

# Combination of clinical characteristics and transrectal ultrasound-guided biopsy to predict lobes without significant cancer: application in patient selection for hemiablativ focal therapy

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**Purpose:** A major limitation of performing hemiablativ focal therapy (FT) for prostate cancer (PCa) is the possibility of accompanying significant cancer in the contralateral side of the prostate that is missed on prostate biopsy. We attempted to verify whether clinical and biopsy-related parameters can be used to predict the absence of significant cancer in the prostate lobe.

**Methods:** We assumed that hemiablativ FT could be performed in patients with low-risk PCa, with unilateral tumors as assessed by transrectal ultrasound-guided biopsy. We evaluated 214 patients who had undergone radical prostatectomy (RP) and fulfilled the eligibility criteria. Seemingly preserved lobes, defined by the absence of cancer on biopsy, were classified as lobes with no cancer (LNC), lobes with insignificant cancer (LIC), and lobes with significant cancer (LSC) according to RP pathology. Cases with an estimated tumor volume of <0.5 mL, a Gleason score of <7, and organ confinement without Gleason pattern 4 were classified as LIC. Univariate and multivariate logistic regression analyses were performed to identify predictors for LSC. Predictive accuracies of the multivariate models were assessed using receiver operating characteristic curve-derived areas under the curve.

**Results:** Of 214 evaluated lobes, 45 (21.0%), 62 (29.0%), and 107 (50.0%) were classified as LNC, LIC, and LSC, respectively. Among the clinical and biopsy-related parameters, prostate-specific antigen density and prostate volume were identified as significant predictors for LSC in univariate regression analysis. However, multivariate analysis did not identify an independent predictor. Predictive accuracies of the multivariate models did not exceed 70.4%.

**Conclusions:** Conventional parameters have limited value in predicting LSC in patients who are candidates for hemiablativ FT.

**Keywords:** Prostatic neoplasms, Tissue preservation, Patient selection

## INTRODUCTION

In the era of prostate-specific antigen (PSA) measurement, prostate cancer (PCa) is increasingly being detected at an early stage and with a low risk, but the management of local-

ized PCa remains controversial because early detection and conventional treatment do not seem to be able to reduce mortality and improve the quality of life [1,2]. Radical whole gland surgery or radiation therapy can result in substantial side effects. Urinary incontinence (5%–20%), erectile dys-

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function (30%–50%), and bowel toxicity (5%–10%) are typical complications of radical treatment [3,4]. For the treatment of low-risk PCa, active surveillance (AS) can be a treatment option; however cancer-related anxiety is the major drawback to this course [5].

Focal therapy (FT) is receiving increasing attention as a middle ground between AS and radical treatment, to selectively eradicate localized PCa while preserving uninvolved structures to minimize treatment-related side effects [6-8]. Hemiablativ FT, which involves ablation of the entire half of the prostate associated with cancer, might be the most feasible and straightforward form of FT [9]. Hemiablativ FT can be used even in cases of bilateral PCa with a significant unilateral lesion and an insignificant lesion on the contralateral side. This is because the index lesion determines the clinical outcome, and the secondary lesions are unlikely to result in disease progression [10,11]. Some authors claim that FT targeting an index lesion alone may be sufficient when supplemented with AS for the untreated insignificant lesions [7,12,13].

For the performance of appropriate hemiablativ FT, the side contralateral to the ablated lobe is supposed to contain no significant lesions. We attempted to identify conventional prostate biopsy and clinical characteristics that could predict the presence of significant cancer in the seemingly preserved lobe, contralateral to the lobe with the index lesion.

## MATERIALS AND METHODS

Between January 2008 and October 2012, 1,140 men underwent RP for PCa at Seoul National University Bundang Hospital, Seongnam, Korea. Clinical data for these men had previously been entered into a prospectively maintained computerized database. After obtaining Institutional Review Board approval, we reviewed the data on 832 of these patients who had undergone prostate biopsy using a single technique at our institution. After the measurement of prostate volume, all patients underwent transrectal ultrasound (TRUS)-guided 12-core biopsy of the prostate. The prostate was biopsied at both sides near the base, midgland, and apex, with at least six biopsy specimens obtained per side. In cases of lesions suspicious for PCa based on TRUS, one or two additional targeted biopsy specimens were obtained. Low-risk patients (clinical stage  $\leq$  T2a; Gleason score [GS]  $\leq$  6; and PSA level  $<$  10 ng/mL) with a unilateral tumor as proven by TRUS biopsy were selected as candidates for hemiablativ FT. Of the 832 patients who underwent RP using a single technique, 310 had low-risk PCa, and of these 310 patients, 214 had unilateral tumors as proven by biopsy.

All biopsy and RP specimens were analyzed by a single genitourinary pathologist (G.C.), and RP specimens were processed according to the Stanford Protocol [14]. Tumor volume was measured by multiplying the X and Y diameters and tumor depth, which was calculated according to the thicknesses of subsequent sections that showed the presence of tumor, as previously described and validated [15,16]. We classified the preserved lobes as lobes with no cancer (LNC), lobes with insignificant cancer (LIC), and lobes with significant cancer (LSC) according to the RP pathologic reports. Using the Epstein criteria [17], cases with a total tumor volume accounting for all foci of  $<$ 0.5 mL, a GS of  $<$ 7, and organ confinement without Gleason pattern 4 on one side were classified as LIC. If the index tumor was located between both lobes, we considered it to be present on the preserved side. To evaluate the possibility of preserving one lobe of the prostate by performing hemiablativ FT, LNC or LIC was considered suitable for hemiablativ FT.

## 1. Statistical analyses

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean  $\pm$  standard deviation. Age, PSA level, percentage of positive cores among the total biopsy cores (% of positive cores), and the maximum percentage of tumor length in positive cores (% of tumor length) were entered into the models as continuous variables. Clinical T stage, PSA density (PSAD), and GS were treated as dichotomous variables. Logistic regression models were conducted for univariate and multivariate analyses to identify significant predictors of LSC. Receiver operating characteristic (ROC) curve-derived areas under the curve (AUCs) were calculated for each parameter in the multivariate model for estimating LSC. All statistical analyses were performed using IBM SPSS ver. 20.0 (IBM Co., Armonk, NY, USA). A two-tailed *P*-value of  $<$ 0.05 was considered significant for all analyses.

## RESULTS

The clinical and biopsy-related characteristics of patients are shown in Table 1. The mean patient age was  $65.14 \pm 6.82$  years. cT1b, cT1c, and cT2a disease were identified in 1 (0.5%), 174 (81.3%), and 39 patients (18.2%), respectively. The mean PSA level was  $5.56 \pm 1.20$  ng/mL, and the PSAD was  $0.16 \pm 0.08$  ng  $\cdot$  mL $^{-1} \cdot$  cm $^{-3}$ . The mean prostate volume was  $38.36 \pm 13.84$  cm $^3$ . Further, 159 (74.3%), 32 (15.0%), and 22 patients (10.3%) underwent 12-, 13-, and 14-core biopsy, respectively, and 126 patients (58.9%) showed only one positive core on TRUS-

guided biopsy. The percentage of positive cores was  $14.34\% \pm 10.01\%$ . The maximum core and tumor lengths were  $16.80 \pm 7.16$  and  $2.90 \pm 2.35$  mm, respectively, and the percentage of tumor length was  $17.95\% \pm 14.93\%$ .

Of the 214 preserved lobes, 45 (21.0%) were found to have no cancer and cancer was detected in the RP specimens of the other 169 lobes. The GS was  $\leq 3+3$  in 87 lobes (40.7%) and  $\geq 3+4$  in 82 lobes (38.8%). Nine lobes (4.2%) showed extra-prostatic extension, and 67 lobes (31.3%) had a tumor volume of  $\geq 0.5$  cm<sup>3</sup>. Accordingly, 45 (21.0%), 73 (34.1%), and 96 lobes (44.9%) were classified as LNC, LIC, and LSC, respectively (Table 2).

We examined the associations between clinical and biopsy-related variables and the lobe category. Of the clinical and biopsy-related parameters, GS was excluded from regression analysis because all patients showed a GS of 6 except for 1 who had GS of 5 based on the analysis of TRUS-guided biopsy specimens. Univariate logistic regression analysis showed

**Table 1.** Clinical and biopsy-related characteristics of the patients

Characteristic	Value
Age (yr)	65.14 ± 6.82
Body mass index (kg/m <sup>2</sup> )	24.35 ± 2.56
Clinical state	
≤T1c	175 (81.8)
T2a	39 (18.2)
PSA level (ng/mL)	5.56 ± 1.20
PSAD (ng · ml <sup>-1</sup> · cm <sup>-3</sup> )	0.16 ± 0.08
Prostate volume (cm <sup>3</sup> )	38.36 ± 13.84
Gleason score	
5	1 (0.5)
6	213 (99.5)
% of positive core	14.34 ± 10.01
% of tumor length	17.95 ± 14.93

Values are presented as mean ± standard deviation or number (%). PSA, prostate-specific antigen; PSAD, PSA density.

that PSAD and prostate volume were significant predictors of LSC, but multivariate analysis did not identify any parameter as an independent predictor (Table 3).

To estimate the predictive accuracy of each parameter for LSC, ROC curve-derived AUCs were calculated. AUCs for all parameters were less than 64%, the largest being for PSAD, at 63.9%. The predictive accuracy of a multivariate model, including age, PSAD, prostate volume, and the other variables mentioned here, for predicting LSC was 70.4% (Table 3). The predictive accuracies of other multivariate models incorporating age and PSAD with various combinations of the other variables were <70%.

## DISCUSSION

Recent studies including ours showed that 17%–22% of men undergoing RP have PCa confined to one side of the gland, although the populations in these studies were different [9,18,19]. In our cohort of 214 patients with low-risk PCa, 107 (55.1%) did not have significant cancer in the seemingly preserved side. Thus, a substantial proportion of men with

**Table 2.** Pathologic features of preserved lobes as assessed on the basis of the radical prostatectomy permanent report

Variable	Preserved prostate lobes
Gleason score	
≤3+3	87 (40.7)
≥3+4	82 (38.3)
Extraprostatic extension	9 (4.2)
Tumor volume ≥0.5 cm <sup>3</sup>	67 (31.3)
Lobe category	
LNC	45 (21.0)
LIC	73 (34.1)
LSC	96 (44.9)

Values are presented number (%).

LNC, lobe with no cancer; LIC, lobe with insignificant cancer; LSC, lobe with significant cancer.

**Table 3.** Univariate and multivariate logistic regression analysis for the prediction of lobes with significant cancer

Variable	Univariate			Multivariate		
	OR (95% CI)	P-value	AUC (%)	OR (95% CI)	P-value	AUC (%)
Age	1.03 (0.99–1.07)	0.19	54.3	1.04 (1.00–1.09)	0.06	
Body mass index	0.91 (0.82–1.01)	0.08	57.2	0.95 (0.84–1.07)	0.38	
Clinical stage (T2a vs. ≤T1c)	0.48 (0.23–1.01)	0.05	54.8	0.48 (0.22–1.04)	0.06	
PSA	1.09 (0.95–1.25)	0.21	56.1	1.07 (0.86–1.34)	0.55	
PSAD (≥0.15 vs. <0.15)	3.13 (1.79–5.48)	<0.01	63.9	1.95 (0.74–5.11)	0.18	
Prostate volume	0.97 (0.95–0.99)	0.03	63.2	0.97 (0.94–1.01)	0.13	
% of positive core	1.01 (0.98–1.04)	0.43	53.6	1.01 (0.98–1.04)	0.63	
% of tumor length	1.00 (0.98–1.02)	0.98	52.4	0.99 (0.97–1.02)	0.56	
Total						70.4

PSA, prostate-specific antigen; PSAD, PSA density; AUC, area under the curve; OR, odds ratio; CI, confidence interval.

clinically low-risk PCa can be treated with hemiablativ FT. Here, we attempted to identify the clinical and biopsy-related parameters that could predict the presence of pathologically significant cancer in the lobe contralateral to the side treated with ablation. However, no independent predictors were identified in multivariate regression analysis. In addition, none of the parameters or multivariate models showed satisfactory predictive accuracies in ROC curve-derived AUC analysis.

Previous studies reported that PSA, taking more prostate biopsy cores, maximum cancer length and family history of PCa were predictor factor of tumor unilaterality based upon RP [9,18-20]. As for the prediction of pathologically insignificant or unfavourable PCa among low-grade PCa cancers, some reported that PSAD and age were correlated with insignificant PCa [21,22]. On the other hand, other authors failed to identify clinical or biopsy-related parameters predicting such pathological outcome [23,24]. There are still controversies to find predictor factor of tumor laterality and clinical significance in PCa patients with preoperative parameters. The differences of experimental group, biopsy protocol and pathologic reporting system were thought of main causes of those results.

Prebiopsy magnetic resonance imaging (MRI) has the benefit of facilitating prior detection of lesions not expected to be identified by systematic prostate biopsy. However, in a large study, Giannarini et al. [25] showed that differentiation between PCa and normal prostatic tissue, not only in the transition zone but also in the peripheral zone, is very difficult based on T2-weighted images. The conventional approach to managing cases with a high PSA level is TRUS-guided prostate biopsy followed by MRI for PCa staging. Conditions other than PCa such as postbiopsy hemorrhaging, scarring, positional and inflammatory changes, and dystrophic changes can interfere with the accuracy of MRI investigations [26,27]. Therefore, we did not include MRI parameters in our evaluations for identifying predictive factors and estimating predictive accuracies.

Matsuoka et al. [28] reported that a combination of diffusion-weighted imaging and extended prostate biopsy can efficiently be used to predict lobes without significant cancer. In their study, the negative predictive value for predicting LSC was 95.7%. However, indolent cancer was defined as organ-confined disease with a tumor volume of  $<0.5 \text{ cm}^3$  and a GS of  $\leq 3+4$  without Gleason pattern 5. Although definitions of significant cancer vary, a GS of 3+4 seems too high to accept as representative of insignificant cancer. FT represents a potential compromise between AS and radical therapy, offering advantages of the resolution of anxiety and the avoidance of urinary and sexual side effects associated with whole gland treatment [9]. The management strategy must not only meet

the curative intent of treatment, but must also account for the safety of AS. Thus, strict criteria may be required in determining the clinical significance of the preserved side based on pathologic reports of RP specimens.

The current study has several limitations. First, we did not include all patients with low-risk PCa detected at our institution. Those treated with AS or radiation therapy were excluded from this study, because we were unable to obtain final pathologic reports for them. Application of FT is not limited to patients who are due to receive RP, and so our study may contain a selection bias associated with the inclusion criteria. In addition, in a hypothetical study based on a database of RP patients, we attempted to determine appropriate selection criteria for FT. However, this therapy was not administered to patients with PCa, and so we were unable to assess biochemical recurrence and cancer-specific survival, which might be more important than pathological features for selection of FT.

In conclusion, among patients with low-risk PCa who had unilateral tumors based on conventional multicore ( $\geq 12$ ) biopsy, 44.9% had pathologically determined LSC and 34.1% harbored LIC. However, no independent predictors of LSC in patients who are candidates for hemiablativ FT were identified. In addition, our data showed that the clinical and biopsy-related parameters currently available have limited value in the prediction of pathologically determined LSC. Further efforts should be made to identify more accurate predictors of actual pathological characteristics and prognosis of PCa to ultimately improve the selection of candidates for hemiablativ FT.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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