Figure 6 show the distribution of the prostate-PTV margins for patients with typical T1–2 tumors treated with IGRT. Prostate or metal marker matching tended to produce slightly smaller margins than bone matching.

DISCUSSION

This study provides a clear picture of present practices of IMRT and/or IGRT for prostate cancer in Japan.

Simulations and treatments were performed in the supine position at most facilities. However, facilities employed various fixation methods. In most facilities, some kind of fixation method was used, although immobilization devices for body malignancies are not covered by health insurance in Japan. In the patterns of care study on prostate cancer patients who were treated with EBRT from 2003 to 2005, immobilization devices were used on only 15% of patients (7). One reason for the high frequency of the usage of patient immobilization devices in this study could be the gradual popularization of fixation methods over time. An additional reason is probably the fact that some sort of fixation method tends to be used in more precise radiation treatment, because patient immobilization can be an important contributor to the reproducibility and accuracy of radiotherapy (9).

The pretreatment condition of the bladder and rectum also varied greatly among facilities. Although fixation of the prostate is frequently conducted with a rectal balloon in Western countries (10), this method has not been used at all in Japan.

In this study, we did not investigate PTV margins when IGRT was not used. Therefore, we were unable to clarify whether IGRT causes decreased margins. However, PTV margins tended to be slightly smaller with prostate or fiducial marker matching than that with bone matching. PTV margins should be determined at each facility taking into account position errors caused not only by the IGRT method, but also by the patient position, fixation method and pretreatment condition of the bladder and rectum. Enmark et al. (11) demonstrated that a margin of 4 mm in all directions was adequate to account for uncertainties including the inter- and intrafraction motions, if IGRT with fiducial markers is performed on a daily basis. Some facilities have chosen prostate-PTV margins of <4 mm. Because of uncertainties such as intrafraction motion or uncertainty of the target delineation, decreases in the PTV margin should be carefully performed even when IGRT is applied.

The radiation dose administered at most facilities was 2 Gy per fraction. The median value of the total radiation dose was 76 Gy with IMRT and 70 Gy with 3DCRT. It is well known that the radiation dose is a strong independent predictor of failure (12), and IMRT can reduce the unwanted doses to nearby organs at risk. Therefore, as IMRT becomes more widespread in Japan, more appropriate higher dosages of radiation should be utilized. However, a significant problem is the fact that the IMRT dose prescription varies. It is necessary to define and develop recommended guidelines for dose prescription and a dose reporting system for IMRT in Japan (13).

IMRT and IGRT were being conducted at approximately half of the facilities in this study. However, our survey targeted large-scale facilities. If all radiation therapy facilities in Japan were to be surveyed, this proportion would probably be smaller (3). At present, high-precision radiation therapy devices such as IMRT and IGRT are being rapidly introduced (3,14), and an increasing number of facilities will surely come to adopt IMRT and IGRT. The results of the survey in this study will provide beneficial information to those facilities as they begin treatment.

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Conflict of interest statement

None declared.

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Clinical Investigation: Breast Cancer

Identifying Patients Who Are Unsuitable for Accelerated Partial Breast Irradiation Using Three-Dimensional External Beam Conformal Techniques

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Summary

Fifty consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) accelerated partial breast irradiation (APBI) techniques. Dose–volume histogram (DVH) constraints were satisfied in 20% of patients with a long cranio-caudal surgical clip distance (CCD; ≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Patients with long CCDs might be unsuitable for 3D-CRT APBI due to nonoptimal DVH constraints.

Purpose: Several recent studies reported that severe late toxicities including soft-tissue fibrosis and fat necrosis are present in patients treated with accelerated partial breast irradiation (APBI) and that these toxicities are associated with the large volume of tissue targeted by high-dose irradiation. The present study was performed to clarify which patients are unsuitable for APBI to avoid late severe toxicities.

Methods and Materials: Study subjects comprised 50 consecutive patients with Stage 0–II unilateral breast cancer who underwent breast-conserving surgery, and in whom five or six surgical clips were placed during surgery. All patients were subsequently replanned using three-dimensional conformal radiotherapy (3D-CRT) APBI techniques according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39 and Radiation Therapy Oncology Group (RTOG) 0413 protocol. The beam arrangements included mainly noncoplanar four- or five-field beams using 6-MV photons alone.

Results: Dose–volume histogram (DVH) constraints for normal tissues according to the NSABP/RTOG protocol were satisfied in 39 patients (78%). Multivariate analysis revealed that only long craniocaudal clip distance (CCD) was correlated with nonoptimal DVH constraints ($p = 0.02$), but that pathological T stage, anteroposterior clip distance (APD), site of ipsilateral breast (IB) (right/left), location of the tumor (medial/lateral), and IB reference volume were not. DVH constraints were satisfied in 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD ($p < 0.0001$). Median IB reference volume receiving ≥50% of the prescribed dose (IB-V_{50}) of all patients was 49.0% (range, 31.4–68.6). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$), but other factors were not.

Conclusion: Patients with long CCDs (≥5.5 cm) might be unsuitable for 3D-CRT APBI because of nonoptimal DVH constraints and large IB-V_{50}. © 2012 Elsevier Inc.

Keywords: Partial breast irradiation, Breast cancer, Radiotherapy, 3D-conformal radiotherapy, Toxicity

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Introduction

Breast-conserving therapy including partial resection and postoperative whole breast irradiation has constituted standard care for patients with early breast cancer (1). Some Phase III trials of postoperative radiotherapy and systematic reviews have revealed that omission of postoperative radiotherapy increases recurrence in breasts by threefold, and increases absolute breast cancer mortality by more than 5% (1, 2). Several reasons, including the long-term radiation schedule, level of surgeon involvement in the radiation decision, patient refusal, and comorbidity, lead to omission of postoperative radiotherapy. In fact, approximately 25% of patients who underwent conservative surgery did not receive postoperative radiotherapy in the United States (1991–2002) (3).

Approximately 85% of breast recurrences after breast conservative therapy develop in the vicinity of the tumor bed; several percent appear "elsewhere" in the breast, and the absolute number of such failures is very low (4). In the past decade, prospective clinical trials and retrospective studies evaluated the efficacy and safety of accelerated partial breast irradiation (APBI) using small radiation fields and a large fraction size. These studies reported good treatment outcome and minimal late toxicities after a short follow-up duration (4–6). However, two recent studies reported that the large volume of irradiated breast tissue was correlated with higher incidences of late severe toxicities including soft-tissue fibrosis and fat necrosis of the breast, which were clearly associated with marked cosmetic compromise (7, 8). Appropriate eligibility criteria and treatment schedules for APBI should be established to avoid late severe toxicities. The present study aimed to identify patients who are unsuitable for APBI because of the potential risk of late toxicities including soft-tissue fibrosis and fat necrosis after APBI using three-dimensional conformal radiotherapy (3D-CRT).

Methods and Materials

Patients

The study population consisted of 50 consecutive patients with unilateral breast cancer, at Union for International Cancer Control 7th Stage 0–II, who received breast-conserving therapy between April 2009 and September 2009. Median patient age was 49 years (range, 33–73). The right-to-left ratio of the ipsilateral breast (IB) was 25:25, and the medial-to-lateral ratio of the tumor location was 19:31. All patients underwent partial breast resection, and five or six surgical clips were placed at the borders of the surgical bed. Thirty-one patients had pathological T stage 1 (pT1), 7 patients had pT2, and 12 patients had pTis. Sentinel node biopsy and/or axillary node dissection revealed that 47 patients had pathological N stage 0 (pN0), and 2 patients had pN1. pN stage was not evaluated for 1 patient.

