

Prostate cancer detection with MRI: is dynamic contrast-enhanced imaging necessary in addition to diffusion-weighted imaging?

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PURPOSE

To assess the feasibility of using magnetic resonance imaging for prostate cancer detection without using a contrast material.

MATERIALS AND METHODS

T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), and dynamic contrast-enhanced imaging (DCEI) were performed using a phased-array coil at 1.5 T. These examinations were performed in 178 patients with elevated serum prostate-specific antigen levels (>4.0 ng/mL) before systematic needle biopsy. Two radiologists independently evaluated images from DWI, DCEI, and a combination of the two techniques by referring to a T2WI image and by using a predefined confidence scale for cancer detection. The right and left halves of the peripheral zone and the central gland were separately rated. The diagnostic performance (A_z) of each technique was assessed by analyzing their associated area under the receiver operating characteristic curves. The results of a biopsy served as a reference standard.

RESULTS

Prostate cancer was detected in 72 (40.4%) of the 178 patients. For the entire prostate, the diagnostic performances of DWI ($A_z = 0.848$) ($P < 0.001$) and the combined technique ($A_z = 0.845$) ($P < 0.001$) were significantly more accurate than that of DCEI ($A_z = 0.746$). DWI (74.8%) ($P < 0.001$) and the combined technique (72.9%) ($P < 0.001$) were significantly more sensitive than DCEI (52.8%). The numbers of cancer lesions that were interpreted using only DWI or DCEI were 83 (26.1%) and 13 (4.1%) of the 318 study lesions, respectively.

CONCLUSION

DWI and the combined technique are more accurate and sensitive than DCEI in the detection of prostate cancer; however, DWI and DCEI play complementary roles in the accurate detection of prostate cancer.

Key words: • magnetic resonance imaging • prostate • neoplasms

Recently, prostate-specific antigen (PSA) has been identified as a useful tumor marker for the primary screening of prostate cancer; however, previously reported positive predictive values (PPV) for patients with elevated serum PSA levels (>4.0 ng/mL) are only 30.5–41.4% (1, 2). Prostate magnetic resonance imaging (MRI) plays an important role in the determination of tumor localization, characteristics, and extent (3). With regard to detecting prostate cancer, recent studies have reported that diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCEI) achieve improved diagnostic performance in comparison to T2-weighted imaging (T2WI) (4–8). The previously reported detection sensitivities of DWI and DCEI are 71–84% and 60–74%, respectively; however, the diagnostic performances that were evaluated in these prior studies varied depending on the field strength of the MR scanner, the type of coil, and the reference standard that was used in each study (4–8). Unlike DWI, DCEI requires the intravenous injection of a contrast material. Contrast material usage requires a longer setup time, and it includes the potential risk of adverse effects.

The purpose of this study was to compare the diagnostic performances of DWI, DCEI, and a combination of both techniques by referring to T2WI while using a phased-array coil at 1.5 T. The diagnostic performances of these methods were compared in the detection of prostate cancer in patients with elevated serum PSA levels. This study also assessed the feasibility of using prostate MRI without using a contrast material.

Materials and methods

Patients

We retrospectively reviewed 178 consecutive patients (mean age, 68.8 y; age range, 41–86 y) with elevated serum PSA levels (>4.0 ng/mL) who underwent MRI before systematic transrectal prostate biopsy between September of 2008 and October of 2009. Systematic needle biopsies were conducted to acquire 10–12 specimens (three specimens for each half of the peripheral zone, two specimens for each half of the central gland, and up to two specimens for the targeted biopsy) within 44 days (median, eight days) after MRI. Histopathological results of the biopsied tissue served as a reference standard. The presence of prostatic intraductal neoplasia or atypical ducts was interpreted as “true negative” in this study. This study proceeded in accordance with the guidelines of our Institutional Review Board, and written informed consent for contrast-enhanced MRI and transrectal prostate biopsy was obtained from each patient.

