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Prostate resected weight and postoperative prostate cancer incidence after transurethral resection of the prostate

A population-based study

Fu-Chao Liu, MD, PhD[a,b], Kuo-Chun Hua, MD[a,b], Jr-Rung Lin, PhD[c], See-Tong Pang, MD, PhD[d], Huang-Ping Yu, MD, PhD[a,b,e,*]

Abstract

To analyze whether different volumes of tissue resected during transurethral resection of the prostate (TURP) would associate with the subsequent development of prostate cancer.

This population-based retrospective cohort study recruited 49,206 patients with benign prostate hyperplasia (BPH) undergoing TURP between 2005 and 2012. Patients were recruited from the Taiwan National Health Insurance Research Database. Patients were separated into three groups, based on different volumes of tissue resected during TURP (5–15 g, 15–50 g, >50 g).

Of the 49,206 patients, 633 patients were diagnosed with new onset of prostate cancer following TURP. Older age was a risk factor contributing to the onset of prostate cancer ($P = .0196$) and different volumes of tissue resected were significantly related to the incidence of postoperative prostate cancer ($P = .0399$). The group of patients with a smaller volume of prostate resected had a higher risk of prostate cancer with a hazard ratio (HR) of 1.221 (95% confidence interval [CI]: 1.035, 1.440; $P = .0179$). However, the risk in the group of patients with a larger volume of prostrate resected was not significantly different, with an HR of 1.277 (95% CI: 0.981, 1662; $P = .0690$). The incidence of prostate cancer in Taiwanese males over 30 years of age has previously been reported to be 0.0560%; the mean incidence was 0.2282% in our present study.

This study shows that BPH patients who had a smaller volume of tissue resected during TURP show a higher incidence of prostate cancer postoperatively. Currently, no clear mechanism is shown to demonstrate the relationship between resected prostate weight and the incidence of tumors. Patients with a larger prostate volume might have lower urinary tract symptoms earlier and then seek professional help. It is possible that surgical procedures might remove the potentially carcinogenic prostate tissue and thus reduce the risk of an aggressive tumor developing in the future.

Abbreviations: BPH = benign prostate hyperplasia, ICD-9-CM = International Classification of Disease, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PSA = prostate specific antigen, Revision 9, TURP = transurethral resection of the prostate.

Keywords: benign prostate hyperplasia, cohort study, population-based study, prostate cancer, transurethral resection of the prostate

1. Introduction

Prostate cancer represents one of the most common cancers in men in the United States of America and remains the third-leading cause of cancer death in 2017.[1] More than 80% of men with prostate carcinoma also have benign prostate hyperplasia (BPH).[2] BPH and prostate cancer share many factors in common, including hormone-dependent growth and response to antiandrogen therapy, and the fact that they both predominantly occur in elderly males.[3] Furthermore, studies have shown that chronic inflammation, metabolic disorder, and genetic variation are all risk factors for both of these diseases.[4–7]

Even though BPH and prostate cancer have so many factors in common, current studies remain controversial in that some refer to BPH as a precursor of prostate cancer; instead, BPH may increase the chance of diagnosing an incidental prostate cancer because patients seek treatment for the relief of their symptoms.[8–12] Transurethral resection of the prostate (TURP) has been widely used as the primary surgical choice to treat obstructive uropathy. TURP-induced surgical trauma could promote the growth of tumor cells,[13] although a 10-year cohort study showed that neither BPH, nor TURP, would increase the risk of developing prostate cancer in patients with BPH.[14] However, the surgical procedures also could resect the potentially

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[a] The Department of Anesthesiology, Chang Gung Memorial Hospital, [b] College of Medicine, [c] Clinical Informatics and Medical Statistics Research Center and Graduate Institute of Clinical Medicine, Chang Gung University, [d] Department of Urology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [e] Department of Anesthesiology, Xiamen Chang Gung Hospital, Xiamen, China.

[*] Correspondence: Huang-Ping Yu, Department of Anesthesiology, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Kwei-Shan, Taoyuan, Taiwan 333 (e-mail: yuhp2001@adm.cgmh.org.tw).

