Table 2. *Continued*

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
	diagnostic observations only; intervention not indicated	function; limiting instrumental ADL	elective operative intervention indicated; limiting self care ADL; disabling	urgent operative intervention indicated	
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	–	–
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region.					
Rectal perforation	–	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall.					
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum.					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

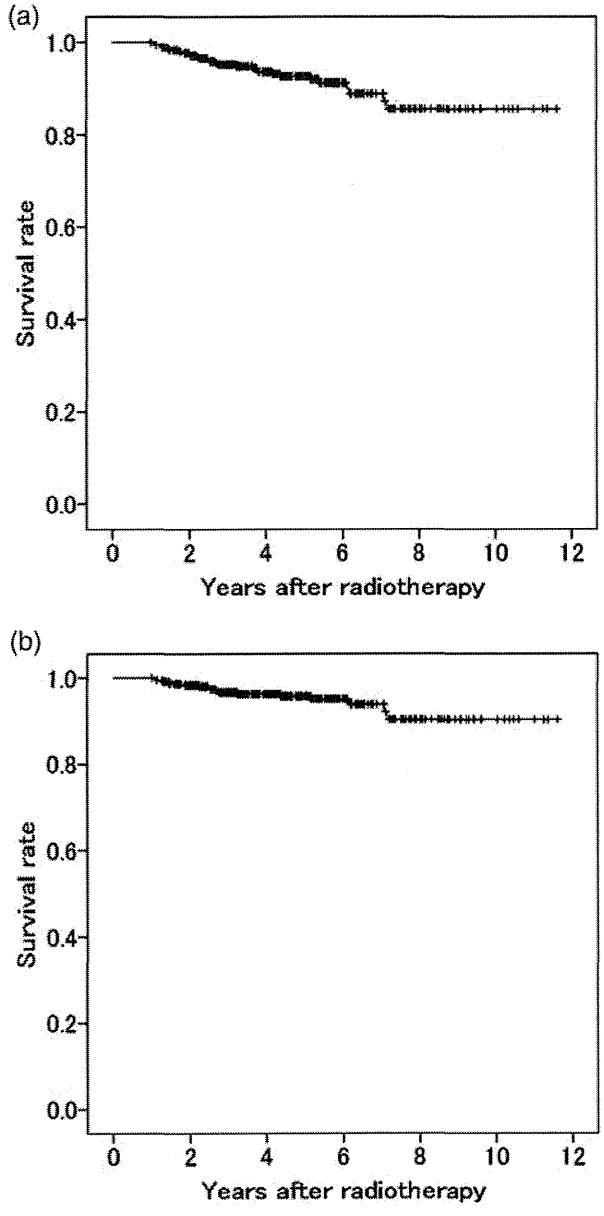

Fig. 1. (a) The 5-year overall survival rate was 93%. (b) The 5-year prostate cancer-specific survival rate was 96%.

field-shrinking technique was used for almost all patients (357 of 362, or 99%), once for 340 (94%) and twice for the other 17 (5%). The first shrinking was performed at 60 Gy for 219 patients (61%), at 50 Gy for 76 (21%), at 40 Gy for 42 (12%), and at other doses for 20 patients (6%). The second shrinking was performed at 60 Gy for 12 patients (71%), at 66 Gy for 4 (24%), and at 50 Gy for 1 (6%).

For the original irradiation field, three institutions defined the clinical target volume (CTV) as the prostate plus the whole seminal vesicle (SV), and the other two institutions as the prostate plus a part of SV. As for the shrinking field, three institutions defined the CTV as the prostate plus a part of SV, and the other two as the prostate only. In the original field, the median margin (distance from the CTV to the block edge) was 1.5 cm (range, 1.5–3.0) except for in the posterior (rectal) direction, where it was 1.3 cm (range, 1.0–2.0). As for the shrinking field, the median margin was 1.3 cm (range, 1.0–2.0) except for in the posterior direction, where it was 0.8 cm (range, 0.6–1.5). In 2D simulation, a Foley catheter was placed and contrast medium was administered into the bladder and rectum for visualization, trying to keep the definition of CTV and field margin described as above as much as possible. Retrograde urethrography was not performed routinely.

The use of the CT-simulator significantly reduced the irradiation field size compared to that used for 2D simulation (Table 3). The mean ± standard deviation (SD) of the distance between block edges in the right–left (RL) direction was 10.8 ± 1.1 cm for 2D simulation compared to 8.4 ± 1.2 cm for 3D (CT) simulation ($P < 0.001$). The corresponding values in the superior–inferior (SI) direction were 10.2 ± 1.0 cm and 8.2 ± 1.0 cm ($P < 0.001$), and in the anterior–posterior (AP) direction 8.8 ± 0.9 cm and 7.7 ± 1.0 cm ($P < 0.001$).

Findings for toxicity are shown in Table 4. The maximum CTCAE Version 4.0 Grade toxicity was observed in the form of late genitourinary (GU) toxicity, late gastrointestinal (GI) toxicity including rectal bleeding, and late rectal bleeding alone. No Grade 4 or 5 late toxicity was observed; 5 patients (1%) suffered Grade 3 GU late toxicity and 10 (3%) Grade 3 GI late toxicity, all of which consisted of rectal bleeding; 14 patients (4%) suffered Grade 2 GU late toxicity and 35 (10%) Grade 2 late GI toxicity, 32 (9%) of which consisted of rectal bleeding. The actuarial 2-, 3-, and 5-year Grade 1–3 GU late toxicity rates were 13%, 17% and 23%, respectively, and the corresponding figures for Grade 2–3 were 2%, 4% and 6% (Fig. 2). The 2-, 3-, and 5-year Grade 1–3 GI late toxicity rates were 30%, 33% and 36%, respectively, and the corresponding figures for Grade 2–3 were 13%, 14% and 14% (Fig. 3). The 2-, 3-, and 5-year Grade 1–3 late rectal bleeding rates were 26%, 30% and 31%, respectively, and the corresponding figures for Grade 2–3 were 12%, 13% and 13%.

When the patients were divided into a 2D- and a 3D-simulation group, the respective 2-, 3- and 5-year Grade 1–3 GI toxicity rates were 35%, 38% and 41% for 2D, and 27%, 31% and 32% for 3D ($P = 0.083$). The corresponding figures for Grade 2–3 were 21%, 23% and 23% for 2D, and 9%, 9% and 9% for 3D ($P < 0.001$) (Table 3). Similarly, the respective 2-, 3- and 5-year Grade 1–3 rectal bleeding rates were 33%, 38% and 38% for 2D, and 23%, 26% and 28% for 3D ($P = 0.015$), and the corresponding figures for Grade 2–3 were 21%, 23% and 23% for 2D, and 7%, 7% and 7% for 3D ($P < 0.001$) (Fig. 4).

Table 3. Comparison of 2D simulation and 3D (CT) simulation

	2D ($n = 127$)	3D ($n = 235$)	*P*
Median follow-up period (range) (year)	5.9 (1.1–11.6)	4.0 (1.0–8.0)	<0.001
Hormone therapy			<0.001
None	1 (1%)	30 (13%)	
Neoadjuvant only	7 (6%)	43 (18%)	
Adjuvant only	1 (1%)	1 (0%)	
Both neoadjuvant and adjuvant	118 (93%)	161 (69%)	
Multileaf collimator width			<0.001
0.5 cm	0 (0%)	5 (2%)	
1.0 cm	127 (100%)	155 (66%)	
2.0 cm	0 (0%)	75 (32%)	
Portal filed size (cm)[a]			
Right-left (RL)	10.8 ± 1.1	8.4 ± 1.2	<0.001
Superior-inferior (SI)	10.2 ± 1.0	8.2 ± 1.0	<0.001
Anterior-posterior (AP)	8.8 ± 0.9	7.7 ± 1.0	<0.001
Grade 1–3 late gastrointesitinal toxicity rate (%)			0.083
at 2 years	35	27	
at 3 years	38	31	
at 5 years	41	32	
Grade 2–3 late gastrointesitinal toxicity rate (%)			<0.001
at 2 years	21	9	
at 3 years	23	9	
at 5 years	23	9	
Grade 1–3 late rectal bleeding rate (%)			0.015
at 2 years	33	23	
at 3 years	38	26	
at 5 years	38	28	
Grade 2–3 late rectal bleeding rate (%)			<0.001
at 2 years	21	7	
at 3 years	23	7	
at 5 years	23	7	

[a]Mean ± standard deviation.
Grade: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
Late gastrointestinal toxicity included late rectal bleeding.

DISCUSSION

To describe and analyse late toxicity is of the utmost importance for the use of radiation therapy for the treatment of prostate cancer. A number of publications have dealt with late toxicity in prostate radiotherapy [2–13]. However, most of these studies examined mixed populations with respect to prescribed dose, dose fractionation, or beam arrangements (for example, number of beam ports and their gantry angles). Therefore, the quantity of pure data for the effect of portal field size on late toxicity has been insufficient.

In Japan, prostate cancer was not considered to be a commonly occurring cancer until around 2000. Moreover, radical prostatectomy was preferred to radiotherapy by most urologists until that time [14]. However, the rate of prostate cancer incidence has been rapidly increasing recently [15], and at the same time, definitive radiotherapy has become

Table 4. Grade of late toxicity

	Late genitourinary toxicity		Late gastrointestinal toxicity		Late rectal bleeding	
	n	%	*n*	%	*n*	%
Grade 3	5	1	10	3	10	3
Grade 2	14	4	35	10	32	9
Grade 1	59	16	79	22	66	18
Grade 0	281	78	235	65	251	69
Missing	3	1	3	1	3	1
Total	362	100	362	101	362	100

Grade: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.
Late gastrointestinal toxicity included late rectal bleeding.

