Table 2 EPIC subdomain scores of patients treated with IMRT monotherapy

Items	Mean score ± SD	Items	Mean score ± SD
Urinary function		Bowel bother	
Baseline (M)	97.7 ± 5.9	Baseline (M)	96.1 ± 6.4
3	97.1 ± 6.8	3	93.3 ± 8.3
6	97.5 ± 6.6	6	93.5 ± 8.1
12	97.8 ± 5.0	12	94.0 ± 7.8
24	96.5 ± 7.6	24	90.8 ± 13.7
Urinary bother		Sexual function	
Baseline (M)	89.0 ± 11.0	Baseline (M)	22.8 ± 20.5
3	89.3 ± 12.0	3	19.5 ± 19.6
6	90.2 ± 10.6	6	17.0 ± 17.6
12	89.3 ± 11.8	12	15.1 ± 16.6
24	88.1 ± 11.6	24	15.5 ± 16.9
Incontinence		Sexual bother	
Baseline (M)	97.3 ± 7.4	Baseline (M)	83.9 ± 22.2
3	96.9 ± 8.7	3	85.1 ± 21.3
6	98.1 ± 7.3	6	82.8 ± 23.6
12	97.3 ± 7.7	12	79.1 ± 26.3
24	96.1 ± 11.1	24	81.1 ± 24.6
Irritative/obstructive		Hormonal function	
Baseline (M)	91.4 ± 9.1	Baseline (M)	90.3 ± 13.6
3	91.5 ± 9.6	3	91.4 ± 10.9
6	91.8 ± 9.0	6	91.9 ± 11.5
12	91.8 ± 9.0	12	91.8 ± 10.5
24	90.3 ± 10.4	24	91.5 ± 12.2
Bowel function		Hormonal bother	
Baseline (M)	94.0 ± 5.9	Baseline (M)	94.1 ± 9.2
3	91.3 ± 9.1	3	95.9 ± 5.9
6	92.1 ± 7.4	6	95.8 ± 8.1
12	92.5 ± 7.8	12	95.4 ± 6.8
24	90.5 ± 10.2	24	95.0 ± 9.3

EPIC Expanded Prostate Cancer Index Composite, *IMRT* intensity-modulated radiation therapy, *SD* standard deviation, *M* month

These scores remained constant until 12 months after IMRT and decreased again at 24 months after IMRT, and they did not return to those at baseline, particularly the urinary bother score ($p = 0.007$).

Sexual function and bother scores after IMRT for potent patients at baseline (Fig. 3)

Of the 91 patients, 27 (30 %) were potent before IMRT. The age of the potent patients was younger than that of the impotent patients ($p = 0.008$) and the use of PDE-5-I was more common in the potent patients ($p = 0.03$) (Table 1). The mean sexual function score at baseline was 47.3. As shown in Fig. 3, this score began to decrease at 3 months after IMRT and then stabilized until 24 months ($p < 0.001$). Although the sexual bother score slowly decreased throughout the 2 years after IMRT, there was not a significant change.

Predictors of QOL (Table 3)

Table 3 shows the multivariate logistic regression analysis of the association between the variables and QOL score decrement at 24 months after IMRT. BMI ($p = 0.02$) and total IPSS score at baseline ($p = 0.003$) were identified as significant predictors of a decrease in EPIC urinary irritative/obstructive scores. Incontinence at baseline ($p = 0.008$) and having smoking history ($p = 0.03$) were identified as significant predictors of a decrease in EPIC incontinence scores. Sexual function at baseline ($p = 0.0005$) was associated with a decrease in sexual function, and age ($p = 0.02$) was associated with a decrease in PCS. No predictor of bowel function and MCS was identified.

Discussion

To the best of our knowledge, this is the first time that longitudinal changes in HRQOL after IMRT monotherapy have been evaluated in patients with clinically localized PCA using EPIC, which measures urinary irritative symptoms and hormonal function as well as urinary incontinence and bowel function.

We found that overall urinary function, including urinary irritative/obstructive symptoms, did not change within the 2 years after IMRT. Recently, Goineau et al. [2] reported that urinary symptoms worsened at 2 months after IMRT, but then improved with time in a QOL study after high-dose IMRT. Since our study questionnaire was not administered within 2 months after IMRT, the speculation that impaired urinary function present at 2 months improves by 3 months cannot be conclusively denied. Namiki et al. [6] reported that the urinary function and bother scores were similar after IMRT and conformal radiation therapy (CRT) and did not change for 5 years after treatment. However, the urinary irritative and obstructive symptoms, which are considered to be the main urinary complications of EBRT, were not evaluated because they used the UCLA-PCA, which contains only questions about urinary incontinence. Quon et al. [10] also reported that all four EPIC urinary subscale scores in the patients treated with hypofractionated IMRT did not change in the 2 years after treatment. However, they studied a cohort of patients who underwent ADT for 2–3 years, and the reduction in prostate size due to ADT might have contributed to their urinary function. Therefore,

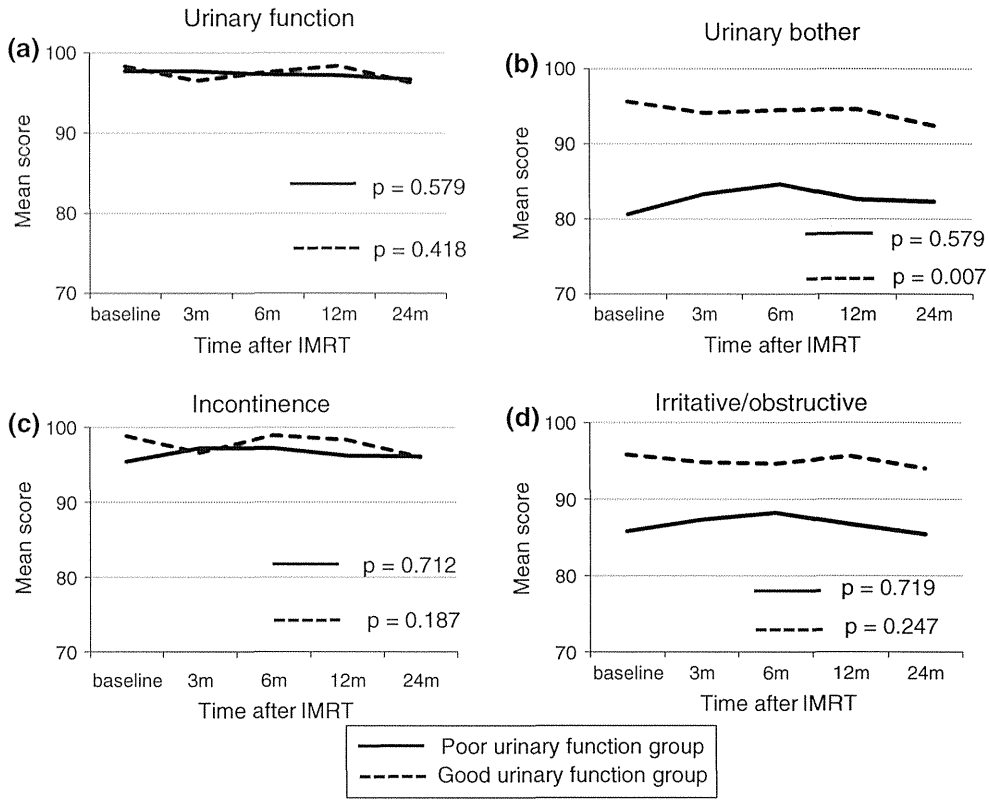

Fig. 2 Longitudinal changes in urinary subscales of the EPIC according to pretreatment urinary function. High scores indicate better functional outcomes. Baseline means pretreatment state. Good and poor urinary functions are defined as < 8 points and 8 or more points of pretreatment IPSS score, respectively. **a** urinary function, **b** urinary bother, **c** incontinence, and **d** irritative/obstructive

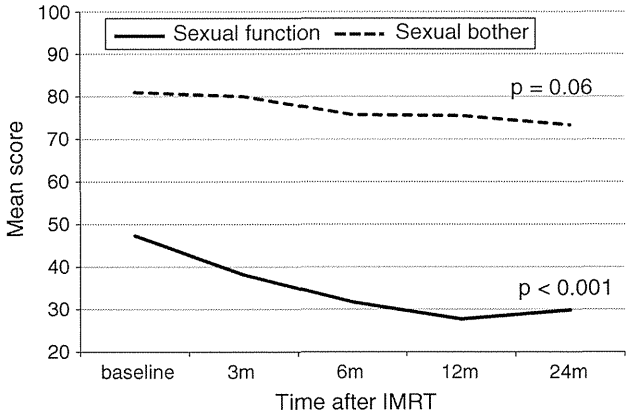

Fig. 3 Longitudinal changes in sexual function and bother scores of the EPIC in patients with potency at baseline. High scores indicate better outcomes (sexual function: *solid line*; sexual bother: *dotted line*)

it might be difficult to evaluate true urinary function after EBRT precisely in patients who undergo ADT plus EBRT. In our study, although the changes did not reach significance, urinary symptoms after IMRT tended to improve in patients who had poor urinary function before IMRT. In contrast, patients with good urinary function before IMRT tended to have worse urinary function after IMRT, in particular urinary bother. The reason for this is unclear. This outcome differs from that of patients undergoing brachytherapy, in which transient irritative and obstructive urinary symptoms usually occur for 3–6 months after treatment [22]. Our finding that urinary function after IMRT is affected by pre-IMRT voiding status is significant for patients who wish to undergo IMRT. Improvement of urinary status after surgery in patients with poor urinary symptoms is one of the important advantages of RP [23]. Thus, IMRT may be suitable for patients with poor urinary symptoms before treatment.

Several investigators have reported that bowel function and bother are worse after EBRT than at baseline [13, 24]. Namiki et al. [6] reported that at 5 years after treatment, bowel function and bother in the patients treated with CRT were significantly worse than those at baseline. However, there were no significant differences between the baseline scores and any of the post-radiation scores at any of the time periods in the patients treated with IMRT. In contrast, bowel function and bother scores after IMRT were lower than those at baseline in our cohort and in the cohort studied by Brassell et al. [11]. Although the reason for the discrepancy between these two studies and the results reported by Namiki et al. is unclear, we propose that there might be slight differences in radiation exposure to the rectum among the three studies in question.

