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審査学位論文
（博　士）

Three-dimensional summation of rectal doses in brachytherapy combined with external beam radiotherapy for prostate cancer

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Key Words

Prostate cancer, Brachytherapy, External beam radiotherapy, Rectal bleeding, Dose-volume histogram

Abstract

Background and Purpose: To determine the dose constraints for rectal bleeding in brachytherapy (BRT) combined with external beam radiotherapy (EBRT). *Materials and Methods*: Post-BRT, pelvic computed tomography images were used for subsequent EBRT planning and BRT postplans in 37 patients. The physical doses for each plan were converted to biologically effective doses, and corresponding voxel doses were integrated to plot the summed dose-volume histogram (sum-DVH). Between 5 patients with (bled-pts) and 32 without (spared-pts) grade 2 or 3 rectal bleeding, the differences in the mean minimal dose (rDn) covering the rectal volume of 0.5–10.0 cc and the rectal volume (rVn) receiving the calculated dose of 20–150 Gy were compared. *Results*: The differences in the summed-rDn were determined by BRT exposure, while those of the summed-rVn were determined in the low-dose range and superimposed in the high-dose range by EBRT exposure. Of the 13 patients with rV_{150} of >1.2 cc, 4 were bled-pts (30.8%). Of the 24 patients with rV_{150} of ≤1.2 cc, 1 was a bled-pts (4.2%) ($p = 0.024$; odds ratio, 10.2; CI [95%], 1.0–104.3). *Conclusions*: The mono-scale DVH analysis is a promising method for exploring the threshold for rectal bleeding in combined radiotherapy.

Introduction

Both external beam radiotherapy (EBRT) and brachytherapy (BRT) are effective therapies for low-risk prostate cancer, yielding more than 90% biochemical relapse-free rates (bRFRs) [1, 2]. However, both therapies achieve only 60–70% bRFRs in cases of high-risk prostate cancer [3, 4]. To improve the bRFRs in patients with high-risk prostate cancer, a combination of BRT with EBRT (combined-RTx) has shown promising results owing to dose escalation and/or eradication of extracapsular tumor extensions [5, 6, 7]. In addition, androgen deprivation treatment, in conjunction with combined-RTx, has recently emerged as another effective treatment option [8]. Combined-RTx is, therefore, becoming a standard radiotherapy modality for patients with high-risk prostate cancer.

Owing to the proximity of the anterior rectal wall to the prostate, the wall is inevitably exposed to full-dose irradiation, even in modern BRT. Snyder et al. found a significantly high frequency of grade 2 proctitis in patients receiving a rectal irradiation volume at a prescribed dose (rV_{100}) higher than 1.3 cc [9]. Waterman et al. also reported that the probability of late rectal morbidity depends on both the dose and the rectal surface area exposed to 100-Gy radiation [10]. Compared to monotherapy, combined-RTx has more frequently been associated with rectal toxicity [11]. In a study involving 458 patients, Shiraishi et al. reported that the rectal dose-volume threshold in combined-RTx for rectal bleeding of grade 2 or more was rV_{100} >0.5 mL in BRT or V_{30} >35% in EBRT [12]. However, the total rectal dose tolerability has not been completely assessed because of the discrepancies between BRT and EBRT in the geometry of the at-risk organs, biological toxicity per physical dose, and the treatment planning system (TPS).

In a sequence of combined-RTx, geometric consistency is confirmed by using a set of pelvic computed tomography (CT) images, acquired 4 weeks after BRT, for subsequent EBRT planning, as well as BRT post-implant evaluation (postplan) for definitive dosimetry. By taking advantage of the same geometry for both EBRT planning and BRT postplanning, Cao et al. exported a dose map from a BRT TPS into another EBRT TPS to visualize the underdosed area to be embedded via intensity-modulated radiotherapy (IMRT) dose painting [13]. The dose map exchange between the BRT and EBRT TPSs was performed by either DICOM export or import. When the DICOM exhibits a biologically effective dose (BED) instead of a physical dose in the same frame, a summed dose-volume histogram (DVH) can be plotted to rationally disclose dose constraints for rectal toxicity. We applied these hypotheses to patients treated with combined-RTx in order to prove its effectiveness for exploring probable dose-volume indexes as thresholds for rectal toxicity.