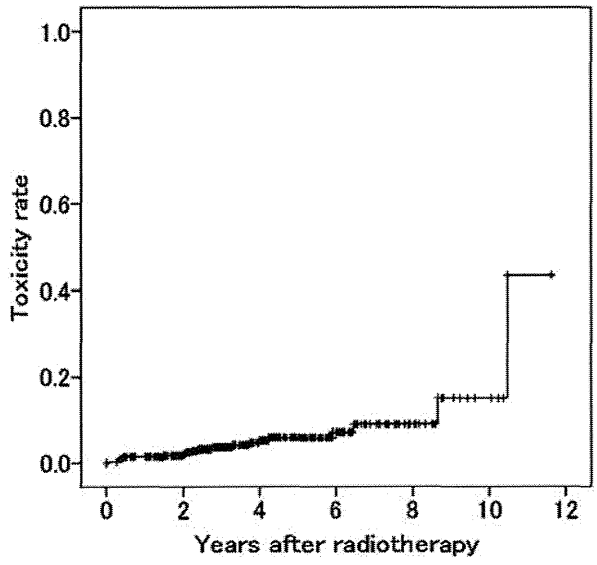

Fig. 2. Grade 2–3 late genitourinary toxicity. The 2-, 3- and 5-year toxicity rates were 2%, 4% and 6%, respectively.

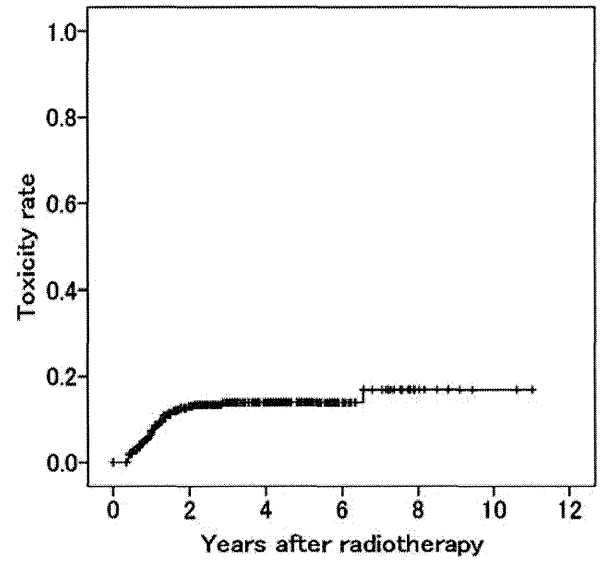

Fig. 3. Grade 2–3 late gastrointestinal toxicity. The 2-, 3- and 5-year toxicity rates were 13%, 14% and 14%, respectively.

the prevailing treatment mode. For these reasons, quite a few institutions did not have much experience with definitive radiotherapy for prostate cancer around 2000, when the subjects of our study were treated (1998–2006). Five representative institutions in the Osaka area, where radiation oncologists who had been trained at Osaka University were employed, participated in this study. These oncologists principally followed the same procedure as the one used at Osaka University, that is, the classical 4-field technique using anterior–posterior and lateral beams with 70 Gy in 35 fractions regardless of T-stage, Gleason Score or pretreatment prostate-specific antigen level. In fact, we found that 378 of all 436 patients (87%) enrolled in the previous survey study of ours had been treated with the same dose-fractionation of 70 Gy in 35 fractions. In view of this finding, we decided to embark upon this second survey to investigate solely the relationship between portal field size and late toxicity for a uniform setting of dose and beam arrangements.

To the best of our knowledge, our study cohort is one of the largest series treated with a uniform dose-fractionation and irradiation technique (classical 4-field technique). Moreover, all the institutions changed their simulation method from simple X-ray film-based simulation (2D) to CT simulation (3D) by the end of data acquisition for this study, which enabled us to compare the field size of 3D and 2D simulation. The results were very clear and easy to understand: 3D simulation reduced the field size significantly, as well as the rate of GI late toxicity, especially rectal bleeding. The reason for this improvement is deemed

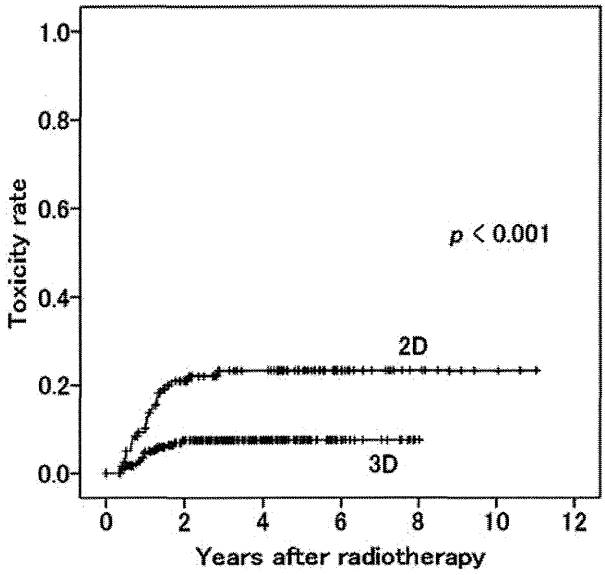

Fig. 4. Grade 2–3 late rectal bleeding. The 2-, 3- and 5-year occurrence rates were 21%, 23% and 23% for 2D simulation, and 7%, 7% and 7% for 3D simulation, respectively ($P < 0.001$).

to be simply that with the smaller irradiation field the rectum could be largely avoided. There might be a speculation that not only field sizes but also the width of the MLC made an impact on the toxicities. We analysed the influence of the width of the MLC, but no statistically significant impact was detected (data not shown), we think because the number of patients treated with other than 1 cm-width MLC was too small compared to the 1 cm-width group. This issue should be addressed with other cohorts in other studies.

A strength of this study may well be that the surveyors were all physicians: no non-physicians participated. Moreover, they were mostly the same physicians that had treated the patients who were the subject of this paper. This makes a high degree of accuracy likely for the data collection, although it should be noted that this study was of a retrospective nature. On the other hand, a variation was observed in the incidence rate of Grade 1 toxicity among the five institutions as follows; 14–33% for 5-year Grade 1 GU late toxicity, 17–36% for GI and 13–30% for rectal bleeding. This variation might indicate that the incidence rate of Grade 1 depended on and was influenced by the physicians who followed up patients, especially in a retrospective analysis; therefore, the significance of the figures presented as Grade 1 toxicity should be considered as relatively low.

The rate of Grade 2–3 late toxicity detected in our study was similar to, or slightly higher than, the findings of other studies in the literature. Dearnaley *et al.* [6] reported that, in their randomized controlled trial in which all patients were treated with 64 Gy, radiation-induced Grade 2 or higher proctitis and bleeding occurred in 5% in the conformal group compared to 15% in the conventional group ($P = 0.01$). They found no difference between groups in bladder function after treatment (20 vs. 23% for Grade 2 or more, $P = 0.61$). It should be noted, however, that the toxicity scales used for their study were the Radiation Therapy Oncology Group (RTOG) criteria [16]. Morris *et al.* [7] conducted an evidence-based review of 3-dimensional conformal radiotherapy (3D-CRT) as part of an American Society for Radiation Oncology (ASTRO) outcomes initiative. In the Task Force Conclusion, they stated that 3D-CRT reduces late morbidity, particularly GI late morbidity, with the dose to the rectum limited. No benefits in terms of GU symptoms or sexual function were observed. Their conclusion thus shows good agreement with ours. Zelefsky *et al.*, in their reports of the long-term results for 3D-CRT [8] and intensity-modulated radiotherapy (IMRT) [9] noted that, with 3D-CRT, the 5-year actuarial likelihood of Grade 2 and 3 late GI toxicities was 11% and 0.75%, respectively, while the corresponding findings for GU were 10% and 3%. With IMRT, the 10-year actuarial likelihood of Grade 2 and 3 late GI toxicities was 2% and 1%, respectively, while the corresponding findings for GU were 11% and 5%. The shapes of their actuarial toxicity curves resembled those of ours. That is, the GI toxicity curve reached a plateau at 2 or 3 years after radiotherapy, while the GU toxicity curve gradually rose until 10 years or more after radiotherapy. However, none of these studies provided detailed information on portal field size or its relation to late toxicity.

Dearnaley *et al.* had addressed this issue by a prospective randomized trial comparing 1.0 and 1.5 cm margins, arriving at the conclusion that the larger margin had been associated with the significantly higher incidence of toxicities [2]. However, their study had included only 126 patients, who had been assigned to 2×2 arms (64 Gy and 74 Gy groups, and, 1.0 and 1.5 cm margin groups). Moreover, their treatment planning had included two phases comprising a 3-field (anterior and left/right lateral or posterior oblique fields) phase and a 6-field (left and right, anterior/posterior oblique and lateral fields) phase. Although those patients had been randomly assigned, such critical heterogeneity of the cohort in total dose (64 Gy and 74 Gy) and treatment planning approach (3-field and 6-field) might make the interpretation complicated in terms of reproducibility. We considered that our current study could still add information and complement the conclusion drawn by Dearnaley *et al.*, because it included a significantly larger number of patients (362 patients) and the treatment was in a more homogeneous manner (all with 70 Gy by 4-field) in spite of its weakness as a retrospective study.

The main criticism of our study might be that the kind of data on which it is based is so classical that no direct clinical indicators such as V_{40Gy} or V_{65Gy} of the rectum, could

be provided as dose-volume constraints for modern 3D treatment planning for 3D-CRT or IMRT. However, the authors believe that the data presented here are still meaningful in terms of (i) describing a certain era of Japanese standard practice, (ii) providing radiation oncologists and treatment planners with a valuable reference because of the clear correspondence between a given portal field size (as a final block-to-block distance that would be relevant even for the most up-to-date irradiation technology) and a given rate of late toxicity, and (iii) providing suggestions for newly emerging irradiation technique in terms of a tolerance level that should not be exceeded, as detailed next.