Sexual function scores after IMRT gradually decreased compared to baseline, but had stabilized by 2 years after IMRT. Brassell et al. [11] also recently reported QOL

Table 3 Multivariate analysis of predictors associated with urinary irritative/obstructive, incontinence, bowel, sexual, physical, and psychological functions at 24 months after IMRT

Variable	Irritative/obstructive		Incontinence		Bowel function		Sexual function		MCS		PCS	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Age	1.01 (0.91–1.13)	0.78	1.10 (0.94–1.35)	0.22	1.08 (1.00–1.19)	0.07	1.11 (0.99–1.26)	0.10	1.10 (0.96–1.30)	0.23	1.13 (1.02–1.29)	0.02
HT (yes vs. no)	1.15 (0.33–3.97)	0.82	2.01 (0.28–15.4)	0.47	0.45 (0.14–1.38)	0.18	0.24 (0.05–0.93)	0.05	1.21 (0.21–6.18)	0.82	0.94 (0.27–3.10)	0.92
DM (yes vs. no)	2.41 (0.50–11.4)	0.26	4.78 (0.50–175.8)	0.22	1.27 (0.32–4.92)	0.73	2.58 (0.54–14.0)	0.24	0.54 (0.03–3.88)	0.60	0.91 (0.18–3.66)	0.90
CVD (yes vs. no)	1.91 (0.08–21.7)	0.62	9.96 (0.38–224.1)	0.15	3.02 (0.24–37.7)	0.37	4.82 (0.35–124.9)	0.25	NA	1.00	1.38 (0.06–13.5)	0.80
Having smoking history (yes vs. no)	1.29 (0.40–4.27)	0.67	8.86 (1.15–169.1)	0.03	1.63 (0.57–4.92)	0.37	2.41 (0.64–10.6)	0.21	0.59 (0.11–2.76)	0.51	0.99 (0.31–3.16)	0.98
									0.86 (0.60–1.15)	0.34	1.15 (0.94–1.42)	0.18
BMI (kg/m^2)	1.32 (1.06–1.73)	0.02	1.05 (0.74–1.50)	0.77	0.97 (0.80–1.18)	0.78	1.02 (0.82–1.31)	0.83	–	–	–	–
Use of PDE-5-I (yes vs. no)	–	–	–	–	–	–	2.89 (0.54–18.1)	0.23	–	–	–	–
Pre-sexual function (yes vs. no)	–	–	–	–	–	–	0.92 (0.88–0.96)	0.0005	–	–	–	–
Pre-IPSS (≤8 vs. ≥7)	8.48 (2.33–41.1)	0.003	–	–	0.94 (0.31–2.78)	0.91	1.56 (0.45–5.65)	0.49	–	–	–	–
Pre-UIR score at baseline	–	–	0.85 (0.73–0.94)	0.008	–	–	–	–	–	–	–	–

MCS mental component summary, *PCS* physical component summary, *OR* odds ratio, *CI* confidence interval, *HT* hypertension, *DM* diabetes mellitus, *CVD* cerebral vascular disease, *NA* not appreciable, *BMI* body mass index, *PDE-5-I* phosphodiesterase-5-inhibitor, *IPSS* International Prostate Symptom Score, *UIR* urinary incontinence

changes at 2 years after IMRT monotherapy using EPIC and concluded that sexual function at 2 years after IMRT monotherapy was slightly decreased. In contrast, Namiki et al. [6] reported that, despite the inclusion of some patients in the cohort who received ADT combined with IMRT, sexual function scores did not change for 5 years after treatment. The reason for this controversial finding is unclear, but the percentage of patients with pretreatment potency in each cohort may have differed.

In our study, sexual bother after IMRT of the patients with potency at baseline did not significantly change for 2 years after IMRT. This result may be explained by the theory that since most Japanese originally have low sexual function [25], they are not concerned about sexual function even if their sexual function decreases further after IMRT. Namiki et al. also investigated sexual function and bother before localized PCA treatment in Japanese and Americans, and concluded that Japanese had poorer overall ability to function sexually than Americans, but there was no difference in sexual bother between Japanese and Americans [26].

In previous reports that used the EPIC [9, 10], evaluation of hormonal function and bother have been greatly affected by ADT because of EBRT and ADT combination treatment. In addition, hormonal function and bother have not been evaluated in the previous reports using UCLA-PCI and EORTC QLQ-PR25 [6, 7, 9]. Accordingly, we believe that our hormonal findings will be very useful for patients who are treated with IMRT alone. Brassell et al. [11] showed that hormonal bother was worse 2 years after treatments in patients with lower incomes and indicated that the effect of economic stress on patients with PCA is one of a few reasons for poorer hormonal bother after treatment in these patients. In contrast, hormonal bother tended to increase after IMRT in this study. The effect of economic stress on hormonal bother might be lower in Japanese patients because the National Universal Health Insurance System covers IMRT for PCA in Japan. In Japan, low-income patients <70 years old can receive IMRT for about 600 US dollars, while those more than 70 years old can receive it for less than 150 US dollars.

To date, there have been few reports on PCS and MCS scores in PCA patients who underwent EBRT. Sugimoto et al. [27] reported that there were no significant differences relative to time after EBRT. They reported that the PCS score, which was decreased in the early period after EBRT, returned to the baseline score at 24 months. In contrast, the MCS score, which was increased in the early period after EBRT, remained stable until 24 months. Despite the differences between EBRT and IMRT, this tendency was the same as our study findings.

On multivariate analysis, pre-IMRT urinary and sexual functions were identified as significant predictors of urinary

irritative/obstructive, incontinence, and sexual functions at 24 months after IMRT, respectively. Morton et al. [28] also previously reported the same results as ours. Furthermore, Hashine et al. [22] reported that low pretreatment IPSS scores significantly predicted urinary irritative/obstructive function at 3 years after RP or brachytherapy. Therefore, pretreatment urinary function may be significant to predict urinary function after treatment, regardless of the treatment method.

This study has some limitations. First, the cohort was relatively small and the follow-up period relatively short. It is well known that radiation therapy has late toxicities [29], so a longer follow-up period is required. Second, the dose of radiation may not have been sufficient to eradicate PCA, because 34 % of the patients received 72 Gy or less. Third, it is unclear whether the definition of potency was suitable, because it was not clearly specified. Fourth, the hormonal function domain of the EPIC has usually been used for patients treated with ADT; however, it has also been used for patients who did not receive ADT in previous reports [13, 30]. Despite these limitations, there have been few previous reports on the longitudinal changes in general and disease-specific HRQOL after IMRT monotherapy for patients with localized PCA, and the results of this study should be useful for patients deciding on treatment strategies. In particular, we should inform patients that urinary function after IMRT is not markedly poor, and that bowel and sexual functions that deteriorate after IMRT do not return to those at baseline. Future studies should include more patients evaluated for a longer period.

Conclusions

For 2 years, we prospectively evaluated the longitudinal changes in general and disease-specific HRQOL after IMRT monotherapy with the EPIC, SF-8, and IPSS in patients with localized PCA. Urinary functions, including irritative/obstruction symptoms, and hormonal functions were not affected by IMRT monotherapy, but bowel and sexual functioning decreased after IMRT.

It is important for patients to evaluate the impact that treatment will have on their quality of life and to make an informed choice based on their pretreatment function when they consider undergoing IMRT monotherapy.

Conflict of interest None declared.

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ORIGINAL ARTICLE

Long-term oncological outcome in men with T3 prostate cancer: radical prostatectomy versus external-beam radiation therapy at a single institution

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Abstract
Background This study was designed to compare the long-term oncological outcome of patients with clinical T3 (cT3) prostate cancer (PCA) treated with either radical prostatectomy (RP) or external-beam radiation therapy (EBRT) and to identify predictors of oncological outcomes.
Methods A total of 231 patients with cT3 PCA underwent either RP ($n = 112$) or EBRT ($n = 119$). Local progression-free (LPFS), distant metastasis-free (DMFS), cancer-specific (CSS), and overall survival curves were generated with the Kaplan–Meier method, and the differences in survival rates between the two groups were assessed with a log-rank test. Cox proportional stepwise multivariate analysis was used to assess the association of variables to the oncological outcomes.
Results The median follow-up of the RP and EBRT groups was 93 and 85 months, respectively ($p = 0.004$).The 10-year LPFS, DMFS, and CSS rates were not statistically different between the two groups (90.2, 73.9, and 93.7 % in the RP group and 82.7, 88.2, and 85.1 % in the EBRT group; $p = 0.25$, 0.10, and 0.10, respectively). The Cox proportional multivariate analysis revealed that clinical T3b (cT3b) ($p = 0.001$) and a biopsy Gleason score of 7–10 ($p = 0.043$) were significant predictors of cancer-specific mortality and that cT3b was also a significant predictor of local progression and all-cause mortality.
Conclusion In cT3 PCA, both RP and EBRT provide an excellent long-term oncological outcome. cT3b was the strongest predictor of oncological outcome for the patients with locally advanced PCA who underwent the definitive therapy.

Keywords Locally advanced prostate cancer · Radical prostatectomy · External-beam radiation therapy · Oncological outcome

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Introduction

Optimal definitive treatment [either radical prostatectomy (RP) or external-beam radiation therapy (EBRT)] for patients with clinical T3 (cT3) prostate cancer (PCA) remains controversial because of a lack of well-conducted prospective randomized studies. It is, however, ethically very difficult to perform such randomized studies. To our knowledge, although there has been one prospective randomized study reported by Akakura et al. [1], the study cohort size was too small, and clinical T2b (which is not "true" locally advanced PCA) was included in the study eligibility. Therefore, at the present time, attending physicians have been forced to utilize the information of prior retrospective studies [2–4] to assist with patient counseling and to decide upon the best course of treatment for patients with cT3 PCA. Unfortunately, some bias existed between

the RP and EBRT cohorts in these previous studies, and the follow-up periods were too short. Boorjian et al. [3] did, however, retrospectively compare the long-term survival rates after RP or EBRT for patients with high-risk PCA, but the study cohort consisted of two centers and there was a lack of a central pathology review. Moreover, the Charlson score data in the two groups were not available. Arcangeli et al. [4] also reported a retrospective comparison of oncological outcomes after EBRT and RP for patients with high-risk localized PCA. Although the study was performed at a single center, the median follow-up times of the RP and EBRT groups were only 33.8 and 38.6 months, respectively. Such a short follow-up time makes it difficult to draw accurate conclusions.

