Original paper

Acute and late toxicities in localized prostate cancer patients treated with low-dose ^{125}I brachytherapy (110 Gy) in combination with external beam radiation therapy versus brachytherapy alone (160 Gy)

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Abstract

Purpose: The aim of this analysis was to compare acute and late toxicities between low-dose-rate brachytherapy (LDR-BT) (110 Gy) in combination with 45 Gy in 25 fractions external beam radiation therapy (EBRT) and LDR-BT (160 Gy) alone for localized prostate cancer.

Material and methods: One hundred five consecutive patients with localized prostate cancer treated from May 2014 to May 2017 were included in this retrospective analysis. Sixty patients received combination therapy and 45 patients received BT monotherapy. The LDR-BT procedure was performed using ^{125}I seeds.

Results: The median follow-up time was 28 months in both groups. Three-year effect rates were overall survival: 100% in both groups. The biochemical failure rate was 2.3% in the combination group and 0% in the monotherapy group (p = 0.373). No patients died during the study period. In both groups, almost all the patients experienced acute urethritis. There was a significant difference between the combination therapy group (8.3%) and BT monotherapy group (11.1%) in late genitourinary (GU) toxicities ≥ grade 2 (p = 0.035). Only 2 patients (3.3%) in the combination therapy group developed late ≥ grade 2 rectal hemorrhage. There were no significant differences between two groups in hematuria ≥ grade 2 (p = 0.068) or rectal hemorrhage ≥ grade 2 (p = 0.206).

Conclusions: To our knowledge, this is the first report to compare the GU and gastrointestinal toxicities between the combination therapy and BT monotherapy (160 Gy) for localized prostate cancer. Unexpectedly, there were more late GU toxicities (except for hematuria) in the BT monotherapy group.

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Key words: low-dose-rate brachytherapy, prostate cancer, radiation therapy, toxicity.

Purpose

Patients with low-risk clinically localized prostate cancer are confronted with multiple curative treatment options such as radical prostatectomy (RP), low-dose-rate brachytherapy (LDR-BT) as monotherapy, definitive external beam radiation therapy (EBRT) using three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and active surveillance (AS) [1,2].

Low-dose-rate BT has been shown to be an acceptable, effective, and safe therapy for localized prostate cancer [3]. This approach has lower complications and is less invasive than RP. In comparison with EBRT, LDR-BT can deliver higher dose with lower exposure to organs at risk. It is relatively well-tolerated by elderly patients because seed insertion can be completed under general or spinal anesthesia in a few hours.

In some institutions, LDR-BT is initiated in an outpatient setting or during a brief hospital stay, after which patients can be discharged some hours after treatment [4]. Most patients may return to work and perform normal activities within a few days after the treatment. This makes

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it an attractive option for patients in terms of convenience and minimal interference with daily activity and lifestyle.

Recently, LDR-BT has been found to be adaptable to include a dose escalation or to being combined with EBRT to supply a boost. Although there is room for interpretation, some reports have implied that dose escalation may improve results [5,6]. At our institution, low-risk patients have been prescribed 145 Gy in LDR-BT. Intermediate-risk and intermediate-tier high-risk (intermediate-to-high-risk) patients have been managed with dose escalation LDR-BT prescribed 160 Gy, or with LDR-BT in combination with EBRT (3D-CRT or IMRT).

As mentioned above, LDR-BT has the great advantage of minimal interference with lifestyle. It is important to choose LDR-BT methods not only considering the remaining life expectancy but also comorbidity, age at diagnosis, and quality of life (QOL).

Both the negative effects of the treatment and possible effects on QOL should be considered in the decision-making process. The aim of this analysis was to compare the acute and late toxicities between LDR-BT (110 Gy) in combination with EBRT and LDR-BT (160 Gy) as monotherapy for localized prostate cancer.

Material and methods

Patients

From May 2014 to May 2017, 105 consecutive locally advanced prostate cancer patients were treated with LDR-BT (160 Gy) as BT monotherapy (the monotherapy group) or LDR-BT (110 Gy) in combination with EBRT (the combination therapy group).