MRI

All MRI examinations were performed using a 1.5-T MR scanner (Magnetom Symphony; Siemens Medical Solutions, Erlangen, Germany). T2-weighted turbo spin echo imaging (TR/TE, 3000/120 ms; turbo, 9; matrix

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size, 512 × 352; acquisition time, 165 s), diffusion-weighted echo planar imaging (TR/TE, 3700/83 ms; matrix size, 128 × 114; average, 6; acquisition time, 91 s), and gadolinium-enhanced dynamic MRI (volumetric interpolated breath-hold examinations [VIBE]; TR/TE, 5.39/2.15; flip angle, 15°; bandwidth, 300 Hz/Px) were acquired using eight-channel phased-array coils. Modified sensitivity encoding (mSENSE) using a reduction factor of two was applied in the in-plane phase-encoding direction for the parallel imaging technique. Diffusion gradients with two b values (0 and 1000 s/mm²) were selected to acquire DWI along the three directions of the motion-probing gradients because high b-value DWI provides greater tissue diffusivity and less T2 shine-through effect without losing detection performance for prostate cancer (9, 10). In order to acquire DCEI, a 0.1-mmol/kg bolus of gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma, Osaka, Japan) was administered at a rate of 1.5 mL/s followed by a 20-mL saline flush using a power injector. Images were acquired before contrast and at 30, 60, and 180 s after the contrast injection was initiated. The slice thickness/interslice gap was 5 mm/1 mm for T2WI, 4 mm/0.8 mm for DWI, and 2.5 mm/0.5 mm for DCEI. The field of view was 30 and 23 cm for DWI and the other sequences, respectively.

Image analysis

Two experienced abdominal radiologists, each unaware of the results of the biopsies, reviewed all of the DWI, DCEI, and DWI and DCEI in combination with T2WI images on a commercial workstation (eFilm Workstation; Infocom, Tokyo, Japan). The observers understood that the patients might have prostate cancer, but they were blinded to the number and location of the lesions. The DWI images were analyzed first, followed by an analysis of a combination of DWI and DCEI images in the same reading session, whereas the DCEI images were interpreted two weeks later to minimize any learning bias. All of the images that were obtained from the three imaging techniques were shown to each observer in a random order by the same presenter. Apparent diffusion coefficient (ADC) maps were displayed to the observers during the interpretation sessions for the DWI images. For visual assessment, the prostate was di-

vided into four regions: two peripheral zones and two inner glands. The prostate was divided because the precise location of the cancer was difficult to determine with only a schematic drawing of the needle biopsy. The detected prostate lesions were then rated using the following confidence scale: 1, definitely not cancer; 2, probably not cancer; 3, probable cancer; 4, definite cancer. Only lesions that were rated as 3 or 4 were considered to be statistical positives. If the observer detected two or more suspected cancer lesions in a single prostate region, the highest rating score was assigned for the region. Receiver operating characteristic (ROC) analysis was performed for each imaging technique by plotting the true-positive fraction against the likelihood of obtaining a false-positive image at each confidence level. The diagnostic accuracy of each imaging technique was compared via the area under each ROC curve (A_z) for the central gland, the peripheral zone, and the entire prostate. The sensitivity, specificity, PPV, and negative predictive value (NPV) for each imaging technique were also assessed for the central gland, the peripheral zone, and the entire prostate. The statistical significance of the A_z value was assessed using Student's *t*-test. The sensitivity and specificity of each technique were statistically compared using the McNemar test. PPV and NPV were statistically compared using Fisher's exact test.