Materials and Methods

Patients

Between June 2006 and February 2009, 37 consecutive patients with intermediate-risk (PSA = 10–20 ng/mL and/or Gleason score =7 and/or stage T2b stage disease) or high-risk (PSA>20 ng/mL, or Gleason score of >7, or ≥T2c stage disease), localized prostate cancer underwent combined-RTx at Iwate Medical University Hospital (Morioka, Japan). The patients' characteristics are shown in Table 1. Thirty-one patients were previously treated with androgen deprivation treatment for a median period of 5 months (range, 3–29

months). All patients were included in this prospective cohort study, approved by the institutional review board of Iwate Medical University Hospital, with follow-up consisting of interval history, physical examination, and measurement of PSA, every 3 months, for 5 years.

Definition of rectal bleeding

Routine pre-treatment colonoscopic assessments of rectal mucosal lesions were not performed. Rectal toxicity was graded according to the modified National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (CTC-AE, ver. 3.0). The adverse events were classified as grade 0, without adverse events; grade 1, if they occurred less than once a week and terminated without treatment; grade 2, if they occurred more than once a week, and continued for more than a month, or required medications, such as suppositories; grade 3, if treatment was required, such as photocoagulation; grade 4, if urinary diversion or colostomy was needed owing to the presence of a rectal fistula or urethrorectal fistula; or grade 5, if the patient died. Rectal bleeding episodes were scored to the highest grade as a toxicity indicator during a median follow-up period of 42 months (range, 22–57 months) after radiotherapy. The patients were divided into groups of those with rectal bleeding ≥grade 2 (bled-pts) and those with <grade 2 rectal bleeding (spared-pts). There were 19 patients with grade 0, 13 with grade 1, 4 with grade 2, and 1 with grade 3 rectal bleeding scores.

BRT

The BRT methods used are described in detail in a previous study [14]. In brief, transrectal ultrasound-guided radioactive seed implantation was performed with interactive optimization at a prescribed dose of 110 Gy using a BRT-TPS (Interplant version 3.2, CMS Japan; Tokyo, Japan; or Variseed version 7.2, Varian Medical Systems, Palo Alto, CA, USA). The intraoperative prostate volume obtained by ultrasound planimetry determined the radiation activity required, based on a volume-dose nomogram [15], and the approximated number of seeds (0.28–0.335 mCi; SourceTec 125I NIST99, Bard, Murray Hill, NJ, USA). Modified peripheral seed loading, using a Mick applicator (Mick Radio-Nuclear Instruments, Mount Vernon, NY, USA), was completed by insertion of three-quarters of the seeds into the periphery of the prostate and one-quarter into the center. Each seed deposition resulted in DVH indexes being converged to dose constraints, such as prostate dose pD_{90} >110 Gy, prostate volume pV_{100} >95%, pV_{150} <60%, and rectal volume rV_{100} <1.0 cc (intraoperative_BRT_plan).

Computed tomography (CT) (Aquilion; Toshiba, Tokyo, Japan) images of the pelvis, with a 3-mm pitch, with the patients in the supine position were acquired 30 days after BRT (CT_30 dys) and imported into the BRT-TPS. Rectal preparation was not performed prior to the examination. The same physician delineated both the prostate and the rectum, as a solid structure defined by an outer wall, without differentiating the inner wall or contents. The rectum was delineated between the superior and inferior limits of the prostate. All doses were defined using the standard TG43 format [16] from a 1-mm grid at each seed location, determined by the seed finder module (BRT_postplan). Table 2 shows the implant quality of the intraoperative_BRT_plan and BRT_postplan.

EBRT

The CT_30dys data were also imported into another TPS (Eclipse version 6.5; Varian Medical Systems) for subsequent EBRT planning. The clinical target volume (CTV) included the prostate and the seminal vesicle. The planning target volume (PTV) was defined by adding a 2-cm margin to the volume surrounding the CTV, except on the rectal side at a which a 1-cm margin was added, as described in previous reports [11, 17]. Irradiation was delivered with 10MV-photons from a linear accelerator (Clinac 2100C; Varian Medical Systems) by using a conformal 4-field technique with a dose of 2.0 Gy per fraction, at the rate of 5 fractions per week, with a total dose of 40 Gy (EBRT_plan). The dose per fraction was changed to 1.8 Gy per fraction, 5 fractions per week, and a total of 45 Gy, in the middle of the study period. The doses delivered to the target and at-risk organs were calculated with a 5-mm grid. The rectum was contoured in the slices between the superior and inferior limits of the PTV.

