JOURNAL OF
Endoluminal Endourology

Original Article
DOI:10.22374/jeleu.v3i2.87

CAN TRANSURETHRAL RESECTION OF THE PROSTATE (TURP) BE ANOTHER GATEWAY TO THE FOCAL THERAPY OF LOCALIZED PROSTATE CANCER?

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Submitted: May 4, 2020. Accepted: June 23, 2020. Published: July 14, 2020.

ABSTRACT

Background and Objectives

Minimally invasive methods are expected to avoid the risk of overtreatment and overtreatment of radical therapy to manage the increased number of patients with low-volume, low-grade localized prostate cancer. Based on our experience of radical transurethral resection of prostate cancer (TURPCa) as a radical treatment, we studied the efficacy and safety of focal TURPCa as a focal therapy for patients with localized prostate cancer.

Materials and Methods

We performed focal TURPCa in 49 patients during the period from July 2007 to August 2016 and followed them with prostate-specific antigen (PSA) testing for the mean period of 68.0 months. We selected the patient as a candidate for the study if the biopsy revealed that cancer foci were limited in one lobe, or the foci were several or less even found in both lobes. Standard TURP was followed by further resection and fulguration of the peripheral zone where cancer was considered to exist. We selected one of our three methods of focal TURPCa as follows: one lobe radical TURPCa, radical resection of the affected lobe with unaffected lobe being resected less vigorously; nerve-sparing radical TURPCa, radical resection of both lobes except for the posterolateral part of the prostate; target radical TURPCa, radical resection of the cancer focus and the surrounding prostate when the target is suggested single.

Results

Twelve patients were in the low-risk group (D'Amico), 29 in the intermediate-risk group, and 8 in the high-risk group. Pathological stages were as follows: pT0, three cases; pT2a-b, 17 cases; pT2c, 29 cases. The preoperative PSA of 6.15±2.73 ng/mL (mean±SD) dropped to 0.172±0.283 ng/mL postoperatively. PSA failure occurred in only two patients (4.1%). Incontinence did not develop and erectile function was preserved in eight (44.4%) of the 18 potent patients. The most frequent complication was bladder neck contracture (20.4%). Other complications included acute epididymitis (8.1%), bladder tamponade (2.0%). No patients died of prostate cancer.

Conclusions

Though the final assessment of efficacy will require long-term follow-up results with more cases, we may think focal TURPCa can be another treatment option as a focal therapy for localized prostate cancer.

Key Words: *advanced TURP, prostate cancer, focal therapy, focal TURPCa, radical TURPCa*

After the introduction of prostate-specific antigen (PSA) testing to a health checkup program, the number of patients with low-volume, low-grade localized prostate cancer has been increasing. In these patients, standard radical therapy of radical prostatectomy or radiation therapy may cause such complications as micturition disorder including incontinence, erectile dysfunction, and rectal disorders. To avoid possible overdiagnosis and overtreatment of radical therapy resulted from prostate cancer screening,[1] active surveillance or watchful waiting[2,3] has been introduced. Focal therapy has been also proposed[4,5,6] as another means of treatment. Cryotherapy [7,8] and high-intensity focused ultrasound (HIFU)[9,10] are currently available modalities but reported clinical results are still controversial.[11] They may seem somewhat difficult to be a standard therapy until methods are established to determine the accurate cancer localization. Mapping biopsy[12,13] and multiparametric magnetic resonance imaging[14–16] seem very helpful but still incomplete for the precise cancer localization.

We already reported our clinical results of radical transurethral resection of prostate cancer (TURPCa) as a radical treatment of both localized[17] and incidental prostate cancer.[18] We then proposed, as a focal therapy, the possibility of focal TURPCa by applying the technique of radical TURPCa.[19] We would like to report our results of focal TURPCa, namely the results of radical transurethral resection of cancer foci based on the rough cancer mapping obtained from prostate biopsy.