To date, most previous studies have used prostate-specific antigen (PSA) failure as a surrogate endpoint of oncological outcome for patients with PCA [5–7]. There are, however, two problems with using PSA failure to evaluate oncological outcome. First, since PSA failure does not always translate into systemic progression, PCA-related death, and all-cause mortality [8, 9], PSA failure might not be a suitable choice as a surrogate endpoint of oncological outcome. Second, it is very difficult to compare PSA failure among the different treatment groups because the definition of PSA failure varies based on the treatment method [10]. Additionally, all patients with cT3 PCA are not completely cured using only first-step treatment. Accordingly, distant metastasis-free survival (DMFS) and cancer-specific survival (CSS) rates are much more suitable endpoints of oncological outcome. Needless to say, longer follow-up times are needed to calculate DMFS and CSS rates.

In this study, we retrospectively compared the oncological outcomes, including long-term DMFS and CSS, between RP and EBRT for patients with cT3 PCA and identified the predictor of oncological outcomes. To minimize bias, all patients had been treated at a single institution from 1994 to 2005.

Patients and methods

Patient population

Between January 1994 and July 2005, a total of 231 Japanese men with cT3 PCA underwent either RP ($n = 112$) or EBRT ($n = 119$) at the Cancer Institute Hospital in Tokyo, Japan. Clinical staging was determined according to the 1997 TNM classification. Digital rectal examination (DRE), abdominopelvic computed tomography (CT), and bone scan were performed for all patients. Since 1999, pelvic magnetic resonance imaging (MRI) has also been carried out to determine the T-stage. All MRI and CT scan findings were determined by a single radiologist (AK). Diagnostic criteria of extraprostatic extension [clinical stage T3a (cT3a)] on MRI T2-weighted images included broad (>12 mm) tumor contact, smooth capsular bulge, irregular capsular bulge, obliteration of the rectoprostatic angle, and asymmetry or direct involvement of the neurovascular bundle [11]. In addition, diagnostic criteria for the presence of seminal vesicle involvement (SVI) [clinical T3b (cT3b)] on MRI T2-weighted images included disruption or loss of the normal architecture of the SV, focal or diffuse areas of low signal intensity within the SV, low signal intensity within the SV causing a mass effect, or direct extension of the low signal intensity of a tumor from the base of the prostate to the SV. An enhanced SV wall on dynamic T1-weighted MR images was also defined as one of the diagnostic criteria for SVI [12]. When cT3 (a or b) findings on either the MRI image or DRE were identified, the patient was diagnosed as having cT3 (a or b). PSA measurements after the definitive treatments and histopathological grading of both the biopsy and RP specimen were performed as reported previously [13–16]. In total, 187 (75 %) patients received neo-adjuvant androgen deprivation therapy (NADT) before the definitive treatments. Combined androgen blockade (consisting of a luteinizing hormone-releasing hormone agonist and a nonsteroidal anti-androgen agent) was used as the ADT in the majority of the patients in the current study.

Radical prostatectomy

During the study period, RP was performed as reported previously [13–16]. Only two of the 112 patients (1.8 %) underwent a unilateral nerve sparing procedure. Eighty-six (76.8 %) patients received NADT for a median of 8 (range 3–18) months before surgery (Table 1). Because of the retrospective nature of the study, the use and period of NADT were decided at the discretion of the attending physician. After RP, 99 patients (88.4 %) were prospectively observed without any adjuvant treatment until PSA failure was confirmed. Exceptions to this protocol were 11 patients who received salvage ADT for persistently elevated PSA following RP due to adverse pathological findings (lymph node metastasis and SVI) and two patients who concurrently underwent orchiectomy as adjuvant ADT (AADT) with RP. At last follow-up, five (4.5 %) and 35 (31.2 %) patients received salvage EBRT and salvage ADT after PSA failure, respectively. The median time from RP to the salvage treatments was 2.0 (range 0.29–12.6) years. PSA failure was defined as a PSA level of >0.2 ng/mL.

External beam radiotherapy

All patients receiving EBRT were treated at 2 Gy per fraction using an opposing bilateral 120° arc technique or

Table 1 Patient characteristics

Variable	RP ($n = 112$)	EBRT ($n = 119$)	p
Median age, years (range)	67 (51–80)	72 (55–85)	<0.001
Median PSA, mg/mL (range)	24.3 (4.0–720.0)	36.0 (2.1–400.0)	0.17
BxGS, *n* (%)			0.23
5–6	14 (12.5)	15 (12.6)	
7	53 (47.3)	47 (39.5)	
8–10	45 (40.2)	57 (47.9)	
Clinical T-stage, *n* (%)			0.08
3a	90 (80.4)	83 (69.7)	
3b	22 (19.6)	33 (27.7)	
NADT, *n* (%)	86 (76.8)	114 (95.8)	<0.001
AADT, *n* (%)	2 (1.8)	25 (21.0)	<0.001
Charlson score, *n* (%)			0.38
0	56 (50.0)	50 (42.0)	
1	29 (25.9)	40 (33.6)	
≥2	27 (24.1)	29 (24.4)	
Median follow-up, months (range)	93 (3.0–214.0)	85 (2.1–162.0)	0.004

RP Radical prostatectomy, *EBRT* external beam radiotherapy, *PSA* prostate-specific antigen, *BxGS* biopsy Gleason score, *NADT* neo-adjuvant androgen deprivation therapy, *AADT* adjuvant androgen deprivation therapy

three-dimensional conformal radiation therapy (3DCRT). The median dose was 70 Gy (range 60–72 Gy; <70 Gy in 6 and ≥70 Gy in 113 patients). The clinical target volume (CTV) was defined as the prostate for the patients with clinical T3a lesions and was extended to include the seminal vesicles in their entirety for those patients with cT3b lesions. The margins of the planning target volume to CTV were 6 mm posteriorly, and 10 mm in all other directions. No pelvic lymph nodes were included in the radiation field.

Of the 119 patients, 114 (95.8 %) received NADT before EBRT and concomitant with ADT for a median of 9 (range 4–34) months (Table 1); 25 (21.0 %) of the 119 patients also received AADT for a median of 27 (range 3–78) months following concomitant ADT (Table 1). Because of the retrospective nature of the study, the use and period of NADT and AADT were decided upon at the discretion of the attending physician. At last follow-up, of the 94 patients who did not receive AADT after EBRT, 32 (26.9 %) had received salvage ADT after PSA failure. The median time from EBRT to salvage ADT was 3.1 (range 0.81–10.3) years. PSA failure was defined as the PSA nadir + 2 ng/mL.

Oncological outcomes

Oncological outcomes in terms of local progression-free survival (LPFS), DMFS, CSS, and overall survival (OAS) rates were evaluated. Local progression was defined as an intrapelvic recurrent mass irrespective of the histological confirmation of cancer cells in targeted biopsies at the bladder–urethral anastomosis. Distant metastasis was defined as a positive finding on radiological examinations. Cause of death was identified from death certificates or physician correspondence.

Statistical analysis

Local progression-free survival , DMFS, CSS, and OAS curves were generated with the Kaplan–Meier method, and the difference in these rates between the RP and EBRT groups was assessed with a log-rank test. The differences in clinicopathological variables between the two groups were analyzed by the chi-square test and the Mann–Whitney *U* test. Cox proportional stepwise multivariate analysis was used to assess the association of variables to LPFS, DMFS, CSS, and OAS. Age (continuous), Charlson score (0–1 vs. ≥2), PSA (continuous), clinical T-stage (T3a vs. T3b), biopsy Gleason score (GS) (5–6 vs. 7–10), NADT (yes vs. no), AADT (yes vs. no), and treatment type (RP vs. EBRT) were evaluated as possible predictors.

All p values were two-sided. A p value of <0.05 was considered to be statistically significant. Statistical analyses were performed with JMP ver. 5.1.1 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics and pathological findings after RP

Patient characteristics are shown in Table 1. The patients in the RP group were significantly younger than those in the EBRT group ($p < 0.001$). Although patients in the EBRT group had higher pretreatment PSA levels ($p = 0.17$), higher biopsy GSs ($p = 0.23$), and a more advanced T-stage ($p = 0.08$) than patients in the RP group, there were no significant differences between the two groups. Approximately 90 % of all patients had high-grade cancers (GS ≥7) on biopsy. The median follow-up time of the RP and EBRT groups was 93 and 85 months, respectively ($p = 0.004$).

