Integral radiation dose to normal structures with conformal external beam radiation

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ABSTRACT

Background: This study was designed to evaluate the integral dose (ID) received by normal tissue from intensity modulated radiotherapy (IMRT) for prostate cancer.

Materials and Methods: Twenty-five radiation treatment plans, including MRT using a conventional linac with both 6 (6MV-IMRT) and 20 MV (20MV-IMRT) as well as 3DCRT using 6 (6MV-3DCRT) and 20 MV (20MV-3DCRT), and IMRT using tomotherapy (6MV) (Tomo-IMRT), were created for five patients with localized prostate cancer. The ID (mean dose X tissue volume) received by normal tissue (NTID) was calculated from dose-volume histograms.

Results: 6MV-IMRT resulted in 5.0% lower NTID than 6MV-3DCRT; 20MV beam plans resulted in 7.7-11.2% lower NTID than 6 MV-3DCRT. Tomo-IMRT NTID was comparable to 6 MV-IMRT. Compared to 6MV-3DCRT, 6MV-IMRT reduced IDs to the rectal wall and penile bulb by 6.1% and 2.7%, respectively. Tomo-IMRT further reduced these IDs by 11.9% and 16.5%, respectively. 20MV did not reduce IDs to those structures.

Conclusions: The difference of NTID between 3DCRT and IMRT is small. 20MV plans somewhat reduced NTID compared to 6MV plans. The advantage of tomotherapy over conventional IMRT and 3DCRT for localized prostate cancer was demonstrated in regard to dose sparing of rectal wall and penile bulb without increasing NTID.

(199 words)

Key words

(1) Radiation, (2) IMRT, (3) Tomotherapy, (4) Prostrate cancer, (5) Integral dose

INTRODUCTION

Intensity modulated radiotherapy (IMRT) is being increasingly used worldwide for a variety of cancers. IMRT achieves better conformity of radiation dose to the target than conventional three-dimensional conformal radiotherapy (3DCRT). The basic principle of IMRT involves irradiation from a number of different directions with beams of nonuniform energy fluences, which have been optimized to deliver a high dose to the target volume and acceptably low dose to the surrounding normal structures. The treatment-planning program divides each beam into a large number of beamlets and determines the optimum setting of their energy fluences or beam weights. IMRT increases the volume of normal tissue exposed to some radiation but can reduce the total dose received by critical structures [**1**].

Integral dose (ID) is the volume integral of the dose deposited in a patient and is equal to the mean dose times the volume irradiated to any dose. The ID is also the area under the curve of a differential absolute-dose absolute-volume histogram [**2**]. It is often stated that the large number of beamlets and monitor units used in IMRT leads to an increase in ID [**1, 3**], and that higher energy photon beams substantially reduce the NTID [**4**]. In contrast, an alternative hypothesis suggests that the total energy deposited in a patient during irradiation (ID) is relatively independent of treatment planning parameters [**2, 5**]. D'Souza et al [**2**] reported that with four or more beams and the clinical margin values, the variation in NTID

was <1% as a function of number of beams. With eight or more beams, the variation was <0.5%. As expected, higher energy beams reduced the NTID, but the variation in NTID was rather small, especially considering the large changes in beam energy, 1.5% - 1.7% for the nasopharynx, 0.9% - 1.0% for the pancreas, and 0.3% - 0.4 % for the prostate. The effect of the number of beams on NTID was independent of beam energy. For the two-, four-, and eight-field plans with different relative beam weights, the NTID varied by 1.4% - 2.1% for the nasopharynx, 0.2% - 1.3% for the pancreas, and 0.5% for the prostate. For the body sites studied, the majority of ID was deposited in normal tissue. For the prostate cancer example, a very large portion of the integral dose was deposited in normal tissue (91% - 97%). These results support the expectation from geometric considerations that the NTID decreases with increasing tumor size for similar anatomic sizes and increases with increasing size of the anatomical region for similar tumor sizes. Pirzkall et al. [**5**] addressed this issue in a study comparing IMRT plans with 6-, 10-, and 18-MV photons, in which they observed NTIDs varying less than 5% among plans.