Diagnostic criteria

The rating criteria for prostate cancer in the peripheral zone for T2WI were as follows: 1, normal signal; 2, mild low signal with a diffuse or wedged-shaped appearance; 3, moderate low signal with a focal appearance; and 4, signal loss with a mass-like appearance. The rating criteria of inner gland cancer for T2WI were as follows: 1, no nodules; 2, heterogeneous nodule with a well-defined border; 3, homogeneous nodule with an ill-defined border; and 4, homogeneous nodules with capsular invasion. For the interpretation of DWI, any lesions in the prostate that exhibited an apparent decrease in the ADC upon visual assessment were to be considered malignant. The rating criteria were as follows: 1, normal signal; 2, a moderate and irregular decrease in signal with a diffuse or linear appearance; 3, an apparently low signal and a small focal appearance; and 4, an apparently

low signal and a large mass-like appearance. The ADC value for each suspected lesion was not measured during the film-reading session. For the interpretation of DCEI, the rating criteria were as follows: 1, no focal enhancement; 2, gradual enhancement without early enhancement; 3, early and prolonged enhancement; and 4, an early enhanced mass with washout in the delayed phase. In the interpretation of the combined images, when the imaging techniques were rated with different scores for the same lesion, the highest rating score was used.

Results

Systematic needle biopsy demonstrated that 72 (40.4%) of the 178 patients had prostate cancer. The histopathological results of the 106 patients who did not have cancer included the following: prostatitis (n=38), benign prostatic hyperplasia (n=21), normal prostate tissue (n=20), atypical ducts (n=19), prostatic intraductal neoplasia (n=7), and adenomatous hyperplasia (n=1). Among the 712 prostate regions that were examined in the 178 patients, prostate cancer was histopathologically confirmed with biopsy in 67 (18.8%) of the 356 regions in the central gland, 92 (25.8%) of the 356 regions in the peripheral zone, and 159 (22.3%) of the 712 regions in the entire prostate. Serum PSA levels for all 178 patients ranged from 4.04 to 568.50 ng/mL (mean, 20.51 ng/mL). Mean PSA levels in patients with and without cancer were 38.53 ng/mL and 7.68 ng/mL, respectively. Patients with cancer had significantly higher serum PSA levels than those without cancer according to the Mann-Whitney test ($P < 0.001$). The Gleason scores of the detected cancer in this study population were 6 (26 patients), 7 (30 patients), 8 (3 patients), and 9 (13 patients). The mean Gleason score was 7.04. The clinical T stages of detected cancer were T1c (3 patients), T2a (24 patients), T2b (14 patients), T2c (17 patients), T3a (8 patients), T3b (4 patients), and T4 (2 patients).

The A_z values for DWI, DCEI, and DWI in combination with DCEI were 0.821, 0.678, and 0.800, respectively, for the central gland; 0.866, 0.797, and 0.882, respectively, for the peripheral zone; and 0.848, 0.746, and 0.845, respectively, for the entire prostate (Table 1). Diagnostic performances were significantly better for DWI and for DWI

in combination with DCEI than for DCEI alone for the central gland ($P = 0.002$ for DWI vs. DCEI, $P = 0.012$ for DWI + DCEI vs. DCEI), peripheral zone ($P = 0.009$ for DWI vs. DCEI, $P = 0.001$ for DWI + DCEI vs. DCEI), and entire prostate ($P < 0.001$ for DWI vs. DCEI, $P < 0.001$ for DWI + DCEI vs. DCEI). No statistical significances in diagnostic performance were observed between DWI and DWI in combination with DCEI for the central gland ($P = 0.511$), peripheral zone ($P = 0.446$), or entire prostate ($P = 0.866$).