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carcinogenic prostate tissue and decrease the development of early aggressive tumor.[15]

Previous studies are primarily focused on the potential adverse effects of TURP.[16–23] To the best of our knowledge, there has been no previous cohort study which has examined the association between resected prostate weight and the post-operative incidence of prostate cancer. The purpose of our study was to examine whether different weight of tissue

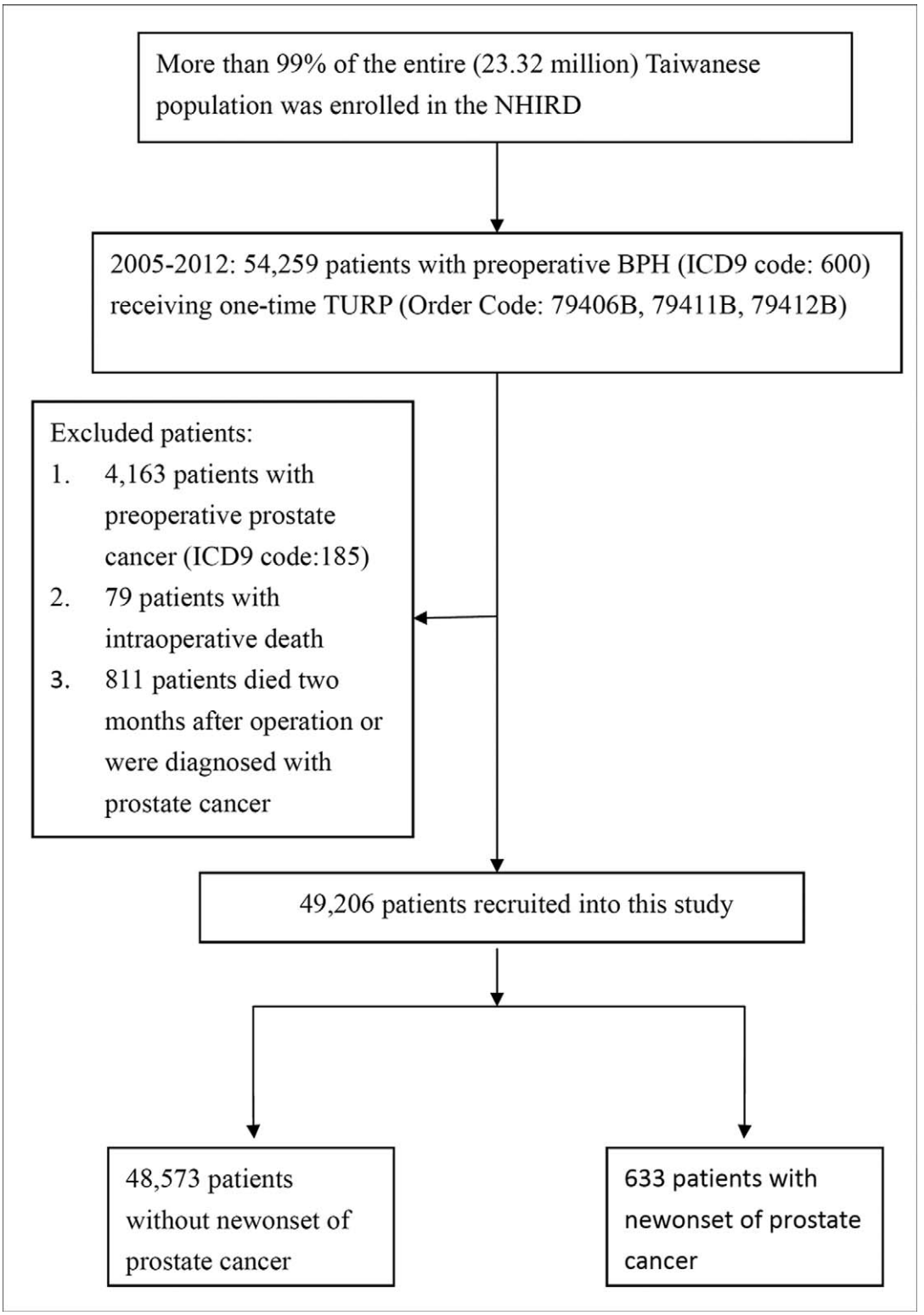

Figure 1. Study design and flowchart for patient selection featuring patients with preoperative BPH diagnosis receiving one-time TURP surgery between 2005 and 2012. BPH = benign prostate hyperplasia, NHIRD = the National Health Insurance Research Database, TURP = transurethral resection of the prostate.

resected during TURP would affect the development of prostate cancer postoperatively.