Helical tomotherapy is a unique radiotherapy delivery method that utilizes intensity modulated fan beams to deliver highly conformal dose distributions in a helical pattern [**6**]. Compared to IMRT treatments with a conventional linac, it has an advantage of using a higher number of independent beam directions. Additionally, the MLC used for tomotherapy

is designed to minimize transmission, and therefore it has the potential to reduce the component of NTID due to leakage [**7**]. Leakage measurements were not a part of this study.

This treatment planning study was designed to address two important issues: whether IMRT using either conventional linac or tomotherapy increase the NTID compared to 3DCRT, and whether the use of higher energy photon beams (20MV) reduces the NTID substantially compared to 6MV. IDs to rectal wall and penile bulb were also evaluated separately due to their documented clinical relevance.

MATERIALS AND METHODS

Five consecutive patients who had been treated with external beam radiation therapy for localized prostate cancer were selected for the analysis. All patients were both planned and treated with a rectal balloon and a bladder filling of 200 cm^3 [**8**]. The clinical target volume (CTV) was defined as the entire prostate in this study. As all of the prostate patients at our institution are treated with image-guidance, a 5-mm margin was used to expand the CTV to the planning target volume (PTV), based on measured localization uncertainties, inter-user reproducibility and intra-fraction motion [**9**]. For 6 MV, the beam margin, accounting for the beam penumbra, was set to be 0.5 cm from the PTV in the coplanar direction and 0.7 cm

from the PTV for the direction perpendicular to the beam direction plane (along the z-direction). For 20 MV planning, these values were set to be 0.5 cm and 1.0 cm, respectively, for the co-planar and the z-direction. Normal structures including bladder, penile bulb, and rectal wall were outlined on the planning CT images. The contoured rectal wall extended from the bottom of the ischial tuberosities to the rectosigmoid flexure. The "normal tissue" volume was defined as the whole patient volume minus the CTV.

For each patient, IMRT using conventional linear accelerator of 6MV (6MV-IMRT) or 20 MV (20MV-IMRT), three-dimensional conformal radiation therapy (3D-CRT) using 6 MV (6MV-3DCRT) or 20 MV (20MV-3DCRT) plans were generated. The Philips Pinnacle^{TM} (Milpitas CA) Version 6.2 was used to contour all of the structures and to compute the dose distribution for plans based on the convolution/superposition algorithm. Seven non-opposing co-planar beams were used for these plans. Inverse treatment plans for IMRT were generated using the same dose-volume constraints for all plans. The dose constraints were set for the rectal wall, penile bulb, bladder, and unspecified normal structure (**Table 1**). Additionally, IMRT plans using helical tomotherapy (Hi-Art^{TM}, Madison, WI) were created using an inverse treatment planning system (TomoTherapy Inc., Madison, WI) also based on the superposition/convolution dose calculation. The fan beam thickness was of 24.6 mm and a pitch (the ratio of distance traveled per rotation to the fan beam thickness) was

0.216. The plans were optimized keeping the mean dose to the PTV the same as that of 6MV-3DCRT. The prescription was normalized to encompass 95 % of the PTV at a dose of 70 Gy for all plans. The doses were calculated using heterogeneous tissue density corrections. Representative treatment plans are shown in **Figure 1**. NTID and IDs of the rectal wall, penile bulb and bladder were compared to 6MV-3DCRT as a standard conformal technique. The ID was calculated as a product of mean dose multiplied by the volume of each structure. It would be possible to compute the density corresponding to the average CT number for the calculation of ID; however, we have chosen to use the definition of ID as a volume integral rather than a mass integral. Even though a mass integral would be best to determine the energy deposited in the structure, using a mass integral is both an extra step and would misrepresent the contribution of a structure with highly heterogeneous density to non-target integral dose. A percent difference of IDs for each plan against 6MV-3DCRT was also calculated using the equation of (ID – ID of 6MV-3DCRT) divided by the ID of 6MV-3DCRT.

RESULTS

The mean IDs of PTV, bladder, rectal wall, penile bulb and normal tissue are summarized in **table 2**. The percent difference of the ID for the PTV of each plan ranged from -0.1% to

+0.2%, compared with 6MV-3DCRT; therefore all plans were clinically equivalent in terms of PTV coverage. **Figure 2** shows the mean NTID for the five treatment plans. Compared to 6MV-3DCRT, the percent difference of 6MV-IMRT and Tomo-IMRT was –5.0% (student t test, P=0.51) and –4.0% (P=0.58) respectively. The use of 20MV somewhat reduced NTID by 7.7% with 3DCRT (P=0.33) and 11.2% (P=0.15) with IMRT compared to 6MV-3DCRT.

