

# Incidental Prostate Cancer from Prostate with Benign Biopsies: A Predictive and Survival Analysis from Cohort Study

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**Purpose:** This cohort was to evaluate incidental prostate cancer (iPCa) from men with preoperative benign biopsies and demonstrate their outcomes under different managements.

**Patients and Methods:** Between 2015 and 2017, we analyzed the risk factors having iPCa from surgical specimens from men provided with benign preoperative biopsies of their prostates. Furthermore, we compared the survival outcomes according to the different managements after iPCa was diagnosed. Receiver operating characteristic (ROC) curve was utilized to find the best thresholds. Univariable and multivariable nested logit regression were performed to estimate the effect size of different independent variables. Odds ratio (OR) was expressed with 95% confidence interval, and the alpha level was 5%.

**Results:** In 295 men we enrolled, there were 57 (19%) men having iPCa from surgical specimens. In univariable logit regression, we found significant variables of age, PSA, prostatic volume, PSA velocity  $\geq 0.75$  ng/mL/year for 3 years, taking 5 $\alpha$  reductase inhibitors, abnormal digital rectal examination, cores of biopsy and surgical methods. In multivariable model, PSA was the strongest variable predicting iPCa (OR 3.81 [2.04–7.07]; Wald: 17.75;  $p < 0.001$ ). In ROC curve, the best threshold was 9.025 ng/mL (area under curve: 0.95; sensitivity: 0.947; specificity: 0.866). In Kaplan–Meier curve of 27.89-month follow-up, robot-assisted simple prostatectomy (RASP) can provide similar PSA progression-free period as robot-assisted radical prostatectomy (RARP) following transurethral surgeries in organ-confined cancer (Log rank test,  $p = 0.293$ ), and both of them were better than external-beam radiation therapy (RT) following transurethral surgeries (Log rank test,  $p < 0.001$ ).

**Conclusion:** PSA was the strongest variable to predict iPCa out of prostate with preoperative benign biopsies. RASP was parallel to RARP following transurethral surgeries in organ-confined cancer in the short term.

**Keywords:** incidentally diagnosed prostatic carcinoma, prostatic hyperplasia/surgery, prostatectomy/methods, robotic surgical procedures/methods, follow-up studies

## Introduction

The rate of incidental prostate cancer (iPCa) is directly proportional to the age.<sup>1</sup> In the era before prostate-specific antigen (PSA) screening was adopted, this rate had been reported to be 18.5% on average in patients aged 60 to 69 years old (yo) and as high as 60% in those aged 90 to 99 yo.<sup>1</sup> After the introduction of PSA, decreasing trends on the rate of iPCa as well as age-specific mortality were observed.<sup>2</sup> In a large retrospective cohort study including 3942 men, the total iPCa rate was observed to decrease to 5.5% clinically and the age was still the determining factor. The incidental rates were 4.8%, 7.6%, and 10.1% in the age groups of 60 to 69 yo, 70 to 79 yo, and 80 to 89 yo, respectively.<sup>3</sup>

Several risk factors were associated with iPCa from prostate with preoperative benign biopsies, including the elderly age, prostatic volume, preoperative PSA, PSA velocity and family history, have been studied.<sup>3–7</sup> Recently, the rate of

iPCa has been increasing in developed countries in Asia, especially in Japan and Korea, suggesting the possible emerging factors such as changes of lifestyle, population ageing, and exposure to new carcinogens.<sup>8</sup> Similar changes in the rate of iPCa may extend to other underdeveloped Asian countries in the future.

Although the application of different devices, either bipolar or laser, does not affect the pathologists in judging an iPCa from specimens,<sup>9</sup> the scope of tissue removal may affect the iPCa detection. In this way, the detection rate of iPCa is higher in specimens collected with Holmium laser enucleation of the prostate (HoLEP) than with the bipolar device.<sup>10</sup> Simple prostatectomy was reasonably the most comprehensive surgical method to investigate the risk factors of iPCa, but it was rarely included into analysis among the current studies. Moreover, there were few studies comparing the survival outcomes of different postoperative managements after iPCa was diagnosed. Our study is the first one incorporating robotic-assisted simple prostatectomy (RASP) into analyzing the iPCa predictive model and demonstrating the outcomes among different managements after iPCa was diagnosed.

