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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 gastro-intestinal (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 mega-voltage 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.

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

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

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.

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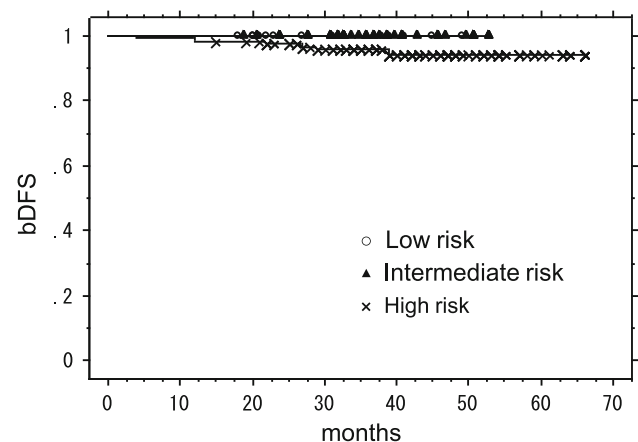
Fig. 1 The 3-year biochemical disease-free survival (bDFS) for low, intermediate, and high-risk group patients

(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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