RESEARCH COMMUNICATION

Preoperative Prediction of Neurovascular Bundle Involvement of Localized Prostate Cancer by Combined T2 and Diffusion-weighted Imaging of Magnetic Resonance Imaging, Number of Positive Biopsy Cores, and Gleason Score

Taku Naiki[1,2]*, Takehiko Okamura[3], Daisuke Nagata[1], Yuji Mori[4], Noriyasu Kawai[1,2], Kumiko Ogawa[4], Hidetoshi Akita[3], Yoshihiro Hashimoto[5], Keiichi Tozawa[2], Kenjiro Kohri[2]

Abstract

Because recovery of erectile function and avoidance of positive surgical margins are important but competing outcomes with prostate cancer therapy, the decision to preserve or resect a neurovascular bundle (NVB) during laparoscopic radical prostatectomy (LRP) should be firmly based on information concerning the presence and location of extracapsular extension. In the current retrospective study, the propriety of actual decisions was assessed using preoperative magnetic resonance imaging (MRI), combining T2-weighted imaging (T2WI) with diffusion-weighted imaging (DWI), the apparent diffusion coefficient (ADC), numbers of positive biopsy cores, tumor volume and the Gleason score. MRI before prostate biopsy was performed in 35 patients who underwent LRP for clinically localized prostate cancer. A single radiologist retrospectively assessed whether the tumor localization, capsular penetration, seminal vesicle invasion, NVB involvement, and MRI findings correlated with the postoperative histological results. With the postoperative specimens, 83 lesions demonstrated a Gleason score of 6 or more. Using T2WI with and without DWI and ADC, 39 and 27 of 54 lesions were correctly identified, respectively, the difference being significant. For cancers in the transitional zone, using a threshold Gleason score of 3 or greater, sensitivity was also significantly higher for T2+DWI+ADC than for T2WI alone. Of 35 patients, using all available clinical information (biopsy results including Gleason score, tumor location, percentage of positive biopsy cores, and the percentage of tumor-involved core tissue), we found that the preoperative and postoperative staging were concordant in 25 cases. There is no universal consensus for nerve-sparing LRP; therefore, we performed an additional analysis using simplified clinically defined selection criteria (PSA level >15ng/mL, cT2, less than two positive biopsy scores in the unilateral lobe and less than 30% tumor volume, and a Gleason score of 6). Using this criteria, we selected 12 of 35 patients, and the detection rate of NVB involvement by MRI combined T2WI + DWI + ADC maps was 100% in their 30 lesions, and therefore we consider it safe to perform nerve-sparing LRP using our criteria. Our findings suggest that NVB can be safely preserved in patients with low-grade tumors using simplified clinically defined selection criteria to determine margin involvement.

Keywords: Prostate cancer - MRI - erectile dysfunction - laparoscopic prostatectomy

Asian Pacific J Cancer Prev, **12**, 909-913

Introduction

Early detection of prostate cancer has recently significantly improved, and a rapid increase in incidence during the past two decades has been noted (Sarma et al., 2002). Nowadays, men who are still sexually active are diagnosed with prostate cancer. There are also now a number of disease-targeted therapies, such as intensity-modulated radiation therapy, interstitial brachytherapy, and cryosurgery (Carroll et al., 1997). Especially, radical retropubic prostatectomy (RP) provides excellent long-term disease control for patients with clinically localized prostate cancer (Hull GW et al., 2002), but erectile dysfunction (ED) is one of the important associated complications. Recovery of ED after RP is quantitatively related to the preservation of the neurovascular bundle (NVB) (Rabbani et al., 2000). However, prostate cancer most commonly arises in the peripheral zone (PZ), often posteriorly, just beneath the capsule. Among patients with extracapsular extension (ECE), the tumor is most often