## Patients and Methods

### Patient

Between 2015 and 2017, we identified men with preoperative benign biopsies but iPCa in surgical specimens obtained from transurethral resection of the prostate (TURP) with bipolar device, HoLEP, and RASP conducted for benign ailments. RASP of fixed surgical steps ([Supplementary 1](#)) was carried out by a single urologist with da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA). Men being included in this study need to have traceable medical records for at least 3 years before surgeries, including data of PSA, performance of digital rectal examination, histories of prescriptions and surgical intervention. Preoperative PSA in analysis was drawn from the latest data before surgeries and PSA velocity was considered significant if exceeding 0.75 ng/mL/year for serial 3 years.<sup>11</sup> Medical records regarding 5 $\alpha$  reductase inhibitors (5 $\alpha$ RI), either finasteride or dutasteride, were considered meaningful when they were prescribed for at least 6 months before surgeries without discontinuation. Systematic biopsies were done via transrectal ultrasound-guided fashion and prostatic volume was measured by transrectal ultrasonography (height  $\times$  width  $\times$  length  $\times$  0.52) before surgeries.<sup>12</sup> Information regarding family histories of prostate cancer was collected from grandfather to their brothers.

### Postoperative Surveillances

A specimen of iPCa would be confirmed by pathologists' peer review. For iPCa, PSA would be routinely assessed after surgeries. The first postoperative appointment was arranged 1 month after RASP, and then, clinical visits were arranged trimonthly. For those with positive surgical margins (PSM), external-beam radiation therapy (RT) or active surveillance would be provided to them. For men with iPCa after transurethral surgeries, robot-assisted radical prostatectomy (RARP), external-beam RT or active surveillance was provided to them.

Regarding the primary endpoint of PSA progression, we defined the same (elevation of PSA above 0.2 ng/mL from the nadir in two successive measurements in one month) for men with RASP or RARP following transurethral surgeries, and the definition was changed to 2 ng/mL for men with external-beam RT.

### Statistical Methods

Parametric and nonparametric methods were performed after evaluating the skewness and kurtosis. Univariable and multivariable logit model were employed to predict the outcome of iPCa. Receiver operating characteristic (ROC) curves were utilized to source the threshold for the most distinguished variable in the predictive model and Kaplan-Meier (KM) curve was used to compare survival outcome of PSA progression among different managements. Statistical work was accomplished by Stata (version 17, StataCorp LLC, College Station, TX, USA) and Statistical Package for the Social Sciences (version 26, IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant, and effect size and data were presented with 95% confidence interval (CI).

## Results

### General Data

After reviewing the medical charts, men with incomplete records (n=12) and loss of follow-ups (n=21) were excluded and a total of 295 men were enrolled in our analysis. The included men were all Asians living in Taiwan. Their general data were presented at Table 1 (data distribution: [Supplementary 2](#)) and the dichotomy was made according to the existence of iPCa. Regarding the resected prostatic weight by iPCa, the median (interquartile range) was 44.55 (25.6) and 40.29 (25.89) grams in non-iPCa and iPCa group, respectively. Cohen's d was 0.25 (-0.04–0.54) for non-iPCa with reference to iPCa. Regarding the resected prostatic weight by different surgeries, the median (interquartile range) was 35.67 (16.54), 65.44 (26.78) and 43.56 (22.34) grams from bipolar TURP, RASP and HoLEP, respectively. Cohen's d was 1.98 (1.64 –2.32) and 0.70 (0.42–0.98) for RASP and HoLEP with reference to bipolar TURP, respectively. It was -1.12 (-1.46 - -0.78) for HoLEP with reference to RASP.

### Logit Model and ROC Curve

In Table 2, we demonstrated logit model of univariable regression analysis and the significant variables would be further incorporated into independent variables in multivariable regression analysis. In Tables 3 and 4, multivariable nested model was constructed. For the reason of Ockham's Razor, model of multivariable logit regression-3 was the most suitable one of this cohort. In this model, PSA was the most significant independent variable among all in all conditions.