Of the 105 patients, 60 patients received combination therapy and the remaining 45 patients received BT

Table 1. Patient and treatment characteristics

	Combination therapy group	BT monotherapy group	*P* value
The number of patients	60	45	
Age (years)			
Median	68 (range: 44-81)	68 (range: 53-81)	0.99
PS (ECOG)			
0	57	41	0.34
1	3	3	(PS = 0)
2	0	1	
Clinical stage (TNM Classification of Malignant Tumors, 8th edition)			< 0.001
Stage I	20	29	
Stage II	32	16	
Stage III	8	0	
Initial PSA (ng/ml)			
Median	9 (range: 4-54.6)	7.46 (range: 4-20.6)	0.08
< 10	38	33	
10-20	16	10	
≥ 20	6	2	
Gleason score			< 0.001
4 + 5 = 9	4	0	
4 + 4 = 8	20	5	
4 + 3 = 7	13	11	
3 + 4 = 7	20	19	
3 + 3 = 6	3	10	
Number of positive cores	4/12 core (30%)	3/12 core (20%)	< 0.001
NCCN risk classification criteria			< 0.001
High	34	7	
Intermediate	25	35	
Low	1	3	

BT – brachytherapy; PS – performance status; ECOG – Eastern Cooperative Oncology Group; PSA – prostate-specific antigen; NCCN – National Comprehensive Cancer Network

monotherapy. We retrospectively reviewed the medical records. Determination of the clinical stage was based on physical examination, chest X-ray, chest-pelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI), and bone scan.

All patients were examined before treatment by urologists and radiation oncologists, and they were classified according to the International Union Against Cancer staging system and categorized according to the National Comprehensive Cancer Network (NCCN) risk classification criteria (TNM Classification of Malignant Tumors, 8th edition). The disease characteristics of the 105 patients are summarized in Table 1. All patients had pathologically confirmed adenocarcinoma and underwent Gleason score histological grading.

This study was approved by the institutional review board (B180700026), and informed consent was obtained from all patients prior to treatment.

Treatment

All patients were treated with curative intent. In the combination therapy group (43.3%) and in BT monotherapy group (42.2%), neoadjuvant androgen deprivation therapy (ADT) 3 months before BT or BT/RT was administered to reduce prostate volume, and 18.3% and 13.3% respectively, received adjuvant hormone therapy after BT or BT/RT.

Methods of LDR-BT

The LDR-BT procedure was performed at our institution using ^{125}I seeds (Onco-Seed®, Nihon Medi-physics, Kobe, Japan). The target volume of the implant was the prostate gland and the implantation was based on intraoperative planning with real-time dynamic dose calculation using commercial software (VariSeed®, Varian Medical Systems, Palo Alto CA, USA). Implantation was performed under general anesthesia using real-time transrectal ultrasound (TRUS) and a standard template, and the seeds were individually deposited using a Mick applicator. The LDR-BT constraints are shown in Table 2. All patients underwent chest and pelvic radiography just after the implantation to assess seed distribution in the prostate and to detect seed migration.

Table 2. Low-dose-rate brachytherapy constraints

		Combination therapy group	BT monotherapy group
BT prescribed dose		110 Gy	160 Gy
Prostate	D_{90}	≥ 110 Gy (> 100%)	180-200 Gy
	V_{100}	≥ 95%	
	V_{150}	< 60%	≤ 150%
Urethra	U V_{150}	= 0 cc (165 Gy)	≤ 10%
	U D_{10}	< 150%	
	U D_{30}	< 130%	≤ 150%
Rectum	R V_{100}	≤ 0.1 cc	≤ 1 cc
	R $D_{2\ cc}$	≤ 110 Gy	

BT – brachytherapy; D_{90} – dose received by 90% of the prostate volume; V_{100} – volume of prostate receiving 100% of the prescribed dose; V_{150} – volume of prostate receiving 150% of the prescribed dose; U V_{150} – volume of urethra receiving 150% of the prescribed dose; U D_{10} – dose received by 10% of the urethra volume; U D_{30} – dose received by 30% of the urethra volume; R V_{100} – volume of rectum receiving 100% of the prescribed dose; R $D_{2\ cc}$ – dose received by 2 cc of the rectum volume

Post-dosimetric evaluation

Both post-implant CT and MRI were obtained, and post-implant dosimetric study was performed approximately 3 weeks after the LDR-BT. The biologically effective dose (BED) from the post-plan D_{90} was calculated using an α/β ratio = 2. The total BED for the combination therapy group was a sum of the BEDs from the LDR-BT and that from the EBRT [7] (Table 3).

