and effective in the monitoring of prostate cancer patients and in the detection of recurrence after EBRT. Therein, DCE T1-weighted MRI is more reliable than T2-weighted MRI.

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