**Table 1** General Data

	iPCa (n= 57)	Non-iPCa (n= 238)	p-value
Age (years old; mean ± SD)	69.14±5.94	62.52±4.46	<0.001 <sup>a</sup> **
BMI (kg/m <sup>2</sup> ; mean ± SD)	25.57±2.24	25.20±3.18	0.411 <sup>a</sup>
PSA (ng/mL)	Median: 12.18; IQR: 5.39	Median: 5.35; IQR: 4.30	<0.001 <sup>b</sup> **
PSA velocity (n, %)			<0.001 <sup>c</sup> **
≥ 0.75 ng/mL/year	45 (79%)	121 (51%)	
< 0.75 ng/mL/year	12 (21%)	117 (49%)	
Prostate volume (mL)	Median:47.18 IQR:26.29	Median:69.48 IQR:22.36	<0.001 <sup>b</sup> **
5α reductase inhibitors (n, %)			<0.001 <sup>c</sup> **
Yes	36 (63%)	208 (87%)	
No	21 (37%)	30 (13%)	
Family history of prostate cancer (n, %)			<0.001 <sup>c</sup> **
No	36 (63%)	219 (92%)	
Yes	21 (37%)	19 (8%)	
Abnormal Digital Rectal Examination (n, %)			<0.001 <sup>c</sup> **
No	37 (65%)	211 (89%)	
Yes	20 (35%)	27 (11%)	
Cores of biopsy (n, %)			<0.001 <sup>c</sup> **
≥ 12 cores	38 (67%)	233 (97%)	
< 12 cores	19 (33%)	5 (3%)	
Surgical method (n, %)			<0.001 <sup>d</sup> **
Bipolar TURP	14 (24%)	126 (53%)	
RASP	30 (53%)	45 (19%)	
HoLEP	13 (23%)	67 (28%)	

**Notes:** In continuous variables, PSA and prostate volume were analyzed with non-parametric method. Statistical method: <sup>a</sup>Student's t-test; <sup>b</sup>mann-Whitney U-test; <sup>c</sup>Pearson's chi-square test with Yates' Correction; <sup>d</sup>Pearson's chi-square test; \*\*p<0.001.

**Abbreviations:** SD, standard deviation; IQR, interquartile range; TURP, Transurethral Resection of Prostate; RASP, Robot-assisted simple prostatectomy; HoLEP, Holmium laser enucleation of the prostate.

**Table 2** Univariable Logit Regression

	Univariable Logit Analysis		
	Odds Ratio (95% CI)	Wald	p-value
Age (years old)	1.32 (1.22–1.42)	47.82	<0.001**
PSA (ng/mL)	1.84 (1.57–2.15)	58.90	<0.001**
3-year PSA velocity	Reference		
≥ 0.75 ng/mL/year	Reference		
< 0.75 ng/mL/year	0.28 (0.14–0.55)	13.56	<0.001**
Prostate volume (mL)	0.94 (0.92–0.96)	32.33	<0.001**
5αreductase inhibitors	Reference		
Yes	Reference		
No	0.17 (0.09–0.38)	28.47	<0.001**
Family history of prostate cancer	Reference		
No	Reference		
Yes	6.72 (3.29–13.73)	27.39	<0.001**
Abnormal Digital Rectal Examination	Reference		
No	Reference		
Yes	4.22 (2.15–8.30)	17.47	<0.001**
Cores of biopsy	Reference		
≥ 12 cores	Reference		
< 12 cores	23.30 (8.21–66.12)	34.99	<0.001**
Surgical method	Reference		
Bipolar TURP	Reference		
RASP	6.00 (2.92–12.33)	23.80	<0.001**
HoLEP	1.75 (0.78–3.93)	1.82	0.178

**Notes:** Dependent variable was “yield of iPCa” and significant independent variables of univariable logit regression would be further incorporated into multivariable logit nested model. Statistics: \*\*p<0.001.

**Abbreviations:** TURP, Transurethral Resection of Prostate; HoLEP, Holmium laser enucleation of the prostate; RASP, Robot-assisted simple prostatectomy.

In **Figure 1**, we detected the best threshold values for PSA and age. A dichotomy was made according to the threshold value of age and we further detected the threshold values of PSA in each of them (**Figure 2**).

### Survival Comparison Among Different Managements

Out of iPCa (n=57), there were 34 (60%), 19 (33%) and 4 (7%) in Gleason grade group 1, 2 and 3, respectively. Among iPCa out of RASP (n=30), it occupied 6.4 ±2.3% in specimens and 3 (10%) of them had PSM. Two of them chose adjuvant external-beam RT following RASP. Although the other one did not reach PSA nadir (<0.008 ng/mL) after RASP, he chose surveillance. All other (n=27) men after RASP reached PSA nadir and only surveillance was adopted.

In men after bipolar TURP (n=14), 6 (43%) of them chose RARP, 7 (50%) of them chose external-beam RT, and the rest one (7%) selected surveillance only. In men after HoLEP (n=13), 7 (54%) men chose RARP, one (8%) man chose external-beam RT, and 5 (38%) men chose surveillance only. Either following bipolar TURP or HoLEP, all of specimens after RARP were organ-confined cancer without PSM.