METHODS

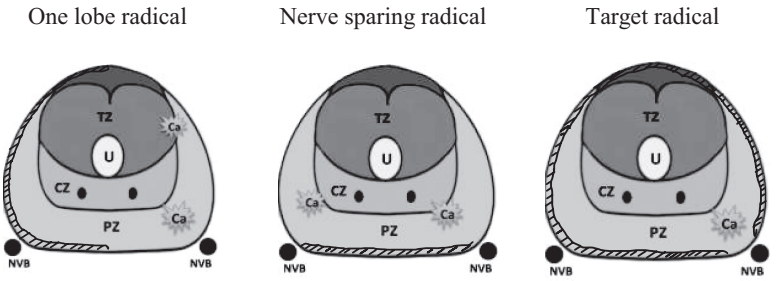
Patient Characteristics

We performed focal TURPCa in 49 patients with localized prostate cancer between July 2007 and August 2016 and followed the patients with PSA until November 2018. A rough map of cancer foci was obtained through ultrasound-guided transrectal biopsy of 14 samples. If patients were suggested by a biopsy to have scattered cancer foci in both lobes of the prostate, they were excluded from the study. We selected the patient as a candidate for the study if the biopsy revealed that cancer foci were limited in one lobe, or the foci were several or less even found in both lobes. To select the final candidates, we applied more strict criteria as follows: 5 positive cores or less out of 14 samples; tumor length of 5mm or less in each core; patients with a small volume of cancer in the low- to intermediate-risk group. We did not check preoperatively N and T categories with computed tomography (CT) or bone scan because we selected patients with a clinical stage of T1 or T2. We informed the patients that the procedure was not a standard radical treatment, and also informed the result of our previous experience of more than 200 cases of radical TURPCa, and the possibility of the additional second TURP operation. Patients who did not agree with this procedure were excluded from the study. We also excluded patients who might not tolerate standard transurethral resection of the prostate (TURP) for benign prostatic hyperplasia.

Operative Procedures and Pathological Examination

One certified urologist (MM) performed all of the operations under spinal anesthesia using a standard setup of monopolar TUR. After resecting the transition (TZ) and central zone (CZ) through the standard procedure of TURP, the peripheral zone (PZ) was resected with one of the methods described below. Resected specimens were collected separately for pathological examination by dividing the prostate into 6 parts starting from the 12 o'clock position clockwise. Because it was difficult to distinguish between pT2a and pT2b we adopted pTa-b and pTc in the T category. We selected one of our three methods of focal TURPCa as follows (Figure 1): one lobe radical TURPCa, radical resection of the affected lateral lobe, with the other lobe being resected less vigorously, the lobe which contained no tumor or secondary lesion of limited size and number; nerve-sparing radical TURPCa, radical resection of both lobes except for the posterolateral part of the prostate (near the 4 and/or 8 o'clock position) when patients were eager to preserve the erectile function; target radical TURPCa, aggressive resection of the cancer focus and the surrounding prostate when cancer is suggested single by biopsy and confirmed during the operation. To PZ that was not resected radically, we applied advanced TURP to check whether the resected tissue contained cancer or not.

FIG. 1 Three types of focal TURPCa method.



Ca: cancer focus
TZ: transition zone
PZ: peripheral zone
CZ: central zone
NVB: neurovascular bundle
U: urethra
▨: rest of PZ after advanced TURP
Drawings in gray: resected part by radical TURPCa

Radical TURPCa means the resection of CZ and TZ followed by further aggressive resection and fulguration of most of the entire PZ. Advanced TURP means a little deeper resection of PZ following standard TURP, obtaining pathological specimens not to overlook incidental prostate cancer. Of our 995 patients that underwent advanced TURP, 226 patients (22.7%) were diagnosed to have incidental cancer. The frequency was almost the same as the reported rate of latent cancer diagnosed by autopsy.[20] Concerning the localization of cancer, we performed the surgery based mainly on the results of transrectal ultrasonography and systematic biopsy, without information from MRI. The patients in the target TURPCa group met the condition that the cancer focus was confirmed by systematic biopsy, by the change of colour and firmness of the prostate tissue during resection and by postoperative pathology.

Patient Follow-up

PSA was measured every 2 months starting 2 months after surgery. PSA did not necessarily reach the undetectable level because some prostate tissue remained in focal TURPCa. Because the residual tissue should be a part of PZ without cancer, the gradual and successive elevation of PSA seldom occurs over a long period. When PSA shows a continuous rise in patient follow-up, we must consider the indication of prostate biopsy suspecting PSA failure [21].

