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Low-risk Prostate Cancer Patients Without Visible Tumor (T1c) On Multiparametric MRI Could Qualify for Active Surveillance Candidate Even If They Did Not Meet Inclusion Criteria of Active Surveillance Protocol

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Introduction: We compared the pathologic outcomes of prostate cancer patients who did not qualify for active surveillance according to the tumor visibility on multiparametric magnetic resonance imaging.
Material and methods: We retrospectively analyzed 464 prostate cancer patients who underwent multiparametric magnetic resonance imaging before radical prostatectomy between 2006 and 2012. All the patients had clinically localized prostate cancer with Gleason score $\leq$6 and prostate-specific antigen $\leq$10 ng/ml. Of these patients, 238 were eligible for active surveillance (group A) and 226 were not. We divided these 226 patients into two groups according to the result of multiparametric magnetic resonance imaging: 59 (26.1%) patients without visible tumor (group B) and 167 (73.9%) patients with visible tumor (group C). We evaluated the pathologic outcomes of organ-confined Gleason $\leq$6 disease and unfavorable disease in each group.
Results: The proportions of organ-confined Gleason $\leq$6 disease and unfavorable disease were 63.9 and 11.3% in group A, 59.3 and 10.2% in group B, and 38.9 and 22.8% in Group C. Comparing group A and B, these proportions were not statistically different ($P = 0.549$ and $P = 1.000$, respectively). However, comparing group A and C, those were significantly different ($P < 0.001$ and $P = 0.002$, respectively). In multivariate logistic regression analysis, no visible tumor on multiparametric magnetic resonance imaging was an independent predictor of organ-confined Gleason score 6 disease (odds ratio 0.426, $P = 0.007$) but there was no statistically independent predictor for unfavorable disease.
Conclusions: The tumor visibility on multiparametric magnetic resonance imaging could be a predictor of favorable disease for the prostate cancer patients who did not meet active surveillance criteria. Multiparametric magnetic resonance imaging could help to determine treatment modality for the low-risk prostate cancer patients who consider active surveillance even if they did not meet active surveillance criteria.

Key words: low-risk prostate cancer – magnetic resonance imaging – active surveillance

INTRODUCTION

The increase in diagnosis of low-risk prostate cancer due to widespread prostate-specific antigen (PSA) screening triggered the investigation for an alternative treatment with fewer morbidities and complications than radical prostatectomy (RP). To this end, active surveillance (AS) was recently developed (1–5). Ideal candidates for AS are low-risk prostate cancer patients with insignificant prostate cancer. And also, low-risk prostate cancer patients with organ-confined Gleason score $\leq$6 disease could be AS candidates considering the indolent quality of prostate cancer (6,7). To identify AS candidates, several investigators developed their own methods, which have been independently validated and compared with regard to effectiveness (1–5).

Current patient inclusion criteria for AS programs are typically based on the profiles of prostate biopsy result, prostate-specific antigen (PSA), PSA density (PSAD) and clinical staging. According to the pathologic results of RP specimens of AS candidates, the diagnostic accuracy was similar between AS protocols (8,9). However, urologist frequently experienced the low-risk prostate cancer patients who had insignificant prostate cancer or organ-confined Gleason score $\leq$6 disease after RP even if they did not meet the AS protocols.

To overcome this misclassification according to typical AS inclusion criteria, multiparametric-MRI (MP-MRI) was received attention recently. Several investigators reported that MP-MRI might help to predict tumor size, tumor aggressiveness and also to select AS candidates (10–14). Taken these recent results together, we supposed that simple tumor visibility on MP-MRI could help to identify the misclassified AS candidates who has favorable prostate cancer among prostate cancer patients who did not meet AS criteria. The aim of present study is to identify whether MP-MRI could help to predict organ-confined Gleason score $\leq$6 disease among the non-AS criteria according to tumor visibility.

