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Original Article

Combining prostrate-specific antigen and Gleason score increases the diagnostic power of endorectal coil magnetic resonance imaging in prostate cancer pathological stage

Chih-Wei Tsao [a], Ming-Hung Lin [b], Sheng-Tang Wu [a], En Meng [a], Shou-Hung Tang [a], Hong-I Chen [a], Guang-Huan Sun [a], Dah-Shyong Yu [a], Sun-Yran Chang [a,c], Tai-Lung Cha [a,*]

[a] *Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC*
[b] *Division of Urology, Department of Surgery, Taichung Hospital, Taichung, Taiwan, ROC*
[c] *Taipei City Hospital, Taipei, Taiwan, ROC*

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Abstract

Background: The proper use of endorectal coil MRI (eMRI) images provide detailed information for the real extent of locally prostate cancer invasion and involvement of pelvic lymph nodes. This study evaluated the accuracy of endorectal coil magnetic resonance imaging (eMRI) results, combining the preoperative prostate-specific antigen (PSA), and the biopsy Gleason score to improve the diagnostic accuracy of prostate cancer (PCa) with organ-confined disease (OCD) or extracapsular extension (ECE)/seminal vesicle invasion (SVI).
Methods: Between 2001 and 2007, 94 PCa patients received eMRI testing during presurgical evaluation and underwent radical prostatectomy. As a part of routine patient workup, serum PSA level and Gleason score after pathology examination were recorded. The eMRI images were used to help assess patient PCa staging status regarding OCD or ECE/SVI. These stage assessments as evaluated through the use of MRI were compared with the final specimen pathological stage after the patients underwent radical prostatectomy.
Results: Of the total 94 patients in our study, 65 had stage pT2, 12 had stage pT3a, and 17 had stage pT3b PCa. In patients with clinical stage T2 PCa, the Gleason score significantly improved the discriminative ability of eMRI to successfully predict PCa at the OCD stage. Otherwise, in cases of clinical stage T3 PCa, accurate determination of PSA levels significantly improved eMRI predictive ability to assess ECE or SVI staging.
Conclusion: In clinical stage T2 PCa patients, integrating the biopsy Gleason score improved the discriminative ability to assess OCD PCa staging. Additionally, combining the preoperative PSA levels of clinical T3 prostate cancer cases with Gleason scores significantly improved the sensitivity and accuracy of eMRI diagnosis to distinguish ECE from SVI.

Keywords: endorectal coil magnetic resonance imaging; Gleason grade; prostate cancer; prostate-specific antigen

1. Introduction

Accurate staging is critical for the treatment and prognosis of patients with prostate cancer (PCa). The choice of an effective treatment modality for organ-confined disease (OCD) or locally advanced PCa remains controversial. If extracapsular extension (ECE) can be accurately identified before surgery, the ipsilateral neurovascular bundle can be either preserved to maintain organ function, or widely excised in order to prevent positive surgical margins. If seminal vesicle invasion (SVI) can be accurately identified, alternative treatments such as radiation therapy or hormone therapy may be preferable to surgical intervention. However, the current methods used to distinguish precisely between clinically OCD

* Corresponding author. Dr. Tai-Lung Cha, Division of Urology, Department of Surgery, Tri-Service General Hospital, 325, Section 2, Cheng-Gung Road, Neihu, Taipei 114, Taiwan, ROC.
E-mail address: tlcha@ndmctsgh.edu.tw (T.-L. Cha).

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and locally advanced PCa, with either ECE or SVI, are suboptimal. Endorectal coil magnetic resonance imaging (eMRI) offers the single most valuable imaging capability to assess OCD or locally advanced diseases. However, the accuracy of eMRI in evaluation of OCD or localized PCa has been varied. It has been shown that up to 40% to 50% of patients with clinically determined OCD PCa have, based on eMRI results, undergone radical prostatectomy, but were subsequently identified as having locally advanced diseases.[1−4] Conversely, about 20% to 25% of patients receiving radiotherapy or undergoing androgen deprivation therapy were overstaged by eMRI, and consequently lost the opportunity to undergo radical surgery to cure the disease.[5,6] In order to improve the diagnostic accuracy of eMRI in distinguishing OCD or ECE/ SVI, we investigated the diagnostic capability of eMRI testing by integrating preoperative prostate-specific antigen (PSA) level and patient Gleason score, to compare the final results of pathological examination with OCD or locally advanced prostate cancers.

