Incidental prostate cancer: Predictors of progression and strategies of management based on prostate-specific antigen

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Abstract: We studied predictors for the progression of incidental prostate cancer (PCa) to optimize the management strategies that are still controversial in the era of prostate-specific antigen (PSA). We performed advanced transurethral resection of the prostate (TURP) in 995 patients with benign prostate hyperplasia (BPH). Of these, 226 patients (22.7%) had incidental PCa. Included in the present study were 146 patients followed up for two years or longer. In the treated group of 26 patients whose PSA elevated, we performed radical transurethral resection of PCa (TURPCa) in 23 patients, palliative TURP in one, and endocrine therapy in two. Between the observed and treated groups, statistical differences were noted in PSA related parameters: preoperative PSA (Pre PSA), PSA three months after surgery (Post PSA), % Post PSA/Pre PSA (%PSA ratio), and PSA density (PSAD). No differences were noted in the clinical stage (T1a, T1b) and Gleason scores. Of 23 patients underwent radical TURPCa, one had pT0 disease, one showed PSA failure, and 19 had stable PSA. It may be rational and practical to decide the treatment strategy of incidental PCa based on PSA changes before and after TURP rather than Gleason scores or clinical stages.

Keywords: Incidental Prostate Cancer, Benign Prostate Hyperplasia, Advanced Transurethral Resection of the Prostate, Prostate-Specific Antigen, Radical Transurethral Resection of Prostate Cancer

1. Introduction

Incidental prostate cancer is now classified into T1a and T1b, based on the report which was published about 30 years ago [1] when PSA testing was not as sensitive, considering the pathologic result that percent cancer tissue detected in the resected tips is greater or less than 5%, together with the differentiation of cancer [2]. According to this classification, patients with T1a cancer are usually observed through periodical follow-up and patients with T1b cancer can be candidates of active treatment [3]. These simple criteria have become inappropriate because there are some patients with T1a disease which shows progression to advanced cancer [4]. The selection of proper management of T1a cancer still remains controversial and difficult because there are sometimes pT0 cancer and considerable number of insignificant cancer.

When patients have received a diagnosis of incidental cancer, current standard technique of transurethral resection of

the prostate (TURP) does not provide sufficient pathological information about the peripheral zone where most of cancer arises. We previously reported advanced TURP for benign prostate hyperplasia (BPH) in order not to overlook incidental cancer by adding a slightly deeper resection of the peripheral zone [5]. Advanced TURP can be considered to give more information about Gleason's scores and the distribution of incidental cancer compared with the usual TURP. In the present study, we compared clinical parameters that could be potential predictors of the cancer progression in order to evaluate the validity of treatment selection.

2. Patients and Methods

We performed advanced TURP in 995 patients with BPH between April 2004 and January 2010. Patient's age ranged from 50 to 97 years (mean ± SD, 73.2 ± 7.8 years; median,

74.0). We first resected most of the transition zone, central zone, central zone and anterior fibromuscular stroma, and then made a slightly deeper additional resection of the residual adenoma and the peripheral zone. A clockwise resection was made dividing the residual prostate into six equal parts starting from the 12 o'clock position, and the resected specimens from each part were separately collected for pathological examination. We enrolled 146 patients in the study who were diagnosed to have incidental cancer by advanced TURP and followed up for two years or longer.

PSA was first measured three months after advanced TURP and every two months thereafter. Patients whose PSA showed three consecutive rises from the nadir were treated by radical TURPCa [6] or endocrine therapy with a steroidal progestin of chlormadinone acetate (Treated group) depending on the conditions of the patients. We informed the patients that radical TURPCa was not a standard radical surgery, and those who did not agree with the procedure were excluded from the study. We conducted radical TURPCa in 23 patients, while palliative TURP in one patient who suffered from urinary retention. Two patients chose to take endocrine therapy. PSA follow-up policy was selected in 120 patients who had showed stable PSA (Observed group). In the treated (26 patients) and the observed (120 patients) groups, Mann-Whitney or chi-square tests were applied to patient age, preoperative PSA (Pre PSA), PSA 3 months after TURP (Post PSA), % Post PSA/Pre PSA (%PSA ratio), PSA density (PSAD), Gleason scores, and cancer occupying rate (%Cancer tips). Gleason scores were determined based on the Gleason system of "Gleason's Modification 1974 & 1977". PSA density is calculated by preoperative PSA divided by the resected weight, and %Cancer tips by the number of tips that contain cancer divided by the total number of resected tips.