PATIENTS AND METHODS

We reviewed the records of 464 prostate cancer patients who underwent MP-MRI before RP between 2006 and 2012. All the patients had clinically localized Gleason score 6 prostate cancer with preoperative prostate-specific antigen (PSA) $\leq$10 ng/ml. And they had complete medical records including prostate biopsy profiles. We stratified these patients according to AS protocol as defined by Prostate Cancer Research International: Active Surveillance (PRIAS). The inclusion criteria of PRIAS includes: Gleason score $\leq$6 on biopsy, clinical stage T1c-T2, PSA $\leq$10 ng/ml, PSAD $\leq$0.2 ng/ml/cm^3 and no more than two positive cores. We used the PRIAS protocol to select AS candidates because our previous analyses show that this protocol is the most helpful in our cohort (9). Among them, we identified 238 (51.3%) patients who met the AS criteria and defined these patients as group A. The remaining 226 (48.7%) patients who did not meet AS criteria; 89 patients did not meet AS criteria due to number of positive biopsy cores, 84 patients due to PSAD and 53 patients due to both criteria. We divided these 226 non-AS candidates into two groups according to the presence of visible tumor on MP-MRI: 59 (26.1%) patients had no visible tumor (group B), and 167 (73.9%) patients had visible tumor (group C).

For clinical staging, all patients were imaged using a 3.0-T MRI system (Intera Achieva 3.0 T, Phillips Medical System, Best, The Netherlands), equipped with a phased-array coil (six-channel). All patients underwent diffusion-weighted (DW) MRI in addition to the routine prostate MRI protocol of our institution. Two *b* values (0–1000) were used, and the restriction of diffusion was quantified by apparent diffusion coefficient mapping. T_2-weighted (T2W) turbo spin-echo images were acquired in three orthogonal planes (axial, sagittal and coronal), and dynamic contrast-enhanced MRI (DCE-MRI) was also obtained. The average period between prostate biopsy and MRI was 27.4 $\pm$ 19.1 days. All images were reviewed by two experienced uroradiologists who were blinded to the pathologic results. Patients who were suspected extraprostatic extension (ECE) and/or seminal vesicle invasion on MP-MRI, were excluded from study cohort even if they had normal digital rectal examination finding.

We collected the following clinicopathologic outcomes: age, prostate volume, preoperative PSA, PSAD, number of total biopsy cores, number of positive biopsy cores, maximal tumor diameter on MP-MRI, postoperative Gleason score, pathologic stage, ECE, SVI, tumor volume and biochemical recurrence (BCR).

To compare the clinicopathologic outcomes, the chi-square test and independent *t*-test were used for statistical comparison of categorical and continuous variables, respectively. To assess the efficacy of tumor visibility on MP-MRI to reclassify AS candidate among non-AS group (groups B and C), we compared the proportion of organ-confined Gleason score $\leq$6 disease and unfavorable disease with those of AS candidate (group A) as the standard criteria. Unfavorable disease features were defined as prostate cancer with postoperative Gleason score 8–10 and/or ECE and/or SVI. Multivariate logistic regression analysis was performed to identify predictors for organ-confined Gleason score $\leq$6 disease and unfavorable disease features in the RP specimens. The actual risk of BCR was calculated using the Kaplan–Meier method. All statistical analyses were performed using SPSS v.18.0 software (SPSS, Chicago, IL, USA). A *P* value of $\leq$0.05 was considered statistically significant.

RESULTS

The baseline characteristics of patients are shown in Table 1. Among 464 prostate cancer patients, the mean preoperative

Table 1. Baseline patient characteristics of active surveillance (AS) candidates (group A), non-AS candidates without visible tumor on MP-MRI (group B), non-AS candidates with visible tumor on MP-MRI (group C)

