Table 7 Clinical characteristics of patients with venous tumor thrombus treated by hepatic arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and systemic interferon (IFN)-α (HAIC-5-FU/IFN) with and without radiotherapy to venous tumor thrombus, Pearson's χ^2 test

Clinical characteristics	Category	Total ($n = 33$)	HAIC alone ($n = 19$)	HAIC plus radio therapy ($n = 14$)	*P*-value
Sex	Male/female	30/3	18/1	12/2	0.373
Age (years)	<65/≥65	15/18	11/8	4/10	0.024
ECOG PS	0/1	23/10	14/5	9/5	0.561
HCV Ab	+/−	16/17	6/13	10/4	0.024
HBs Ag	+/−	7/26	7/12	0/14	0.011
Child–Pugh stage	A/B	25/8	16/3	9/5	0.187
Previous treatment	Yes/no	9/24	3/16	6/8	0.084
α-fetoprotein (ng/mL)	<5 000/≥5 000	17/16	8/11	9/5	0.208
des-γ-carboxy prothrombin (mAU/mL)	<10 000/≥10 000	14/19	9/10	5/9	0.503
Platelet count (/mm^3)	<150 000/≥150 000	19/14	11/8	8/6	0.966
size of largest tumor (mm)	<100/≥100	16/17	11/8	5/9	0.208
Tumor liver occupying rate (%)	<50/≥50	20/13	11/8	9/5	0.710
Grade of venous invasion (Vv)†	Vv 2/3	13/20	12/7	1/13	0.001
Grade of portal invasion (Vp)‡	Vp 0,1,2/3,4	12/21	6/13	6/8	0.506
Extrahepatic metastasis	Yes/no	16/17	9/10	7/7	0.881

†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.

required platelet transfusion. Cutaneous ulcerations developed in the inguinal region in four patients, requiring implantation of reservoir system. Furthermore, two patients developed bleeding esophageal varices at one month after completion of HAIC-5-FU/IFN. Three patients developed radiation esophagitis, which required hospitalization as CTCAE grade 3. Of the latter group, one developed esophageal stenosis requiring endoscopic dilatation at 2 months after completion of radiotherapy. None of the patients who received the combination of HAIC-5-FU/IFN and radiotherapy developed hepatic failure that fulfilled the criteria of RILD.[29] On the other hand, three patients who did not receive 3D-CRT developed hepatic failure with hyperbilirubinemia; the cause of hepatic failure was considered to be the rapid progression of intrahepatic HCC.

Causes of death

At the time of analysis, six patients were still alive, whereas 27 patients had died. All 27 deaths were cancer-related, with the majority being due to progression of intrahepatic HCC. Among them, three patients died of HCC rupture and intra-abdominal bleeding. Two patients who did not receive 3D-CRT died of esophageal variceal bleeding. None died directly of extrahepatic metastases, and one patient died of septic necrotizing limb fasciitis. During the periods of treatment, we have no sudden death patient, which was clinically suspected to be due to pulmonary artery embolism.

DISCUSSION

INVASION OF A major vessel, especially the trunk of PVTT, is a poor prognostic factor in patients with advanced HCC.[14–19] Furthermore, the best available treatment for advanced HCC with PVTT is considered HAIC-5-FU/IFN.[9–13] Based on the lack of sufficient information on the efficacy of HAIC-5-FU/IFN for advanced HCC with VTT in the hepatic vein trunk (Vv2) or inferior vena cava (Vv3), we investigated the efficacy of HAIC-5-FU/IFN for HCC with VTT in this retrospective study. We also investigated the response to the combination of HAIC-5-FU/IFN and 3D-CRT to VTT of Vv3. In 33 patients, the intrahepatic response rate to HAIC-5-FU/IFN was 30%,

Table 8 Univariate analysis for determinants of effect of treatment on venous tumor thrombus after two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment, Pearson's χ^2 test

Factors	Category	*n*	*P*-value
Sex	Female vs. male	3/30	0.658
Age (years)	≥65 vs. <65	18/15	0.112
ECOG PS	0 vs. 1	23/10	0.730
HCV Ab	Presence vs. absence	16/17	0.112
HBs Ag	Absence vs. presence	26/7	0.120
Child–Pugh stage	A vs. B	25/8	0.767
Previous treatment	No vs. yes	24/9	0.943
α-fetoprotein (ng/mL)	<5 000 vs. ≥5 000	17/16	0.611
des-γ-carboxy prothrombin (mAU/mL)	<10 000 vs. ≥10 000	14/19	0.335
Platelet count (/mm^3)	<150 000 vs. ≥150 000	19/14	0.010
Size of largest tumor (mm)	<100 vs. ≥100	16/17	0.112
Tumor liver occupying rate (%)	<50 vs. ≥50	20/13	0.027
Grade of venous invasion (Vv)†	2 vs. 3	13/20	0.135
Grade of portal invasion (Vp)‡	0, 1, 2 vs. 3, 4	12/21	0.290
Extrahepatic metastasis	No vs. yes	17/16	0.227
Radiotherapy to venous tumor thrombus	Yes vs. no	14/19	0.017

†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.

with MST of 7.9 months. Multivariate analysis (Table 6) identified two factors that influenced the intrahepatic response to HAIC-5-FU/IFN: tumor liver occupying rate of >50% ($P = 0.016$) and positivity for HCV Ab ($P = 0.010$). The combination of HAIC-5-FU/IFN with 3D-CRT to VTT had a significantly better treatment effective rate of VTT (79%) than HAIC-5-FU/IFN alone (37%). Multivariate analysis (Table 4) identified three independent factors that influenced survival: treatment-related reduction in VTT ($P = 0.0006$), largest tumor size <100 mm ($P = 0.013$), and CR/PR for intrahepatic response ($P = 0.030$). While 3D-CRT did not significantly improve the survival times, it significantly reduced VTT, thus indirectly contributing to the high intrahepatic response and presumably improving the survival rate. Among 16 patients with disadvantageous conditions (VTT-Vv3 and non-CR/PR), effective 3D-CRT resulted in significant prolongation of survival time compared with patients who did not receive or showed ineffective response to 3D-CRT ($P = 0.028$, Fig. 4). This result suggests the prognostic value of radiotherapy to VTT for advanced HCC patients treated by HAIC-5-FU/IFN.