Summation of BRT and EBRT doses

Standard radiotherapy files in the DICOM format (DICOM-RT) for both the BRT_postplan and EBRT_plan were exported to another computer in which an in-house software program was installed for the following process.

1. The physical doses of the voxels in the DICOM-RT were replaced by those converted to BEDs using the following equation, with an α/β ratio of 3 in both the BRT_postplan and EBRT_plan.

BRT: $BED = (R0/\lambda)\{1 + [R0/(\mu + \lambda)(\alpha/\beta)]\}$ [18]

R0: the value of the physical dose in each voxel * λ

λ: radioactive decay constant = $0.693/T_{1/2}$

$T_{1/2}$: radioactive half-life of isotope = 60 days

μ: repair rate constant = $0.693/t_{1/2}$

$t_{1/2}$: tissue repair half-time = 1 hour

EBRT: $BED = nd[1 + d/(\alpha/\beta)]$

n: fraction number

d: physical dose of each voxel/fraction

2. The modified DICOM-RT files were exported into the EBRT-TPS to recalculate the DVHs, including the BRT-DVH and EBRT-DVH. The BEDs of the corresponding voxels from each plan were summed using a 1-mm grid via its sumplan module to build another DVH (sum-DVH) (Fig. 1) [19]. The EBRT_plan, with a 5-mm grid, was applied to that with a 1-mm grid before the summation.

3. By using the 3 DVHs, the following rectal doses were obtained: (1) *rDn (Gy);* the minimal BED dose covering n (cc) of the rectal volume ranging from 0.5 to 1.0 for 10.0 cc: $rD_{0.5}$, rD_1, rD_2, rD_3, rD_4, rD_5, rD_6, rD_7, rD_8, rD_9, rD_{10}, (2) *rVn (cc);* the rectal volume receiving n (Gy) of the calculated BED dose ranging from 20 to 150 Gy: rV_{20}, rV_{30}, rV_{40}, rV_{50}, rV_{60}, rV_{70}, rV_{80}, rV_{90}, rV_{100}, rV_{110}, rV_{120}, rV_{130}, rV_{140}, rV_{150}. The rectal volumes of the sumplan were used those of the EBRT_plan.

Study Design

Background: The mean age of the bled-pts and the spared-pts was compared by Mann-Whitney test. The distributions of comorbidities, such as diabetes mellitus or diseases necessitating anticoagulants were determined by chi-square tests. The statistical software that was used was SPSS 15.0J for Windows (SPSS, Chicago, IL, USA).

DVH parameters: Between the bled-pts and the spared-pts, the differences in the mean rDn or rVn values in BRT-DVH, EBRT-DVH, and sum-DVH were evaluated. For each parameter, the bled-pts and spared-pts were plotted separately, with corresponding variables, in an ascending order to qualitatively compare the magnitude and profile of the differences. The patients were divided into 2 groups on the basis of the provisional parameters and the differences in the ratios of the bled-pts to the spared-pts were tested by chi-square tests; their odds ratios were also calculated.

Results

No significant differences were apparent, for any of the background factors, between the bled-pts and the spared-pts. For the rDn, between $rD_{0.5}$ and rD_{10}, those of the bled-pts were consistently larger than those of the spared-pts in the BRT-DVH. There was almost no difference between patient groups in the EBRT-DVH, and the difference showed a sum-DVH profile similar to that in the BRT-DVH (Fig. 2 $_{a)-c)}$). With regard to the rVn, there was almost no difference in the BRT-DVH between the patient groups. From rV_{30} to rV_{80}, those of the bled-pts were larger than those in the spared-pts in the EBRT-DVH. In addition the superimposed difference

also appeared from rV_{90} to rV_{150}, which was absent in either the BRT-DVH or EBRT-DVH (Fig. 2 $_{d)-f)}$). Exploration of the dose-volume thresholds for the sum-DVH revealed that 4 of the 13 patients (30.8%) with an rV_{150} of >1.2 cc were in the bled-pts group, while only 1 of the 24 patients (4.2%) with an rV_{150} of ≤1.2 cc was included in this group. The difference was significant ($p = 0.024$), and the odds ratio was 10.2 (95% CI: 1.0–104.3) (Fig. 3).

