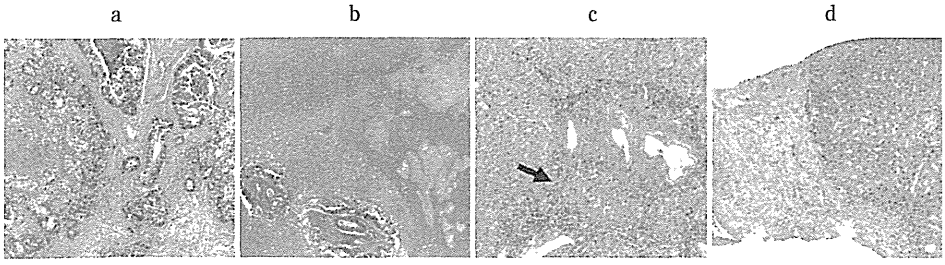

図3　病理所見
a: 腫瘍部。楕円形の核をもつ異形細胞が不整な管腔構造を形成し，直腸癌肝転移として矛盾のない腺癌の所見。
b: 腫瘍壊死部。照射部に腫瘍の壊死部が確認された。
c: 照射部背景肝。門脈域の線維性拡大と架橋形成（矢印）がみられ新犬山分類 f3 相当の線維化が認められた。
d: 非照射部背景肝。線維化は認められず，f0 の所見。

渋し，また出血も来しやすかった（図2b）。術後は合併症なく経過は良好であった。

病理所見: 主腫瘍は転移性肝癌であった（図3a）。主腫瘍周囲の粒子線照射部は腫瘍の壊死巣がみられ，治療効果のあった部分と考えられた（図3b）。また，粒子線照射部の背景肝には架橋形成を伴う新犬山分類 f3 相当の線維化がみられた。非照射部の肝生検は f0 であり，この線維化は粒子線照射の影響であると推測された（図3c, d）。

Ⅱ．考　察

HCC に関して，粒子線治療は高い局所制御率が得られたとの報告も多く[1,2]，肝切除困難例に対する効果的な治療法といえる。一方，転移性肝癌に関しては，原発癌の種類にもよるが一般に放射性感受性が低いため[3]，奏効率は HCC より低いとされている。肝腫瘍に対する通常の放射線治療において，放射線肝障害が合併症としてあげられ，剖検例においてではあるが照射部に強い肝の線維化が生じたとの報告[4]もある。粒子線治療は，bragg peak といわれる体内深部で線量がピークに達する特性を利用することで高い抗腫瘍効果を得つつ副作用を軽減できる治療であり，一般的な放射線治療と比較し肝障害は少ないとされているが[5,6]，その影響の詳細に関しては明らかでない。われわれが検索し得る範囲で粒子線治療後の外科切除の報告はほとんどないが，本症例では手術所見において照射部の癒着や肝の硬化はみられ，病理所見においても背景肝の線維化が確認された。照射目標となる腫瘍部以外への影響が比較的少ないとされる粒子線療法においても，照射野内での肝実質障害は無視できないものであることが示唆された。

おわりに

粒子線照射部位における再発肝腫瘍に対するサルベージ手術は，施行可能であるものの高難度の手術となった。粒子線照射部位は周囲との癒着だけでなく，照射野内の肝実質にも線維化がみられ，切除に伴う合併症のリスクが上がると予想される。低侵襲，高い奏効率などのメリットから局所治療の第一選択肢として粒子線治療が選ばれる症例は増えてくると思われるが，その治療効果が不十分である症例もあり，再発時の治療選択が限定される可能性もある。サルベージ手術前の切除可否の評価はもちろんながら，粒子線治療選択時にも特に慎重な適応の検討が必要である。

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FULL PAPER

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Keywords: prostate cancer; carbon ion radiotherapy; phase I/II clinical trial; radiotherapy

Phase I/II trial of definitive carbon ion radiotherapy for prostate cancer: evaluation of shortening of treatment period to 3 weeks

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Background: The purpose of this study was to evaluate the feasibility of a new shortened 3-week treatment schedule of carbon ion radiotherapy (CIRT) for prostate cancer.

Methods: Beginning in May 2010, patients with T1b–T3bN0M0, histologically proven prostate adenocarcinoma were enrolled in the phase II trial of CIRT. Patients received 51.6 GyE in 12 fractions over 3 weeks (protocol 1002). The primary end point was defined as the incidence of late adverse events that were evaluated based on the Common Terminology Criteria for Adverse Events version 4.0. Biochemical failure was determined using the Phoenix definition (nadir $+2.0\,ng\,ml^{-1}$).

Results: Forty-six patients were enrolled, and all patients were included in the analysis. The number of low-, intermediate-, and high-risk patients was 12 (26%), 9 (20%), and 25 (54%), respectively. The median follow-up period of surviving patients was 32.3 months. Two patients had intercurrent death without recurrence, and the remaining 44 patients were alive at the time of this analysis. In the analysis of late toxicities, grade 1 (G1) rectal haemorrhage was observed in 3 (7%) patients. The incidence of G1 haematuria was observed in 6 (13%) patients, and G1 urinary frequency was observed in 17 (37%) patients. No $\geqslant$G2 late toxicities were observed. In the analysis of acute toxicities, 2 (4%) patients showed G2 urinary frequency, and no other G2 acute toxicities were observed.