The pathological T-stage of the patients who underwent RP was T0, T2, T3a, T3b, and T4 in three (3 %), 41 (37 %), 34 (30 %), 32 (29 %), and two (2 %) patients,

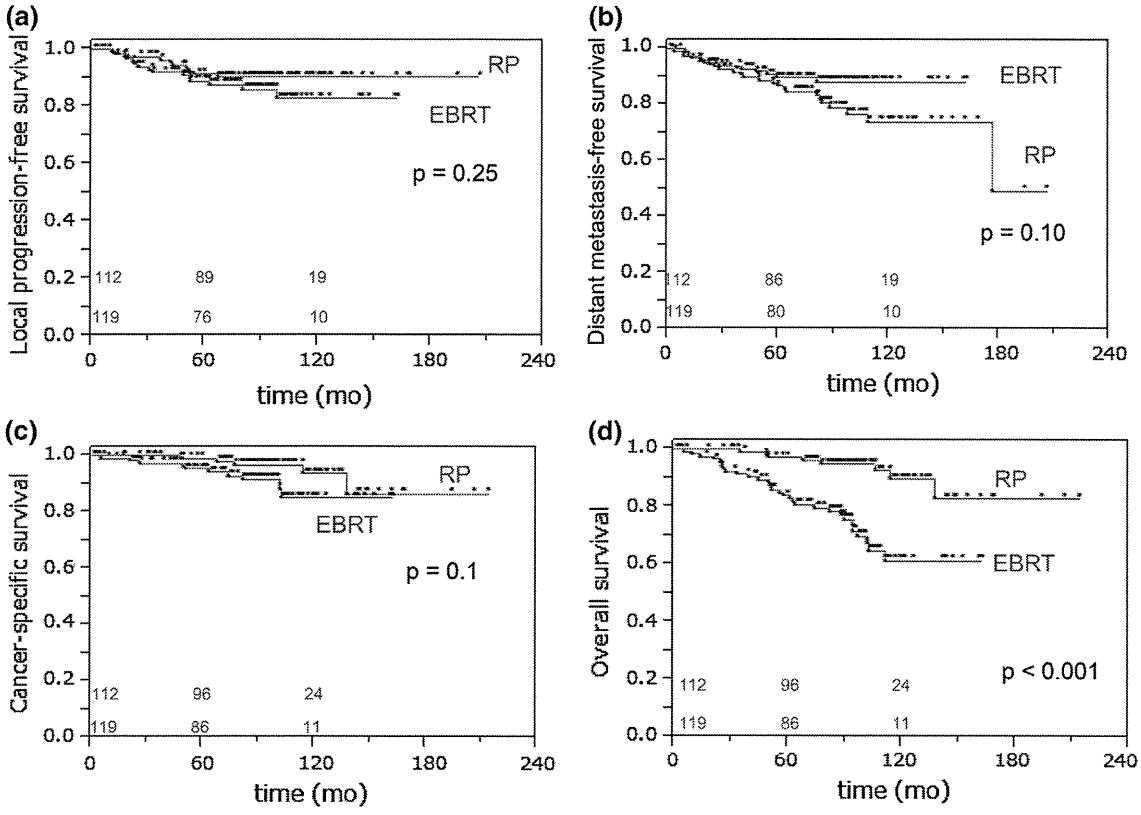

Fig. 1 Kaplan–Meier local progression-free (**a**), distant metastasis-free (**b**), cancer-specific (**c**) and overall (**d**) survival curves of patients with clinical T3 prostate cancer treated by radical prostatectomy (*RP*) or external-beam radiation therapy (*EBRT*). *Numbers above X-axis* (*red* EBRT, *blue* RP) Numbers of patients at risk at 0, 5, and 10 years

respectively. Sixteen patients (14 %) had lymph node metastasis, and 31 (28 %) were found to have positive surgical margins.

Oncological outcomes

The local progression of the RP and EBRT groups was observed in ten (8.9 %) and 15 (12.6 %) patients, respectively ($p = 0.37$). As shown in Fig. 1a, the 10-year LPFS of the RP and EBRT groups was 90.2 and 82.7 %, respectively ($p = 0.25$).

Twenty-three (20.5 %) patients of the RP group and 12 (10.1 %) of the EBRT group experienced a distant metastasis during the follow-up period ($p = 0.03$). The 10-year DMFS of the RP and EBRT groups was 73.9 and 88.2 %, respectively ($p = 0.10$) (Fig. 1b).

During the follow-up period, there were 39 deaths (16.9 %), including 15 PCA-related deaths (6.5 %). The RP group (93.7 %) showed only a tendency towards a better CSS rate than the EBRT group (85.1 %) ($p = 0.10$) (Fig. 1c), yet the 10-year OAS rate was significantly different between the RP (89.7 %) and EBRT (61.5 %) groups ($p < 0.001$) (Fig. 1d).

Predictors of the oncological outcomes in the entire cohort

Table 2 shows the Cox proportional stepwise multivariate analysis of the association between the eight variables and the oncological outcomes. Among the eight variables, cT3b ($p = 0.018$) and non-NADT ($p = 0.016$) were identified as significant predictors of local progression. cT3b ($p = 0.001$) and a biopsy GS of 7–10 ($p = 0.043$) were identified as predictors of a significantly increased risk of cancer-specific mortality, and EBRT ($p = 0.013$), older age ($p = 0.005$), and cT3b ($p = 0.002$) were also identified as significant predictors of all-cause mortality.

Discussion

Our retrospective study revealed two important findings.

First, patients with cT3 PCA treated with either RP or EBRT were able to obtain an excellent long-term oncological outcome. To date, there have been several published reports on the long-term oncological outcome of RP and EBRT series for patients with cT3 PCA [17–21]. Ward

Table 2 Cox proportional stepwise multivariate analysis of predictors associated with oncological outcome in patients with clinical T3 prostate cancer

Variable	Local progression-free survival				Distant metastasis-free survival			
	Full model		Reduced model		Full model		Reduced model	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*
Age	1.02 (0.91–1.05)	0.50	–	–	1.00 (0.94–1.06)	0.91	–	–
Charlson score (0–1 vs. ≥2)	1.06 (0.66–1.86)	0.83	–	–	2.34 (0.91–7.94)	0.08	–	–
PSA (ng/mL)	1.00 (0.99–1.01)	0.78	–	–	1.40 (0.03–20.1)	0.84	–	–
Clinical T (3a vs. 3b)	1.56 (0.42–0.99)	0.05	1.64 (0.41–0.92)	0.018	1.84 (0.84–3.83)	0.12	–	–
BxGS (5–6 vs. 7–10)	1.02 (0.49–1.74)	0.96	–	–	2.38 (0.71–14.7)	0.18	–	–
NADT (yes vs. no)	2.03 (1.24–3.26)	0.006	1.76 (1.12–2.64)	0.016	1.95 (0.78–4.44)	0.15	–	–
AADT (yes vs. no)	1.36 (0.70–3.49)	0.39	–	–	1.06 (0.24–3.37)	0.92	–	–
Treatment (RP vs. EBRT)	1.65 (1.01–2.77)	0.05	–	–	1.64 (0.73–3.87)	0.23	–	–
Variable	Cancer-specific survival				Overall survival			
	Full model		Reduced model		Full model		Reduced model	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*
Age	1.03 (0.88–1.08)	0.57	–	–	1.07 (1.00–1.14)	0.05	1.09 (1.02–1.15)	0.005
Charlson score (0–1 vs. ≥2)	1.72 (0.75–7.41)	0.24	–	–	1.24 (0.55–2.63)	0.58	–	–
PSA (ng/mL)	1.01 (0.98–1.00)	0.17	–	–	1.00 (0.99–1.01)	0.25	–	–
Clinical T (3a vs. 3b)	2.50 (0.22–0.69)	0.001	2.38 (0.23–0.70)	0.001	1.64 (0.43–0.87)	0.006	1.67 (0.44–0.83)	0.002
BxGS (5–6 vs. 7–10)	NA	0.04	NA	0.043	1.06 (0.51–1.51)	0.83	–	–
NADT (yes vs. no)	1.08 (0.50–1.08)	0.84	–	–	1.24 (0.73–1.96)	0.40	–	–
AADT (yes vs. no)	1.20 (0.42–1.85)	0.63	–	–	1.01 (0.64–1.77)	0.96	–	–
Treatment (RP vs. EBRT)	1.50 (0.76–3.04)	0.24	–	–	1.93 (1.23–3.22)	0.004	1.65 (1.11–2.59)	0.013

HR hazard ratio, *CI* confidence interval, *NA* not appreciable

et al. [18] reported the long-term oncological outcome of RP in the largest ever cT3 PCA cohort. In this study, at a median follow-up of 10.3 years, the 10- and 15-year CSS rates of the 841 men with cT3 PCA who underwent RP were 90 and 79 %, respectively, yet because half of the patients in the cohort immediately received additional forms of treatment after surgery, the direct impact of RP on patients with cT3 PCA was unclear [18]. More recently, Hsu et al. [19] also reported that, at a median follow-up of 8.3 years, the 10-year CSS and OAS rates of 164 men with cT3 PCA who underwent RP were 80 and 67 %, respectively. Although the CSS and OAS rates among our patient cohort were slightly better than those of these previous studies [17–19], in general, the 10-year CSS and OAS rates of RP for patients with cT3 PCA range from 80 to 90 %, and values ranging from 70 to 80 % were obtained in the previous studies [17–19] and in our study. Furthermore, some studies have showed the benefit of adjuvant radiation therapy after RP for patients with adverse pathological features; however, it may be controversial to perform adjuvant radiation therapy routinely [20, 21]. In contrast, Zelefsky et al. [22] reported that the 10-year CSS and OAS rates of 296 patients with cT3 PCA treated with 3DCRT or intensity modulated radiotherapy (IMRT) were 83 and 65 %, respectively. Alicikus et al. [23] also reported the oncological outcome of 170 patients with PCA treated with 81 Gy IMRT. In their study, the 10-year CSS rate of patients with high-risk PCA was 86 %, and the 10-year actuarial risks of these men later developing greater than Grade 2 genitourinary and gastrointestinal toxicities were only 17 and 3.7 %, respectively. The oncological outcomes of these two studies [22, 23] are nearly comparable to those of the previous RP series [17–19] for cT3 PCA.

To our knowledge, there are only three retrospective studies which have compared the oncological outcome between RP and EBRT for patients with either high-risk or locally advanced PCA [2–4]. Zelefsky et al. [2] reported the oncological outcome of 1,318 patients with cT1c-3b PCA who underwent RP and 1,062 patients with cT1c-3b PCA who underwent IMRT at the Memorial Sloan-Kettering Cancer Center. The 8-year CSS rates of RP and IMRT for all patients were 98.6 and 95.3 %, respectively, yet the 8-year cancer-related mortality rates of RP and IMRT in patients with high-risk PCA were 3.8 and 9.5 %, respectively. These authors therefore concluded that the CSS rate of RP was superior to that of IMRT in cases of

high-risk PCA. Boorijan et al. [3] conducted a comparison of the long-term survival between RP and EBRT for patients with high-risk PCA and concluded that RP is an independent positive predictor of OAS. These authors suggested that one potential explanation for this result might be an imbalance between the two treatment groups in terms of medical co-morbidities and unmeasured confounding variables. They also suggested that another potential explanation for the result might be an adverse impact of ADT on patients who received EBRT because ADT might result in adult diseases, such as cardiac disease, diabetes, and hypercholesterolemia. In our study, while treatment type was also identified as a significant predictor of all-cause mortality, it was not a significant predictor of CSS. One possible explanation for this finding may be that there was bias in terms of age between the two groups and that the EBRT group had more advanced features than the RP group, regardless of a lack of statistical significance. Also, only approximately 20 % of the EBRT group received adjuvant ADT after EBRT in our cohort, and only one patient died of heart failure in our entire patient cohort. We therefore believe that any adverse impact resulting from ADT use was not associated with the oncological outcome in our study.