Table 1. *Clinical parameters of the patients with incidental prostate cancer*

Group	Age (years)	Resected weight (grams)	PSA (ng/mL)			PSAD (ng/mL per resected gram)	%Cancer tips in resected samples	Clinical stage (cases)	
			Pre PSA (Before TURP)	Post PSA (after TURP)	% PSA Ratio (After/Before)				
			Mean±SD / Median / (range)					T1a	T1b
Observed Group n=120	73.50±7.14	20.44±9.82	3.94±4.32	0.27±0.23	10.64±9.80	0.18±0.14	6.40±7.53		
	74	17	2.60	0.22	7.30	0.15	4.30	54	66
	(57-90)	(8-65)	(0.32-35.41)	(0.012-1.178)	(0.2-52.0)	(0.02-1.11)	(1.4-64.3)		
Treated Group n=26	76.62±5.87	24.0±14.45	6.07±6.15	0.71±0.57	18.44±13.53	0.28±0.31	4.41±2.89		
	74.5	18.5	4.64	0.63	16.80	0.19	3.60	9	17
	(68-89)	(8-61)	(0.70-29.21)	(0.069-2.082)	(0.8-51.8)	(0.05-1.72)	(1.4-13.6)		
P value	0.100	0.470	0.018	0.00001	0.005	0.032	0.448	0.372	

Table 2. *Preoperative Gleason scores of prostate cancer in the observed and treated groups*

| Gleason Score | Overall patients | | Patients with preoperative PSA value of lower than 4.0 ng/mL | |
	Observed Group n=120 (100%)	Treated Group n=26 (100%)	Observed Group n=81 (100%)	Treated Group n=12 (100%)
5	13 (3.8%)	1 (3.8%)	12 (14.8%)	1 (8.3%)
6	69 (57.5%)	13 (50.0%)	46 (56.8%)	7 (58.3%)
7	33 (27.5%)	8 (30.8%)	20 (24.7%)	3 (25.0%)
8	5 (4.2%)	4 (15.4%)	3 (3.7%)	1 (8.3%)
P value	0.065		0.534	

3. Results

All the studied patients were followed for a period between 25 and 106 months (mean ± SD, 68.7 ± 25.4 months; median, 66.0). The follow-up periods were 27 to 106 months (mean ± SD, 69.2 ± 25.2 months; median, 67.1) in the observed group, and 25 to 106 months (mean ± SD, 66.4 ± 23.9 months; median, 64.2) in the treated group.

Table 1 shows clinical characteristics of 120 cases of the observed and 26 cases of the treated group and Table 2 shows Gleason scores in each group. Statistically significant differences were noted in PSA related parameters: Pre PSA, Post PSA, %PSA ratio, and PSAD. Two patients with high PSA values (29.21 and 35.41 ng/mL) had urinary retention and prostatitis respectively, and PSA became low values after TURP. No significant differences were noted in patient age, resected weight, and %Cancer tips. And we could not find any significant differences in clinical stage and Gleason scores.

Table 3. *Clinical parameters of the patients with preoperative PSA value of lower than 4.0 ng/mL*

Group	Age (years)	Resected weight (grams)	PSA (ng/mL)			PSAD (ng/mL per resected gram)	%Cancer tips in resected samples	Clinical stage (cases)	
			Pre PSA (Before TURP)	Post PSA (after TURP)	% PSA Ratio (After/Before)				
			Mean±SD / Median / (range)					T1a	T1b
Observed Group n=81	73.53±7.38	17.27±7.38	1.97±0.96	0.25±0.22	13.42±10.60	0.12±0.05	5.33±4.31		
	75	15	1.80	0.15	11.60	0.12	4.30	38	43
	(57-90)	(8-65)	(0.32-3.75)	(0.012-1.040)	(0.2-52.0)	(0.02-0.25)	(1.4-21.4)		
Treated Group n=12	78.08±5.72	16.75±7.93	2.24±0.85	0.55±0.31	25.00±12.41	0.15±0.06	3.42±1.99		
	77.5	15.5	2.16	0.63	22.60	0.16	2.90	7	5
	(68-87)	(8-40)	(0.70-3.62)	(0.138-1.218)	(6.7-51.8)	(0.05-0.24)	(1.4-7.1)		
P value	0.066	0.696	0.300	0.00061	0.00205	0.093	0.229	0.460	