2. Methods

Between January 2001 and October 2007, a total of 461 patients who came to our hospital were diagnosed with PCa. The indications of transrectal ultrasound prostate biopsies included elevated PSA, or a palpable nodule of the prostate. All patients underwent bilateral prostatic biopsies with an 18-gauge spring-loaded biopsy gun with 10 to 12 core biopsies. One-hundred and sixty patients underwent eMRI for staging. Based on clinical criteria (age, performance status, comorbidity, chest X-ray) and standard preoperative tests (PSA and bone scan), 94 of the 160 patients were selected for surgery, with a mean PSA level of 16.92 (0.12−107) ng/mL. The eMRI procedure was carried out using a 1.5 T MRI unit with T2- and T1-weighted images before and after gadolinium enhancement (Magnetom Vision 1.5T; Siemens, Munich, Germany). Written informed consent was obtained from all patients and the study protocol was approved by the appropriate ethics committees.

A low-signal-intensity lesion on T2-weighted images was regarded as the indicator for prostate neoplasm. The appearance of irregular contour deformity, asymmetry of the neurovascular bundles, and obliteration of the recto-prostatic angle were indicative of capsular penetration. Similarly, SVI presented as a low-signal-intensity infiltration of these structures; whereas on T2-weighted images of noninvasion, SVI presented with a bright signal as a result of the fluid content. In addition to postbiopsy lesion assessment, hematoma can be differentiated from prostate neoplasm by their corresponding appearance on T1-weighted eMRI.

In all cases, the waiting period between prostate biopsies and eMRI study was maintained at an interval of >6 weeks in order to reduce the likelihood of a false positive MRI study. None of the above PCa patients had received hormone or pelvic radiation therapy. Serum PSA levels and Gleason grades were recorded. All the eMRI images were interpreted by a single radiologist with expertise in the field of urology. All surgical interventions involving radical prostatectomy were completed no more than 2 weeks after eMRI studies were completed. The preoperative eMRI results were correlated with the final histopathological findings after patients underwent radical prostatectomy.

3. Results

Data were collected from a total of 94 consecutive patients with clinically localized PCa who underwent preoperative eMRI studies, and the correlation with the final staging assessments after pathological examination was analyzed. The average age of subjects was 68.9 (50−85) years. There were 58 patients included with clinical stage T2, 27 with clinical stage T3a, and nine with clinical stage T3b PCa. The final histopathological results showed that a total of 65 subjects were diagnosed with stage pT2, 12 with pT3a, and 17 with stage pT3b PCa (Table 1). The age distribution was not significantly different among different stage PCa. According to the diagnostic results of eMRI, the preoperative PSA levels and Gleason scores were statistically lower in pT2 than pT3a or pT3b PCa ($p < 0.001$). The sensitivity rates of eMRI in identifying OCD, ECE, and SVI were 63.08%, 25.0%, and 35.29%, respectively. The specific rates of eMRI in distinguishing OCD, ECE, and SVI were 41.38%, 70.73%, and 96.10%, and the accuracy in differentiating OCD, ECE, and SVI were 56.38%, 68.09%, and 85.11%, respectively.

The patients were divided into three groups—those with cT2, cT3a, and cT3b PCa cases—according to the eMRI diagnosis. The preoperative Gleason grade and serum PSA were investigated as to enhance the prognostic efficiency of eMRI for differentiation of localized and locally advanced PCa (Table 2). Of the preoperatively diagnosed cT2 PCa, 70.69% (41/58) cases were later proved to be pT2 stage, and 29.31% (17/58) as pT3 stage, which meant that 29.31% of the cases were understaged by a single imaging tool (eMRI). In the cT3a PCa cases, 77.78% (21/27) were later proved to be pT2 as OCD, 11.11% (3/27) to be pT3a as ECE, and 11.11% (3/27) to be pT3b as SVI. Most cT3a PCa cases diagnosed by eMRI were overstaged. In other cT3b PCa cases, 33.33% (3/9) were diagnosed to be pT2 as OCD and 66.7% (6/9) to be pT3b as SVI. The proportion of cT3b PCa cases overstaged by the diagnostic tool of eMRI was 33.33%.

Table 1
Characteristics of 94 PCa between preoperative eMRI diagnosis and postoperative pathologic stage.