Regarding the IDs of sensitive normal structures, the use of 20MV rather than 6 MV had limited influence on the ID for rectal wall, penile bulb or bladder. In comparison to 6MV-3DCRT, the percent difference in the IDs were 0% (student t test, P=0.99) for rectal wall, 4.8% (P=0.81) for penile bulb, and –2.9% (P=0.88) for bladder when 20MV-3DCRT was used. When 20MV-IMRT was used, these values were –1.8% (P=0.87), -0.3% (P=0.95), and –0.7% (P=0.99), respectively. The use of 6MV-IMRT reduced the ID only modestly, by –6.1% (P=0.59) for rectal wall, –2.7% (P=0.93) for penile bulb, and –7.5% (P=0.51) for bladder whereas Tomo-IMRT resulted in somewhat greater reduction of –11.9% (P=0.33) for rectal wall, –16.5% (P=0.58) for penile bulb, and –6.0% (P=0.69) for bladder as shown in **Figure 2b, 2c and 2d**.

DISCUSSION

The treatment outcome, measured as PSA-progression free rate, for prostate cancer patients has improved in recent years. Both radiation dose escalation [**10**] and the addition of androgen suppression therapy to conventional 70Gy radiation therapy [**11, 12**] have contributed to the improvement. Radiation dose escalation over 70Gy requires precise patient set-up and modern radiation techniques in order to avoid late radiation toxicity, especially rectal bleeding [**8, 9**]. Late rectal bleeding is well established as a key dose-limiting end point in prostate radiotherapy. In a randomized-controlled dose-escalation trial at the M.D. Anderson Cancer Center, patients who received 78Gy showed a higher incidence of rectal complications than those receiving 70Gy. For patients in the 78Gy-arm, Grade 2 or higher rectal toxicity correlated strongly with the proportion of the rectum receiving more than 70Gy [**10**]. The importance of the dose-volume relationship for rectal complications is also demonstrated in two large randomized dose-escalation studies from Europe [**13, 14**]. Peeters et al., [**13**] observed that hormonal therapy was associated with a significantly increased risk of grade 2+ late genito-urinary toxicity. With an increasing proportion of prostate cancer patients receiving hormonal therapy, this observation would encourage further efforts to spare the urinary bladder in prostate radiation therapy The dose to the penile bulb is increasingly recognized as a risk factor for erectile dysfunction following

high-dose radiation [**15, 16**]. Wernicke et al. demonstrated the existence of a relationship between penile bulb dose and the prevalence of erectile dysfunction after radiotherapy [**15**]. Roach et al. examined the dose-response relationship in patients studied in the Radiation Therapy Oncology Group (RTOG) 9406 trial. Patients whose median penile bulb dose was 52.5Gy or greater had a greater risk of erectile dysfunction compared with those receiving less than 52.5Gy [**16**]. Our study demonstrated a clear advantage of tomotherapy over IMRT using conventional Linac or higher dose photon beams in regard to dose reduction to surrounding radiation sensitive structures. Both 3DCRT and IMRT using 20 MV failed to show a benefit in the dose reduction in rectal wall and penile bulb. IMRT utilizing conventional Linac showed only modest reduction (6.1% for rectal wall and 2.7% for penile bulb), In contrast, tomotherapy could further reduce IDs of those structures (11.9% for rectal wall and 16.5% for penile bulb).