The sensitivity, specificity, PPV, and NPV for this study are shown in Table 2. DWI and DWI in combination with DCEI were significantly more sensitive than DCEI alone for every prostate region ($P < 0.001$ for DWI vs. DCEI, $P < 0.001$ for DWI + DCEI vs. DCEI). No statistical significances in sensitivity

were observed between DWI and DWI in combination with DCEI for the central gland ($P = 0.611$), peripheral zone ($P = 1.000$), or entire prostate ($P = 0.651$). NPVs for DWI and DWI in combination with DCEI were significantly higher than those for DCEI alone for the central gland ($P = 0.004$ for DWI vs. DCEI, $P = 0.016$ for DWI + DCEI vs. DCEI), peripheral zone ($P = 0.004$ for DWI vs. DCEI, $P = 0.005$ for DWI + DCEI vs. DCEI), and entire prostate ($P < 0.001$ for DWI vs. DCEI, $P < 0.001$ for DWI + DCEI vs. DCEI). No statistical significances in NPV were observed between DWI and DWI in combination with DCEI for the central gland ($P = 0.749$), peripheral zone ($P = 0.900$), or entire prostate ($P = 0.685$). There were no significant differences in the specificity and PPVs among the three imaging techniques for any of the prostate regions.

The number of true lesions that were only interpreted using DWI and DCEI was 83 (26.1%) and 13 (4.1%) of the 318 study lesions, respectively. For DWI, 41 (49.4%) and 42 (50.6%) of 83 lesions were located in the central gland and the peripheral zone, respectively. All 13 lesions that were only interpreted via DCEI were located in the peripheral zone (Fig. 2). The number of true lesions that were not detected by either DWI or DCEI was 43 (13.5%) for the central gland and 24 (7.5%) for the peripheral zone of the 318 study lesions. Two representative cases are shown in Figs. 1 and 2.

Discussion

This study demonstrates that both DWI and DWI in combination with DCEI are superior to DCEI and are more accurate and sensitive in detecting prostate cancer. In fact, 26.1% of the cancer lesions were not detected by DCEI alone; however, 4.1% of the cancer lesions were also missed when detection was attempted by DWI alone. Thus, excluding DCEI from routine prostate MRI incurs a risk of failure in the detection of prostate cancer, especially for lesions in the peripheral zone. Based on our current results, unenhanced MRI, (comprised of DWI and T2WI) cannot be replaced by contrast-enhanced MRI (comprised of DWI, DCEI, and T2WI) for the accurate detection of prostate cancer although the accuracies and sensitivities of both imaging techniques were not significantly different. These results also suggest that every central-gland cancer that was detected via DCEI was also detectable with DWI alone. In contrast to peripheral zone cancer, the detection of central-gland cancer by T2WI or DCEI is often difficult because the zonal T2 contrast between cancer and normal tissues is relatively low. In addition, central-gland tissues are more susceptible to enhancement with gadolinium, resulting in insufficient contrast between cancer and normal tissues (6). In this respect, DWI is superior to T2WI or DCEI for delineating central-gland cancer by yielding sufficient contrast to distinguish cancer from normal tissues.

The improved performance of DWI in the detection of prostate cancer is predominantly attributable to the difference in ADC values between cancer and normal tissues. ADC measurement has been reported to be useful for distinguishing between malignant and

Table 1. A_z values for the three imaging techniques for detecting prostate cancer in different prostate regions

	Central gland	Peripheral zone	Whole prostate
DWI	0.821 [0.778–0.858]	0.866 [0.835–0.893]	0.848 [0.823–0.871]
DCEI	0.678 [0.591–0.756]	0.797 [0.750–0.838]	0.746 [0.704–0.784]
DWI + DCEI	0.800 [0.749–0.845]	0.882 [0.849–0.910]	0.845 [0.816–0.871]

Data in brackets denote 95% confidence intervals.

DWI, diffusion-weighted imaging; DCEI, dynamic contrast-enhanced imaging.

Diagnostic performances are significantly better for DWI and DWI+DCEI than for DCEI alone for every prostate region.