	Group A		Group B	Group C	*P* value
No. of patients	238		59	167	
Age	63.6 ± 6.9		61.9 ± 7.5	63.5 ± 7.2	0.158[a]
PSA	5.32 ± 1.6		5.74 ± 1.9	6.48 ± 1.7	0.009[a]
Prostate volume	42.9 ± 15.7		30.3 ± 11.7	30.5 ± 10.7	0.916[a]
PSA density	0.13 ± 0.04		0.20 ± 0.07	0.23 ± 0.09	0.012[a]
MRI result	No visible tumor	Visible tumor	–	–	–
	76	162	–	–	–
Maximal tumor diameter (mm)	–	14.2 ± 6.8	–	16.6 ± 7.9	0.004[b]
No. of biopsy cores	11.8 ± 2.4		11.6 ± 2.6	11.6 ± 1.7	0.998[a]
No. of positive cores	1.35 ± 0.5		3.00 ± 1.9	3.43 ± 2.2	0.152[a]

MRI, magnetic resonance imaging; PSA, prostate-specific antigen.
[a]Group B versus group C.
[b]Group A and group C.

PSA was 5.79 ng/ml and the mean PSAD was 0.18 ng/ml/cm^3. In overall study cohort, no visible tumor on MP-MRI was found in 135 (29.1%) patients and 329 (70.9%) patients had visible tumor. Among AS candidates, 76 of 238 (31.9%) had no visible tumor on MP-MRI. Comparing the clinical parameters between non-AS groups (group B and group C), preoperative PSA and PSAD were significantly different. The mean preoperative PSA was 5.74 ± 1.9 ng/ml in group B and 6.48 ± 1.7 ng/ml in group C ($P = 0.009$), and the mean PSAD was 0.20 ± 0.07 in group B and 0.23 ± 0.09 in group C ($P = 0.012$). However, there were no statistically significant differences in age, prostate volume, number of positive biopsy cores between two groups. To compare maximal diameter of visible tumor on MP-MRI, we compared visible tumors between group A and group C. Group A had a smaller tumor diameter than group C (14.2 ± 6.8 versus 16.6 ± 7.9 mm, $P = 0.004$).

Table 2 shows the pathologic outcomes according to tumor visibility on MP-MRI in AS candidates (group A). In group A, the proportion of organ-confined Gleason score ≤6 disease and unfavorable disease features were 67.1 and 11.8% in AS candidates who had no visible tumor and 62.3 and 11.1% in AS candidates who had visible tumor. These proportions were not significantly different ($P = 0.476$ and $P = 0.868$). However, tumor volume was significantly smaller in AS candidates without visible tumor than those with visible tumor (0.61 ± 0.81 versus 0.98 ± 1.05, $P = 0.007$).

In the overall study cohort, the proportion of organ-confined Gleason score ≤6 disease and unfavorable disease features were 54.3 and 15.3% (Table 3). Comparing between group A and group B, there were no statistical differences in the distribution of postoperative Gleason scores, pathologic stages, tumor volume, organ-confined Gleason ≤6 disease and unfavorable disease features. However, comparing between group A and group C, there were statistical differences in the distribution of postoperative Gleason scores, pathologic stages, tumor volume. And the proportion of organ-confined Gleason ≤6 disease and unfavorable disease were also significantly different (63.9 versus 38.9%, $P < 0.001$ and 11.3 versus 22.8%, $P = 0.002$). After a mean postoperative follow-up of 30 months, a log-rank test of the Kaplan–Meier survival curves demonstrated no significant difference in overall BCR rate across each groups (Fig. 1, log rank $P = 0.500$).

Table 2. Comparison of pathologic outcomes according to tumor visibility on MP-MRI among AS candidates (group A)

	No visible tumor	Visible tumor	*P* value
Postoperative Gleason score			
≤6	55	110	0.713
7	20	48	
8–10	1	4	
Pathologic stage			
pT2	68	145	0.994
pT3	8	17	
Extracapsular extension	8 (10.5%)	16 (9.9%)	0.877
Seminal vesicle invasion	0 (0.0%)	1 (0.6%)	0.492
Tumor volume	0.61 ± 0.81	0.98 ± 1.05	0.007
Organ-confined Gleason score 6 disease	51 (67.1%)	101 (62.3%)	0.476
Unfavorable prostate cancer	9 (11.8%)	18 (11.1%)	0.868
Biochemical recurrence	4 (5.3%)	14 (8.7%)	0.358