There has been concern about the increase of normal tissue integral dose with multiple beam radiation therapy as a potential risk factor of the development of secondary malignancies [**1**]. It is commonly believed that the large number of beamlets and monitor units lead to an increase in ID [**1, 3**], and that higher energy photons reduce the NTID [**4**]. Our data are consistent with the publications of D'Souza [**2**] and Pirzkall et al. [**5**]. In our study, the NTID of 6MV-IMRT and Tomo-IMRT showed a negligible difference of 4-5%

compared to the NTID from 6MV-3DCRT. The small difference between 3D-CRT and IMRT is likely due to the ability of the optimizer to reduce the effective field boundary and thereby reduce the area of the beam. Both 3DCRT and IMRT using 20MV resulted in 7.7% and 11.2% lower NTID compared to 6MV. However, like most other RTP systems, Pinnacle^{TM} does not fully take into account leakage, and hence these reductions of 7.7 and 11.2 % are potential overestimates. Another aspect, mostly neglected, is the neutron peripheral dose that occurs when LINAC energies above 8 MeV are used. [**3**] Therefore, the decrease in NTID of 20MV in our study would be even less dissimilar than the 6MV NTID if dose equivalent contribution for neutrons and the transmission through the collimator leaves were fully accounted for. The reduced integral dose from the buildup portion is limited by the higher exit dose and the need for a larger beam area to accommodate the wider penumbra of the high-energy beam (**Figure 3**). In effect, the benefit of greater longitudinal electron transport in the buildup region is counteracted somewhat by greater lateral electron transport in the penumbra. The conventional wisdom regarding lower NTID from higher beam energies arose from the use of two opposed field directions, which often deposits the maximum dose for low energy beams outside of the target volume. The use of multiple non-opposed fields reduces the need for high-energy photon beams because the summing effect of multiple beams is far more important than the difference in attenuation between low

and high-energy beams. Radiation leakage is another factor influencing integral dose. There are two distinct sources of leakage directed at the patient. The first is due to transmission through the collimator leaves or blocks. The second is due to leakage through the primary collimation system. Leakage through the leaves of a conventional collimator will add substantially to the integral dose. The average leakage is about 2.5% for 6-MV and 3.5% for 20-MV photon beam [**17**]. Conventional MLC systems were originally designed as block replacements whereas the Hi-Art^{TM} (Madison WI) tomotherapy binary MLC was designed to deliver only IMRT and has a thickness of 10 cm of 95% tungsten, which results in a leaf leakage of under 0.5% [**18**].

Radiation-induced secondary malignancies are rare. However, as the treatment outcome improves, these became important considerations, as evidenced by the experience with Hodgkin's lymphoma. It is still controversial whether pelvic radiation increases the likelihood of developing a secondary malignancy. Hall et al., using biological modeling, estimated that the risk of secondary malignancies in 10-year survivors could be doubled by the use of IMRT compared with 3D-CRT [**1**]. Movsas et al. assessed the second malignancy issue through a surveillance study [18]. 1,053 of 18,135 patients (5.8%) in the Connecticut Tumor Registry developed secondary primary cancer compared with 31 of 543 (5.7%) patients treated for prostate radiation (P=0.99). They concluded that there is no increased risk of

developing a second primary cancer following prostate irradiation compared to the baseline rate from prostate cancer itself, at least in the first 10 years of follow-up [**20**]. Brenner et al. surveyed 122,123 men with prostate carcinoma, of whom 51,584 received radiotherapy and 70,539 were treated with surgery. Radiotherapy for prostate carcinoma was associated with a small, statistically significant increase in the relative risk of subsequent solid tumors (6%; P=0.02) compared with treatment of surgery. Among patients who survived for >= 5 years, the increased relative risk of developing all solid tumors reached 15%, and was 34% for patients surviving >= 10 years. The most significant tumors resulting in this increased risk in the irradiated group were carcinomas of the bladder, rectum and lung, and sarcomas within the treatment field. However, no significant increase in rates of leukemia was noted [**21**]. There is an interesting difference in the secondary malignancies in patients treated by radiation therapy. First, carcinomas are observed in the lining cells in the body and often in tissues and organs that received lower doses because they were remote from the treatment site. Second, sarcomas are induced in heavily irradiated tissues in or close to the radiation field [**1**]. All the population-based studies including patients who had received traditional two- or four-field radiation techniques, in which surrounding normal structure were exposed to a high radiation dose support this observation. Multiple field radiation tends to decrease the volume receiving high radiation dose, and increase the volume receiving low dose radiation.

Therefore, theoretically, there may be an increased risk of non-sarcomatous solid tumors. However, this can be rather difficult to interpret when we apply it to modern radiation techniques in which multiple radiation fields are utilized.