Regarding the survival analysis, we included men of RASP without PSM, RARP following transurethral surgeries and external-beam RT following transurethral surgeries. After an average of 27.89 ±4.50 months’ follow-ups, comparison of PSA progression-free survival of them was demonstrated in **Figure 3**.

**Table 3** Multivariable Nested Models (Multivariable Logit Regression-1 and Multivariable Logit Analysis-2)

	Multivariable Logit Regression-1			Multivariable Logit Analysis-2		
	Odds Ratio (95% CI)	Wald	p-value	Odds Ratio (95% CI)	Wald	p-value
Age (years old)	1.33 (1.02–1.74)	4.38	0.036*	1.38 (1.05–1.80)	5.30	0.021*
PSA (ng/mL)	3.98 (1.86–8.51)	12.63	<0.001**	3.73 (1.97–7.07)	16.39	<0.001**
3-year PSA velocity	Reference			Reference		
≥ 0.75 ng/mL/year	Reference			Reference		
< 0.75 ng/mL/year	0.01 (0.00–0.32)	6.47	0.011*	0.02 (0.01–0.35)	6.88	0.009*
Prostate volume (mL)	0.89 (0.82–0.97)	7.11	0.008*	0.89 (0.82–0.96)	8.17	0.004*
5 $\alpha$ reductase inhibitors	Reference			Reference		
Yes	Reference			Reference		
No	0.11 (0.01–1.37)	2.96	0.085			
Family history of prostate cancer	Reference			Reference		
No	Reference			Reference		
Yes	46.73 (1.56–79.08)	4.91	0.027*	26.01 (1.18–57.47)	4.26	0.039*
Abnormal Digital Rectal Examination	Reference			Reference		
No	Reference			Reference		
Yes	7.28 (0.45–17.65)	1.96	0.162			
Cores of biopsy	Reference			Reference		
≥ 12 cores	Reference			Reference		
< 12 cores	5.57 (2.03–30.26)	4.65	0.031*	9.69 (0.17–55.37)	1.21	0.271
Surgical method	Reference			Reference		
Bipolar TURP	Reference			Reference		
RASP	39.05 (1.21–63.58)	4.27	0.039*	26.15 (1.54–44.38)	5.10	0.024*
HoLEP	19.19 (0.67–29.37)	2.99	0.084	4.39 (0.33–38.15)	1.26	0.262

**Notes:** With the dependent variable of “yield of iPCa”, nested model was constructed to source the simplest predictive model. Statistics: \*p<0.05 \*\*p<0.001.

**Abbreviations:** TURP, Transurethral Resection of Prostate; HoLEP, Holmium laser enucleation of the prostate; RASP, Robot-assisted simple prostatectomy.

## Discussion

In a cohort, the rise of iPCa rate was postulated to be the results from the changes of clinical practice, and they found that the increasing iPCa rate was accompanied with a decreasing confirmation of benign biopsies prior to the surgeries of obstructive prostatic enlargement.<sup>13</sup> Nevertheless, the sensitivity and specificity of transrectal ultrasound guided-biopsy was around 44% and 73%,<sup>14</sup> respectively. Herein, even though confirming benign tissues from biopsies, urologists would still encounter iPCa. In our cohort, the rate was estimated to be 19% totally and this would remarkably fluctuate with different surgical methods. The highest one, 40%, was in RASP and the lowest one, 10%, was in bipolar TURP. In HoLEP, the rate in our study was 16%. However, according to the meta-analysis out of 50 studies and a total of 27,925 men after HoLEP,<sup>15</sup> iPCa rate was assessed to be around 8.1%, suffering from remarkable heterogeneity among studies. Some of studies included in the meta-analysis were conducted before the US Food and Drug Administration (FDA) approved the use of PSA in testing asymptomatic men for prostate cancer, and some of them were conducted before the yearly PSA screening was encouraged in men aged over 50 yo. In this aspect, a unified study protocol for future observational studies is needed to evaluate the true incidence.

We assumed that the different detection rate among surgical methods might be explained by the amounts of tissues removal. In a large-scale observations study, smaller resection weight in TURP would be associated with future detection of prostate cancer, especially low-grade one.<sup>16</sup> However, out of 6 studies of transurethral surgeries,<sup>15</sup> one of them

**Table 4** Multivariable Nested Model (Multivariable Logit Regression-3)

	Multivariable Logit Regression-3		
	Odds Ratio (95% CI)	Wald	p-value
Age (years old)	1.36 (1.06–1.73)	5.95	0.015*
PSA (ng/mL)	3.81 (2.04–7.07)	17.75	<0.001**
3-year PSA velocity	Reference		
≥ 0.75 ng/mL/year	Reference		
< 0.75 ng/mL/year	0.01 (0.00–0.29)	7.67	0.006*
Prostate volume (mL)	0.90 (0.84–0.92)	7.11	0.002*
Family history of prostate cancer	Reference		
No	Reference		
Yes	22.77 (1.26–31.00)	4.49	0.034*
Surgical method	Reference		
Bipolar TURP	Reference		
RASP	25.25 (1.80–35.42)	5.74	0.017*
HoLEP	8.80 (0.77–10.05)	3.07	0.080

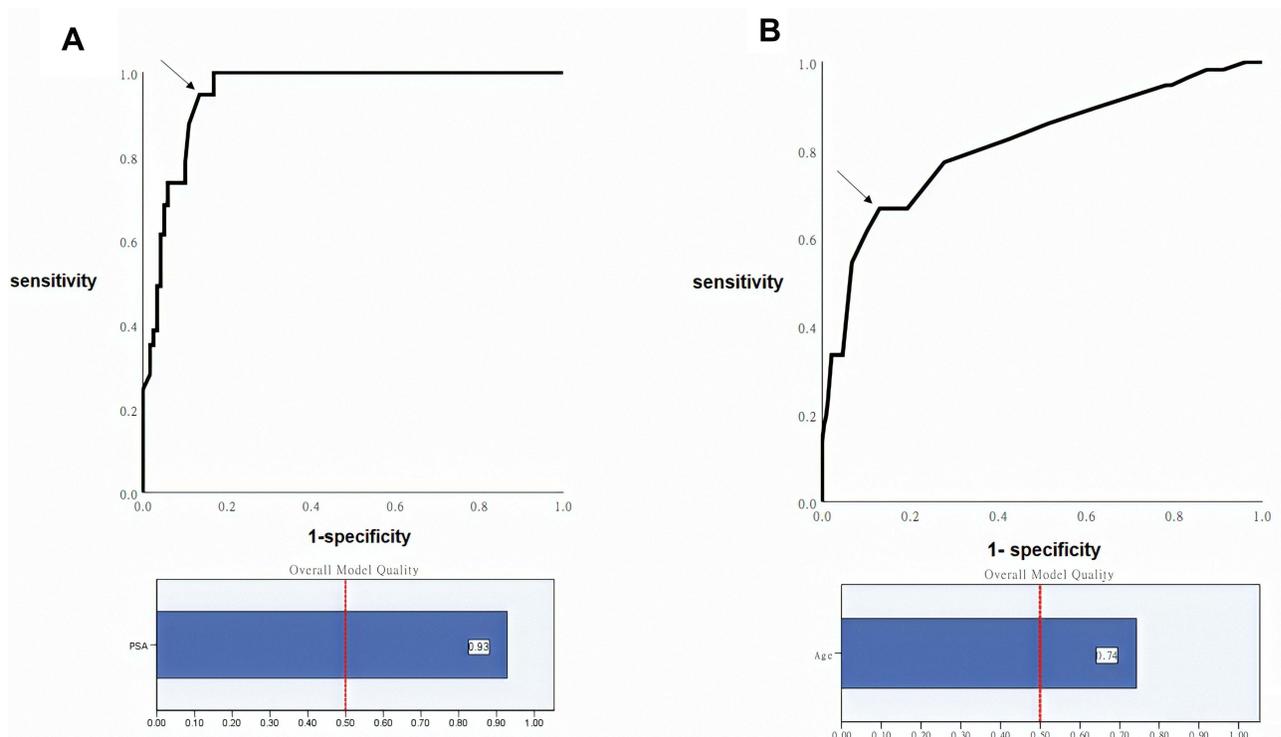
**Notes:** With the dependent variable of “yield of iPCa”, nested model was constructed to source the simplest predictive model. Statistics: \*p<0.05 \*\*p<0.001.

**Abbreviations:** TURP, Transurethral Resection of Prostate; HoLEP, Holmium laser enucleation of the prostate; RASP, Robot-assisted simple prostatectomy.

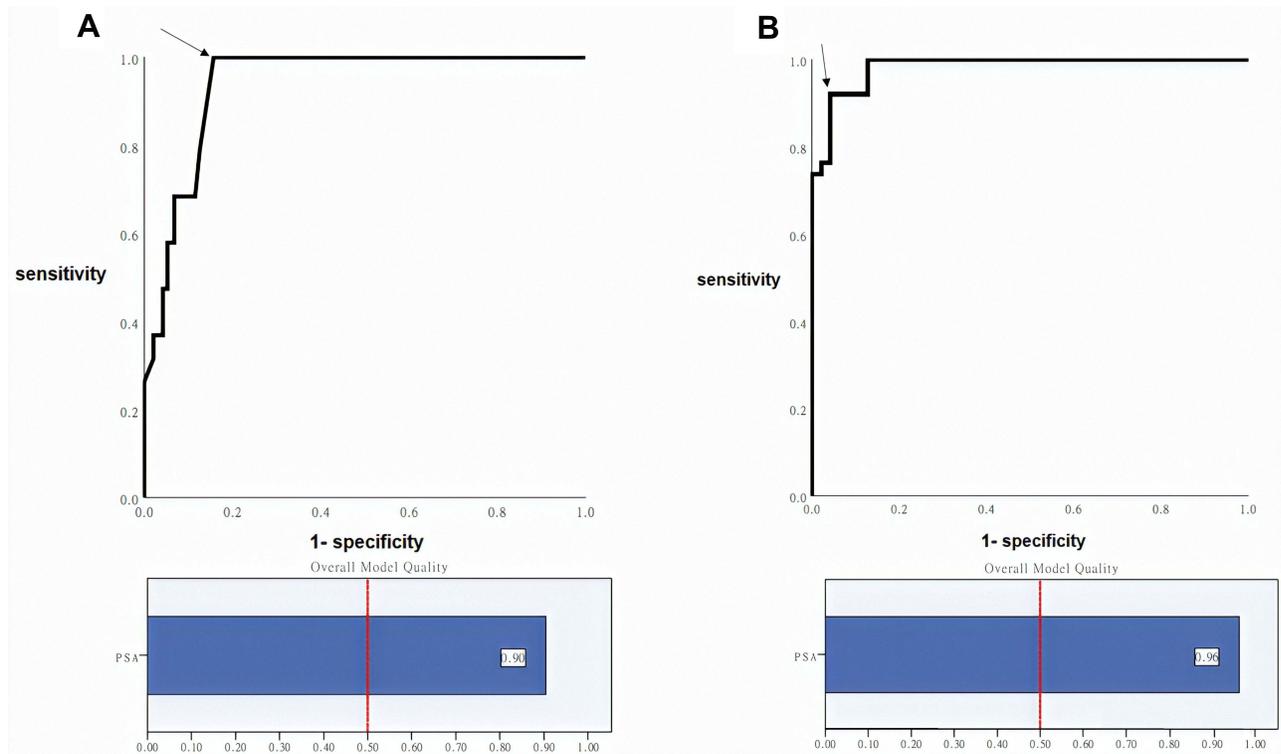
demonstrated the inverse relation between resected weight and iPCa and the others could not conclude significant relations. Herein, the assumption that the resected weight would be related to the detection of iPCa was still inconclusive and undetermined in current medical evidence. In our study, although HoLEP could remove more tissues than bipolar TURP, its odds in predicting iPCa was not different from that of bipolar TURP.

In ours and previous study,<sup>13</sup> iPCa was mostly low-grade and clinically insignificant prostate cancer. Nowadays, fewer and fewer diagnostic biopsies in solid cancers were taken without targeting to certain suspicious lesions. However, the prostate cancer was one of the few occasions. Recently, several alternatives have been proposed, and among them, 3T multi-parametric magnetic resonance imaging (mpMRI), interpreted by the Prostate Imaging-Reporting and Data System (PI-RADS), is one of the frequently mentioned and discussed ones. The PI-RADS is composed of scores 1 to 5, with 5 being the most suspicious malignant lesion. A PI-RADS 5 represents 93% sensitivity to detect prostate cancer and 80% sensitivity to clinically significant prostate cancer.<sup>17</sup> Additionally, a PI-RADS 3, indicating equivocal likelihood, was corresponded to around 40% sensitivity of cancer detection.<sup>18,19</sup> Based on clinical trial,<sup>20</sup> incorporating 3T mpMRI-targeted into standard biopsy, known as fusion biopsy, could increase diagnosis of low risk prostate cancer, the major constituent of iPCa, by around 18%. Moreover, more detailed clinical clues could be incorporated into biopsies such as prostatic volume. In analyzing prostate cancer from transrectal-ultrasound guided biopsies, prostate volume is an independent variable detecting prostate cancer.<sup>21</sup> As a continuous variable, the odds of prostate cancer detection would be inversely proportional to it. In PSA from 4 to 20 ng/mL, prostatic volume could be further stratified according to 35 and 50 mL when considering biopsies.<sup>22</sup> Likewise, in the meta-analysis of current 13 studies, smaller prostate volume was related to iPCa after surgeries. A large prostate volume in preoperative assessment might indicate the true hyperplasia and the odds would decrease with every 10-mL change in prostatic volume.<sup>15</sup> This conclusion was similar to that in our study. As for tools for assessment, previous literature demonstrated that although both transabdominal and transrectal ultrasounds could provide information to predict the resected weight of prostate, the latter could provide the closer approximation.<sup>12</sup> In our multivariable logit model, assessment of prostatic volume via transrectal ultrasound could also be associated with iPCa.