External beam radiation therapy

In the combination therapy group, the planning CT was obtained approximately one month after the LDR-BT. In this group, patients received 45 Gy in 25 fractions using a four-field box technique with 15 MV 3D-CRT or IMRT using TomoTherapy system (Accuray Inc., Sunnyvale, CA).

The clinical target volume (CTV) consisted of the whole prostate and the proximal one-third of the seminal vesicles (SV). PTV was defined as the CTV with a 3-5 mm expansion margin posteriorly, and 8-10 mm expansion margins inferiorly, superiorly, anteriorly, and laterally. The maximum allowable dose delivered to the PTV was 107% of the prescribed dose, and the minimum allowable dose delivered to the PTV was 95% of the prescribed dose. The dosimetric goals to the rectum were: V_{40} < 20% (no more than 20% of the rectal volume should receive > 40 Gy), and V_{35} < 30% and V_{30} < 40%. The maximum acceptable dose delivered to the bladder was < 110% of the prescribed dose.

Evaluation criteria and statistical analysis

The patients were followed up 3-6 months after the treatment. During these visits, serum PSA levels and toxicity data were collected.

Comparison of clinical variables between the two groups was performed using Mann-Whitney's *U*-test. The

Table 3. The total biologically effective dose (BED) at implant phase and post-implant phase

	Combination therapy group	BT monotherapy group
Implant phase		
BED (α/β = 2)	220.6	209.6
EQD2	110 Gy	104 Gy
Post-implant phase		
BED (α/β = 2)	211.1	191.8
EQD2	106 Gy	96 Gy

BT – brachytherapy; BED – biologically effective dose; EQD2 – equivalent dose in 2 Gy fractions

overall survival (OS) rate and biochemical relapse-free survival (BRFS) rate from the beginning of LDR-BT were calculated with Kaplan-Meier curves, and differences between curves were tested by the log-rank test. Biochemical failure (BF) was defined as the nadir PSA level + 2 ng/ml.

Acute and late genitourinary (GU) and gastrointestinal (GI) toxicities associated with treatment were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.0, 2009). Acute toxicities were defined as therapy-related adverse events that occurred within 3 months after the beginning of the treatment, and late toxicities as those occurring after 3 months. These statistical analyses were performed using commercial software (the Statistical Package for the Social Sciences [SPSS®] for Windows, version 23.0 IBM Inc., Armonk NY, USA). A p value < 0.05 was considered significant.

Results

The median follow-up time was 28 months (range: 11-48 months) in the combination therapy group, and 28 months (range: 12-48 months) in the BT monotherapy group.

The treatment characteristics of the study group are summarized in Table 4. Seed migrations were observed (combination therapy group/BT monotherapy group) in the lung (n = 3/n = 5), pelvis (n = 8/n = 15), seminal vesicle (n = 6/n = 6), and other sites (n = 0/n = 2). Table 3 also shows the post-implant data of the study groups. CT data could not be obtained in 3 patients; 102 patients were analyzed in the post-implant phase.