The second significant finding was that the cT3b stage was determined to be a very strong predictor of local progression and cancer-specific mortality, which meant that patients with cT3b PCA had a poor prognosis regardless of treatment method. To date, there have been few reports of definitive treatment for cT3b PCA. Joniau et al. [24] reported that the 10-year clinical progression-free survival and CSS rates of their 51 patients with cT3b-4 treated with RP were 73 and 92 %, respectively, leading them to the conclusion that RP was a reasonable first step in selected patients with cT3b-4 PCA and no tumor fixation to the pelvic wall or invasion into the urethral sphincter. Zelefsky et al. [24] reported that the 10-year PSA failure-free survival and DMFS of the cT3b PCA patients treated with EBRT were 32 and 32 %, respectively, and that the oncological outcome of cT3b PCA patients was significantly worse than that of cT3a PCA patients. Based on the findings of the previous studies and our current study, the development of any effective additional treatment after definitive treatment is urgently needed for cT3b PCA patients in the near future.

There were several limitations to the present study: First, this was a relatively small retrospective study, so there were quite a few biases, such as age and follow-up period. Although it is very difficult to perform such randomized prospective studies due to ethical concerns, this study is one of the largest studies conducted to date in an Asian population, and the findings of this study resulted from multivariate analysis; we therefore believe our overall findings are of value. Second, because many patients received NADT before the definitive treatments, it is unclear whether they were true cT3 PCA cases. The results of this study, however, are at least comparable to those of other studies, and as it has been reported that approximately 70–80 % of men diagnosed with cT3-4 disease show a concordance between the clinical stage and the pathological stage [25], we believe that only a few patients without cT3 disease were included in our cohort. As a rule, we have been performing RP without NADT for locally advanced PCA since 2008 because it has been demonstrated that NADT before RP does not improve OAS or disease-free survival [26]. Third, AADT was not performed on all patients of the EBRT group, regardless of the existence of cT3PCA, and even if the patients received AADT, the ADT periods were possibly too short. Fourth, the radiation dose might not have been sufficient to eradicate cT3 PCA. At present, all patients with locally advanced PCA are treated by IMRT with 78 Gy in our hospital. Lastly, the quality of life after the treatments was not evaluated.

In conclusion, despite some limitations, RP as well as EBRT for men with cT3 PCA provide an excellent long-term oncological outcome. cT3b was a very strong predictor of the oncological outcome our patients with locally advanced PCA who underwent the definitive treatment. Finally, it is necessary to add some forms of additional treatment to the definitive treatment regimen for cT3b PCA patients.

Conflict of interest None declared.

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Original article

Preparation of pediatric patients for treatment with proton beam therapy

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ABSTRACT

Purpose: Anesthesia is often used in proton beam therapy (PBT) for pediatric patients and this may prolong the treatment time. The aim of the study was to examine preparation of pediatric patients to allow smooth performance of PBT.

Material and methods: Preparation was initiated 1–2 days before treatment planning CT and continued for 10 days. The patient first visited the facility to become familiar with the treatment room and staff. As the second step, the patient stayed in the treatment bed for a certain time with their mother, and then stayed on the treatment bed alone. Special fixtures painted with characters, music, and gifts were also prepared.

Results: From 2010 to 2014, 111 pediatric patients underwent PBT. These patients were divided into 3 groups: 40 who could follow instructions well (group A, median age: 13.6 years old), 60 who could communicate, but found it difficult to stay alone for a long time (group B, median age: 4.6 years old), and 11 who could not follow instructions (group C, median age: 1.6 years old). Preparation was used for patients in group B. The mean treatment times in groups A, B and C were 13.6, 17.1, and 15.6 min, respectively, on PBT treatment days 2–6, and 11.8, 13.0, and 16.9 min, respectively, for the last 5 days of PBT treatment. The time reduction was significant in group B ($p = 0.003$).

Conclusion: Preparation is useful for pediatric patients who can communicate. This approach allows PBT to be conducted more smoothly over a shorter treatment time.

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Radiotherapy is frequently used for pediatric tumors to improve disease control. However, many pediatric patients cannot remain still on the treatment bed during radiotherapy, and these patients often require sedatives or general anesthesia [1,2]. Proton beam therapy (PBT) is widely used in pediatric patients to reduce toxicities [3–5], but the treatment time for PBT can be longer than that for photon radiotherapy and similar sedatives or anesthesia are required. Buchsbaum et al. showed that anesthesia is safe and efficient in pediatric patients receiving PBT [6] and Owusu-Agyemang et al. showed that non-invasive anesthesia is effective and safe for pediatric patients, with a seizure/laryngospasm/bronchospasm rate of 0.05% [7]. However, daily sedation or anesthesia has several difficulties, including the need for specialized staff and an extension of the treatment time.

In our hospital, anesthesiologists are unavailable on a regular basis and there is no room to perform anesthesia near the PBT treatment room. A pediatric physician induces anesthesia or administers sedatives, accompanies the patient to the treatment room, observes the PBT, and remains with the patient on transfer back to the ward. Pediatric patients also receive PBT in the same treatment room as adult patients; therefore, we have to minimize anesthesia and shorten the occupancy time in the treatment room. It would be advantageous if the need for sedation could be reduced in pediatric patients who cannot remain still, but can communicate, and we have developed a preparation process for these patients that allow PBT to be conducted smoothly and rapidly. In this report, we retrospectively investigated the effect of this process on performance of PBT for pediatric patients.

Methods and materials

Patients

A total of 111 pediatric patients received PBT at our hospital from April 2010 to April 2014. Prior written informed consent was obtained from the parents of all patients. The patients

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comprised 55 boys and 56 girls, and had a median age of 6.2 years old (range: 0.7–19.6 years old). The sites of irradiation were the brain ($n = 40$), head and neck ($n = 33$), and body ($n = 38$). The diagnoses were rhabdomyosarcoma ($n = 23$), neuroblastoma ($n = 16$), Ewing sarcoma ($n = 13$), pons glioma ($n = 10$), ependymoma ($n = 8$), germ cell tumor ($n = 7$), retinoblastoma ($n = 4$), glioma ($n = 4$), arteriovenous malformation ($n = 3$), chordoma ($n = 3$), yolk sac tumor ($n = 3$), and other tumors ($n = 17$). The patient and tumor characteristics are shown in Table 1.

Patient groups

Of the 111 patients, 40 could follow instructions and did not require preparation for PBT (group A; median age 13.6 (range 7.1–19.6) years old); 60 had difficulty staying in the treatment bed for a long time, but could communicate (group B; median age 4.6 (range 2.0–12.6) years old); and 11 could not follow instructions and required anesthesia (group C; median age 1.6 (range 0.7–3.0) years old). The preparation process described below was performed for patients in group B. The number of preparation sessions was limited to 10.

Proton beam therapy

Computed tomography (CT) images were taken at 2- to 5-mm intervals for brain or head and neck tumors, and at 5-mm intervals for body trunk tumors. A respiratory gating system (Anzai Medical Co., Tokyo, Japan) was used as required [8]. The clinical target volume was defined based on the tumor diagnosis. An additional margin of 5–10 mm was added to cover the entire CTV by enlarging the multileaf collimator and adjusting the range shifter. Proton beams from 155 to 250 MeV generated through a linear accelerator and synchrotron were spread out and shaped with ridge filters, double-scattering sheets, multicollimators, and a custom-made bolus to ensure that the beams conformed to the treatment planning data. During each treatment session, the patient position was monitored using an orthogonal fluoroscopy unit attached to the treatment unit under direct vision. On the first treatment day, a therapeutic radiologist and a radiotherapy technologist both checked the fluoroscopy images, while in routine treatment only a radiotherapy technologist checked these images. The relative biological effectiveness (RBE) of the PBT was assumed to be 1.1 [9].

Table 1
Characteristics of patients.

Characteristics	Number	%
Age (years)	0.7–19.6	6.2 (median)
Gender		
Boy	55	50
Girl	56	50
Irradiated site		
Brain	40	36
Head and neck	33	30
Body	38	34
Diagnosis		
Rhabdomyosarcoma	23	21
Neuroblastoma	16	14
Ewing sarcoma	13	12
Pons glioma	10	9
Ependymoma	8	7
Germ cell tumor	7	6
Retinoblastoma	4	4
Glioma	4	4
Arteriovenous malformation	3	3
Chordoma	3	3
Yolk sac tumor	3	3
Others	17	15

Preparation

The purpose of the preparation process was to allow the patient to remain still while alone in the treatment bed during PBT. Preparation was scheduled and performed by a radiation technologist and a nurse who were in charge of the actual treatment. Preparation was performed using a step-by-step schedule (see Supplementary File-1). The first step was to become familiar with the treatment room and staff. This step mainly consisted of visiting the PBT facility and playing with the radiation technologist and nurse. The second step was to stay still in the treatment bed for a period of time with a well-known person (mother in most cases). The final step was to remain still on the treatment bed for the required treatment time while alone (see Supplementary File-2). An immobilization bed and mask (those actually used during PBT) were utilized during preparation to allow the patient to become used to fixation. A picture book was usually used from the first visit as an aid to preparation. In this book, well-known characters provide a simple explanation of PBT. To reduce anxiety, a special treatment area was prepared for pediatric patients. Favorite characters were painted on the treatment mask and the body fixture was decorated as the patient wished (Fig. 1). A favorite video or music CD was played during position adjustment and irradiation, and a sticker was placed on the treatment calendar on every treatment day as a gift.

Treatment planning CT was performed about 1 week before the first day of PBT and preparation was initiated on this day or 1–2 days earlier. The average time of preparation was about 15 min per day and was limited to a maximum of 30 min. Preparation was performed about 5–6 times before PBT. Some patients who could not remain still on the treatment bed alone on the first treatment day continued preparation during the treatment period up to a total of 10 times overall.