The response rate to HAIC-5-FU/IFN in HCC with VTT (30%) was similar to the previously reported response

Table 9 Multivariate analysis for factors that contributed to the effect of treatment on venous tumor thrombus after two cycles of hepatic arterial infusion chemotherapy (HAIC) treatment. Logistic regression analysis

	Category	OR	95% CI	*P*-value
Platelet count (/mm^3)	<150 000	16.087	1.704–151.861	0.015
	≥150 000	1		
Radiotherapy to venous tumor thrombus	Yes	14.982	1.508–148.827	0.021
	No	1		

95% CI, 95% confidence interval; OR, odds ratio.

rate to HAIC-5-FU/IFN in HCC with PVTT (29–52%).[9,12,13] Multivariate analysis found that tumor liver occupying rate ($P = 0.016$) and positivity for HCV Ab ($P = 0.010$) contributed to intrahepatic response of CR/PR (Table 6). Two previous studies[9,13] also reported that positivity for HCV Ab was also a pretreatment predictive factor for response and survival of advanced HCC treated with HAIC-5-FU/IFN. The exact reason for the correlation between HCV positivity and the response to HAIC-5-FU/IFN is not clear. Several studies have investigated the differences between the HCV and HBV in relation to HCC, such as the mechanism of hepatocarcinogenesis[30,31] and cytokine pattern in hepatitis.[32] These factors could influence the tumor response to therapy.

Similar to a previous report on advanced HCC with PVTT treated by HAIC-5-FU/IFN,[9,12,13] 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). Multivariate analysis showed that survival correlated with effect of treatment VTT ($P = 0.0006$), tumor size ($P = 0.013$) and CR/PR based on intrahepatic response ($P = 0.030$) (Table 4).

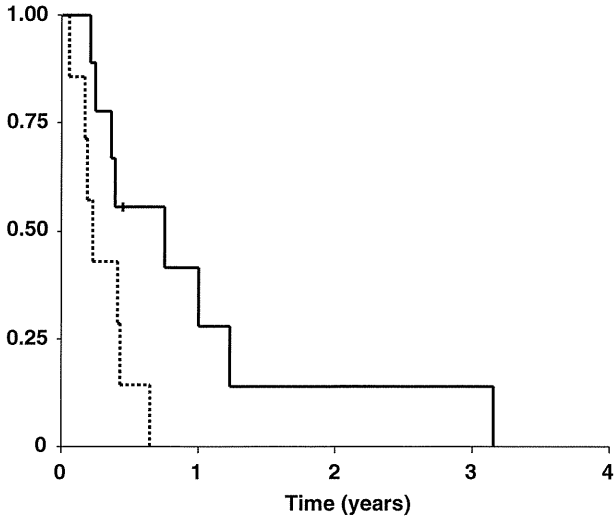

Figure 4 Cumulative survival rate of 16 patients with advanced hepatocellular carcinoma (HCC) and venous tumor thrombosis (VTT) of Vv3 who were not evaluated as complete or partial response (non-CR/PR). Solid line: nine patients who underwent arterial infusion chemotherapy (HAIC) and responded to 3-D conformal radiotherapy (3D-CRT), resulting in a decrease in VTT and significantly longer median survival time (MST) of 9.2 months ($P = 0.028$, log rank test). Dashed line: seven patients who underwent HAIC without or with ineffective radiotherapy, resulting in increase of VTT and MST of 3.1 months. ——, Effective 3D-CRT to VTT; ·····, No or ineffective 3D-CRT to VTT.

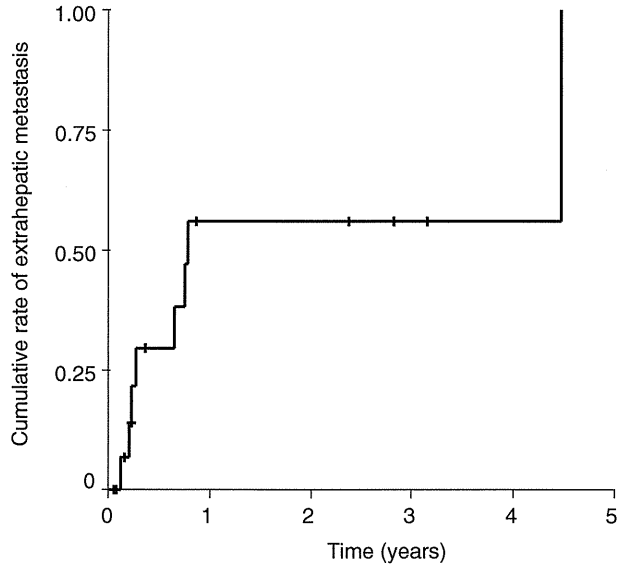

Figure 5 Cumulative rate of extrahepatic metastasis in 17 patients who were negative for extrahepatic metastasis at baseline (before treatment). The median time to metastasis was 7.1 months. The 6- and 12-month cumulative rate of metastasis was 30% and 56%, respectively. HAIC, hepatic arterial infusion chemotherapy; non-CR/PR, not evaluated complete or partial response on intrahepatic response evaluation; VTT, venous tumor thrombus; Vv3, tumor thrombus in the inferior vena cava.

The highest response rate was registered with the combination of HAIC-5-FU/IFN and 3D-CRT to VTT (79%, Fig. 3). This finding is similar to that reported by Katamura *et al.*[27] who reported a rate of 75% for HAIC-5-FU/IFN with radiotherapy to PVTT. Although 3D-CRT was considered, in general, tolerable to allow continuation of HAIC-5-FU/IFN without the development of RILD in our study, radiotherapy caused severe esophageal complications in three out of 14 patients (21%). This finding suggests that it is often difficult to avoid the harmful effect of irradiation to the radiosensitive esophagus, which is anatomically close to VTT of Vv3. Careful planning of 3D-CRT and reduction of radiation dose as much as possible might avoid esophageal complications associated with 3D-CRT of Vv3.

