Effect of Thermosensitization with Parthenolide in Thermotherapy of Early Prostate Cancer Combined with Androgen Deprivation ; with an Emphasis on Histopathologic Findings

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Abstract : Parthenolide (PTL), a nuclear factor- κ B (NF- κ B) inhibitor, has been known to have a significant thermo-enhancement effect. The purpose of this study is to report our clinical experiences of using PTL in perioperative period of transurethral microwave thermotherapy (TUMT) for the treatment of early prostate cancer and to compare the results with those of the patients who were treated in the similar manner without PTL administration. All the patients who underwent TUMT for early prostate cancer were pretreated with androgen deprivation therapy (ADT) at least for 3 months to reduce volume of the prostate to render the TUMT more effective. PTL, daily oral dose of 0.5 mg, was administered during the perioperative period of TUMT.

Forty-five patients with early prostate cancer, clinical stage T1c~T2cN0M0 were included in this study. Significant reduction in volume of the prostate (mean 34.6%) was noted after ADT for 3 months. Transurethral resection of the prostate in radical fashion was then performed at least 3 months after TUMT to wait for maturation of histopathologic changes of the prostate glands.

Thorough histopathologic study of all the transurethral resection of the prostate (TURP) chips revealed no cancer cell in 41 of 45 patients. Among 4 patients who were found to have remnant cancer cells in TURP chips, 1 was with non-viable cancer cells. Whereas, 3 were with probably viable cancer

cells, but apparently degraded in malignancy. These results were apparently superior to those of the 75 patients who were treated in similar manner before administration of PTL. Analyses were performed using Student's *t*-test, chi-square test and Fisher's exact test and ANOVA.

Key Words : parthenolide, thermosensitization, prostate cancer, androgen deprivation, TUMT

Introduction

Parthenolide (PTL), a sesquiterpen isolated from feverfew (*Tanacetum parthenium*), a medical herb, has been known to have antitumor activity¹⁻³⁾. Besides, PTL is used in the west to treat such conditions as migraine and inflammation^{4,5)}. However, there was no known study of its effect in combination with hyperthermia until 2008, when Hayashi *et al*⁶⁾ reported thermo-enhancement effect of PTL towards human lung cancer A549 cells. Furthermore Hayashi *et al*⁷⁾ reported its significant thermo-enhancement effect towards human prostate cancer androgen-independent cell lines PC3 and DU145 in 2011.

Transurethral microwave thermotherapy (TUMT) was introduced as a minimally invasive clinical management for the treatment of benign prostatic hyperplasia (BPH) in 1990s. Although TUMT was originally introduced for the treatment of prostatic hyperplasia, its significant effectiveness on the treatment of early stage prostate cancer after reduction of volume of the prostate by androgen deprivation had recently been reported⁸⁾.

In this study, clinical effect of PTL was evaluated by thorough histopathologic study of all the transurethral resection of the prostate (TURP) chips which were taken 3 months after TUMT on 45 patients. The findings were compared with those of 75 patients who were treated before the use of thermosensitization with PTL.

Materials and methods

Patients

Between October 2008 and April 2011, 45 patients with biopsy proven adenocarcinoma of the prostate, clinical stage T1c~T2c N0M0, were enrolled in this study. The mean age of the patients was 71.8 (range 53~83) years. The mean serum prostate antigen (PSA) was 9.2 (range 4.0~34.1) ng/ml. The mean prostatic volume (total volume including fibrous capsule of the prostate) at initial transrectal ultrasound (TRUS) measurement was 30.1 ml (range 15.6~59.4). Gleason scores⁹⁾ at initial TRUS biopsy were 6 or less in 17, 7 (3+4) in 13, 7 (4+3) in 7, 8 in 3, 9 in 4 and 10 in 1 patient. Clinical stages were T1c in 25, T2a in 9, T2b in 7 and T2c in 4 patients according to the 1992 TNM Staging System (Table I).

Table I. Baseline characteristics of 45 patients with parthenolide.