2. Materials and methods

2.1. Data resource

This study collected data from the National Health Insurance Research Database (NHIRD), provided by the National Health Research Institutes (NHRI), which holds detailed hospital records for every patient visit, including diagnostic codes, procedure orders, and medical expenses. BPH was coded as "600" and prostate cancer was coded as "185," according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Procedure order codes for TURP were applied based on the obtained tissue weight (79406B: 5–15 g; 79411B: 15–50 g; 79412B: >50 g).

This study was evaluated and approved by the NHIRD research committee (NHIRD-103-103) and the Institutional Review Board of Chang Gung Medical Foundation (104-6697B).

2.2. Study population

Figure 1 shows a flowchart which describes the way in which patients were selected. The NHIRD recorded the patient's date of diagnosis, the date of the medical procedure, and the date of ICD-9. Thus, between January 2005 and December 2012, we collated 54259 patients with a BPH code and a TURP date following diagnosis. The dates of TURP for BPH were defined as the index date; this also represented the start of the follow-up time during which we were looking for the occurrence of prostate cancer. Of these, 4163 patients with prostate cancer coded before the TURP date, we excluded 79 patients with intraoperative death and 811 patients who died post operatively, or were newly diagnosed with prostate cancer within two months postoperatively.[24] Thus, 49,206 patients remained in our cohort study. We separate these patients into three groups, based on the different weight of tissue resected during TURP (5–15 g, 15–50 g, >50 g). Table 1 shows the proportion of patients assigned to these three groups. Over the course of the follow-up time, there were 633 patients diagnosed with newly onset prostate cancer, but no prostate cancer coded for the remaining 48,573 patients.

Preoperative comorbidity was ascertained from medical records held by the inpatient or outpatient departments using ICD-9-CM codes for further analyses: diabetes mellitus (250), disorders of lipid metabolism (272), hypertension (401-405), acute kidney failure (584), chronic renal failure (585-586) and liver disease (456, 571-572).

2.3. Statistical analysis

We used SAS statistical software, version 9.3, (SAS institute Inc, Cary, NC) to evaluate our data. We set a *P*-value <.05 as statistically significant. The Pearson's chi-squared test, and two-sample *t*-tests, were performed to evaluate if patient's age, different resected tissue weight, and preoperative comorbidity, contributed any risk to the new onset of prostate cancer. Cox proportional hazards regression modeling was also conducted to estimate the hazard ratios for new onset of prostate cancer with the 15–50 g group as the baseline to compare with the 5–15 g and >50 g groups. Finally, Kaplan–Meier analysis was used to estimate the cumulative probability of prostate cancer developing during the follow-up period in patients who received TURP.

Table 1

Groups by resected volume.

Tissue weight	5–15 g (79406B)	15–50 g (79411B)	>50 g (79412B)	Total
Number of patients (%)	19392 (39.41)	25448 (51.72)	4366 (8.87)	49206

Numbers of patients in each group. Values are presented as n (%) unless otherwise indicated.

3. Results

Of the 49,206 patients recruited into our study, 633 patients were diagnosed with new onset of prostate cancer following TURP while the remaining 48,573 patients had no occurrence of prostate cancer during the study period (2005–2012). We separated these patients into two groups; Table 2 shows the demographic data for these patients. Older age was shown to be a risk factor contributing to the onset of prostate cancer, with a mean age of 72.25 versus 73.01 years ($P=.0196$). Different weight of tissue resected were also statistically significant and reflected the idea that resected weight might be a risk factor contributing the occurrence of prostate cancer ($P=.0399$). All other preoperative comorbidities showed no statistical difference between these two groups ($P>.05$).