Statistical analysis

Two measurements were used to evaluate the efficacy of the preparation process: the daily occupancy time of the treatment room, and the number of patients who needed anesthesia during PBT. The occupancy time was defined as the time from patient entry into the treatment room until completion of irradiation. One-way analysis of variance (ANOVA) was performed to compare occupancy times among groups A, B and C. The numbers of patients who needed anesthesia during PBT were recorded for treatment planning CT, on the first day of PBT, and on the last day of PBT.

Results

Of the 60 patients who underwent the preparation process (group B), 36 needed anesthesia for treatment planning CT (essentially prior to preparation), 31 needed anesthesia on the first day of PBT (after the preparation process was initiated), and 17 needed anesthesia within the first 5 treatment days (after preparation was complete). The dose of anesthetic agent also decreased in 9 of these 17 patients. Changes in the number of patients who needed anesthesia in group B are shown in Fig. 2a.

In all 111 patients, 47 needed anesthesia for treatment planning CT (median age 3.4, range 0.7–8.7), 41 needed anesthesia on the first day of PBT (median age 3.0, range 0.7–8.7), and 27 needed anesthesia on the last day of PBT (median 2.5, range: 0.7–8.7). The dose of anesthetic agent was decreased in 9 of these 27 patients. Anesthesia was required in 41% of all patients for treatment planning CT (100%, 93%, 70% and 56% in 2-, 3-, 4-, and 5-year old patients, respectively), but only in 24% after preparation (75%, 57%, 10% and 0% in the respective age groups). Changes in the num-

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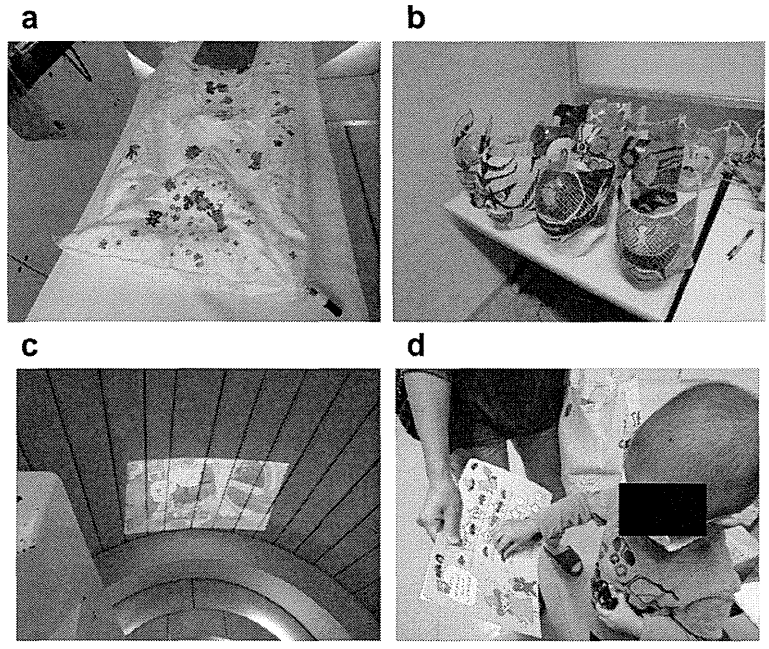

Fig. 1. (a) Decorated treatment bed. (b) Painted treatment mask. (c) A favorite video is shown on the ceiling or music is played during position adjustment and irradiation. (d) A sticker is placed on the calendar on every treatment day. All decorations and paintings are handmade at the patient's request.

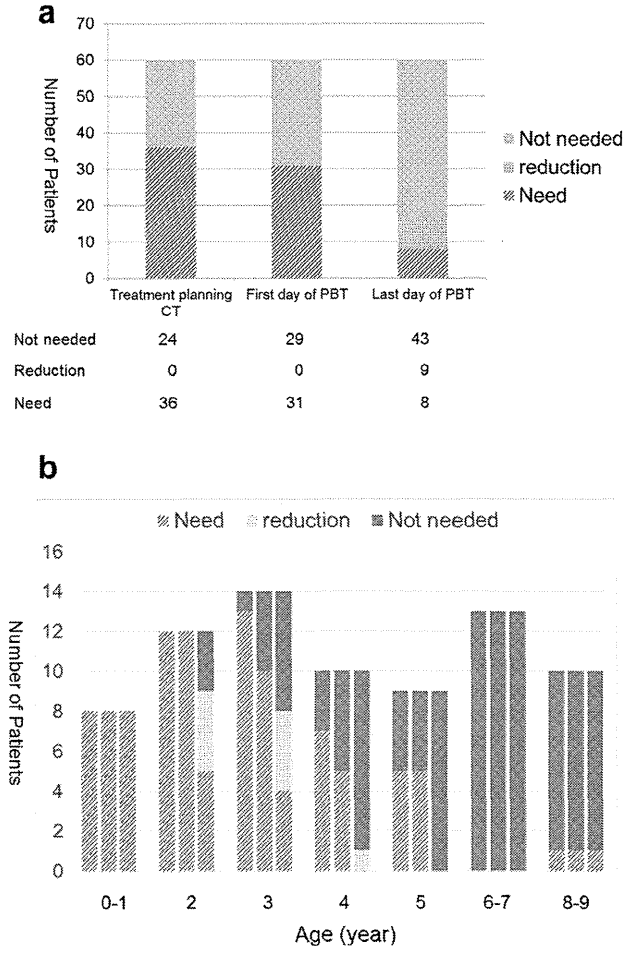

Fig. 2. (a) Process of anesthesia in group B ($n = 60$, underwent preparation). (b) Process of anesthesia in age groups in all patients. The age-grouped bar charts indicate (from left to right) the number of patients who required anesthesia for planning CT, on the first day of PBT, and on the last day of PBT, respectively. The number of patients requiring a reduced dose of anesthesia is also indicated.

ber of patients who needed anesthesia in each age group are shown in Fig. 2b.

The mean treatment times on the first day of PBT were 24.5 (range 8.5–80.2, 95% CI 21.7–27.3) min for all patients, and 20.9 (range 10.2–52.2, 95% CI 17.9–24.0), 26.5 (range 8.5–80.2, 95% CI 22.1–30.9) and 26.6 (range 12.4–72.5, 95% CI 15.5–37.8) min in groups A, B and C, respectively. These times are longer than those on subsequent days because of body adjustments performed on day 1 by the physician and radiation technologist. There were no significant differences among the three groups ($p = 0.161$ by ANOVA). The mean treatment times on all PBT days (localization by a radiation technologist only) were 14.6 (range 7.4–46.1, 95% CI 13.3–15.8) min for all patients, and 13.3 (range 7.4–35.3, 95% CI 11.3–15.4), 15.1 (range 8.4–46.1, 95% CI 13.4–16.9) and 16.0 (range 10.1–25.3, 95% CI 12.8–19.1) min in groups A, B and C, respectively, again with no significant difference among the groups ($p = 0.304$). Treatment times on the first and following days of PBT are shown in Supplementary File-3a and 3b.

A comparison of treatment times on days 2–6 and on the last 5 days of PBT was performed to evaluate the impact of familiarization with the PBT procedure. The mean treatment times on days 2–6 were 13.6, 17.1, and 15.6 min in groups A, B and C, respectively, with no significant differences among the groups ($p = 0.068$). In contrast, for the last 5 days, the mean treatment times were 11.8, 13.0, and 16.9 min, respectively, and there was a significant difference among the groups ($p = 0.03$). The changes in treatment times for the last 5 days compared to days 2–6 were −1.7 (range −11.1–5.3, 95% CI −2.9 to −0.4), −4.2 (range −27.1 to 4.1, 95% CI −5.7 to −2.7) and 1.4 (range −4.8 to 5.7, 95% CI −0.8 to 3.6) min in groups A, B and C, respectively (see Supplementary File-3c). ANOVA showed a significant difference among the groups ($p = 0.001$) and multiple comparison showed significant differences between groups A and B ($p = 0.047$) and between groups B and C ($p = 0.003$).

Discussion

PBT is performed for various malignancies [10–14] and PBT for pediatric patients may be particularly beneficial due to reduction

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of late toxicities such as disturbance of growth and second malignancies [15,16]. Brodin et al. found that PBT reduces the risk of a second malignancy in irradiation of the whole spine [15] and Sethi et al. showed a reduced risk of a second malignancy in patients with retinoblastoma who were treated with photon and proton radiotherapy, with 10-year actual cumulative incidences of radiotherapy-induced in-field second malignancy of 0% (proton) and 14% (photon) [16]. However, PBT requires accurate daily localization, and therefore has an equal or longer treatment time compared to photon radiotherapy. In an evaluation of radiotherapy and treatment planning CT, Bois et al. found that the mean time per person for routine irradiation from entering to leaving the treatment room was 19 min [19]. This is similar to our occupancy time of 15 min, particularly because our time did not include the time from the end of PBT to leaving the treatment room.

Anesthesia for pediatric patients during radiotherapy is commonly used and is considered to be safe and effective [1,2]. In a study of anesthesia in pediatric patients receiving PBT, Buchsbaum et al. found that the total time under anesthesia was about 50 min and that the average time from the start of anesthesia to the start of PBT was about 7 min [6]. These data indicate that anesthesia greatly lengthens the total treatment time, but does not have a major influence on the time of occupancy of the treatment room. However, in practice, there are problems with use of anesthesia. Staff resources may limit performance of anesthesia to a maximum of 2–3 patients each day. Also, anesthesia is performed by a pediatric doctor for all except high-risk patients, and this doctor remains with the patient throughout the anesthesia and pre- and post-PBT period, which may take more than 30 min. A treatment schedule is also required for anesthesia, including performance of anesthesia at least 3 h after lunch in our hospital. Ideally, PBT for all patients is finished earlier, but PBT for pediatric patients under anesthesia is performed later and some patients cannot eat dinner because of insufficient recovery from anesthesia. This causes a disruption in the rhythm of everyday life.