CONCLUSION

In conclusion, we investigated late toxicity associated with EBRT for prostate cancer under conditions of a uniform setting of classical 4-field 70 Gy in 35 fractions. The use of CT simulation and the resultant reduction in the portal field size were significantly associated with diminished GI late toxicity, especially with less rectal bleeding. Typically, the field size was significantly reduced from $10.8 \times 10.2 \times 8.8$ cm (2D simulation) to $8.4 \times 8.2 \times 7.7$ cm (3D simulation), and at the same time, the rate of Grade 2–3 late rectal bleeding was significantly reduced from 23% to 7%. In view of the high overall and cause-specific survival rates observed in our study, any novel innovative radiotherapy should not exceed a late toxicity level of 7% for Grade 2–3 rectal bleeding in order to improve the quality of life of the patients or at least keep it the same as with "classical radiotherapy".

FUNDING

This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI (21791192).

ACKNOWLEDGEMENTS

This study is dedicated to the late Professor Takehiro Inoue, who was Chair of the Osaka Urological Tumor Radiotherapy Study Group, in recognition of his outstanding contribution to radiation oncology.

REFERENCES

1. Yoshioka Y, Suzuki O, Kobayashi K *et al.* External-beam radiotherapy for clinically localized prostate cancer in Osaka, Japan, 1995-2006: time trends, outcome, and risk stratification. *Strahlenther Onkol* 2009;**185**:446–52.
2. Dearnaley DP, Hall E, Lawrence D *et al.* Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005;**92**:488–98.
3. Pilepich MV, Asbell SO, Krall JM *et al.* Correlation of radiotherapeutic parameters and treatment-related morbidity analysis of RTOG Study 77-06. *Int J Radiat Oncol Biol Phys* 1987;**13**:1007–12.
4. Smit WGJM, Helle PA, van Putten WL *et al.* Late radiation damage in prostate cancer patients treated by high dose external radiotherapy in relation to rectal dose. *Int J Radiat Oncol Biol Phys* 1990;**18**:23–9.
5. Schultheiss TE, Hanks GE, Hunt MA *et al.* Incidence of and factors related to late complications in conformal and conventional radiation treatment of cancer of the prostate. *Int J Radiat Oncol Biol Phys* 1995;**32**:643–9.
6. Dearnaley DP, Khoo VS, Norman AR *et al.* Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomized trial. *Lancet* 1999;**353**:267–72.
7. Morris DE, Emami B, Mauch PM *et al.* Evidence-based review of three-dimensional conformal radiotherapy for localized prostate cancer: an ASTRO outcomes initiative. *Int J Radiat Oncol Biol Phys* 2005;**62**:3–19.
8. Zelefsky MJ, Cowen D, Fuks Z *et al.* Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. *Cancer* 1999;**85**: 2460–8.
9. Alicikus ZA, Yamada Y, Zhang Z *et al.* Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2011;**117**:1429–37.
10. Takahashi Y, Koizumi M, Sumida I *et al.* What is the optimum minimum segment size used in step and shoot IMRT for prostate cancer? *J Radiat Res* 2010;**51**: 543–52.
11. Ogino I, Kaneko T, Suzuki R *et al.* Rectal content and intrafractional prostate gland motion assessed by magnetic resonance imaging. *J Radiat Res* 2011;**52**:199–207.
12. Aoyama H, Azuma Y, Inamura K. Comparison of daily prostate positions during conformal radiation therapy of prostate cancer using an integrated CT-linear accelerator system: in-room CT image versus digitally reconstructed radiograph. *J Radiat Res* 2011;**52**:220–8.
13. Tanaka H, Hayashi S, Ohtakara K *et al.* Usefulness of CT-MRI fusion in radiotherapy planning for localized prostate cancer. *J Radiat Res* 2011;**52**:782–8.
14. Arai Y, Egawa S, Tobisu K *et al.* Radical retropubic prostatectomy: time trends, morbidity and mortality in Japan. *BJU Int* 2000;**85**:287–94.
15. Center for Cancer Control and Information Services, National Cancer Center, Japan. Trend in age-standardized cancer incidence rate (world pop, major sites) [male 1975-2005]. http://ganjoho.ncc.go.jp/professional/statistics/index.html (26 December 2011, date last accessed, in Japanese).
16. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**:1341–6.

Cancer Chemother Pharmacol (2012) 69:1499–1505
DOI 10.1007/s00280-012-1853-7

ORIGINAL ARTICLE

Neoadjuvant chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil for esophageal cancer

Manabu Emi · Jun Hihara · Yoichi Hamai · Yoshiro Aoki · Morihito Okada · Masahiro Kenjo · Yuji Murakami

Received: 27 January 2012 / Accepted: 14 February 2012 / Published online: 2 March 2012

Abstract
Purpose We aimed to evaluate the safety, tolerability, and efficacy of combination preoperative chemoradiotherapy as first-line treatment in patients with advanced esophageal cancer.
Methods We performed a phase I dose-escalation trial of docetaxel at 25–40 mg/m^2 in four planned dose levels in 3–6 patient cohorts on days 1, 15, 29, and 43 administered in combination with cisplatin (70 mg/m^2 on days 1 and 29) and 5-fluorouracil (70 mg/m^2/day on days 1–4 and 29–32) and concurrent radiation therapy (40 Gy). The tumors were resected during weeks 10–13.
Results This study included 7 patients with esophageal cancer. The dose-limiting toxicity was observed at a biweekly docetaxel dose of 30 mg/m^2 when patients developed grade 3 febrile neutropenia, grade 4 thrombocytopenia, and grade 4 pain/esophagus, resulting in a maximum tolerated dose of 25 mg/m^2. Grade 3/4 hematological toxicity was observed in 71% of the patients and grade 3/4 non-hematological toxicity in 57%. The overall tumor response rate was 86% (complete, 57% and partial, 29%). All patients underwent surgery, and there were no deaths as a result of postoperative complications.
Conclusions This preoperative chemoradiotherapy regimen using triplets is feasible but results in moderate toxicity. It is noteworthy that this regimen was associated with a high rate of pathological complete remission.

Keywords Esophageal cancer · Chemoradiotherapy · Docetaxel · Cisplatin · 5-Fluorouracil

M. Emi (✉) · J. Hihara · Y. Hamai · Y. Aoki · M. Okada
Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8553, Japan
e-mail: moaista@wish.ocn.ne.jp

M. Kenjo · Y. Murakami
Department of Radiology, Graduate School of Biomedical Sciences, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8553, Japan

Introduction

Esophageal cancer is the sixth leading cause of cancer deaths in Japanese men. An estimated 12,000 individuals die due to esophageal cancer every year [1]. The incidence of esophageal adenocarcinomas is increasing in Western Europe and the United States, whereas esophageal squamous cell carcinomas are the most commonly encountered type of esophageal cancer in Japan. Most patients with newly diagnosed carcinoma of the esophagus present with locally advanced disease. Since the incidence of locoregional and distant failure is high, considerable interest has been generated in combining local and systemic therapy. Preoperative chemoradiotherapy and surgery are potentially curative for patients with locoregional disease, and this treatment is probably superior to surgery alone [2–4]. However, prognosis for these patients remains poor. In an effort to improve treatment results, newer combinations of chemotherapy with radiotherapy have been evaluated.

5-Fluorouracil and cisplatin (CF) are the most commonly used agents in combination chemotherapy and radiotherapy. A V325 phase III study on gastric cancer demonstrated that adding docetaxel to CF significantly improved the time to progression, survival, and overall response rate as compared to treatment with CF alone [5]. A randomized trial of squamous cell carcinoma of the head and neck illustrated the advantages of combining docetaxel, cisplatin, and 5-fluorouracil as induction

chemotherapy compared to cisplatin and 5-fluorouracil, when followed by chemoradiotherapy [6]. On the basis of these studies, it was hypothesized that a preoperative therapy consisting of a chemotherapy combining docetaxel, cisplatin, and 5-fluorouracil, followed by radiotherapy, could significantly improve the prognosis of patients with localized esophageal cancer. The present work is a phase I clinical trial designed to evaluate the safety and efficacy of this neoadjuvant chemotherapy. The primary end point was dose-limiting toxicity (DLT) during chemoradiation. Secondary objectives were feasibility and efficacy of the neoadjuvant chemoradiotherapy.

Methods

Eligibility

Previously untreated patients with histological proof of squamous cell carcinoma of the thoracic esophagus or gastroesophageal junction (GEJ), with clinical T2–T3 N0–3, and M0 (including supraclavicular or celiac lymph node involvement) disease according to the American Joint Committee on Cancer (AJCC), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were eligible to participate in this study.

The patients were required to have measurable disease by radiological or endoscopic evaluation at the time of enrollment. Other eligibility criteria included age $\leq$75 years, adequate organ function (white blood cell count [WBC], $\geq$3,000/μL; platelet count, $\geq$100 $\times$ 109/L; serum bilirubin, $\leq$1.5 $\times$ the upper limit of normal (UNL); serum, AST/ALT less than 1.5 $\times$ the UNL; alkaline phosphatase, <2.5 $\times$ the UNL; and serum creatinine, $\leq$1.2 mg/dL; or calculated creatinine clearance, $\leq$60 mL/min). The exclusion criteria included history of hypersensitivity to docetaxel, cisplatin (CDDP), 5-fluorouracil (5-FU), or polysorbate 80; infection with fever elevation; peripheral neuropathy >grade 1; any other serious preexisting medical illnesses; pregnancy or lactation; and prior invasive malignancy within 5 years. This study was approved by the Institutional Ethics Committee, and all the patients provided their written informed consents prior to the enrollment.