RESULTS

Patients' age ranged from 56 to 84 years (average, 71.0). No patients had received hormone therapy preoperatively. The follow-up periods of 49 patients was 68.0±28.0 (mean±SD) months (median, 72.9; range, 20.7–136.4), the operation time 92±17 (mean±SD) minutes (median, 100; range, 60–120), and the resected weight 18.0±7.0 (mean±SD) grams (median, 18.0; range, 4–30). The preoperative PSA value was 6.15±2.73 (mean±SD) ng/mL (median, 5.32; range, 1.72–13.35) and postoperative latest PSA was 0.172±0.283 (mean±SD) ng/mL (median, 0.070; range, 0.001–1.550).

Table 1 shows the summary of the preoperative evaluation of the enrolled patient indicating their PSA and Gleason score (GS) for each risk group.

For each method of focal TURPCa, GS, clinical stage, pathological stage, and D'Amico's risk group are shown in Table 2. Table 3 and Table 4 show the PSA value before and after the surgery grouped by the methods of focal TURPCa and D'Amico's risk group respectively. PSA failure occurred in two patients who underwent one lobe radical TURPCa. Both patients received secondary radical TURPCa. One patient with GS 6, GS 9 cancer being detected in the residual lobe, has a low and stable PSA of 0.01 ng/mL at the latest follow-up. Another patient with GS 9, no cancer is detected in the residual prostate, is now on maximum androgen blockade. The other 47 patients showed a stable and low PSA value (mean, 0.172; median, 0.070 ng/mL; range, 0.001-1.550) depending on the amount of the residual prostate tissue. Finally confirmed tumor multiplicity was shown in Table 5, indicating that 34 patients (69.3%) had multiple tumors. The tumour was localized in one

TABLE 1 Preoperative Evaluation of Risk Group, PSA and Gleason Score

Risk group (D'Amico)	Number of patients (49 cases)	PSA before FTURPCa (ng/mL)	Gleason Scores
		Mean ± SD	
		Median (Range)	
Low	24	4.86 ± 1.62	6
		4.76 (1.72–8.21)	
Intermediate	25	7.40 ±2.99	7
		7.11 (3.29–13.35)	

TABLE 2 Gleason Scores, Cancer Stages and Risk Groups of the Patients Treated by Each Method of Focal TURPCa

Methods of Focal TURPCa	Number of Patients	Gleason scores					Clinical stage (T)				Pathological stage (pT)			Risk group (D'Amico)		
		6	7	8	9	10	1a	1b	1c	2b	0	2a-b	2c	Low	Inter-mediate	High
One lobe radical	29 cases	11	13	1	4	0	3	2	23	1	2	12	15	9	15	5
Nerve-sparing radical	13 cases	3	8	1	1	0	1	2	10	0	1	4	8	3	8	2
Target radical	7 cases	0	6	0	1	0	0	0	7	0	0	1	6	0	6	1
Total	49 cases	14	27	2	6	0	4	4	40	1	3	17	29	12	29	8

TABLE 3 PSA Values Before and After Focal TURPCa in the Patients Grouped by Each Method of Focal TURPCa

Methods of focal TURPCa	Number of patients (49 cases)	PSA before FTURPCa (ng/ml)	Latest PSA after FTURPCa (ng/mL)	PSA failure (2 cases)
		Mean ± SD		
		Median (Range)		
One lobe radical	29	6.33 ± 2.98	0.202 ± 0.320	2
		5.47 (2.46–13.35)	0.086 (0.001–1.550)	
Nerve-sparing radical	13	5.27 ±2.03	0.179 ± 0.253	0
		4.97 (1.72–9.06)	0.079 (0.008–0.910)	
Target radical	7	9.08±2.29	0.044 ±0.053	0
		6.45 (4.24–11.26)	0.030 (0.003–0.170)	

TABLE 4 PSA Values Before and After Focal TURPCa in the Patients Grouped by the Risk Group of D'Amico

Risk group (D'Amico)	Number of patients (49 cases)	PSA before FTURPCa (ng/ml)	Latest PSA after FTURPCa (ng/ml)	PSA failure (2 cases)
		Mean ± SD		
		Median (Range)		
Low	12	4.99 ± 2.07	0.231 ± 0.427	1
		5.06 (1.72-10.00)	0.090 (0.012-1.550)	
Inter-mediate	29	6.22 ±2.71	0.145 ± 0.198	0
		5.10 (2.77-13.35)	0.079 (0.001-0.910)	
High	8	7.67±2.89	0.190 ± 0.280	1
		8.81 (3.29-12.53)	0.020 (0.008-0.741)	