Conclusions: The new shortened CIRT schedule over 3 weeks was considered as feasible. The analysis of long-term outcome is warranted.

The morbidity in prostate cancer is the second highest in the world, and the mortality in prostate cancer is the fifth highest in the world (Ferlay *et al*, 2012). There are many treatment modalities for prostate cancer including radical prostatectomy (Roehl *et al*, 2004), laparoscopic surgery (Touijer *et al*, 2009), three-dimensional (3D)-conformal radiotherapy (CRT) by photons (Zelefsky *et al*, 2008), intensity-modulated radiotherapy (IMRT) (Cahlon *et al* 2008), low-dose rate (LDR) brachytherapy (Peinemann *et al*, 2011), high-dose rate brachytherapy (Masson *et al*, 2012), proton beam therapy (Zietman *et al*, 2010), carbon ion radiotherapy (CIRT) (Ishikawa *et al*, 2006), hormone therapy (Souhami *et al*, 2009), and robot-assisted laparoscopic prostatectomy (Menon *et al*, 2010). A high dose of 78–80 Gy is generally used in 3D-CRT or IMRT for prostate cancer, and definitive radiotherapy using photons or proton beam requires ~8 weeks (Zelefsky *et al*, 2008; Cahlon *et al* 2008; Zietman *et al*, 2010). This treatment duration appears to be one of the disadvantages for patients, and *some* patients choose radical prostatectomy or LDR brachytherapy because of the

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treatment duration. Although treatment duration for radiotherapy tends to increase with the increase in the total irradiation dose, because of the biological characteristics of photons and proton beams, it is not easy to shorten the treatment duration by increasing the dose/fraction (Furusawa *et al*, 2000). Recent studies have reported stereotactic radiotherapy (SRT) for prostate cancer using 35–50 Gy/5 fractions (Boike *et al*, 2011; King *et al*, 2013). However, the efficacy and the safety (in higher dose) have not yet been established.

Carbon ion radiotherapy for prostate cancer has been in use since 1995, and an initial clinical trial was initiated using a schedule of 20 fractions over 5 weeks (Akakura *et al*, 2004). The clinical trial of CIRT for prostate cancer was initiated with a shorter duration than that typically used with photons. The efficacy and the feasibility were established with that schedule (Tsuji *et al*, 2005; Ishikawa *et al*, 2006). A new treatment schedule of 16 fractions over 4 weeks was initiated in 2003. This treatment schedule has also shown favourable outcomes and feasibility despite approximately half the duration compared with that of radiotherapy by photons (Okada *et al*, 2012). The possibility of shortening the treatment duration is one of the advantages of CIRT; however, it is also one of the challenges of CIRT (Tsujii *et al*, 2004). The purpose of this study (protocol 1002) was to evaluate the feasibility of a clinical trial using a new shortened treatment schedule of 12 fractions over 3 weeks.

MATERIALS AND METHODS

The primary end point was defined as the incidence of late adverse events. Late adverse events were defined as adverse events occurring in more than 6 months after the start of radiotherapy. Adverse events were evaluated based on the Common Terminology Criteria for Adverse Events version 4.0 (National Cancer Institute, 2009). The secondary end points were (1) biochemical failure-free survival, (2) overall/cause-specific survival, and (3) quality of life. Biochemical failure was determined using the Phoenix definition (nadir $+2.0\,\mathrm{ng\,ml^{-1}}$) (Roach *et al*, 2006). Biochemical failure-free survival, cause-specific survival, and overall survival were calculated from the day CIRT was started. Risk categories of prostate cancer were defined as follows: low-risk group, initial prostate-specific antigen (PSA) $<20\,\mathrm{ng\,ml^{-1}}$ and T1b–T2bN0M0 and Gleason score $\leqslant 6$; intermediate-risk group, initial PSA $<20\,\mathrm{ng\,ml^{-1}}$ and/or T2cN0M0 and/or Gleason score $=7$; and high-risk group, initial PSA $\geqslant 20\,\mathrm{ng\,ml^{-1}}$ or T3a/3bN0M0 or Gleason score $\geqslant 8$. The T stage was determined based on TNM classification 7th edition (Sobin *et al*, 2009). Clinical stage was determined by digital rectal examination, magnetic resonance imaging, computed tomography, bone scintigraphy, and other diagnostic images. Adverse effects were evaluated by interview of symptoms from patients, urine analysis, stool analysis, cystoscopy, and colonoscopy.