Table 3. Comparison of pathologic outcomes between overall AS candidates (group A), non-AS candidates without visible tumor on MP-MRI (group B), non-AS candidates with visible tumor on MP-MRI (group C)

	Group A	Group B	Group C	*P* value*	*P* value**
Postoperative Gleason score					
≤6	165	36	82	0.426	<0.001
7	68	22	80		
8–10	5	1	5		
Pathologic stage					
pT2	213	54	130	0.643	0.001
pT3	25	5	37		
Extracapsular extension	24 (10.1%)	5 (8.5%)	33 (19.8%)	0.709	0.006
Seminal vesicle invasion	1 (0.4%)	0 (0.0%)	4 (2.4%)	0.618	0.076
Tumor volume	0.81 ± 0.78	0.93 ± 0.85	1.66 ± 1.33	0.959	<0.001
Organ-confined Gleason score 6 disease	152 (63.9%)	35 (59.3%)	65 (38.9%)	0.549	<0.001
Unfavorable prostate cancer	27 (11.3%)	6 (10.2%)	38 (22.8%)	1.000	0.002
Biochemical recurrence	18 (7.5%)	5 (8.5%)	16 (9.7%)	0.788	0.473

**P* value, group A versus group B.
***P* value, group A versus group C.

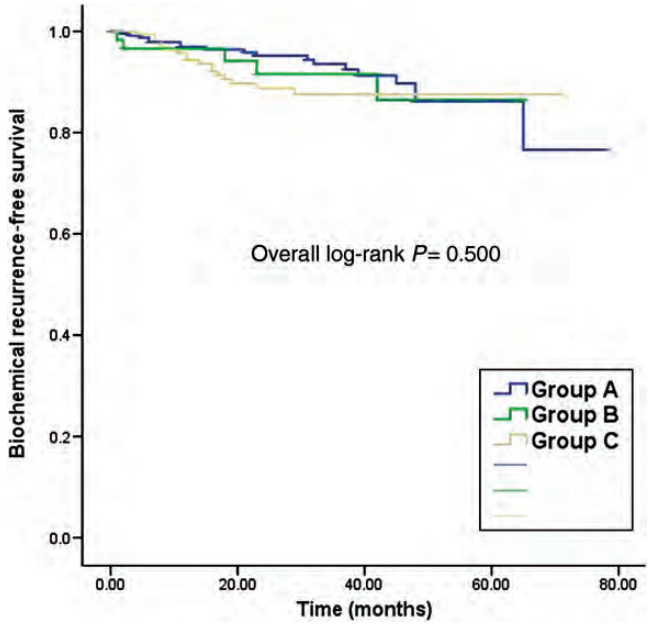

Figure 1. Comparison of Kaplan–Meier biochemical recurrence-free survival curves among the three groups after radical prostatectomy. Active surveillance (AS) candidates (group A), non-AS candidates without visible tumor on MP-MRI (group B), non-AS candidates with visible tumor on MP-MRI (group C).

Using multivariate logistic regression analysis to predict pathologic appearance in the non-AS candidates (group B and C) according to the tumor visibility on MP-MRI, we found that no visible tumor on MP-MRI was an independent predictor of organ-confined Gleason score ≤6 disease (odds ratio = 0.426, $P = 0.007$). However, no preoperative parameter was an independent predictor of unfavorable disease features. Even though there was no statistically significance, PSAD had higher odds ratio than other preoperative parameters (Table 4).

Table 4. Multivariate logistic regression analysis to predict organ-confined Gleason score ≤6 disease and unfavorable disease features using preoperative variables in the non-AS candidates

	Organ-confined Gleason ≤6 disease		Unfavorable prostate cancer[a]	
	Odds ratio	*P* value	Odds ratio	*P* value
Age	1.011	0.569	1.008	0.500
PSA	0.980	0.831	0.903	0.401
PSA density	1.329	0.880	58.385	0.070
MRI result				
No visible tumor	Ref.	–	Ref.	–
Visible tumor	0.426	0.007	2.527	0.053
No. of positive cores	0.999	0.993	0.963	0.666

[a]Extracapsular extension and/or seminal vesicle invasion and/or Gleason score 8–10.