Preoperative parameter	Pathologic finding			p
	T2 ($n = 65$)	T3a ($n = 12$)	T3b ($n = 17$)	
Mean age (y)	67.60 ± 7.40	73.25 ± 6.40	64.80 ± 7.10	0.583
PSA (ng/mL)	12.08 ± 8.61	20.85 ± 18.61	33.32 ± 30.00	<0.01
Gleason grade	3.12 ± 0.65	3.50 ± 0.80	3.82 ± 0.88	<0.01
Gleason score	6.42 ± 1.20	7.42 ± 1.44	7.41 ± 1.62	<0.01
MRI finding				<0.01
T2	41/58 (70.7)	9/58 (15.5)	8/58 (33.3)	
T3a	21/27 (77.78)	3/27 (11.1)	3/27 (11.1)	
T3b	3/9 (33.3)	0/9 (0)	6/9 (66.7)	

Table 2
Comparisons of PSA level and Gleason grade in the diagnostic power of PCa pathologic stage between cT2 and cT3 patients.

	Pathologic finding		p
	pT2 *n* (%)	pT3 *n* (%)	
cT2 patients ($n = 58$)			
PSA level			
<10	22 (53.7)	9 (52.9)	0.512
≥10	19 (46.3)	8 (47.1)	
<15	30 (73.2)	10 (58.8)	0.354
≥15	11 (26.8)	7 (41.2)	
<20	37 (90.2)	13 (76.5)	0.334
≥20	4 (9.8)	4 (23.5)	
Gleason grade			0.001
≤3	37 (90.2)	8 (47.1)	
>3	4 (9.8)	9 (52.9)	
Gleason score			0.138
≤7	37 (90.2)	12 (70.6)	
>7	4 (9.8)	5 (29.4)	
cT3 patients ($n = 36$)			
PSA level			
<10	10 (41.7)	0 (0)	0.015
≥10	14 (58.3)	12 (100)	
<15	15 (62.5)	1 (8.3)	0.004
≥15	9 (37.5)	11 (91.7)	
<20	19 (79.2)	2 (16.7)	0.001
≥20	5 (20.8)	10 (83.3)	
Gleason grade			0.081
≤3	16 (66.7)	4 (33.3)	
>3	8 (33.3)	8 (66.7)	
Gleason score			0.148
≤7	17 (70.8)	5 (41.7)	
>7	7 (29.2)	7 (58.3)	

In the cT2 PCa patients, eMRI results in conjunction with the Gleason grade from biopsy report had statistically significant correlation with the pathologic stages ($p = 0.002$). However, the same population integrating preoperative PSA level showed no statistical relationship between the eMRI findings and final pathological stages. On the other hand, in the cT3a/cT3b PCa cases, the preoperative PSA levels, but not the Gleason grade, revealed a statistically significant correlation between eMRI findings and final pathologic stages, respectively (Table 3; $p = 0.032$, $p = 0.012$). In cT3a and cT3b PCa cases with PSA levels above 20 ng/ml and 15 ng/ml, respectively, the eMRI findings significantly correlated with the final pathological stages. These parameters were compared to improve the eMRI diagnostic accuracy involving capsule invasion. The area under receiver operating characteristic curves of the Gleason score and grade had a larger area than the PSA level, with statistical significance in the clinical T2 stage. However, the under receiver operating characteristic curve area of PSA has a significantly larger area than Gleason score and grade in the clinical T3 stage (T3a and T3b) cases (Fig. 1; Tables 4a–4b).

For patients with cT2 PCa, combining the parameters of Gleason Grade ≤3 with the eMRI findings improved the sensitivity of the staging capability of eMRI from 63.08% to 90.24% ($p = 0.004$), specificity from 41.38% to 52.94% ($p = 0.65$), and accuracy from 56.38% to 82.76%

Table 3
Comparisons of different cutoffs of PSA in diagnosis of the pathologic stage between cT3a and CT3b PCa.

	Pathologic finding			p
	T2 *n* (%)	T3a *n* (%)	T3b *n* (%)	
cT3a patients ($n = 27$)				
PSA level				
<10	9 (42.9)	0 (0)	0 (0)	0.058
≥10	12 (57.1)	3 (100)	3 (100)	
<15	12 (57.1)	1 (33.3)	0 (0)	0.087
≥15	9 (42.9)	2 (66.7)	3 (100)	
<20	16 (76.2)	1 (33.3)	1 (33.3)	0.032
≥20	5 (23.8)	2 (66.7)	2 (66.7)	
cT3b patients ($n = 9$)				
PSA level				
<10	1 (33.3)	0 (0)	0 (0)	0.333
≥10	2 (66.7)	0 (0)	6 (100)	
<15	3 (100)	0 (0)	0 (0)	0.012
≥15	0 (0)	0 (0)	6 (100)	
<20	3 (100)	0 (0)	0 (0)	0.012
≥20	0 (0)	0 (0)	6 (100)	

($p = 0.007$). For patients with cT3a PCa, we also noticed that using 10 ng/ml of preoperative PSA as a cut-off significantly increased the sensitivity of eMRI from 25% to 100% but specificity and accuracy were compromised. In cT3b patients with preoperative serum PSA levels above 15 ng/ml, the eMRI showed high sensitivity (100%), specificity (100%), and accuracy (100%). Overall, for the patients with cT3 PCa, combining the PSA level above 15 ng/ml to improve the sensitivity of eMRI diagnoses from 41.38% to 91.7% ($p = 0.004$), specificity from 63.08% to 62.5% ($p = 0.96$), and accuracy from 56.38% to 72.2% ($p = 0.099$). In the same population, combining the PSA level above 20 ng/ml with the eMRI findings improved sensitivity from 41.38% to 83.33% ($p = 0.035$), specificity from 63.08% to 79.17% ($p = 0.237$), and accuracy from 56.38% to 80.56% ($p = 0.019$).

4. Discussion

Accurate staging of PCa is crucial for guiding appropriate definitive treatment. Endorectal coil MRI is one of the most effective pre-treatment staging methods available for distinguishing between clinically localized and locally advanced prostate cancers. MRI can accurately detect locally advanced prostate cancer in 56% to 86% of cases.[7–12] Factors responsible for this variation may include patient population size, use of an endorectal coil, MR sequences, and reader experience.[13] Our study was conducted to survey the comparisons between eMRI results and final pathologic stages by integrating the Gleason grade from biopsies and serum PSA levels.

One of the pivotal factors contributing to the accuracy of MRI detection in PCa is tumor size. Typically, tumor size is related to the risk of extracapsular spread,[14] relapse after radical prostatectomy[15] and PSA progression[16]: the larger the tumor, the higher the risk of treatment failure. Previous studies have shown

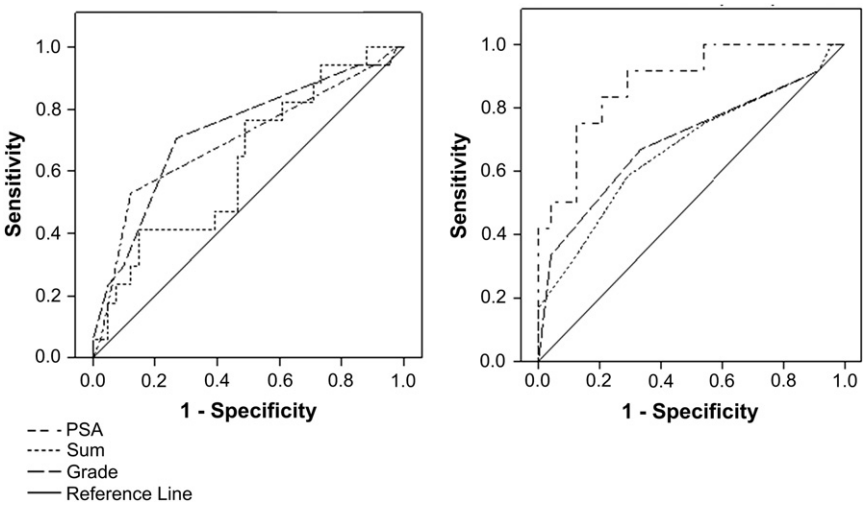

Fig. 1. The receiver operating characteristic curve of clinical stage T2 (left) and T3 (right) patients.

that 89% of tumors <0.5 cm^3 in diameter have a Gleason score of ≤6.[17] Such tumors are likely to be indolent. This suggests that the tumor size cutoff of 4 mm in diameter is sufficient to detect significant cancers in a large proportion of patients.[16,17]

Most errors reported in assessing ECE by eMRI have been false-negative results that occur because microscopic penetration of the capsule is identified when pathology results are reviewed, but cannot ultimately be detected by eMRI. However, PCa with microscopic penetration of the capsule without SVI or positive surgical margin might not differ from pathologically diagnosed OCD treated with radical prostatectomy[8,9] in the disease-free survival rate. In 36 patients, capsular thickening, bulging, and minimal irregularity were interpreted as possible capsular penetration or seminal vesicle involvement. However, upon review of final pathology results, only 12 patients were identified as ECE or SVI (sensitivity 33%). Importantly, the necessity to obtain a highly specific diagnosis precludes the type of less-rigorous 'possible T3' sometimes diagnosed by eMRI, and is highly beneficial in helping patients avoid undergoing neurovascular bundle preservation prostatectomy.

Previous studies found that eMRI had a low sensitivity and accuracy for predicting locally advanced PCa. Our analyses showed that the sensitivity, specificity, and accuracy of eMRI was 25%, 70.73%, and 68.09% for cT3a PCa; and 35.29%, 96.1%, and 85.11% for tumors at the cT3b stage. The eMRI was limited in its ability to distinguish microscopic invasion of prostate cancer.

Our study also found a low sensitivity and accuracy of eMRI diagnoses for the prediction of locally advanced PCa, similar to previously published studies. One explanation for the low sensitivity of eMRI for cT3 stage tumors may be associated with the difficulty in detection of microscopic invasion. We combined the preoperative serum PSA with the eMRI for the diagnoses of cT3 stage tumors, and successfully improved imaging sensitivity from 41.38% to 83.33% ($p = 0.035$) and accuracy from 56.38% to 80.56% ($p = 0.019$).

For patients with cT3 PCa, it is generally accepted that radiation therapy, with or without hormonal therapy, should be considered as first line intervention. Recently, surgical treatment has been employed for selected cases with a low risk of advanced disease. Accurate preoperative staging could also assist urologists in deciding whether or not to preserve the neurovascular bundles.

In our prospective study, the sensitivity, specificity, and accuracy (63.08%, 41.38%, and 56.38%) of eMRI diagnoses for cT2 PCa were unsatisfactory. Of PCa patients who were predicted to have OCD tumors, 29.31% (17/58) were proven to be stage pT3 PCa. Additionally, the Gleason grade of prostate biopsies were significantly higher than those subjects with pT2 tumors, but PSA level was not statistically different between pT2 and pT3 PCa patients. Integrating the Gleason grade from prostate biopsy significantly improved the sensitivity (90.24%, $p = 0.004$) and accuracy (79.31%, $p = 0.007$) of eMRI diagnoses in cT2 stage tumors.

It is interesting to note that each parameter varied in importance, depending upon the clinical stage analysed. The Gleason grade from prostate biopsy is important for cT2 PCa, but not for cT3 tumors. Otherwise, the preoperative PSA levels

Table 4a
Area under the receiver operating characteristic curve in clinical stage T2.

	Area	Standard error	*p*	95% confidence interval
PSA	0.631	0.079	0.118	0.476–0.787
Gleason score	0.727	0.077	0.007	0.577–0.878
Gleason grade	0.699	0.082	0.018	0.538–0.860

Table 4b
Area under the receiver operating characteristic curve in clinical stage T3.

	Area	Standard error	*p*	95% confidence interval
PSA	0.878	0.059	<0.001	0.763–0.994
Gleason score	0.668	0.102	0.104	0.469–0.868
Gleason grade	0.694	0.102	0.060	0.494–0.895

play a much more important role for the diagnoses in cT3 PCa, but not for the cT2 tumors. The working hypothetical theory indicated that locally advanced PCa patients initially have higher levels of PSA, and play a key role in improving the discriminative ability of eMRI to predict ECE or SVI. However, the PCa subjects of clinical OCD have no significant preliminary PSA levels, so pathological factors such as Gleason score were pivotal in improving the clinical diagnostic ability of eMRI. The recent study of Roethke et al concluded that eMRI is effective in predicting ECE in an intermediate to high-risk group,[18] which is in accordance with our result. The eMRI can more reliably predict locally advanced PCa compared with pelvic phase-array MRI at 1.5 T scan.[19,20] To date, no endorectal coil is available for 3 T imaging; 1.5 T scan using combined endorectal coil is still the most effective for PCa, and is equal to the pelvic phase-array MRI at 3 T scan.[14,15,20−23] In combination with preoperative parameters, including PSA and the Gleason score from prostate biopsy may offer the better predictive value of eMRI diagnoses in OCD or locally advanced PCa.

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