Discussion

We successfully plotted a rectal DVH for combined-RT by fusing both of the comparably transformed dose maps distributed in an identical organ framework. The mono-scale DVH analysis revealed the reciprocal impact of the BRT and EBRT on the total rectal dose-volume indexes, which are suitable measures of the magnitude of supplemental EBRT on the combined dose. Increases in the EBRT rectal exposure induce an increase in the rectal volume exposed to far higher doses than those of BRT, a value that dichotomizes subjects by different rectal bleeding ratios. When the threshold was re-assessed using a conclusive number of patients, it might be used as a dose constraint in the subsequent EBRT.

The usefulness of this hybrid dose calculation method is apparent when compared to the methods proposed for individual dose constraints in BRT or EBRT. In practice, the rectal dose, determined by the BRT_postplan, should be considered when planning the subsequent EBRT. Some brachytherapists alter the posterior PTV margin of the prostate according to the gravity classification of rV_{100} in the BRT_postplan [12]. In contrast to this stepwise margin reduction, we can assess the sub-optimizing EBRT dose, which is variable in each case.

This seamless quantification optimizes EBRT planning with regard to the antecedent BRT dose delivery. As an EBRT adjunct to BRT, three-dimensional (3D)-conformal radiotherapy is expected to be replaced by IMRT, which causes fewer side effects than 3D-conformal radiotherapy [20,21]. Because IMRT does not eliminate rectal exposure, the prostate coverage is optimized by trading off the safety range of the rectal dose registered in the inverse planning table.

Certain conditions, required for dose summation, contraindicate the use of the current method. Dose summation cannot be adopted when EBRT precedes BRT or when EBRT is performed in the prone position. To overcome these restrictions, a more advanced algorithm is required for matching the CTV pairs acquired at separate intervals with accurate dose accumulation [22]. When 3D dose distributions can be transferred with deformable image registration, the advantage of our concept of dose accumulation through BED conversion will be applicable to radiotherapies that combine different modalities.

This study has the following limitations. First, the small number of patients inevitably results in some uncertainty with respect to the threshold for rectal bleeding. The sumplan is based on CT images acquired only once; therefore, each dose distribution may change during treatment as a result of implant-induced prostate edema, rectal filling, and changes in rectal position [23]. Integration of DICOM-RT with different grid sizes might have also introduced some geometrical inaccuracies. The absence of routine endoscopic examination could lead to discrepancies in the severity of rectal mucosal damage and the CTC-AE grading. This study therefore needs to be repeated with many more patients in order to draw a definitive conclusion.

In conclusion, we have developed a new method for the 3D quantitation of the rectal exposure dose in

combined-RTx, enabling it to be measured on a single scale. At a minimum, this method clearly revealed how each radiotherapy fraction escalates the total rectal dose and the dose-volume index suitable for exploring the threshold in the subsequent EBRT. This method is also useful for IMRT optimization after BRT.

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Conflict of interest

The authors have no conflict of interest to disclose.

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Figure legends

Fig. 1. Comparison of the dose distributions in the brachytherapy postplan (BRT_postplan) (a), external beam radiotherapy plan (EBRT_plan) (b), and sumplan (c), after biologically effective dose (BED) conversion.

Fig. 2. Comparison of the mean exposed rectal doses (BED, Gy) on $rD_{0.5}$–rD_{10} between patients with (bled-pts) or without (spared-pts) grade 2 or 3 rectal bleeding for brachytherapy postplan (BRT-DVH) (a), external beam radiotherapy plan (EBRT-DVH) (b), and sumplan (sum-DVH) (c). Comparison of the mean exposed rectal volumes (cc) on rV_{20}–rV_{150} between bled-pts and spared-pts for BRT-DVH (d), EBRT-DVH (e), and sum-DVH (f).

Abbreviations: BED = biologically effective dose; rDn = the minimal dose covering n (BED, Gy) of the rectal volume (cc); rVn = the rectal volume receiving n (cc) of the calculated dose (BED, Gy).

Fig. 3. Odds ratio for patients with (bled-pts) or without (spared-pts) grade 2 or 3 rectal bleeding, with 95% CI led by each provisional rV_{150}; * $p < 0.05$

Table

Table 1: Patient characteristics

Characteristic		Patients (n=37)	% of total
Age (years)	≦65	12	32.4
	＞65	25	67.6
Pretreatment PSA (ng/ml)	＜10	22	59.5
	10-＜20	13	35.1
	≧20	2	5.4
Gleason Score	≦6	1	2.7
	7	24	64.9
	≧8	12	32.4
Tumor classification	≦T2a	19	51.4
	T2b	4	10.8
	T2c≦	14	37.8
Risk group	intermediate	12	32.4
	high	25	67.6
Diabetes	Yes	5	13.5
	No	32	86.5
Antiplatelet or Anticoagulant	Yes	6	16.2
	No	31	83.8
Neoadjuvant hormone therapy	Yes	31	83.8
	No	6	16.2
Hemorrhoids	Yes	13	35.1
	No	24	64.9

Abbreviation: PSA = prostate-specific antigen.