CONCLUSION

There is little difference between 3D-CRT and conventional IMRT, for both 6 MV and 20 MV, in the ID to the PTV, penile bulb, and rectal wall. There was some reduction of NTID (whole body – CTV) for IMRT over 3D-CRT and some further improvement in NTID for 20 MV vs. 6MV. However, this difference in NTID may be smaller if detailed leakage and neutron dose were accounted for. The tomotherapy NTID was very similar to the 6MV conventional IMRT NTID. The advantage of tomotherapy over conventional IMRT and 3D-CRT for localized prostate cancer was demonstrated in regard to dose sparing of rectal wall and penile bulb without increased in NTID to non-target tissues.

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FIGURE LEGENDS:

Figure 1: Isodose distribution for a typical patient. Dose distribution of (**a**) 6MV-3DCRT, (**b**) 6MV-IMRT, (**c**) Tomo-IMRT, (**d**) 20MV-3DCRT, (**e**) 20MV-IMRT

Figure 2: Mean value and standard error of the integral dose of (**a**) nontumor tissue, (**b**) rectal wall, (**c**) penile bulb, and (**d**) bladder.

Figure 3: The role of electron transport in integral dose. Left side of dashed line is high energy and left side in low energy.

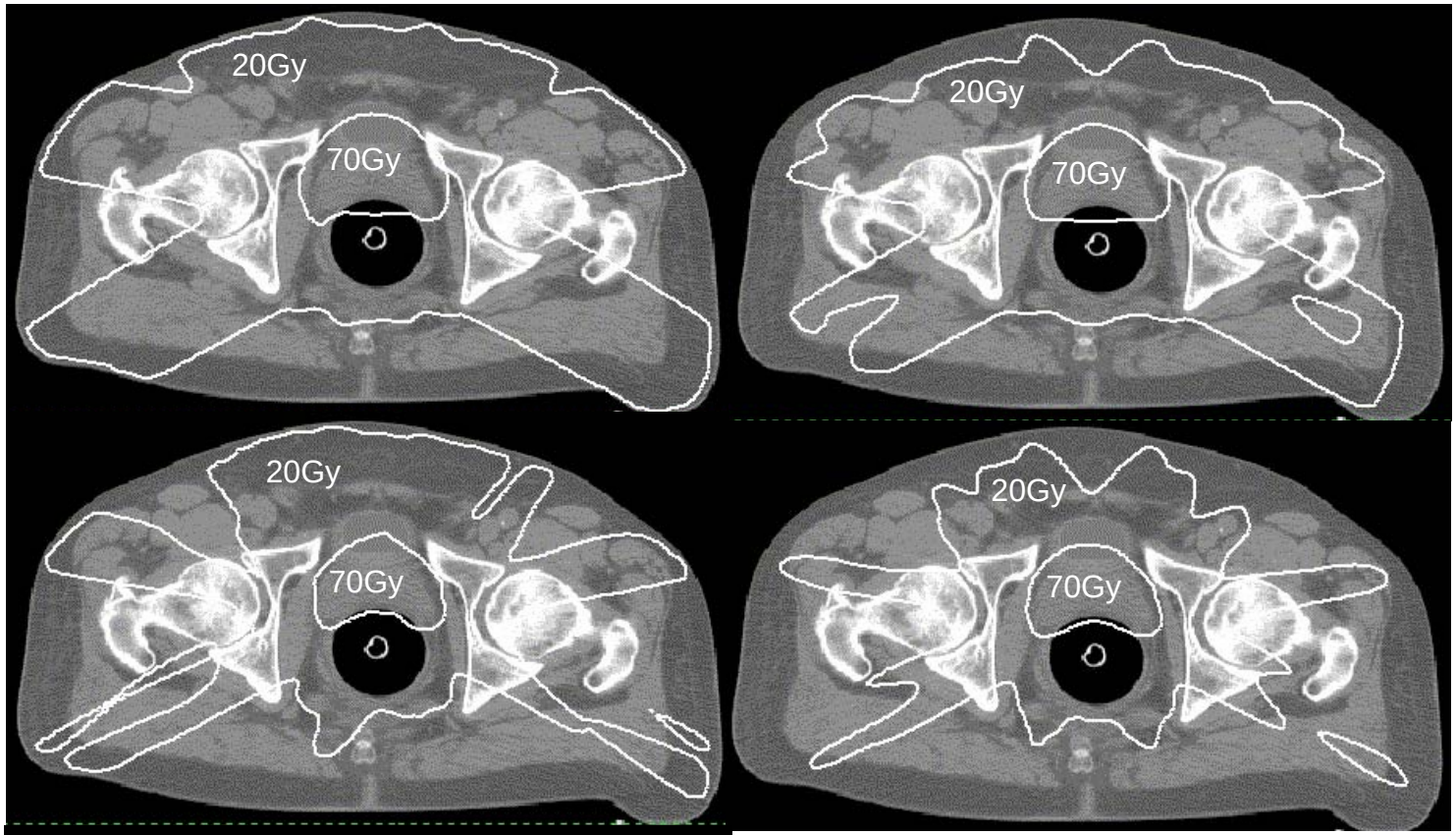
TABLE 1. Optimization parameters for IMRT treatment plans.