Although the response of VTT to radiotherapy was high in this study, the addition of 3D-CRT to the management of advanced HCC with VTT did not improve survival ($P = 0.667$, log rank test). This result could be causally related to the existence of five patients in HAIC-

5-FU/IFN alone group who achieved CR/PR without 3D-CRT and obtained prolonged survival (MST 34.3 months). These long-term survivors in the HAIC-5-FU/IFN alone group might balance out the benefit of additional 3D-CRT in the HAIC-5-FU/IFN plus radiotherapy group. With regard to the prognostic effect of 3D-CRT, radiotherapy and the associated reduction of VTT significantly improved the survival time in patients of non-CR/PR (intrahepatic response) group with VTT of Vv3 ($P = 0.028$, Fig. 4). In other words, patients who fail to show a response to HAIC-5-FU/IFN, 3D-CRT should be applied with the hope of improving survival. Conversely, the response to radiotherapy would be rather questionable in patients who show CR/PR response to HAIC-5-FU/IFN alone. Because the response of HCC with VTT to HAIC-5-FU/IFN cannot be predicted before treatment, it is important to monitor the patients on HAIC-5-FU/IFN for the response to such treatment as soon as possible, and introduce 3D-CRT to VTT to those who show non-CR/PR.

Despite the relatively high efficacy of the HAIC-5-FU/IFN regimen, the high incidence of extrahepatic metastasis is a poor prognostic sign. In the seven patients who were confirmed to be metastasis-free at baseline and developed extrahepatic metastasis during HAIC-5-FU/IFN treatment, the MST was 4.4 months after the detection of metastasis. In other words, the prognosis of these patients was similar to those who presented with extrahepatic metastasis before HAIC-5-FU/IFN (MST, 3.0 months). Various chemotherapies have been used for HCC extrahepatic metastasis though a standard regimen has not yet been established. Nevertheless, some investigators reported an objective response rate of 17–25% using systemic combination chemotherapy of S1 and IFN.[33,34]

Recent studies have praised the benefits of sorafenib tosilate in unresectable advanced HCC, reporting relatively long MST of 6.5–10.7 months and slowing of radiological progression in nearly 3 months.[35,36] While sorafenib seems to have survival benefits, the reported response rate is less than 2%. Compared with our results, with MST of 7.9 months, systemic RR of 24% and intrahepatic RR of 30% for advanced HCC with VTT, HAIC-5-FU/IFN seems to be characterized by higher response rate than sorafenib monotherapy, while MST was similar. Because the intrahepatic CR/PR patients by HAIC-5-FU/IFN could obtain significantly longer survival than the non-CR/PR patients (18.7 vs. 4.4 months, respectively), it might be meaningful to sort out HAIC-5-FU/IFN effective HCC patients who have potentially prolonged prognosis by HAIC-5-FU/IFN before introducing sorafenib treatment. There seemed to be a limitation of HAIC-5-FU/IFN that extrahepatic metastasis frequently occurred as a poor prognostic sign. In others, the benefits of sorafenib were reported to be consistent including patients with extrahepatic spread.[35,36] Sorafenib might be one of the most prospective modalities for extrahepatic metastasis after ineffective HAIC-5-FU/IFN.

The present study has certain limitations. These include data generated from a single institution, small population size and retrospective study design. For example, patients had a tendency to be elderly, HBV negative and HCV positive in comparison between the HAIC-5-FU/IFN alone group and the HAIC-5-FU/IFN plus 3D-CRT group (Table 7). There seemed to be no doubt about some clinicopathologic biases in patient background due to our study design. However, our results provide material for future large scale studies to determine the usefulness of the combination of HAIC-5-FU/IFN and 3D-CRT for advanced HCC with VTT.

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ORIGINAL ARTICLE

Long-term outcomes of intraluminal brachytherapy in combination with external beam radiotherapy for superficial esophageal cancer

Yuji Murakami · Yasushi Nagata · Ikuno Nishibuchi · Tomoki Kimura · Masahiro Kenjo · Yuko Kaneyasu · Tomoyuki Okabe · Yasutoshi Hashimoto · Yukio Akagi

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Abstract
Background The aim of this study was to assess the long-term outcomes of combining high-dose-rate intraluminal brachytherapy (IBT) with external beam radiotherapy (EBRT) for superficial esophageal cancer (SEC).
Methods From 1992 to 2002, 87 patients with T1N0M0 thoracic esophageal cancer received IBT in combination with EBRT. Of these, 44 had mucosal cancer and 43 had submucosal cancer. For patients with tumor invasion within the lamina propria mucosa, IBT alone was performed ($n = 27$). IBT boost following EBRT was performed for patients with tumor invasion in the muscularis mucosa or deeper ($n = 60$). No patient received chemotherapy.
Results The median follow-up time was 94 months. For mucosal cancer, the 5-year locoregional control (LRC), cause-specific survival (CSS) and overall survival (OS) rates were 75, 97 and 84%, respectively, and 49, 55 and 31%, respectively, for submucosal cancer. Tumor depth was a significant factor associated with LRC ($p = 0.02$), CSS ($p < 0.001$) and OS ($p < 0.001$) by univariate analysis. Multivariate analysis revealed that tumor depth was the only significant predictor for OS ($p = 0.003$). Late toxicities of grade 3 or higher in esophagus, pneumonitis, pleural effusion and pericardial effusion were observed in 5, 0, 0 and 1 patients, respectively. Grade ≥ 3 events of cardiac ischemia and heart failure after radiotherapy were observed in 9 patients, and history of heart disease before radiotherapy was the only significant factor ($p = 0.002$).
Conclusion There was a clear difference in outcomes of IBT combined with EBRT between mucosal and submucosal esophageal cancers. More intensive treatment should be considered for submucosal cancer.