Radiation treatment planning

All patients were placed in the supine position and underwent computed tomography (CT) as part of the standard planning for whole breast irradiation. CT scanning was performed using a 2-mm thick-slice and a slice step of 2 mm; slices extended to completely cover the bilateral whole breast, lung, heart, thyroid, and a 5-cm margin in the cranial and caudal directions. No respiratory control was used. The following structures were contoured for the planning of 3D-CRT: surgical clips, clinical target volume (CTV), planning target volume (PTV), ipsilateral whole breast (IB) reference, IB reference excluding PTV (IB-PTV), contralateral breast, heart, bilateral lungs, and thyroid. To keep the probability of comparison consistent with outcomes of other studies, the contouring of IB reference was made up using an automated contouring method applied by the National Surgical Adjuvant Breast and Bowel Project (NSABP B-39) and Radiation Therapy Oncology Group (RTOG 0413) protocol (9). CTV was defined as the volume bound by uniform expansion of surgical clips by 1.5 cm in all dimensions, excluding the pectoralis muscles, chest wall, lung, heart, pericardial fat, and 5 mm beneath the skin (9). PTV was defined as the volume bound by uniform expansion of CTV by 1.0 cm in all dimensions. PTV_EVAL, the volume for dose–volume histogram (DVH) analysis, was defined as the volume of PTV excluding the first 5 mm of tissue under the skin, the posterior breast tissue extent (chest wall and pectoral muscles), lung, heart, and pericardial fat.

All 50 patients were replanned using 3D-CRT planning system software (Pinnacle^3 version 8.0m, Pinnacle Treatment System; Philips, Milpitas, CA). To correctly evaluate heterogeneous tissue density, the convolution algorithm was used. The NSABP B-39/RTOG 0413 protocol dose limitation was used as a guideline for specified normal tissue constraints (9). Beam arrangements included noncoplanar mainly four- or five-field beams using 6-MV photons referring to the method reported by Vicini *et al.* (10). No electron beam was used. The exertion of simulation planning was for minimizing doses to organs at risk, and improving a homogeneous dose to the target volume. Beam weights, beam angle, and wedge angles were manually optimized, such that the targeted goal was to cover $\geq$90% of the PTV_EVAL by a dose $\geq$90% of the prescribed dose (9). The DVH constraints adopted for plan optimization are shown in Table 1.

A total dose of 30 Gy in five fractions was prescribed to the International Commission on Radiation Units and Measurements 50 reference point dose (isocenter) (11). The isocenter was placed in the center of the PTV. This treatment schedule was proposed by the Department of Radiation Oncology at New York University using the prone position and parallel-opposed minitangents external beam therapy (12). The New York University study demonstrated that this abbreviated regimen was well tolerated, with only mild acute adverse events and excellent or good cosmetic outcome. However, given the typical Japanese woman's breast size and shape, we had patients assume a supine position and used a noncoplanar three-, four-, five-, and six-beam technique.

Data analysis

IB volume, target volumes, and distance of surgical clips were measured by CT images on the radiation treatment planning (RTP) system. The craniocaudal surgical clip distance (CCD) was defined as the longitudinal distance along the body axis between head-side clip and foot-side clip, and the anteroposterior surgical clip distance (APD) was defined as the vertical distance between anterior-side clip and posterior-side clip. The IB reference volume receiving 50% of the prescribed dose (IB-V_{50}) was calculated. The homogeneity index (HI) was defined as the ratio of maximum dose

Table 1 DVH constraints for planning

IB reference	≤60%	≥50% of the prescribed dose	IB-V50 ≤60%
	≤35%	≥100% of the prescribed dose	IB-V100 ≤35%
Contralateral breast	Any point	≤3% of the prescribed dose	0.9 Gy
Ipsilateral lung	≤15%	≥30% of the prescribed dose	V30 ≤15%
Contralateral lung	≤15%	≥5% of the prescribed dose	V5 ≤15%
Heart			
Right-sided lesions	≤5%	≥5% of the prescribed dose	V5 ≤5%
Left-sided lesions	≤40%	≥5% of the prescribed dose	V5 ≤40%
Thyroid	Any point	≤3% of the prescribed dose	0.9 Gy

Abbreviations: DVH = dose–volume histogram; IB = ipsilateral breast.

of PTV_EVAL to minimum dose of PTV_EVAL. The conformity index (CI) was defined as the ratio of volume that was covered by the minimal dose of PTV_EVAL to the volume of PTV. The associations between categorical variables (*e.g.*, site of IB) and patient and tumor characteristics at baseline were analyzed using Fisher's two-tailed exact test. Statistically significant differences between two sample means and medians for continuous variables (*e.g.*, IB reference volume) were analyzed using the Student's unpaired *t*-test. A p value of less than 0.05 was considered statistically significant. Multivariate analysis of prognostic factors was performed with the Cox proportional hazards model. Statistical analyses were performed with JMP software, version 5.1 (SAS Institute, Cary, NC).

Results

Outcome of 3D-CRT planning

Median IB reference volume of all patients was 824 cm^3 (range, 425–1868) (Table 2). Median right IB reference volume was 794 cm^3 (range, 463–1556) and the left IB reference volume was 849 cm^3 (range, 425–1868), respectively ($p = 0.63$). Median CCD and APD for all patients were 4.5 cm (range, 2.0–9.5) and 4.2 cm (range, 0.8–7.6), respectively.

Median CTV for all patients was 56.3 cm^3 (range, 11.3–83.6), and median PTV for all patients was 246.9 cm^3 (range, 113.4–370.9) (Table 3). The median ratio between IB-PTV and IB reference volume was 74.9% (range, 54.0–86.9). The number of external beams ranged from three to six; the four-beam technique was mainly used for patients with the right breast region, and the five-beam technique was mainly used for patients with the left breast region. The median value of mean dose of PTV_EVAL was 30.2 Gy (range, 29.5–30.8). The median value of HI for all patients was 1.24 (range, 1.14–1.39), and the median value of CI for all patients was 1.38 (range, 1.01–2.40).

Unsuitable patients for the NSABP B-39/RTOG 0413 protocol

DVH constraints for organs at risk according to the NSABP B-39/RTOG 0413 protocol were satisfied in 39 patients (78%). Seven patients showed nonoptimal DVH for the ipsilateral lung; 5 patients for the contralateral breast; 4 patients for IB-V_{50}; 2 patients for the heart; and 1 patient for the thyroid. Univariate logistic regression analysis revealed that long CCD and medial tumors were correlated with nonoptimal DVH constraints ($p < 0.0001$ and $p = 0.007$, respectively), but pathological T stage excluding pTis (T1a/T1b/T1c/T2), APD, site of IB (right/left), and IB reference volume were not ($p = 0.98$, $p = 0.54$, $p = 0.73$, and

Table 2 Patients characteristics

				Univariate analysis
	All patients ($n = 50$)	Optimal DVH ($n = 39$)	Nonoptimal DVH ($n = 11$)	p value
Pathological T stage				
pTis/pT1/pT2	12/31/7	10/24/5	2/7/2	0.82
pT1a/pT1b/pT1c/pT2*	5/5/20/7	4/4/15/5	1/1/5/2	0.98
Site of IB				
Right/left	25/25	20/19	5/6	0.73
Location of tumor				
Mediolateral	19/31	11/28	8/3	0.007
IB reference volume (cm^3)				
Median (range)	824 (425–1868)	828 (425–1868)	725 (528–1032)	0.10
CCD (cm)				
Median (range)	4.5 (2.0–9.5)	3.5 (2.0–5.5)	6.0 (4.5–9.5)	<0.0001
APD (cm)				
Median (range)	4.2 (0.8–7.6)	4.2 (0.8–7.6)	4.6 (1.0–7.5)	0.54

Abbreviations: APD = anteroposterior clip distance; CCD = craniocaudal clip distance; DVH = dose–volume histogram; IB = Ipsilateral breast.
* 1 patient was not classified according to subcategory of pathological T stage.

Table 3 Dosimetric characteristics

Dosimetric characteristics	Mean	Median	Range
CTV (cm^3)	55.5	56.3	11.3–83.6
PTV (cm^3)	247.4	246.9	113.4–370.9
IB–PTV/IB reference (%)	74.3	74.9	54.0–86.9
IB-V_{100} (%)	12.7	12.5	5.6–23.4
IB-V_{95} (%)	24.7	24.6	14.6–44.8
IB-V_{50} (%)	48.6	49.0	31.4–68.6
Ipsilateral mean lung dose (Gy)	4.1	4.2	1.2–7.6
Ipsilateral lung-$V_{9\ Gy}$ (%)	12.5	12.6	3.6–23.1
Contralateral lung-$V_{1.5\ Gy}$ (%)	0.3	0	0–10.1
Heart-$V_{15\ Gy}$ (%)	1.0	0	0–7.4
Heart-$V_{6\ Gy}$ (%)	2.7	0	0–17.1
Thyroid-$V_{0.9\ Gy}$ (%)	0.5	0	0–25.5
Contralateral breast-$V_{0.9\ Gy}$ (%)	0.1	0	0–3.6
Mean dose of PTV_EVAL (Gy)	30.2	30.2	29.5–30.8
PTV_EVAL-$V_{27\ Gy}$ (%)	99.4	99.7	96.2–100
Homogeneity index	1.23	1.24	1.14–1.39
Conformity index	1.45	1.38	1.01–2.40

Abbreviations: CTV = clinical target volume; IB = ipsilateral breast; PTV = planning target volume; PTV_EVAL = volume of PTV for evaluation.