Given these problems, a strategy for smooth PBT for pediatric patients is required. In photon radiotherapy, Tsai et al. showed that play reduces the anxiety of pediatric patients with a brain tumor treated by radiotherapy [17]. Haederli et al. showed that a psycho-educational intervention reduced the need for anesthesia during radiotherapy for pediatric patients [18], with anesthesia required for most patients aged 3–4, but few aged 4–5, without the intervention, and in most patients aged 2–3, but few aged 3–4, with the intervention. For photon radiotherapy, Fortney et al. showed that anesthesia was required in 86% of patients aged 2–3, but in only 49% of those aged 3–4 [2].

In our study, anesthesia was required for all patients aged 2 or less, but only for about half of the patients aged 3 years old. Thus, we can perform PBT for pediatric patients with minimum use of anesthesia, even though the time for PBT is generally equal to or longer than that for photon radiotherapy. The treatment time on PBT days 1 and 2–6 was longer in patients in groups B and C than in group A (although without a significant difference), but this time was significantly reduced in group B (patients who underwent preparation) in the last 5 days of PBT. The mean time of 13.0 min for group B in this period was similar to that of 11.8 min in group A (patients who could communicate well). This indicates that patients in group A underwent PBT more smoothly in earlier sessions, but that preparation smoothened performance of PBT in group B in later sessions. These findings show that the preparation process described in this study is useful for reducing the need for anesthesia, allowing PBT to be performed in less time, and permitting regular daily life activities in pediatric patients who can communicate, but find it difficult to stay alone on the treatment bed.

Conflict of interest

None.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.01.007.

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Particle beam therapy

Association between pretreatment retention rate of indocyanine green 15 min after administration and life prognosis in patients with HCC treated by proton beam therapy

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ABSTRACT

Purpose: The Child-Pugh score is often used to judge the outcome of radiotherapy for hepatocellular carcinoma (HCC). The retention rate of indocyanine green 15 min after administration (ICG R15) can also be used to predict prognosis after liver resection. We evaluated the utility of ICG R15 for prediction of outcomes after proton beam therapy (PBT) for HCC.

Methods and materials: A retrospective evaluation was performed in 250 patients who received PBT between 2002 and 2007. The patients (178 males and 72 females) had a median age of 71 years (range: 43–88). Child-Pugh categories were A (score 5–6), B (7–9), and C (10–15) in 197, 51, and 2 patients, respectively. ICG scores were 0–<10, 10–<20, 20–<30, 30–<40 and ⩾40 in 27, 99, 59, 28 and 37 patients, respectively; including 26, 92, 45, 16 and 18 Child-Pugh A patients and 1, 8, 14, 11, and 17 Child-Pugh B patients, respectively. Survival times from the start of PBT were compared between Child-Pugh A and B patients, and among each ICG group.

Results: The median survival times were 61 months (95% CI: 50–72 months) in all patients, and 64 and 20 months in Child-Pugh A and B patients, respectively ($p = 0.001$), The 3-year survival rates were 72%, 72%, 75%, 63%, and 26% in patients with ICG scores of 0–<10, 10–<20, 20–<30, 30–<40, and ⩾40 ($p = 0.001$); 70%, 75%, 77%, 65%, and 38% in these respective groups in Child-Pugh A patients ($p = 0.02$); and 100%, 57%, 67%, 36%, and 14% in Child-Pugh B patients ($p = 0.173$, not significant). Multivariate analysis showed that low ICG R15 and the absence of portal vein tumor thrombus were associated with good survival.

Conclusions: Pretreatment ICG R15 is a useful prognostic factor for prediction of outcome of PBT in HCC patients, especially in those with Child-Pugh A liver function.

Hepatocellular carcinoma (HCC) is a common malignancy [1,2] that is currently treated curatively using surgery, radiofrequency ablation and liver transplantation [3–9]. Transarterial chemoembolization and systemic therapy (such as sorafenib) may be used in cases in which standard treatments are not applicable [10–13]. However, the indication for curative treatment for HCC is limited by the size and number of tumors and by residual liver function. Radiotherapy was originally not used as curative treatment for HCC because of the low tolerance dose of normal liver [14], but recent advances in technology, such as stereotactic radiotherapy and proton beam therapy (PBT), have enabled curative radiotherapy for HCC [15–19]. PBT is particularly effective for achieving good local control of HCC without severe late toxicity [20–23]. Pretreatment Child-Pugh class is strongly associated with prognosis after PBT and the 5-year local control rate after PBT is 80–90% [24–31].

The retention rate of indocyanine green for 15 min (ICG R15) is commonly used for evaluation of liver function and as an indication for surgical resection [40]. However, some patients with high ICG R15 are not candidates for surgical resection, even with Child A liver function. Stenmark et al. showed that changes in ICG R15 during treatment are an early indicator of tolerance to hepatic irradiation [32]. For radiotherapy, however, pretreatment ICG R15 is not always evaluated and the association between ICG R15 and treatment outcome has not been examined [33]. In the current study, we retrospectively investigated pretreatment ICG R15 as a predictor of prognosis and liver function after PBT.

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Methods and materials

Patients

From January 2002 to November 2009, 383 patients received PBT for HCC at our hospital. Written informed consent was obtained from all patients prior to performance of PBT. All 383 patients met criteria of (1) no active tumors outside the target volume; (2) a performance status (PS) ⩽2; (3) hepatic function characterized by a Child-Pugh score ⩽10; (4) no extrahepatic metastasis; (5) white blood cell count ⩾1000/mm^3, hemoglobin level ⩾6.5 g/dl, platelet count ⩾25,000/mm^3; (6) no uncontrolled ascites. However, only 250 of the patients underwent an indocyanine green clearance test for measurement of pretreatment ICG R15. These patients were enrolled in the study.

The 250 patients comprised 178 men and 72 women, and had a median age of 71 years old (range: 43–88 years old). The Eastern Cooperative Oncology Group (ECOG) PS was 0, 1 and 2 in 162, 82 and 6 patients, respectively. The Child-Pugh category for impairment of liver function was class A in 197 patients (114 had a score of 5, and 83 had a score of 6), class B in 51 (29, 18 and 4 with scores of 7, 8 and 9, respectively), and class C in 2 (all with a score of 10). The median pretreatment ICG R15 was 19 (range: 0–91). The ICG R15 scores were 0–<10, 10–<20, 20–<30, 30–<40, and ⩾40 for 27, 99, 59, 28, and 37 patients, respectively.

Twenty-six patients were positive for hepatitis B virus (HBV), 177 for hepatitis C virus (HCV), 6 for both HBV and HCV, and 41 had neither type of infection. There were 124 patients with a solitary mass and 126 with multiple tumors prior to PBT. The maximum tumor diameters ranged from 6 to 130 mm, with a median value of 35 mm. Clinical target volume (CTV) ranged from 3 to 1398 cm^3, with a median volume of 43 cm^3. Of the 250 patients, 36 had portal vein tumor thrombus (PVTT) and 120 received another treatment (RFA, TAE, or surgery) before PBT. The patient and tumor characteristics are shown in Table 1.

Table 1
Characteristics of patients and tumors.

Characteristics	Number	%
Age (years)	43–88	71 (median)
Gender		
Male	178	71
Female	72	29
ECOG performance status		
0	162	65
1	82	33
2	6	2
Etiology of liver disorder		
Hepatitis B virus	26	10
Hepatitis C virus	177	71
Both Hepatitis B and C virus	6	2
No	41	16
Child-Pugh classification		
A	197	79
B/C	53	21
Tumor size (mm)	6–130	35 (median)
CTV (cm^3)	3–1398	43 (median)
Prior treatment		
Yes	120	48
No	130	52
PVTT		
Yes	36	14
No	214	86
ICG R15		
<10	27	11
10–19	99	40
20–29	59	24
30–39	28	11
<40	37	15

ECOG, Eastern Cooperative Oncology Group; CTV, clinical tumor volume; PVTT, portal vein tumor thrombus.

Proton beam therapy

The physical properties of the proton beams used in this study have been described elsewhere [34]. Prior to treatment planning, patients had metallic fiduciary markers (iridium seeds of 0.8 mm in diameter and 2 mm in length) implanted in the vicinity of the tumor to aid in positioning. After making an individual immobilization cradle, CT images were taken at 5-mm intervals during the expiratory phase under a respiratory gating system (Anzai Medical Co., Tokyo, Japan) [35,36]. The CTV encompassed the gross tumor volume with a 5- to 10-mm margin in all directions. We determined the CTV to cover the GTV plus 10 mm or more when the GTV included a portal vein tumor thrombus. An additional 5-mm margin was included on the caudal axes to compensate for uncertainty due to respiration-induced hepatic movements. An additional margin of 5–10 mm was added to cover the entire CTV by enlarging the multileaf collimator and adjusting the range shifter. Proton beams from 155 to 250 MeV generated through a linear accelerator and synchrotron were spread out and shaped with ridge filters, double-scattering sheets, multicollimators, and a custom-made bolus to ensure that the beams conformed to the treatment planning data.

The proton beam schedule was selected depending on tumor location. A total dose of 77.0 GyE in 35 fractions or 74 GyE in 37 fractions was selected for tumors within 2 cm of the gastrointestinal tract, 72.6 GyE in 22 fractions was selected for tumors within 2 cm of the porta hepatis, and 66 GyE in 10 fractions was selected for tumors that were not adjacent to the gastrointestinal tract or porta hepatis. The gastrointestinal tract was avoided as far as possible after 40–50 GyE. Using this approach, we essentially ensure that at least 50 GyE in 25 fractions is delivered to the CTV. The dose for the CTV changes according to the space between the CTV and gastrointestinal tract (about 50 GyE in 25 fractions when the space is zero and close to 74 GyE in 37 fractions when the space is ⩾1.5 cm). The relative biological effectiveness (RBE) of the PBT was assumed to be 1.1 [37].

Follow-up procedures

During treatment, acute treatment-related toxicities were assessed weekly in all patients. After completion of PBT, physical examinations, CT or MRI, and blood tests were performed every 3 months for the first 2 years and every 6 months thereafter.

