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Research Article

Definitive Therapy of Early Prostate Cancer with Transurethral Microwave Thermotherapy after Prostate Volume Reduction by Androgen Deprivation: A 17-Year Experience of a Potential Alternative to Radical Surgery

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ABSTRACT

Background: Transurethral Microwave Thermotherapy (TUMT) has shown limited efficacy as a treatment for prostate cancer, mainly because of the inability of microwaves to reach the peripheral region of the prostate. Pre-treatment with Androgen Deprivation Therapy (ADT) may increase TUMT efficacy by reducing the prostate size.

Objective: To examine the clinical outcomes of patients undergoing TUMT after at least 3 months of ADT.

Design, setting, and participants: One hundred twenty-three men with early, non-metastatic prostate cancer and Prostate-Specific Antigen (PSA) levels of 4.0 ng/mL or higher were enrolled between 2001 and 2011 and followed up until 2017. TUMT was performed after at least 3 months of ADT and the efficacy of this treatment was confirmed by radical Transurethral Resection of the Prostate (TURP) performed at least 3 months after TUMT.

Intervention: ADT and TUMT, Outcome Measurements and Statistical Analysis, Post-intervention prostate volume, presence of remnant cancer cells, and clinical outcomes.

Results and limitations: Prostate volume was significantly reduced (mean, 35.2%) after 3 months of ADT. Histopathological examination of TURP chips revealed no cancer cells in 102 of 123 patients. Twenty-one patients demonstrated remnant cancer cells; in 13 patients these were non-viable, and in 8 they were degraded. During the 17-year follow-up period, 28 patients received regular or intermittent anti-androgen therapy to maintain PSA levels below 4.0 ng/mL. No patients died of prostate cancer.

Conclusion: Combination ADT and TUMT therapy in 123 patients suggests that early prostate cancer is easily destroyed by heat. A significant reduction of prostate volume after ADT increased TUMT efficacy in the peripheral zone and apex.

Patient summary: In this study, ADT reduced the volume of the prostate gland by around 35%, enhancing the ability of TUMT to kill cancer cells. This approach should be further evaluated as a less-invasive alternative to current, conventional therapies.

Keywords: Prostate Cancer; Androgen; Radical Surgery; Thermotherapy; Deprivation

INTRODUCTION

Transurethral Microwave Thermotherapy (TUMT) was introduced in the 1990s for the minimally invasive clinical management of benign prostatic hyperplasia (BPH) as an alternative to Transurethral Resection of the Prostate (TURP). Transurethral microwave application is able to destroy prostate gland tissue up to a radial distance of 15 to 16 mm from the prostatic urethra, which allows for treatment of prostate glands

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with volumes of approximately 30 mL or smaller. Of note, TUMT can be performed as a single 60 min procedure under local anesthesia.

Few studies have examined the curative treatment of prostate cancer with TUMT [1,2] and conclusions have been disappointing, mainly because of the inability of microwaves to reach the peripheral region of the prostate. In the present study, we successfully managed localized prostate cancer with TUMT after first significantly reducing the prostate volume with androgen deprivation therapy (ADT) for 3 months or longer. The treatment effects were confirmed by TURP, which was performed at least 3 months after TUMT to allow time for thermal effects to induce satisfactory degenerative changes in prostatic tissue.

In 2011, we reported results from the first 8 years of this trial in 75 patients [3]. After 9 more years of clinical experience and follow-up, we here report the clinical outcomes of 123 patients with follow-up periods of 6 years or longer as of the end of December 2017.

METHODS

Patients

A total of 123 Japanese patients with biopsy-proven adenocarcinoma of the prostate, clinical stage T1-2 N0 M0, were enrolled between December 2001 and December 2011 and followed up until the end of 2017. Initial bone scans were negative for metastatic disease in all patients.

All treatments used in this study (ADT, TUMT, and TURP) are considered to be standard therapies and are approved worldwide. The specific protocol used was approved by The Ethical Committee of the Saitama Ken-oh Hospital in 2001. Thorough discussion was held with each patient and written informed consent was obtained.

The mean patient age was 70.2 years (range, 57-89) at the start of therapy. The mean PSA level was 9.1 ng/mL (range, 4.0-49.5), and the mean prostate volume (total volume including fibrous capsule) at initial Transrectal Ultrasonography (TRUS) was 34.8 mL (range, 13.6–85.0). Gleason scores 4 at biopsy diagnosis were 6 or less, 7 (3+4), 7 (4+3), 8, and 9 in 67,29,11,10 and 6 patients, respectively. According to the 1992 TNM staging system, clinical stages were T1c, T2a, T2b, and T2c in 86,23,11 and 3 patients, respectively (Table 1).