Characteristics	
Age (mean $\pm$ SD) (years)	71.8 $\pm$ 5.6
PSA (mean $\pm$ SD) (ng/ml)	9.2 $\pm$ 7.8
PSA level number (%)	
4-10 (ng/ml)	33 (73.3)
> 10-20 (ng/ml)	8 (17.7)
> 20 (ng/ml)	4 (8.9)
Prostate volume (mean $\pm$ SD)	
< 20 (ml)	8 (17.8)
20.1-30 (ml)	15 (33.3)
30.1-40 (ml)	16 (35.6)
40.1-50 (ml)	4 (8.9)
> 50 (ml)	2 (4.4)
Clinical stage number (%)	
T1c	25 (55.5)
T2a	9 (20.0)
T2b	7 (15.6)
T2c	4 (8.9)
Gleason score number (%)	
< 6	17 (37.8)
7	20 (44.4)
8	3 (6.7)
9	4 (8.9)
10	1 (2.2)

PSA, Prostate specific antigen; Prostate volume, Total gland volume including fibrous capsule of the prostate measured by ultrasonography.

A thorough discussion was held with each patient regarding this illness, the plan of this treatment, potential choice of other treatment modalities regarding this illness and written informed consent was obtained.

The histopathologic findings of their TURP chips which were obtained at least 3 months after TUMT with use of UroWave™ (Dornier MedTech Systems GmbH, Munich, Germany) were compared by thorough histopathologic examination with those of 75 patients⁸⁾ who were treated in a similar procedure before the administration of PTL.

Androgen deprivation therapy

The therapy started with oral administration of non-steroidal anti-androgen (bicalutamide 80 mg/day) and was followed by subcutaneous administration of luteinizing hormone-releasing hormone (LH-RH) agonist (leuporelin acetate 3.75 mg/4 weeks in 31 patients and goserelin acetate 10.8 mg/12 weeks in 14 patients) 2 weeks after starting oral administration of non-steroidal anti-androgen. High-energy TUMT was performed at least 12 weeks (mean 14.6) after initiation of LH-RH agonist therapy to wait for satisfactory reduction in prostate volume to render the thermotherapy more effective. The counting of length of androgen deprivation therapy (ADT) was started at the first LH-RH agonist administration and terminated at 6th months (4 weeks×6) after TURP in radical fashion. Total length of ADT was 15.7 ± 2.5 (mean $\pm$ SD) months.

Thermosensitization by parthenolide

PTL is a nuclear factor- κ B (NF- κ B) inhibitor. It was investigated in the human prostate cancer androgen-independent cell lines PC3 and DU145 and its significant thermo-enhancement effect was confirmed by Hayashi *et al*⁷⁾. We have utilized Tanacet 125® (Ashbury Biologicals, Toronto, Canada) as a remedy for this purpose. It is a standardized feverfew (*Tanacetum parthenium*) leaf product, which is a recognized traditional herbal remedy mainly for prevention of migraine as well as anti-tumor activity. According to Curry III *et al*¹⁰⁾, feverfew, with up to 4 mg of PTL, given daily as an oral tablet is well tolerated without dose-limiting toxicity.

In this study, Tanacet 125®, which contains a minimum of 0.2% PTL, was used as a thermosensitizing remedy. We have administered 2 oral tablets daily (PTL 0.5 mg/day). For the initial 30 patients, 2 tablet daily for 30 days were given orally to examine any physiological and biochemical changes due to PTL administration and it was followed by 15 days of oral administration during and after TUMT with UroWave™. Since we have noticed no detectable side effect of PTL on these 30 patients, pretreatment PTL administration has reduced to 15 days and followed by 30 days during and post-treatment period after TUMT. The total dose of PTL administration was 22.5 mg in perioperative period of TUMT.

