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Original

Association of radiation doses to individual part of periprostatic area in cases of iodine-125 prostate brachytherapy with erectile dysfunction

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Abstract

To explore the correlation of radiation exposure of the periprostatic area (PPA) with erectile dysfunction (ED) after seed implant brachytherapy (BT), we compared DVH parameters of the PPA obtained from the postplan, considering alterations of the International Index of Erectile Function 6 questionnaire score (IIEF-6) after BT, among 34 patients with IIEF-6 ≧ 22 before BT. We delineated the PPA manually as the extracapsular rind of 3 mm width, which was divided into 36 parts on 12 sectors of the apex, middle and base of the prostate (ROIs). We divided patients into two groups: the non-ED group (n = 23) with IIEF-6 ≧ 22 at 12 months after BT, and the ED group (n = 11), who had IIEF-6 ≦ 11 at the same time point as the non-ED group. We performed statistical comparison between the non-ED group and ED group for the mean D90 of each ROI (roiD90) and the variables belonging to patients' backgrounds and DVH parameters. In known variables, there was no significant difference between the ED and non-ED groups in terms of patients' backgrounds and DVH parameters. The mean roiD90 of the ED group was significantly larger than that of the non-ED group at the middle and apex of left side of the prostate. These findings indicate that that excessive doses on a specific site of the PPA may induce ED due to radiation damage on the pelvic splanchnic nerve passing through the area.

Key words : *prostate cancer, I-125 prostate brachytherapy, erectile dysfunction, radiation dose, neurovascular bundle*

I. Introduction

The prevalence of prostate cancer (PC) in developed nations has been gradually increasing since the 1990s, along with increasing incidence worldwide. In 2015, PC was the most common cancer among Japanese men [1)]. Because the incidence of localized PC has exceeded that of metastatic PC, the rate of local therapy of curative intent, such as radical prostatectomy (RP) or radiation therapy including external beam radiotherapy

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(EBRT) and brachytherapy, has become higher than that of systemic therapy such as androgen deprivation therapy (ADT). Both RP and EBRT are associated with erectile dysfunction (ED); however, it is predominant in RP patients [2]. The mechanism of ED in RP is believed to be physical damage of the neurovascular bundles (NVBs) lying between the prostatic fascia and the levator fascia [3]. ED is less likely to occur due to radiotherapy because the pelvic splanchnic nerve is preserved. In prostate seed implant brachytherapy (BT), the placement of a radioactive source within the prostate seems to have an advantage over RP in the urinary and sexual domains and also in patients' satisfaction, as indicated in QOL assessments. Nevertheless, not all BT patients necessarily avoid ED [4].

The cause of post-BT ED has been investigated with a focus on the possible association of the prostate radiation dose with ED. Merrick et al. [5] found no significant association between the dose of the prostate and the NVB and ED. Likewise, Meyer et al. discovered no significant differences between post-BT radiation dose at the base or apex of the prostate and fluctuations in erectile function [1]. Thus, no clear relationship between post-BT ED and radiation dose has yet been established despite the fact that BT avoids unnecessary declines of erectile function score [2]. We believe that one of the reasons for this might be that the region of interest used in previous studies did not comprehensively and accurately reflect the path of the pelvic splanchnic nerve. In the present study, we analyzed the dose distribution on the periprostatic area (PPA).

II. Materials and methods

Patients in this study underwent BT monotherapy for localized PC of low or intermediate risk [1] in our hospital from December 2004 to October 2016. They were included in a prospective cohort study (J-POPS) (Ito K et al., Int J Clin Oncol 2018) with a follow-up protocol comprising interval history, physical examination, adverse effects, and measurement of PSA every 3 months for 5 years. In addition, we evaluated disease-related QOL using the International Index of Erectile Function (IIEF)-6 questionnaire before and after BT annually. Further eligibility criteria included completion of the IIEF-6 questionnaire before and a year after BT; indication or not of mild ED by IIEF-6 score prior to BT; and absence of ADT for any purpose.