In the combination therapy group, the median EBRT duration time was 35 days (range: 32-41), and the du-

Table 4. The treatment characteristics at implant phase and post-implant phase

(Average ± standard deviation)	Combination therapy group	BT monotherapy group	*P* value
Median follow-up time (months)	28 (range: 11-48)	28 (range: 12-48)	NS
The days from diagnosis to BT (days)	136.5 ±287.75	69 ±173.26	0.939
Anticoagulant drug (*n*)	6	6	NS
Implant phase			
Seeds number (*n*)	60 (range: 35-75)	80 (range: 55-100)	0.001
Migrations (*n*)	0.4 ±0.7	0.7 ±0.9	0.06
D_{90} (Gy)	129.3 ±5.6	196.2 ±6.5	< 0.001
Activity (mCi)	0.33 (range: 0.26-0.35)	0.33 (range: 0.33-0.35)	
Prostate volume at implant (cc)	27.7 ±7.2	27.5 ±6.5	0.74
R V_{100} (cc)	0.08 ±0.2	0.2 ±0.3	< 0.001
R $D_{2\ cc}$ (Gy)	73.1 ±7.7	109.3 ±12.5	< 0.001
R D_{30} (Gy)	68.2 ±6.9	110.3 ±15.1	< 0.001
U V_{150} (cc)	0 ±0.02	0 ±0.12	0.02
U D_{90} (Gy)	89.2 ±18.6	114.8 ±28.7	< 0.001
U D_{30} (Gy)	136.0 ±6.7	200.8 ±8.3	< 0.001
Post-implant phase			
CT not available	1	2	
Prostate volume	28.9 ±7.2	27.3 ±6.0	0.426
D_{90} post (Gy)	120.4 ±9.3	180.4 ±14.9	< 0.001
R V_{100} post (cc)	0.2 ±0.2	0.3 ±0.3	0.098
R $D_{2\ cc}$ post (Gy)	70.7 ±10.3	103.4 ±17.4	< 0.001
R $D_{30\ Gy}$ post (Gy)	35.6 ±8.1	49.4 ±12.8	< 0.001
U $V_{150\ cc}$ post (cc)	0.01 ±0.5	0.01 ±0.4	0.15
U $D_{90\ Gy}$ post (Gy)	90.1 ±17.0	126.0 ±29.7	< 0.001
U $D_{30\ Gy}$ post (Gy)	138.2 ±10.7	208.0 ±14.8	< 0.001

BT – brachytherapy; NS – not significant; D_{90} – dose received by 90% of the prostate volume; R V_{100} – volume of rectum receiving 100% of the prescribed dose; R D_2 – dose received by 2 cc of the rectum volume; R D_{30} – dose received by 30% of the rectum volume; U V_{150} – volume of urethra receiving 150% of the prescribed dose; U D_{90} – dose received by 90% of the urethra volume; U D_{30} – dose received by 30% of the urethra volume; CT – computed tomography

ration time from LDR-BT to start of EBRT was 36 days (range: 26-64).

Twelve patients who received BT monotherapy alone had been advised to undergo combination therapy but selected monotherapy due to work schedule (n = 10), or because of age (n = 1) or comorbidities (n = 1). Six patients in the BT monotherapy group required dose escalation because of age < 60 years. In the combination therapy group, 51 patients received EBRT in the form of 3D-CRT, and the remaining 9 patients underwent IMRT.

The survival and tumor control

Three-year OS in this cohort was 100% in both groups; the BRFS rate in the combination group was 97.7% and in the monotherapy group was 100% (Figure 1) (p = 0.373). No patients died during the study period.

Only one patient developed BF in the combination therapy group. This patient's nadir PSA was recorded at 12 months after the end of the treatment; subsequently, the PSA began increasing. At 24 months after the treatment, PSA level = nadir PSA level + 2 ng/ml, and he was diagnosed with BF. At that time, CT, MRI, and bone scan were performed but there was no evidence of metastasis. Hormonal therapy (luteinizing hormone-releasing hormone – LHRH) was started at that time at the patient's request. At the latest visit, there was no further PSA increase.

Toxicity

Table 5 shows the acute and late toxicities. In the BT monotherapy group, one patient had already had a urinary catheter inserted before the BT, preventing evaluation of voiding symptoms except hematuria. This patient had no hematuria. In both groups, almost all the patients experienced acute urethritis. The median times that late GU toxicity ≥ grade 2 occurred in the combination therapy group and the BT monotherapy group were 19 months (range: 6-23 months) and 18 months (range: 3-19 months), respectively. Late GI toxicity ≥ grade 2 occurred in the combination therapy group only at 9 and 12 months, respectively.