Table 1: Baseline characteristics of 123 patients.

Characteristics	
Age (mean ± SD) (years)	70.2 ± 6.5 (range, 57-89)
PSA level (mean ± SD) (ng/mL)	9.1 ± 6.6range, 4.0-45.9)
PSA level (%)	
4-10 (ng/mL)	93 (75.6)
10.1-20 (ng/mL)	19 (15.4)
>20 (ng/mL)	11 (8.9)
Prostate volume (mean ± SD)	34.8 ± 14.7 (range, 13.6-85.0)
<20 (mL)	12 (9.8)
20.1-30 (mL)	39 (31.7)
30.1-40 (mL)	39 (31.7)
40.1-50 (mL)	17 (13.8)
>50 (mL)	14 (11.4)
unknown	2 (1.6)
Clinical stage (%)	
T1c	86 (69.9)
T2a	23 (18.7)
T2b	11 (8.9)
T2c	3 (2.4)
Gleason score at biopsy (%)	
<6	67 (54.5)
7 (3+4)	29 (23.6)
7 (4+3)	11 (8.9)
8	10 (8.1)
9	6 (4.9)

PSA: Prostate-Specific Antigen; Prostate Volume; Total Gland Volume (Including the Fibrous Capsule) as Measured by Ultrasonography.

Androgen deprivation therapy

Patients first received an oral non-steroidal anti-androgen (bicalutamide 80 mg/day in 122 patients and flutamide 3.75 mg/day in 1 patient). Two weeks after the first anti-androgen treatment, a luteinizing hormone–releasing hormone (LH-RH) agonist was administered subcutaneously (leuprorelin acetate 3.75 mg/4 weeks in 110 patients and goserelin acetate 10.8 mg/12 weeks in 13 patients). Patients underwent TUMT at least 12 weeks (mean, 15.5) after the initial LH-RH agonist dose to allow time for prostate volume reduction and thereby increase TUMT efficacy. The duration of ADT was calculated from the initial administration of the LH-RH agonist to 6 months (4 weeks×6) after TURP. The final ADT duration was 13.8 ± 1.2 (mean ± SD) months.

Transurethral microwave thermotherapy

The UroWave™ system (Dornier MedTech Systems GmbH, Munich, Germany) used for TUMT is a high-energy device designed for treatment of benign prostatic hyperplasia [4-6]. It consists of a microwave power generator, a cooling system, and a control and monitoring system. The microwave power generator operates at a frequency of 915 MHz and requires no special shielding. The generator is capable of delivering up to 90 W of power to the targeted tissue. The treatment antenna is integrated into a disposable delivery system based on a balloon angiography design. It is inserted into the urethra with the balloon deflated to a catheter size of approximately 9 Fr. The balloon is then inflated in the urinary bladder with 6-10 mL of sterile water to keep the helical coil antenna positioned appropriately during the treatment. When the system is turned on, the pressure and flow provided by the water-cooled circuit inflates the applicator to 18 Fr. Cooling water is infused into a separate chamber that provides uninterrupted circumferential cooling to the pain-sensitive urethral mucosa. This reduces discomfort and enables high-energy treatment to be applied, and also preserves the urethral mucosa by preventing tissue sloughing. Two urethral applicators, both helical coil antennas, are available: UA20 is 17.5 mm long while UA30 is 24.5 mm long. The choice of antenna is based on the length of each patient's prostatic urethra. The system features a rectal probe, with a series of 3 thermal couples mounted on the anterior midline that continuously monitors the temperature at the rectal mucosa closest to the posterior aspect of the prostate. It serves as a key safety feature to prevent excessive heating of the rectal wall.

In the present study, the safety threshold was set at 43.5°C in the urethral mucosa and 43°C in the rectum. These settings resulted in a peak intraprostatic temperature of up to 65°C. The temperature reaches approximately 55°C at a radial distance of 4 mm from the urethral mucosa and remains at 45°C or higher up to a distance of 16 mm. The fibrous capsule serves as a barrier to microwaves and thus prevents excessive heating of the rectal wall and external urethral sphincter, and also helps elevate the temperature within the capsule to facilitate destruction of prostatic cancer cells. The median power used in this series was 64 W (range, 25-90).