BT: iodine-125 loose seeds of 0.28–0.335 mCi (Source Tec 1251 NIST99; Bard, NJ) or custom-build linked seeds (Bard Medical, Covington, GA, USA) were inserted by a Mick applicator system (Mick Radionuclear Instruments, New York, USA) under interactive planning using transrectal ultrasound imaging [9]. The prescription dose (PD) was escalated from 145 Gy to 160 Gy during the study period. Modified-peripheral loading was optimized by a BT-treatment planning system (TPS; VariSeed version 7.2; Varian Medical Systems, Palo Alto, CA) to pV_{100} (% prostate volume exposed to PD) > 95%; pV_{150} (% prostate volume exposed to 1.5 PD) < 60% and rV100 (rectal volume exposed to PD) < 1.0 cc. [10].

Postplan: Computed tomography (CT, Aquillion, Toshiba, Tokyo, Japan) images with a 3-mm pitch of the pelvis in the supine position were acquired 4 weeks after BT

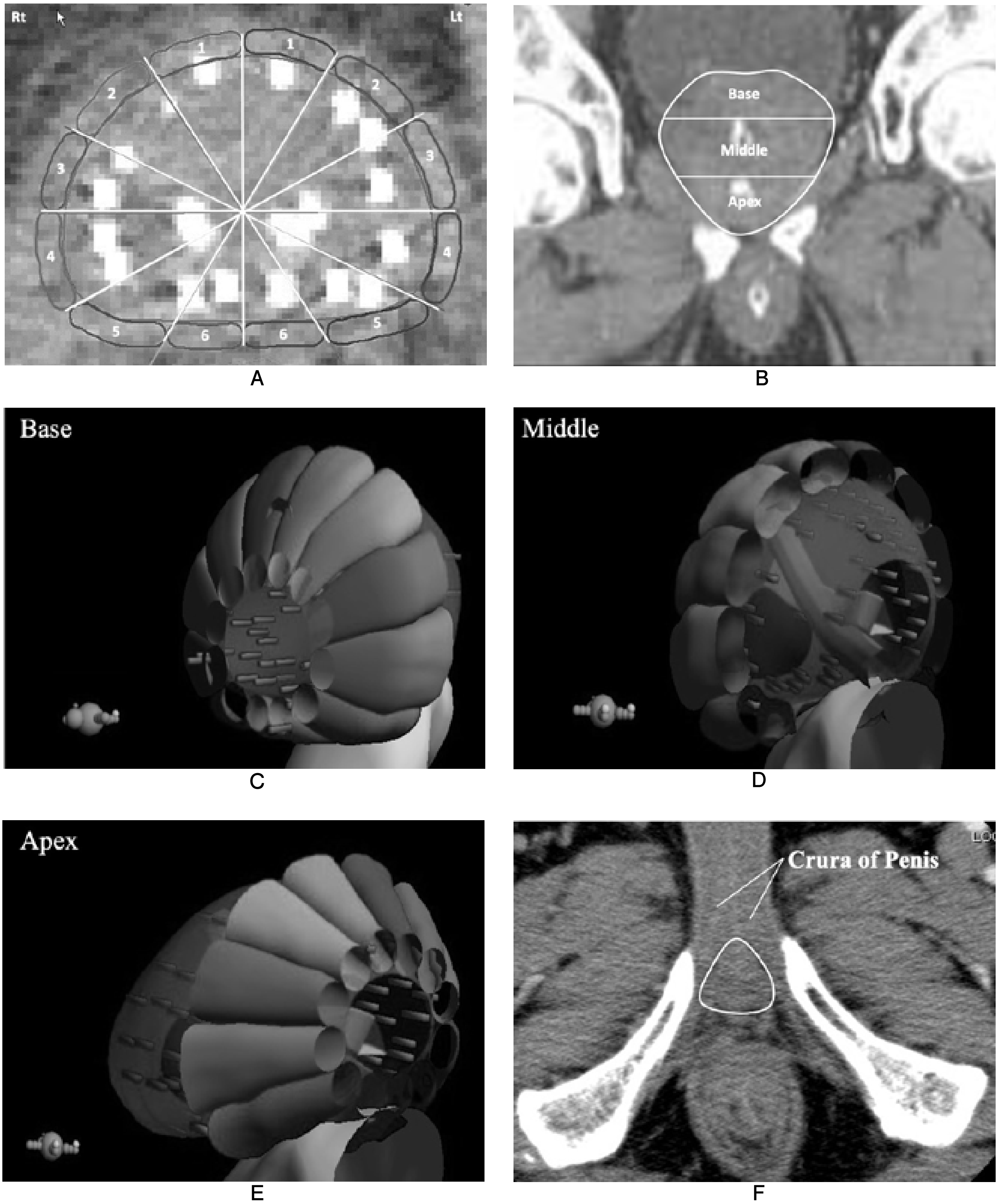

Fig. 1. Method of measuring the site-specific radiation dose of the periprostatic areas. A: The regions surrounding the prostate was divided into 12 sections using CT images on the radiotherapy planning system. The regions of interest (ROIs) were set with 3 mm thickness. B: The prostate was divided into three equal sections: base, middle and apex. C-E: ROIs of the periprostatic area (C: base, D: middle, E apex, respectively). F: The urethral bulb region into which the peritoneal seeds were implanted was set as the ROI.

Table 1. Changes in IIEF-6 scores at pre-treatment and 12 months post-treatment

IIEF-6 score range Pre-treatment	n	IIEF-6 score range 12 month	n	Group*
26–30 (No ED)	33	26–30	12	non-ED
		22–25	5	non-ED
		17–21	4	
		11–16	2	ED
		06–10	3	ED
		No sexual intercourse	7	
22–25 (Mild ED)	23	26–30	4	non-ED
		22–25	2	non-ED
		17–21	6	
		11–16	4	ED
		06–10	2	ED
		No sexual intercourse	5	
17–21 (Mild-Moderate ED)	18	26–30	1	
		22–25	0	
		17–21	4	
		11–16	6	
		06–10	0	
		No sexual intercourse	7	
11–16 (Moderate ED)	7	26–30	1	
		22–25	0	
		17–21	0	
		11–16	1	
		06–10	1	
		No sexual intercourse	4	
06–10 (Severe ED)	0			

Scoring categories are based on a maximum of 30 points scored according to the International Index of Erectile Function (IIEF) specific area of erectile function (15).
*, Group assignments of the study; ED, erectile dysfunction.

and were imported into the TPS. All doses were defined using the TG43 formalism from a 1-mm grid size at each seed location determined by the seed finder module to present pD_{90}, pV_{100} and pV_{150}.

To evaluate the effect of radiation exposure on the pelvic splanchnic nerve around the prostate, we performed DVH analysis of the PPA defined as 3-mm-thick extracapsular rind surrounding the prostate to cover all structures of nerve fibers (Figs. 1A, B). The PPA was divided into 36 parts on 12 sectors of the apex, middle and base of the prostate (ROIs) (Figs. 1C, D, E). They were numbered 1 - 6 clockwise on the left-hand side and counter-clockwise on the right-hand side. One urologist manually delineated the prostate, ROIs and the corpus cavernosum (CV) (Fig. 1f). The radiation exposure dose of 36 ROIs was individually expressed as $roiD_{90}$.

Those who had an IIEF-6 score equal to or greater than 22 at 12 months after BT were assigned to the preserved sexual function (non-ED) group. Those patients who had a score

Table 2. Comparison of clinical background characteristics in the non-ED and ED groups

	non-ED (n = 23)	ED (n = 11)	Total (n = 34)	p value
2Mean age at diagnosis (years)	60.9	62.1	61.3	0.61
PSA level at diagnosis (ng/mL)	6.13	6.42	6.22	0.727
Gleason score				
6 or less	16	7	23	0.178
3 + 4	4	4	8	
4 + 3	3	0	3	
Clinical T stage				
T1c	20	11	31	0.115
T2a	3	0	3	
Past history				
Hypertension	7	1	8	0.144
Dyslipidemia	1	1	2	0.594
Diabetes mellitus	0	1	1	0.372
Smoking	9	2	11	0.278
Obesity (BMI is 25 kg/m^2 or less)	3	9	12	0.437
Mean pre-treatment IIEF-6	26.6	25.4	26.36	0.141

IIEF, International Index of Erecrile Function; ED, erectile dusfunction.

Table 3. Comparison of the brachytherapy parameters in the non-ED and ED groups

	non-ED (n = 23)	ED (n = 11)	Total (n = 34)	p value
Mean preoperative volume (mL)	23.5	28.9	25.3	0.198
Mean number of needles	22.9	24	23.2	0.261
Mean number of seeds	73.3	79.5	75.4	0.325
Use of Linkseed	6	4	10	0.409
Prescription dose				
145 Gy	6	4	10	0.542
160 Gy	17	7	24	
Total dose to 90% of the prostate. (D90, Gy)	181.2	189.3	183.8	0.4
Percentage of the volume of the prostate receiving 100% of the prescription dose. (V_{100}, %)	93.1	94.8	93.7	0.626
Percentage of the volume of the prostate receiving 150% of the prescription dose. (V_{150}, %)	66	67.9	66.6	0.702

ED, erectile dusfunction.

equal to or less than 16 were assigned to the declined sexual function (ED) group. Those patents who had scores from 17 to 21 (the equivocal) were excluded from this study to emphasize the difference between the groups. Between the ED group and the non-ED group, statistical comparison was performed in multiple values such as patient backgrounds, classification of the tumor, therapeutic parameters and postplan DVH parameters,

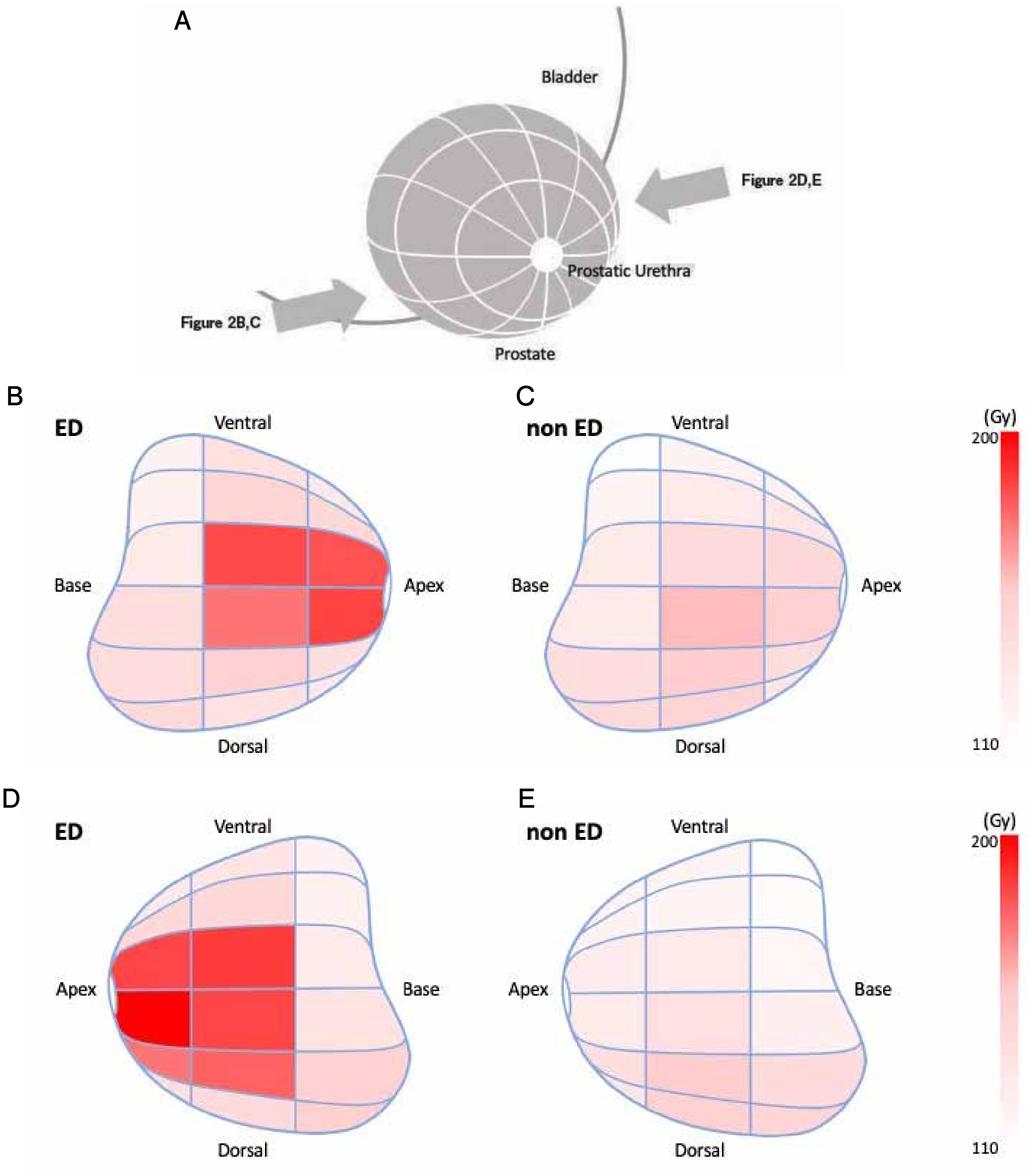

Fig. 2. Radiation doses specific to sites of the periprostatic areas. (A): Diagram of the radiation doses specific to the sections of the prostate. The dose distribution for the 18 sections on the right-hand side in the ED group (B) and the non-ED group (C) and the dose distribution for the 18 sections on the left-hand side in the ED group (D) and the non-ED group (E) are shown. The D90 (Gy) for all sections on the heatmap are shown with 200 Gy in red and 110 Gy in white.

including D_{90}, V_{100} and V_{150} of the prostate and the ROIs. The patient backgrounds included age, hypertension [11], diabetes [12], history of smoking [13] and obesity [14].

Statistical analyses were conducted using Student's t-test and the chi-squared test. Statistical significance was set at $p < 0.05$. We examined whether it would be possible to predict post-BT ED using the radiation doses recorded in ROIs, by creating a receiver operating characteristic curve (ROC) for the onset of post-BT ED. The analytical software package used was JMP 13.2.1 (SAS Institute Inc., Cary, NC, USA). Post-BT PSA failure was

Table 4. Dose distribution in 36 prostate sections in the non-ED, the equivocal and ED groups (D90, Gy)

		Base (Mean ± SD, Gy)	Middle (Mean ± SD, Gy)	Apex (Mean ± SD, Gy)
ED Rt Surface	1 (Ventral)	131.8 ± 24.0	150.0 ± 23.8	140.5 ± 34.7
	2	133.2 ± 17.6	162.7 ± 33.9	159.1 ± 44.6
	3	140.0 ± 19.0	187.3 ± 57.3	186.4 ± 72.0
	4	154.1 ± 39.2	182.3 ± 46.3	188.2 ± 65.5
	5	153.6 ± 46.3	165.9 ± 45.0	151.4 ± 31.2
	6 (Dorsal)	156.8 ± 39.8	148.2 ± 19.5	141.4 ± 27.8
the equivocal Rt Surface	1 (Ventral)	123.5 ± 28.0	128.0 ± 33.5	118.0 ± 36.0
	2	134.0 ± 25.0	141.5 ± 32.1	139.5 ± 31.8
	3	147.5 ± 30.9	151.5 ± 25.4	145.0 ± 30.5
	4	163.0 ± 49.0	173.5 ± 33.5	154.0 ± 39.5
	5	144.0 ± 18.9	181.0 ± 29.6	145.5 ± 36.2
	6 (Dorsal)	149.5 ± 24.5	169.0 ± 24.3	132.0 ± 30.3
non-ED Rt Surface	1 (Ventral)	116.7 ± 26.7	130.7 ± 28.8	130.7 ± 31.8
	2	128.9 ± 28.4	140.2 ± 29.5	144.6 ± 36.7
	3	140.4 ± 30.8	155.7 ± 32.7	158.0 ± 38.2
	4	141.3 ± 25.4	173.9 ± 46.9	167.2 ± 41.7
	5	152.8 ± 29.1	170.4 ± 34.7	154.1 ± 34.9
	6 (Dorsal)	156.7 ± 26.3	163.7 ± 24.3	141.7 ± 29.7
ED Lt Surface	1 (Ventral)	130.9 ± 33.3	143.6 ± 26.0	140.9 ± 35.3
	2	133.6 ± 29.2	159.1 ± 29.4	160.0 ± 40.0
	3	141.4 ± 20.3	189.1 ± 52.1	187.7 ± 41.6
	4	147.7 ± 28.8	187.7 ± 45.6	195.9 ± 55.4
	5	165.9 ± 45.8	184.5 ± 43.1	182.3 ± 60.5
	6 (Dorsal)	168.6 ± 42.7	157.7 ± 24.7	151.4 ± 32.6
the equivocal Lt Surface	1 (Ventral)	128.0 ± 32.1	128.0 ± 39.3	130.0 ± 22.8
	2	131.0 ± 34.0	136.5 ± 29.8	139.0 ± 20.7
	3	140.5 ± 25.1	146.5 ± 25.0	142.5 ± 25.1
	4	142.5 ± 25.6	151.0 ± 31.7	137.0 ± 26.4
	5	154.5 ± 35.9	178.5 ± 42.7	138.0 ± 35.2
	6 (Dorsal)	153.5 ± 27.7	166.5 ± 21.0	129.5 ± 26.8
non-ED Lt Surface	1 (Ventral)	116.3 ± 28.8	129.3 ± 30.8	129.3 ± 28.9
	2	121.7 ± 29.1	127.4 ± 26.2	131.3 ± 26.0
	3	127.0 ± 25.3	140.9 ± 27.9	138.9 ± 31.8
	4	134.3 ± 28.9	151.1 ± 39.8	141.1 ± 33.8
	5	156.5 ± 31.2	172.0 ± 33.7	152.6 ± 42.5
	6 (Dorsal)	162.4 ± 33.6	167.2 ± 29.8	145.4 ± 34.8
ED Bulb			51.8 ± 15.2	
the equivocal Bulb			41.0 ± 18.1	
Non-ED Bulb			39.1 ± 18.3	

ED, erectile dusfunction.

estimated by the Phoenix definition [15].

This study was approved by the Ethics Committee of Iwate Medical University School of Medicine (H17-7).

III. Results

Between December 2004 and October 2016, 81 men with prostate cancer underwent BT. The IIEF-6 distribution for these

Table 5. Relation between the radiation doses in the 36 prostate sections and erectile dysfunction (p values)

	Right surface (p value)			Left surface (p value)			Bulb (p value)
	Base	Middle	Apex	Base	Middle	Apex	
1 (Ventral)	0.122	0.062	0.420	0.197	0.194	0.317	
2	0.651	0.056	0.322	0.273	0.003	0.017*	
3	0.966	0.048*	0.141	0.109	0.001*	0.001*	
4	0.260	0.629	0.264	0.215	0.023*	0.001*	0.055
5	0.951	0.749	0.824	0.487	0.359	0.107	
6 (Dorsal)	0.995	0.074	0.972	0.645	0.370	0.639	

*, Indicates statistical significance ($p < 0.05$).

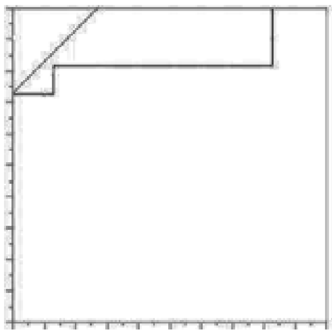

Fig. 3. A receiver operating characteristic curve to investigate the predictive ability for the onset of post-BT ED. The results demonstrated a high degree of accuracy, with an area under the curve of 0.838. Using the radiation dose at the middle and the apex of both lateral side of PPA, it was possible to predict post-BT ED with a high degree of probability. When the cutoff (defined as mean D_{90} for the identified region) was set at 167.1 Gy, ED onset was predicted with a sensitivity of 0.73 and a specificity of 1.00.

patients is shown in Table 1. Fifty-six of the sexually active patients selected for further analysis [16] were divided into groups of 23 (the non-ED group), 11 (the ED group) and 22 (the equivocal). The patient background characteristics for the non-ED and ED groups are shown in Table 2 with no significant intergroup differences. No significant difference was found in the mean pre-BT IIEF-6 scores between the non-ED and ED groups ($p = 0.141$). No cases presented with post-treatment PSA recurrence. The therapeutic variables and postplan DVH parameters of the prostate are shown in Table 3, with no significant differences. In addition, although linked seeds were also used, there was no difference in the frequency of their usage.

The mean roiD90 of each ROI of PPA and the urethral bulb (D_{90}, Gy) are shown in Fig. 2 and Table 4. The mean roiD_{90} of the ED group tended to be higher than that of the non-ED group. In all ROIs, the mean roiD_{90} of the ED group was equal to or higher than that of the non-ED group except for those of the right-middle 5 and 6 ROIs. The p value of the t-test comparing mean roiD90s between the ED and non-ED groups is shown in Table 5. In this comparison, p value at each ROI was less than 0.05 at right-middle 3 o'clock; left-middle 2, 3 and 4 o'clock; and left apex 2, 3 and 4 o'clock. Although the mean D_{90} of the corpus cavernosum of the ED group was greater than that of the non-ED group, the difference was not statistically significant ($p = 0.055$).

The ROC analysis demonstrated a high degree of accuracy with an area under the curve of 0.838, and by using the radiation dose at the middle and the apex of both lateral sides of the PPA, it was possible to predict post-BT ED with a high degree of probability. When the cutoff (defined as mean D90 for the identified region) was set at 167.1 Gy, ED onset was predicted with a sensitivity of 0.73 and a specificity of 1.00. We calculated the cutoff using the ROC curve in Fig.3.

Ⅳ. Discussion

The cancer-specific survival rate for low-to-moderate-risk PC is extremely high after either RP or radiotherapy, including EBRT and BT [8, 17]. BT was used in cases of low-to-moderate-risk PC in the beginning and is now used even in cases of high-risk PC in conjunction with EBRT or ADT [18]. The post-BT erectile function is perceived as being favorable for patients willing to live with erectile function [2] instead of undergoing surgery causing frequent and irreversible damage to the pelvic splanchnic nerve fibers that run through the lateral pelvic fascia adjacent to the prostate [3]. Malcom reported that BT avoids unnecessary declines of erectile function scores [7]. On the other hand, Zelefsky reported that patients undergoing brachytherapy developed post-treatment impotence [19]. Nolan et al. reported histological changes of the nerves in dogs, such as severe hollowing and lesion formation followed by a decrease in nerve fibers, after radiation exposure of 50 Gy per 5 fractions [20]. There is a high probability that a similar phenomenon may occur by way of BT wherein peripheral seed loading escalates the extracapsular region dose up to the range of a biologically effective dose (BED) of 200 Gy, approximating to the threshold dose of 50 Gy in 5 fractions corresponding to 217 Gy when the Linear-Quadratic model is adoptable.

The correlation of radiation exposure of several organs with post-BT ED has been studied. Meyer et al. [6] investigated the correlation of the mean dose to the prostate base, apex and the urethral bulb with the IIEF-5 (a basic index of erectile function). However, although their univariate analysis showed positive correlation in pD_{90}, pV_{100} of the apex and pV_{100} at the base, multivariate analysis failed to prove a significant relationship. Merrick et al. investigated as to whether a relationship exists between the postplan dose to the CV or the NVB and the possibility of vaginal intercourse [21]. Although they found a significant correlation between D_{95} of CV and the possibility of vaginal intercourse ($p = 0.001$), their further investigation did not show a significant relationship between radiation dose to the NVB and ED [5]. Thus, there is still room for debate on the issue of the relationship between the magnitude of radiation exposure because of BT and ED.

Regarding the anatomical location of the NVB, recent studies have found that the path of the pelvic splanchnic nerve is quite variable and that it runs a wide path across the surface of the prostate [7]. Therefore, it is rationally presumed that the ROIs of the PPA in the present study accurately cover the path of the pelvic splanchnic nerve. Our study is the first to measure the radiation dose of the PPA.

In the PPA, the radiation dose at the left-middle 2 to 4 and the right-middle 3 ROIs of the prostate correlated with the incidence of ED. This suggests that the path of the pelvic splanchnic nerve may fall in this region. In their investigation of the course of the

NVB, Kaiho et al. assessed the intra-urethral pressure when electrophysiological stimulation was applied to the surface of the prostate during radical prostatectomy to study the physical path of the nerves associated with erection. They found that stimulation applied to the middle prostate at between 4 and 5 o'clock led to the highest intra-urethral pressure and concluded that the distribution of nerves in this region was the most dense [22]. The results of our study support these findings, and clearly indicate that the radiation dose to this same region is related to ED.

In the present study, roiD90s of the left-hand-side of the PPA were larger than those of the right-hand-side ones (Table 4). For our right-handed surgeons, it might be easier to insert peripheral needles into the left prostate lobe and cause the laterality in the dose distribution. The ROIs showed significant differences in roiD90 between the ED and non-ED groups predominantly located in the left-hand side of the PPA (Table 5). Eichelberg et al. conducted a study on the course and distribution of nerve fibers using post-prostatectomy specimens. They found no difference in the number of nerve fibers between the right and left lobes of the prostate [23]. These conflicting findings indicate the need for further study. The mean radiation doses at the apex and middle on both lateral sides certainly predict ED at 12 months after BT with a high degree of accuracy. Mapping the high-dose area in the PPA is expected to enhance prediction of post-BT ED.

Current standard BT delivers eradication doses covering the entire prostate. Based on recent concerns for tissue preservation, focal therapies have received a great deal of attention as another therapeutic option. Dose de-escalation in the specific predictive area might ensure the preservation of erectile function as well as therapeutic efficacy. In cases where a cancer lesion is outside the site associated with ED, the use of these methods may allow the avoidance of seed implantation. By contrast, in cases with a cancer lesion in a site that is associated with ED, the physician should consider early intervention using phosphodiesterase type 5 inhibitors, which may be useful in preserving erectile function.

This study has several limitations. First, we have few patients. Second, we had an insufficient basis for setting 3 mm as the thickness for the ROI on the surface of the prostate. Third, because we used the IIEF-6 score at 12 months after BT, the study period was relatively short, whereas post-treatment erectile function has been reported to improve after at least 2 years [24]. Thus, we plan to conduct further study over a longer period of time. Fourth, our predictions of ED onset were not validated using independent samples, and it therefore remains necessary to conduct further investigation with additional patients to avoid the problem of over-fitting. Fifth, because erectile function was evaluated by patient-oriented inquiry, this study is perhaps contaminated by nonstructural alterations in erectile function. It is therefore necessary to investigate the relationship between radiation doses to individual parts of the PPA and quantitative assessment of erectile function, using an objective method such as RIGISCAN®. Nevertheless, in the present study, we clearly identified the location of the PPA where radiation dose is related to

ED, and this information is important for the preservation of post-BT erectile function.

V. Conclusion

Erectile function score was degraded in patients who had high radiation exposure to the lateral periprostatic area of the middle and apex during seed implant brachytherapy. This suggests that excessive radiation delivery to these sites should be avoided to preserve erectile function.

Conflict of Interest: The authors have no conflict of interest to declare.

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I-125 前立腺癌密封小線源療法における 前立腺表面の部位別放射線量と勃起不全の関連

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要旨

我々は今回，前立腺表面を 36 分割した部位別放射線量を詳細に測定し，前立腺癌密封小線源療法後の勃起不全との関連を明らかにする．当院で前立腺癌密封小線源療法単独治療を施行した症例 81 例より，治療前の international index of erectile function（IIEF）– 6 スコアが 21 点以上の 56 例を抽出した．治療後 12 ヵ月における IIEF– 6 が 22 点以上の症例 23 例と 16 点未満の症例 11 例を選択し，それぞれ維持群，低下群と定義した．小線源療法 1 ヵ月後の CT 画像上の前立腺を尖部・中部・底部に 3 分割，各々の領域を 12 分割した計 36 ヵ所の前立腺表面線量を測定，維持群と低下群で比較検討をおこなった．患者背景比較では治療前 IIEF – 6 スコアで群間に差を認めなかった．ポストプランの放射線量パラメータ比較では維持群と低下群で差は認められなかった．治療後の各部位における部位別放射線量の平均値を維持群，低下群で検討すると，低下群では前立腺中部〜尖部 2-4 時方向での放射線量が有意に高値をとり，この部分への過剰被曝が小線源療法後の勃起不全に影響すると思われた．