There was a significant difference between the combination therapy group (8.3%) and the BT monotherapy group (11.1%) in late GU toxicities ≥ grade 2 (p = 0.035). In the BT monotherapy group, one patient required a catheter 7 months after the treatment because of prostatitis that was associated with urinary retention. He experienced repeated urinary tract infections and had required an indwelling bladder catheter until the last follow-up. Late grade 3 hematuria occurred in one patient (1.7%) in the combination therapy group; he had not been treated with anticoagulants. Two patients (3.3%) in the combination therapy group developed late grade 2 rectal hemorrhage.

Hematuria and rectal hemorrhage (grade 1-2) frequently developed in the combination therapy group: hematuria, n = 5 (8.3%); rectal hemorrhage, n = 17 (28.3%). Whereas, in the monotherapy group, there was no hematuria and only one patient developed grade 1 rectal hemorrhage. There was no significant difference between two groups in hematuria ≥ grade 2 (p = 0.068) and in rectal hemorrhage ≥ grade 2 (p = 0.206).

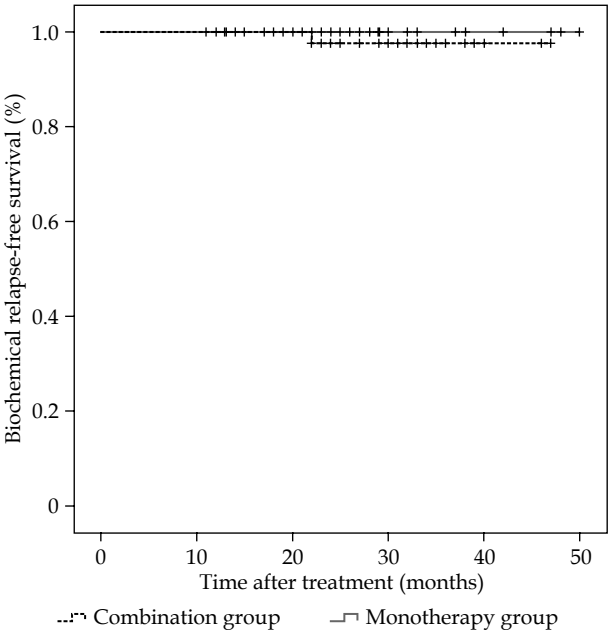

Fig. 1. Kaplan-Meier curves for biochemical relapse-free survival rate. Biochemical relapse-free survival of patients treated with combination therapy and monotherapy

In patients who experienced bleeding, one patient with hematuria and one patient with rectal hemorrhage had used anticoagulants. There was no significant difference between medications with anticoagulants and hematuria ≥ grade 2 (p = 0.896) or rectal hemorrhage ≥ grade 2 (p = 0.317). One patient in the BT monotherapy group developed grade 1 rectal hemorrhage. All rectal bleeding was assessed with colonoscopy.

In the combination therapy group, we analyzed the 3D-CRT and IMRT groups but found no significant differences between them in late GU toxicity (p = 0.13). No late GI ≥ grade 2 toxicity occurred in the IMRT group.

Discussion

To our knowledge, this is the first report to compare the acute and late toxicities between ^{125}I LDR-BT 110 Gy in combination with EBRT and ^{125}I LDR-BT 160 Gy as monotherapy for localized prostate cancer.

There have been several reports to compare the treatment outcomes and GU or GI toxicities [8,9,10,11,12,13,14]. However, they included a variety of LDR-BT modalities or sources, or different prescribed doses such as mixed ^{125}I and ^{103}Pb [8,15,16]. In one study, the LDR-BT procedure included both pre-operative planning and intraoperative planning [12], and in another only pre-operative planning was used [8]. The prescribed dose of LDR-BT was not uniform, ranging from 137-160 Gy [8,12,13].

In this study, LDR-BT used only ^{125}I, the prescribed dose was only 160 Gy in monotherapy and 110 Gy in combination therapy, and all LDR-BT was intraoperatively planned. The treatment had high uniformity. In addition, most previous reports targeted low-to-intermediate-risk prostate cancer patients, whereas ours focused on localized intermediate-to-high-risk patients.