Each patient underwent a 60 min TUMT treatment in an outpatient setting. Prior to insertion of the urethral thermotherapy applicator, local anesthesia was administered *via* lidocaine jelly in the urethra, a diclofenac sodium suppository (50 mg) in the rectum, and 20 mL of 2% lidocaine hydrochloride infused into the urinary bladder. A 14 Fr indwelling urethral catheter was kept in place for 3 days after the treatment. Most patients complained of no difficulty in urination after catheter removal, with the exception of 2 patients who required that the catheter be kept in place for an additional 2 days.

Transurethral resection of the prostate

Transurethral resection was performed to remove as much glandular prostate tissue as possible up to the fibrous capsule, both to excise remnant cancer tissue and to confirm the treatment effects of thermotherapy under ADT. Our policy was to avoid resecting the verumontanum since early prostate cancer rarely occurs in this area, and the structure is also an important landmark to identify the location of the external urethral sphincter. In all cases, TURP was conducted at least 3 months after TUMT, as the fibrous capsule was thick and firm by this time and tissue degeneration due to thermotherapy was maximized. Since a significant reduction in prostate volume was achieved by ADT and TUMT, the TURP procedure was straightforward and safe, with a clear field of vision and less blood loss than ordinary TURP for BPH. All TURP chips were subjected to thorough histopathologic examination (Figure 1).

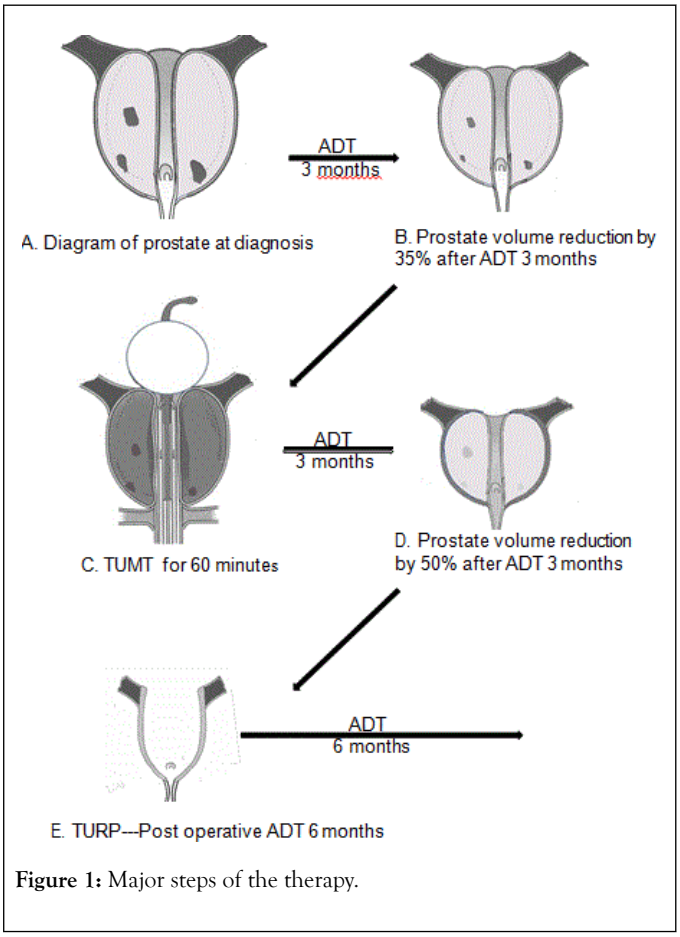

Figure 1: Major steps of the therapy.

RESULTS

Reduction in prostate volume

At diagnosis, the mean volume of the prostate, including the fibrous capsule, was 34.8 mL (range, 13.6-85.0) as measured by TRUS. A significant reduction in prostate volume (mean, 35.2%) was noted after 3 months of ADT. At TUMT, the mean prostate volume was 22.1 mL. This was thought to be small enough to allow the peripheral prostate (up to the fibrous

capsule) to be thoroughly heated by high-energy microwaves in most patients. By 3 months after TUMT with continued ADT, the prostate volume was approximately 50% of that at diagnosis. The mean weight of TURP chips was 9.8 g (Table 2).

Table 2: Reduction in prostate volume as measured by ultrasonography (123 patients).

Volume	Before treatment TRUS (mL)	12 weeks after ADT TRUS (mL)	12 weeks after TUMT TRUS (mL)	TURP Wt (g)
(mean ± SD)	34.8 ± 14.7	22.1 ± 9.5	17.2 ± 15.8	9.8 ± 7.4
Percent reduction		35.2 ± 15.8%	50.6 ± 12.5%	

ADT: Androgen Deprivation Therapy; TUMT: Transurethral Microwave Thermotherapy; TURP Wt: Total Chip Weight Following Transurethral Resection of the Prostate; TRUS: Transrectal Ultrasonography.