TABLE 5 Number of Cancer Foci Finally Confirmed by Pathological Examination after Focal TURPCa

Number of cancer foci	Number of patients (%)
Single focus	12 (24.5%)
Multiple foci	34 (69.3%)
No tumor (T0)	(6.1%)
Total	49 (100%)

lobe in 19 patients (38.8%). And the preoperative diagnosis of cancer localization was correct in 16 patients (32.6%) assessed by the pathological result. GS of the biopsy specimen was consistent with that of the resected tissue in 24 patients (49.0%), upgraded in 21 (42.9%), downgraded in one (2.0%), and unknown (T0) in three (6.1%).

In the nerve-sparing radical TURPCa group, all five patients preserved the erectile function that had enough function preoperatively. Out of eight patients with insufficient preoperative function, erection became more weakened in seven and lost in one. Of three with enough erectile function in the one lobe radical TURPCa group, it was preserved in two (66.7%) and weakened in one. One patient in the target radical TURPCa group preserved the function. No patients received phosphodiesterase 5 (PDE5) inhibitor postoperatively.

There were no patients who needed a perioperative blood transfusion, and TUR syndrome did not develop. As for the postoperative complications, some patients experienced urinary incontinence immediately after the removal of a urethral catheter on the third post-operative day. Incontinence gradually improved and disappeared within 3 months. Bladder neck contracture (BNC) developed in 10 patients (20.4%) mostly about 3 months after the surgery. But it was easily treated with direct vision cold knife incision under caudal block on a day surgery basis. Other complications included acute epididymitis (four patients, 8.1%) and bladder tamponade (one patient, 2.0%). Out of 49 patients, two died of cerebrovascular accident and one of renal failure with low and stable PSA values of 0.406, 0.086, and 0.003 ng/mL. No patients died of prostate cancer.

DISCUSSION

It is almost 20 years since cryotherapy and HIFU were first reported as a focal therapy, but the evaluation of the clinical results is still controversial.[5,6,11,22] As for the patients with localized prostate cancer, there has been a growing concern about the risk of overdiagnosis and overtreatment because many of such patients die of the diseases other than prostate

cancer. This forced some urologists and radiologists to study and discuss the focal therapy for localized prostate cancer, and new methods or devices of focal ablation combined with imaging guidance are emerging and developing.[23–27] But these procedures as well as cryosurgery and HIFU still seem to have some drawbacks. First, there remain difficulties to control the necessary extent of the treatment in the prostate, namely to recognize the target lesion and the safety margin. We think we can by TURPCa control more precisely the extent that must be eliminated because in most cases we can distinguish during resection the cancer lesion, TZ, PZ, and even prostate capsule. Second, pathological samples cannot be obtained, resulting in an inadequate final pathological diagnosis. We also understand that there are common drawbacks among TURPCa, cryotherapy, and HIFU. Concerning the preoperative staging, the appropriate method of patient selection base on the accurate clinical stage has to be established early in the future because current methods of imaging and biopsy cannot always predict the precise cancer foci.

We already applied radical TURPCa to the focal treatment of prostate cancer and reported a preliminary result.[19] In the procedure, we radically resected the main cancer focus predicted by biopsy followed by the resection of the residual PZ with advanced TURP. We could thus resect other cancer foci, if any, which were not predicted preoperatively, resulting in postoperative long-term, stable PSA. In another of our experiences, we followed 146 patients with T1 cancer detected by advanced TURP for 27 to 106 months (median, 67.0). Twenty-six (17.8%) patients showed a gradual PSA elevation and were given a diagnosis of prostate cancer by biopsy.[21] We think we can resect and control tiny cancer lesions by advanced TURP, but long-term follow-up should be required because we did not resect the prostate tissue completely. Thus, focal TURPCa, by resecting most of the prostate tissue, is thought to be practical and useful in the point that we can resect and find even tiny cancer foci.[20] As for the patient selection, to aim at resecting cancer tissue completely, low cancer volume and a smaller number of cancer foci are considered more important for this operation. Because the preoperative determination of cancer foci is still insufficient,[28–30] progress in the field of imaging and biopsy is expected to make our procedure more practical. Postoperative GS upgraded in 21 patients (42.9%). Because we had selected the patients with small cancer focus with ultrasound-guided biopsy, we could not find the secondary lesion of unexpected tiny high-grade cancer that was detected in the resected tissue. We had better consider MRI fusion biopsy or something to improve the accuracy of biopsy and therefore focal TURPCa. Focal TURPCa, a less invasive, low-cost procedure, can be performed repeatedly after the failure of the first-line focal TURPCa, and we can use PSA for follow-up after operation.[21] Though higher operative technique with more experience is necessary to perform focal TURPCa than TURP for BPH, it would be a challenging technique to acquire for urologists that are earnest about transurethral surgery.