Inclusion and exclusion criteria. Patients who met all the following conditions were included: histologically diagnosed prostate adenocarcinoma, without any previous surgery or radiotherapy for prostate cancer, and T1bN0M0 to T3bN0M0. In addition, the following patients were included in this trial (excluded from another CIRT trial 9904): (1) low-risk patients who underwent hormonal therapy, (2) intermediate/high-risk patients who refused hormonal therapy, and (3) intermediate/high-risk patients who received longer than 6 months of hormonal therapy. Exclusion criteria included the following: (1) having a history of pelvic irradiation; (2) having prognosis for survival of $<$ 6 months; (3) performance status of 3 or 4; (4) receiving other treatments for prostate cancer, with the exception of hormonal therapy; (5) having uncontrolled malignancy(ies) other than prostate cancer; (6) having uncontrolled infectious disease near the irradiation area; (7) medical/psychological/other reasons; and (8) showing PSA elevation during prior hormonal therapy. Patients who met the above inclusion criteria and who had provided informed consent were enrolled in the trial. All enrolled patients were examined before CIRT by the institutional review board including external committee members. The target number of patients was 45 and the registration period was 2 years. Once the target number of patients was reached, the clinical trial was closed. Analysis of the primary end point was performed at least 2 years after registration of the last patient. After CIRT, all patients are followed by measuring serum PSA level every 3 months.

Carbon ion radiotherapy. Clinical target volume (CTV) was defined as the whole prostate and proximal one third of seminal vesicles (gross tumour volume was not contoured). However, all seminal vesicles were included in the CTV in T3b cases. Planning target volume (PTV) was defined as the CTV with 10 mm margins in the anterior and lateral directions, and with 5 mm margins in the superior, inferior, and posterior directions. The prophylactic area (pelvic lymph nodes) was not included in the PTV. Rectum was delineated as organ at risk from 10 mm above the upper margin of the PTV to 10 mm below the lower margin of the PTV. The prescribed dose was 51.2 GyE/12 fr., and $>95\%$ of the prescription dose were planned to be irradiated to the CTV. The recommended (not restricted) dose constraints for rectum are V53GyE (rectal volume to be irradiated 53 GyE) $\leqslant 0\%$, V50GyE $\leqslant 7\%$, and V40GyE $\leqslant 16\%$.Other dose constraints were not defined. The two-fields technique (opposing lateral fields) was routinely used for the CIRT planning. Compensators were individually made for each port, and irradiation fields were shaped using multi-leaf collimators. Purgatives or enema was used so that patients have bowel movements at least once a day. All patients were treated with a resinous shell and an image-guided irradiation system under shallow natural breathing, and irradiation was performed 4 days per week. The total irradiation dose was calculated on the basis of the past irradiation schedules. The past protocols of CIRT (63.0 GyE in 20 fractions in protocol 9904[2] and 57.6 GyE in 16 fractions in protocol 9904[3]) showed favourable outcomes with limited toxicity; the total dose of this clinical trial was estimated to be equivalent to the biological effect observed in the past protocols (Okada *et al*, 2012). Assuming the alpha–beta ratio of prostate cancer is 1.5–3.0 (Akimoto *et al*, 2005; Fowler, 2005; Khoo, 2005; Pollack *et al*, 2006), biologically effective dose when $\alpha/\beta = 1.5$ ($BED_{1.5}$) of 63.0 GyE/20 fr. was calculated as 195.3, $BED_{1.5}$ of 57.6 GyE/16 fr. was 195.8, and $BED_{3.0}$ of 63.0 GyE/20 fr. was 129.2, and biologically effective dose when $\alpha/\beta = 3.0$ ($BED_{3.0}$) of 57.6 GyE/16 fr. was 126.7. Similarly, $BED_{1.5}$ and $BED_{3.0}$ of 51.6 GyE/12 fr. were calculated as 199.5 and 125.6, respectively.

Statistical analysis. Time to event was calculated from the first day of CIRT to the date of the event. The follow-up period was calculated from the first date of CIRT to the date of last follow-up. The Kaplan–Meier method was used for survival analyses.

RESULTS

The phase I/II clinical trial of CIRT in 12 fractions for prostate cancer (protocol 1002) was approved by the research ethics review board of our institution on May 2010, and then the clinical trial was open for enrollment. Although the scheduled registration period was 2 years, registration was closed on October 2011 because the number of patients reached 46. Between May 2010 and October 2011, 282 prostate cancer patients were enrolled in CIRT protocols. Of the 282 patients, 197 patients were eligible for the protocol 9904(3) phase II clinical trial. In all, 46 of 85 patients who did not meet the eligibility criteria for protocol 9904(3), but wished

to participate in clinical trial (protocol 1002) were enrolled in this clinical trial. The remaining 39 patients who did not meet the eligibility criteria for protocol 9904(3) and who did not wish to participate in the protocol 1002 trial were treated in the protocol 0507 G trial with the same dose fractionation as 9904(3) (Figure 1).

The characteristics of 46 patients are shown in Table 1. According to the risk classification, patients with T1c–T2b, T2c, and T3a/b were 25, 6, and 15, respectively. The number of patients with initial PSA $<20\,ng\,ml^{-1}$ and $\geqslant 20\,ng\,ml^{-1}$ were 34 and 12, respectively. The number of patients with Gleason score $\leqslant 6$, $=7$, and $\geqslant 8$ was 12, 15, and 19, respectively. Finally, 12 patients (26%) were classified as low risk, 9 patients (20%) were classified as intermediate risk, and 25 (54%) patients were classified as high risk. Forty-five patients underwent hormonal therapy, and one of the forty-five patients underwent castration due to liver function failure after LH-RH analogue injection. One patient who was intermediate risk did not undergo hormonal therapy because he refused hormonal therapy.