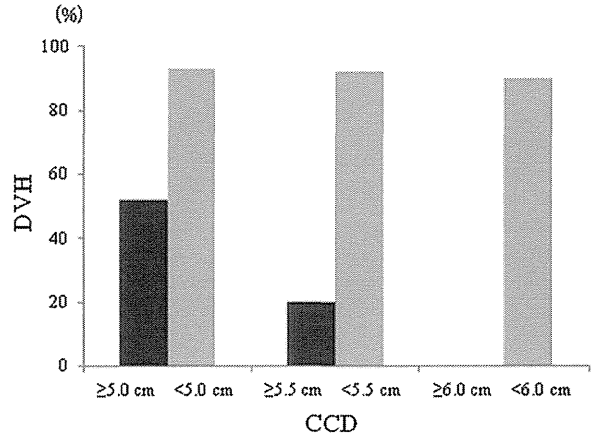

Fig. 1. Frequency of optimal dose–volume histogram (DVH) constraints according to craniocaudal surgical clip distance (CCD). Left column indicates that 52% of patients with long CCD (≥5 cm) satisfy DVH constraints, whereas the center and right columns show that only a few patients with long CCD of ≥5.5 cm and those with long CCD of ≥6.0 cm satisfy DVH constraints.

$p = 0.10$, respectively). Multivariate analysis revealed that only a long CCD was correlated with nonoptimal DVH constraints ($p = 0.02$). DVH constraints were satisfied in only 20% of patients with a long CCD (≥5.5 cm) and 92% of those with a short CCD (<5.5 cm) ($p < 0.0001$) (Fig. 1). Of the 2 patients with a short CCD (<5.5 cm), 1 patient with a left upper-inner primary tumor and a 5-cm CCD, did not satisfy optimal DVH for the ipsilateral lung and contralateral breast, and the other patient, who had a right upper-outer primary tumor and a 4.5-cm CCD, did not satisfy optimal DVH for the heart and IB-V_{50}. DVH constraints were satisfied in 52% of patients with a long CCD (≥5.0 cm) and 93% of those with a short CCD (<5.0 cm) ($p = 0.0007$). DVH constraints were satisfied in 0% of patients with a long CCD (≥6.0 cm) and in 90% of those with a short CCD (<6.0 cm) ($p < 0.0001$). A long CCD was correlated with not only nonoptimal DVH constraints, but also a large ipsilateral mean lung dose (MLD) ($r = 0.48$, $p = 0.0003$).

High-risk patients with large IB-V_{50}

Median IB-V_{50} of all patients was 49.0% (range, 31.4–68.6). Univariate logistic regression analysis revealed that long CCD ($r = 0.72$, $p < 0.0001$) and medial tumors ($p = 0.02$) were correlated with large IB-V_{50} (Fig. 2, 3). The site of the IB (right/left), pathological T stage (T1a/T1b/T1c/T2), IB reference volume, and APD were not correlated with a large IB-V_{50} ($p = 0.47$, $p = 0.92$, $p = 0.13$, $p = 0.10$, respectively). Multivariate analysis revealed that only a long CCD was correlated with large IB-V_{50} ($p < 0.0001$).

Discussion

The Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology Breast Cancer Working Group and the American Society for Radiation Oncology Health Services Research Committee proposed the patient selection criteria for use of APBI based on available clinical evidence complemented by expert opinion (13, 14). The main eligibility criteria proposed by these task groups included patient age (≥60 years), pathological tumor size (≤3 cm), negative surgical margin, unicentric lesion, and pN0 (13, 14). These recommendations were mainly based on the probability of breast recurrence after APBI. To maintain the efficacy and safety of APBI, potential risk for late severe toxicities should be considered in addition to the probability of breast recurrence. The NSABP B-39/RTOG 0413 protocol requires that the ratio of lumpectomy cavity to IB volume must be <30% based on postoperative/prerandomization CT

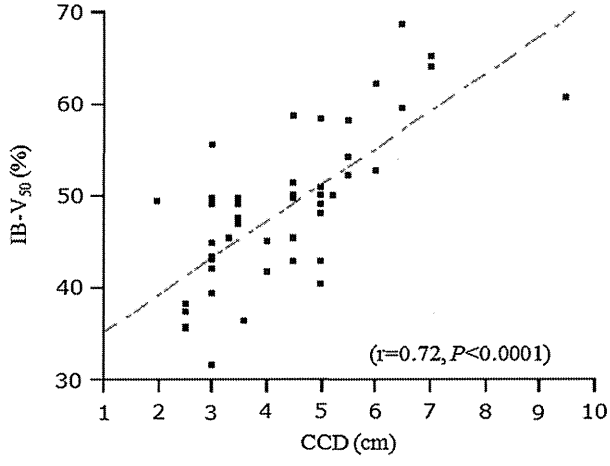

Fig. 2. Scatter plots for craniocaudal surgical clip distance (CCD) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-V_{50}). Long CCD was strongly correlated with large IB-V_{50} ($r = 0.72$). IB-V_{50}. The dotted line indicates the fitting line.

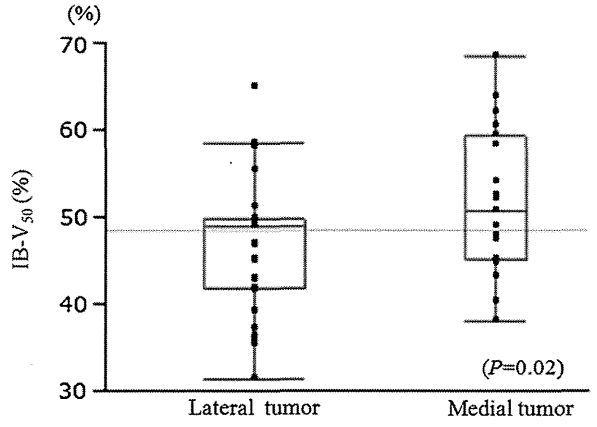

Fig. 3. Box plots for tumor location (lateromedial) and ipsilateral breast reference volume receiving ≥50% of the prescribed dose (IB-V_{50}). The gray line indicates the median value of IB-V_{50}.

imaging (9). Unfortunately, the ratio of lumpectomy cavity to IB volume and that of PTV to IB reference volume are not calculated until the RTP system operation. Thus, eligibility criteria that require complex calculations serve as obstacles toward seamless execution of clinical trials. In the majority of contemporary APBI series, patients for whom the maximal tumor size is less than 3 cm have been eligible (5, 14). In our study, pathological T stage (pT1a/pT1b/pT1c/pT2), which was classified according to pathological maximum diameter of the invasive carcinoma component, was not associated with nonoptimal DVH constraints of the NSABP B-39/RTOG 0413 protocol. Some likely explanations for this are that the pathological T stage does not include the noninvasive carcinoma component and that it does not correlate with specimen shape (*e.g.*, fan shape, slender oval) or the direction of the long axis of the specimen. On the other hand, the distance of surgical clips is directly associated with the size of the resected specimen, and the CCD strongly correlated with the field length in the craniocaudal direction and the breast irradiated volume. Distances between surgical clips are easy to measure with digital chest X-rays rather than the RTP system operation and they serve as tools to help predict which patients are unsuitable for 3D-CRT APBI. However, APD was not closely correlated with either nonoptimal DVH constraints or large IB-V_{50}. We applied the noncoplanar beam technique using tangential beam with a 10–20° steeper gantry angle and couch angles of 0–30°. With this technique, the gantry angle arrangement allows one to reduce the field width in the anteroposterior direction and the irradiated volume, in which case APD does not correlate closely with field size, irradiated volume, or nonoptimal DVH constraints.