In this small cohort of 49 cases, we reported the results of focal TURPCa as a focal therapy for localized prostate cancer. The result seems satisfactory with the non-recurrence rate of 95.9% during the mean follow-up period of 68.0 months. No patients died of prostate cancer. Preserved in eight (44.4%) of 18 potent patients, erectile function reached about the same level as TURP for BPH by applying less resection to PZ near the neurovascular bundle. Thus, the proper choice of TURPCa method may solve the issues of erectile function.

Most frequent postoperative morbidity was BNC, and no patients experienced long-lasting incontinence. The incidence of BNC following TURP can reach as high as about 12%.[31] In the present study, we resected PZ aggressively though partially as well as bladder neck and TZ. This may cause impaired blood supply and low tissue perfusion affecting the wound healing leading to BNC.

There remain problems to be solved concerning focal TURPCa. First, the criteria for PSA failure have not been established yet. In our focal TURPCa, following complete resection of TZ, we aggressively resect and fulgurate PZ where cancer is located based on the biopsy results. We applied advanced TURP to PZ without cancer and checked the resected tissue pathologically. Because some prostate tissue remains, though it must be a part of PZ without cancer, PSA

does not necessarily drop to the undetectable level. When the gradual and successive elevation of PSA occurs over a long time, PSA failure must be considered and confirmed by biopsy.[21] Second, another drawback of focal TURPCa is the possibility of residual cancer resulting from residual PZ. A small amount of residual PZ tissue may not show a continuous rise of PSA. In addition to the regular check of PSA, standard follow-up criteria and methods after surgery have to be also established such as bone scan, CT, MRI, and periodical biopsy for each patient appropriately. The validity of current criteria must be evaluated by the results of a longer follow-up of more cases.

Current ordinary radical treatment of localized prostate cancer includes radical prostatectomy and radiation therapy. Concerning the focal therapy, in addition to generally accepted cryotherapy and HIFU, we proposed a new approach that may expand the treatment option for both patients and urologists. We think we could demonstrate, in the era filled with high-tech medical devices, that we could manage the patients with localized prostate cancer successfully and safely by the low-tech but traditional procedure that was very familiar to all urologists.

CONCLUSIONS

In this study of the patients with localized prostate cancer treated with focal TURPCa, PSA failure occurred in only 2 out of 49 patients. No perioperative mortality was encountered and postoperative morbidities were acceptable. We fully understand that the final assessment of efficacy will require long-term follow-up results with more cases as well as the resolution of patient selection based on information on cancer localization with biopsy and imaging. Even so, we may think focal TURPCa can be another treatment option as a focal therapy for localized prostate cancer.

STATEMENT OF ETHICS

Patients who gave the written informed consent were eligible to participate in the focal TURPCa program. The study was approved by the institutional review board (Medical Research Ethics Committee of Matsubara Tokushukai Hospital; Reference number, EC-14-04) after a preliminary study and registered at the University Hospital Medical Information Network Clinical Trials Registry in Japan (UMIN-CTR; Study ID, UMIN000016924).

DISCLOSURE STATEMENT

The authors declare that there are no conflicts of interest regarding the present study.

FUNDING SOURCES

No funding was obtained in this study.

AVAILABILITY OF DATA AND MATERIALS

All data used and/or analyzed during the current study are included in this published article and the database is available from the corresponding author (MM) on reasonable request.

AUTHORS CONTRIBUTION

The contribution of the authors is as follows: MM, protocol development, data collection and management, and manuscript preparation; AM, data collection and analysis; TM, data management, and manuscript writing.

All of the authors have read and approved the final manuscript

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