An Advanced but Traditional Technique of Transurethral Resection of the Prostate in Order not to Overlook Stage T1 Prostate Cancer

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Key Words

BPH • Incidental prostate cancer • Latent prostate cancer • TURP

Abstract

Introduction: A little deeper resection was done during transurethral resection of the prostate (TURP) for benign prostate hyperplasia (BPH) to fill the disparities of reported prevalence rates between latent and incidental prostate cancer, as well as in order not to overlook clinically significant incidental cancer. **Patients and Methods:** We performed TURP in 995 patients who were diagnosed to have BPH. With a routine TUR setup, first most of the transition and central zones were resected. Then a slightly deeper resection of the residual adenoma and the peripheral zone than in the usual TURP was made. Pathological specimens were collected from 6 different parts. **Results:** Incidental cancer was diagnosed in 226 patients (22.7%). Gleason scores were distributed as follows: 6 or less in 150 cases (66.4%), 7 in 68 cases (30.1%), and 8 in 8 cases (3.5%). Even in the patients with lower prostate specific antigen (PSA), patients with incidental cancer and Gleason scores of 7 or more were 142 (21.2%) and 41 (28.9%) respectively at $0 < \text{PSA} < 4.0$ ng/ml, and 95 (18.7%) and 26 (27.4%) respectively at $0 < \text{PSA} < 2.5$ ng/ml. Multifocal/diffuse cancer was detected in 84 (37.2%) patients. **Conclusions:** With our method of advanced TURP, we detected incidental cancer at almost the same rate as reported in latent cancer. When TURP is performed, incidental cancer as well as to relieve voiding difficulties must not be overlooked,

because there must be a considerable number of clinically significant incidental cancer of higher Gleason scores, and of multifocal/diffuse lesions.

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Introduction

Since the introduction of prostate specific antigen (PSA) into clinical practice, the rate of incidental prostate cancer, which is detected with the specimen from transurethral resection of the prostate (TURP) for benign prostate hyperplasia (BPH), has gradually decreased and has been reported as 5.3–10.0% [1–9]. On the other hand, the prevalence of latent prostate cancer, which is incidentally detected at autopsy, has been reported as 19.7–24.2% in Japan [10–12]. There is a clear and considerable disparity in the reported rate of incidental cancer compared to latent cancer. In addition, prostate cancer is reported to develop in 2–3% of the patients who previously underwent TURP for BPH, and it tends to be diagnosed at an advanced stage [4,13]. These facts suggest that, in some of these patients, prostate cancer might be treated more appropriately if it was detected at the time of TURP. Urologists, as a result, have to perform TURP with the intention to detect incidental cancer as well as to relieve voiding difficulties. We previously reported radical TURP for prostate cancer (RTUR-PCa)

Table 1. Patient age, preoperative PSA, operation time and resected weight in patients with BPH (n = 769) or incidental prostate cancer (n = 226).

	Mean $\pm$ SD			Median (range)		
	BPH	Incidental cancer	p	BPH	Incidental cancer	p
Age, years	72.7 $\pm$ 7.9	74.9 $\pm$ 7.3	0.00017	73.0 (50–97)	75.0 (51–93)	0.00012
PSA, ng/ml	4.12 $\pm$ 5.72	4.33 $\pm$ 4.46	0.569	2.2 (0.11–81.14)	3.1 (0.32–35.41)	0.00093
Operation time, minute	76 $\pm$ 17	72 $\pm$ 16	0.0013	70 (40–140)	65 (50–125)	0.00005
Resected weight, g	23 $\pm$ 12	21 $\pm$ 11	0.0138	18 (5–82)	17 (7–65)	0.0180

P values were calculated with Student' t test and Man Whitney U test comparing BPH cases with incidental cancer cases.

[14]. And using the similar technique, we think a little deeper additional resection during TURP for BPH can help detect clinically significant T1 prostate cancer that might be overlooked.

Patients and Methods

TURP was performed in 995 patients under a diagnosis of BPH between April 2004 and February 2010. We informed the patients of the prevalence rate of incidental prostate cancer and of our procedure to improve the detection rate of cancer before performing TURP to relieve voiding difficulties. Patients who agreed with the procedure were eligible for the present study.

In patients with PSA values more than 4.0 ng/ml, ultrasound guided transrectal prostate biopsy was conducted if the patient had a PSA density (PSAD) of 0.15 or greater [15] to exclude prostate cancer before enrolling the patient in the study. We obtained a total of 14 samples per case including the far lateral part where the prostate was divided into the base, upper middle part, lower middle part and apex.

With a routine TUR setup using D-sorbitol solution, we first resected most of the transition and central zone, and then made a slightly deeper resection of the residual anterior fibromuscular stroma, transition zone and peripheral zone. A clockwise resection was made dividing the residual prostate into 6 parts starting from the 12 o'clock position, and the resected specimens were separately collected from each part for pathological examination. The number of examined specimens was around 80–90 chips per case. We used 34 β E12, p63 and AMACR (P504S) for immunohistological staining to confirm prostate cancer in all patients with a Gleason score of 6 or less.

Results

Incidental cancer was diagnosed in 226 (22.7%) out of 995 patients who underwent TURP under the diagno-

sis of BPH. One patient was given a diagnosis of prostate ductal cancer. The age of patients ranged from 50 to 97 years (mean $\pm$ SD, 73.2 $\pm$ 7.8 years; median, 74.0); preoperative PSA, 0.11–81.14 ng/ml (4.17 $\pm$ 5.45 ng/ml; 2.5); operation time, 40–140 minutes (75 $\pm$ 17 minutes; 70); resected weight, 5 - 82 g (23 $\pm$ 12 g; 18). Table 1 shows patients' characteristics of the BPH group and the incidental cancer group. A PSA value of 81.14 ng/ml in a patient was as a result of urinary retention and urinary tract infection due to BPH.

Age distribution of patients with BPH or incidental cancer is shown in table 2. Gleason scores (GS) are also shown in the cancer group. Incidental cancer was diagnosed in 12.5% of patients in the fifth decade of life, 17.5% in the sixth, 23.4% in the seventh, 29.9% in the eighth, and 23.5% in the ninth. Gleason scores were as follows: 4 in 7 cases (3.1%), 5 in 18 (8.0%), 6 in 125 (55.3%), 7 in 68 (30.1%), and 8 in 8 (3.5%).

Table 3 shows age distribution of patients with BPH or incidental cancer who had preoperative PSA values less than 4.0 ng/ml. In this subgroup (PSA < 4.0 ng/ml), incidental cancer was diagnosed in 142 (21.2%) out of 669 patients. The rate of incidental cancer for each age was as follows: 16.1% of patients in the fifth decade, 16.1% in the sixth, 21.7% in the seventh, 26.9% in the eighth, and 23.1% in the ninth. Gleason scores in this lower PSA subgroup were as follows: 4 in 7 cases (4.9%), 5 in 14 (9.9%), 6 in 80 (56.3%), 7 in 36 (25.4%), and 8 in 5 (3.5%).

Table 4 shows PSA distribution of patients with BPH or incidental cancer. The number of cases with incidental cancer were as follows: 95 (18.7%) in 508 patients with PSA < 2.5 ng/ml and 131 (26.9%) of 487 patients with PSA > 2.5 ng/ml. Incidental cancer comprised 19

Table 2. Age distribution of patients with BPH or incidental cancer who underwent TURP. Gleason scores are also shown

	Age, years					Total
	50–59	60–69	70–79	80–89	90~	
BPH, n (%)	42 (87.5%)	193 (82.5%)	390 (76.6%)	131 (70.1%)	13 (76.5%)	769 (77.3%)
Incidental cancer, n (%)	6 (12.5%)	41 (17.5%)	119 (23.4%)	56 (29.9%)	4 (23.5%)	226 (22.7%)
GS						
4	1	2	3	0	1	7 (3.1%)
5	0	0	18	0	0	18 (8.0%)
6	3	24	61	35	2	125 (55.3%)
7	2	14	32	19	1	68 (30.1%)
8	0	1	5	2	0	8 (3.5%)

Table 3. Age distribution of patients with BPH or incidental cancer who have PSA levels less than 4.0 ng/ml. Gleason scores are also shown

	Age, years					Total
	50–59	60–69	70–79	80–89	90~	
BPH, n (%)	26 (83.9%)	125 (83.9%)	271 (78.3%)	95 (73.1%)	10 (76.9%)	527 (78.8%)
Incidental cancer, n (%)	5 (16.1%)	24 (16.1%)	75 (21.7%)	35 (26.9%)	3 (23.1%)	142 (21.2%)
GS						
4	1	2	3	0	1	7 (4.9%)
5	0	0	14	0	0	14 (9.9%)
6	2	15	37	25	1	80 (56.3%)
7	2	7	18	8	1	36 (25.4%)
8	0	0	3	2	0	5 (3.5%)

Table 4. PSA distribution of patients with BPH or incidental prostate cancer who underwent TURP. Gleason scores are also shown

	PSA, ng/ml								Total
	0.11~	1.0~	2.0~	2.5~	3.0~	4.0~	10.0~	20.0~	
BPH, n (%)	168 (87.0%)	189 (80.4%)	56 (70.0%)	39 (70.9%)	72 (69.9%)	172 (72.6%)	50 (76.9%)	23 (85.2%)	769 (77.3%)
IC, n (%)	25 (13.0%)	46 (19.6%)	24 (30.0%)	16 (29.1%)	31 (30.1%)	65 (27.4%)	15 (23.1%)	4 (14.8%)	226 (22.7%)
GS									
4	0	4	0	1	2	0	0	0	7 (3.1%)
5	2	6	3	0	3	3	1	0	18 (8.0%)
6	17	20	17	8	18	34	8	3	125 (55.3%)
7	5	14	4	6	7	25	6	1	68 (30.1%)
8	1	2	0	1	1	3	0	0	8 (3.5%)

IC = Incidental cancer.

Fig. 1. Location of the collected prostate tissues and the distribution of cancer. Around the urethra, the prostate was divided into six parts starting from the 12 o'clock position clockwise. The detection rate of cancer in each part was indicated, but no significant differences were noted (chi square test, $p = 0.133$).

(20.7%) out of 92 patients with a PSA level of 10.0 ng/ml or more, indicating that there was no significant difference compared to the patients with PSA less than 2.5 ng/ml ($p = 0.66$, chi square test).

Figure 1 shows the distribution of incidental cancer detected in each part of the six parts of the prostate. No significant statistical difference was noted concerning the location of cancer (chi square test, $p = 0.133$). Localized cancer (cancer detected in 1 part or in 2 adjacent parts) was diagnosed in 142 patients (62.8%), while diffuse cancer (cancer detected in more than 2 parts that were not side by side, or detected in 3 parts or more) was diagnosed in 84 patients (37.2%). There were 112 (11.3%) patients with stage A1 cancer and 114 (11.5%) with stage A2 (Whitmore-Jewett).

We checked PSA values 3 months after TURP in 212 of the patients with incidental cancer. PSA values decreased to a level between 0.001 and 2.005 ng/ml (mean $\pm$ SD, 0.342 ± 0.327 ng/ml; median, 0.247). Radical TUR-PCa was performed [14] in 16 patients who showed gradual PSA elevation.

No patient received a transfusion or did water intoxication develop perioperatively. Postoperative morbidities include epididymitis in 35 patients (3.5%), bladder neck contracture in 10 patients (1.0%) and late hemorrhage in 9 patients (0.9%). These morbidities were almost at the same rate as those reported in usual TURP for BPH. Stress incontinence and erectile dysfunction did not develop.

Discussion

During routine TURP for BPH, resected specimens for pathological examination are mainly collected from the transition and central zone, but enough specimens may not necessarily be collected from the peripheral zone. Prostate cancer is reported to originate from the transition and central zone in 30% of patients and from the peripheral zone in 70% [16]. Detection rate of prostate cancer in patients who undergo usual TURP, therefore, may become lower with some of them being missed in diagnosis. The Association of Directors of Anatomic and Surgical Pathology recommends a method of examination of TURP specimens [17]. But Trpkov et al. [18] reported that pathological examination with a limited amount of specimen was enough to make a correct diagnosis and also was cost effective. We precisely examined cancer in the peripheral zone by resecting a little more prostate tissue in the peripheral zone than in usual TURP. We reduced the number of examined chips by omitting most of the chips from the transition and central zone. If diagnosis of cancer in the transition zone was missed by omitting the chips to be examined, enough deeper resection could eliminate cancer tissues resulting in a satisfactory clinical result.