Table 5. Acute and late toxicities

	Combination therapy group			BT monotherapy group		
	Grade 1	Grade 2	Grade ≥ 3	Grade 1	Grade 2	Grade ≥ 3
Acute toxicities						
GU						
Urethritis	1	59	0	0	45	0
Urinary urgency	45	0	0	23	0	0
Urinary incontinence	6	0	0	4	2	0
Urinary retention	2	0	0	1	0	0
Urinary tract pain	19	0	0	13	0	0
Hematuria	0	0	0	1	0	0
GI						
Proctitis	4	0	0	0	0	0
Diarrhea	3	0	0	3	0	0
Anal pain	23	0	0	5	0	0
Late toxicities						
GU						
Urinary urgency	2	0	0	10	1	0
Urinary incontinence	1	2	0	4	2	0
Urinary retention	0	0	0	0	1	0
Urinary tract pain	1	2	0	5	3	0
Hematuria	1	3	1	0	0	0
GI						
Proctitis	10	0	0	0	0	0
Anal pain	1	0	0	1	0	0
Rectal hemorrhage	15	2	0	1	0	0

BT – brachytherapy; GU – genitourinary; GI – gastrointestinal

Almost all patients (99%) sustained acute grade 2 GU toxicities, a higher incidence compared with previous reports [2,10]. However, in our study, they were categorized as grade 2 GU because they were medicated for urinary symptoms.

It was similar to previous reports that there were no acute GI toxicities ≥ grade 2 [12]. As we mentioned above, the variety of LDR-BT procedures used in prior studies makes comparison difficult.

In this study, late GU toxicities ≥ grade 2 in the combination therapy group showed a rate of 8.3% and the BT monotherapy group 11.1%. In the previous reports of BT monotherapy, the late GU toxicity rate was 8.1-22.3% [17,18], and late urinary retention was reported in 0.6% [4]. By contrast, a study of BT and EBRT combination therapy reported a late GU grade 2 toxicity rate of 17% and grade 3 – 3% [10]. The GU toxicity rate was similar to previous reports in both groups. In this study, late grade 2 GU toxicity was significantly higher in the BT monotherapy group (p = 0.035). With regard to bladder catheterization, in our study, only one patient (2.2%) in the BT monotherapy group required long-term bladder catheterization. There have been some reports of rates of the need for bladder catheterization between 0.2-6.1% [4,18,19] for acute GU toxicity in BT monotherapy.

In this study, 2 patients (3.3%) in the combination therapy group, developed rectal hemorrhage as late grade 2 GI toxicity. It was comparable to previous reports of late grade 2 GI toxicity rates of 0.3-1.3% [3,18] in BT monotherapy studies, and 2.8-6.8% [8,12] in the studies including EBRT combination therapy.

There was a significant difference between EBRT combination therapy and BT monotherapy in late GU and GI toxicity rates in one study [12]; estimated G2 rectal bleeding with monotherapy was 18% and 22% with combined therapy in another report [13]. In studies of HDR-BT, HDR-EBRT combination therapy was associated with a higher rate of bleeding than HDR-BT mono-

therapy [20]. In our study, there was a high incidence of rectal hemorrhage and hematuria in the combination therapy group; however, there were no significant differences between the two groups in hematuria ≥ grade 2 (p = 0.068) or in rectal hemorrhage ≥ grade 2 (p = 0.206), respectively. We also analyzed the relationship between anticoagulant medicine use and bleeding, and found no significant association. There have been no reports about it in combination therapy vs. BT monotherapy. In BT monotherapy, there has been one report of a late hematuria rate of 15.4% [17], and several reports of late rectal hemorrhage rates of 6-16% [3,4,17]. In our study, only one late grade 1 rectal hemorrhage in the monotherapy group was recorded.

We analyzed the 3D-CRT and IMRT groups in combination therapy group but found no significant differences between them in late GU toxicity (p = 0.13). The failure to reach statistical significance is likely attributable to the small patient numbers (only nine patients received IMRT).

