

Risk factors for rectal bleeding associated with I-125 brachytherapy for prostate cancer

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(Received 3 April 2012; revised 26 June 2012; accepted 26 June 2012)

The purpose of this study was to determine the risk factors for rectal bleeding after prostate brachytherapy. Between April 2005 and September 2009, 89 patients with T1c-2cN0M0 prostate cancer were treated with permanent I-125 seed implantation alone. The prostate prescription dose was 145 Gy, and the grade of rectal bleeding was scored according to the Common Terminology Criteria for Adverse Events version 4.0. Post-treatment planning was performed with fusion images of computerized tomography and magnetic resonance imaging 4–5 weeks after brachytherapy. Patient characteristics and dosimetric parameters were evaluated to determine risk factors for bleeding. The calculated parameters included the rectal volume in cubic centimeters that received >50–200% of the prescribed dose (RV50–200) and the minimal doses received by 1–30% of the rectal volume (RD1–30). The median follow-up time was 42 months (ranging 18–73 months). Grade 1 rectal bleeding occurred in 24 (27.0%) patients, but no Grade 2 or severe bleeding was observed. Usage of anticoagulants had a significant correlation with the occurrence of bleeding ($P = 0.007$). The RV100–150 and RD1–10 were significantly higher in patients with rectal bleeding than in those without bleeding. The RV100 was identified as a possible threshold value; the 3-year rectal bleeding rate in patients with an RV100 > 1.0 cm³ was 36%, whereas that with an RV100 ≤ 1.0 cm³ was 14% ($P < 0.05$). Although no Grade 2 morbidity developed in this study, the RV100 should be kept below 1.0 cm³, especially in additional dose-escalated brachytherapy.

Keywords: prostate cancer; brachytherapy; rectal bleeding; dose-volume-histogram; anticoagulant

INTRODUCTION

The incidence of prostate cancer in Japan has been increasing in recent years [1]. Radiation therapy (RT) has been playing an important role in the curative treatment of prostate cancer, because recent novel RT techniques, such as intensity-modulated radiotherapy (IMRT), stereotactic radiotherapy, and particle radiotherapy with protons and carbon ions, can deliver a large dose to the target while sparing the surrounding normal tissues.

Permanent implants for prostate cancer have proved to be useful as an alternative highly conformal and high-dose RT

approach. Since the Japanese government legalized the use of the iodine-125 (¹²⁵I) seed source in July 2003, ¹²⁵I-brachytherapy has been a popular treatment method, mainly for low- to intermediate-risk prostate cancer in Japan. It is well known that the actual benefits of prostate brachytherapy compared with external beam radiation therapy (EBRT) are lower incidences of sexual dysfunction and incontinence and a shorter treatment period [2]. Regarding rectal morbidity, however, radiation-induced rectal bleeding is still a problem in brachytherapy as well as in EBRT because of the close borders of the rectum and the prostate. Several reports have shown improved

outcomes of prostate cancer when higher irradiation doses are delivered both in EBRT and brachytherapy [3–9]. It is possible that increasing the irradiation dose to the target volume improves biochemical disease control, but it has a risk of increasing the rectal morbidity of RT for prostate cancer. Therefore, the purpose of this study was to identify predictive factors associated with rectal bleeding after brachytherapy to carry out future dose escalation safely.

MATERIALS AND METHODS

A total of 98 patients with T1–T2 prostate cancer (according to the International Union Against Cancer TNM Classification of Malignant Tumours 6th edition [10]) underwent ^{125}I permanent radioactive seed implantation between April 2005 and September 2009 at Isesaki Municipal Hospital. Among them, 90 patients who did not receive adjuvant EBRT were followed up for more than 36 months. One was excluded from this study, because the computed tomography (CT) data for post-implant dosimetry could not be used. Hence, 89 patients were evaluated, and their clinical and treatment characteristics are shown in Table 1. According to the National Comprehensive Cancer Network Guidelines [11], 48 and 39 patients had low-risk and intermediate-risk prostate cancer, respectively. The median age was 70 years (range 51–80 years), and the median initial prostate specific antigen (PSA) level before biopsy was 5.5 ng/ml (range 3.0–34.0 ng/ml). A total of 17 patients (19%) received anticoagulant therapy for various reasons. Neoadjuvant androgen deprivation therapy (ADT) was given to 43 patients (48.3%) for a median of 9 months (range 1–39 months). ADT consisted of a luteinizing hormone releasing hormone agonist alone in 40 patients or in conjunction with an anti-androgen in 2 patients or an anti-androgen alone in 1 patient. Written informed consent was obtained from each patient before treatment.