In the treated group, 23 patients underwent radical TURPCa 6 to 72 months (mean ± SD, 29.2 ± 20.3 months; median, 23.5) after given a diagnosis of incidental prostate cancer. Another two patients were treated by endocrine therapy, in whom consecutive PSA rises had been noted at 16 and 66 months after the diagnosis of incidental prostate cancer. One of the two patients refused radical therapy and the other patient was selected to give endocrine therapy because of the age of 94 years. Palliative TURP (partial minimal resection of the enlarged prostate to relieve voiding difficulties) was performed in one patient in the treated group. Though his PSA had shown consecutive rises 42 months after the diagnosis of incidental cancer with Gleason score of 3 + 4, he refused to take any treatment and did not come back to the clinic, but urinary retention developed 52 months later. Gleason scores of palliative TURP samples were 4 + 5.

Clinical stages of the 23 patients who underwent radical TURPCa were T1a in 8 cases and T1b in 15 cases, and pathological stages were pT0 in 1 case, pT2a in 15 cases, and pT2b in 7 cases. PSA failure after radical TURPCa occurred in one patient with stage pT2a disease and Gleason scores of 4 + 4. PSA failure was suspected when PSA showed a consecutive rise more than 0.2 ng/mL. If the PSA level reached a plateau between 0.2 and 1.0 ng/mL, we did not immediately think

treatment failure had occurred because there may be residual prostate tissue after TURPCa [6]. One patient never returned to the clinic and was lost to follow up after radical TURPCa. In 21 out of 23 patients, PSA remained stable between the period of 5 and 83 months (mean ± SD, 44.6 ± 21.5 months; median, 49.0) after radical TURPCa. The latest PSA values were as follows: PSA≤0.01 ng/mL, 9 cases; ≤0.02, 3 cases; ≤0.03, 3 cases; ≤0.04, 3 cases; ≤0.4, 1 case. Two patients died during the follow-up period. One died of hematological disease at 79 months and the other of pneumonia at 23 months postoperatively, with low PSA levels of 0.013 ng/mL and 0.028 ng/mL respectively. There were no patients who died of prostate cancer.

No patient received a transfusion or water intoxication did not develop around advanced TURP. Postoperative morbidities include epididymitis (3.5%), bladder neck contracture (1.0%) and late hemorrhage (0.9%). Stress incontinence and erectile dysfunction did not develop. After radical TURPCa, bladder neck contracture occurred in 13 patients (56.5%), and rectourethral fistula in one (4.3%). We successfully treated bladder neck contracture by optical urethrotomy. Rectourethral fistula healed after indwelling of a catheter for 10 months.

Table 4. *Gleason scores of prostate cancer determined by advanced TURP and radical TURPCa*

Clinical Stage	Gleason Score			T0
	Same	Different		
		Upgrade	Downgrade	
T1a n=8 (100%)	2(25.0%)	6(75.0%)	0(0%)	0(0%)
T1b n=16 (100%)	7(43.8%)	4(25.0%)	4(25.0%)	1(6.3%)
Total n=24 (100%)	9(37.5%)	10(41.7%)	4(16.7%)	1(4.2%)

We investigated predictive factors in the subgroup of patients with preoperative PSA value of lower than 4.0 ng/mL (Table 2, 3) because 12.9% of patients even in this subgroup finally required radical TURPCa. Significant differences were noted in Post PSA and %PSA ratio, but not in Pre PSA, Gleason scores and clinical stage. In Table 4, Gleason scores of the cancer tissue obtained by advanced TURP are compared with those by radical TURPCa. Consistency of Gleason scores was noted in only 9 patients (37.5%). In the other 14 patients (58.3%), Gleason scores were upgraded in 10 patients (41.7%)

and downgraded in 4 patients (16.7%). One patient with T1b cancer (4.2%) finally received a diagnosed of pT0 cancer.