All 46 enrolled patients completed the scheduled irradiation. The median overall treatment time (OTT) of CIRT was 20 days (range, 16–21 days), and there were no treatment interruptions or treatment delays. The median follow-up period of surviving patients from the start of CIRT was 32.3 months (range, 23.5–38.9 months), and the median follow-up period of surviving patients from the start of treatment including hormonal therapy was 40.0 months. Two deaths were observed during the follow-up period. There were no deaths due to disease and no treatment-related deaths. The two deaths were due to intercurrent disease. One of the intercurrent deaths was in a 64-year-old patient who had hypertension, hyperlipidaemia, diabetes mellitus, hyperuricemia, cardiovascular disease, and an abdominal aortic aneurysm (AAA). This patient suddenly died from AAA rupture 4 months after CIRT without elevation of PSA. No relationships were found among CIRT, hormonal therapy, and the death; therefore, this case was determined to be intercurrent death without recurrence. A 78-year-old patient who had been diagnosed with interstitial pneumonitis (IP) before treatment for prostate cancer also died. Although IP was stable during the treatment for prostate cancer, the patient died from exacerbation of IP and pneumothorax 24 months after the start of hormonal therapy and 17 months after CIRT, without elevation of PSA. No relationships were found between hormonal therapy, CIRT, and exacerbation of IP; therefore, this case was also determined as intercurrent death without recurrence.

The acute and late toxicities observed with CIRT are shown in Table 2. The most frequent acute toxicity, grade 1 (G1) urinary frequency was observed in 34 out of 46 (74%) cases. Grade 2 (G2) urinary frequency was observed in 2 out of 46 (4%) cases. One of the patients with G2 urinary frequency had been diagnosed with benign prostatic hypertrophy before being diagnosed with prostate cancer, and the patient had pollakiuria before CIRT. The urine sample of the other patient tested positive for bacteria; therefore, G2 urinary frequency was considered to be due to CIRT and a complication of urinary infection. No $\geqslant$G2 toxicities were observed. The most frequent late toxicity observed was G1 urinary frequency in 17 out of 46 (37%) cases. The second most frequent late toxicity was G1 haematuria observed in 6 out of 46 (13%) cases. The median time to occurrence of G1 haematuria was 20.7 months (range, 3.5–34.4 months). Grade 1 rectal haemorrhage was observed in 3 (7%) patients and G1 proctitis was observed in

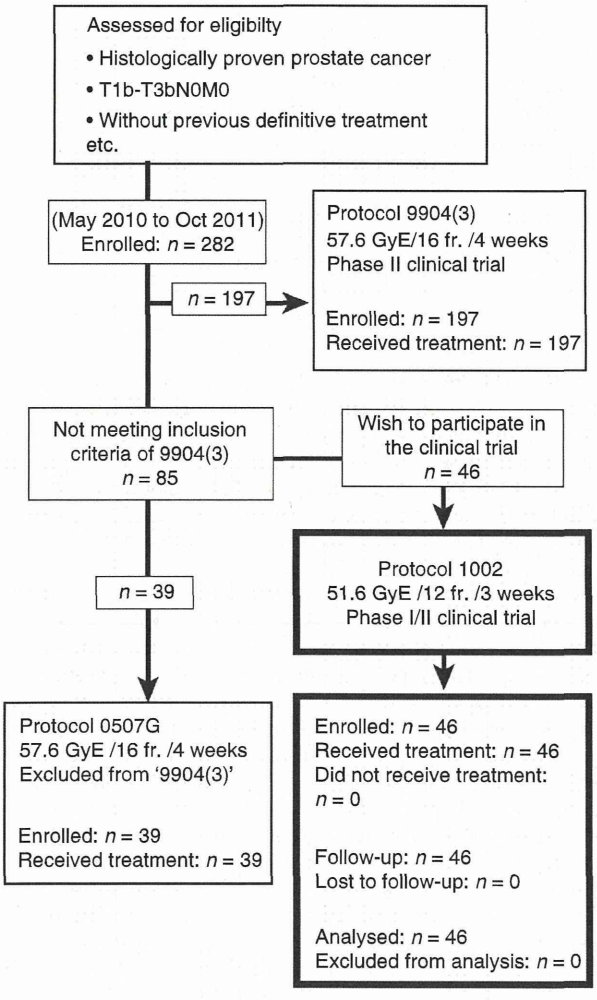

Figure 1. Chart of the trial. The patients who did not meet the inclusion criteria of 9904(3) (CIRT over 4 weeks) and who wished to participate were enrolled in the study (1002).