To compare the hazard ratios with regards to the new onset of prostate cancer by different weight of tissue resected, Table 3 shows the result of three groups. The medium weight of 15–50 g group was set as the baseline and used for comparison with the other two groups. In the age-unadjusted comparison, the group with the smaller weight (5–15 g) had a higher risk of prostate cancer with a hazard ratio (HR) of 1.210 (95% confidence interval [CI]: 1.026, 1.428); $P=.0235$). For the larger weight group (>50 g), although the HR was 1.294 (95% CI: 0.994, 1.684), there was no statistical significance ($P=.0553$). In the age-adjusted comparison, the smaller weight group had a higher risk of prostate cancer with an HR of 1.221 (95% CI: 1.035, 1.440; $P=.0179$) and the group with a larger weight was not statistically significant with an HR of 1.277 (95% CI: 0.981, 1662; $P=.0690$).

For reference, Table 4 shows the comparison between our study group and the general population in terms of the

Table 2

Preoperative comorbidity analysis.

Risk factor	New onset prostate cancer		*P*-value
	No (n=48,573)	Yes (n=633)	
Age (mean [SD])	72.25 (8.68)	73.01 (8.14)	.0196
Tissue size			.0399
5–15 g (79406B)	19,125 (39.37)	267 (42.18)	
15–50 g (79411B)	25,150 (51.78)	298 (47.08)	
>50 g (79412B)	4298 (8.85)	68 (10.74)	
Diabetes mellitus	10,477 (21.57)	118 (18.64)	.0750
Disorders of lipid metabolism	11,419 (23.51)	145 (22.91)	.7226
Hypertension	27,666 (56.96)	369 (58.29)	.4999
Acute kidney failure	301 (0.62)	4 (0.63)	.7999
Chronic renal failure	1731 (3.56)	18 (2.84)	.3309
Liver disease	6316 (13.00)	81 (12.80)	.8778

Pearson's chi-squared test and the two-sample *t*-test were used to examine differences in the demographic characteristics of patients with BPH receiving TURP. Values are presented as n (%) unless otherwise indicated.

BPH = benign prostate hyperplasia, SD = standard deviation, TURP = transurethral resection of the prostate.

Table 3

Hazard ratios of new onset of prostate cancer based on resected volume.

	Age unadjusted		Age adjusted	
Factor	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Order code group		.0329		.0306
5–15 g (79406B)	1.210 (1.026, 1.428)	.0235	1.221 (1.035, 1.440)	.0179
15–50 g (79411B)	—	—	—	—
>50 g (79412B)	1.294 (0.994, 1.684)	.0553	1.277 (0.981, 1.662)	.0690

Cox proportional hazardous regression modeling was used to estimate the hazard ratios for new onset of prostate cancer with the 15–50 g group as the baseline to compare with the other groups.
HR = hazard ratio.

occurrence of prostate cancer during the period elapsing from 2005 to 2013. During this period, the mean incidence of prostate cancer for Taiwanese males over 30 years of age was 0.0560%. In our present cohort, the mean incidence rate was 0.2282%. The Standardized Incidence Ratio (SIR) between our study group and the general population was 4.08 (95% CI: 3.92, 4.24).

To understand the association between different sizes of tissue resected and the incidence of prostate cancer, Figure 2 shows unadjusted Kaplan–Meier curves for the cumulative probability of prostate cancer occurring during the follow-up period after patients had undergone TURP.

Some previous studies have shown that there is an inverse relationship between prostate size and the incidence of prostate cancer,[25–27] which means that the larger the prostate size, the lower the risk of developing prostate cancer. Hong et al[28] used preoperative magnetic resonance imaging (MRI) to assess preoperative prostate volume in 1756 men and examined their pathological outcome after radical prostatectomy. The results showed that smaller prostate volume was associated with a higher pathological Gleason score (≥7). Another study also found that patients with a smaller resected prostate volume had a higher grade of tumor and were at increased risk of biochemical progression following radical prostatectomy.[29]

4. Discussion

This study demonstrated that the smaller the weight of prostate tissue resected during TURP, the higher the risk of prostate cancer developing postoperatively. However, for those who were already diagnosed with prostate cancer, undergoing TURP would increase the risk of metastasis.[30] For this reason, we excluded patients from our initial data collection who were diagnosed with prostate cancer within two months of undergoing TURP.