4. Discussion

Radical prostatectomy for incidental prostate cancer, open or laparoscopic, is reported to have satisfactory oncologic outcome but functional outcome is inferior compared with the patients without history of TURP [7-11]. Thus, in the management of incidental prostate cancer, postoperative

morbidities resulted from probable overtreatment might become more important compared with T1c cancer. Capitanio et al., studying the predictive factors related to the progression of incidental cancer, reported that PSA before and after surgery and the Gleason scores of resected tissues were important factors, while the stage of the disease such as T1a or T1b was not [12]. Descazeaud et al. also reported that the predictive factors of progression of T1a cancer were PSA before and after surgery, prostate volume, resected weight and Gleason scores [4]. Melchiors et al. pointed out that there was considerable disparity of Gleason scores between specimens obtained from TURP and those from radical prostatectomy [13]. Epstein et al. also reported that it was difficult to predict the clinical significance of incidental cancer by Gleason scores [14]. Some reports, therefore, state that the current staging system may need reassessment [12,13,15].

Most incidental prostate cancers are low-volume and early stage ones, but there are actually some clinically important cancers that can be progressive [4,9]. Predictive factors of the clinically important incidental cancer have not been clarified because its biological behavior is still difficult to understand. Similar issue is present concerning T1c cancer, the issues that results of prostate biopsy or PSA values cannot necessarily indicate the whole state of cancer. More precise pathological information can be obtained by advanced TURP compared with usual TURP for BPH as far as incidental cancer is concerned [5]. We could get a higher detective rate by advanced TURP, but in the present study pathological results were not necessarily consistent with those obtained by radical TURP. This might be attributed to the time lag of each TURP (median, 23.5 months), or an unresolved disposition of latent cancer.

Pathological findings are considered to be the most important points in the active surveillance for T1c cancer and periodical biopsy, which is relatively an invasive procedure, is mandatory. PSA changes are thought to reflect the whole state of changes in the peripheral, transition and central zones as well as changes in the cancer focus. On the contrary, PSA changes after advanced TURP, in which we resect almost all of the transition and central zones, mainly reflect the state of the peripheral zone. PSA changes even as minimal as one decimal place can be considered to reflect the state of residual cancer. Biopsy cannot always detect the cancer cells when cancer focus is small. In the present study, 22 out of 23 patients who showed consecutive rise of PSA had residual cancer and only one (4.3%) had T0 disease. We therefore consider that it is appropriate to follow patients with incidental prostate cancer by periodical PSA check after advanced TURP.

Our present study on the predictive factors for the progression of incidental prostate cancer indicated that PSA related parameters were important, but stages of cancer could not be an predictive factor as other reports stated [12,13,15]. In the patients who showed consecutive PSA rises, we selected aggressive therapies such as radical TURPCa [6] or endocrine therapy. In these 23 patients who underwent radical TURPCa, 22 patients had residual cancer with one exceptional

case (4.3%) of pT0. Oncological and functional outcomes were considered satisfactory. These results might support the validity of the treatment strategy against incidental PCa, the strategy that should be decided based on the PSA related parameters. More careful follow-up is needed especially in patients with high Post PSA and high %PSA ratio.

Patients in the observed group must be followed up for a longer period because we cannot evaluate residual cancer. Some of these patients may need radical treatment in the future. Though patients with Gleason Score of 8 had a tendency to receive an additional treatment, these patients may not miss appropriate chance of radical treatment with the strict regular check of PSA.

5. Conclusions

The present study with mean follow-up period of 69.2 months might suggest that the important predictive factors for the probable progression of incidental PCa are PSA related parameters: PSA before and after TURP, %PSA ratio, and PSAD. And it seems difficult to decide the treatment strategy by Gleason scores or clinical stages. Further study remains to be done with a larger number of patients and a longer period of follow-up before obtaining persuasive conclusions.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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