Treatment plan

Radiation therapy

External beam radiotherapy was given at 5 fractions per week for 4 weeks (total dose, 40 Gy) [7]. Radiotherapy was delivered using 10-MV X-rays. A computed tomography (CT) simulator was used for three-dimensional treatment planning. The radiation field for upper thoracic tumors included the region from the supraclavicular, cervical, and mediastinal lymph nodes to the carina. The field for mid-thoracic or lower thoracic tumors included the cervical, mediastinal, and perigastric lymph nodes, and the supraclavicular fossa was included if the cervical nodes tested positive. The field for GEJ tumors included the mediastinal (lower than subcarinal), perigastric, and celiac lymph nodes. The primary tumor was included with a craniocaudal margin of 2–3 cm.

Concurrent chemotherapy

During radiotherapy, all patients received intravenous docetaxel (days 1, 15, 29, and 43), CDDP (days 1 and 29), and 5-fluorouracil (days 1 thorough 4 and days 29–32), as shown in Fig. 1. Initial dose levels were influenced by dose levels reported as a phase I trial of definitive chemoradiotherapy by Higuchi et al. [8]. They used docetaxel (20–40 mg/m^2) and an infusion of cisplatin (40 mg/m^2) on day 1 plus a continuous infusion of 5-fluorouracil (400 mg/m^2/day) on days 1–5, administered every other week and recommend the following dosage for phase II studies of DCF plus radiotherapy: docetaxel 35 mg/m^2, cisplatin 40 mg/m^2, and 5-fluorouracil 400 mg/m^2/day with 61.2 Gy of concurrent radiotherapy. We reduced the dose with respect to neoadjuvant chemoradiotherapy. We used a conventional dose-escalation schema with the primary end point of defining the DLT of docetaxel that can be delivered with CDDP, 5-fluorouracil, and radiotherapy, as shown in Table 1. Steroids and antiemetic premedication were administered to all the patients.

Definition of dose-limiting toxicities (DLTs): The following toxicities (according to the Common Terminology Criteria for Adverse Events (version 3.0) of the National Cancer Institute) that occurred during chemoradiotherapy or before surgery were defined prospectively as DLTs:

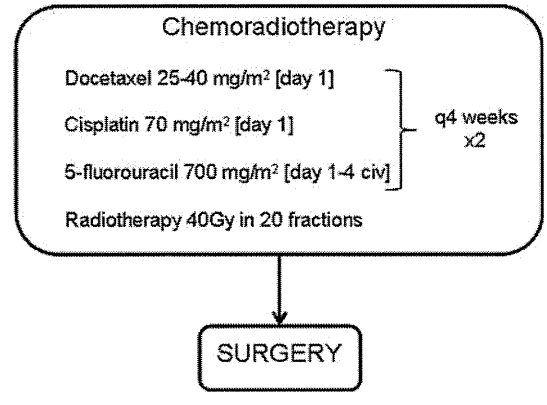

Fig. 1 A schematic showing the treatment and the dosage of different drugs

Table 1 Chemotherapy dose levels

	Docetaxel (mg/m^2) Day 1, 15	Cisplatin (mg/m^2) Day 1	5-FU (mg/m^2/day) Days 1–4
Level 1	25	70	700
Level 2	30	70	700
Level 3	35	70	700
Level 4	40	70	700

(1) grade 4 neutropenia or leucopenia (persisting for 5 days or longer); (2) grade 4 thrombocytopenia; (3) grade 3 or 4 febrile neutropenia; (4) other grade 3 or 4 non-hematological toxicity, except for grade 3 esophagitis, nausea, vomiting, anorexia, and diarrhea within 3 days, dyspepsia, hyperglycemia, and abnormalities of sodium, potassium, and calcium; (5) omission of chemotherapy >1 week; (6) interruption of radiotherapy for >1 week.

Dose-escalation schema

At least three patients were enrolled at each level. If no DLT was observed, the next dose level was opened for enrollment. If DLT was observed in one or two patients, then up to three additional patients were enrolled. Intrapatient dose escalation was not permitted. If 3 or more patients experienced DLTs, the dose escalation was stopped and that dose was regarded as the maximum tolerated dose (MTD). The recommended dose (RD) for the phase II study of docetaxel was determined to be one dose level below the MTD.

Suspended criteria of chemoradiotherapy: In the case of toxicity, no dose modification was allowed in this study. If hematological toxicity ≥grade 3 occurred, administration of the chemotherapy was delayed until the platelet count was $\geq 10 \times 10^4/mm^3$, and absolute neutrophils were $\geq 2 \times 10^3$. Radiotherapy continued despite chemotherapy interruptions. Radiotherapy, together with chemotherapy, was suspended if the patient experienced grade 4 esophagitis until improvement to grade 2.

Surgery

Patients were underwent definitive surgical resection from weeks 10–13. The patients in whom the primary tumor was located in the upper or middle thoracic esophagus underwent transthoracic esophagectomy (involving laparotomy, right thoracotomy, and cervical anastomosis) with three-field lymph node dissection (thoracic, abdominal, and cervical). Those whose primary tumor was located in the lower thoracic or abdominal esophagus underwent transthoracic esophagectomy with two-field lymph node dissection. Reconstruction was usually carried out via a gastric tube through the posterior mediastinal or retrosternal route.

Definition of response

The tumors, nodes, and metastases were staged according to the International Union against Cancer criteria [9]. Clinical staging was carried out using results of endoscopy, endoscopic ultrasound, barium swallow, computed tomography scanning of the abdomen and thorax, and positron-emission tomography.

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to evaluate the responses in all the patients. The final response category assigned to the patients represented the best response obtained during treatment. All the patients were reassigned into stages 3–4 weeks after completing combined therapy (week 9) using results of CT scans, endoscopy and, where available, endoscopic ultrasound and positron-emission tomography. Histopathological response, a secondary end point, was based on the pathological findings after esophagectomy. Pathological complete remission (pCR) was defined as the complete disappearance of the tumor on histological examination.

Monitoring procedures and follow-up

During treatment, patients were reviewed weekly, and their weight, patient performance status (PS), and physical examination were measured, and acute toxicities were recorded. Biochemical analysis and creatinine clearance were measured weekly from blood samples obtained from the patients every week.

After active treatment, the patients were examined (including CT scan) every 3 months for the first year, every 4 months in the next year, and then every 6 months in the next 3 years. Endoscopic examination was carried out annually.

Results

Patients

Between December 2009 and November 2010, we enrolled 7 patients with esophageal cancer into this study. Patient characteristics are summarized in Table 2. There were 5 male and 2 female subjects of ages ranging from 38 to 71 years (median, 61 years). The PS was 0 in all cases. Of these, 5 patients had stage IIIA esophageal cancer and 2 had stage IIIB esophageal cancer. All the patients had squamous cell carcinoma.

Table 2 Patient characteristics

Age (year)	
Median	61
Range	38–71
Gender (*n*, %)	
Male	5 (71.4)
Female	2 (28.6)
ECOG performance (*n*, %)	
0	6 (85.7)
1	1 (14.3)
AJCC TNM stage (*n*, %)	
IIIA	5 (71.4)
IIIB	2 (28.6)
Histological type (*n*, %)	
Squamous cell	7 (100)

ECOG Eastern Cooperative Oncology Group, *AJCC* American Joint Committee on Cancer

Treatment delivery and toxicity

All the patients were evaluated for toxicity weekly during radiotherapy and concurrent chemotherapy. The adverse effects of the treatment are summarized in Table 3. The patients completed planned radiotherapy without any treatment interruptions. Hospitalization and intravenous fluids were required in the case of 4 patients with grade 3 esophagitis.

Among the 3 patients who were administered level 1 docetaxel, none had DLTs. Of the 3 patients who were administered level 2 docetaxel, 2 had DLT. One patient in dose level 2 experienced grade 3 febrile neutropenia. This event caused a delay in chemotherapy; however, radiotherapy was completed without any interruption. Despite the use of opioids, 1 patient at dose level 2 experienced severe pain due to esophagitis after the completion of radiotherapy. Since the pain resulted in the patient becoming confined to bed, we deemed it as grade 4 pain and DLT. However, these symptoms disappeared after approximately 2 weeks of central venous nutrition. Therefore, a fourth patient was treated. This additional patient had grade 4 thrombocytopenia. Therefore, DLT occurred in 3 of the 4 patients, and the level 2 dose was designated as the MTD and the level 1 dose was designated as the RD for phase II studies. One patient who was administered level 2 docetaxel had grade 4 hyponatremia and was diagnosed with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), but this patient recovered after water restriction, and Na supplements were applied.

All the patients underwent definitive surgical resection during weeks 10–13. Four patients underwent transthoracic esophagectomy with three-field lymph node dissection and 3 underwent transthoracic esophagectomy with two-field lymph node dissection. Infections were the predominant complication of surgery (Table 4) and occurred in 3 patients (43%). One patient (14%) developed anastomotic leakage, which was resolved with conservative measures. There were no deaths at 30 days after the surgery. Furthermore, there was no in-hospital mortality during the 6-month follow-up, and there were no treatment-related deaths.