Histopathologic characteristics at biopsy diagnosis

Transrectal ultrasonography-guided needle biopsy of the prostate was performed in all patients. A total of 6-14 systemic needle biopsy samples were taken from the right and left apex, mid gland, and base. In patients with large prostate, more than 6 systemic cores were taken from the mid gland, including from the transition zone. The biopsy specimens of each patient were reviewed by a single urological pathologist who assigned Gleason scores to cancer foci. Fifty-four percent (66/123) of patients demonstrated multifocal disease. Also, 24% (30/123) had cores with different Gleason scores, in which case the highest score was recorded. Overall, Gleason scores were 6 or less, 7 (3+4), 7 (4+3), and 8 or greater in 67, 29, 11, and 16 patients, respectively (Table 1).

Histopathologic features of turp chips

Transurethral resection of the prostate was performed at least 3 months (range, 3-10) after TUMT and continued ADT, and all TURP chips were examined histopathologically by the same urological pathologist who performed biopsy diagnoses. Each TURP chip was classified by region of origin: median, anterior, right lateral, left lateral, and apex. Most TURP chips revealed marked degenerative changes associated with fibrosis. In 102 (83%) of 123 patients, no cancer focus was detected in TURP chips. In 13 patients, a small number of TURP chips contained apparently non-viable cancer foci with necrosis and severe degenerative changes, as well as intensely eosinophilic cytoplasm with homogeneous nuclear pyknosis. We assumed that these cells were undergoing degradation and would soon disappear. In 8 (6.5%) patients, however, degenerated but probably viable cancer cells were detected in a small number of TURP chips. The characteristics of patients with remnant cancer foci are shown in Table 3.

Table 3: Characteristics of 21 patients with remnant cancer cells in TURP chips.

At Diagnosis									At TURP			
Patient	Age (years)	PSA (ng/mL)	P.Vol (mL)	Gleason Score	Location	Stage	P.Vol (mL)	Wt (G)	Location	N-Chips	Gleason Score	Pathology Viability
1	67	8.9	21.8	2+2=4	4	T2a	12	7	Md	1/6 (139)	2+3=5	Viable
2	63	6.3	33.6	2+1=3	2	T1c	16	5	RL	1/22 (85)		Non-Viable
				3+4=7	4				LL	4/22 (85)		Non-Viable
3	77	6.3	28.6	2+3=5	6	T1c	16	10	LL	1/38 (106)		Non-Viable
				3+4=7	5							
4	70	9.1	43.5	3+4=7	1,2,3	T2b	30	21.6	RL	2/22 (189)		Non-Viable

5	60	20	18.4	3+3=6	6	T1c	7.6	4.8	LL	1/20 (69)		Non-Viable
				4+4=8	5				Ap	2/14 (69)		Non-Viable
6	65	6.3	22.1	3+4=7	1	T1c	9.1	5	LL	2/10 (58)	3+3=6	Viable, Degraded
7	60	8.5	14.7	3+2=5	2	T2a	13	4.9	LL	3/25 (75)		Non-Viable
				3+4=7	5,6							
8	69	11	21.9	4+5=9	1,2,3	T2b	10	8.7	RL	7/20 (67)	4+3=7	Viable, Degraded
9	70	6.2	34.2	2+3=5	1	T1c	21	12	RL	5/49 (135)		Non-Viable
10	72	4.4	19.2	3+3=6	1,2	T1c	19	9	LL	1/25 (97)	2+3=5	Viable, Degraded
11	70	11	27.9	4+5=9	4	T1c	13	9.8	Ap	1/30 (101)	2+2=4	Viable, Degraded
12	62	7.8	22.8	2+3=5	5	T2a	10	5	LL	3/16 (50)		Non-Viable
				3+3=6	4							
13	70	7.9	32.7	2+2=4	1	T2a	16	8.1	LL	2/18 (76)	2+2=4	Viable, Degraded
14	72	12	24.4	4+3=7	2	T1c	15	5.5	RL	4/25 (72)	3+4=7	Viable, Degraded
									Ap	3/7 (72)	3+4=7	Viable, Degraded
15	71	7.8	25.8	3+3=6	1	T1c	8.8	5.1	RL	3/15 (73)		Non-Viable
16	83	12	28.8	4+4=8	1,2,3	T2b	14	12.9	LL	1/23 (147)		Non-Viable
17	73	6.5	23.6	3+3=6	3,4	T2a	8.7	4.9	LL	3/20 (79)		Non-Viable
				3+4=7	5							
18	76	8.6	26.0	4+4=8M	4	T1c	13.1	5.8	Ap	1/22 (77)	4+4=8	Viable
19	71	6.2	14.5	3+3=6	5	T2a	7.2	3.6	LL	1/25 (74)		Non-Viable
				3+4=7	4				Ap	3/30 (74)		
20	70	13.1	38.0	3+3=6	1,2,3	T2a	12.7	5.0	RL	3/35 (101)		Non-Viable
21	76	4.8	19.7	3+3=6	2,5	T1c	9.6	4.2	RL	3*		Non-Viable
									LL	2*		Non-Viable