Table

Table 2: Results of dosimetry in brachytherapy

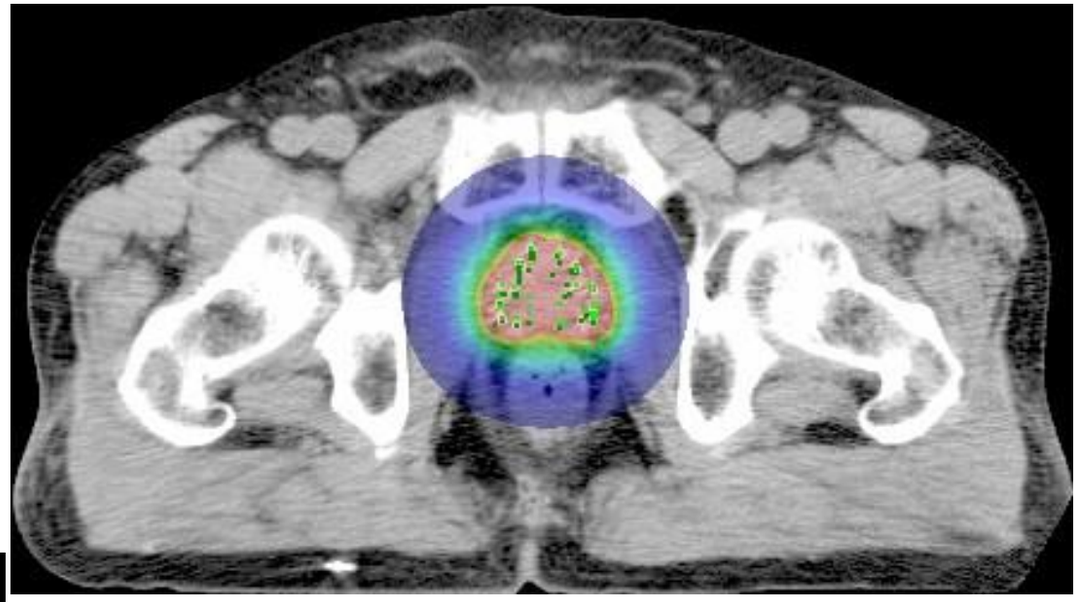
		intraoperative_BRT_plan				BRT_postplan			
		Volume (mean ± SD)	Median	Min	Max	Volume (mean ± SD)	Median	Min	Max
Prostate	pD90 (Gy)	24.5±14.1	139	123	164	23.7±6.2	122	101	145
	pV100 (%)		97.8	95	100		93.1	82.1	99.4
	pV150 (%)		69.7	19.7	82.5		63.2	30.9	76.9
Urethra	uV200 (%)	—	0	0	0.27	—	0.011	0	0.17
Rectum	rV100 (cc)	—	0.24	0	2.45	52.6±17.1	0.2	0	2.06
	rV150 (cc)		0.01	0	0.5		0	0	0.33

Abbreviations: SD = standard deviation; BRT = brachytherapy;
D90 = minimal dose covering of the 90% of structure volume;
V100 = structure volume receiving 100% of the calculated dose.