Response

All the 7 patients are included in the response analyses (Table 5). Complete pathological response was seen in 3 patients and partial response in 4 patients with an overall response rate of 86%. One patient had progressive disease. Complete tumor resection with microscopically clear

Table 3 Common toxicities (NCI-CTC version 3)

	Level 1 ($n = 3$)			Level 2 ($n = 4$)			Overall ($n = 7$)		
	Any	G3	G4	Any	G3	G4	Any	G3	G4
Leukopenia	3	2	0	4	3	0	7	5	0
Neutropenia	3	1	0	4	3	0	7	4	0
Anemia	3	0	0	4	1	0	7	1	0
Thrombocytopenia	1	0	0	2	1	1[a]	3	1	1
Febrile neutropenia	0	0	0	1	1[a]	0	1	1	0
Creatinine	1	0	0	1	0	0	2	0	0
Anorexia	3	1	0	4	0	0	7	1	0
Nausea	3	0	0	4	0	0	7	0	0
Vomiting	0	0	0	0	0	0	0	0	0
Esophagitis	3	2	0	4	2	0	7	4	0
Pain/esophagus	3	2	0	3	1	1[a]	6	3	1
Diarrhea	1	0	0	0	0	0	1	0	0
Fatigue	3	0	0	2	1	0	5	1	0

[a] Three patients in dose level 2 experienced dose-limiting toxicity

Table 4 Post-operative complications (within 30 days of surgery) in patients undergoing resection

Complications	Thoracic surgery ($n = 7$)
Postoperative infection	2
Anastomotic leakage	1
Anastomotic stricture	1
Recurrent nerve paralysis	2
Recurrent nerve paralysis	3
Pneumonia	1
Re-operation	0

Anastomotic leakage: The condition resolved with conservative treatment

There were no deaths as a result of postoperative complications during the study

margins (R0 resection) was achieved in 6 of the 7 patients (86%).

Discussion

Gebski et al. [10] conducted a recent meta-analysis of neoadjuvant chemoradiotherapy for resectable esophageal cancer; they reported that a significant survival benefit was evident for preoperative chemoradiotherapy and suggested that evidence-based treatment be used for esophageal cancer. Tepper et al. [4] used chemotherapeutic agents—100 mg/m^2 cisplatin and 1,000 mg/m^2/for 4 days 5-fluorouracil with radiotherapy (50.4 Gy total dose)—and reported favorable results for neoadjuvant chemoradiation followed by surgery. In particular, the 5-year survival was 16% (95% CI, 5–33%) in the surgery-alone group versus 36% (95% CI, 21–57%) in the neoadjuvant chemoradiation group. In addition, the use of neoadjuvant chemoradiation did not appear to increase operative mortality, and the preoperative therapy was associated with manageable toxicity.

Because the achievement of pCR in the primary tumor after preoperative CRT is a positive long-term outcome [11, 12], regimens of new drug combinations containing docetaxel, paclitaxel, and/or other molecular target agents have been tested to achieve higher rates of pCR and improve survival benefit of preoperative chemoradiation for resectable esophageal cancer [13].

In this study, to improve the therapeutic effect of standard cisplatin plus 5-FU concurrent chemoradiotherapy, we focused on docetaxel incorporation into the therapy, which has been extensively used with radiation for the treatment of patients with non-small lung cancer and head and neck cancer [14, 15]. Although not powered to demonstrate improvements in cancer outcomes, this study shows that the addition of docetaxel to the current preoperative chemotherapy plans combining cisplatin and 5-FU provides a high response rate. Pathological CR rate of 43% compares favorably with other chemoradiotherapy studies using cisplatin and 5-FU [3, 4].

Esophagitis was the most frequent toxicity in this study. Hospitalization was required in 2 of 3 level 1 patients and 2 of 4 level 2 patients who experienced grade 3 esophagitis.

Spigel et al. [16] used a triplet regimen consisting of oxaliplatin, docetaxel, and capecitabine in combination with radiation therapy. Grade 3 esophagitis occurred in 20% of all cases. Day et al. [17] conducted a phase I trial of cisplatin and docetaxel concurrent with 50 Gy radiotherapy. In this trial, grade 3 radiation esophagitis was found to be the most common acute toxicity (37.5%). In our study, regional lymph nodes were included in the clinical target volume (CTV) as a prophylactic irradiation field for patients with no clinical evidence of lymph nodes metastases, which was larger than the irradiation field used in previous trials. This increased irradiation field could be attributed to the occurrence of esophagitis, which was the most commonly encountered adverse event.

In radiotherapy, there is no clear consensus about the CTV, especially regarding inclusion of regional lymph nodes in the CTV when there is no clinical evidence of lymph node metastases of esophageal cancer.

A recent publication has suggested that the 5-year survival improves with the number of lymph nodes removed and that this effect is observed for the removal of over 40

Table 5 Histopathological response and clinical course

Patient no.	Dose level	Stage	Clinical response		Pathological response		Status (month)
			Primary	LN	Primary	LN	
1	1	IIIB (T3N2)	PR	PR	CR	CR	ADF (18)
2	1	IIIA (T3N1)	PR	PR	PR	CR	AWD (17)
3	1	IIIB (T3N2)	PR	PR	CR	PR	ADF (17)
4	2	IIIA (T3N1)	CR	CR	CR	CR	ADF (14)
5	2	IIIA (T3N1)	CR	CR	CR	PR	ADF (11)
6	2	IIIA (T3N1)	PD	NC	PD	NC	AWD (10)
7	2	IIIA (T3N1)	CR	PR	CR	CR	ADF (6)

AWD alive with disease, *ADF* alive and disease free, *CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease

nodes [18]. Another study showed that the total number of surgically resected lymph nodes is independently associated with the overall and disease-free survival in esophageal cancer [19, 20]. We believe that neoadjuvant chemoradiotherapy aims to resect not only primary tumors but also lymph nodes and surrounding tissues with microscopically clear margins that may be potentially involved, and neoadjuvant chemoradiotherapy is associated with improved lymphadenectomy. Therefore, regional lymph nodes were included as a prophylactic irradiation field in the CTV.

In this trial, the 3 agents—docetaxel, cisplatin, and 5-fluorouracil—were found to be well tolerated when combined with radiation in patients with potentially resectable esophageal cancer. The antitumor efficacy, as demonstrated by the high pathological response rate, was also extremely encouraging. Moreover, it is noteworthy that there was no indication of increased operative mortality and morbidity in our trial.

A phase II study in esophageal cancer using the doses found in this study (25 mg/m^2 docetaxel on days 1, 15, 29, and 43; 70 mg/m^2 cisplatin on days 1 and 29; 700 mg/m^2/day 5-FU on days 1–4 and 29–32; and 40 Gy radiotherapy) is currently underway at our institution.

References

1. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T, Japan Cancer Surveillance Research Group (2011) Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol 41:139–147
2. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N (1999) A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335:462–467 ([Erratum: N Engl J Med 341: 384, 1999])
3. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M (2001) Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 19:305–313
4. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, Willett C, Sugarbaker D, Mayer R (2008) Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 26:1086–1092
5. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML, Ajani JA, V325 Study Group (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 24:4991–4997
6. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglio Rdel C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM Jr, Haddad RI (2007) Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357:1705–1715
7. Natsugoe S, Okumura H, Matsumoto M, Uchikado Y, Setoyama T, Yokomakura N, Ishigami S, Owaki T, Aikou T (2006) Randomized controlled study on preoperative chemoradiotherapy followed by surgery versus surgery alone for esophageal squamous cell cancer in a single institution. Dis Esophagus 19:468–472
8. Higuchi K, Koizumi W, Tanabe S, Sasaki T, Katada C, Ishiyama H, Hayakawa K (2008) A phase I trial of definitive chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) for advanced esophageal carcinoma: Kitasato digestive disease and oncology group trial (KDOG 0501). Radiother Oncol 87:398–404
9. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) (2010) AJCC cancer staging manual, 7th edn. Springer, New York
10. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J, Australasian Gastro-Intestinal Trials Group (2007) Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 8:226–234
11. Rohatgi PR, Swisher SG, Correa AM, Wu TT, Liao Z, Komaki R, Walsh GL, Vaporciyan AA, Rice DC, Bresalier RS, Roth JA, Ajani JA (2006) Histologic subtypes as determinants of outcome in esophageal carcinoma patients with pathologic complete response after preoperative chemoradiotherapy. Cancer 106: 552–558
12. Rizk NP, Seshan VE, Bains MS, Ilson DH, Minsky BD, Tang L, Rusch VW (2007) Prognostic factors after combined modality treatment of squamous cell carcinoma of the esophagus. J Thorac Oncol 2:1117–11123
13. Ruhstaller T, Pless M, Dietrich D, Kranzbuehler H, von Moos R, Moosmann P, Montemurro M, Schneider PM, Rauch D, Gautschi O, Mingrone W, Widmer L, Inauen R, Brauchli P, Hess V (2011) Cetuximab in combination with chemoradiotherapy before surgery in patients with resectable, locally advanced esophageal carcinoma: a prospective, multicenter phase IB/II Trial (SAKK 75/06). J Clin Oncol 29:626–631
14. Kiura K, Ueoka H, Segawa Y, Tabata M, Kamei H, Takigawa N, Hiraki S, Watanabe Y, Bessho A, Eguchi K, Okimoto N, Harita S, Takemoto M, Hiraki Y, Harada M, Tanimoto M, Okayama Lung Cancer Study Group (2003) Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer 89:795–802
15. Tsao AS, Garden AS, Kies MS, Morrison W, Feng L, Lee JJ, Khuri F, Zinner R, Myers J, Papadimitrakopoulou V, Lewin J, Clayman GL, Ang KK, Glisson BS (2007) Phase I/II study of docetaxel, cisplatin, and concomitant boost radiation for locally advanced squamous cell cancer of the head and neck. J Clin Oncol 24:4163–4169
16. Spigel DR, Greco FA, Meluch AA, Lane CM, Farley C, Gray JR, Clark BL, Burris HA 3rd, Hainsworth JD (2010) Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy in localized carcinoma of the esophagus or gastroesophageal junction. J Clin Oncol 28:2213–2219
17. Day FL, Leong T, Ngan S, Thomas R, Jefford M, Zalcberg JR, Rischin D, McKendick J, Milner AD, Di Iulio J, Matera A, Michael M (2011) Phase I trial of docetaxel, cisplatin and concurrent radical radiotherapy in locally advanced oesophageal cancer. Br J Cancer 104:265–271
18. Schwarz RE, Smith DD (2007) Clinical impact of lymphadenectomy extent in resectable esophageal cancer. J Gastrointest Surg 11:1384–1394