DISCUSSION

The increasing incidence of low-risk prostate cancer is an ongoing worldwide phenomenon, and the increased number of diagnoses of clinically localized prostate cancer is remarkable in comparison with the number in past decades (15). Using definitive therapy such as RP, clinically localized prostate cancer might be curatively treated, especially in

low-risk prostate cancer patients. However, for the low-risk prostate cancer patient with insignificant prostate cancer, RP is obviously an overtreatment considering the morbidities, postoperative complications and the oncologic features of insignificant prostate cancer. Considering the long-term follow-up result of AS, it could be one of the treatment options for low-risk prostate cancer patients (6).

To reduce overtreatment of these patients, several investigators have promoted their AS programs (1–5). Several AS protocols were developed with clinical results based on their study cohort and the predictive accuracy for organ-confined Gleason $\leq$6 disease and insignificant prostate cancer were not bad and quite similar according to their inclusion criteria (8,9). Nevertheless, the dilemma of AS is still how to select the ideal candidates more accurately. To select the ideal AS candidates is important in the aspect of oncological safety of AS. However, it is also important to reduce the number of misclassified AS candidates who had favorable disease among the patients who did not meet the AS inclusion criteria in the aspect of the benefits of AS. In clinical practice, we frequently experienced that the patients who had organ-confined Gleason $\leq$6 disease including insignificant prostate cancer among the low-risk prostate cancer patients who excluded from AS inclusion criteria. So, many urologists believe that typical AS inclusion criteria are not insufficient to identify AS candidates and have tried to investigate ways to improve the accuracy of patient selection for AS. For these reasons, the effectiveness of MP-MRI has been a focus of current studies.

Prostate MRI has significant value for the identification of ECE and SVI (16–18). However, these benefits were primarily seen in intermediate- and high-risk prostate cancer patients, and the role of MRI for low-risk prostate cancer patients was unclear (19). Several investigators raised variety of opinions about the efficacy of MRI for low-risk prostate cancer patients. Vargas et al. (20) reported that tumor visualization on T2W-MRI could help to assess eligibility for AS. However, Guzzo et al. (21) concluded that tumor visibility on T2W-MRI is not predictive of pathologic feature at RP specimens, and that T2W-MRI could not provide additional information for the selection of AS candidate. And also, Ploussard et al. (22) concluded that T2W-MRI did not improve the prediction of unfavorable prostate cancer under the extended 21-core biopsy scheme. However, these articles were based on the findings of T2W-MRI. The authors discussed additionally that other MRI techniques such as MP-MRI including DW-MRI, MR spectroscopy might improve the prediction of pathologic outcomes for AS.

With the technical advantages of MRI, the recent studies with MP-MRI had received new consideration in low-risk prostate cancer. Delongchamps et al. (12) concluded that MP-MRI could help predict tumor size and bilateral tumor in unilateral low-risk prostate cancer patients. Furthermore, Turkbey et al. (13) reported that MP-MRI could estimate index tumor volume and had better accuracy in prediction of prostate tumor volume larger than 0.5 cm^3 than other clinical variables. Rouse et al. (23) also reported that MP-MRI could rule in and rule out clinically significant prostate cancer in men at risk prior to biopsy. Based on these recent findings, we supposed that low-risk prostate cancer patients who did not meet AS inclusion criteria would have different pathologic outcomes using tumor visibility on MP-MRI.