About one month before the actual implant procedure, a volumetric study of the prostate was performed for all patients with transrectal ultrasound (TRUS) with patients in the dorsal lithotomy position. The prostate was scanned at 5-mm intervals from the proximal seminal vesicles to the apex. The captured images were digitized with a planning computer. Treatment planning was performed with the brachytherapy planning system VariSeed 7.1 (Varian Medical Systems, Palo Alto, CA, USA) to calculate the well-designed dose volume histogram (DVH). The gross target volume (GTV) was defined as the prostate itself visualized on the TRUS images. The planning target volume (PTV) was determined from the GTV plus a treatment margin of 3 mm in the bilateral and anterior directions but no margin posteriorly. We set the treated volume to include the PTV within the prescribed isodose (145 Gy), using a modified peripheral loading technique. Implantation was performed under general anesthesia, via TRUS

Table 1. Clinical characteristics of patients

Median (range)	
Age (years)	70 (51–80)
Follow up (months)	42 (18–73)
Number of patients (%)	
Clinical stage	
T1c	60 (67.4%)
T2a	18 (20.2%)
T2b	10 (11.2%)
T2c	1 (1.1%)
Gleason score	
3 + 3	55 (61.8%)
3 + 4	33 (37.1%)
4 + 3	1 (1.1%)
Initial PSA	
<10 ng/ml	75 (84.3%)
10–20 ng/ml	12 (13.5%)
>20 ng/ml	2 (2.2%)
Neoadjuvant hormonal therapy	43 (48.3%)
Diabetes mellitus	15 (16.9%)
Usage of anticoagulants	17 (19.1%)

PSA = prostate specific antigen.

guidance of the preplanned seeds, with the patient in the extended lithotomy position, similar to the volumetric study. A Mick applicator (Mick Radionuclear Instruments, Bronx, NY, USA) was used to deposit the seeds.

One month after implantation, both computerized tomography (CT) and magnetic resonance imaging (MRI) were carried out for dosimetric analysis. A urinary catheter was placed during these examinations. Axial CT images 2.5 mm in thickness were obtained at 1.25-mm intervals, and T2-weighted images 2 mm in thickness were acquired within 1 h after CT examination. The CT and MR images were electronically fused using the manual-fusion procedure of the Variseed fusion system by fitting the urethra, and then the prostate, rectum and urethra were contoured. To provide consistency in defining rectal volumes, all rectal outlining was redone by one person (K.H.). Volumes were contoured as a solid structure defined by the outer wall from one slice above and below the prostate.

The calculated dosimetric parameters included the % volume of the post-implant prostate receiving 100 and 150% of the prescribed dose (V100 and V150, respectively) and values of the minimal dose received by 90% of the prostate volume (D90). The urethral dose was expressed as values of the minimal dose received by 5% of the urethral

volume (UD5). The rectal volumes in cubic centimeters that received >50, 75, 100, 125, 150, 175 and 200% of the prescribed dose (RV50, RV75, RV100, RV125, RV150, RV175 and RV200, respectively) and the minimal doses received by 1, 2, 5, 10 and 30% of the rectum volume (RD1, RD2, RD5, RD10 and RD30, respectively) were determined.

After brachytherapy, patients were followed-up at 3-month intervals to record information concerning disease status, rectal bleeding and cause of death. If patients were unable to visit our hospital due to various reasons, the information was obtained through letters or telephone contact directly with patients or relatives or through communication with the referring physicians. Rectal bleeding was confirmed by rectal digital examination and endoscopy and was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [12] (Table 2). All time intervals were measured from the day of brachytherapy to occurrence of the rectal bleeding. The median follow-up time for this study was 42 months (range 18–73 months).

The student's *t* test and a chi-square test were used to compare the distribution of clinical and dosimetric parameters between the two groups. The cumulative incidence of rectal bleeding was calculated with the Kaplan-Meier method, and differences in cumulative incidence were compared with the log-rank test. Statistical significance was set at $P < 0.05$.