Table 1. The characteristics of 46 patients

Enrolled patients		46
Gender	Male	46 (100%)
Age (years)	Median	66 (range 54–83)
Stage (UICC2009)	T1c 17 T2a 5, T2b 3, T2c 6 T3a 13, T3b 2	T1 17 (37%) T2 14 (30%) T3 15 (33%)
Initial PSA ($ng\,ml^{-1}$)	Median	11.1 (range 3.559–242.7)
Gleason score	3+3=6 3+4=7 4+3=7 4+4=8 4+5=9	12 (26%) 6 (13%) 9 (20%) 8 (17%) 11 (24%)
Risk	Low Intermediate High	12 (26%) 9 (20%) 25 (54%)
ADT	With ADT Castration Without ADT	45 (98%) (1) (2%) 1 (denied) (2%)
Median (range) duration of ADT by risk (months)	Low risk Intermediate risk High risk	7.7 (5.5–25.2) 10.0 (7.3–28.3) 26.7 (9.7–52.9)[a]

Abbreviations: ADT = androgen deprivation therapy; PSA = prostate-specific antigen.
[a]One patient who underwent castration was excluded (duration of ADT: 3.5 months).

Table 2. Follow-up data and toxicity

Follow-up period of surviving patients	Median (months) (range)	32.3 (23.5–38.9)
Survival	Alive	44 (96%)
	Dead	2 (4%)
Cause of death	Intercurrent death	2 (100%)
	Death from primary disease	0 (0%)
	Treatment-related death	0 (0%)

	Grade			
Toxicity	**G0**	**G1**	**G2**	**Total**
Acute				
Skin (radiation dermatitis)	44 (96%)	2 (4%)	0 (0%)	46
Rectum (haemorrhage)	46 (100%)	0 (0%)	0 (0%)	46
GU (urinary frequency)	10 (22%)	34 (74%)	2 (4%)	46
Acute toxicity by risk				
Low	1 (2%)	11 (24%)	0 (0%)	12
Intermediate	1 (2%)	6 (13%)	2 (4%)	9
High	7 (15%)	18 (39%)	0 (0%)	25
Late				
Skin (radiation dermatitis)	46 (100%)	0 (0%)	0 (0%)	46
Rectum (haemorrhage)	43 (94%)	3 (7%)	0 (0%)	46
Rectum (proctitis)	45 (98%)	1 (2%)	0 (0%)	46
GU (haematuria)	40 (87%)	6 (13%)	0 (0%)	46
GU (urinary frequency)	29 (63%)	17 (37%)	0 (0%)	46
GU (urinary stricture)	46 (100%)	0 (0%)	0 (0%)	46
Late toxicity by risk				
Low	5 (11%)	7 (15%)	0 (0%)	12
Intermediate	4 (9%)	5 (11%)	0 (0%)	9
High	16 (35%)	9 (19%)	0 (0%)	25

Abbreviation: GU = genitourinary. Acute grade 2 urinary frequency was seen in two patients (4%). There were no grade 2 or more toxicities in the late toxicity.

1 (2%) patient. No G2 late toxicities were observed during the follow-up period.

Treatment outcomes are shown in Table 3. There were no biochemical failures (PSA nadir +2.0) during the follow-up period. Almost all patients showed a good response to the hormonal therapy, and the PSA nadir was $<0.1\,ng\,ml^{-1}$ in 43 out of 46 (94%) patients. Two (4%) patients had a PSA nadir in the range of $0.1–1.0\,ng\,ml^{-1}$, and 1 patient who refused to undergo hormonal therapy had a PSA nadir of $1.91\,ng\,ml^{-1}$. At the last follow-up date, 26 (57%) patients had rising PSA ($\geqslant 0.1\,ng\,ml^{-1}$) after cessation of hormonal therapy, and the remaining 20 patients, including 5 patients undergoing hormonal therapy. One patient who underwent castration did not show rising PSA. None of the patients showed rising PSA during the hormonal therapy.

DISCUSSION

Gastrointestinal adverse events. In definitive radiotherapy for prostate cancer, late adverse effects tend to be more problematic than acute adverse effects. The rate of ⩾G2 rectal toxicity after radiotherapy has been reported as 5.1% in the analysis of patients who enrolled in the RTOG 75-06 and 77-06 trials (Pilepich *et al*, 1984). However, a lower total dose of radiation of ~65 Gy was used in those trials, so their results cannot be compared with recent data. The results of a randomised controlled trial by Pollack *et al* (2002) suggested that the rates of ⩾G2 rectal toxicity were 12% in patients who received 70 Gy/35 fr. and 26% in patients who received 78 Gy/39 fr., and the rate of rectal toxicity was significantly higher in the high-dose group. Those results may be higher than those of recent studies because the trial was performed from 1993 to 1998, before image-guided radiotherapy (IGRT) or IMRT had been developed. Vargas *et al* (2005) analysed 331 patients treated with a median dose of 79.7 Gy by 3D-CRT and reported that the rate of ⩾G2 rectal toxicity was 20% and the rate of G3 rectal toxicity was 4% at 3 years. Rectal toxicity has improved compared with the report of Pollack *et al.*, despite using a higher total dose of radiation, seemingly due to development of radiotherapy techniques. In the analysis of 743 patients treated with 75.6–81.0 Gy by 3D-CRT at Memorial Sloan-Kettering Cancer Center, it was reported that the incidence of ⩾G2 rectal toxicity was 15% (Zelefsky *et al*, 1999). Although the incidence of rectal toxicity is approximately twice as high as that in the lower dose group (64.8–70.2 Gy), the rate of rectal toxicity has been improving. In a subsequent trial at the same institution that compared 3D-CRT and IMRT using a total dose of 81 Gy, the rate of rectal toxicity of IMRT was significantly lower than that of 3D-CRT (2% *vs* 14%) (Zelefsky *et al*, 2001). A similar result has been reported in the study on GI toxicity comparing 79.2 Gy by IMRT and 79.2 Gy by 3D-CRT (⩾G2 GI toxicity at 3 years; 15% *vs* 22%, $P = 0.039$) (Michalski *et al*, 2013). Although dose escalation is inevitable from the viewpoint of treatment outcomes for prostate cancer, IMRT or IGRT allows for a high dose of radiation with feasible toxicity.