Hepel *et al.* reported that high-, intermediate-, and low-dose volumes (IB-V_5–IB-V_{80}) all correlated with incidence of breast fibrosis after 3D-CRT APBI (7). Improved target coverage with external beam techniques comes at the cost of a higher integral dose to the remaining normal breast. With the 3D-CRT APBI technique, the volume of high-dose region (*e.g.*, IB-V_{100}, IB-V_{80}) and that of low-dose region (*e.g.*, IB-V_2, IB-V_{20}) are closely related. Jagsi *et al.* reported on the unacceptable cosmesis that developed in 7 patients among 34 patients after APBI using Intensity-modulated radiotherapy, noting that IB-V_{50} and IB-V_{100} correlated with cosmetic outcome (8). They indicated that there seemed to be a possible threshold at 40%, in which the 5 of 10 patients (50%) with an IB-V_{50} >40% experienced unacceptable cosmesis vs. the 2 of 22 (9%) below that threshold who experienced it ($p = 0.02$). On the other hand, Formenti *et al.* reported good cosmetic outcomes in most patients after performing APBI with the 3D-CRT technique in a prone position with 30 Gy in five fractions, noting that IB-V_{50} ranged from 23 to 75%, and IB-V_{100} ranged from 10 to 45% (12). In our simulation study, median IB-V_{50} of patients with optimal DVH constraints was 46.9% (31.4–58.1), and that for patients with nonoptimal DVH constraints was 59.4% (49.9–68.6) ($p < 0.0001$, data not shown). The appropriate threshold of IB-V_{50} and that of other parameters (*e.g.*, IB-V_{20}, IB-V_{80}, maximum dose) as predictive factors of late soft tissue toxicities has yet to be clarified. Further studies should be conducted to clarify predictive factors for late soft tissue toxicities.

Recht *et al.* reported that the risk of pneumonitis appeared to be related to the irradiated ipsilateral lung volume treated, and recommended that ipsilateral lung volume receiving 20 Gy or higher should be lower than 3%, and that receiving 5 Gy lower than 20% (6). They indicated that relatively low-dose lung irradiation might better help to determine the risk of pneumonitis after radiotherapy. In our study, a long CCD was correlated with large ipsilateral MLD ($r = 0.48$, $p = 0.0003$), and ipsilateral lung volume receiving 6 Gy or higher (≥20% of the prescribed dose) ($r = 0.63$, $p < 0.0001$).

A limitation of the present study was that we used simulation data rather than clinical outcomes. A prospective clinical trial should be conducted to evaluate the utility of these eligibility criteria and treatment outcomes. In addition, we could not verify the geometric couch and gantry angle limitations for the Varian linear accelerator in all patients. However, before the beginning of this study, we did verify the geometric couch and gantry angle limitations using a human-body phantom placed on a couch.

Conclusions

Patients with a long CCD, especially 5.5 cm or longer, might be unsuitable for 3D-CRT APBI from nonoptimal DVH constraints and large IB-V_{50}. Pathological T stage, APD, site of IB (right/left), tumor location (medial/lateral), and IB reference volume could not predict whether patients were unsuitable for 3D-CRT APBI.

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ORIGINAL ARTICLE

The relationship between the bladder volume and optimal treatment planning in definitive radiotherapy for localized prostate cancer

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Abstract

Background. There is no current consensus regarding the optimal bladder volumes in definitive radiotherapy for localized prostate cancer. The aim of this study was to clarify the relationship between the bladder volume and optimal treatment planning in radiotherapy for localized prostate cancer. *Material and methods.* Two hundred and forty-three patients underwent definitive radiotherapy with helical tomotherapy for intermediate- and high-risk localized prostate cancer. The prescribed dose defined as 95% of the planning target volume (PTV) receiving ≧ 100% of the prescription dose was 76 Gy in 38 fractions. The clinical target volume (CTV) was defined as the prostate with a 5-mm margin and 2 cm of the proximal seminal vesicle. The PTV was defined as the CTV with a 5-mm margin. Treatment plans were optimized to satisfy the dose constraints defined by in-house protocols for PTV and organs at risk (rectum wall, bladder wall, sigmoid colon and small intestine). If all dose constraints were satisfied, the plan was defined as an optimal plan (OP). *Results.* An OP was achieved with 203 patients (84%). Mean bladder volume (± 1 SD) was 266 ml (± 130 ml) among those with an OP and 214 ml (±130 ml) among those without an OP ($p = 0.02$). Logistic regression analysis also showed that bladder volumes below 150 ml decreased the possibility of achieving an OP. However, the percentage of patients with an OP showed a plateau effect at bladder volumes above 150 ml. *Conclusions.* Bladder volume is a significant factor affecting OP rates. However, our results suggest that bladder volumes exceeding 150 ml may not help meet planning dose constraints.

The bladder is filled to various volumes during fractionated radiotherapy. Changing bladder volumes affects both bladder dose volumes and the position of adjacent organs (the prostate, seminal vesicles, small intestine and sigmoid colon) [1]. Furthermore, significant variations in bladder volume can affect planned three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) dose distributions. For all these reasons, bladder volumes must be kept consistent throughout planning and treatment to reduce positional uncertainties related to the prostate and the risk of increased toxicity to the surrounding normal tissue.

There is no current consensus regarding the optimal bladder volumes in definitive radiotherapy for localized prostate cancer. One possible advantage of maintaining a full bladder is that part of the bladder moves away from the target volume, thereby reducing bladder toxicity [2,3]. A full bladder also moves the small intestine and the sigmoid colon out of the irradiation field, reducing toxicity in these organs [1,4–7]. However, if we target larger bladder volumes on planning using computed tomography (CT) and during radiotherapy, such volumes tend to show marked variability [8–10]. On the other hand, excessively small bladder volumes make it difficult to meet planning dose constraints for the bladder and adjacent organs. For these reasons, the optimal bladder volume may be the minimum bladder volume that can satisfy dose constraints. Based on this reasoning, several institutions target a half-full bladder or a comfortably full bladder [8,9]. However, no previous

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reports have focused on the relationship between the bladder volume and optimal treatment planning.

We evaluated the relationship between the bladder volume on planning CT and the percentage satisfying the dose constraints as a reference what bladder volumes should be targeted.

Material and methods

Between June 2007 and February 2009, 243 patients underwent definitive radiotherapy with helical tomotherapy using the Hi-Art System (Tomotherapy Inc.) for intermediate- and high-risk localized prostate cancer (cT1-4N0M0) according to D'Amico's classification at Edogawa Hospital (Tokyo, Japan) (Table I).

The patients were irradiated in a supine position, with a knee support. They were instructed to refrain from urinating for 60–90 minutes before the planning computed tomography (CT) scan and before daily irradiation. They were also encouraged to drink an unspecified volume of water to ensure a clear but tolerable urge to urinate before the planning CT scan and before daily irradiation. They were instructed to take laxatives before the planning CT scan, although no specific instructions were issued regarding bowel movements before daily irradiation.

Table I. Patient characteristics.

	no.
cT stage (TNM 6th ed.)	
1–2a	101(42%)
2b	32 (13%)
2c	40 (16%)
3a	61 (25%)
3b	8 (33%)
4	1 (0.4%)
Gleason score	
2–6	41 (17%)
7	102 (42%)
8–10	100 (41%)
Pretreatment PSA	
0–10	104 (43%)
10–20	67 (28%)
>20	72 (30%)
D'Amico's risk group	
Intermediate	71 (29%)
High	172 (71%)
Neoadjuvant hormone therapy	
No	81 (33%)
Yes	162 (67%)
Mean age (range)	70 (42–85)
Mean prostate volume (range)	21 ml (6–178)
Mean PTV (range)	112 ml (61–273)
Mean bladder volume (range)	235 ml (45–653)

cT stage, clinical tumor stage; PSA, prostate-specific antigen; PTV, planning target volume.

The clinical target volume (CTV) was defined as the prostate that was delineated by the fusion images of CT and magnetic resonance imaging (MRI) with a 5-mm margin and 2 cm of the proximal seminal vesicle. Exceptionally, the whole seminal vesicle was included in the CTV for cases of clinical T3b stage disease. The planning target volume (PTV) was defined as the CTV with a 5-mm margin. The prescribed dose defined as 95% of the PTV receiving ≧100% of the prescription dose (D95) was 76 Gy in 38 fractions. The treatment plans were optimized to satisfy the dose constraints defined by in-house protocols for the PTV and organs at risk (OAR) (Table II). No specific protocols were used for the order of prioritization among the constraints. Cases in which all dose constraints were satisfied were defined as an optimal plan (OP).