Statistical methods

Overall survival and local control were evaluated in all 250 patients. The Kaplan–Meier method was used for calculation of local control and survival rates, with a Log-rank test used to evaluate differences between groups [38]. Overall survival and local control were classified based on the ICG R15 and Child-Pugh score. Acute and late treatment-related toxicities were assessed using the National Cancer Institute Common Criteria v.3.0 [39] and the RTOG/EORTC late radiation morbidity scoring scheme. The following potential prognostic factors were evaluated with respect to overall survival: age, liver function (ICG R15), PS, gender, prior treatment, number of tumors, tumor size, CTV, and presence of PVTT. Prior treatments were defined as those performed for HCC included in the proton beam field. Groups were established by dividing age, ICG R15, tumor size or CTV using the median value. Multivariate analyses were performed using a Cox proportional hazard model.

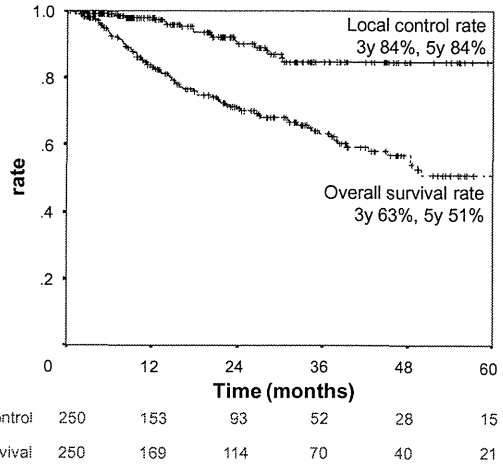

Fig. 1. Kaplan–Meier estimates of overall survival and local control for all patients.

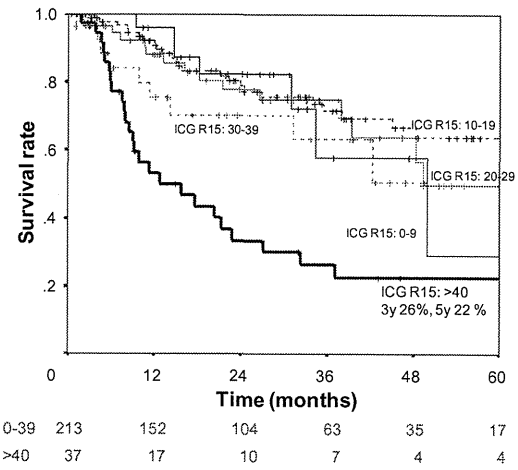

Fig. 3. Kaplan–Meier estimates of overall survival in all patients in groups with ICG R15 scores of 0–<10, 10–<20, 20–<30, 30–<40, and ⩾40, respectively.

Results

One patient with a treatable intratumor hemorrhage did not complete PBT according to the treatment protocol. All other patients completed PBT as scheduled and all were followed up until death or until December 2013.

The overall 1-, 3- and 5-year survival rates for all patients were 83% (95% CI: 78–88%), 63% (56–70%), and 51% (42–60%), respectively (Fig. 1). The median survival times were 61 months (95% CI: 50–72 months) for all patients, and 64 and 20 months for Child-Pugh A and B patients, respectively, with a significant difference between these groups ($p = 0.001$; Fig. 2). The 3-year survival rates were 72%, 72%, 75%, 63%, and 26% for patients with an ICG R15 of 0–<10, 10–<20, 20–<30 30–<40, and ⩾40, respectively, and survival differed significantly among these groups ($p = 0.001$; Fig. 3). The median survival times were 63 and 16 months for patients with ICG R15 ⩽39 and ⩾40, respectively. In Child-Pugh A patients, the 3-year survival rates were 70%, 75%, 77%, 65%, and 38% in the respective ICG groups, with significant differences in survival among these groups ($p = 0.02$; Fig. 4). In Child-Pugh B patients, the respective 3-year survival rates were 100%, 57%, 67%, 36%, and 14%, but survival did not differ significantly among groups ($p = 0.173$).

Multivariate analysis for all patients ($n = 250$) showed that ICG R15 and PVTT were significantly associated with overall survival (Table 2). Multivariate analysis for patients with Child-Pugh class A ($n = 197$) similarly showed that ICG R15 and PVTT were significantly associated with overall survival (Table 3).

At the time of analysis, 165 patients were alive and 85 patients had died: 62 due to HCC, 12 due to hepatic failure, and 11 due to other causes. The pretreatment ICG R15 of the patients who died due to hepatic failure ranged from 13% to 76% (median 42%) and the Child-Pugh score was 5–10 (median 6.5). Death due to hepatic failure occurred in 5 of 57 patients (9%) with a pretreatment ICG R15 ⩽39 compared to 7 of 28 (25%, 2 Child A, 5 B/C) with a pretreatment ICG R15 ⩾40; and in 6 of 55 patients (11%) with a Child-Pugh score of 5 or 6 compared to 6 of 30 (20%) with a Child-Pugh score of 7–10. Of the 12 patients who died due to liver failure, 4 died within 6 months after PBT (defined as treatment-related toxicity) and 8 died more than 6 months after PBT (defined as progressive cirrhosis). The 1- and 2-year overall survival rates of 12 patients who died due to liver failure without tumor recurrence were 33% and 8%, respectively (median 9 months, 95% CI: 8–10 months) (Fig. 5).

The 1-, 3- and 5-year local control rates were 98% (95% CI: 96–100%), 85% (95% CI: 78–91%), and 85% (95% CI: 78–91%), respectively (Fig. 1). There was no significant difference in local control between Child-Pugh A and B/C patients. In contrast, pretreatment

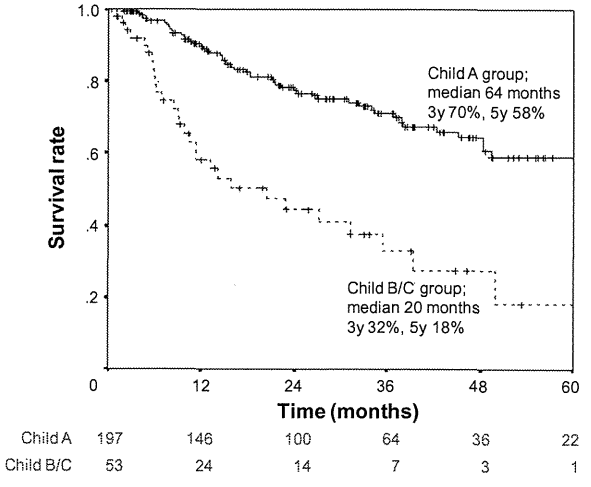

Fig. 2. Kaplan–Meier estimates of overall survival in Child-Pugh A and B/C patients.

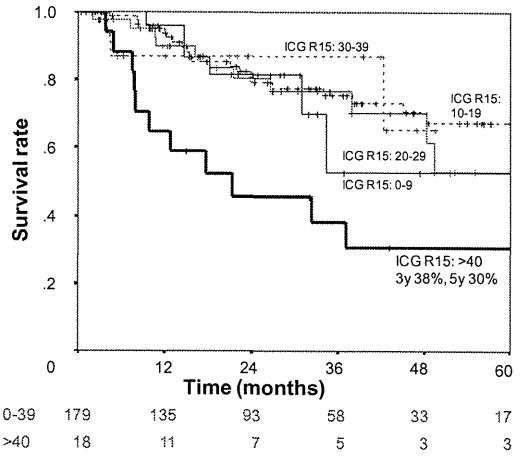

Fig. 4. Kaplan–Meier estimates of overall survival in Child-Pugh A patients with ICG R15 scores of 0–<10, 10–<20, 20–<30, 30–<40, and ⩾40, respectively.

Table 2
Multivariate analysis of potential predictive factors for overall survival of all patients.

	Number of patients	Multi-variate P	Hazard ratio	95% CI
CTV (cm^3)		0.214	1.48	0.80–2.77
<43	124			
⩾43	126			
Age		0.444	1.19	0.76–1.86
<71	116			
⩾71	134			
Gender		0.412	0.80	0.48–1.35
Male	178			
Female	72			
PS		0.495	0.85	0.52–1.37
0	162			
1/2	88			
Diameter (cm)		0.758	1.10	0.59–2.05
<3.5	124			
⩾3.5	126			
PVTT		0.003	2.44	1.34–4.44
No	214			
Yes	36			
ICG R15		0.001	2.49	1.57–3.96
<20	126			
⩾20	124			
Tumor		0.294	1.27	0.82–1.96
Single	124			
Multiple	126			
Prior treatment		0.750	1.08	0.69–1.68
No	130			
Yes	120			

Table 3
Multivariate analysis of potential predictive factors for overall survival of patients with Child-Pugh A liver function (n = 197).

	Number of patients	Multi-variate P	Hazard ratio	95% CI
CTV (cm^3)		0.539	0.78	0.35–1.74
<43	97			
⩾43	100			
Age		0.228	1.42	0.80–2.51
<71	88			
⩾71	109			
Gender		0.093	0.53	0.26–1.11
Male	144			
Female	53			
PS		0.287	0.71	0.38–1.33
0	131			
1/2	66			
Diameter (cm)		0.11	1.95	0.87–4.40
<3.5	94			
⩾3.5	103			
PVTT		0.011	2.77	1.26–6.09
No	169			
Yes	28			
ICG R15		0.030	1.88	1.06–3.34
<20	118			
⩾20	79			
Tumor		0.333	1.31	0.76–2.27
Single	104			
Multiple	93			
Prior treatment		0.199	1.44	0.83–2.51
No	101			
Yes	96			

ICGR15 was significantly associated with local control. Thus, the 1-, 3- and 5-year local control rates of patients with ICG R15 <30 were 98%, 88% and 88%, respectively; whereas these rates were 98%, 67% and 67% in patients with ICG R15 ⩾30.

Discussion

Previous studies of PBT for patients with HCC [24–31] have suggested that pretreatment Child-Pugh score is well correlated with life prognosis after PBT. However, there are few reports describing pretreatment ICG R15 for radiotherapy. Stenmark et al. showed that ICG R15 is an early indicator of tolerance to hepatic irradiation and that ICG R15 in patients with radiation-induced liver disease (RILD) tends to worsen soon after radiotherapy [32]. In the current study, ICG R15 was not evaluated post-PBT, and thus we cannot evaluate ICG R15 as a possible indicator for RILD. In 30 patients who received PBT, Kawashima et al. suggested that pretreatment ICG R15 was a prognostic factor, as well as Child-Pugh classification, and that high ICG R15 may be a risk factor for proton-induced