RESULTS

One patient died of cerebral infarction 43 months after brachytherapy. Biochemical PSA failures as defined by the nadir + 2 definition were observed in two patients (2.2%). No Grade 2 or greater rectal bleeding was observed, but 24 (27.0%) patients developed Grade 1 bleeding. The median onset of the bleeding was 20 months (range 3–63 months), and it was resolved without treatment from 1–33 months (median 11 months). Post-treatment planning data showed

Table 2. CTCAE version 4.0 rectal hemorrhage criteria

Grade	Description
1	Mild, intervention not indicated
2	Moderate symptoms; medical intervention or minor cauterization indicated
3	Transfusion, radiologic, endoscopic, or elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

CTCAE = Common Terminology Criteria for Adverse Events.

that D90, V100 and V150 of the implanted prostate were 157.5 ± 13.4 Gy, $92.9 \pm 3.4\%$, and $58.1 \pm 12.0\%$, respectively.

The distributions of clinical parameters and treatment-related factors were compared between patients who did or did not develop rectal bleeding (Table 3). There was a significant relationship between the occurrence of bleeding and taking anticoagulants ($P = 0.007$). There was no significant difference between the two groups regarding age, medical history of diabetes mellitus (DM), neoadjuvant hormonal therapy, prostate volume and number of seeds.

The comparison of the mean values of dosimetric parameters between the 24 patients who presented with rectal bleeding and the 65 patients who did not is shown in Table 4. There were significant differences in the RD1 and RD2 between the two groups. Dosimetric risk factors for rectal bleeding were further analyzed in 72 patients who did not take anticoagulants, and a comparison of the mean values of dosimetric parameters between the 15 patients with and the 57 patients without rectal bleeding is shown in Table 5. The means of the RV100, RV125, R150, RD1, RD2, RD5 and RD10 in patients with rectal bleeding were significantly higher than in those without bleeding. The most significant statistical difference was observed in the RV100 ($P = 0.02$). An RV100 $> 1.0 \text{ cm}^3$ was possibly a threshold value; the cumulative incidence of rectal bleeding in patients with an RV100 $> 1.0 \text{ cm}^3$ was significantly higher than that with an RV100 $\leq 1.0 \text{ cm}^3$ (36% vs 14% at

Table 3. Correlation of clinical parameters

Clinical parameter	Rectal bleeding		<i>P</i> -value
	Yes (<i>n</i> = 24)	No (<i>n</i> = 65)	
Age (years)			0.525
≥70	14	33	
<70	10	32	
Neoadjuvant hormonal therapy			0.250
Yes	14	29	
No	10	36	
Diabetes mellitus			0.542
Yes	5	10	
No	19	55	
Usage of anticoagulants			0.007
Yes	9	8	
No	15	57	
Treatment-related factor			
Prostate volume (ml)	23.0 ± 8.8	24.3 ± 8.8	0.548
Number of Seeds	71 ± 14	72 ± 15	0.738

Table 4. Correlation of dosimetric parameters with rectal bleeding in all patients

Dosimetric parameter	Rectal bleeding		P-value
	Yes (n = 24)	No (n = 65)	
RV50 (ml)	5.6 ± 2.0	5.2 ± 1.8	0.350
RV75 (ml)	2.6 ± 1.3	2.2 ± 1.1	0.109
RV100 (ml)	1.1 ± 0.8	0.80 ± 0.64	0.064
RV125 (ml)	0.44 ± 0.42	0.29 ± 0.34	0.078
RV150 (ml)	0.17 ± 0.19	0.11 ± 0.15	0.101
RV175 (ml)	0.07 ± 0.09	0.05 ± 0.08	0.188
RV200 (ml)	0.03 ± 0.05	0.02 ± 0.04	0.307
RD1 (Gy)	202.6 ± 50.4	182.0 ± 39.9	0.047
RD2 (Gy)	178.9 ± 39.5	162.3 ± 33.0	0.048
RD5 (Gy)	147.1 ± 30.4	135.4 ± 25.6	0.072
RD10 (Gy)	120.8 ± 26.3	111.5 ± 20.8	0.083
RD30 (Gy)	71.7 ± 19.7	66.0 ± 14.1	0.131
D90 (Gy)	156.3 ± 11.6	157.9 ± 14.1	0.639
V100 (%)	93.0 ± 3.2	92.8 ± 3.5	0.869
VI50 (%)	57.6 ± 11.1	58.2 ± 12.4	0.847
UD5 (Gy)	223.8 ± 30.7	226.9 ± 42.4	0.742

RV50, RV75, RV100, RV125, RV150, RV175 and RV200 = the rectal volumes in cubic centimeters that received >50, 75, 100, 125, 150, 175 and 200% of the prescribed dose, respectively; RD1, RD2, RD5, RD10 and RD30 = the minimal doses received by 1, 2, 5, 10 and 30% of the rectal volume, respectively; D90 = values of the minimal dose received by 90% of the prostate volume; V100 and V150 = the percent volume of the prostate receiving 100 and 150% of the prescribed dose, respectively; UD5 = values of the minimal dose received by 5% of the urethral volume.

36 months, $P < 0.05$; Fig. 1). Table 6 shows dosimetric parameters of patients taking anticoagulants. There was no significant difference between the two groups.

DISCUSSION

Rectal bleeding is one of the major dose-limiting factors in curative RT for prostate cancer. Table 7 summarizes the results of the incidence of rectal morbidities after prostate brachytherapy without EBRT reported by several investigators. The rates of Grade 1, 2 and >3 rectal morbidities ranged from 4.2–16.7%, 0–10.4% and 0–1.4%, respectively [13–19]. The incidence of morbidities in the current study was almost comparable (Grade 1, 27% and Grade 2–4, 0%). In addition, the rates were lower than those observed after 3D-conformal RT and similar to those after current

Table 5. Correlation of dosimetric parameters with rectal bleeding in patients not taking anticoagulants

Dosimetric parameter	Rectal bleeding		P-value
	Yes (n = 15)	No (n = 57)	
RV50 (ml)	5.8 ± 1.9	5.1 ± 1.8	0.176
RV75 (ml)	2.8 ± 1.2	2.2 ± 1.0	0.053
RV100 (ml)	1.2 ± 0.8	0.77 ± 0.58	0.022
RV125 (ml)	0.48 ± 0.40	0.26 ± 0.28	0.029
RV150 (ml)	0.18 ± 0.19	0.09 ± 0.13	0.040
RV175 (ml)	0.08 ± 0.10	0.04 ± 0.06	0.085
RV200 (ml)	0.04 ± 0.06	0.02 ± 0.04	0.121
RD1 (Gy)	207.7 ± 51.7	179.5 ± 37.8	0.020
RD2 (Gy)	182.2 ± 38.5	160.6 ± 31.8	0.028
RD5 (Gy)	149.8 ± 29.0	134.2 ± 24.9	0.041
RD10 (Gy)	123.1 ± 24.8	110.4 ± 20.0	0.042
RD 30 (Gy)	72.8 ± 19.5	65.0 ± 13.1	0.072
D90 (Gy)	157.2 ± 12.9	157.5 ± 13.4	0.944
V100 (%)	93.1 ± 3.6	92.8 ± 3.4	0.736
V150 (%)	56.4 ± 12.3	57.6 ± 12.0	0.745
UD5 (Gy)	221.9 ± 34.7	223.7 ± 41.3	0.877

RV50, RV75, RV100, RV125, RV150, RV175 and RV200 = the rectal volumes in cubic centimeters that received >50, 75, 100, 125, 150, 175 and 200% of the prescribed dose, respectively; RD1, RD2, RD5, RD10 and RD30 = the minimal doses received by 1, 2, 5, 10 and 30% of the rectal volume, respectively; D90 = values of the minimal dose received by 90% of the prostate volume; V100 and V150 = the percent volume of the prostate receiving 100 and 150% of the prescribed dose, respectively; UD5 = values of the minimal dose received by 5% of the urethral volume.

IMRT studies [3–5, 20–22]. In brachytherapy, the incidence of rectal bleeding seems to be tolerable because most cases can be managed with conservative therapy.

Several randomized trials have shown improved outcomes when higher external beam radiation doses are delivered [3–5, 23]. In general, dose levels of 78 Gy or higher were associated with better biochemical no evidence of disease rates for prostate cancer. Similarly to EBRT, dose-response relationships were found in brachytherapy [6–9]. Stock *et al.* [6] demonstrated that higher doses resulted in a lower incidence of positive cancer cells from post-radiation biopsies. Positive biopsies were found in 24% of patients who received a D90 < 140 Gy, 6% for 140–160 Gy, 7% for 160–180 Gy, and 1–3% for > 180 Gy. In this study, no cases of Grade 2 or worse rectal bleeding were observed. However, the rate of bleeding would

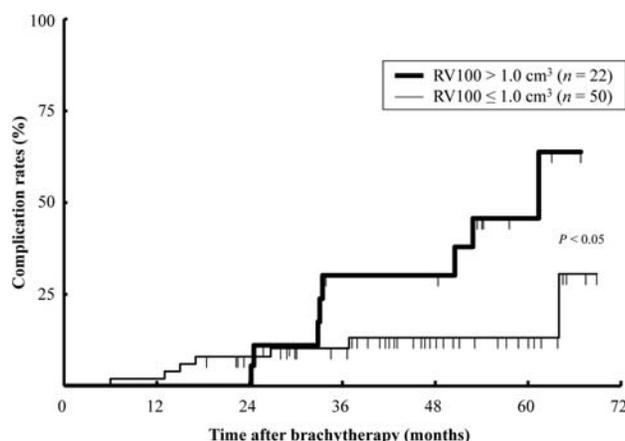


Fig. 1. Cumulative late Grade 1 rectal bleeding rates according to receipt of 100% of the prescribed dose to the rectum (RV100) in patients who did not receive anticoagulation therapy ($n=72$). The 3-year bleeding rate of patients with an $RV100 > 1.0 \text{ cm}^3$ was 36%, compared with 14% for patients with an $RV100 \leq 1.0 \text{ cm}^3$ ($P < 0.05$).

probably increase if higher prescription doses to the prostate were given. As dose escalation to $D90 = 160 \text{ Gy}$ was actually performed in our institution based on Stone's data [7–9], identification of risk factors for mild bleeding at the rectum with the prescription dose of $D90 = 145 \text{ Gy}$ is very important for safe delivery of higher doses to the prostate.

In this study, the $RV75$ – 125 and $RD1$ – 10 were predictors for rectal bleeding, and $RV100$ was thought to be the most significant predictor ($P = 0.02$). The cumulative incidence of rectal bleeding in patients with an $RV100 > 1.0 \text{ cm}^3$ was significantly higher than that with an $RV100 \leq 1.0 \text{ cm}^3$ (36% vs 14% at 36 months, $P < 0.05$; Fig. 1). Snyder *et al.* [13] reported that the risk of developing Grade 2 proctitis following ^{125}I brachytherapy with rectal DVH analysis, and the volume thresholds for <math>< 5\%</math> risk of morbidity were 3 cm^3 at 100 Gy , 2 cm^3 at 140 Gy , 1.3 cm^3 at 160 Gy , and 0.8 cm^3 at 200 Gy . Furthermore, Waterman *et al.* [18] showed that the rectum could tolerate doses of 100, 150, and 200 Gy to approximately 30%, 20% and 10% of the rectal surface, respectively, with a <math>< 5\%</math> risk of late morbidity. It is difficult to compare our results with theirs because a different definition of rectal dose and a different grade of criteria for rectal bleeding were used. However, to a varying degree, our results agree with theirs from the viewpoint of prediction for rectum morbidity.

Recent studies have shown that patients taking anticoagulation therapy have a substantial risk of bleeding toxicity with EBRT [24, 25]. Our results show that rectal bleeding occurred in 9 of 17 patients with anticoagulation therapy, and usage of anticoagulants was one of the predictors for bleeding induced by irradiation. DVH parameters of the rectum were associated with the incidence of bleeding in all patients as well as in patients not taking anticoagulants,

Table 6. Correlation of dosimetric parameters with rectal bleeding in patients not taking anticoagulants

Dosimetric parameter	Rectal bleeding		P-value
	Yes ($n = 9$)	No ($n = 8$)	
RV50 (ml)	5.2 ± 2.2	5.6 ± 2.0	0.700
RV75 (ml)	2.4 ± 1.4	2.5 ± 1.4	0.857
RV100 (ml)	0.96 ± 0.86	1.0 ± 0.97	0.894
RV125 (ml)	0.38 ± 0.45	0.43 ± 0.55	0.836
RV150 (ml)	0.16 ± 0.21	0.20 ± 0.27	0.737
RV175 (ml)	0.07 ± 0.09	0.10 ± 0.14	0.594
RV200 (ml)	0.03 ± 0.04	0.05 ± 0.08	0.438
RD1 (Gy)	194.2 ± 50.0	200.0 ± 51.8	0.816
RD2 (Gy)	173.2 ± 42.6	174.1 ± 41.1	0.967
RD5 (Gy)	142.6 ± 33.9	143.6 ± 30.8	0.954
RD10 (Gy)	117.1 ± 29.6	119.2 ± 25.7	0.880
RD30 (Gy)	69.9 ± 21.1	72.6 ± 19.7	0.791
D90 (Gy)	154.9 ± 9.8	160.7 ± 19.0	0.437
V100 (%)	92.6 ± 2.5	92.9 ± 4.8	0.886
V150 (%)	59.6 ± 8.9	62.5 ± 14.8	0.627
UD5 (Gy)	227.0 ± 24.2	250.1 ± 45.9	0.206

$RV50$, $RV75$, $RV100$, $RV125$, $RV150$, $RV175$ and $RV200$ = the rectal volumes in cubic centimeters that received >50, 75, 100, 125, 150, 175 and 200% of the prescribed dose, respectively; $RD1$, $RD2$, $RD5$, $RD10$ and $RD30$ = the minimal doses received by 1, 2, 5, 10 and 30% of the rectal volume, respectively; $D90$ = values of the minimal dose received by 90% of the prostate volume; $V100$ and $V150$ = the percent volume of the prostate receiving 100 and 150% of the prescribed dose, respectively; $UD5$ = values of the minimal dose received by 5% of the urethral volume.

but this observation was not detected in patients taking anticoagulants. Taking these findings into consideration, it is important to evaluate DVH parameters of the rectum to predict rectal bleeding. Additionally, a usage of anticoagulants seems to be an independent risk factor for the occurrence of bleeding after brachytherapy using this dose level.

Several investigators have shown that DM and ADT are risk factors for rectal bleeding in RT for prostate cancer [26–29]. However, no relationship of bleeding with DM and ADT was observed in our study. This discrepancy is probably explained by the following reasons: (i) this study included a small number of cases, (ii) other studies focused on Grade 2 but not Grade 1 rectal bleeding, and (iii) ADT was used as only short-term neoadjuvant therapy in this study. A previous Phase II trial of carbon-ion RT, which can deliver excellently localized irradiation doses to the target like brachytherapy, also revealed that the use of

Table 7. Reports of late rectal morbidity after prostate brachytherapy

Study	No. of patients	Period (years)	Median follow-up (months)	Criteria	Incidence of late rectal morbidity (%) Grade			
					1	2	3	4
Snyder ^[13]	212	1995–1998	28	Modified RTOG	NR	10.4	0	0
Shah ^[14]	135	1996–2001	41	NCI CACTE	7.3	0	0	0
Zelevsky ^[15]	248	1988–1997	48	Modified RTOG	NR	9	0	0.4
Zelevsky ^[16]	367	1993–2002	63	NCI CACTE	16.7	7.1	1.4	0.3
Gelblum ^[17]	685	NR	NR	Modified RTOG	8.9	6.5	0.4	0
Waterman ^[18]	98	1997–1999	32	Modified RTOG	NR	10.2	0	0
Martin ^[19]	213	1994–2001	60	Modified RTOG	4.2	0	0	0

RTOG = radiation therapy oncology group.

NCI CTCAE = national cancer institute common toxicity criteria for adverse events.

NR = not reported.

short-term ADT was not correlated with rectal and urogenital complications [24].

Brachytherapy with ¹²⁵I is an effective treatment modality for localized prostate cancer. Rectal DVH analysis is a practical and predictive method for assessing the risks of late rectal morbidity after treatment. To maintain less than 1 cm³ of the RV100 is very important to decrease rectal morbidity after brachytherapy. Although we used a prescribed dose of 145 Gy, the predictive risk factors proposed in this analysis may be useful tools for safely and effectively delivering higher doses to the target when dose escalation to 160 Gy is also included.

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