We assessed the relationship between the bladder volumes on planning CT and the percentage of patients achieving an OP. Univariate logistic regression analysis was used to examine the predictive value of covariates including clinical T stage (T1–2a, T2b, T2c, T3a, T3b, and T4), Gleason score (2–6, 7, 8–10), pretreatment PSA (0–10, 10–20, and >20), D'Amico's risk group (intermediate or high), neoadjuvant hormone therapy (yes or no), age, PTV, and bladder volume. Those showing significant associations in univariate logistic regression analysis were further tested by multivariate logistic regression analysis.

We used GraphPad Prism version 5 (GraphPad Software Inc.) and SPSS version 17 (IBM) for statistical analysis. Differences were deemed significant when two-tailed p-values were less than 0.05.

Results

Of the subjects, 203 patients (84%) met the definitions for an OP. Among these patients, the mean of

Table II. Dose constraints.

Target/Organ		Dose constraint
PTV	D95	100% (76 Gy)
	Maximum	<110% (83.6 Gy)
	Mean	<105% (79.8 Gy)
Rectum wall*	V40	<65%
	V60	<35%
	V70	<25%
	V78	<10%
Bladder wall	V40	<60%
	V70	<35%
Sigmoid colon	V65	<0.5 ml
Small bowel	V60	<0.5 ml

*Rectum wall within 5 mm above and below the PTV, Vx<y% (or ml) means that no more than y% (or ml) of the volume of the organ receive a dose>x Gy.
PTV, planning target volume.

the mean PTV dose and the maximum dose were 77.4 Gy (range 76.7–79.2 Gy) and 80.7 Gy (range 78.2–83.3 Gy), respectively.

The mean bladder volume (±1 standard deviation; SD) was 266 ml (±130 ml) among those with an OP and 214 ml (±130 ml) among those without an OP ($p = 0.02$, by unpaired t-test).

Logistic regression analysis also showed that bladder volumes below 150 ml decreased the possibility of achieving an OP (Table III). Figure 1 shows the percentage of patients with an OP according to bladder volumes, indicating that the percentage of patients with an OP showed a plateau effect at bladder volumes above 150 ml. On univariate analysis, higher clinical T stage, younger age, treatment with neoadjuvant hormone therapy, and larger bladder volume were predictors for achieving an OP (Table IV). On multivariate analysis, larger bladder volumes ($p = 0.04$), younger age ($p = 0.01$), and higher clinical T stage ($p = 0.03$) were independent predictors for achieving an OP.

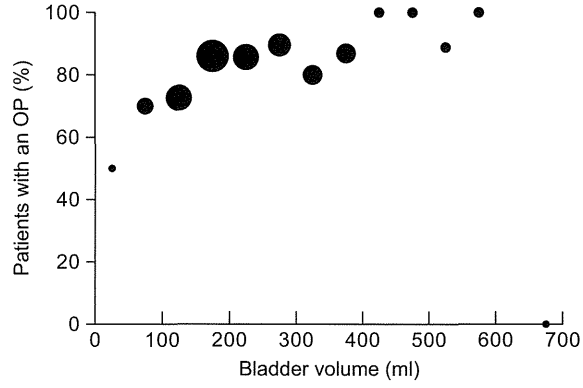

Figure 1. The percentage of patients with an OP according to bladder volume. Patients were divided into subgroups according to their bladder volume by 50 ml. The percentage of patients with an OP was defined by dividing the number of patients with an OP by the number of patients in each subgroup. The size of each dot represents the number in each subgroup.
n, number of patients; OP, optimal plan.

Discussion

We found that bladder volumes among patients with an OP were significantly larger than among patients without an OP. This indicates that bladder volume is a significant factor affecting whether OP is achieved. However, we also found that bladder volumes larger than 150 ml did not contribute to OP rates. We could meet the dose constraints on the bladder even with considerably small bladder volumes. However, small bladders moved the small intestine and the sigmoid colon inside the irradiation field, which made it impossible to meet the dose constraint on those organs. This may explain why we found the plateau effect at bladder volumes above 150 ml.

Table III. Logistic regression analysis between bladder volume and the percentage of patients with an optimal plan.

Bladder volume	Number of patients	Patients with an OP	p	Odds ratio (95% CI)
<100 ml	21	15 (71%)	0.069	0.34 (0.11–1.09)
100–149 ml	34	24 (71%)	0.028	0.33 (0.12–0.89)
150–199 ml	43	37 (86%)	0.761	0.85 (0.29–2.50)
200–249 ml	35	30 (86%)	0.739	0.82 (0.26–2.61)
250–299 ml	27	24 (89%)	0.896	1.10 (0.28–4.31)
>300 ml	83	73 (88%)		1

OP, optimal plan.

Our logistic regression analysis did not show a statistically significant difference in the percentage of patients with an OP in the subgroup with the smallest bladder volume. We think the relatively small number of subjects in the subgroup caused the false negative.

Our results suggested that younger age and higher clinical T stage were also independent predictors for achieving an OP. It is difficult to interpret why age affects OP achievement. There may be some anatomic features among younger patients that make it easier to achieve an OP. It is also difficult to interpret why clinical T stage affects OP achievements although we used the same definition of CTV for all clinical T stages except for the few cases of clinical T3b.

The existence of a clear dose effect for genitourinary (GU) toxicity is well-known in cases in which the entire bladder is irradiated [11]. In the case of prostate irradiation, the cranial portion of the bladder is generally spared, whereas the bladder neck and urethra are irradiated at levels close to the prescribed dose. Most of the published results fails to support a correlation between bladder dose volume histograms (DVH) and GU toxicity [12,13], whereas several studies indicate that the absolute volume of the bladder receiving >78 Gy to 80 Gy is most predictive of late GU toxicity [14,15]. Regarding GU toxicity, a half-full bladder and an empty bladder appear to be acceptable bladder volumes [16]. However, an excessively small bladder volume may move the small intestine and sigmoid colon within the high dose irradiated field [1,4–6]. Therefore, we also imposed dose constraints on the small intestine and sigmoid colon.

Table IV. Univariate logistic regression analysis of association with achieving an optimal plan.

	Patients with an OP (n, 203)	Patients without an OP (n, 40)	p
cT stage (TNM 6th ed.)			0.03
1–2a	77 (38%)	24 (60%)	
2b	26 (13%)	6 (15%)	
2c	35 (17%)	5 (13%)	
3a	57 (28%)	4 (10%)	
3b	7 (3%)	1 (3%)	
4	1 (0.5%)	0 (0%)	
Gleason score			NS
2–6	39 (19%)	2 (5%)	
7	83 (41%)	19 (48%)	
8–10	81 (40%)	19 (48%)	
Pretreatment PSA			NS
0–10	85 (42%)	19 (48%)	
10–20	58 (28%)	9 (23%)	
>20	60 (30%)	12 (30%)	
D'Amico's risk group			NS
Intermediate	60 (30%)	11 (28%)	
High	143 (70%)	29 (73%)	
Neoadjuvant hormone therapy			0.10
No	63 (31%)	18 (45%)	
Yes	140 (69%)	22 (55%)	
Mean age (range)	70 (42–85)	73 (59–83)	0.01
Mean prostate volume (range)	21 ml (6–178)	22 ml (12–103)	NS
Mean PTV (range)	109 ml (61–225)	115 ml (77–273)	NS
Mean bladder volume (range)	266 ml (45–594)	214 ml (48–653)	0.04

cT stage, clinical tumor stage; OP, optimal plan; PSA, prostate-specific antigen; PTV, planning target volume.

Several previous studies have reported that the greatest variation in bladder volume is found in patients with large initial bladder volumes [8,9,17]. Significant variations in bladder volume can confound planned dose distributions. A half-full bladder of 150 ml or slightly larger may represent a reasonable target, offering the potential to improve bladder volume consistency without compromising the dose constraints for the adjacent organs.