In the present study, no visible tumor (cT1c) on MP-MRI was an independent predictor for organ-confined Gleason score 6 disease among the non-AS candidates. Our result supports that MP-MRI could aid the identification of suitable candidates for AS and reduce the misclassification using typical AS inclusion criteria. However, one difference with other studies is that our concept of misclassification is to identify the low-risk prostate cancer patients who could be enrolled AS program among non-AS candidate who did not meet AS criteria. Some readers could raise a question why the present study focused on the effectiveness of MP-MRI to identify misclassified AS candidate among non-AS candidate. In fact, almost published literatures had attentions to increase predictive accuracy for organ-confined Gleason $\leq$6 disease and/or insignificant prostate cancer among the AS candidate. In these literatures, how to identify the unfavorable disease among the AS candidates for the predictive diagnostic accuracy is the main concern (20–23). However, we investigated it the other way round. Considering there were clearly considerable proportion of favorable disease patients among the non-AS candidates whether the AS inclusion criteria are stringent or lenient (8,9), it is also important to reclassify AS candidate among non-AS candidates.

Another possible question is the pathologic result of AS candidate who had visible tumor. The proportion of organ-confined Gleason $\leq$6 disease and unfavorable disease features in the AS candidates were not significantly different according to tumor visibility. A notable point to explain this finding is that the pathologic tumor volume was statistically different between AS candidate with visible tumor in group A and non-AS candidate with visible tumor (0.98 ± 1.05 versus 1.66 ± 1.33 cc, $P < 0.001$). This difference was also observed on MRI findings. The AS candidates had a smaller tumor diameter on MP-MRI than non-AS candidates (14.2 ± 6.8 versus 16.6 ± 7.9 mm, $P = 0.004$). Considering that AS programs were developed to identify favorable disease features with low Gleason score and low tumor volume, it is hardly surprising that group A patients would had more favorable disease features than group C patients even though both groups had visible tumor on MRI.

Recently, Margel et al. (14) reported that MP-MRI could help to predict disease reclassification among prostate cancer patients who elected to undergo AS. They performed MP-MRI and confirmatory prostate biopsy to identify disease progression. In this prospective study, they found that the patients who had no visible tumor on MP-MRI were more likely to maintain AS regardless of the confirmatory biopsy; however, those who had visible tumor were to be reclassified from AS program after the confirmatory biopsy. We believe that their conclusion has similar implications to

our findings. As the tumor visibility on MP-MRI was an important indicator for the reclassification among the low-risk prostate cancer patients who elected to undergo AS, it was also an important indicator for the prediction of organ-confined Gleason $\leq$6 disease among the non-AS candidates. Our finding could help urologists agonized the treatment modality between RP and AS for the low-risk prostate cancer patients who did not meet the AS criteria. Especially, for the patients who want AS even though they did not meet AS criteria, tumor visibility on MP-MRI would be helpful with close surveillance in the clinical practice.

Our study had several limitations. (1) Our study was retrospective design and (2) we simply analyzed MP-MRI with the simple tumor visibility. If we stratified visible tumors into more detailed size using maximal tumor diameters, we could gain more yields of MP-MRI from the study cohort about AS candidate selection. Actually, we started the analysis using maximal tumor diameters on MP-MRI and we could be able to report more meaningful findings on the role of MP-MRI in planning treatment for low-risk prostate cancer patients. However, to measure tumor diameters on MRI is difficult without accurate interpretation of well-experienced uroradiologist. So, we reported the efficacy of MP-MRI according to simple tumor visibility and we thought that this was meaningful. (3) The question could be raised whether the reclassification of AS candidates using MP-MRI among non-AS candidate by current AS protocol is needed. Frankly, the definite management would be needed for the non-AS candidate who excluded from AS protocols. However, as we mentioned above, we focused on the possibility of favorable disease among non-AS candidates in the aspect of increase of beneficiaries of AS. Within this concept, we emphasized that the non-AS candidate without visible tumor on MP-MRI would have one more options; AS.

In conclusion, our analysis suggests that low-risk prostate cancer patient who may not meet AS criteria but who have no visible tumor on MP-MRI could be selected as AS candidate with close surveillance. There were no significant differences in outcome between AS candidates and non-AS candidate without visible tumors. Therefore, we propose that the absence of visible tumor on MP-MRI may be reasonably used in a urologist's clinical decision when considering a patient for AS.

Conflict of interest statement

None declared.

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