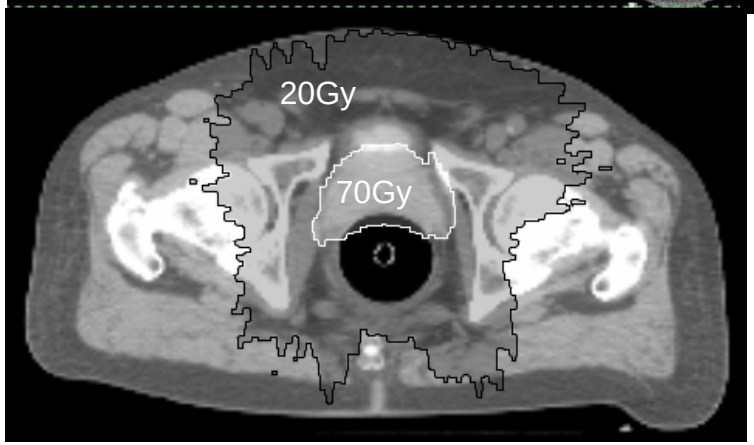
Structure	Criterion	Weight
PTV	Min dose = 70Gy	30
	Uniform dose = 70Gy	20
Rectal wall	Max dose = 63.63Gy	5
	Max DVH: 36.36Gy to 30%	5
	Max DVH: 45.54Gy to 20%	5
	Max DVH: 54.54Gy to 15%	5
Penile bulb	Max DVH: 45Gy to 50%	3
	Max DVH: 37Gy to 70%	3
Bladder	Max dose = 63.63Gy	1
Normal tissue outside PTV+5mm	Max dose = 20Gy	3

TABLE 2. Integral dose and percent difference compared to 6MV-3DCRT

	3D-CRT 6MV	IMRT 6MV		3D-CRT 20MV		IMRT 20MV		Tomo-IMRT	
	ave.†(liter-gray)	ave.(liter-gray)	p.d.‡(%)	ave.(liter-gray)	p.d.(%)	ave.(liter-gray)	p.d.(%)	ave.(liter-gray)	p.d.(%)
PTV	8.27	8.27	0.0	8.28	0.2	8.27	-0.1	8.26	-0.1
Rectal wall	2.53	2.37	-6.1	2.53	0.0	2.43	-1.8	2.23	-11.9
Penile bulb	0.201	0.196	-2.7	0.211	4.8	0.201	-0.3	0.168	-16.5
Bladder	4.99	4.61	-7.5	4.84	-2.9	4.95	-0.7	4.69	-6.0
Non-tumor tissue	122.85	116.66	-5.0	113.38	-7.7	109.06	-11.2	117.89	-4.0