A limitation of this investigation is the lack of the clinical correlation. We need to investigate the correlation between bladder volumes on planning CT and clinical outcomes in a future study. In most cases, we use a shrinking PTV if we can not satisfy the dose constraints for OARs. Our concern is that the compromise might cause inferior local control and survival rates. However, long-term follow-up is necessary to clarify the clinical impact. We consider achieving an optimal plan a surrogate marker for clinical outcomes; therefore, we report the correlation between bladder volumes and achieving an optimal plan as the first step.

While optimal bladder volumes vary from institution to institution according to the protocol used, we believe that each institution must seek to recognize what bladder volumes are optimal in definitive radiotherapy for localized prostate cancer.

In conclusions, bladder volume is a significant factor affecting the achieving of an optimal plan. However, our results suggest that bladder volumes exceeding 150 ml may not help meet planning dose constraints.

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ORIGINAL PAPER

Preliminary results of intensity-modulated radiation therapy with helical tomotherapy for prostate cancer

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Abstract
Purpose We present the preliminary results of intensity-modulated radiation therapy with helical tomotherapy (HT) for clinically localized prostate cancer.
Methods Regularly followed 241 consecutive patients, who were treated with HT between June 2006 and December 2010, were included in this retrospective study. Most patients received both relatively long-term neoadjuvant and adjuvant androgen deprivation therapy (ADT). Patients received 78 Gy in the intermediate high-risk group and 74 Gy in the low-risk group. Biochemical disease-free survival (bDFS) followed the Phoenix definition. Toxicity was scored according to the Radiation Therapy Oncology Group morbidity grading scale.
Results The median follow-up time from the start date of HT was 35 months. The rates of acute Grade 2 gastrointestinal (GI) and genitor-urinary (GU) toxicities were 11.2 and 24.5 %. No patients experienced acute Grade 3 or higher symptoms. The rates of late Grade 2 and 3 GI toxicities were 6.6 and 0.8 %, and those of late Grade 2 and 3 GU toxicities were 8.3 % and 1.2 %. No patients experienced late Grade 4 toxicity. The 3-year bDFS rates for low, intermediate, and high-risk group patients were 100, 100, and 95.8 %, respectively. We observed clinical relapse in two high-risk patients, resulting in a 3-year clinical DFS of 99.4 %.
Conclusions This preliminary report confirms the feasibility of HT in a large number of patients. We observed that HT is associated with low rates of acute and late toxicities, and HT in combination with relatively long-term ADT results in excellent short-term bDFS.

Keywords Prostate cancer · Intensity-modulated radiation therapy · Image-guided radiation therapy · Helical tomotherapy

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Introduction

High-dose external beam radiation therapy (EBRT) with intensity-modulated radiation therapy (IMRT) has been shown to improve disease-free survival in patients with localized prostate cancer over the past decade (Zelefsky et al. 2002; Alicikus et al. 2011). Helical tomotherapy (HT) is a novel IMRT treatment modality. HT is a form of 3D conformal radiation therapy in which treatment beams are spatially and temporally modulated to maximize the dose delivered to tumors while minimizing the dose delivered to normal structures (Kapatoes et al. 2001). In addition, detectors within the tomotherapy system provide megavoltage computed tomographic (MVCT) images of the patient, which can be obtained immediately before treatment for setup, registration, and repositioning [i.e., image-guided radiation therapy (IGRT)]. Thus, we believe that HT provides excellent target coverage with dose uniformity while sparing the organs at risk (OAR) and would avoid severe toxicity in patients with prostate cancer. On the other hand, IMRT has been used in Japan recently, especially for prostate cancer. However, to our knowledge, Japanese data of prostate cancer treated with IMRT have not been reported. In this report, we present the preliminary

results of IMRT with HT for clinically localized prostate cancer in Japan.

Materials and methods

Patients

Between June 2006 and December 2010, 251 patients with clinically localized prostate cancer were treated with HT at our institution. Of these, 10 patients were followed at their local hospital. Another 241 consecutive patients, who were followed regularly at our institution, were included in this retrospective study. Pretreatment diagnostic evaluations were performed by serum prostate-specific antigen (PSA), digital rectal examination, magnetic resonance imaging of the pelvis, computed tomography (CT) of the chest to the pelvis, and bone scintigraphy. All patients had histological diagnosis of prostatic adenocarcinoma, classified according to the Gleason grading system. The American Joint Committee on Cancer 2002 clinical staging was used, and patients were classified into three prognostic risk groups defined by the National Comprehensive Cancer Network criteria (http://www.nccn.org/) as follows: low, pretreatment PSA < 10 ng/ml, T1–T2a, and Gleason score ≤ 6; intermediate, T2b–T2c or Gleason score 7 or PSA 10–20 ng/ml; high, T3a or Gleason score 8–10 or PSA > 20 ng/ml. We classified patients with T3b–T4 clinical stage as a high-risk group in this study. Table 1 describes patient characteristics.

Table 1 Patient characteristics

Characteristic	$n = 241$
Age (years)	69 (49–81)
PSA level (ng/ml)	
<10	79 (32.8 %)
10–20	65 (27.0 %)
>20	97 (40.2 %)
Median	15.17
Range	1.40–502.00
Gleason score	
2–6	47 (19.5 %)
7	97 (40.2 %)
8–10	97 (40.2 %)
Tumor stage	
T1–T2a	73 (30.3 %)
T2b–T2c	36 (14.9 %)
T3a	97 (40.2 %)
T3b–T4	35 (14.6 %)
Risk group	
Low	17 (7.0 %)
Intermediate	53 (22.0 %)
High	171 (71.0 %)

Age data are presented as median values

Hormonal therapy

All patients were given neoadjuvant androgen deprivation therapy (N-ADT). A combination of a luteinizing hormone releasing hormone (LHRH) analogue and anti-androgen treatment (i.e., maximum androgen blockade) was performed as N-ADT. N-ADT time depended on the IMRT reservation in principle, and the median time of N-ADT was 9 months (range 2–68 months). Adjuvant ADT (A-ADT) consisted of only the LHRH analogue. Patients were given A-ADT for 1–2 years at the discretion of the urologists. Eight patients (3.3 %) did not receive A-ADT because they experienced adverse effects associated with N-ADT such as liver dysfunction, and 29 patients (12.0 %) continue to receive A-ADT at the time of this analysis. The median time of A-ADT in another patient was 20 months (range 1–37 months).

IMRT treatment

All patients were immobilized in a supine position with the Esform vacuum type immobilization system (Engineering System, Matsumoto, Japan) and simulated by pelvic computed tomography (CT) with a 2.5-mm slice thickness. On the day of CT simulation and during IMRT, all patients defecated where possible every morning and discharged urine about one hour before CT simulation and IMRT to minimize daily variations in the shape and anatomical location of the prostate. Outlines of the target were delineated on a 3-dimensional radiation treatment planning system (Pinnacle3 workstation, Hitachi Medical Corporation, Tokyo, Japan) using the abdominal CT window setting. Clinical target volume (CTV) was defined as the entire prostate and proximal seminal vesicle. In the case of seminal vesicle invasion, CTV included the entire seminal vesicle. Planning target volume 1 (PTV1) included CTV with a 6–8 mm margin except at the prostatorectal interface, where a 4–6 mm margin was used. PTV2 was defined as the seminal vesicle with a similar margin as PTV1 outside of PTV1. Normal structures including the rectum, bladder, femoral head, penile bulb, pubic bone, bowel, and sigmoid colon adjacent to PTV were considered to be OAR. The rectum was delineated only around PTV1 with 10 mm on the cranio-caudal direction. CT images and structure sets were transferred to the Tomotherapy Hi-Art System workstation (TomoTherapy Inc., Madison, WI, USA). Normal structures were constrained on an individual basis using maximum and dose–volume histogram (DVH) dose constraints without compromising PTV1 coverage.

The dose constraints required to achieve an acceptable HT plan in our institution were as follows: (1) PTV1 D95 (i.e., dose delivered to 95 % of PTV1): 74 Gy in the low-risk group, 78 Gy in intermediate and high-risk groups, maximum dose < 107 % of the prescribed dose, minimum dose > 90 % of the prescribed dose; (2) PTV2 D95: 64 Gy, minimum dose > 90 % of the prescribed dose; (3) rectum: the percentage of the entire rectum covered by at least 70 Gy (V70) < 15 %, V60 < 25 %, and V40 < 45 %; (4) bladder: the percentage of the entire bladder covered by at least 60 Gy (V60) < 25 % and V40 < 50 %; (5) femoral head: maximum dose < 40 Gy; (6) bowel, sigmoid colon: the volume covered by 55 Gy < 0.5 cc; (7) penile bulb: mean dose < 52.5 Gy; and (8) pubic bone: V70 < 20 %.