Table 3. Biochemical failure and the changes of serum PSA level

Biochemical failure	Failure (−)	46 (100%)
(PSA nadir +2.0)	Failure (+)	0 (0%)
PSA nadir	Median	0.01 ng ml^{-1}
	<0.01	20 (44%)
	⩽0.01 to <0.1	23 (50%)
	⩽0.1 to <1.0	2 (4%)
	⩽1.0 to <2.0	1 (2%)
	<2.0	0 (0%)
PSA value at latest follow-up date	<0.01	7 (15%)
	⩽0.01 to <0.1	12 (26%)
	⩽0.1 to <1.0	23 (50%)
	⩽1.0 to <2.0	4 (9%)
	<2.0	0 (0%)
PSA rise ⩾0.1	+	26 (57%)
	−	20 (43%)
Local recurrence		0 (0%)
Distant metastasis		0 (0%)

Abbreviation: PSA = prostate-specific antigen. Although almost all patients show PSA rise after termination of ADT, none of the patients showed biochemical failure.

In the present phase I/II study of hypofractionated CIRT, the incidence of G1 late rectal toxicity was 7% (3 out of 46) and that of G2 late rectal toxicity was 0%. There were no acute rectal toxicities. The dose distribution of CIRT using Bragg-peak is better than that of photons, and the dose distribution of CIRT with less beam scattering is also better than that of protons. The ability to easily decrease the irradiated rectal volume is considered to be one of the reasons for lower rectal toxicity.

Genitourinary adverse events. Frequent GU adverse events include haematuria, urinary stricture, and urinary frequency. The incidence of ⩾G2 late GU toxicity was ~5% in the RTOG 75-06 and 77-06 trials (Pilepich *et al*, 1984). In the abovementioned phase III clinical trial reported by Pollack *et al* (2002), the rates of G2 and G3 late GU toxicities in the 151 patients in the 78 Gy group were 10% and 3%, respectively, whereas the rates of G2 and G3 late GU toxicities in the 150 patients in 70 Gy group were 7% and 1%, respectively. The GU toxicity tended to increase according to the irradiation dose, but there were no significant differences. The study at the Memorial Sloan-Kettering Cancer Center reported that the rates of ⩾G2 late GU toxicity of the high-dose group (75.6–81.0 Gy) at 3 and 5 years were 10% and 15%, respectively (Zelefsky *et al*, 1999). In the following study comparing IMRT and 3D-CRT in 1100 patients, the rates of G2 and G3 late GU toxicities were 13% and 1.5%, respectively, in the group who received ⩾75.6 Gy (Zelefsky *et al*, 2001). Unlike the rates of rectal toxicity, there was no significant difference between 3D-CRT group and IMRT group in the late GU toxicity ($P=0.32$). In a recent study, ⩾G2 GU toxicity at 2 years of 3D-CRT group (76 Gy) and IMRT group (78 Gy) were 40% and 30%, respectively ($P=0.011$) (Sveistrup *et al*, 2014). Although significant difference was shown in GU toxicity in that study, the difference is smaller than that of rectal toxicity. In another study on SRT for prostate cancer, a total of two patients (7%) show grade 3 genitourinary (GU) toxicity in the arm of 47.5 and 50 Gy in five fractions (Boike *et al*, 2011). Further, because the median follow-up time of 47.5-Gy group and 50-Gy group is 18 and 12 months, respectively, the incidence of late adverse effect may increase in the future. It is believed that sufficient data are needed when performing the short-term irradiation by X-rays.

In the present study of CIRT, the rate of ⩾G2 late GU toxicity was 0% (Table 2). Grade 1 haematuria was observed in 6 (13%) patients and G1 urinary frequency was observed in 17 (37%) patients. None of these patients required any treatment, and symptoms were improved with observation. No other ⩾G2 late toxicities were found. However, GU late toxicity sometimes occurs ⩾36 months after radiotherapy; therefore, the follow-up period of the present study was not sufficient to observe all late GU adverse events (Zelefsky *et al*, 1999). However, because the long-term incidence of late GU toxicity can be predicted from the incidence at 2–3 years (Zelefsky *et al*, 1999), the rate of late GU toxicity of this phase I/II CIRT study is highly favourable.