Keywords Esophageal cancer · Superficial esophageal cancer · Squamous cell carcinoma · Radiotherapy · Brachytherapy

Y. Murakami (✉) · Y. Nagata · I. Nishibuchi · T. Kimura · M. Kenjo · Y. Kaneyasu
Department of Radiation Oncology, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
e-mail: yujimura@hiroshima-u.ac.jp

Y. Nagata
e-mail: nagat@hiroshima-u.ac.jp

I. Nishibuchi
e-mail: ikuno@hiroshima-u.ac.jp

T. Kimura
e-mail: tkimura@hiroshima-u.ac.jp

M. Kenjo
e-mail: kenjom@hiroshima-u.ac.jp

Y. Kaneyasu
e-mail: kaneyasu@hiroshima-u.ac.jp

T. Okabe
Department of Radiology, Hiroshima City Hospital, 7-33 Motomachi, Naka-ku, Hiroshima 730-8518, Japan
e-mail: t-okabe@pd6.so-net.ne.jp

Y. Hashimoto
Department of Radiology, Chugoku Rosai General Hospital, 1-5-1 Tagaya, Kure, Hiroshima 737-0193, Japan
e-mail: yasu06340829@yahoo.co.jp

Y. Akagi
Hiroshima Heiwa Clinic, 1-21 Kawaramachi, Naka-ku, Hiroshima 730-0856, Japan
e-mail: akagi@aoikai.jp

Introduction

Advances in endoscopic equipment have enabled the treatment of increasing numbers of patients with superficial esophageal cancer (SEC) [1–3], which can be divided into mucosal and submucosal cancers. In SEC patients treated by surgery, pathological analyses have shown significant differences in rates of lymph node (LN) metastasis according to tumor depth: 0–6% in the mucosa and 38–53% in the submucosa [4–9]. Among mucosal cancer patients, when tumor cells were found within the lamina propria mucosa there was almost no LN metastasis (0–1.4%), whereas in patients with tumors invading to the muscularis mucosa, a ratio of LN metastases of more than 10% was reported [4]. Endoscopic resection is generally indicated for patients with tumors invading within the lamina propria mucosa. For patients with tumors invading the muscularis mucosa or deeper, esophagectomy with systematic LN dissection is the main treatment. However, due to the extent of surgery, the alternative of radiotherapy (RT) is often selected for patients in poor medical condition or advanced age, and its efficacy has been reported by several authors [10–14].

Brachytherapy is a RT technique that can deliver a high dose to local tumors while sparing exposure to the surrounding normal tissues. Intraluminal brachytherapy (IBT) has been used mainly for SEC in Japan, while in Western countries IBT has been used with palliative intent for malignant esophageal strictures. The efficacy of IBT combined with external beam radiotherapy (EBRT) for SEC has been reported [15–19], and this method was considered an effective treatment in Japan in the 1990s. We performed IBT combined with EBRT for SEC patients until 2002, following the introduction in 1991 of the high-dose-rate iridium-192 remote afterloading system (micro-Selectron HDR from Nucletron, Netherlands). Subsequently, the protocol was changed and chemoradiotherapy (CRT) was introduced for SEC. In this study, the long-term outcomes of IBT combined with EBRT for SEC were evaluated.

Patients and methods

Patient and tumor characteristics

Patient and tumor characteristics are listed in Table 1. There were 87 patients eligible for this study with T1N0M0 (International Union Against Cancer TNM system, 1997) thoracic esophageal cancer who received IBT combined with EBRT between 1992 and 2002. The median age was 70 years (range 43–89), with 80 males and 7 females. Sixty-nine patients had Karnofsky performance status (KPS) of 90 or more. RT was selected in 54 patients who were judged medically inoperable and in 33 patients who declined surgery. Medically inoperable factors included concurrent illnesses, advanced age and coexisting malignancies. Main concurrent illnesses included heart disease in 14, hepatic disease in 18 and pulmonary disease in 9. Coexisting malignancies were observed in 28 patients, and 16 had malignancies within 5 years before the diagnosis of esophageal cancer. Among them, 12 had active malignancies. Taken together, these malignancies were distributed as follows: gastric cancer in 11, head and neck cancer in 10, hepatocellular carcinoma in 4, colorectal cancer in 3 and lung cancer in 2. Histologically, 86 patients had squamous cell carcinoma and one had adenocarcinoma. Tumor sites were upper thoracic in 8 patients, middle thoracic in 65 and lower thoracic in 14. Forty-four had mucosal cancer and 43 had submucosal cancer. Of the 44 mucosal cancer patients, 25 received incomplete endoscopic mucosal resection (EMR) for tumors within the lamina propria mucosa, i.e., positive margin or partial resection of multiple or large lesions for the purpose of diagnosing tumor depth.

Table 1 Patient and tumor characteristics

Characteristics	No. of patients (%)
Age (years)	
Range	43–89
Median	70
Gender	
Male	80 (92)
Female	7 (8)
KPS	
90–100	69 (79)
60–80	18 (21)
Reasons for selecting RT	
Medically inoperable	54 (62)
Patient refused surgery	33 (38)
Double cancer	
All	28 (32)
Within 5 years	16 (18)
Histology	
Squamous cell	86 (99)
Adenocarcinoma	1 (1)
Tumor sites	
Upper thoracic	8 (9)
Middle thoracic	65 (75)
Lower thoracic	14 (16)
Tumor depth	
Mucosal	44 (51)
Submucosal	43 (49)

KPS Karnofsky performance status, *RT* radiotherapy

Treatment

Intraluminal brachytherapy was performed using the high-dose-rate iridium-192 remote afterloading system. The double-balloon applicator was used for IBT. The outer diameter of the applicator was either 16 or 20 mm, and the latter was mainly used. A prescribed dose was calculated at a depth of 5 mm from the surface of the esophageal mucosa.

EBRT was administered with 6 or 18 MV X-rays. After irradiation with 45–46 Gy using a fractional dose of 1.8–2.0 Gy to the primary tumor and regional LN area with anterior–posterior opposed beams, a planned dose was delivered to the primary tumor with oblique opposed beams to spare the spinal cord.

For patients with tumors within the lamina propria mucosa who had almost no risk of LN metastases, IBT alone was performed ($n = 27$). IBT was performed 5 days per week and irradiation doses were 35 Gy/14 fractions in 15 patients, 36 Gy/18 fractions in 9, 30 Gy/15 fractions in 2 and 25 Gy/5 fractions in 1.

Intraluminal brachytherapy boost following EBRT was performed for patients with tumors in the muscularis mucosa or deeper who had risk of LN metastases ($n = 60$). Irradiation doses of EBRT were 50–58 Gy/25–29 fractions (median 54 Gy) in cases of tumors in the muscularis mucosa or inner one-third of the submucosa and 54–61 Gy/27–33 fractions (median 60 Gy) in cases of tumors in the outer two-thirds of the submucosa. The IBT boost was generally performed immediately after EBRT using a schedule of 5 days per week. IBT boost doses were 10 Gy/4 fractions in 29, 10 Gy/5 fractions in 25, 10 Gy/2 fractions in 3, 7.5 Gy/3 fractions in 1, and 15 Gy/3 fractions in 1.