In tomotherapy treatment conditions, a 2.5-cm field width was used in all patients. Other common parameters were a pitch of 0.430 and a normal modulation factor of 2.0. The inverse planning system performed a variable number of iterations, which ranged from 100 to 300, during the optimization process for each plan. All patients began treatment with daily MVCT acquisitions for setup, registration, and repositioning on the basis of the location of the prostate. Patients inserted a tube or were encouraged to defecate when their rectums were dilated on MVCT and were checked on MVCT again.

Follow-up

Follow-up evaluations after treatment were performed at intervals of 3 months. Serum PSA was measured at each follow-up. The length of follow-up was calculated from the start date of IMRT. Biochemical disease-free survival (bDFS) followed the Phoenix definition (i.e., a post-treatment nadir plus 2.0 ng/ml Roach et al. 2006). A clinical relapse comprised local disease, and lymph node, bone, or parenchymal metastases detected by CT scan and/or bone scintigraphy. Patients began ADT again after documentation of biochemical relapse. Distributions of bDFS, disease-free survival (DFS), and overall survival were calculated according to the Kaplan–Meier method. The Student's t test was used in the analysis of prognostic factors for biochemical control. A p value of <0.05 was considered significant. Toxicity was scored according to the Radiation Therapy Oncology Group morbidity grading scale (Cox et al. 1995). In brief, Grade 1 toxicity represents minimal side effects not requiring medication for symptom control, Grade 2 toxicity indicates symptoms requiring medication, Grade 3 indicates complications requiring minor surgical intervention (i.e., transurethral resection, laser coagulation, or blood transfusion), and Grade 4 requires hospitalization and major intervention. The time to develop late toxicity was the interval from the start date of IMRT.

Results

The prescribed dose was slightly reduced to 74 or 70 Gy in 16 patients (6.6 %) because of their antithrombogenic medications (6 patients), failure in OAR dose constraints (4 patients, especially in those whose bowel or sigmoid colon invaginated into the surrounding area of PTV1), patients' request or physicians' suggestion for their acute rectal symptoms (3 patients), financial reasons (one patient), and unspecified in 2 patients. The median IMRT period was 57 days (range 51–95 days). The median follow-up time from the start date of IMRT was 35 months (range 13–66 months).

Acute toxicity

Table 2 shows the incidence of acute gastro-intestinal (GI) and genitor-urinary (GU) toxicities treated with IMRT with HT. Of 27 patients (11.2 %) who developed acute Grade 2 rectal toxicity requiring medication such as suppositories, the main symptoms were pain on defecation in 17 patients (7.1 %) and rectal bleeding with bowel movements in 10 patients (4.1 %), respectively. Of 59 patients (24.5 %) who developed acute Grade 2 urinary toxicity, most symptoms (55, 22.7 %) were dysuria such as urinary frequency, and other symptoms were gross hematuria in 3 patients (1.2 %) and pain with urination in 2 patients (0.8 %). No patients experienced acute Grade 3 or higher acute symptoms.

Late toxicity

The incidence of late GI and GU toxicities is also shown in Table 2. Of 16 patients (6.6 %) who developed late Grade 2 rectal toxicity, 13 patients (5.4 %) developed Grade 2 rectal bleeding at a median of 18 months (range 10–39 months) after the start date of IMRT. Other symptoms were pain on defecation in 2 patients (0.8 %) after 9 and 11 months and subtle fecal incontinence in one patient (0.4 %) after 9 months. Two patients (0.8 %) developed Grade 3 rectal bleeding requiring laser coagulation at 11

Table 2 Incidence of acute and late Grade 2 or higher gastro-intestinal (GI) and genitor-urinary (GU) toxicity among patients treated with intensity-modulated radiation therapy (IMRT) with helical tomotherapy ($n = 241$)

	Acute toxicity		Late toxicity	
	GI	GU	GI	GU
Grade 2	27 (11.2 %)	59 (24.5 %)	16 (6.6 %)	20 (8.3 %)
Grade 3	0 (0 %)	0 (0 %)	2 (0.8 %)	3 (1.2 %)
Grade 4	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Total	27 (11.2 %)	59 (24.5 %)	18 (7.4 %)	23 (9.5 %)

Table 3 Patient characteristics with or without biochemical relapse after intensity-modulated radiation therapy (IMRT) with helical tomotherapy

Characteristic	Biochemical relapse group ($n = 6$)	Biochemical control group ($n = 169$)	p value
Age (years)	65 (51–77)	69 (49–81)	0.041
PSA level (ng/ml)	38.26 (24.88–153.00)	15.17 (1.40–502.00)	0.057
Gleason score	9 (8–10)	7 (5–10)	0.0030
Tumor stage			0.00022
T1–T2c	0 (0 %)	82 (50.3 %)	
T3a	2 (33.3 %)	63 (38.7 %)	
T3b–T4	4 (66.7 %)	18 (11.0 %)	
Risk group			0.13
Low	0 (0 %)	14 (8.2 %)	
Intermediate	0 (0 %)	39 (23.0 %)	
High	6 (100 %)	113 (68.8 %)	

and 12 months after the start date of IMRT. No Grade 4 late rectal complications have been observed. Of 20 patients (8.3 %) who developed late Grade 2 urinary toxicity, 16 patients (6.6 %) experienced dysuria requiring medication at a median of 19 months (range 7–47 months) after the start date of IMRT. Other symptoms were gross hematuria in 2 patients (0.8 %) and cystitis in 2 patients (0.8 %). Two patients (0.8 %) experienced Grade 3 urinary retention requiring self-catheterization or dilation at 14 and 17 months after the start date of IMRT. One patient developed a bladder ulcer (Grade 3) requiring laser coagulation after 14 months. No patients experienced late Grade 4 urinary symptoms.

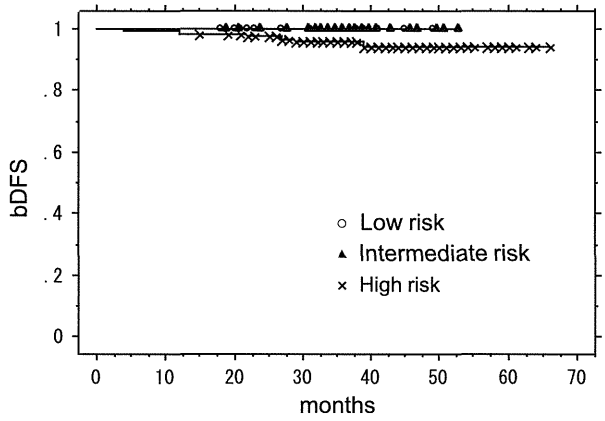

Fig. 1 The 3-year biochemical disease-free survival (bDFS) for low, intermediate, and high-risk group patients

Biochemical control, clinical relapse, and overall survival

Biochemical control was estimated in only 175 patients followed for at least 6 months after the completion of A-ADT. Six patients in the high-risk group developed biochemical relapse at a median of 25 months (range 4–39) after the start date of IMRT. No patients in low and intermediate risk groups experienced biochemical relapse. Table 3 shows each patient's characteristics with or without biochemical relapse. Age, Gleason score, and T-stage were significant factors of biochemical relapse in patient characteristics ($p = 0.041$, 0.0030, and 0.00022, respectively). PSA in the biochemical relapse group seemed to be higher than those in the biochemical control group, but PSA and the risk group had no significant impact on the biochemical control.

The 3-year bDFS rate was 96.9 % (95 % confidence interval (CI): 94.2–99.6 %) in all groups. The 3-year bDFS rates for low, intermediate, and high-risk group patients were 100, 100, and 95.8 % (CI: 92.1–99.5 %), respectively. The bDFS for each risk group are shown in Fig. 1. We observed clinical relapse in two patients in the high-risk group, resulting in a 3-year clinical DFS of 99.4 % (CI: 98.2–100 %). One patient developed bone metastasis of the humerus after 4 months, and the other patient developed pelvic node metastases after 39 months. Each patient received ADT after clinical relapse. No patient died at the time of analysis, resulting in a 3-year OS of 100 %.