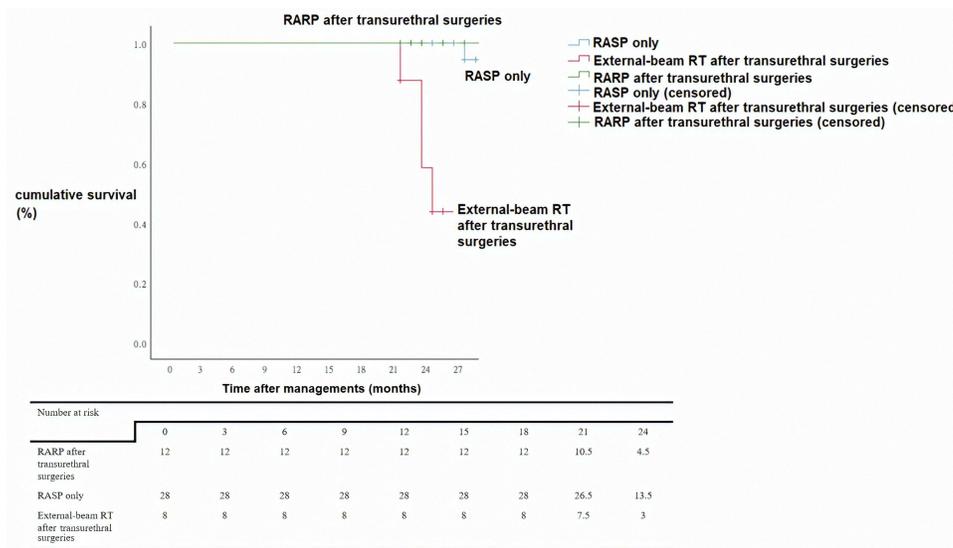
In current 17 studies, PSA possessed a solid role in predicting iPCa out of surgeries for benign prostate.<sup>15</sup> In our multivariable logit model, preoperative PSA remained to be the most powerful one predicting the existence of iPCa from



**Figure 1** Receiver-operating curve of PSA level and age.  
**Notes:** (A) The area under curve was 0.95 and the best threshold was 9.025 ng/mL (sensitivity: 0.947, specificity: 0.866) for PSA. (B) The area under curve was 0.82 and the best threshold was 65.5 years old (sensitivity: 0.667, specificity: 0.807) for age. The arrows in the both figures indicated the detected threshold values.



**Figure 2** Receiver-operating curve of PSA level by age (<65.5 or ≥ 65.5 years old).  
**Notes:** (A) The area under curve was 0.94 and the best threshold was 9.025 ng/mL (sensitivity: 1.000, specificity: 0.843) for age < 65.5 years old. (B) The area under curve was 0.983 and the best threshold was 9.025 ng/mL (sensitivity: 0.921, specificity: 0.951) for age ≥ 65.5 years old. The arrows in the both figures indicated the detected threshold values.



**Figure 3** The Kaplan Meier curve among different managements.

**Notes:** The primary endpoint of PSA progression was made according to their definition of recurrence. Median time to PSA progression was 24 (IQR:3) months in men choosing external-beam RT after transurethral surgeries. Log rank test: RASP after transurethral surgeries vs External-beam RT after transurethral surgeries ( $p < 0.001$ ); RASP only vs External-beam RT after transurethral surgeries ( $p < 0.001$ ); RASP after transurethral surgeries vs RASP only ( $p = 0.293$ ).