*[1]Department of Urology, [4]Department of Radiology, [5]Department of Pathology, East Medical Center Higashi Municipal Hospital City of Nagoya, Nagoya, [2]Department of Nephro-urology, Nagoya City University, Nagoya, [3]Department of Urology, Anjo Kosei Hospital, Anjo, Japan *For correspondence: rx-nike@hotmail.co.jp naiki@med.nagoya-cu.ac.jp*

present posteriolaterally in the region of the NVB (McNeal et al., 1992; Rosen et al., 1992). Therefore, preservation of the latter may compromise disease control and result in a positive surgical margin, which markedly increases the probability of recurrence. Consequently, surgeons often resect widely in areas of suspected ECE (Sofer et al., 2002). In spite of all precautions, positive margins still occur in approximately 23-31% of RP specimens. Efforts to preserve sexual function after curative treatment with RP by means of nerve-sparing (NS) techniques are receiving increasing attention. But their efficacy depends on the ability to determine the presence and location of tumor ECE, which are difficult to predict from the clinical stage, serum prostate specific antigen (PSA) level, and biopsy Gleason score, even when quantitative assessment of the extent of the tumor in systematic biopsies is considered (D' Amico et al., 1997).

Magnetic resonance imaging (MRI) widely used for pretreatment workup in patients with prostate cancer (Nakashima et al., 2004; Hricak et al., 2007), may be of assistance however. On conventional T2WI, areas with cancer involvement show decreased signal intensity relative to normal peripheral gland tissue because of increased cell density and loss of prostatic ducts (Dhingsa R et al., 2004), although this is non-specific and may also be observed with hyperplasia or prostatitis. MRI ability to detect prostate cancer is dependent on tumor size, with reported T2WI for values for sensitivity and specificity of 45-80% and 27-80%, respectively. Diffusion-weighted imaging (DWI) provides indirect tissue information based on changes in the random motion of water protons at the cellular or physiologic level and has been widely used to evaluate acute cerebral ischemia. This technique is noninvasive, does not involve radiation exposure or intravenous contrast material, and requires little additional examination time, and from DWI parametric maps, apparent diffusion coefficient (ADC) can be calculated. Recently, a number of investigators have reported the potential usefulness of DWI for detecting prostate cancer because it shows a lower ADC than normal PZ (Kozlowski et al., 2006). In the present study, in order to examine the utility of DWI and ADC for assessment of margin involvement, we compared the detection rate of multiple cancer regions with volume and Gleason scores on a lesion-by-lesion basis.

Materials and Methods

Study population

During the period from January 2006 through October 2008, 35 male patients (mean age: 67.7 years; age range: 49-78 years) in whom prostate cancer had been diagnosed by transrectal ultrasound (TRUS) - guided systematic transrectal prostate biopsy underwent LRP at the East Medical Center Higashi Municipal Hospital. All patients were referred for MR imaging of the pelvis before biopsy. A total of 10 - 12 prostate gland specimens, eight from the PZ and two-four from the TZ, from each patient were obtained during the biopsy. The biopsy sites were the lateral right region and lateral left region of the PZ from the apex to the bladder neck, and the bilateral regions of the TZ. A single pathologist diagnosed the Gleason score, and cancer volume in each core was recorded along with the number of cores and the location and tumor volume of each core. None of the patients underwent hormonal or radiation therapy during the interval between MRI and biopsy. Their mean serum PSA level at diagnosis was 12.8ng/mL (range: 2.78 - 67.3ng/mL). Their medial preoperative Gleason score was 7 (range: 5 - 10). Table 1 shows clinical and pathological findings for all 35 patients. Clinical stage was assigned using the 1997 International Union Against Cancer (UICC) TNM staging system.

MRI technique

MRI was performed using a 1.5-T MR unit (MAGNETOM Symphony; Siemens). A body coil was used for signal excitation, and a multichannel phased-array coil for signal reception. The MRI examination included transverse and coronal T2-weighted fast spin-echo imaging, transverse T2-weighted echo-planar imaging, transverse nonenhanced and contrast-enhanced T1-weighted fast spin-echo imaging, and transverse DW imaging. Transverse T2-weighted fast spin-echo imaging was performed under specific conditions of Repetition Time/Echo Time [TR/TE]=7040/129 msec, signal average of 1, echo train length of 29, 130Hz/Px bandwidth, 23cm × 23cm field of view, 5-mm section thickness, 1-mm intersection gap, and a 256 × 256 matrix, and transverse T1-weighted fast spin-echo imaging was performed in conditions of TR/TE=450/11 msec, signal average of 1, echo train length of 7, 150Hz/Px bandwidth, 23cm × 23cm field of view, 5-mm section thickness, 1-mm intersection gap, and a 256 × 256 matrix through the prostate gland and seminal vesicles.

Transverse DWI was performed using a multisection spin-echo sequence (TR/TE=1400/80 msec, signal average of 6, 90° flip angle, 2298Hz/Px bandwidth, parallel imaging factor of 2, 32cm × 32cm field of view, 5-mm section thickness, 1-mm intersection gap, and a 128 × 128 matrix). Images were acquired with motion-probing gradient pulses that were applied sequentially along three orthogonal orientations with two b factors (0 and 800 sec/mm^2).

LRP and pathological evaluation

A single surgeon with 8 years experience of LRP performed the operations. Once the prostate had been removed, the specimen was fixed in 10% buffered formaldehyde. After removal of the apex and the bladder neck resection margins, the prostate was sectioned axially

Table 1. The Clinical and Pathological Findings of the 35 Patients

	Clinical Characteristic		Pathological Stage	
			pT2	pT3
PSA (ng/ml)	<10	22	17	5
	10≤15	4	4	0
	15≤	9	7	2
Gleason Score	4-6	16	15	1
at Biopsy	7	9	5	4
	8-10	10	8	2
Clinical Stage	cT1c	6	3	3
	cT2	29	25	4

to match the MRI plane of sectioning at regular intervals of 5mm or less, yielding serial slices of tissue. A ruler was used to ensure that no single slice was more than 5mm in thickness. These slices were sectioned into two lobes (left and right) to fit on a standard slide. On each slide, a pathologist outlined the region of cancer and assigned a Gleason score. The MRI results were blinded to the pathologist. In our studies, preoperative androgen deprivation therapy was performed in only one patient, whose preoperative serum PSA was 67.3ng/mL.

Image interpretation and data analysis

All images were retrospectively reviewed by a single radiologist with 13 years of experience of interpreting body MRI. The T2WI were initially reviewed. DWI and ADC maps were subsequently reviewed in conjuction with the T2-weighted images. For the purpose of radiologic-pathologic correlation, a region was considered positive for cancer if it contained a tumor with a cross-sectional area that was greater than 0.14cm2 for the specimens with a Gleason score of 6 or higher. Assuming an ellipsoid shape of the tumor and accounting for tissue shrinkage after fixation and processing (linear factor = 1.14), this was equivalent to a geometric mean diameter of 4 mm and an area of 0.13cm2 (Schned et al., 1996). In cases in which a sextant contained more than one tumor intersection, the largest one was used. The radiologist reviewed the pathologic specimens in conjuction with the MR images to spatially match tumors in each zone. Each pathological slice was visually matched to a corresponding MR image on the basis of the location of the ejaculatory ducts, diameter of the prostate, and approximate distance from the base of the apex. To be considered as a match, a tumor not only had to be in the same region from superior to inferior in the prostate but also to lie in the same anterior or posterior half of the prostate. All images were transferred to a workstation using digital imaging and communications in medicine format.

The sensitivity of MRI and positive predictive value (PPV) were calculated using pathologic results as the standard of reference. The concordance between MRI and pathologic findings was established on a lesion-by-lesion basis. True- and false positive findings on T2WI without and with DWI and ADC were compared using the Student's t test, with $p<0.05$ considered to denote significance.

Results

From pathologic study of the prostatectomy specimens, 83 lesions were found to have a Gleason score of 6 or more, 54 lesions (mean size: 14.1mm × 8.6mm; range 5 - 33mm × 5 – 26mm) of which contained tumors with an area of more than 0.14cm2 in 35 patients. Of 29 lesions with tumors 0.13cm2 or smaller, 25 (86.2%) had a Gleason score of 6, and 4 had a Gleason score of 7. On T2WI without and with DWI and ADC, 27 and 39 of the 54 lesions were correctly identified, respectively. The sensitivity of T2+DWI+ADC for prostate cancer detection was significantly better than that of T2WI alone (Table 2).

In a comparison between the PZ and TZ, both sensitivity and PPV were improved, particularly in the TZ. For cancers in the TZ, using a threshold score of 3+3 or greater, sensitivity was significantly higher for T2+DWI+ADC than for T2WI alone (Figure 1). Of the 35 patients, using all available clinical information (biopsy results including Gleason score, tumor location, percentage of positive biopsy cores, and the percentage of tumor-involved core tissue), concordance was found between the preoperative and postoperative staging in 25 patients (Table 3). Four of 29 patients diagnosed as cT2 were found to be pT3a in 1 patient and pT3b (seminal vesicle invasion) in 3 patients. Only 4 of the 35 patients (whose postoperative staging was pT3) demonstrated PSA recurrence and received postoperative adjuvant radiation therapy. Their biopsy positive cores were more than three in unilateral lobes or had more than 50% percentage tumor volume. In further retrospective reviews, 6 patients as cT2 and pT2 patients had positive SMs.

All the positive SM sites in the apex were tiny lesions (<4mm tumor diameter), and 2 of 6 patients had a positive SM in the posteriolateral margin. (This region was able to be detected by T2+DWI+ADC.) There is no universal consensus for NSRP; therefore, we performed an additional analysis using simplified clinically defined selection criteria (PSA level >15ng/mL, cT2, less than two positive biopsy scores in a unilateral lobe, less than 30% tumor volume, and a Gleason score of 6). Using this criteria, in the 12 chosen cT2 patients, we could

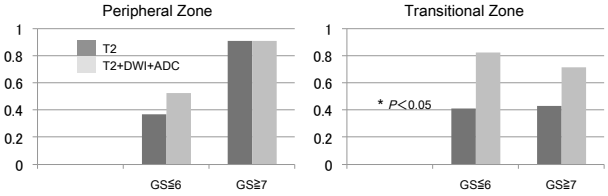

Figure 1. Detection Rate in Each Zone among Different MRI Methods Using a Gleason Score of 6 as the Threshold

Table 2. Differences in Prostate Cancer Detection among Different MRI Methods

		Lesion Number	True Positive	False Negative	False Positive	Sensitivity (%)	Positive Predictive Value (%)
T2WI	PZ	30	17	13	12	57	59
	TZ	24	10	14	4	42*1	71
	Overall	54	27	27	16	50*2	63
T2+DWI+ADC	PZ	30	20	10	5	67	80
	TZ	24	19	5	1	79*1	95
	Overall	54	39	15	6	72*2	87

T2WI, T2-weighted Omaging; DWI, Diffusion-Weghted Imaging; ADC, Apparent Diffusion Coefficient; PZ, Peripheral Zone; TZ, Transitional Zone

Table 3. Surgical Margin Status in 35 Patients

Clinical Stage	Pathological Stage	Surgical Margin	Pt. No.
cT1c	pT2	(+)	2
		(-)	1
	pT3	(+)	3
		(-)	0
cT2	pT2	(+)	6
		(-)	19
	pT3	(+)	3
		(-)	1

detect that the cancer foci were tend to proliferate to TZ from PZ by MRI combined T2WI+DWI+ADC, and the detection rate of NVB involvement by MRI combined T2WI+DWI+ADC maps was 100% in the 12 patients, and so it is considered that NSRP can be performed safely. Consequenly, the probability that the tumor is pathologically confined to the prostate is very high if a patient's condition suggests this preoperative criteria using DWI for NSRP.

Discussion

Several investigators have assessed the tumor detectability rendered with methods involving combined T2WI, dynamic imaging, and DWI. Kozlowski et al. reported that combining DWI with dynamic imaging yielded better sensitivity, with a small decrease in specificity for the differentiation between tumor and normal prostate tissue. In addition, Shimofusa et al. (Shimofusa et al., 2005) investigated combined MRI, including imaging of TZ cancer, and reported that combining T2WI and DWI facilitated improved tumor detectability: to 86% sensitivity and 84% specificity. Our present results are comparable to these results and indicate that high tumor detectability is achievable for prostate cancer.

Regarding tumor detectability in different areas of the prostate, sensitivity and specificity were lower for the TZ than for the PZ in T2WI. This could be partly because the signal intensity of prostate cancer on T2WI resembles that of the normal TZ. Due to the improvement of detection rates with T2WI and DWI and ADC, particularly in the TZ, we were able to detect tumor foci that mainly show proliferation towards the TZ from the PZ. Regions smaller than 4mm in tumor diameter were difficult to detect with the present MRI technique, but based on the selection criteria of this study, there is a high possibility of the detection of NBV involvement; and therefore, NSRP can be safely performed.

Serum PSA level, Gleason score, tumor volume, and perineural invasion have been studied in an effort to predict extracapsular disease. As serum PSA increases, so does the likelihood of ECE. Studies (Partin et al., 1993; Hudson et al., 1989) have shown that serum PSA levels higher than 10ng/mL were frequently associated with ECE (35%). Serum PSA levels higher than 30ng/mL were almost always associated with ECE in cases of PZ tumors. In our study, 2 of 9 patients (22.2%) with preoperative serum PSA levels higher than 15ng/mL displayed evidence of capsular perforation and/or seminal vesicle invasion. Tumor volume is also correlated with ECE and prognosis (McNeal et al., 1992; Epstein et al., 1993). Mc Neal et al demonstrated that capsular penetration was rare for tumors smaller than $4cm^3$, and almost all tumors larger than $12cm^3$ had extensive capsular penetration and a high incidence of positive SM. It is difficult to detect tiny tumor foci with MRI, but by combining T2, DWI, ADC, and preoperative systematic biopsy in addition to preoperative PSA level, our data suggest that the NVB can be safely preserved on a side without evidence of cancer in patients with low-and moderate-grade tumors.

High-grade tumors are less likely to be organ confined. Partin et al. evaluated 72 men with high-grade tumors (Gleason score 8, 9, or 10) and found that only 8% of these tumors were organ confined (Partin et al., 1994). Similarly, we observed ECE and/or seminal vesicle invasion in 20% of these tumors in 10 patients with high-grade tumors. Most posteriolateral ECE are thought to be spread by way of natural perineural tissue planes. It is believed that the perineural invasion seen in preoperative prostate biopsy specimens may reflect tumor involvement of NVB on the same side, but perineural invasion on preoperative biopsy was not addressed in this study. Bastacky et al. (1993) reported that the perineural invasion seen on preoperative biopsy specimens had a sensitivity of 27%, a specificity of 96%, and a PPV of 93% in predicting the presence of ECE. This may provide a promising adjunct to other clinical parameters for selecting candidates for NSRP.

Currently, the relevant surgical techniques remain difficult to perform, but LRP has offered better results than open RP in terms of urinary continence and erectile function recovery, with similar positive SM rates (Salomon et al., 2002; Gettman et al., 2006). Contemporary series have shown better outcomes according to transfusion rates and the length of catheter duration. In our study, 4 of 35 patients (11%) showed biochemical recurrence, but 2 of 4 patients may have not been indication for operation because of extremely high levels of preoperative serum PSA levels (33ng/mL and 67.26ng/mL in each patient). We have to reestimate the indication of LRP, but almost all the patients have survived over 2 years with a good outcome. An additional prospective study is needed to evaluate whether minimally invasive approaches provide distinct advantages over open surgery, but LRP has the advantage of improved magnification and lighting, which may facilitate dissection around the prostate apex and NVB. Therefore, in comparison to NSRP, the NSLRP procedure might result in a regression of the rate of positive SM especially on the posteriolateral aspect of the specimen and might increase the quality of life of low-risk patients using our selection criteria.

In this study, MR imaging was performed with a phased-array coil only rather than with a combination of a phased-array coil and an endorectal coil. Use of an endorectal coil yields a substantial increase in the signal-to-noise ratio (Hosseinzadeh et al., 2004), and DWI was performed using b factors of 0 and $800sec/mm^2$. Whether these are the most appropriate b factors for DWI of the prostate remains unclear. Further studies with various b factors and imaging sequence modifications are needed. Although NS modification can be applied to RP with

relatively low morbidity, it is clear that not all patients are candidates for this procedure. Our data suggest that in patients with low-grade tumors, NVB can be safely preserved, after having obtained less than two positive biopsy scores on the lesion side (in addition to the cancer volume being less than 30 %) without evidence of cancer involvement of the NVB on the basis of MRI findings. No safe subset for NS surgery could be identified for a side that shows no evidence of tumor foci on MRI or either side in the presence of high-grade disease on biopsy. Although some of the subsets are small, with cancer control as a primary goal, wide excision of the NVB would appear indicated on any side where a large volume cancer region is present in some cores at biopsy or bilaterally with high-grade disease on biopsy. The conclusion of our study is that pretreatment imaging and clinical estimation can assist treatment planning and the prediction of prognosis, which is clearly beneficial to both clinicians and patients. With this mind, it is important to further define reliable preoperative parameters that can be used to identify those patients that can safely undergo NSLRP without compromising cancer control.

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