There are potential adverse effects in patients receiving TURP. Postoperative complications include bleeding, urethral strictures, infection, and urge incontinence.[16–23] To our knowledge, there is no long-term cohort study to evaluate the association of resected weight of prostate and post-operative prostate cancer incidence in patients receiving TURP. Currently, there is no clear mechanism to demonstrate the relationship between prostate volume and the incidence of tumors. Some of the possible explanations are described below. First, serum androgen level may be a causative factor. Since the growth of prostate volume is androgen-dependent,[3] Schatzl et al[31] found that patients with a high Gleason score for prostate cancer had lower levels of testosterone and estradiol. Therefore, patients with a smaller prostate volume might have a more aggressive tumor. However, Monda et al.[32] found that serum testosterone level was unable to predict either prostate volume or tumor grading. Second, another factor might be difficult in spreading. Enlargement of the BPH-related transition zone might restrict the epithelial cells on the peripheral zone, thus causing atrophy or apoptosis of these epithelial cells and therefore reducing the risk of a tumor developing in the transition zone.[28] Finally, another factor might be the surgical removal of prostate tissue. Patients with a larger prostate volume might develop lower urinary tract symptoms earlier and then seek professional help. Surgery represents a way to remove the obstruction and thus relieve discomfort. As a result, it is possible that surgical procedures might remove the potentially carcinogenic prostate tissue and thus reduce the risk of an aggressive tumor developing in the future.[15]

Table 4

Comparison between patients with new onset of postoperative prostate cancer and the general population with prostate cancer.

	General population		Study group		
Year	**Cases of prostate cancer**	**Number of male population**	**Cases of prostate cancer**	**Number of TURP recipient**	**Cumulative person-year of follow-up**
2005	2703	6,541,107	15	6709	60,381
2006	3072	6,675,495	26	6156	109,629
2007	3365	6,780,384	39	6151	152,686
2008	3601	6,898,210	44	6448	191,374
2009	4013	7,018,403	49	6749	225,119
2010	4392	7,132,821	63	6400	250,719
2011	4628	7,247,815	80	5437	267,030
2012	4735	7,356,773	146	5156	277,342
2013	4801	7,455,081	171	—	277,342
Total	35,310	—	633	49206	

All men are above 30 years of age; the number in each year represents the number of cases of new onset of prostate cancer or the total numbers of each group.
TURP = transurethral resection of the prostate.