Biochemical failure and metastases. There were no biochemical failures or distant metastases as of the last follow-up date. The PSA nadir of almost all patients (94%) showed good response to the treatment (<0.1 ng ml^{-1}), which may be due to the fact that all but one patient received hormonal therapy. Hormonal therapy to the low-risk patients may be overtreatment, but this trial was designed to be able to include these patients. Twenty-six of forty-six (57%) patients showed rising PSA ⩾0.1 ng ml^{-1} after cessation of hormonal therapy, but there were no patients with rising PSA >2.0 ng ml^{-1} above the PSA nadir. Several studies have reported on PSA bouncing after radiotherapy or PSA rising after hormonal therapy (Crook *et al*, 2007; Pinkawa *et al*, 2007). It has been reported that long-term PSA rising after hormonal therapy is a concern for the recovery of serum testosterone level (Pickles *et al*, 2002). After completion of CIRT, the PSA level was not so different from that in patients treated with radiotherapy by photons and hormonal therapy. Long-term outcomes will be reported in the future.

Treatment period. The standard total dose of definitive radiotherapy for prostate cancer by photons is considered to be ⩾70 Gy. In the EORTC (European Organisation for Research and Treatment of Cancer) 22 863 trial, 70 Gy/35 fr. over 7 weeks was used (Bolla *et al*, 2010). After which, the total dose was increased to 75.6–81.0 Gy for intermediate- or high-risk patients. These treatments require 8.5–9 weeks to complete the irradiation (Zelefsky *et al*, 2001). In proton therapy as well as photon radiotherapy, 7.5 weeks are required for the completion of the treatment of 74 GyE, and >8 weeks are required for the dose-escalated treatment using 82 GyE (Slater *et al*, 1998; Coen *et al*, 2011). Although there are few studies that evaluated OTT of radiotherapy and prognosis in the treatment of prostate cancer, a significant relationship between OTT of radiotherapy and recurrence rate has been reported in a recent study (D'Ambrosio *et al*, 2008). Although there were no significant differences between the short-OTT group and the long-OTT group in the patients who received >74 Gy, patients in the long-OTT group tended to have a higher rate of biochemical failure than the patients in the short-OTT group (Liauw and Liauw, 2011). From these studies, it can be said that dose escalation contributes to the improvement of local control; however, extension of the treatment period due to the increase in dose is considered to be unfavourable for local control. Recently, SRT for prostate cancer has been suggested as short-term external body radiotherapy (Madsen *et al*, 2007). A study concluded that SRT could be completed with a schedule of five fractions with tolerable toxicity. However, the biological treatment effects and adverse effects can be different from conventional dose/fraction because dose/fraction has a large impact on biological effect in radiotherapy by photons. But the long-term follow-up results of SRT have not been reported.

Although the median follow-up period was 31 months, the results of the present study demonstrated feasibility and local control at this time point. More than 1600 prostate cancer patients

have been treated with CIRT in the >18 years it has been available. It has been reported that the long-term outcome of CIRT was very favourable even in high-risk prostate cancer (Tsuji *et al*, 2005). Compared with other EBRTs, with the exception of SRT, CIRT for prostate cancer has steadily shortened the treatment time while maintaining good local controllability. The biological characteristics of CIRT are considered to be one of the advantages of this modality. The biological effect of the carbon ion beam is less susceptible to dose/fraction than that of photons (Kanai *et al*, 1999). However, ~2 months of hospital visits and admissions for prostate cancer patients is one of the disadvantages. Shortening the treatment period is favourable not only for treatment outcomes but also for quality of life of the patients.

CONCLUSIONS

The results of the phase I/II clinical trial shortening the treatment period of CIRT for prostate cancer have been reported. The treatment period of irradiation has been shortened from 4 weeks to 3 weeks without occurring ⩾G2 adverse events with a median follow-up of 32 months. Long-term outcomes (e.g., biochemical failure-free survival and local control rate) of the 3-week treatment period are required.

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ORIGINAL ARTICLE

Late toxicity of proton beam therapy for patients with the nasal cavity, para-nasal sinuses, or involving the skull base malignancy: importance of long-term follow-up

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Background Although several reports have shown that proton beam therapy (PBT) offers promise for patients with skull base cancer, little is known about the frequency of late toxicity in clinical practice when PBT is used for these patients. Here, we conducted a retrospective analysis to clarify the late toxicity profile of PBT in patients with malignancies of the nasal cavity, para-nasal sinuses, or involving the skull base.

Methods Entry to this retrospective study was restricted to patients with (1) malignant tumors of the nasal cavity, para-nasal sinuses, or involving the skull base; (2) definitive or postoperative PBT (>50 GyE) from January 1999 through December 2008; and (3) more than 1 year of follow-up. Late toxicities were graded according to the common terminology criteria for adverse events v4.0 (CTCAE v4.0).

Results From January 1999 through December 2008, 90 patients satisfied all criteria. Median observation period was 57.5 months (range, 12.4–162.7 months), median time to onset of grade 2 or greater late toxicity except cataract was 39.2 months (range, 2.7–99.8 months), and 3 patients had toxicities that occurred more than 5 years after PBT. Grade 3 late toxicities occurred in 17 patients (19 %), with 19 events, and grade 4 late toxicities in 6 patients (7 %), with 6 events (encephalomyelitis infection 2, optic nerve disorder 4).