Table 2. Sensitivity, specificity, PPV, and NPV summarized by prostate region and imaging technique

	Imaging technique	Central gland	Peripheral zone	Whole prostate
Sensitivity	DWI	65.6 (88/134)	81.5 (150/184)	74.8 (238/318)
	DCEI	37.3 (50/134)	64.1 (118/184)	52.8 (168/318)
	DWI+DCEI	61.9 (83/134)	80.9 (149/184)	72.9 (232/318)
Specificity	DWI	81.1 (469/578)	78.4 (414/528)	79.8 (883/1106)
	DCEI	85.8 (496/578)	79.9 (422/528)	83.0 (918/1106)
	DWI+DCEI	82.3 (476/578)	77.8 (411/528)	80.1 (887/1106)
PPV	DWI	44.6 (88/197)	56.8 (150/264)	51.6 (238/461)
	DCEI	37.8 (50/132)	52.6 (118/224)	47.1 (168/356)
	DWI+DCEI	44.8 (83/185)	56.0 (149/266)	51.4 (232/451)
NPV	DWI	91.0 (469/515)	92.4 (414/448)	91.6 (883/963)
	DCEI	85.5 (496/580)	86.4 (422/488)	85.9 (918/1068)
	DWI+DCEI	90.3 (476/527)	92.1 (411/446)	91.1 (887/973)

DWI, diffusion-weighted imaging; DCEI, dynamic contrast-enhanced imaging; PPV, positive predictive value; NPV, negative predictive value.

Sensitivities and NPVs are significantly higher for DWI and DWI+DCEI than for DCEI alone for every prostate region. There were no significant differences in the specificity and PPV among the three imaging techniques.