Discussion

We could not find a published report for Japanese outcomes of prostate cancer treated with IMRT in a PubMed search, although there were many reports of permanent brachytherapy. Therefore, to our knowledge, this data may be the first report to compile IMRT-treated patients in Japan and demonstrate the feasibility of high-dose radiotherapy with HT for patients with localized prostate cancer. Localized prostate cancer patients, especially those in the low-risk group, usually have some radical treatment choices such as radical prostatectomy, IMRT, brachytherapy, particle therapy, and recently implemented robotic surgery. This report provided outcomes and toxicities for localized

prostate cancer after IMRT with IGRT (i.e., HT) combined with ADT in one of the Japanese cancer centers, and this could be the basis of comparison with other treatments and will be of assistance for patients and physicians associated with prostate cancer at the time for treatment choice.

Most patients could receive the prescribed total doses, but they were slightly reduced in 16 patients (6.6 %). To our knowledge, the impact of antithrombogenic medication on GI toxicity is still uncertain. The total doses of some patients who took this medication were reduced based on each physician's clinical decision. We will estimate the impact of the antithrombogenic medication on toxicity circumstantially in the near future. Some patients received a reduced total dose because of their acute rectal symptoms. Zelefsky et al. (2008) recently reported that the presence of acute GI and GU symptoms during treatment conferred a fivefold and threefold increased risk of late GI and GU toxicities, respectively, in 1,571 patients with prostate cancer who had a long follow-up after receiving 3-dimensional conformal radiotherapy (3DCRT) or IMRT. Therefore, we think that these patients would have developed severe late GI toxicity if they had received the prescribed total dose. We will also estimate the relationship between acute and late toxicity for patients treated with HT. We reduced the total dose for some patients due to failure in OAR dose constraints, especially in patients whose bowel or sigmoid colon invaginated into the surrounding area of PTV1. We think that these patients should choose other treatments such as surgery if possible.

We observed a satisfactory low rate in acute GI and GU toxicity, and the Grade 2 rates of acute GI and GU toxicity were 11.2 and 24.5 %, respectively. Among patients who developed acute Grade 2 rectal toxicity, the main symptoms were pain on defecation. We think from our clinical experience that these symptoms were not so much due to the doses exposed to the rectum, but rather too much effort from each patient's to empty their bowels because they had inserted a tube or were encouraged to defecate when their rectums were dilated on MVCT. On the other hand, we observed a satisfactory low rate in late GI and GU toxicity, and the rates of late Grade 2 or higher GI and GU toxicity were only 7.4 and 9.5 %, respectively. Data indicate that late rectal toxicity profiles are excellent compared to the incidence of late Grade 2 or higher GU and GI toxicity that reportedly ranged from 24 to 35 % and from 15 to 29 %, respectively, in recent studies with the use of IMRT (Vora et al. 2007; Wong et al. 2009; Sharma et al. 2011). We think that our favorable toxicity rates came partly as a result of IGRT with HT. The significance of IGRT is established in EBRT for localized prostate cancer (http://www.nccn.org/). However, IGRT was conducted at only approximately 60 % of facilities in a recent Japanese national survey on the current status of EBRT for prostate cancer (Nakamura et al. 2012). Another may be the relatively tight margin used between CTV and PTV. Enmark et al. (2006) demonstrated that a margin of 4 mm in all directions was adequate to account for uncertainties including inter- and intra-fraction motions. In a recent report (Crehange et al. 2012), 165 men were treated with daily IMRT with IGRT using a 3D ultrasound-based system and stratified regarding CTV to PTV margin: group A, 5 mm or group B, 10 mm. Their data indicated that the margin had no impact on short-term bDFS in control of IGRT. We also confirmed favorable short-term bDFS in the current report. However, long-term follow-up is required to evaluate the clinical significance of the tight margin with IGRT.

Our preliminary results suggest excellent short-term biochemical out-comes for all risk group patients when treated with HT combined with relatively long-term ADT. Of course, longer follow-up will be necessary to determine whether HT results in an incremental favorable outcome in tumor control. Actually, in our clinical experience of 3DCRT (Tomita et al. 2009), patients develop biochemical relapse 4–5 years after the start date of RT when combined with long-term (>2 years) ADT. All patients who developed biochemical relapse were in the high-risk group in this cohort, and age, Gleason score, and T-stage were significant factors of biochemical relapse in patient characteristics. Ogawa et al. (2011) surveyed the pattern of care study (PCS) for radical EBRT for clinically localized prostate cancer in Japan. They reported that the number of patients in the high-risk group consisted of more than 60 % of the 2003–2005 survey, although the number of patients in the high-risk group decreased gradually. The current study cohort was similar to that of PCS. There is room for consideration of the treatment strategy for high-risk prostate cancer patients in Japan.

In conclusion, this preliminary report confirms the feasibility of HT in a large number of localized prostate cancer patients. We observed that HT is associated with low rates of acute and late toxicities, and HT in combination with relatively long-term ADT results in excellent short-term bDFS. Superior dose distributions and IGRT with HT are better options not only for high-dose EBRT, but also for all treatment choices of localized prostate cancer.

Conflict of interest We declare that we have no conflict of interest.

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Treatment outcomes of definitive chemoradiotherapy for patients with hypopharyngeal cancer

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We analyzed the efficacy of definitive chemoradiotherapy (CRT) for patients with hypopharyngeal cancer (HPC). Subjects comprised 97 patients who were treated with definitive CRT from 1990 to 2006. Sixty-one patients (62.9%) with resectable disease who aimed to preserve the larynx received induction chemotherapy (ICT), whereas 36 patients (37.1%) with resectable disease who refused an operation or who had unresectable disease received primary alternating CRT or concurrent CRT (non-ICT). The median dose to the primary lesion was 66 Gy. The median follow-up time was 77 months. The 5-year rates of overall survival (OS), progression-free survival (PFS), local control (LC), and laryngeal preservation were 68.7%, 57.5%, 79.1%, and 70.3%, respectively. The T-stage was a significant prognostic factor in terms of OS, PFS and LC in both univariate and multivariate analyses. The 5-year rates of PFS were 45.4% for the ICT group and 81.9% for the non-ICT group. The difference between these groups was significant with univariate analysis ($P = 0.006$). Acute toxicity of Grade 3 to 4 was observed in 34 patients (35.1%). Grade 3 dysphagia occurred in 20 patients (20.6%). Twenty-nine (29.8%) of 44 patients with second primary cancer had esophageal cancer. Seventeen of 29 patients had manageable superficial esophageal cancer. The clinical efficacy of definitive CRT for HPC is thought to be promising in terms of not only organ preservation but also disease control. Second primary cancer may have a clinical impact on the outcome for HPC patients, and special care should be taken when screening at follow-up.

Keywords: hypopharyngeal cancer; chemoradiotherapy; survival; laryngeal preservation; local control

INTRODUCTION

Hypopharyngeal cancer (HPC) is usually diagnosed at an advanced stage and treated using multidisciplinary modalities. Chemoradiotherapy (CRT) is currently considered the standard treatment for unresectable head and neck cancer. It is also thought to be a treatment option for patients with resectable locally advanced lesions. Therefore, the number of patients treated with CRT, especially for organ preservation, is increasing. Several types of chemotherapy regimens have been reported to have positive outcomes, and concurrent CRT (CCRT) has become a standard treatment for patients with the aim of preserving the larynx [1, 2]. However, CCRT is reported to be accompanied by markedly increased toxicity compared to radiation alone, and patients who receive CCRT followed by salvage surgery sometimes have serious and intractable complications [3].

Induction chemotherapy (ICT) is often used in clinical practice for patients with advanced HPC and plays a considerable role in organ preservation and reduction of distant metastases [4]. To reduce treatment toxicities and avoid the risk of salvage surgery, we used ICT for patients with resectable tumors with the aim of optimally selecting candidates for larynx preservation.

CCRT regimens with cisplatin (CDDP) and 5-fluorouracil (5-FU) have been used in patients with advanced head and neck cancer. However, severe acute mucositis has been reported with these regimens [2]. For patients treated with