P.Vol: Prostate Volume of Total Gland Measured By Ultrasonography; M: Mucinous Adenocarcinoma; 1: Right Apex; 2: Right Mid; 3: Right Base; 4: Left Apex; 5: Left Mid; 6: Left Base; Wt: Weight Of Total TURP Chips; Md: Median Lobe Area; RL: Right Lateral Area; LL: Left Lateral Area; Ap: Apex Area; N-Chips: Number Of Cancer-Positive Chips / Number Of Chips In The Location (Number Of Total TURP Chips); *3/*2: Number Of Cancer-Negative Chips Were Not Counted; Gleason Scores: Gleason Scores Of The Patients Who Had Viable Cancer Cells In Their Prostates Even After TURP; Other Abbreviations as in Table 1.

Changes in Serum PSA Levels

Serum PSA levels decreased rapidly after 3 months of ADT, and became almost undetectable after TUMT. After ADT (6 × 4 weeks) was discontinued after TURP, serum PSA levels rose gradually but stayed within the normal range (<4.0 ng/mL) in most patients. During the follow-up period, which ended on December 31, 2017, serum PSA levels above 4.0 ng/mL were observed in 32 (26%) patients; of these, 28 (23.5%) were receiving intermittent or continued anti-androgen medication. Of 16 patients with Gleason scores of 8 or greater, 8 exhibited PSA levels elevated to 4.0 ng/mL or higher. Three of these patients were in the third year of the follow-up period and 5 were in the fourth year. The majority were taking anti-androgen medication and exhibited no clinical evidence of disease recurrence.

However, 2 patients died of other causes. The first had a Gleason score of 8 (4+4) at diagnosis and died at age 86, after 9 years of follow-up, due to pneumonia unrelated to prostate cancer. The second died at age 84 due to a cardiovascular accident in the sixth year of follow-up. His Gleason score was 8 (4+4; mucinous) and he had started taking intermittent anti-androgen medication 3 years after completing the therapy. His serum PSA level during the follow-up period reached a maximum of 5.3 ng/mL, and was 0.9 ng/mL at 1 month before his death.

Complications

Five patients complained of difficulty in urination due to posterior urethral stricture. Three were successfully treated by urethral dilatation, but 2 required internal urethrotomy. Three patients complained of mild stress incontinence after TURP, but the condition resolved spontaneously within 6 months. One patient developed left epididymitis 1 year after the therapy, which was successfully treated conservatively. All patients tolerated the scheduled ADT ending 6 months after TURP.

Clinical outcomes

Twenty-five patients (20.3%) died of cause unrelated to prostate cancer. Twelve patients (9.8%) were lost to follow-up for reasons unrelated to disease recurrence, in most cases changes of address. As of December 31, 2017, the remaining 86 patients were alive and still being followed, with a median follow-up period of 121 months (range, 96-188). Fifty-eight of these patients had serum PSA levels below 4.0 ng/mL, and 28 were receiving intermittent or regular anti-androgen therapy to maintain serum PSA levels below 4.0 ng/mL. No patients died of prostate cancer and none were at risk of prostate cancer-related death at the end of December, 2017.

Regarding the 25 patients who died of causes unassociated with prostate cancer, 5 died of cardiac accidents between ages 78 and 88, at least 3 years after finishing the therapy. Two patients were found drowned in the bathtub and another patient died of senile decay at age 95. Four patients died of pneumonia between ages 76 and 102. Three patients died of cerebrovascular accidents between ages 75 and 88. Ten patients died due to other malignant tumors: laryngeal cancer in 1 patient, lung cancer in 2, gastrointestinal cancer in 4, and pancreatic cancer in 2. One patient died of acute myeloid leukemia 8 years after the prostate cancer therapy described here (Table 4). Of note, one patient died of pneumonia in the 12th follow up year, and though he had extensive prostate cancer with bone metastases, this was not the direct cause of death.