The treatment outcome was excellent in this study and at the same time, it may be meaningless because of short period of observation.

The American Brachytherapy Society guidelines (2012) characterize BT and EBRT combination therapy as an option, and recommend it for high-risk disease [8,12]. In the American Society of Clinical Oncology (ASCO) guidelines [21] for low-intermediate risk patients, Gleason score (GS) 7 and PSA < 10, GS 6 and PSA 10-20, LDR-BT may be offered as monotherapy. Additionally, the NCCN guidelines also state that BT and EBRT combination therapy is optional. Recently, several reports on BT and EBRT combination therapy found no difference in the survival of prostate cancer patients [8,13,22,23] compared with BT monotherapy. Stones *et al*. reported, even at a high grade, if the tumor was confined to the prostate gland, BT only is adaptive, but there are also reports with opposite results [9,10,24,25,26].

Conversely, an EBRT boost may be indispensable when there is suspicion of incipient extracapsular or seminal vesicle invasion seen on MRI. We predict that dose escalation for BT monotherapy may be less toxic. Our results show significantly less GU toxicity with combination therapy. Although the definite indications of EBRT combination therapy have not been established, it may be useful for patients with increased risk of GU toxicity.

LDR-BT monotherapy has a great benefit compared to EBRT such as: 1. Higher dose can deliver to prostate with lower exposure to organs at risks; 2. The treatment time became remarkably shorter than EBRT because usually the insertion was completed within one day [14,19,27]. In comparison with EBRT, LDR-BT can deliver a higher dose with lower exposure to organs at risk.

In this study of intermediate-to-high-risk prostate cancer patients, there was no significant difference in BRFS between the combination therapy group and BT monotherapy group (p = 0.373). If there is no apparent invasion outside of the prostate, the dose escalation BT monotherapy may be a good treatment option for intermediate-to-high-risk prostate cancer patients who are elderly, taking anticoagulants, or who cannot follow a schedule of external beam treatments, as long as they understand slightly increased risk of GU toxicities.

The limitations of this study include its retrospective nature, the relatively short follow-up time, and the small number of patients. Further studies are needed to evaluate the long-term prognosis.

Conclusions

To our knowledge, this is the first report to compare the GU and GI toxicities between ^{125}I LDR-BT 110 Gy in combination with EBRT and ^{125}I LDR-BT 160 Gy as monotherapy for localized prostate cancer. In this study, we found significantly higher grade 2 GU toxicity in the BT monotherapy group. It is important to choose a treatment method according to the characteristics of the patient, since there are many treatment options for localized prostate cancer.

Disclosure

Authors report no conflict of interest.

References

1. Kindts I, Stellamans K, Billiet I et al. 125I brachytherapy in younger prostate cancer patients: Outcomes in low- and intermediate-risk disease. *Strahlenther Onkol* 2017; 193: 707-713.
2. Chiumento C, Fiorentino A, Caivano R et al. Low-dose rate brachytherapy of the prostate in elderly patients. *Radiol Med* 2013; 118: 1412-1421.
3. Prada PJ, Cardenal J, García Blanco A et al. Long-term outcomes in patients younger than 60 years of age treated with brachytherapy for prostate cancer. *Strahlenther Onkol* 2018; 194: 311-317.
4. Prada PJ, Juan G, González-Suárez H et al. Prostate-specific antigen relapse-free survival and side-effects in 734 patients with up to 10 years of follow-up with localized prostate cancer treated by permanent iodine implants. *BJU Int* 2010; 106: 32-36.
5. Shiraishi Y, Yorozu A, Ohashi T et al. A dose-response analysis of biochemical control outcomes after (125) I monotherapy for patients with favorable-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2014; 90: 1069-1075.
6. Stone NN, Potters L, Davis BJ et al. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7-10 prostate cancer treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009; 73: 341-346.
7. Strom TJ, Hutchinson SZ, Shrinath K et al. External beam radiation therapy and a low-dose-rate brachytherapy boost without or with androgen deprivation therapy for prostate cancer. *Int Braz J Urol* 2014; 40: 474-483.
8. Serrano N, Moghanaki D, Asher D et al. Comparative study of late rectal toxicity in prostate cancer patients treated with low-dose-rate brachytherapy: with or without supplemental external beam radiotherapy. *Brachytherapy* 2016; 15: 435-441.
9. Tanaka N, Asakawa I, Fujimoto K et al. Minimal percentage of dose received by 90% of the urethra (%UD90) is the most significant predictor of PSA bounce in patients who underwent low-dose-rate brachytherapy (LDR-brachytherapy) for prostate cancer. *BMC Urol* 2012; 14: 12-28.
10. Hathout L, Folkert MR, Kollmeier MA et al. Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for treatment planning. *Int J Radiat Oncol Biol Phys* 2014; 90: 312-319.