In this study, no patient received chemotherapy.

Analysis

The data were updated in June 2009. The median follow-up time for survivors was 94 months (range 28–187) and for all patients 64 months (range 2–187). There were 3 patients who were lost to follow-up within 60 months from RT. The follow-up periods of these 3 patients were 28, 56 and 57 months. Complete response (CR) was defined as the disappearance of the primary tumor by endoscopic biopsy. Overall survival (OS) was defined as the time from the initiation of RT to death from any cause. Cause-specific survival (CSS) was defined as the time from the initiation of RT to death due to esophageal cancer. Locoregional control (LRC) was calculated from the initiation of RT to the earliest events of recurrences in esophageal primary site, esophageal metachronous cancers and regional LN metastases. OS, CSS and LRC rates were calculated using the Kaplan–Meier method. Comparison of data was analyzed by Fisher's exact test. Univariate (UVA) and multivariate analyses (MVA) were performed using the log-rank test and the Cox proportional hazards test. A p value of <0.05 was considered significant. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results

Response and failures

Treatment outcomes are shown in Table 2. Initial response was evaluated 8–181 days (median 31 days) after RT. Two patients were not evaluated because one died in a traffic accident soon after treatment, and concurrent illness

Table 2 Treatment outcomes

Outcomes	No. of patients (%)		
	Mucosal ($n = 44$)	Submucosal ($n = 41$)	Total ($n = 85$)
Initial response (evaluable cases)			
Complete response	43 (98)	40 (98)	83 (98)
Partial response	1 (2)	1 (2)	2 (2)
Recurrences			
Locoregional	14 (32)	19 (46)	30 (39)
Esophagus—primary site	5 (11)	8 (20)	13 (15)
Esophagus—metachronous	8 (18)	4 (10)	12 (14)
Lymph node—in EBRT field	0 (0)	1 (2)	1 (1)
Lymph node—out of EBRT field	1 (2)	4 (10)	5 (6)
Distant	0 (0)	1 (2)	1 (1)
Unknown	1 (2)	1 (2)	2 (2)

EBRT external beam radiotherapy, *RT* radiotherapy

progressed after treatment in the other patient. In 85 evaluable patients, 83 (98%) achieved CR and residual cancer cells were confirmed in 2 patients. Failures were observed in 33: locoregional failures in 30, distant metastasis (malignant pleural effusion) in 1 and unspecified in 2. Among the 30 patients with locoregional failures, one had failure at the primary esophageal site and regional LN metastasis concurrently. Esophageal failures were observed in 25 patients: 13 were primary tumor failures and 12 were metachronous esophageal cancers. There were no differences according to tumor depth in the occurrence rate of all esophageal failures, primary site failures and metachronous esophageal cancers. Regional LN metastases were observed in 6 patients. Although submucosal cancer patients showed a high rate of regional LN metastasis compared with mucosal cancer patients, the difference lacked significance (2% in mucosal and 12% in submucosal cancer, $p = 0.10$). Furthermore, 5 failures were not in the EBRT field and one was in the EBRT field.

Among the 33 patients with failures, an early stage failure detected as a superficial esophageal lesion was observed in 15 patients and an advanced stage failure was observed in 18. According to the depth of tumor, the occurrence rate of advanced stage failures was significantly higher in submucosal cancer patients (7% in mucosal and 37% in submucosal cancer, $p < 0.01$). Regarding salvage treatments for 15 patients with early stage failures, 14 patients were salvaged by esophagectomy or endoscopic resection. For 18 patients with advanced stage failures, only one patient who received lymphadenectomy with adjuvant CRT for LN metastasis out of the EBRT field was salvaged.

Survival rates and prognostic factor

At the time of last follow-up, 49 of 87 patients had died. Seventeen patients had esophageal cancer deaths including one treatment-related death; 2 in mucosal and 15 in submucosal cancer patients. Submucosal cancer patients showed a higher rate of esophageal cancer deaths compared with mucosal cancer patients ($p < 0.01$). Eleven patients died of other malignancies: lung cancer in 3, hepatocellular carcinoma in 3, head and neck cancer in 2, and single cases each of malignant lymphoma, bile duct carcinoma and bladder sarcoma. Among these 11 patients, 3 had esophageal metachronous cancers and 1 had LN recurrence, however, all of them were controlled by salvage treatments. Twenty-one patients died of intercurrent diseases: pulmonary infection in 9, heart disease in 4, hepatic failure in 2, unknown cause in 2 and single cases each of renal failure, suicide, senility and cerebral thrombosis.

The 5-year OS, CSS and LRC for all patients were 58% [95% confidence intervals (CI) 48–69%], 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively (Fig. 1). According to the depth of tumors, the 5-year OS, CSS and LRC for mucosal and submucosal cancers were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), 97% (95% CI 92–100%) and 55% (95% CI 38–73%), and 75% (95% CI 62–89%) and 49% (95% CI 36–67%), respectively (Fig. 2a–c). There were significant differences in OS, CSS and LRC between mucosal and submucosal cancer ($p < 0.01$, $p < 0.01$ and $p = 0.02$, respectively). Prognostic factors according to UVA are summarized in Table 3. The significant factors for LRC were tumor depth ($p = 0.02$) and tumor length ($p = 0.01$), those for CSS were tumor depth ($p < 0.01$) and tumor length ($p = 0.02$), and those for OS were KPS ($p = 0.04$), operability ($p = 0.02$), double cancer within 5 years ($p < 0.01$) and tumor depth ($p < 0.01$). MVA for OS revealed that tumor depth was the only significant prognostic factor ($p < 0.01$).