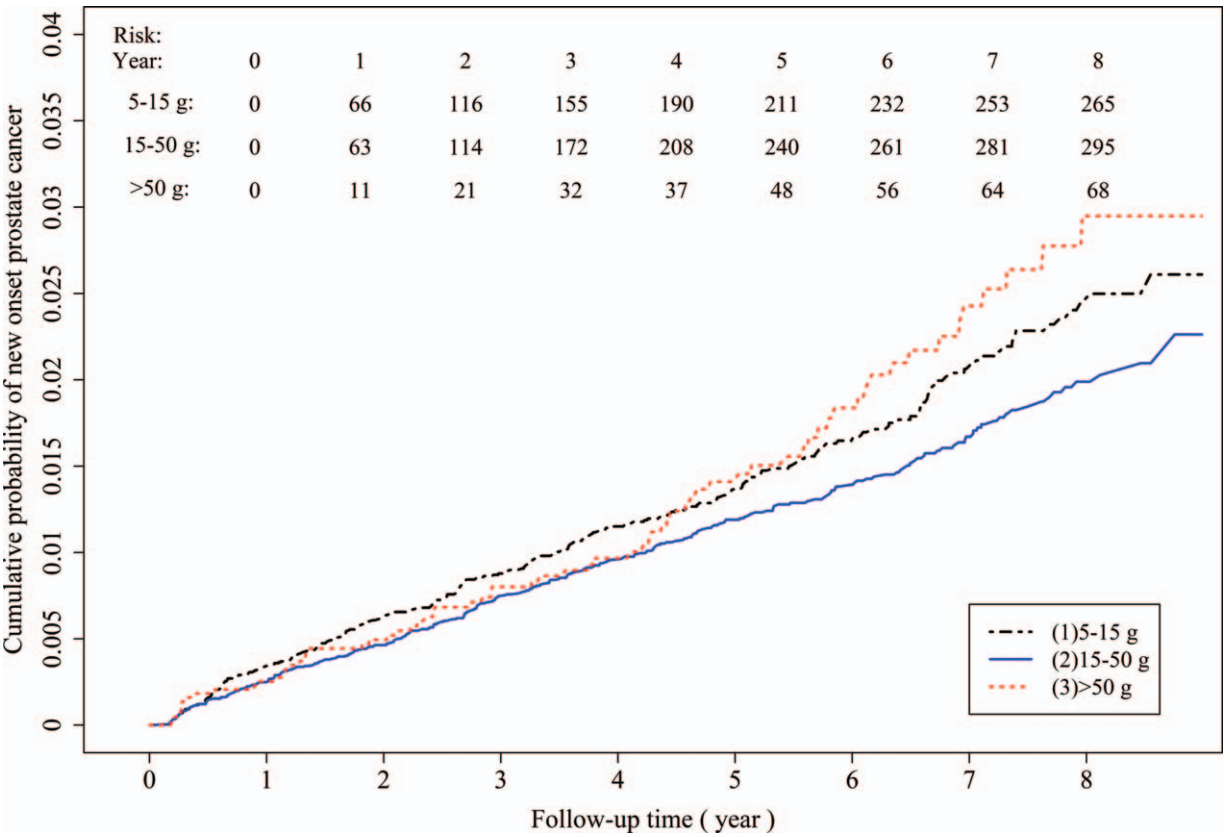

Figure 2. Unadjusted Kaplan–Meier curves for the cumulative probability of prostate cancer during the follow-up period of patients undergoing TURP. TURP = transurethral resection of the prostate.

4.1. Limitations and strengths

This population-based cohort study may have several limitations. First, we used ICD-9-CM codes to collect data from the NHIRD database; we must consider that there may have been coding mistakes due to human error. Thus, incorrectly coded data may have misled our analysis. The major risk factors of prostate cancer are age, race/ethnicity, and family history, and the most common factors trigger prostate biopsy are abnormal PSA and digital rectal examination. However, the database lacked clinical information, including preoperative serum PSA level, androgen level, prostate volume, postoperative pathological reports, and clinical tumor stages. As a result, the relationship between resected prostate weight and the aggressiveness of the prostate tumor could not be confirmed since we lacked the pathological reports to support these investigations. Strengths of the study are the long-term cohort method in a nationwide population. Our study had a relatively large number of patients and a long follow-up duration compared to other studies.

5. Conclusion

This population-based study in Taiwan showed that BPH patients with a smaller weight of tissue resected during TURP had a higher incidence of prostate cancer. Thus, the importance of postoperative surveillance should not be neglected. Future prospective studies are now needed to clarify the relationship between the prostate resected weight and aggressiveness of prostate tumor.

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Author contributions

Conceptualization: Fu-Chao Liu, Kuo-Chun Hua, See-Tong Pang, Huang-Ping Yu.
Data curation: Fu-Chao Liu, Kuo-Chun Hua.
Formal analysis: Kuo-Chun Hua, Jr-Rung Lin.
Funding acquisition: Huang-Ping Yu.
Methodology: Fu-Chao Liu, Jr-Rung Lin.
Supervision: Huang-Ping Yu.
Writing – original draft: Fu-Chao Liu, Kuo-Chun Hua.
Writing – review & editing: See-Tong Pang, Huang-Ping Yu.

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