Table 4: Clinical outcomes: 123 patients with 6- to 17-year follow-up.

Alive at end of scheduled follow-up		86 (69.8%)
Serum PSA <4.0 mg/ml		58
Receiving anti-androgen medication		28
Lost to follow-up		12 (9.8%)
Dead		25 (20.3%)
Cause of death	Prostate cancer	0
	Cancer of other organs	10
	Cardiac accident	5
	Pneumonia	4
	Cerebrovascular accident	3
	Drowned in bathtub	2
	Senile decay	1

DISCUSSION AND CONCLUSION

The first treatment of prostate cancer using localized hyperthermia administered *via* microwave applicator was reported by Mendecki, et al. [7] in 1980. Similar clinical trials were reported by several investigators [8-10] through the late 1980s. However, this technique remained supplementary to radiotherapy and hormone therapy, possibly because the use of the transrectal treatment route resulted in intraprostatic temperatures lower than 43°C.

A newly developed system, TUMT [11], combines heating of the prostate tissue with conductive cooling of the urethral mucosa, the latter accomplished by arranging a chamber around the microwave antenna that is continuously circulated with cooling water. This urethral applicator reduces the temperature of the adjacent tissue, allowing a higher temperature to be used to create sufficient heat deep inside the prostate tissue, while leaving the temperature of the urethral mucosa within a safe range. Microwave treatment is able to destroy prostate tissue to a distance of 16 mm from the urethral mucosa. Moreover, temperatures of 45 or higher for approximately 1 hour cause uniform thermoablation of the prostate tissue [12,13]. Regarding the treatment of localized prostate cancer with TUMT, there were 2 reports [1,2] in the early 2000s. They concluded that the effectiveness of TUMT for localized prostate cancer is disappointing mainly because of limitations in microwaves reaching the peripheral prostatic tissue. In majority of their patients, however, TUMT was performed shortly before radical prostatectomy, and the volume of the prostate was too large to be thoroughly treated by TUMT alone. Further, radical prostatectomy specimens obtained only a few days after TUMT can never demonstrate the true effect of high-energy thermotherapy. At least a few months are needed before the full histologic effects of TUMT are apparent.

According to our clinical experience, when an 18 Fr microwave urethral applicator is placed in the urethra, the radial distance from the urethral mucosa to the external margin of the fibrous capsule of a prostate gland with a total volume of around 30 mL is usually within 15 mm. Regarding neoadjuvant hormone therapy, it is generally accepted that preoperative serum PSA levels and positive surgical margin rates decline significantly but

do not beneficially decrease the risk of PSA recurrence years after surgery [14,15]. However, the reduction in prostate volume is very significant after ADT [16]. According to our experience, 3 months of ADT resulted in a decrease in prostate volume of around 35%, and the mean volume of 22.1 mL was small enough to be thoroughly heated by high-energy TUMT. Regarding the difference in the effect of TUMT between BPH and cancer, Nakajo, et al. [17] focused on histopathologic findings and reported that cancer cells were more irreversibly destroyed than benign hyperplastic cells.

Since the establishment of this therapeutic approach, TURP has been thought to be indispensable to remove remnant cancer foci after TUMT. It is also an important diagnostic measure to determine the therapeutic effect of TUMT at the periphery of the prostate gland adjacent to the fibrous capsule. Though the removal of the glandular component of the prostate can hardly reach 100%, and a needle biopsy is considered to be the gold standard for prostate cancer diagnosis, we believe that findings based on the histologic study of all TURP chips should be more reliable than conventional needle biopsy that examines very small amount of tissue. In one patient, who revealed an elevation of serum PSA level to 5.57 ng/mL in third follow-up year, TRUS detected a tiny nodule with a volume of approximately 0.2 mL in the apex area. It was removed from the surrounding tissue by excisional biopsy using transurethral resectoscope. While pathologic study of the specimen revealed no cancer cells, there were chronic inflammatory changes. This was the only follow-up tissue examination we have performed so far.

The results were confirmed by a histopathological study of all TURP chips. Three months of ADT significantly reduced the prostate volume and resulted in TUMT efficacy even in the peripheral zone and apex. Although the number of patients was limited and longer follow-up is needed, the histopathologic evidence and clinical outcomes in the present series justify further evaluation of this curative therapy as a less-invasive alternative to radical prostatectomy.

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