Toxicity

Toxicities are summarized in Table 4. Grade ≥3 acute toxicities of esophagitis, leucopenia and thrombocytopenia occurred in 2, 1 and 0 patients, respectively. Grade ≥3 late toxicities of esophageal ulcers, pneumonitis, pleural effusion and pericardial effusion were observed in 5, 0, 0 and 1 patients, respectively. Details of Grade ≥3 late toxicities of the esophageal ulcers are shown in Table 5. All of them received IBT boost following EBRT and 3 patients developed esophago-mediastinal fistulas concurrently. One needed bypass surgery (Grade 4) and another died of mediastinitis (Grade 5). The other 3 patients recovered by conservative treatment. The lone patient with Grade 3 pericardial effusion, who was the same patient with Grade 3 esophago-mediastinal fistula, developed Grade 2 pleural effusion concurrently. Both pericardial and pleural effusion decreased after recovery from the fistula. Regarding

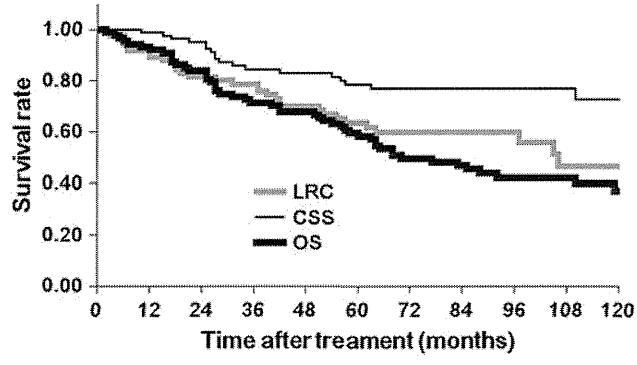

Fig. 1 Curves for overall survival (*OS*), cause-specific survival (*CSS*) and locoregional control (*LRC*) rates for all patients. The 5-year OS, CSS and LRC were 58% (95% CI 48–69%), 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively

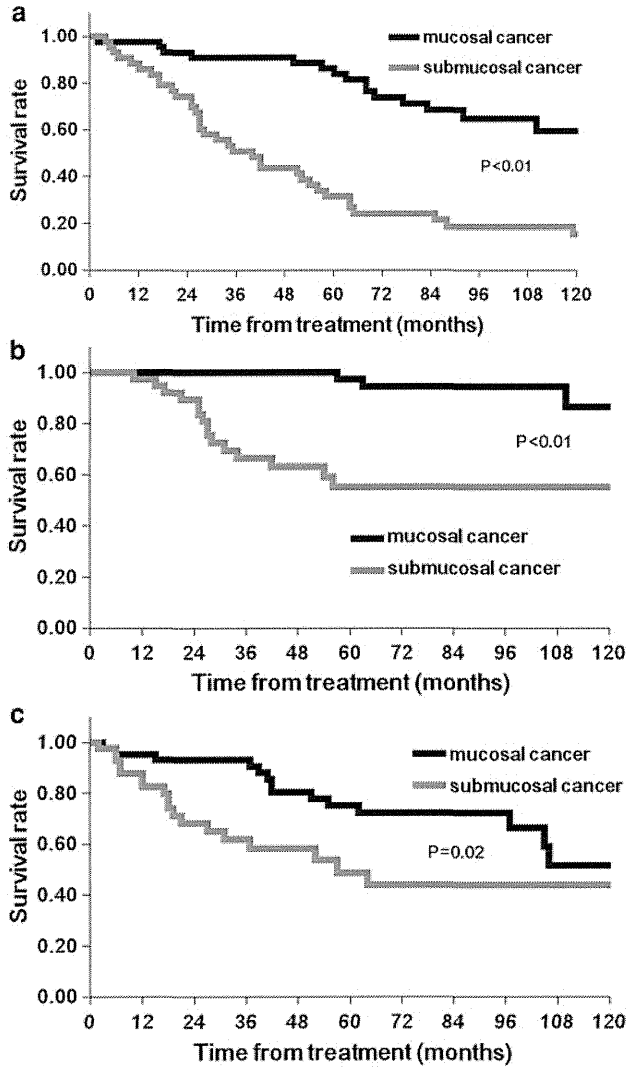

Fig. 2 **a** Curves for OS according to tumor depth. The 5-year OS for mucosal and submucosal cancer were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), respectively ($p < 0.01$). **b** Curves for CSS according to tumor depth. The 5-year CSS for mucosal and submucosal cancer were 97% (95% CI 92–100%) and 55% (95% CI 38–73%), respectively ($p < 0.01$). **c** Curves for LRC according to tumor depth. The 5-year LRC for mucosal and submucosal cancer were 75% (95% CI 62–89%) and 49% (95% CI 36–67%), respectively ($p = 0.02$)

occurrence of Grade ≥3 esophageal ulcers, no significant factor emerged.

We also investigated cardiac ischemia and heart failure after RT (Grade ≥3 according to CTCAE v3.0) (Table 6). Cardiac ischemia occurred in 5 patients. Two patients died of acute myocardial infarction, at 2 and 6 months after RT. One had a history of angina and the other patient had a history of brain infarction and KPS of 60. The time to onset of the other 3 patients was 22, 76 and 151 months after RT. They received stent placement and were alive 65, 24 and 13 months later, respectively. Four patients suffered heart failure. One died of heart failure at 64 months after RT; he had a history of dilated cardiomyopathy. The time to onset of the other 3 patients was 42, 46 and 124 months. They received pacemaker placement; one of them died of malignant lymphoma 9 months later; the other 2 patients were alive 18 and 47 months later. Investigation of significant factors associated with cardiac ischemia and heart failure revealed that a history of heart disease before RT was the only significant factor ($p = 0.002$) (Table 7).

Discussion

With advances in endoscopic equipment, the number of SECs treated has increased. According to the report of the Registry of Esophageal Carcinomas in Japan, SEC accounted for 8.5% of esophageal cancer patients treated in 1979–1982 and 28% in 1998–1999 [1, 2]. In the data of the Japanese Patterns of Care Study, 21% of the esophageal cancer patients who were treated with RT in 1999–2001 had SEC [3].

In our study, there was a clear difference in treatment results depending on the depth of tumor invasion. Tumor depth was a significant factor for OS, CSS and LRC by UVA. Furthermore, tumor depth was the only significant factor for OS by MVA. Favorable treatment outcomes in mucosal cancer were achieved in this study. The CR rate was 98% and the 5-year OS, CSS and LRC were 84, 97 and 75%, respectively. These results were almost equivalent to that reported for surgery [4–9]. Most of the mucosal cancers in this study were large or multiple lesions that were difficult to completely resect by EMR or had margin-positive lesions after EMR. In the 1990s, surgery or radiotherapy was often considered for these lesions. However, remarkable progress in endoscopic techniques has resulted in significant changes. Recently, endoscopic submucosal dissection (ESD) has been increasingly used as a new technique of endoscopic resection. ESD facilitates en-bloc resection even in large lesions where piecemeal resection was needed by EMR. Takahashi et al. [20] reported that ESD reduced the local recurrence rate (0.9% in the ESD group and 9.8% in the EMR group) significantly and that the disease-free survival rate was significantly better with ESD than with EMR. Most mucosal cancers can now be cured by endoscopic treatment alone due to advances in the technique of endoscopic resection. Thus, surgery and RT in the treatment of mucosal cancer have been relegated to a limited role.

Initial response for submucosal cancer was considered equally good as that achieved for mucosal cancer. CR rate was 98% and high long-term LRC and survival rates were anticipated. However, the 5-year OS, CSS and LRC were 31, 55 and 49%, respectively. These results were obviously inferior to those of mucosal cancer, and little difference

Table 3 Prognostic factors

Patient characteristics	*n*	LRC		CSS		OS		
		5-year rate (%)	UVA	5-year rate (%)	UVA	5-year rate (%)	UVA	MVA
Age (years)								
≤70	49	61	n.s.	84	n.s.	65	n.s.	–
>70	38	67		72		51		
Gender								
Male	80	62	n.s.	77	n.s.	58	n.s.	–
Female	7	86		100		57		
KPS								
90–100	71	61	n.s.	79	n.s.	64	0.04	0.222
60–80	16	74		73		37		
Operability								
Operable	33	63	n.s.	86	n.s.	72	0.010	0.076
Inoperable	54	63		73		50		
Double cancer within 5 years								
Yes	16	69	n.s.	90	n.s.	64	0.007	0.485
No	71	63		77		31		
Tumor depth								
Mucosal	44	75	0.023	97	<0.001	84	<0.001	0.003
Submucosal	43	49		55		31		
Tumor length (cm)								
≤3.0	63	72	0.012	85	0.026	63	n.s.	–
>3.0	24	38		63		45		
Circumferential extent								
≤1/2	70	65	n.s.	79	n.s.	60	n.s.	–
>1/2	17	57		78		51		
Multiple Lugol-voiding regions								
Yes	59	58	n.s.	78	n.s.	58	n.s.	–
No	28	74		81		60		
Multiple cancer in esophagus								
Yes	21	69	n.s.	81	n.s.	52	n.s.	–
No	66	62		78		60		

KPS Karnofsky performance status, *LRC* locoregional control rate, *CSS* cause-specific survival rate, *OS* overall survival rate, *UVA* univariate analysis, *MVA* multivariate analysis, *n.s.* not significant

Table 4 Toxicity

	G2	G3	G4	G5	≥G3 (%)
Acute					
Esophagitis	22	2	0	0	2 (2%)
Leukopenia	3	1	0	0	1 (1%)
Thrombocytopenia	1	0	0	0	0 (0%)
Late					
Esophagus	3	3	1	1	5 (6%)
Pneumonitis	2	0	0	0	0 (0%)
Pleural effusion	3	0	0	0	0 (0%)
Pericardial effusion	–	1	0	0	1 (1%)

G grade

was seen when compared with previous reports of RT alone [10–16]. The main pattern of failures was locoregional failures (18 of 19 patients with failures). These outcomes suggest that treatment needs to be intensified to improve the locoregional control rate for submucosal cancer patients.

Table 5 Details of patients with esophageal ulcer (≥Grade 3)

	Depth	Treatment	Complication	Grade	Support
1	Mucosal	EBRT + IBT	Ulcer + perforation	3	TPN
2	Submucosal	EBRT + IBT	Ulcer	3	TPN
3	Submucosal	EBRT + IBT	Ulcer	3	TPN
4	Submucosal	EBRT + IBT	Ulcer + perforation	4	Bypass surgery
5	Submucosal	EBRT + IBT	Ulcer + perforation	5	Death

EBRT external beam radiotherapy, *IBT* intraluminal brachytherapy, *TPN* total parental nutrition

Table 6 Details of patients with heart disease (≥Grade 3)

	Sex	Age	History of HD	Tumor site	Treatment	Complication	Onset (months)	Outcome (months)	
1	Male	69	Angina	Mt	IBT	CI	2	Dead with AMI	2
2	Male	78	–	Mt	EBRT + IBT	CI	5	Dead with AMI	6
3	Male	61	–	Mt	EBRT + IBT	CI	22	Alive	87
4	Male	70	–	Mt	EBRT + IBT	CI	76	Alive	100
5	Male	73	AR	Mt	EBRT + IBT	CI	151	Alive	164
6	Male	84	–	Lt	EBRT + IBT	HF	42	Dead with ML	51
7	Male	65	DCM	Lt	EBRT + IBT	HF	50	Dead with HD	64
8	Male	71	OMI	Mt	EBRT + IBT	HF	46	Alive	64
9	Male	55	AF	Mt	EBRT + IBT	HF	124	Alive	171

HD heart disease, *EBRT* external beam radiotherapy, *IBT* intraluminal brachytherapy, *CI* cardiac ischemia, *HF* heart failure, *AR* aortic regurgitation, *DCM* dilated cardiomyopathy, *OMI* old myocardial infarction, *AF* atrial fibrillation, *AMI* acute myocardial infarction, *ML* malignant lymphoma, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus

Intraluminal brachytherapy is a RT method that can deliver an isolated high dose to local tumors while sparing the surrounding normal tissues. Its efficacy for SEC has been reported by several authors [13–19]. However, a significant advantage of IBT in the treatment of esophageal cancer remains to be demonstrated. The Study Group of the Japanese Society of Therapeutic Radiology and Oncology reported no advantage when IBT was compared with EBRT alone [11]. Recently, some promising results of IBT combined with EBRT for submucosal cancer were reported by Ishikawa et al. [19] from Gunma University. Their study showed a significant difference in the 5-year CSS between the IBT + EBRT group and EBRT alone (86 vs. 62%, $p = 0.04$). However, there were no significant differences in LRC, OS and recurrence-free survival. Furthermore, according to the Japanese Patterns of Care Study, the performance rate of IBT in the treatment of esophageal cancer in Japan has been decreasing [3]. Concurrent CRT has become the standard therapy as a non-surgical treatment for locally advanced esophageal cancer, because randomized controlled trials revealed the efficacy of CRT [21–23]. Recently, the efficacy of CRT for SEC has been studied. Yamada et al. [24] reported that the 5-year OS of CRT for stage I esophageal cancer was 66.4%. Kato et al. reported the outcome of a phase II trial of CRT in patients with stage I esophageal cancer. In their study, the 4-year OS was 80.5% [25]. The survival rates from these studies were equivalent to those of surgery. There has thus been a shift from RT alone to CRT in the RT methods for SEC.