**Abbreviations:** RARP, Robot-assisted radical prostatectomy; RASP, Robot-assisted simple prostatectomy; RT, radiation therapy.

benign biopsies. A threshold of 9.025 ng/mL could serve as a reference to possible iPCa and the sensitivity of this value was more prominent in men below the threshold age. However, although PSA was the most distinguished independent variable predicting iPCa from benign biopsies, its practical use would be affected by several clinical factors. Prescription of 5 $\alpha$ RI was one of them. Based on two renowned clinical trials,<sup>23,24</sup> American Food and Drug Administration issued an announcement that such drugs, daily 5 mg finasteride for 7 years or daily 0.5 mg dutasteride for 4 years, would increase the risk of high-grade prostate cancer. In our multivariable logit model, this kind of prescription was not associated with iPCa from preoperative benign biopsies. We assumed that since low-grade cancer consisted of iPCa in majority, prescription of such drug did not increase the likelihood of iPCa.

Together with PSA, PSA velocity was often discussed as well. Based on the recommendations of the American Urological Association, PSA velocity of 0.75 ng/mL was applied to men with PSA interval of 4–10 ng/mL and was not applied to men with PSA over 10 ng/mL.<sup>25</sup> However, the definition in monitoring PSA velocity varies in a wide range in current literature. In previous analysis from the SEER database, Asian population would more likely have the significant Gleason group and experience the higher PSA when being diagnosed prostate cancer.<sup>26</sup> Herein, the characteristic among races should be considered. In this study, we defined the threshold of PSA velocity according to the previous large-scale study of Chinese society. Regardless of baseline PSA and age, PSA velocity over 0.75 ng/mL would indicate extreme 5% occasion in population.<sup>11</sup> After the multivariable analysis, the PSA velocity of 0.75 ng/mL could be an independent variable associated with the odds of iPCa.

Aside from discussing iPCa, another feature of this study was that we provided the comparison of RASP to other managements following confirming iPCa from transurethral surgeries. In organ-confined prostate cancer with the primary endpoint of PSA progression-free survival, RASP seemed equivalent to RARP in the short term under the condition of complete resection without PSM. Both of them were significantly superior to external-beam RT. However, this result was restricted by the limited statistical power. However, PSM of iPCa should always be kept in mind. In prostate cancer, T stage as well as margin status could determine the PSA progression after radical prostatectomy.<sup>27</sup> For an organ-confined prostate cancer, PSM might be equivalent to extracapsular extension.<sup>27</sup> In our experiences,<sup>28</sup> up to 50% of pT2+ prostate cancer would encounter biochemical recurrence in 10 years and the majority of them occurred in the first 5 years. Herein, tailored strategies were still required for those with iPCa.

There was some obvious bias in this study. Two of them were the distribution of PSA and prostatic volume. From skewness and kurtosis, PSA was remarkably right skewed with leptokurtic and this suggested that our conclusion

regarding it might be affected by some extremely distributed data in some degrees. One of the main explanations postulated to be related to this bias was that we only recruited data under the specific situation and from certain surgical techniques. Herein, some other occasions, such as non-diagnosed and non-treated prostate cancer in autopsies, or surgical specimens from other surgical techniques, such as cystoprostatectomy, were not included. These selection bias would lead to the abovementioned distribution of data to a certain degree. Based on this study and previous literature, prediction of iPCa from prostates with benign biopsies requires more clinical and laboratory parameters and great heterogeneity among studies has masked the evaluation of each independent variable. In order to correctly discuss this topic, more modern cohorts are needed. As for our novel finding regarding survival assessment of RASP, a longer observation study could be launched to compare the PSA-progression free survival between it and RARP after transurethral surgeries in organ-confined prostate cancer without PSM.

## Conclusion

High preoperative PSA was the most powerful sign predicting iPCa from preoperative benign biopsies, especially in those above 9.025 ng/mL. For an organ-confined iPCa without PSM, RASP was similar to RARP following transurethral surgeries in regard to PSA progression-free survival in the short term and external-beam RT was the inferior choice.

## Ethics Approval Statement

This study was conducted in accordance with the declaration of Helsinki and the corresponding regulations (IRB No. TTMHH-C1100014) from the local institutional human research committee of Tungs' Taichung MetroHarbor Hospital. For the retrospective nature, the patient consent was waived and we confirmed that the data was anonymized and maintained with confidentiality.

## Patient Consent Statement

Informed consent was exempt by the local institutional committee.

## Disclosure

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