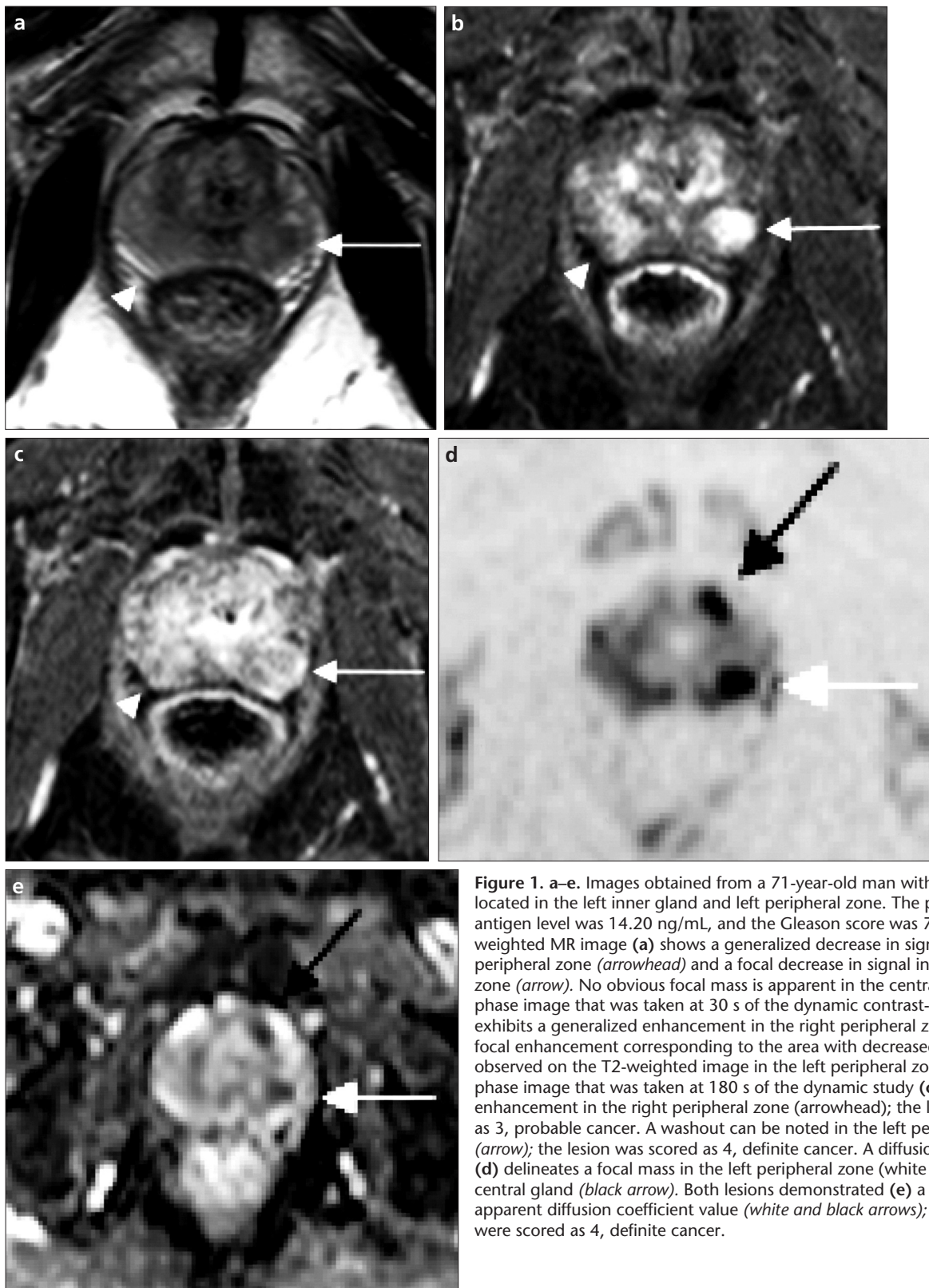


Figure 1. a–e. Images obtained from a 71-year-old man with prostate cancer located in the left inner gland and left peripheral zone. The prostate-specific antigen level was 14.20 ng/mL, and the Gleason score was 7 (3 + 4). A T2-weighted MR image (a) shows a generalized decrease in signal in the right peripheral zone (arrowhead) and a focal decrease in signal in the left peripheral zone (arrow). No obvious focal mass is apparent in the central gland. An early phase image that was taken at 30 s of the dynamic contrast-enhanced study (b) exhibits a generalized enhancement in the right peripheral zone (arrowhead) and focal enhancement corresponding to the area with decreased signal that was observed on the T2-weighted image in the left peripheral zone (arrow). A late phase image that was taken at 180 s of the dynamic study (c) shows prolonged enhancement in the right peripheral zone (arrowhead); the lesion was scored as 3, probable cancer. A washout can be noted in the left peripheral zone lesion (arrow); the lesion was scored as 4, definite cancer. A diffusion-weighted image (d) delineates a focal mass in the left peripheral zone (white arrow) and the left central gland (black arrow). Both lesions demonstrated (e) a decrease in the apparent diffusion coefficient value (white and black arrows); these two lesions were scored as 4, definite cancer.

benign lesions (11). Prior studies have shown that ADC values are significantly lower in prostate cancer (ranging from $0.61\text{--}1.34 \times 10^{-6} \text{ mm}^2/\text{s}$, with a b value of $300\text{--}2000 \text{ mm}^2/\text{s}$) in compar-

ison to normal peripheral-zone values (ranging from $1.01\text{--}1.72 \times 10^{-6} \text{ mm}^2/\text{s}$) (6, 9, 12–14). In this study, higher detection sensitivities for prostate cancer were achieved for the entire prostate

with DWI than with DCEI. The precise reason for DWI's superior performance is uncertain. It is possible that the signal intensity difference between cancer and normal tissues is higher for DWI