Transurethral microwave thermotherapy

The UroWave™ was used for TUMT. It is a high-energy TUMT device designed for treatment of BPH^{11,12)}. It applies 915 MHz microwave energy to the prostate *via* a helical coil antenna enclosed in a transurethral delivery system, which also contains a water-cooling circuit system to provide 360°

uninterrupted circumferential cooling. This prevents urethral mucosa from heat injury. The diameter of the urethral applicator is approximately 18F when inflated with cooling water. Urethral applicator UA20 is a helical coil antenna 17.5 mm in length and UA30 is of 24.5 mm in length. An appropriate length of antenna was chosen according to the length of prostatic urethra of each patient. The system features a rectal probe, with a series of 3 thermal couples mounted on the anterior midline that continuously monitor 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. For the present study, the safety threshold was set at 43.5°C in the urethral mucosa and at 43°C in the rectum. With these settings, peak intraprostatic temperature reaches as high as 65°C. Mean temperature reaches a maximum of 55°C at a radial distance of approximately 4 mm from the urethral mucosa and remained 45°C or higher up to a distance of 16 mm. The fibrous capsule serves as a barrier to pass microwave so as to prevent excessive heating of the rectal wall and external urethral sphincter, and it also helps to accumulate higher temperature to kill cancer cells inside the fibrous capsule of the prostate. This system is capable of delivering up to 90 watts of power to the targeted tissue. The median power we used in this series was 74 watts (range 35~90). The patients were subjected to a 60 min treatment in an outpatient setting under local anesthesia. A 14F indwelling urethral catheter was kept in place for 3 days after the treatment. Majority of the patients complained of no difficulty in urination after removal of the catheter. In 2 exceptional patients, however, longer indwelling catheter was needed, 2 and 3 weeks respectively.

Regional hyperthermia

Three days after TUMT and after removal of indwelling urethral catheter, all the patients underwent one session of regional hyperthermia using a radiofrequency capacitive heating system operated at 8 MHz (Thermotron-RF8, Yamamoto Vinita, Osaka, Japan)^{13,14)} focused on lower pelvic cavity including the prostate at around center of it. Intrarectal temperature was measured using a 4-on the point microthermocouple sensor *via* a rectal tube at the level of the prostate so as to measure the treatment temperature and to record in a real time manner. The output power was set at 800~1,200 watts, based on the patient's tolerance. The heating duration was equally 45 min. In all patients, both the upper and lower electrodes were 30 cm in diameter and placed on opposite sides of lower pelvic region. The treatment posture was prone position in majority of the patients. Patients with subcutaneous adipose tissue thickness greater than 2.5 cm frequently complain of irritating sensation in the skin at the heating site, which cause a decrease in the effectiveness of the RF-capacitive heating device. However, at least one of the 4 intrarectal temperature measurement was reached 41.5°C or higher during the treatment. The upper limit of the temperature was set at 43.5°C.

The purpose of this regional hyperthermia is to expect higher treatment effect by heating fibrous capsule of the prostate and periprostatic region as well. Since preceding TUMT is able to heat whole intraprostatic adenomatous tissue up to 45°C or higher, but microwave poorly penetrates fibrous capsule of the prostate.

Transurethral resection of the prostate

TURP was performed in radical fashion at least 3 months after thermotherapy. This is to remove

glandular tissue of the prostate, as much as possible, until reaching to the fibrous capsule. As our policy, the verumontanum was kept intact, since prostate cancer rarely occurs in this area and also it is an important landmark to identify location of the external urethral sphincter. This procedure is not only to remove remnant cancer tissue, but also to confirm the treatment effect of thermotherapy under ADT and PTL administration. Interval of 3 month is to wait for maturation of tissue degeneration due to thermotherapy combined with ADT and PTL. Significant reduction in volume of the prostate and tissue degeneration due to ADT followed by thermotherapy made TURP easy and safe under clear vision with less blood loss than ordinary TURP for benign prostatic hyperplasia. All TURP chips were subjected to thorough histopathologic study divided into 5 parts; median, anterior, right lateral, left lateral and apex.

Statistical analysis

Data on age, serum PSA, Gleason score, histology and TRUS volume were analyzed with Student's *t*-test, chi-square test, Fisher's exact test and ANOVA. Differences were considered significant with the *P*-value < 0.05. The OR and 95% CI were calculated for histology.

Results

Reduction in volume of the prostate

The mean volume of the prostate including fibrous capsule of the prostate measured by TRUS was 30.1 ml at initial diagnosis. Significant reduction in prostatic volume (mean 34.6%) was noted after ADT for 3 months. At TUMT, the mean volume of the prostate was 19.5 ml. It was thought to be small enough to be thoroughly heated by high-energy microwave down to the peripheral prostate. In another 3 months after TUMT and continued ADT, reduction in volume of the prostate was 51.7% of the original volume at diagnosis. The mean weight of TURP chips was 6.4 grams. These figures are grossly compatible with those of the control group⁸⁾ before PTL administration (Table II).

Table II. Reduction in volume of the prostate measured by ultrasonography (45 patients with use of parthenolide).

	Before treatment TRUS (ml)	12 weeks after ADT TRUS (ml)	12 weeks after TUMT TRUS (ml)	TURP Wt (g)
n =	45	43	45	45
Mean $\pm$ SD	30.1 $\pm$ 9.9	19.5 $\pm$ 7.3	14.6 $\pm$ 7.2 [†]	6.4 $\pm$ 4.9
Reduction rate		34.6 $\pm$ 17.1%	51.7 $\pm$ 16.3%	

ADT, androgen deprivation therapy; TUMT, transurethral microwave thermotherapy; TURP Wt, total chip weight of transurethral resection of the prostate; TRUS, transrectal ultrasonography; [†], one-way ANOVA, repeated measurement, *P* = 0.0003.

Histopathologic features of TURP chips

At least 3 months (mean 3.8 $\pm$ 0.6) after TUMT, continued ADT and administration of PTL for 45 days before and after thermotherapy, TURP was performed in radical fashion. The all TURP chips were subjected to thorough pathologic study in the same manner as the control group by the same single urological pathologist who identified Gleason score of the cancer foci. They revealed remarkable degenerative changes associated with fibrosis in general. In 41 of 45 patients, cancer cell was not detected in TURP chips. In 1 patient, non-viable cancer foci referring to as necrosis and severe

degenerative changes, cell cytoplasm was homogeneous in appearance and intensely eosinophilic with nuclear piknosis, were found in a small number of TURP chips (Fig. 1). In 3 patients, however, degraded but probably viable cancer cells were detected in TURP chips (Figs. 2-4). Number of patients

Fig. 1. 73 yrs. PSA 7.8 ng/ml. **A**, Initial biopsy core from the left mid area: poorly differentiated adenocarcinoma, Gleason score 4+4=8. Reduced from $\times 100$. **B**, A typical area of the above. Reduced from $\times 200$. **C**, Histology of a TURP chip from the apex area, 12 weeks after transurethral microwave thermotherapy pretreated with parthenolide 0.5 mg/daily for 15 days and continued androgen deprivation. Generalized degenerative changes, but with some remnant of probably non-viable cancer cells, in 7 of 20 chips from the apex area. The total number of TURP chips was 73. Reduced from $\times 40$. **D**, A typical area of the above. Reduced from $\times 200$.

Fig. 2. 71 yrs. PSA 4.8 ng/ml. **A**, Initial biopsy core from the left apex area; moderately differentiated adenocarcinoma, Gleason score 3+4=7. Reduced from $\times 100$. **B**, A typical area of from above. Reduced from $\times 200$. **C**, Histology of a TURP chip from the left lateral area, 16 weeks after transurethral microwave thermotherapy pretreated with parthenolide 0.5 mg/daily for 15 days and continued androgen deprivation. Generalized degenerative changes, but with some remnant of probably viable but degraded cancer foci in 1 of 14 chips from the left lateral area. The total number of TURP chips was 63. Reduced from $\times 100$. **D**, A typical area of the above. Reduced $\times 400$.

Fig. 3. 67 yrs. PSA 11.8 ng/ml. **A**, Initial biopsy core from the right apex area ; poorly differentiated mucinous adenocarcinoma, Gleason score 4+4=8. Reduced from $\times 100$. **B**, A typical area of the above. Reduced from $\times 200$. **C**, Histology of a TURP chip from the right lateral area, 16 weeks after transurethral microwave thermotherapy pretreated with parthenolide 0.5 mg/daily for 15 days and continued androgen deprivation. Generalized degenerative changes but with a few remnant of degraded cancer foci, probably of Gleason score 3+4=7, in 1 chip among 19 chips from the right lateral area. The total number of TURP chips was 70. Reduced from $\times 40$. **D**, A typical area of the above. Reduced from $\times 400$.

Fig. 4. 79 yrs. PSA 11.3 ng/ml. **A**, Initial biopsy core from the left base area ; moderately differentiated adenocarcinoma, Gleason score 3+4=7. Reduced from $\times 100$. **B**, A typical area of the above. Reduced from $\times 200$. **C**, Histology of a TURP chip from the left lateral area, 18 weeks after transurethral microwave thermotherapy pretreated with parthenolide 0.5 mg/daily for 15 days and continued androgen deprivation. Generalized degenerative changes, but with scattered remnant of probably viable cancer foci, possibly degraded, in about half of TURP chips from the left lateral and apex area. The total number of TURP chips was 158. Reduced from $\times 100$. **D**, A typical area of the above. Reduced from $\times 200$.

who had remnant cancer foci in TURP chips was apparently smaller than half of the control group without use of PTL and degenerative change was more remarkable in the PTL group than those of the control group (Table III). The characteristics of the 4 patients with remnant cancer foci in TURP chips are listed in Table IV and those of 16 patients of control group are listed in Table V.

Table III. Historologic difference in TURP chips between patients with parthenolide (PTL) and without PTL.

	With PTL (n=45)	Without PTL (n=75)	P-value	(95% CI)
No remnant cancer	41	59	0.061	Chi-squared
Remnant cancer	4	16		OR 0.36 (0.11–1.15)
(viable, non-viable)	(3, 1)	(6, 10)		
	Mean $\pm$ SD (n)	Mean $\pm$ SD (n)		t-test
Age (years)	71.8 $\pm$ 5.6 (45)	70.4 $\pm$ 6.3 (75)	0.054	(-0.09–4.49)
PSA (ng/ml)	9.2 $\pm$ 7.8 (45)	10.1 $\pm$ 6.7 (75)	0.381	(-3.84–1.43)
Prostate volume (ml)	30.1 $\pm$ 9.9 (45)	34.6 $\pm$ 14.2 (72)	0.221	(-6.62–1.65)
Gleason score	n (%)	n (%)		
< 6	17 (37.8)	41 (54.6)	0.189	Fisher's exact test
7	20 (44.4)	23 (30.7)		
> 8	8 (17.8)	11 (14.7)		

Abbreviations as in Table I.

Table IV. Characteristics of 4 patients who had remnant cancer cell in TURP chips (4/45 patients with parthenolide).

Patient	Age (years)	at Diagnosis					sat TURP				Pathology	
		PSA (ng/ml)	P. vol. (ml)	Gleason score	Location	Stage	P. vol. (ml)	Wt (g)	Location	N-chips	Presumed Gleason score	Viability
1	73	7.8	17.3	4+4=8	5,6	T2a	14.8	5.1	Ap	7/20(73)		non-viable
2	71	4.8	20.7	3+4=7	4,5,6	T2a	7.8	3.6	LL	1/14(63)	—	viable, degraded
3	67	11.8	23.1	4+4=8	1	T1c	14.7	5.7	RL	1/19(70)	3+4=7	viable, degraded
4	79	11.3	51.6	3+4=7	5,6	T2a	22.0	11.5	LL	32/58(158)	—	viable, degraded
									Ap	11/34(158)	—	viable, degraded

P. vol., prostate volume including fibrous capsule measured by ultrasonography; **1**, right apex; **4**, left apex; **5**, left mid; **6**, left base; Wt, weight of TURP chips; Ap, apex area; LL, left lateral area; RL, right lateral area; N-chips, number of cancer positive chip/number of chips in the area (number of total TURP chips)

Table V. Characteristics of 16 patients who had remnant cancer cell in TURP chips (16/75 patients before use of parthenolide).

Patient	Age (years)	at Diagnosis					sat TURP				Pathology	
		PSA (ng/ml)	P. vol. (ml)	Gleason score	Location	Stage	P. vol. (ml)	Wt (g)	Location	N-chips	Presumed Gleason score	Viability
1	67	8.9	28.1	2+2=4	4,5	T2a	12.2	7.0	Md	1/6 (139)	2+3=5	viable, degraded
2	63	6.3	33.6	2+1=3	2	T1c	16.0	5.0	RL	1/22 (85)		non-viable
				3+4=7	6				LL	4/22 (85)		non-viable
3	70	9.1	43.5	4+3=7	1,2,3	T2a	30.4	21.6	RL	2/69 (189)		non-viable
4	60	20.2	18.4	3+3=6	4	T2a	13.3	4.8	LL	1/20 (69)		non-viable
				4+4=8	5				Ap	2/14 (69)		non-viable

Table V. (continued).

Patient	Age (years)	PSA (ng/ml)	at Diagnosis				P. vol. (ml)	Wt (g)	sat TURP		Pathology	
			P. vol. (ml)	Gleason score	Location	Stage			Location	N-chips	Presumed Gleason score	Viability
5	60	8.5	14.7	3+4=7	5,6	T2a	13.0	4.9	LL	3/25 (75)		non-viable
6	69	10.6	21.9	4+5=9	1,2,3	T2a	14.5	8.7	RL	7/20 (67)	4+3=7	viable, degraded
7	70	6.2	34.2	2+3=5	3	T1c	21.0	12.0	RL	5/49 (135)		non-viable
8	77	6.3	28.6	2+3=5	4	T1c	15.9	10.0	LL	1/38 (106)		non-viable
				3+4=7	5							
9	72	4.4	19.2	3+3=6	3	T1c	18.8	9.0	LL	1/25 (97)	2+3=5	viable, degraded
10	70	10.9	27.9	4+5=9	4	T1c	12.9	9.8	Ap	1/30 (101)	2+2=4	viable, degraded
11	62	7.8	22.8	3+3=6	5	T2a	20.3	5.0	LL	3/16 (50)		non-viable
				2+3=5	6							
12	72	11.6	24.4	4+3=7	2	T1c	14.5	5.5	RL	4/32 (72)	3+2=5	viable, degraded
									Ap	3/10 (72)		non-viable
13	71	7.8	25.8	3+3=6	1	T1c	8.8	5.1	RL	3/15 (73)		non-viable
14	83	12.2	28.8	4+4=8	1,2,3	T2a	14.1	12.9	LL	1/23 (147)		non-viable
15	76	8.6	26.0	4+4=8M	4	T1c	13.1	5.8	Ap	1/22 (77)	4+4=8	viable
16	73	6.5	23.6	3+3=6	1,6	T1c	8.7	4.9				
				3+4=7	5				LL	3/20 (79)		non-viable
			26.3 ± 6.9					15.5 ± 5.3				

2, right mid ; 3, right base ; Md, median lobe area ; M, mucinous adenocarcinoma ; Other abbreviations as in Table IV.

Changes in serum chemistry and PSA levels

For the initial 30 patients PTL administration was started 30 days before TUMT. Their serum chemistry levels before and after 30days revealed no unfavorable change in any visceral functions and blood components as well. For 15 patients thereafter, PTL administration was started 15 days before TUMT.

Sudden fall in serum PSA was observed after ADT for 3 months. It became almost undetectable after TUMT. After cessation of ADT, 6 months (6×4 weeks) after TURP, serum PSA showed gradual elevation, but stayed within normal range (< 4 ng/ml) in majority of the patients. Regarding 8 patients with biopsy Gleason score 8 or greater, one patient showed elevation of serum PSA up to 6.1 ng/ml, at 12th month after cessation of ADT. He has been on intermittent anti-androgen treatment up to date since then, without any clinical evidence of recurrence of the disease. His biopsy Gleason score was 10 and serum PSA was 34.1 ng/ml at diagnosis (Fig. 5). Although it is still too early to discuss

Fig. 5. Changes in serum PSA level during the therapy and follow up period on 8 patients with Gleason score 8 or greater at biopsy diagnosis. One of them has been on anti-androgen therapy (red line).

on the behavior of serum PSA after this treatment, there has been no statistically meaningful difference between PTL group and control group before administration of PTL.

Complications

Two patients complained of difficulty in urination due to stricture in posterior urethra. One patient was successfully treated by urethral dilation, however, another patient required internal urethrotomy twice. One patient complained of stress incontinence after TURP, but spontaneously cured by 6th postoperative month. All patients tolerated the scheduled ADT until 6th month after TURP.

Clinical outcome

The main purpose of this study is to report differences in the irreversible pathologic changes of TURP chips between PTL administered group and control group before the use of PTL. Therefore it is still too early to compare the long term clinical outcome of both groups in the same standard.

One patient developed mild elevation of serum PSA at 12th month and has been on intermittent non-steroidal anti-androgen administration. One patient, 83 years old, died of cardiac accident at home, in 2 months after finishing all the therapeutic procedure, without any relationship with prostate cancer. His last serum PSA was < 0.1 ng/ml at 2 months before death. The other patients are alive as of February 2013, at a median observation period of 33 months (range 18~51) without any evidence of clinical recurrence of prostate cancer.

Discussion

The therapeutic effectiveness of heat on malignant tumors has been reported since long ago. There were many reports in the early 1900s on the use of applied hyperthermia in treating cancer in which heat was thought to be the most important factor in causing regression of tumors and even cure¹⁵⁾. However, the interest declined in the 1960s possibly due to the decrease of many infectious diseases with the introduction of antibiotics and technical difficulties related to the practical application of hyperthermia.

Localized hyperthermia for prostate cancer using microwave applicator was reported by Mendecki *et al*¹⁶⁾ though the clinical efficacy remained insufficient mainly because of the transrectal treatment route with the intraprostatic temperature lower than 43°C. Development of a new system, TUMT¹⁷⁾ combines the heating of the prostatic tissue with the conductive cooling of the urethra, accomplished by arranging a chamber around the microwave antenna which is continuously circulated with cooled water. It is also acknowledged that high-energy TUMT is able to destroy prostatic tissue up to a radial distance of 16 mm, while maintaining innocuous urethral and rectal temperature. According to our clinical experiences⁸⁾, the radial distance from the urethral mucosa to the fibrous capsule of the prostate with the volume of approximately 30 ml is usually within 15 mm, with an 18F microwave applicator placed in the urethra. However, one should notice that not all TUMT machines are suitable to treat prostate cancer. Majority of them are designed for the treatment of enlarged lateral lobes of prostatic hyperplasia. It is fortunate for us that the TUMT machine we have used in this study is a very suitable one to treat prostate cancer even in the peripheral zone and/or apex of the prostate by helical coil antenna system^{8,18)}.

Though TUMT is capable of heating whole intraprostatic tissue to 45°C or higher, it is insufficient

to deliver therapeutic heat further than 16 mm from the urethral mucosa. The purpose of 8 MHz radiofrequency capacitive regional hyperthermia is to expect higher treatment effect by additional heating to the fibrous capsule of the prostate and periprostatic region, though the maximum temperature is limited to 43.5°C. To date, regional hyperthermia is usually performed in combination with another treatment modality, such as radiotherapy or chemotherapy. In this study, we have utilized PTL expecting its thermo-enhancement effect.

The thermo-enhancement effect of the sesquiterpene lactone PTL, which targets the transcription factor NF- κ B, and hyperthermia at 40, 42 and 44°C on the human lung adenocarcinoma A549 cell line were investigated and reported by Hayashi *et al*⁶⁾ in 2008. They hypothesized that cells treated with PTL had an altered arrangement of stressed cells undergoing the transformation from necrotic cell death to apoptotic cell death *via* another mechanism. Their results suggested that PTL-induced apoptosis of A549 cells was due to the direct suppression of NF- κ B activity in a p53- and hsp72-independent manner based on NF- κ B signaling. Their subsequent investigation results on the thermo-enhancement effect of PTL on human prostate cancer androgen-independent cell lines⁷⁾ encouraged us to use PTL in thermotherapy of prostate cancer.

To date, as far as we know, this is the first clinical report to assess the combination therapy of TUMT, regional hyperthermia, ADT and PTL in patients with prostate cancer. We like to conclude that this combination therapy is feasible and administration of PTL may positively contribute to better clinical outcome in patients with early prostate cancer.

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