Our patients had relatively higher PSA levels (4.17–5.45 ng/ml, median 2.5), but the detected number of incidental cancer was not so different in the lower PSA group compared to the higher PSA group. These results support our biopsy criteria based on a PSAD of 0.15 or more.

In the present study, incidental cancer was diagnosed in 22.7% of the patients, and the rate nearly reached the reported rate of latent cancer. Detection rate of incidental cancer increased as the age of patients increased between 50 and 89 years. The lower rate in patients between 90 and 97 years old was attributable to the small patient number. It is reported that cancer developed after TURP tends to be advanced [13], because a patient with an improved voiding state may seldom visit a clinic to

check PSA, resulting in a delayed diagnosis of prostate cancer. As a historical control in our clinic, 34 (5.3%) patients were diagnosed to have incidental cancer out of 646 patients who underwent usual TURP during the period between January 2001 and May 2004. The rate of incidental cancer was almost the same as other reported rates. Our present method of resecting and collecting specimens during TURP is sure to increase the detection rate of incidental cancer and, as a result, the number of patients who receive a diagnosis of high-stage prostate cancer long after TURP is expected to decrease.

Gleason scores of the patients with incidental cancer were distributed as follows: 6 or less in 150 patients (66.4%), 7 in 68 patients (30.1%), and 8 in 8 patients (3.5%). Concerning latent cancer of the Japanese, well-differentiated cancer accounts for 71% and moderately and poorly differentiated cancer accounts for 29% [12]. These reported figures were comparable to our present results of incidental cancer. More importantly, based on our results that 84 (37.2%) patients had diffuse incidental cancer and 76 (33.6%) patients had Gleason scores of 7 or more, we can conclude that a considerable number of clinically significant incidental cancers may be included in patients who undergo TURP for BPH.

A study reported that, even in patients with a PSA value less than 4.0 ng/ml, there were 13% of stage T3 cases, while lymph node metastasis was detected in 9% of patients and distant metastasis in 11% [19]. Another study reported that indolent cancer [20] was only 26.0–30.8% of patients with prostate cancer and a PSA of 4.0 ng/ml or less [21, 22]. We therefore think that incidental cancer must be detected if it exists in a patient who has a clinical diagnosis of BPH with a low PSA level. In the present study, incidental cancer was diagnosed in 21.2% (table 2) of patients with PSA less than 4.0 ng/ml. This was almost the same rate as the reported 21.9% in the study about latent cancer [22]. Forty-one (28.9%) patients had higher Gleason scores of 7 or more in the present study. And even in the patients with PSA < 2.5 ng/ml, incidental cancer was detected in 18.7%, and 26 (27.4%) of these patients had a Gleason score of 7 or more. Meeks et al. [23] recently reported a similar result in this patient group (PSA < 2.5 ng/ml) that 20 (26.0%) of 77 confirmed prostate cancers by radical prostatectomy had Gleason scores of 7 or greater.

TURP is usually performed to improve voiding difficulties of patients with BPH. In the present study, we detected more cases with incidental cancer by resecting the peripheral zone a little more deeply. The detected rate of incidental cancer was almost the same as that of latent

cancer. But Zigeuner et al. [3] reported that the rate of incidental cancer treated with usual TURP was 6.4% and pathological examination might not necessarily be required because of this low rate. They therefore concluded that treatment procedures that could not obtain tissue sample might be warranted [3]. As for the technique to manage BPH today, many transurethral less invasive procedures are available using LASER, high intensity focused ultrasound, thermotherapy and vaporization. We think such procedures with no pathological samples seem inferior to TURP in the point of improving the detection rate of incidental cancer. For holmium laser enucleation of the prostate or transurethral enucleation with bipolar, a little deeper additional resection after these procedure is possible.

Conclusions

The main purpose of TURP for BPH is to relieve voiding difficulties, but it is also very important to detect incidental cancer. We conclude, based on the results of advanced TURP, that we could show the importance of the method of tissue sampling and pathological examination: the detection rate of incidental cancer reached nearly the reported rate of latent cancer and a considerable number of incidental cancer was clinically significant.

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