† average, ‡ percent difference





a. 6MV-3DCRT	**d. 20MV-3DCRT**
b. 6MV- IMRT	**e. 20MV-IMRT**
c. Tomo-IMRT	

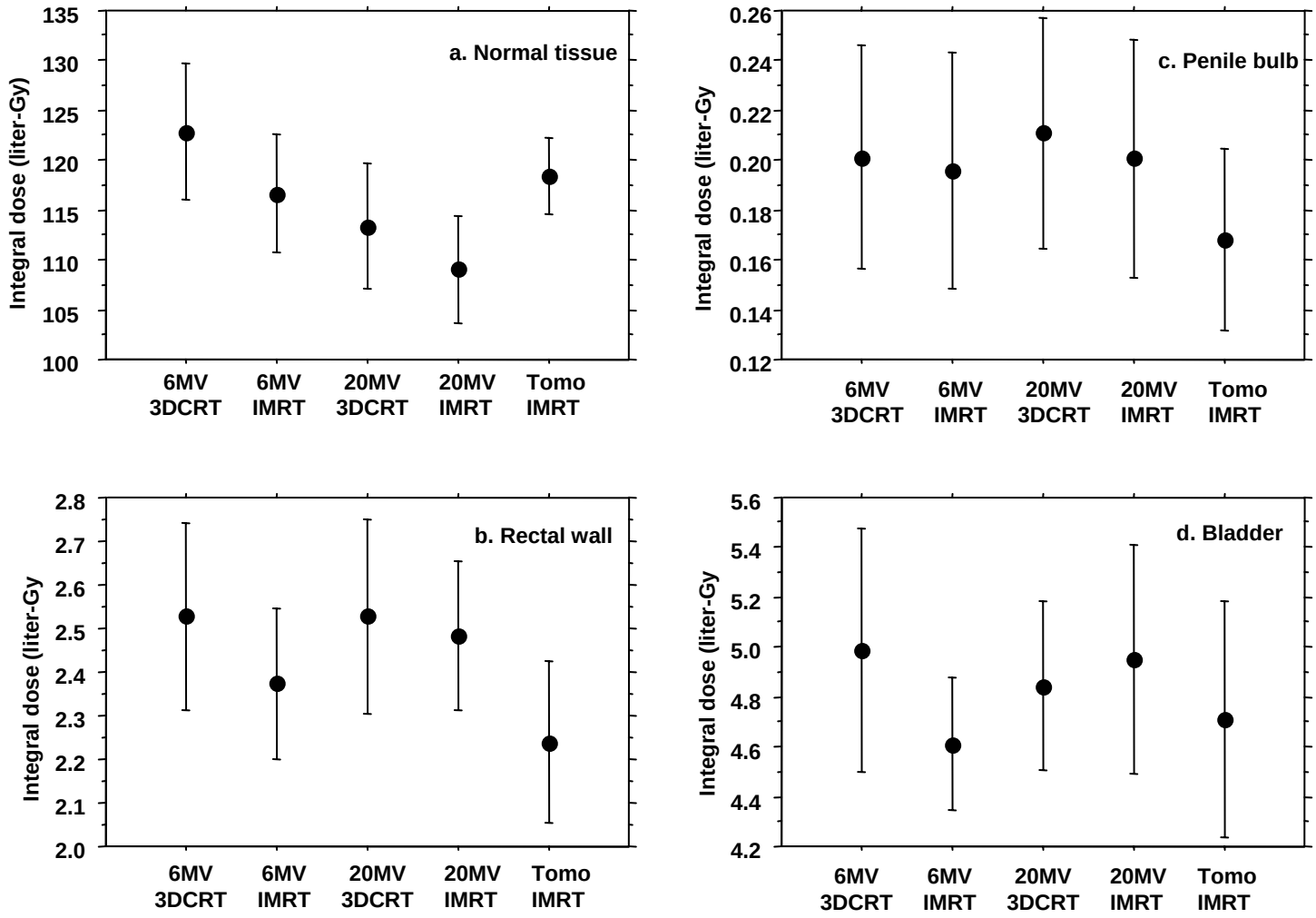

a. Normal tissue
Integral dose (liter-Gy)
135
130
125
120
115
110
105
100
6MV 3DCRT
6MV IMRT
20MV 3DCRT
20MV IMRT
Tomo IMRT
c. Penile bulb
Integral dose (liter-Gy
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
6MV 3DCRT
6MV IMRT
20MV 3DCRT
20MV IMRT
Tomo IMRT
b. Rectal wall
Integral dose (liter-Gy
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
6MV 3DCRT
6MV IMRT
20MV 3DCRT
20MV IMRT
Tomo IMRT
d. Bladder
Integral dose (liter-Gy
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
6MV 3DCRT
6MV IMRT
20MV 3DCRT
20MV IMRT
Tomo IMRT

Figure 3, Aoyama H