Conclusions In conclusion, the late toxicity profile of PBT in patients with malignancy involving the nasal cavity, para-nasal sinuses, or skull base malignancy was partly clarified. Because late toxicity can still occur at 5 years after treatment, long-term follow-up is necessary.

Keywords Proton beam therapy · Late toxicity · Follow-up · Head and neck cancer

Introduction

Malignant tumors that arise in the nasal cavity or paranasal sinuses, or which invade the skull base, usually present a difficult clinical problem.

Most cases are treated by craniofacial surgery and postoperative radiotherapy, either singly or in combination [1–5]. Surgical approaches are often complicated by serious functional deformity and the difficulty of complete resection. In these cases, definitive radiotherapy is performed as an alternative treatment, but aggressive irradiation of the intracranial region increases the risk of severe late toxicity [6–8].

The depth–dose distribution of a proton beam, the Bragg curve, is characterized by an entrance region with a slowly increasing dose followed by a sharp increase near the end of the range, the Bragg peak. This improved dose distribution of proton beam therapy is of therapeutic merit in the

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treatment of deeply seated tumors. The difference between three-dimensional (3D)-conventional radiotherapy (RT) and PBT is clear in dose-painting simulation. Dose coverage to target in intensity-modulated radiotherapy (IMRT) is sufficient; however, the low-dose area is much larger than that of PBT [9].

Therefore, PBT may not be inferior to IMRT or 3D-conventional RT in safety.

Although several reports [10–12] have shown that PBT holds promise for patients with skull base cancer, little is known about the frequency of late toxicity in clinical practice using PBT for these patients.

Here, we conducted a retrospective analysis to clarify the late toxicity profile of PBT for the intracranial region with long-term follow-up.

Patients and methods

Patients

Entry to this retrospective study was limited to patients with (1) malignant tumors of the nasal cavity, para-nasal sinuses, and/or involving the skull base; (2) definitive or postoperative PBT (>50 GyE) from January 1999 through December 2008; and (3) more than 1 year of follow-up. Written informed consent to treatment was obtained from all patients before the initiation of treatment.

Pretreatment evaluation

Pretreatment clinical evaluation was performed using magnetic resonance imaging (MRI), cervical, chest, and abdominal computed tomography (CT), or positron emission tomography (PET)-CT. Tumor staging in the present study was based on the sections on the nasal cavity and paranasal sinuses in the TNM classification of the International Union Against Cancer (UICC 7th), regardless of histology type. Radiologic evaluations for staging were jointly reviewed by radiologists, head-and-neck surgeons, and medical oncologists at our institution.

Late toxicity evaluation

Late toxicity evaluation was mainly performed using MRI and routine physical examination every 3 months until 2 years after treatment, and every 6–12 months thereafter.

Final grade of late toxicities was retrospectively graded by a radiation oncologist based on clinical charts and radiologic findings. Time to onset of toxicity grade 2 or greater was defined as from the day of initiation of treatment to the first day of confirmation of late toxicity of grade 2 or greater.

Proton beam therapy

Treatment planning was performed on a three-dimensional (3D)-CT planning system. In this system, the proton beam was generated with a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biological effectiveness was defined as 1.1, based on our preclinical experiments. Proton beam therapy at our institution is conducted using passive irradiation with dual-ring double-scatter methods. Dose distribution is optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined pretreatment with CT, MRI, and PET-CT, either alone or in combination. Clinical target volume (CTV) was defined for each disease individually. The CTV of patients who had cervical lymph node metastases was defined the same as for those without lymph node metastasis, because this study included only patients who did not have lymph node metastasis or had lymph node metastasis near the primary site. No prophylactic nodal RT was done for any of the patients.

Planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin but could be finely adjusted where necessary in consideration of organs at risk.

Beam energy and spread-out Bragg peak were fine tuned such that the PTV was at least covered in a 90 % isodose volume of the prescribed dosage.

The most common regimen was 65 GyE/26 fr (2.5 GyE/fr), and for only 14 mucosal melanoma patients, a 60 GyE/15 fr (4GyE/fr) regimen was adapted at National Cancer Center Hospital East. Dose constraints for organs at risk in 2.5 GyE fractions were as follows (D_{max}): (1) surface of brainstem, 60 GyE; (2) center of brainstem, 50 GyE; (3) optic nerves of the healthy side/chiasm, 54 GyE; and (4) optic lens, 15 GyE. However, we gave priority to sufficient target coverage when the GTV or CTV was located close to or adjacent to critical organs.

Statistical analysis

Patient demographics and pathological and clinical characteristics were described using descriptive statistics, including mean, standard deviation, median, range, and percentage. Univariate analysis was conducted using the log-rank test. Overall survival and progression-free survival time were estimated by the Kaplan–Meier product–limits method using commercially available statistical software (Stat Mate IV; SAS Institute, Cary, NC, USA).

Definition of local control, progression-free survival, and overall survival

Overall survival time was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival