Preoperative parameters to predict incidental (T1a and T1b) prostate cancer

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Abstract

Introduction: Prostate cancer has been found incidentally in transurethral resection of the prostate (TURP) specimens without prior diagnosis in 5% to 13% of the patients. We evaluated whether incidental prostate cancer (stages T1a and T1b) could be predicted preoperatively.

Methods: TURP was performed in 307 patients between 2006 and 2011. Patient age, prostate-specific antigen (PSA) level, total prostate volume, transitional zone volume, PSA density, history of needle biopsy, and pathological diagnosis on TURP specimen were assessed. We analyzed the association between these parameters and prostate cancer detection.

Results: Incidental prostate cancer was found in 31 patients (10.1%), and 13 cases (4.2%) had cancer with T1b and/or Gleason ≥7. Multivariate analysis demonstrated that age ≥75 years (odds ratio [OR] 2.58, $p = 0.022$), prostate volume ≤50 cc (OR 4.11, $p < 0.001$), and the absence of preoperative needle biopsy despite PSA ≥4 ng/mL (OR 2.65, $p = 0.046$) were independent risk factors. In patients who had 2 or 3 of these risk factors, incidental prostate cancer and cancer with T1b and/or Gleason ≥7 were observed in 25% to 50% and 16% to 25% cases, respectively.

Conclusions: Older patient age, small prostate volume, and the absence of previous needle biopsy (despite a high PSA level) might be independent risk factors for detecting incidental prostate cancer, although external validation is warranted to confirm our results.

Introduction

Transurethral resection of the prostate (TURP) is still standard treatment for lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH). Prostate cancer has been found incidentally in TURP specimens without prior diagnosis in 5% to 13% of patients.[1-3] According to the TNM staging system, incidental tumour in less than 5% of resected prostate tissue is subclassified in clinical stage T1a; tumour found in more than 5% of resected tissue is subclassified as T1b.[4] Although most of the incidental prostate cancers are considered clinically insignificant, recent studies have suggested that in some of them, the clinical course becomes more unfavourable.[5,6]

The main preoperative diagnostic tools to confirm prostate cancer include serum concentration of prostate-specific antigen (PSA), digital rectal examination (DRE), and imaging modalities. The positive predictive values, however, of DRE[7] and transrectal ultrasonography (TRUS)[8] are limited. PSA is considered a better predictor of cancer than DRE or TRUS,[9] and it can be complemented with parameters, such as PSA velocity,[10] PSA density,[11] and free/total PSA.[12] However, serum PSA levels may be elevated in the presence of BPH, prostatitis, and other non-malignant conditions. The role of multiparametric magnetic resonance imaging (MRI) in the diagnosis and staging of prostate carcinoma is rapidly increasing,[13] but routine use of MRI as a cancer screening tool is unrealistic in standard clinical practice. Therefore, in most cases the finding of T1a or T1b prostate cancer has been completely incidental.

The technology related to photoselective laser vaporization of the prostate (PVP) has evolved over the last 10 years, and PVP can produce significant improvement in both clinical and voiding parameters with minimal morbidity.[14-16] However, PVP can miss incidental prostate cancer because prostatic tissues are vaporized; moreover, PVP does not provide a histologic diagnosis. Therefore, on the basis of preoperative prediction for incidental prostate cancer, the indication of preoperative biopsy or the selection of treatment modalities (TURP or PVP) should be discussed prior to treatment. In this study, we evaluated whether prostate cancer detected on TURP (stages T1a and T1b) can be predicted preoperatively.

Methods

After receiving institutional review board approval, we conducted a retrospective chart review of 307 patients with bladder outlet obstruction due to BPH who underwent TURP

between 2006 and 2011 at our institution. All patients were treated with the bipolar transurethral resection in saline (TURIS) system (Olympus, Tokyo, Japan). Clinicopathological variables examined included patient age (year), serum PSA level (ng/mL), total prostate volume (cc), transitional zone volume (cc), PSA density (serum PSA level divided by prostate volume; ng/mL/cc), resected tissue weight (g), history of needle biopsy, and pathological diagnosis on TURP specimen. Prostate and transitional zone volumes were determined by TRUS. For an accurate pathological diagnosis, tumour extent (stage) in TURP specimens was determined by calculating the fraction of all TURP chips involved by tumour, and Gleason scores were assigned based on the 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma.[17]

To identify the factors that influenced the detection of incidental prostate cancer, we performed univariate analyses using a logistic regression model. Next, using factors for which p values were less than 0.10 in univariate analyses, multivariate analyses were performed by applying a logistic regression model with stepwise forward selection. In these multivariate analyses, statistical significance was determined at $p < 0.05$. To categorize continuous measurements, we used the cut-off point that produced the minimum p value, found by testing all possible cut-off points.[18] All such cut-off points were then rounded up or down to clinically relevant values. Receiver operating characteristic (ROC) curve analysis was used to evaluate the performance of the prediction model for incidental prostate cancer. These analyses were performed with SPSS software, version 20 (SPSS Inc, Chicago, IL) and R, version 3.0.2.

Table 1. Patient characteristics

Preoperative parameters	
Total no. patients	307
Age	Mean 69.2 years (range: 49–84)
PSA value	Mean 5.4 ng/mL (range: 0.1–28.5)
Prior prostate needle biopsy: Yes	126 patients (41.0%)
Prior prostate needle biopsy: No	181 patients (59.0%)
Total prostate volume	Mean 61 cc (range: 10–225)
Transitional zone volume	Mean 33 cc (range: 5–154)
PSA density	Mean 0.10 ng/mL/cc (range: 0.01–0.69)
Operative and pathological results	
Resected volume	Mean 24 g (range: 3–98)
Incidental prostate cancer	31 patients (10.1%)
Clinical stage T1a	Total 22 patients
Gleason score 3+3	18 patients
Gleason score 3+4	3 patients
Gleason score 4+4	1 patient
Clinical stage T1b	Total 9 patients
Gleason score 3+3	4 patients
Gleason score 3+4	2 patients
Gleason score 4+4	2 patients
Gleason score 4+5	1 patient

PSA: Prostate-specific antigen. ICU: intensive care unit.

Results

Due to high PSA levels and/or abnormal DRE findings, 126 patients (41.0%) received the transrectal needle biopsy prior to TURP. Eleven patients (3.6%) in our cohort revealed abnormal DRE and all of them received preoperative needle biopsy. Meanwhile, 39 patients with high PSA (≥4 ng/mL) and negative DRE findings did not undergo prostate biopsy because of their older age (mean 71.3), low PSA density (mean 0.12 ng/mL/cc), comorbidity, and/or patient choice (Table 1).

Using multivariate analyses of a logistic regression model, we found that the following 3 factors had independently significant impact on the detection of incidental prostate cancer: (1) patient age (year) as a continuous variable (odds ratio [OR] 1.06; 95% confidence interval [CI] 1.00–1.13, $p = 0.048$); (2) prostate volume (cc) as a continuous variable (OR 0.98; 95% CI 0.96–0.99, $p = 0.011$); and (3) the absence of preoperative needle biopsy despite PSA ≥4 ng/mL (OR 2.68; 95% CI 1.05–6.81, $p = 0.039$). Our cut-off points of age and prostate volume were 75 years and 50 cc, respectively. Again using these categorized variables we performed multivariate analysis and found that the following factors were independent predictors: age ≥75 years (OR 2.58; 95% CI 1.14–5.83, $p = 0.022$), prostate volume ≤50 cc (OR 4.11; 95% CI 1.79–9.44, $p < 0.001$), and the absence of preoperative needle biopsy despite PSA ≥4 ng/mL (OR 2.65; 95% CI 1.02-6.90, $p = 0.046$).

To create a risk stratification model, we used the previously mentioned 3 risk factors (page age, prostate volume and absence of preoperative needle biopsy). This model enabled us to accurately predict not only incidental prostate cancer, but also cancer with T1b and/or Gleason ≥7 (Table 3). Patients with no or one risk factor had a limited probability of incidental prostate cancer on TURP (4%–10%). Meanwhile, some of patients who had 2 or 3 of the risk factors had the risk of incidental prostate cancer (25%–50%), and even cancer with T1b and/or Gleason ≥7 (16%–25%). We calculated ROC curves; the area under the ROC curve of our model for detection of incidental prostate cancer was 0.71 (Fig. 1a); and it was 0.74 for cancer with T1b and/or Gleason ≥7 (Fig. 1b).

Table 2. Univariate and multivariate analyses on preoperative factors associated with incidental prostate cancers on TURP

	Univariate	Multivariate (continuous variable)		Multivariate (categorical variable)	
	p value	*p* value	OR (95% CI)	*p* value	OR (95% CI)
Age					
Continuous variable (years)	0.040	0.048	1.06 (1.00–1.13)		
Category (≥75 years)	0.023			0.022	2.58 (1.14–5.83)
PSA (ng/mL)	0.102				
Prostate volume					
Continuous variable (cc)	0.021	0.011	0.98 (0.96–0.99)		
Category (<50 cc)	0.001			<0.001	4.11 (1.79–9.44)
Transitional zone volume (cc)	0.069				
PSA density (ng/mL/cc)	0.732				
The absence of NBx despite PSA ≥4	0.026	0.039	2.68 (1.05–6.81)	0.046	2.65 (1.02–6.90)

TURP: transurethral resection of prostate: PSA: prostate-specific antigen: NBx; needle biopsy: OR: odds ratio; CI; confidential interval.

Discussion

Routine PSA testing, DRE, and TRUS are widely accepted. Several studies have reported rates of incidental prostate cancer among patients undergoing TURP, and indicated that such preoperative examinations have reduced the incidental finding of prostate cancer on TURP by detecting cancers on preoperative prostate biopsy.[1-3] Jones and colleagues[1] compared the frequency of incidental prostate cancer among patients undergoing TURP between the pre-PSA era and the PSA era, and showed a decrease in frequency from 14.9% (34 of 228) to 5.2% (26 of 501). In another study, Zigeuner and colleagues[2] showed that incidental prostate cancer was diagnosed in 314 (13%) of 2422 patients. However, the rate of incidental prostate cancer in patients with both negative age-specific PSA levels and negative DRE findings was 6.4% (72 of 1127). Yoo and colleagues[3] reported that incidental prostate cancer was found in only 4.8% (78 of 1613) after prostate biopsy in all patients with PSA ≥4.0 ng/mL or with abnormal DRE findings. Meanwhile, despite being performed in the PSA era, our detection rate of incidental prostate cancer on TURP was slightly higher than the other reports (10.1%; 31 of 307); there are 2 possible reasons for this increase. Firstly, in clinical practice, some older patients with high PSA (≥4 ng/mL) undergo TURP without prior prostate biopsy, and our study population also included 39 such patients who omitted prostate biopsy because of their older age, low PSA density, comorbidity and/or patient refusal. Secondly, for an accurate pathological diagnosis, we examined all TURP chips (i.e., not by a random sampling technique), which might also be associated with the high detection rate.

With incidental prostate cancer, it is an important issue whether the cancer diagnosed incidentally during TURP is significant or not. Andren and colleauges[5] observed 240 patients of T1a or T1b prostate cancer without any initial treatment for cancer, and 42 (18%) died due to prostate cancer with a mean follow-up of 108 months. They reported that higher Gleason grade, higher nuclear grade, and larger tumour volume were independent predictors of death in prostate cancer. In another report, Robinson and colleagues[6] found that 33 (17%) of 197 cases of incidental prostate cancer who were managed conservatively died from prostate cancer during the mean 7.8-year follow-up. Again, their data indicated that high Gleason score, T1b, and high immunoreactivity of Ki-67 were independent predictors of disease-specific mortality.

Some studies evaluated the pathological and clinical results in incidental prostate cancer treated with subsequent radical prostatectomy. Melchior and colleagues[19] examined the pathological results of radical prostatectomy in 17 cases with clinical stage T1a and 9 cases with T1b. They found that 11 (65%) in the T1a group and 7 (78%) in the T1b group had residual tumours. Magheli and colleagues[20] investigated biochemical outcomes following radical prostatectomy in 8658 patients with clinical stage T1 prostate cancer, including 85 T1a cases and 156 T1b cases. They found that 5- and 10-year recurrence-free survival rates in T1b were 90% and 86%, respectively, which were similar to those in T1c cases (90% and 84%, respectively), although those in T1a were

Table 3. Risk stratification for incidental prostate cancer and the frequency of incidental prostate cancer

	Risk ratio	No. patients	No. incidental cancer cases	No. incidental T1b or Gleason ≥7
3 risk factors*	28.1	8	4 (50%)	2 (25%)
2 risk factors	6.84-10.9	32	8 (25%)	5 (16%)
1 risk factor	2.58-4.11	158	15 (10%)	4 (3%)
No risk factor	1.00	109	4 (4%)	2 (2%)

*Three risk factors are age ≥75 years, prostate volume ≤50 cc, and the absence of preoperative needle biopsy despite PSA ≥4 ng/mL.

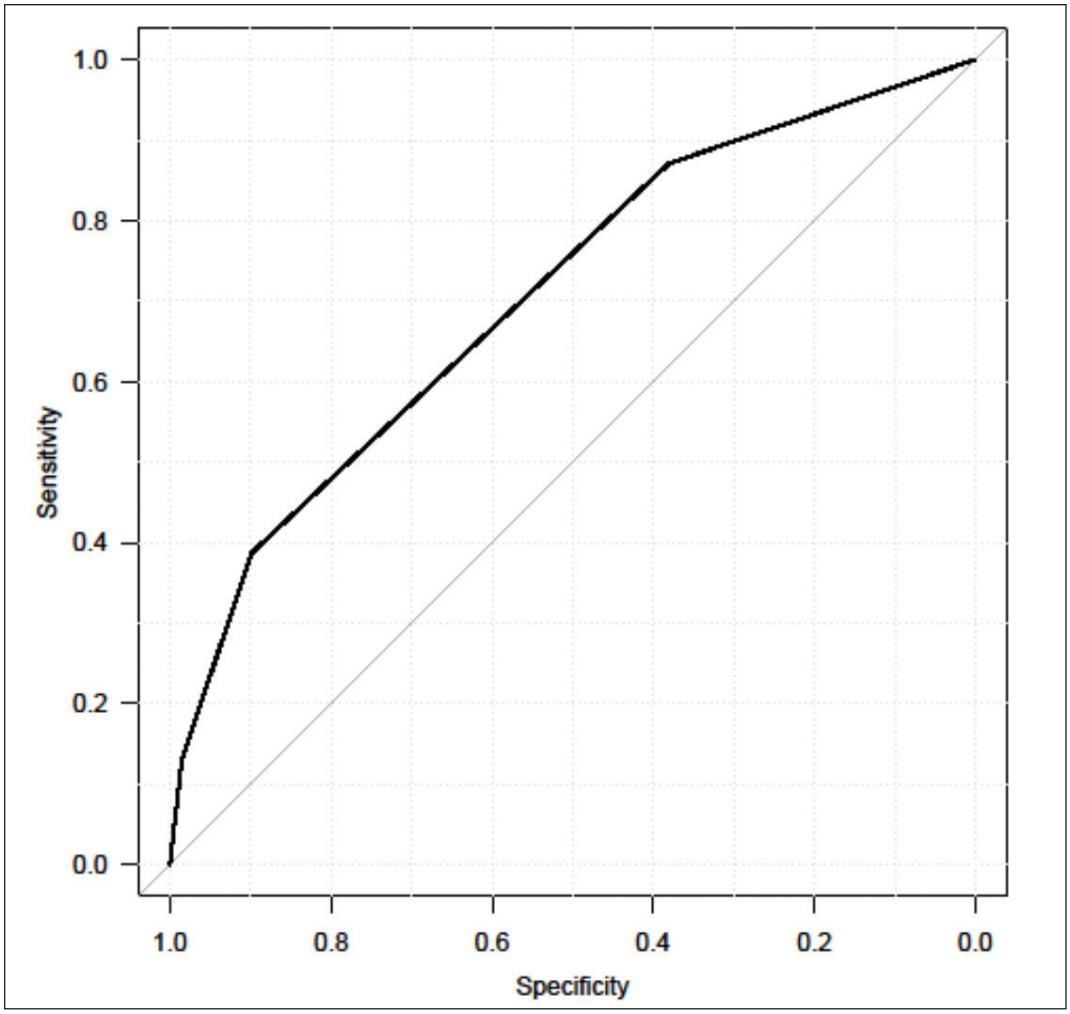

Fig. 1a. Receiver operating characteristic (ROC) curves of our model for detecting incidental prostate cancer.

better (98% and 98%, respectively). These results demonstrate that some incidental prostate cancers (especially cases with high Gleason score and large cancer volume) should be treated as clinically significant cancer.

PVP with a high-performance potassium-titanyl-phosphate (KTP) laser has expanded as a minimally invasive surgery for BPH.[14-16] However, PVP yields no tissue for pathological examination. Therefore, it is mandatory to perform meticulous preoperative examinations and to continue postoperative surveillance. Malek and colleagues[21] reported their results in 94 patients treated with PVP and found that 5 patients (5%) had prostate cancer diagnosed within 6 months to 3 years after surgery. Meanwhile, Ruszat and colleagues[22] achieved a limited rate of subsequent prostate cancer (1.2%; 6 of 500) with a mean follow-up of 31 months by doing thorough preoperative investigations. They performed at least 2 series of prostate biopsies in all cases with an abnormal PSA or DRE findings, although this protocol is thought to be less practical.

In this study, we focused on identifying preoperative risk factors for incidental prostate cancer in the current clinical setting. We found that 3 simple parameters (age ≥75, prostate volume ≤50 cc, and the absence of preoperative needle biopsy despite PSA ≥4 ng/mL) were unfavourably linked to incidental prostate cancers. Yoo and colleagues[3] performed multivariate analyses using a large multicentre cohort of patients treated with TURP, and concluded that high PSA and low transitional zone volume could be used as predictive factors of incidental prostate cancer. The difference from our results is thought to derive from backgrounds. As mentioned above, their indication criteria of prostate biopsy were different from ours. In addition, patients with PSA ≥20 ng/mL were excluded from their study irrespective of their biopsy results, while we included 4 patients with PSA ≥20 ng/mL, all of whom were diagnosed as cancer-negative on prostate biopsy. Furthermore, because our study was performed at a single institution, the measurement of serum PSA and TRUS,

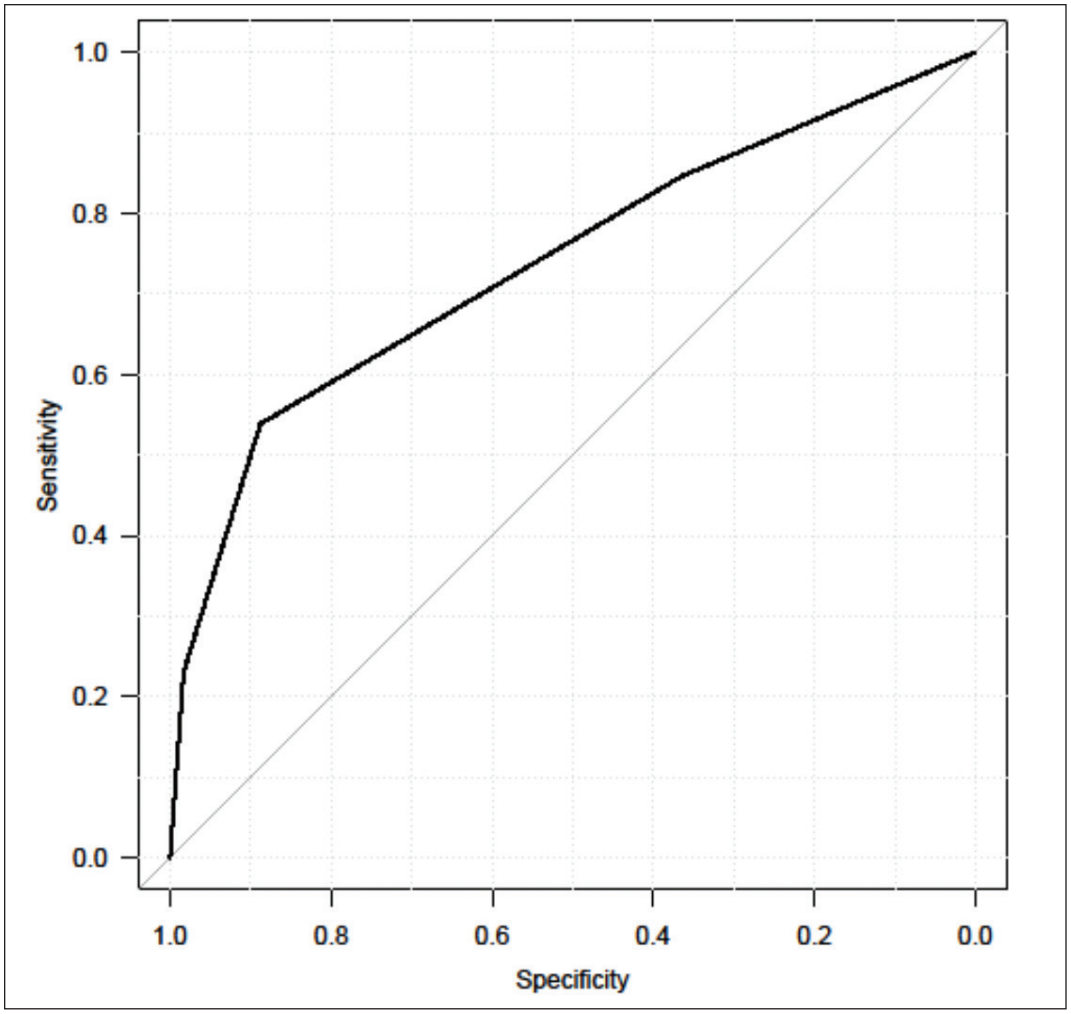

Fig. 1b. Receiver operating characteristic (ROC) curves of our model for detecting cancer with T1b and/or Gleason ≥7.

prostate biopsy, TURP, and pathological diagnosis were all performed in the same manner. We believe our 3 simple parameters could be used to make a decision on preoperative prostate biopsy or selection of treatment modalities (TURP or PVP), because these are generally assessed in routine clinical practice. However, we have not confirmed the performance of this risk stratification in an external data set. Therefore, obtaining definite conclusions concerning the preoperative parameters to predict incidental prostate cancer will require further investigations.

Conclusion

Our data suggest that older patient age, small prostate volume, and the absence of previous needle biopsy despite a high PSA level might be independent risk factors for detecting incidental prostate cancer on TURP, although external validation is warranted to confirm our results.

Competing interests: Dr. Sakamoto, Dr. Matsumoto, Dr. Hayakawa, Dr. Maeda, Dr. Sato, Dr. Ninomiya, Dr. Mukai and Dr. Nakamura all declare no competing financial or personal interests.

This paper has been peer-reviewed.

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