19. Altorki NK, Zhou XK, Stiles B, Port JL, Paul S, Lee PC, Mazumdar M (2008) Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg 248:221–226
20. Rizk NP, Ishwaran H, Rice TW, Chen LQ, Schipper PH, Kesler KA, Law S, Lerut TE, Reed CE, Salo JA, Scott WJ, Hofstetter WL, Watson TJ, Allen MS, Rusch VW, Blackstone EH (2010) Optimum lymphadenectomy for esophageal cancer. Ann Surg 251:46–50

Hepatology Research

Hepatology Research 2012; 42: 442–453 doi: 10.1111/j.1872-034X.2011.00943.x

Original Article

Hepatic arterial infusion chemotherapy using 5-fluorouracil and systemic interferon-α for advanced hepatocellular carcinoma in combination with or without three-dimensional conformal radiotherapy to venous tumor thrombosis in hepatic vein or inferior vena cava

Eisuke Murakami,[1] Hiroshi Aikata,[1] Daisuke Miyaki,[1] Yuko Nagaoki,[1] Yoshio Katamura,[1] Tomokazu Kawaoka,[1] Shintaro Takaki,[1] Akira Hiramatsu,[1] Koji Waki,[1] Shoichi Takahashi,[1] Tomoki Kimura,[2] Masahiro Kenjo,[2] Yasushi Nagata,[2] Masaki Ishikawa,[3] Hideaki Kakizawa,[3] Kazuo Awai[3] and Kazuaki Chayama[1]

Departments of [1]Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, [2]Radiation Oncology, Division of Genome Radiobiology and Medical Science, and [3]Diagnostic Radiology, Division of Medical Intelligence and Informatics, Hiroshima University, Hiroshima, Japan

Aim: We investigated the efficacy of hepatic arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and systemic interferon (IFN)-α (HAIC-5-FU/IFN) for advanced hepatocellular carcinoma (HCC) with venous tumor thrombosis (VTT) in the hepatic vein trunk (Vv2) or inferior vena cava (Vv3).

Methods: Thirty-three patients with HCC/Vv2/3 underwent HAIC with 5-FU (500 mg/body weight/day, into hepatic artery on days 1–5 on the first and second weeks) and IFN-α (recombinant IFN-α-2b 3 000 000 U or natural IFN-α 5 000 000 U, intramuscularly on days 1, 3 and 5 of each week). Three-dimensional conformal radiotherapy (3D-CRT) was used in combination with HAIC-5-FU/IFN in 14 of 33 patients to reduce VTT.

Result: The median survival time (MST) was 7.9 months, and 1- and 2-year survival rates were 30% and 20%, respectively. Evaluation of intrahepatic response after two cycles of HAIC-5-FU/IFN showed complete response (CR) in three (9%) and partial response (PR) in seven (21%), with an objective response rate of 30%. Multivariate analysis identified reduction of VTT ($P = 0.0006$), size of largest tumor ($P = 0.013$) and intrahepatic response CR/PR ($P = 0.030$) as determinants of survival. CR/PR correlated significantly with tumor liver occupying rate ($P = 0.016$) and hepatitis C virus Ab ($P = 0.010$). Reduction of VTT correlated significantly with radiotherapy ($P = 0.021$) and platelet count ($P = 0.015$). Radiotherapy-related reduction in VTT significantly improved survival of 16 patients with Vv3 and non-CR/PR response of HAIC-5-FU/IFN ($P = 0.028$).

Conclusion: As for advanced HCC with VTT of Vv2/3, HAIC-5-FU/IFN responsive patients could obtain favorable survival. Despite ineffective HAIC-5-FU/IFN, the combination with effective radiotherapy to VTT might improve patients' prognosis.

Key words: 5-fluorouracil, hepatocellular carcinoma, interferon, radiotherapy, venous tumor thrombosis

INTRODUCTION

THE PROGNOSIS OF patients with advanced hepatocellular carcinoma (HCC) remains poor,[1–3] although that of patients with HCC has gradually improved following the development of new diagnostic techniques and advancements in therapeutic modalities, such as surgical resection, radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), radiotherapy and hepatic arterial infusion chemotherapy (HAIC).[4–8] Recent advances in implantable drug delivery systems have facilitated repeated arterial infusions of anti-cancer agents to tumors in the corresponding arterial perfusion area. HAIC is considered suitable for HCC patients with poor hepatic reserve due to high drug concentrations in

Correspondence: Dr Hiroshi Aikata, Department of Medicine and Molecular Science, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science, Hiroshima University, 1-2-3 Kasumi, Minamiku, Hiroshima 734-8551, Japan. Email: aikata@hiroshima-u.ac.jp
Received 8 June 2011; revision 19 October 2011; accepted 9 November 2011.

local tissue and late rates of adverse effects of anti-cancer agents. Among several anti-cancer agents, intra-arterial 5-fluorouracil (5-FU) and systemic interferon (IFN) have been reported as one of the most effective combination chemotherapies for HCC with portal vein tumor thrombus (PVTT).[9–13] Vascular invasion of HCC with PVTT, venous tumor thrombosis (VTT) and biliary thrombosis in the liver, represent the worst prognostic factors in patients with advanced HCC, especially PVTT.[14–19] On the other hand, VTT is less commonly recognized poor prognostic factor than PVTT. To define the therapeutic benefits of HAIC-5-FU/IFN for HCC with VTT in the hepatic vein trunk (Vv2), or inferior vena cava (Vv3), we retrospectively analyzed the treatment response, survival time and prognostic factors.

Three-dimensional conformal radiotherapy (3D-CRT) allows the delivery of higher radiation doses to tumors and low radiation dose to normal tissue. 3D-CRT improves the anti-tumor effect of radiotherapy and minimizes damage to normal tissue. This modality is probably suited as local radiotherapy for PVTT in patients with poor hepatic reserves.[20,21] The synergistic effects of the combination of chemotherapy and radiotherapy have been reported in various malignancies such as lung cancer and esophageal cancer.[22–25] Recently, Han *et al.*[26] reported a response rate of 45% in HCC patients with PVTT treated by HAIC with 5-FU/cisplatin and 3D-CRT. Furthermore, Katamura *et al.*[27] reported the efficacy of intra-arterial 5-FU/IFN combined with 3D-CRT for PVTT. To our knowledge, there are no studies on the therapeutic efficacy of radiotherapy for HCC with VTT. In addition, it is still unclear whether radiotherapy has any additional effects on HAIC-5-FU/IFN. Based on the above results, we retrospectively analyzed and compared differences in the clinical course and outcome of HCC patients treated by HAIC-5-FU/IFN with or without 3D-CRT.

METHODS

Study design and eligibility

THE FOLLOWING ENROLLMENT criteria were applied in the study: (i) HCC with VTT in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein (Vv2), or inferior vena cava (Vv3); (ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or PS 1; (iii) Child–Pugh stage A or B; (iv) serum total bilirubin <3.0 mg/dL; (v) leukocyte count >2000/mm^3; (vi) platelet count >50 000/mm^3; (vii) serum creatinine <1.5 mg/dL; (viii) at least a 4-week rest period of no treatment since any previous treatment for HCC; (ix) the initial administration of HAIC for HCC; and (x) no other serious medical condition that would interfere with HAIC. The presence of extrahepatic metastases was not an exclusion criterion when they were not considered prognostic factors. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Hiroshima University. Written informed consent was obtained from each patient after detailed explanation about the therapy. From March 2004 to November 2010, 33 patients met the above criteria for HAIC-5-FU/IFN. The baseline characteristics of these patients are summarized in Table 1.

Treatment protocol

The patients received repeated arterial infusion chemotherapy via drug delivery systems implanted in the subcutaneous inguinal region. The arterial catheter was implanted using the method described previously by our group.[9] One course of chemotherapy represented 2 weeks. 5-FU (500 mg/body weight/day; Kyowa Hakko, Tokyo) was administered using a mechanical infusion pump from day 1 to day 5 on the first and second weeks. Recombinant IFN-α-2b (Intron A, Schering-Plough Pharmaceuticals, Osaka, Japan) at 3 000 000 U (3 MU) or natural IFN-α (OIF, Otsuka Pharmaceuticals, Tokyo) at 5 000 000 U (5 MU), was administered intramuscularly on days 1, 3 and 5 of each week (total dose: 18 and 30 MU, respectively). As for the two types of IFN, similar effects were reported previously between recombinant IFN-α-2b and natural IFN-α when combined with intra-arterial 5-FU for the treatment of advanced HCC.[10] After each treatment course, 2–4 weeks of rest/no treatment period was enforced. HAIC-5-FU/IFN was repeated several times during the treatment as much as possible, until we considered that it was impossible to continue further HAIC-5-FU/IFN based on the following criteria: (i) PS changed to 3 or 4; (ii) adverse events were estimated as grade 4 by Common Technology Criteria for Adverse Events (CTCAE) version 4.0; (iii) patients were evaluated clinically to have progressive disease; and (iv) patient requested termination of treatment. Fourteen out of 33 patients received 3D-CRT to VTT to control VTT progression. 3D-CRT was applied to objective progressive VTT of Vv2/3, which was shown in dynamic computed tomography (CT) before or during two courses of HAIC-5-FU/IFN. From March 2004 to July 2006, when the decision to introduce 3D-CRT was clinically left to the

Table 1 Clinical characteristics of 33 patients with hepatocellular carcinoma (HCC) and venous tumor thrombus (VTT)

Clinical characteristics	Category	
Sex	Male/female	30/3
Age	<65 years/≥65 years	15/18
ECOG PS	0/1	23/10
HCV Ab	+/−	16/17
HBs Ag	+/−	7/26
Child–Pugh stage	A/B	25/8
Previous treatment	Yes/no	9/24
α-fetoprotein (ng/mL)	<5 000/≥5 000	17/16
des-γ-carboxy prothrombin (mAU/mL)	<10 000/≥10 000	14/19
Platelet count (/mm^3)	<150 000/≥150 000	19/14
Size of largest tumor (mm)	<100/≥100	16/17
Tumor liver occupying rate (%)	<50/≥50	20/13
Tumor stage†	IVA/IVB	19/14
Grade of venous invasion‡	Vv 2/3	13/20
Grade of portal invasion§	Vp 0/1/2/3/4	7/1/4/8/13
Extrahepatic metastasis	Yes/no	16/17
Radiotherapy to venous tumor thrombus	Yes/no	14/19

†According to the Liver Cancer Group of Japan.
‡Venous invasion. Vv1, tumor thrombus in peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.
§Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

attending physician, one patient of Vv2 and five patients of Vv3 were enrolled. Since August 2006, the indication of 3D-CRT was limited to objective progressive VTT of Vv3 in principle, eight patients of Vv3 were enrolled. Patients received 3D-CRT in the Division of Radiation Oncology at our hospital. They received high-energy photon beam irradiation using 18, 10 or 6 MV, delivered by a three-dimensional conformal technique (CLINAC 2300 C/D or CLINACiX linear accelerators, Varian Medical Systems Inc., Palo Alto, CA, USA). The planning CT determined the gross tumor volume (GTV) representing only the VTT. The clinical target volume (CTV) was also determined; which included GTV and intrahepatic tumor forming the basal part of VTT. The planning target volume (PTV) represented the CTV plus a 10–20-mm margin in all directions for internal motion and set-up error. Four to five portal fields were used. The outlined target volumes, total liver tissue and organs at risk, including the spinal cord, bilateral kidneys, esophagus, stomach and other nearby intestinal tract targets, were transferred to the treatment planning system (Pinnacle 3, Philips Medical Systems, Eindhoven, The Netherlands) with reference to the diagnostic enhanced CT images. The prescribed dose was 30, 39 or 45 Gy, based on the dose-volume constraint of normal tissues and liver function. Using this protocol, it was estimated that 95% of the PTV should receive at least 95% of the prescribed dose, 50% of the liver tissue should not receive more than 25 Gy, 50% of each kidney not more than 20 Gy and that the maximum dose to the spinal cord, intestinal tract and esophagus was not more than 40 Gy. Finally, five patients received a total dose of 30 Gy, five patients 39 Gy and four patients 45 Gy, in daily doses of 3 Gy per fraction.

Evaluation

Every patient underwent dynamic CT before and after two courses of HAIC-5-FU/IFN, and the therapeutic effect was classified according to Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1[28] after completion of two cycles of the chemotherapy. A complete response (CR) was defined as disappearance of all target/non-target lesions, no appearance of any other lesion within 4 weeks, and normalization of α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP). CR was confirmed at 4 weeks after the first evalu-

ation of CR. A partial response (PR) was defined as a decrease of at least 30% in the sum of the longest diameter of target lesions with the baseline sum of the longest diameter of target lesions as the reference. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameter of target lesions. Stable disease (SD) was defined as meeting neither the PR nor PD criteria. We also evaluated the treatment effect of VTT by measuring the longest diameter to increase or decrease, the response of intrahepatic tumor to the therapy and overall systemic response. Adverse reactions were assessed every week during the treatment using the CTCAE. Radiotherapy-induced liver disease (RILD) exhibited the following criteria:[29] development of anicteric elevation of alkaline phosphatase level of at least twofold, nonmalignant ascites in the absence of documented progressive disease and increased transaminases levels of at least fivefold the upper limit of normal or of pretreatment level.

Statistical analysis

Data were analyzed statistically on 1 March 2011. Differences between background factors were examined for statistical significance using logistic regression test and Pearson's χ^2 test where appropriate. Consecutive data (e.g. α-fetoprotein) was classified by each median value referring to scatter diagram or histogram. Univariate analysis of predictors of survival was assessed by the cumulative survival rate, which was calculated from the initial date of HAIC-5-FU/IFN and assessed by the Kaplan–Meier life-table method, and differences were evaluated by the log rank test. Variables that achieved statistical significance ($P < 0.05$) or those with *P*-values of less than 0.10 on univariate analysis were entered into multivariate analysis. Multivariate analysis of predictors of survival was assessed by Cox proportional hazard model or Logistic regression analysis. All analyses were performed using the Statistical Package for Social Sciences (version 11, SPSS Inc., Chicago, IL). We assessed the survival benefits and safety of HAIC-5-FU/IFN combined with or without 3D-CRT to VTT.

RESULTS

Overall survival and response

FIGURE 1 SHOWS the cumulative survival rate of 33 patients who underwent HAIC using 5-FU/IFN. The median survival time (MST) was 7.9 months. The 1- and 2-year survival rates were 30% and 20%, respectively. The median observation time was 5.5 months (range, 0.7 to 54.9 months). Table 2 shows the response to therapy as evaluated by RECIST. In five patients (shown as NE), CT could not be performed after the HAIC. The systemic (i.e., whole body) response to the treatment was: CR in three cases, PR in five, SD in four and PD in 16, with an overall systemic response rate of 24%. We also defined intrahepatic (i.e., limited to the liver) response as one of the treatment factors in order to evaluate localized therapeutic effects in the liver. The intrahepatic response was: CR in three, PR in seven, SD in six and PD in 12, with an overall intrahepatic response rate of 30%, similar to the systemic response rate.

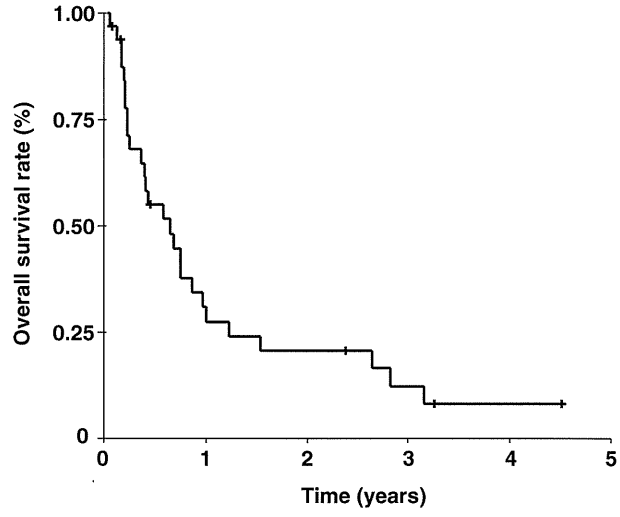

Figure 1 Overall survival of 33 patients with venous tumor thrombosis (VTT) treated by hepatic arterial infusion chemotherapy (HAIC). The median survival time (MST) was 7.9 months, and the 1- and 2-year survival rate were 30% and 20%, respectively. The median observation time was 5.5 months (range, 0.7–54.9 months).

Univariate analysis (Table 3) and multivariate analysis (Table 4) identified three factors that contributed to overall survival; treatment-related reduction in VTT

Table 2 Clinical response to the therapy to hepatocellular carcinoma (HCC) with venous tumor thrombus (VTT)

	CR	PR	SD	PD	NE	RR
Systemic evaluation of response: whole body	3	5	4	16	5	24%
Intrahepatic response: liver only	3	7	6	12	5	30%

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RR, response rate for patients with CR and PR per entire group of patients; SD, stable disease.

Table 3 Univariate analysis of factors that contributed to overall survival (Log rank test)

	Category	*n*	*P*-value
Sex	Female vs. male	3/30	0.567
Age (years)	≥65 vs. <65	18/15	0.326
ECOG PS	0 vs. 1	23/10	0.324
HCV Ab	Presence vs. absence	16/17	0.215
HBs Ag	Absence vs. presence	26/7	0.023
Child–Pugh stage	A vs. B	25/8	0.004
Previous treatment	No vs. yes	24/9	0.414
α-fetoprotein (ng/mL)	<5 000 vs. ≥5 000	17/16	0.559
des-γ-carboxy prothrombin (mAU/mL)	<10 000 vs. ≥10 000	14/19	0.309
Platelet count (/mm^3)	<150 000 vs. ≥150 000	19/14	0.0008
Size of largest tumor (mm)	<100 vs. ≥100	16/17	0.0003
Tumor liver occupying rate (%)	<50 vs. ≥50	20/13	0.0013
Grade of venous invasion (Vv)†	2 vs. 3	13/20	0.274
Grade of portal invasion (Vp)‡	0, 1, 2 vs. 3, 4	12/21	0.224
Extrahepatic metastasis	No vs. yes	17/16	0.040
Radiotherapy to venous tumor thrombus	Yes vs. no	14/19	0.667
Intrahepatic response	CR, PR vs. Other	10/23	0.0029
Effect of treatment on venous tumor thrombus	Decrease vs. increase	18/15	0.0001

†Venous invasion. Vv1, tumor thrombus in a second branch or more of peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.

‡Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

($P = 0.0006$, hazard ratio, HR, 6.611, 95% confidence interval [CI] 2.262–19.322), largest tumor size <100 mm ($P = 0.013$, HR 3.896, 95%CI 1.328–11.432), and intrahepatic response of complete response/partial response (CR/PR) ($P = 0.030$, HR 2.968, 95%CI 1.108–7.951). Patients classified as CR/PR based on intrahepatic response had a significantly longer MST than the non-CR/PR group (18.7 vs. 4.4 months, respectively, $P = 0.0029$, log rank test) (Fig. 2). Univariate analysis (Table 5) and multivariate analysis (Table 6) identified two factors that contributed to intrahepatic response of CR/PR; tumor liver occupying rate of >50% ($P = 0.016$, OR 23.239, 95%CI 1.791–301.508) and positivity for hepatitis C virus antibody (HCV Ab) ($P = 0.010$, OR 16.886, 95%CI 1.969–144.774).

Effect of radiotherapy

The clinical characteristics of patients treated by HAIC-5-FU/IFN with and without radiotherapy to VTT are summarized in Table 7. Patients treated with radiotherapy had a tendency to be elderly, hepatitis B virus

Table 4 Multivariate analysis for factors that contribute to overall survival, Cox proportional hazards model with stepwise selection

	Category	HR	95% CI	*P*-value
Effect of treatment of venous tumor thrombus	Decrease	6.611	2.262–19.322	0.0006
	Increase	1		
Size of largest tumor (mm)	<100	3.896	1.328–11.432	0.013
	≥100	1		
Intrahepatic response	CR, PR	2.968	1.108–7.951	0.030
	Other	1		

95% CI, 95% confidence interval; CR, complete response; HR, Hazard ratio, PR, partial response.

(HBV) negative and HCV positive. About two-thirds of patients with VTT of Vv3 received 3D-CRT. Figure 3 shows the overall response to treatment of all patients classified according to the application of 3D-CRT. In patients who received HAIC alone, five out of 19 patients were classified as CR/PR based on intrahepatic response, with a response rate of 26%. Furthermore, VTT was considered to have decreased in seven out of 19 patients with a VTT-treatment effective rate of 37%. For patients who received HAIC combined with radiotherapy, CR/PR was achieved in five out of 14 patients, with a response rate of 36%, and VTT decreased in 11 out of 14 patients, with a treatment effective rate of up to 79%. Radiotherapy had no significant effect on the intrahepatic response ($P = 0.561$, Pearson's χ^2 test). The combination of HAIC and radiotherapy had a significant effect on VTT ($P = 0.017$, Pearson's χ^2 test). Table 8 shows the results of univariate analysis for factors that contributed to the effect of treatment on VTT. Multivariate analysis (Table 9) two factors that significantly and independently influenced the VTT; platelet count less than 150 000/mm^3 ($P = 0.015$, OR 16.087, 95%CI 1.704–151.861) and response of VTT to radiotherapy ($P = 0.021$, OR 14.982, 95%CI 1.508–148.827). Figure 4 shows the cumulative survival rates of 16 patients with VTT in the inferior vena cava (Vv3), based on the VTT response to 3D-CRT. The nine patients who received HAIC-5-FU/IFN and 3D-CRT to VTT and showed a decrease in VTT had a significantly longer MST of 9.2 months ($P = 0.028$, log rank test), compared with the seven patients who received HAIC-5-FU/IFN without or with ineffective 3D-CRT (these patients showed increases in VTT and MST of 3.1 months).

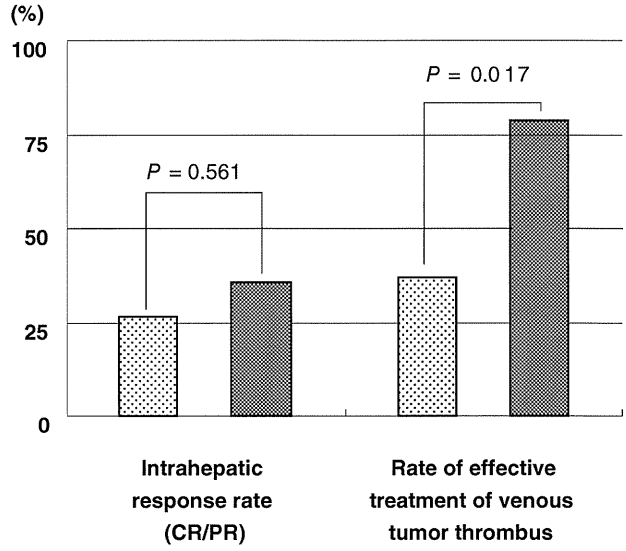

Figure 3 Overall treatment response according to the treatment regimen presence or absence of undergoing radiotherapy to venous tumor thrombus (VTT). ▨, HAIC alone; ▩, HAIC plus 3-D conformal radiotherapy (3D-CRT). HAIC, hepatic arterial infusion chemotherapy.

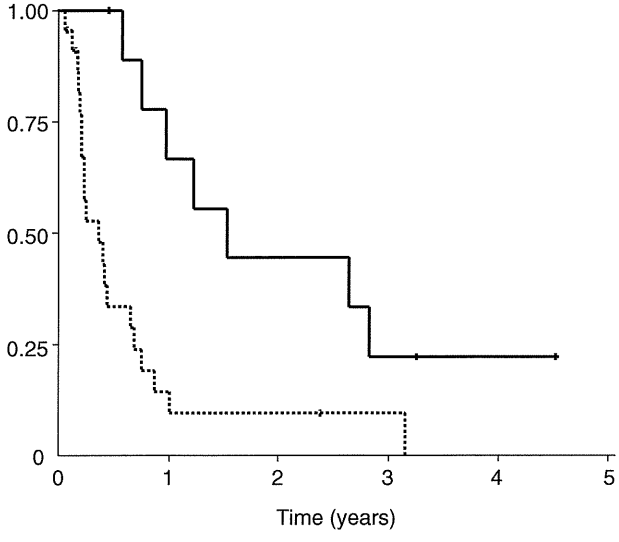

Figure 2 Cumulative survival rate of 33 patients with venous tumor thrombosis (VTT) treated by hepatic arterial infusion chemotherapy (HAIC). Solid line: 10 patients, who underwent HAIC and classified as complete response/partial response (CR/PR) based on intrahepatic response, had a significantly longer median survival time (MST) of 18.7 months ($P = 0.0029$, log rank test). Dashed line: 23 patients who were classified as non-CR/PR based on intrahepatic response resulting in MST of 4.4 months. ——, CR/PR of intrahepatic response; ·····, Non-CR/PR of intrahepatic response.

Incidence of extrahepatic metastasis

Figure 5 shows the cumulative rate of extrahepatic metastases in 17 patients who were negative for extrahepatic metastasis before HAIC-5-FU/IFN. Eight (47%) patients developed extrahepatic metastases after starting HAIC-5-FU/IFN, including seven with lung metastases and one with adrenal gland metastasis. The median time to the diagnosis of metastasis was 7.1 months. The 6- and 12-month cumulative incidence rates were 30% and 56%, respectively. The median survival time was 4.4 months after the diagnosis of extrahepatic metastasis.

Other anti-cancer treatments

Nine out of 33 (27%) patients received additional courses of HAIC with 5-FU/IFN after completing the two

Table 5 Univariate analysis for factors that contribute to intrahepatic response after two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment, Pearson's χ^2 test

	Category	*n*	*P*-value
Sex	Female vs. male	3/30	0.905
Age (years)	≥65 vs. <65	18/15	0.103
ECOG PS	0 vs. 1	23/10	0.980
HCV Ab	Presence vs. absence	16/17	0.017
HBs Ag	Absence vs. presence	26/7	0.299
Child–Pugh stage	A vs. B	25/8	0.208
Previous treatment	No vs. yes	24/9	0.061
α-fetoprotein (ng/mL)	<5 000 vs. ≥5 000	17/16	0.520
des-γ-carboxy prothrombin (mAU/mL)	<10 000 vs. ≥10 000	14/19	0.561
Platelet count (/mm^3)	<150 000 vs. ≥150 000	19/14	0.086
Size of largest tumor (mm)	<100 vs. ≥100	16/17	0.103
Tumor liver occupying rate (%)	<50 vs. ≥50	20/13	0.023
Grade of venous invasion (Vv)†	2 vs. 3	13/20	0.020
Grade of portal invasion (Vp)‡	0, 1, 2 vs. 3, 4	12/21	0.963
Extrahepatic metastasis	No vs. yes	17/16	0.497
Radiotherapy to venous tumor thrombus	Yes vs. no	14/19	0.161

†Venous invasion. Vv1, tumor thrombus in a second branch or more of peripheral branches of hepatic vein; Vv2, tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein; Vv3, tumor thrombus in inferior vena cava.

‡Portal invasion. Vp1, tumor thrombus in a third or more peripheral branches of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in a first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody.

recommended courses. On the other hand, 24 out of 33 (73%) patients did not complete HAIC-5-FU/IFN. Subsequently, 21 (64%) patients received other anti-cancer treatments, and 12 patients (36%) received best supportive care (BSC). The other treatments included TACE in 17 patients (MST 8.3 months), HAIC in six patients (MST 14.9 months) and systemic chemotherapy in six patients (MST 2.8 months). The MST of the additional treatment group was 11.8 months, which was significantly longer than the BSC group (with MST of 3.0 months, $P = 0.0078$, Log rank test). With regard to the regimens of other treatments, trans-arterial treatments tended to be associated with longer survival than systemic chemotherapy and BSC.

Adverse reactions and complications

Fever, fatigue, nausea and anorexia were the most common adverse events, but these were mostly CTCAE grade 1 or 2. CTCAE grade 3 or 4 adverse reactions included leukopenia in five patients (15%), thrombocytopenia in two (6%), anemia in three (9%) and anorexia in two (6%). Six patients required treatment with granulocyte colony-stimulating factor for leukopenia. Three patients required blood transfusion, but none

Table 6 Multivariate analysis for factors that influenced intrahepatic response to two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment. Logistic regression analysis

Factors	Category	OR	95% CI	*P*-value
Tumor liver occupying rate (%)	<50	23.239	1.791–301.508	0.016
	≥50	1		
HCV Ab	Presence	16.886	1.969–144.774	0.010
	Absence	1		

95% CI, 95% confidence interval; HCV Ab, hepatitis C virus antibody; OR, odds ratio.