11. Tanaka N, Asakawa I, Katayama E et al. The biochemical recurrence-free rate in patients who underwent prostate low-dose-rate brachytherapy, using two different definitions. *Radiat Oncol* 2014; 9: 107.
12. Tanaka 1, Asakawa I, Anai S et al. Periodical assessment of genitourinary and gastrointestinal toxicity in patients who underwent prostate low-dose-rate brachytherapy. *Radiat Oncol* 2013; 8: 25.
13. Albert M, Tempany CM, Schultz D et al. Late genitourinary and gastrointestinal toxicity after magnetic resonance image-guided prostate brachytherapy with or without neoadjuvant external beam radiation therapy. *Cancer* 2003; 98: 949-954.
14. Zimmermann JS, Osieka R, Bruns T et al. Five-year effectiveness of low-dose-rate brachytherapy: comparisons with nomogram predictions in patients with non-metastatic prostate cancer presenting significant control of intra- and periprostatic disease. *J Contemp Brachytherapy* 2018; 4: 297-305.
15. Price JG, Stone NN, Stock RG. Predictive factors and management of rectal bleeding side effects following prostate cancer brachytherapy. *Int J Radiat Oncol Biol Phys* 2013; 86: 842-847.
16. Gelblum DY, Potters L. Rectal complications associated with transperineal interstitial brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2000; 48: 119-124.
17. Okazaki E, Kuratsukuri K, Ishii K et al. Correlations of post-implant regional dosimetric parameters at 24 hours and one month, with clinical results of low-dose-rate brachytherapy for localized prostate cancer. *J Contemp Brachytherapy* 2017; 9: 499-507.
18. Shiraishi Y, Yorozu A, Ohashi T et al. A dose-response analysis of biochemical control outcomes after (125) I monotherapy for patients with favorable-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2014; 90: 1069-1075.
19. Martell K, Meyer T, Sia M et al. Parameters predicting for prostate specific antigen response rates at one year post low-dose-rate intraoperative prostate brachytherapy. *J Contemp Brachytherapy* 2017; 2: 99-105.
20. Mohammed N, Kestin L, Ghilezan M et al. Comparison of acute and late toxicities for three modern high-dose radiation treatment techniques for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; 82: 204-212.
21. Chin J, Rumble RB, Loblaw DA. Brachytherapy for patients with prostate cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update Summary. *J Oncol Pract* 2017; 13: 392-394.
22. Yang DD, Muralidhar V, Nguyen PL et al. Lack of benefit from the addition of external beam radiation therapy to brachytherapy for intermediate- and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017; 99: 904-911.
23. Strom TJ, Hutchinson SZ, Shrinath K et al. External beam radiation therapy and a low-dose-rate brachytherapy boost without or with androgen deprivation therapy for prostate cancer. *Int Braz J Urol* 2014; 40: 474-483.
24. Stock RG, Cahlon O, Cesaretti JA et al. Combined modality treatment in the management of high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2004; 59: 1352-1359.
25. Potters L, Morgenstern C, Calugaru E et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2008; 179: S20-24.
26. Davis BJ, Horwitz EM, Lee WR et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012; 11: 6-19.
27. Taussky D, Igidbashian L, Donath D et al. Is intraoperative real-time dosimetry in prostate seed brachytherapy predictive of biochemical outcome? *J Contemp Brachytherapy* 2017; 4: 304-308.