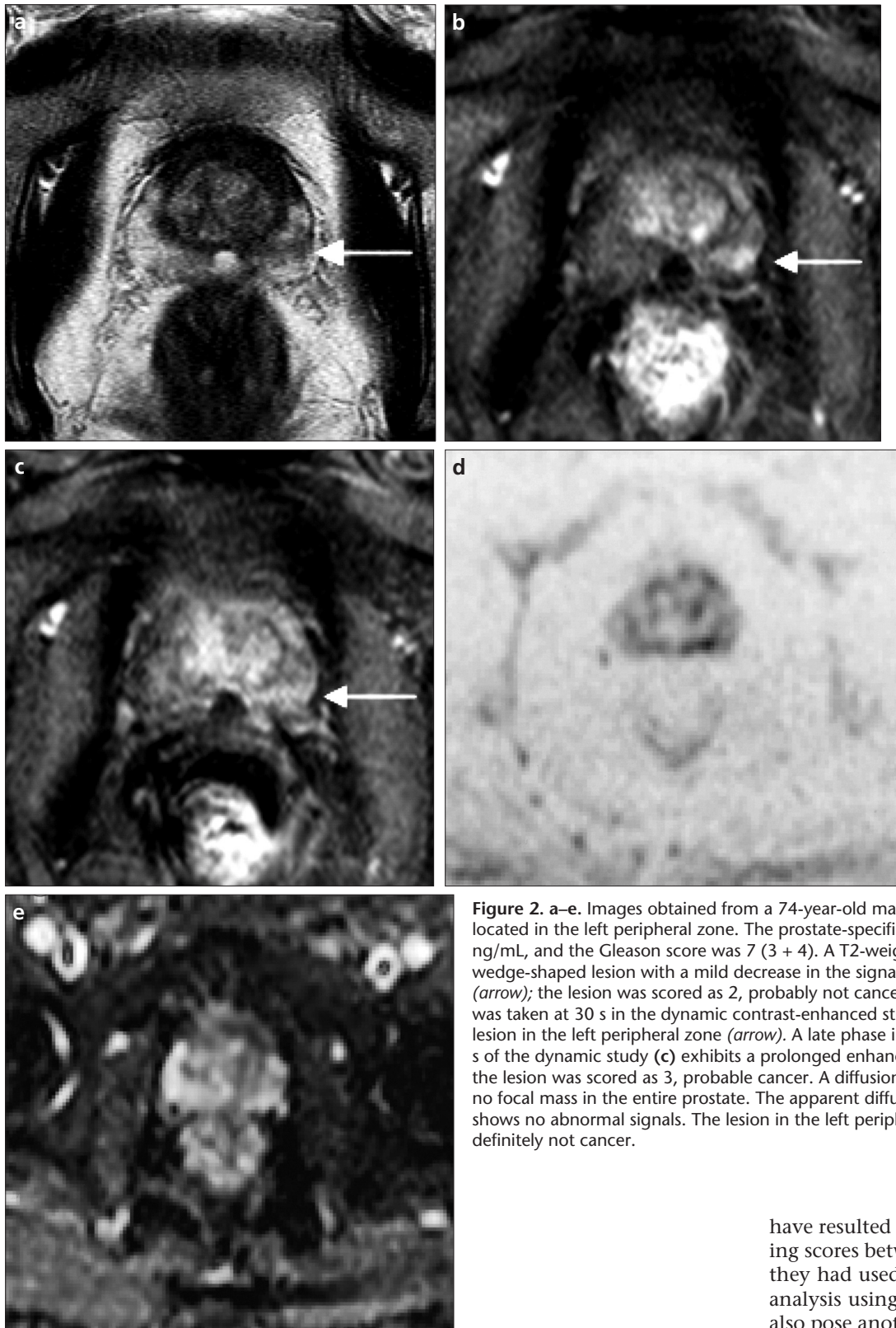


Figure 2. a–e. Images obtained from a 74-year-old man with prostate cancer located in the left peripheral zone. The prostate-specific antigen level was 5.79 ng/mL, and the Gleason score was 7 (3 + 4). A T2-weighted MR image (**a**) shows a wedge-shaped lesion with a mild decrease in the signal in the left peripheral zone (*arrow*); the lesion was scored as 2, probably not cancer. An early phase image that was taken at 30 s in the dynamic contrast-enhanced study (**b**) shows an enhanced lesion in the left peripheral zone (*arrow*). A late phase image that was taken at 180 s of the dynamic study (**c**) exhibits a prolonged enhancement of the lesion (*arrow*); the lesion was scored as 3, probable cancer. A diffusion-weighted image (**d**) shows no focal mass in the entire prostate. The apparent diffusion coefficient map (**e**) shows no abnormal signals. The lesion in the left peripheral zone was scored as 1, definitely not cancer.

than for DCEI. In this study, we did not compare the exact signal-to-noise ratios of DWI and DCEI.