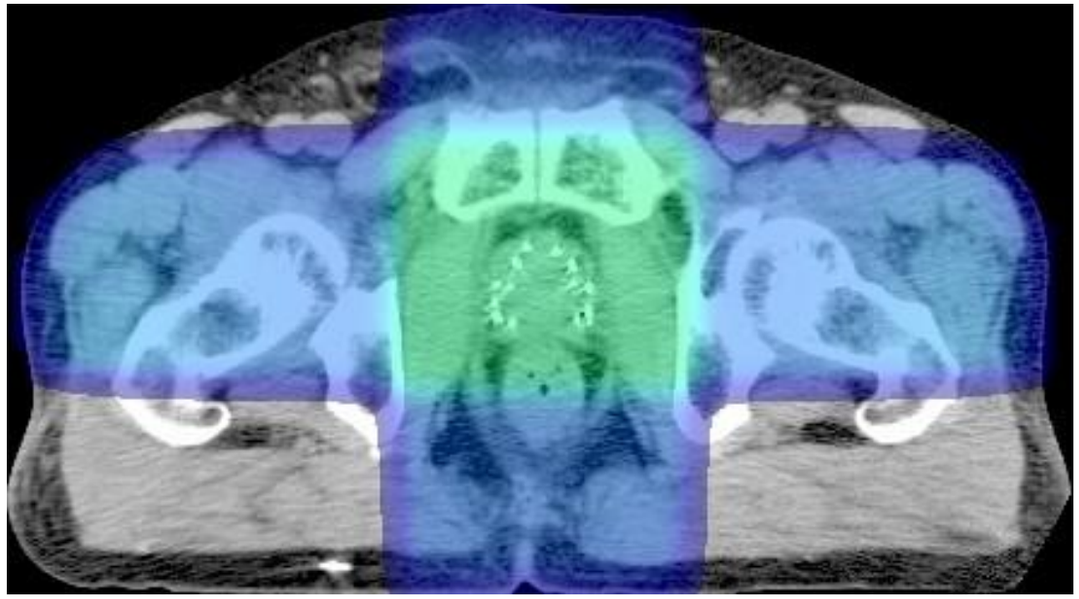
Figure

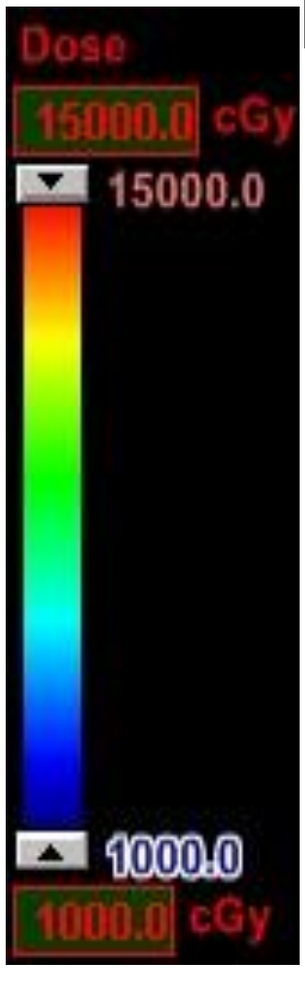
Fig. 1

(a) BRT_postplan (BED)

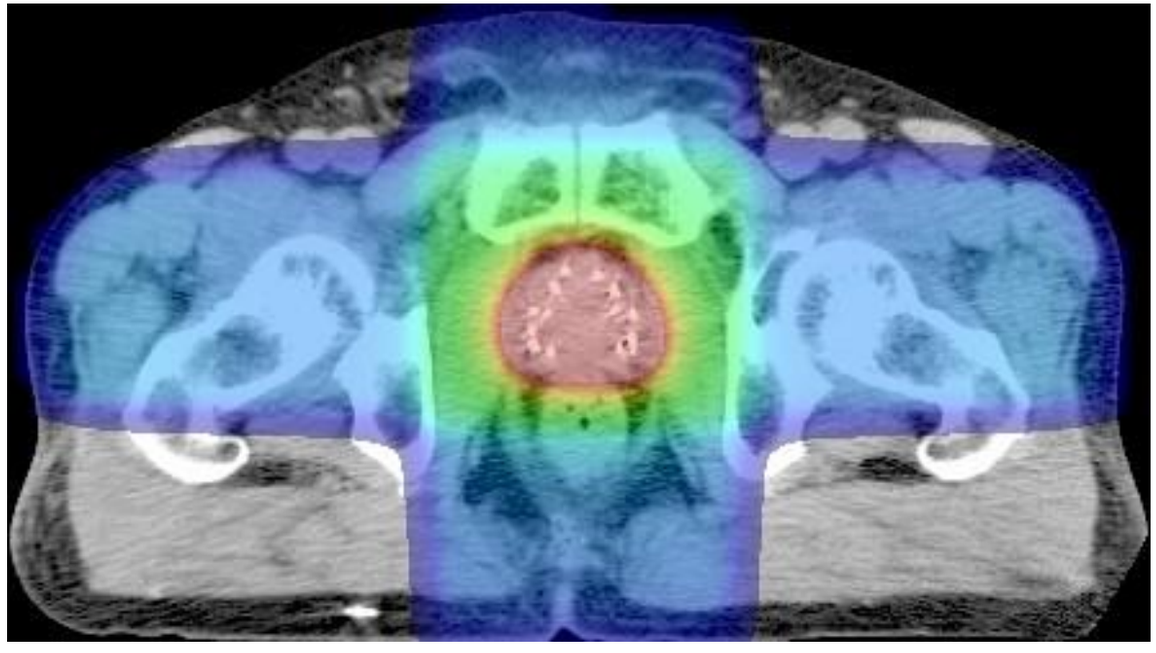


(b) EBRT_plan (BED)



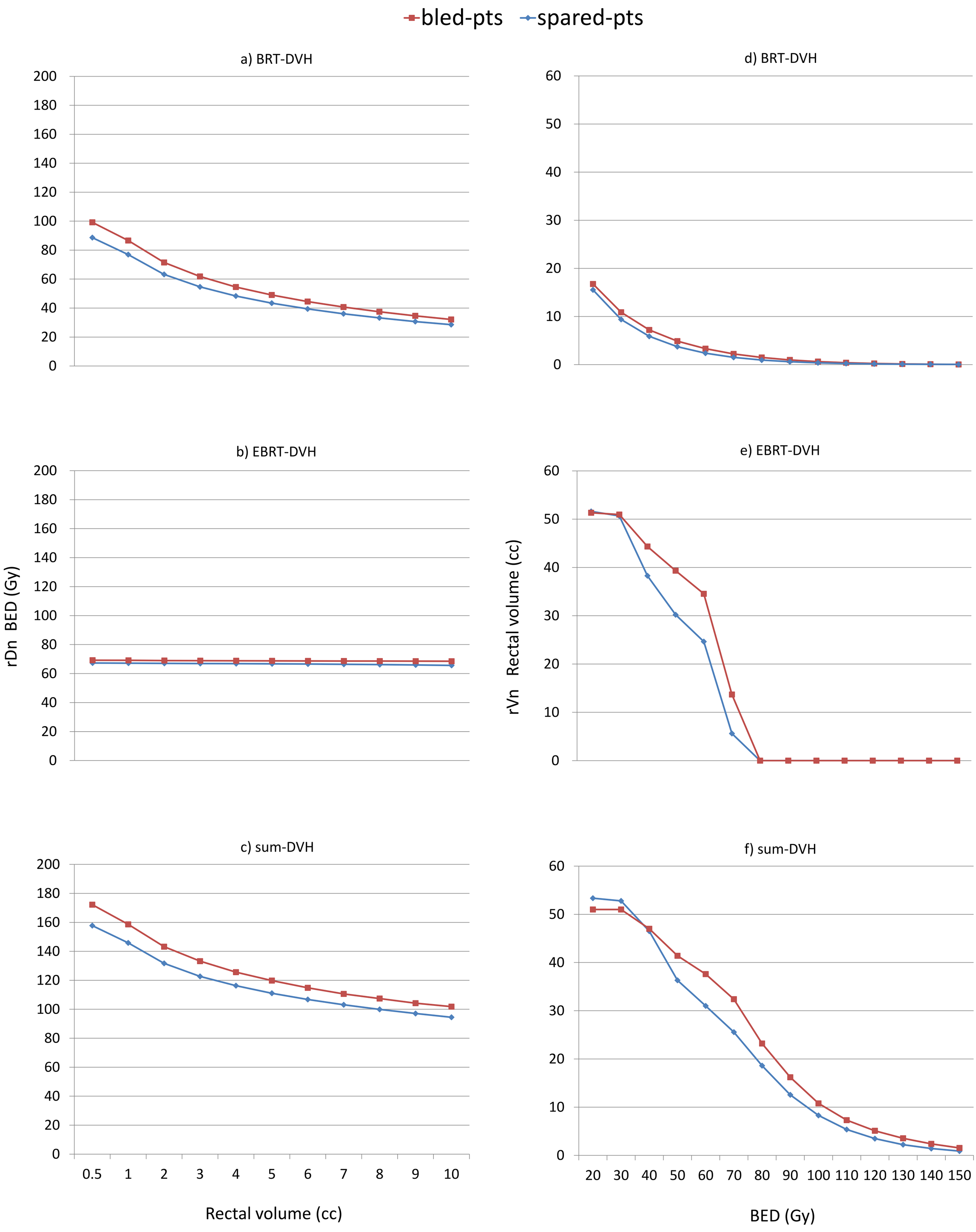


(c) sumplan



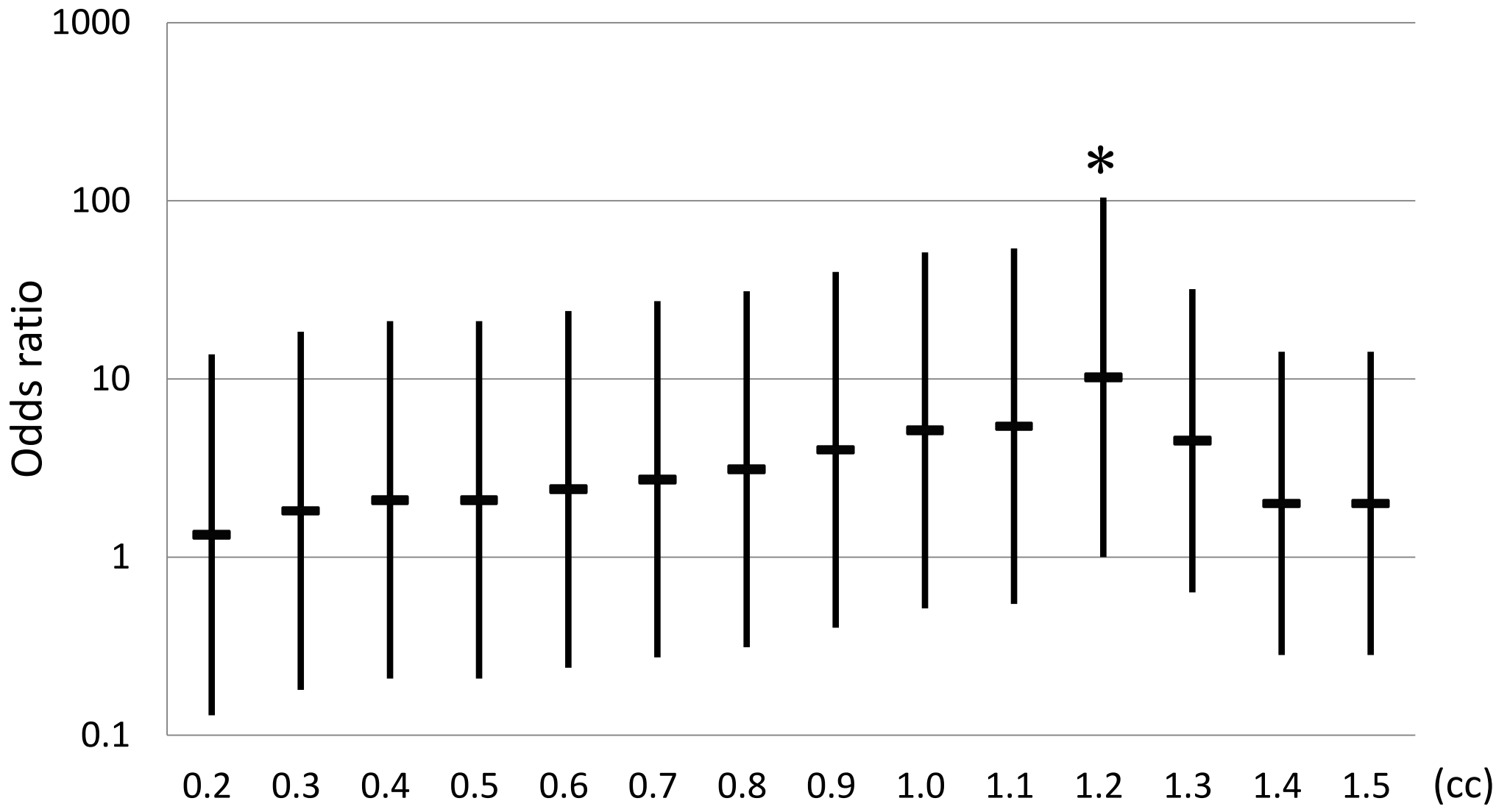
Figure

Fig. 2


bled-pts
spared-pts
a) BRT-DVH
d) BRT-DVH
b) EBRT-DVH
e) EBRT-DVH
c) sum-DVH
f) sum-DVH
rDn BED (Gy)
rVn Rectal volume (cc)
Rectal volume (cc)
BED (Gy)

Figure

Fig. 3



rV_{150}	bled-pts	spared-pts
> 1.2cc	4	9
≤ 1.2cc	1	23