We did not measure the ADC values of the suspected lesions at the film

reading sessions because the rating of suspected lesions based on predefined ADC value criteria for malignancy might have hampered the observer's independence. Such hampering might

have resulted in a perfect match of rating scores between the two observers if they had used these criteria. Objective analysis using ADC measurement may also pose another problem. If DWI was scored by measuring the ADC value during the film reading session without the use of quantitative criteria for other imaging, then a bias toward DWI would be created. The statistical analysis in this study was conducted with subjective ROC analysis; therefore, we

adopted visual assessment for the rating of all imaging.

Most benign prostatic hyperplasia that were located in the inner gland exhibited early enhancement, and it was sometimes difficult to use DCEI alone to discriminate such lesions from early-enhanced true cancers; however, benign prostatic hyperplasia exhibited lesser changes in signal intensity in comparison to those exhibited by cancer via DWI. Inner-gland cancer was more clearly delineated by DWI than by DCEI, possibly because the different ADC values between malignant and benign tissues enabled the observers to visualize the cancer more easily and to distinguish both lesions more confidently. Although prostate cancer in the peripheral zone was enhanced earlier in comparison to normal prostate tissues on DCEI, inflammatory lesions, such as prostatitis, were also enhanced in the early phase of DCEI (Fig. 1). Most similar false-positive lesions were accurately interpreted as benign lesions by DWI because ADC values may be more significantly altered by cancer tissues than by inflammation.

Proton MR spectroscopy is an alternative method with a high detection rate for diagnosing prostate cancer (15, 16); however, the best results are only achieved with modern equipment and a longer acquisition time. In contrast to this method, DWI has the advantages of needing only short image acquisition times and technicians with less training. In comparison to DCEI, DWI requires no setup time for the preparation of a contrast material, the table transfer of the patient, needle insertion, or intravenous injection. The relatively short examination time of DWI enables efficient patient throughput.

This study had certain limitations. MRI examinations were performed using a phased-array coil at 1.5 T. The results may have differed if we had used endorectal coils or a 3-T MRI system. The standards of reference that were used in this study consisted of histological results from transrectal needle biopsies; however, the reported sensitivity and PPV of ultrasound-guided biopsy are 50% and 47%, respectively (17). Thus, the detection performance results of the current study may have been different if the study had proceeded based on the histopathological findings that were noted for whole-mount sections. We did not perform separate

analyses according to the tumor size or Gleason scores that were noted in this study. Prior studies have shown that 89% of tumors that were smaller than 0.5 mm³ in size have a Gleason score of ≤ 6 and that such tumors are indolent (18, 19). Excluding such small lesions from the study group may have resulted in improved diagnostic performance for each imaging technique. We divided the prostate into four regions for ROC analysis, although 10–12 specimens were obtained by biopsy. This discrepancy may have caused an overestimation of a region in the rating score if two or more cancers were independently located in a same region. Interobserver variability was also not assessed in this study; thus, there might have been differences in agreement even though each observer was asked to rate the detected lesions according to standardized diagnostic criteria.

In conclusion, in patients with elevated serum PSA levels, DWI is superior to DCEI in the detection of prostate cancer. DWI is more accurate and sensitive, and a combination of DCEI and DWI does not significantly improve the accuracy or sensitivity of DWI; however, DCEI cannot be excluded from prostate MRI because DWI and DCEI play complementary roles in the detection of prostate cancer.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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