In this study, 13 primary site recurrences and 12 metachronous esophageal cancers were observed. Fifteen of these 25 lesions were detected as superficial lesions and 14 of these were successfully salvaged. Meanwhile, most of the patients who developed advanced recurrences died of esophageal cancer. This suggests that detection of esophageal failures or metachronous cancers as a superficial lesion by periodic endoscopy is very important.

In treating with IBT, avoiding the toxicity of treatment-related esophageal ulcer is of critical importance. Nemoto et al. [10] recommended that the IBT fractional dose should not exceed 5 Gy to prevent esophageal ulcers. Akagi et al. [26] have also recommended a small fractional dose of 2.0 or 2.5 Gy in high-dose-rate IBT to minimize esophageal complications. In our study, Grade ≥3 esophageal ulcer occurred in 5 patients (6%). This incidence rate was comparatively low; however, Grade 4 and 5 ulcers

Table 7 Late toxicities: heart disease

Characteristics	*n*	Heart disease	
		n (%)	*p* value
Age (years)			
≤70	49	5 (10)	n.s.
>70	38	6 (16)	
Gender			
Male	80	9 (11)	n.s.
Female	7	2 (29)	
KPS			
90–100	71	7 (10)	n.s.
60–80	16	4 (25)	
Operability			
Operable	33	2 (6)	n.s.
Inoperable	54	9 (17)	
Tumor depth			
Mucosal	44	6 (14)	n.s.
Submucosal	43	5 (12)	
Tumor length (cm)			
≤3.0	63	7 (11)	n.s.
>3.0	24	4 (17)	
Treatment			
IBT alone	27	2 (7)	n.s.
IBT + EBRT	60	9 (15)	
Diabetes mellitus			
Yes	14	2 (14)	n.s.
No	73	9 (12)	
Heart disease history			
Yes	14	6 (43)	0.002
No	73	5 (7)	
Hypertension			
Yes	15	2 (13)	n.s.
No	72	9 (13)	
Alcoholic drinking			
Yes	64	7 (11)	n.s.
No	23	4 (17)	
Tobacco smoking			
Yes	66	7 (11)	n.s.
No	21	4 (19)	

KPS Karnofsky performance status, *n.s.* not significant

occurred in patients treated with IBT fractional doses of 2.0 and 2.5 Gy. We need to be aware of the occurrence of severe esophageal ulcer even when we perform IBT with a low fractional dose.

In our study, Grade ≥3 pneumonitis, pleural effusion and pericardial effusion developed in 0, 0 and one patient, respectively. This result suggests that RT without chemotherapy was safe regarding these toxicities. We also investigated cardiac ischemia and heart failure after treatment. Nine patients suffered Grade ≥3 events. Two died of AMI and one died of heart failure. Five of them had a history of heart disease, and a history of heart disease was the only significant factor associated with developing events of cardiac ischemia and heart failure after RT ($p = 0.002$). Radiation-induced heart disease is one of the complications after thoracic RT. The effects on various portions of heart, such as pericardium, myocardium or coronary artery, due to RT have been reported [27–29]. In CRT of esophageal cancer, cardiopulmonary toxicities became problems to be solved after the report by Ishikura et al. [30]. We are not sure whether all events of cardiac ischemia and heart failure in this study occurred due to irradiation. However, in the RT for esophageal cancer, irradiation to the heart cannot be avoided. Therefore, efforts should be made to decrease the irradiation dose to the heart as much as possible using the newest technique. Furthermore, follow-up with attention to development of heart disease is important.

As mentioned previously, the role of IBT has been limited in the treatment of SEC. However, we consider that IBT can be a treatment option for mucosal cancer patients who have multiple or large legions that have a risk of severe esophageal stenosis by endoscopic resection and for submucosal cancer patients who have difficulties in receiving surgery or concurrent chemotherapy because of high age or concurrent illnesses.

In conclusion, there was a clear difference in treatment results depending on tumor depth. The outcomes of IBT combined with EBRT for submucosal cancer were not satisfactory and more intensive treatment should be considered. In our institution, CRT was introduced for submucosal cancer after 2002 and the efficacy and safety of CRT are currently under investigation.

Conflict of interest No author has any conflict of interest.

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Clinical Investigation: Normal Tissue

Radiation-Induced Rib Fractures After Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors and Dose–Volume Relationship

Kaori Asai, M.D.,* Yoshiyuki Shioyama, M.D., Ph.D.,† Katsumasa Nakamura, M.D., Ph.D.,* Tomonari Sasaki, M.D., Ph.D.,* Saiji Ohga, M.D.,* Takeshi Nonoshita, M.D.,* Tadamasa Yoshitake, M.D., Ph.D.,† Kayoko Ohnishi, M.D.,§ Kotaro Terashima, M.D.,* Keiji Matsumoto, M.D.,* Hideki Hirata, M.D., Ph.D.,‡ and Hiroshi Honda, M.D., Ph.D.*

*Departments of *Clinical Radiology, †Heavy Particle Therapy and Radiation Oncology and ‡Health Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; and §Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan*

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Summary

Radiation-induced rib fracture (RIRF) is one of the late adverse effects after hypofractionated stereotactic body radiation therapy (SBRT) for lung tumors. However, the incidence and risk factors have not been determined, to our knowledge. We performed this study to assess the clinical features, risk factors, and dose–volume relationship of RIRF after hypofractionated SBRT. The incidence of RIRF after hypofractionated SBRT is relatively high. The

Purpose: The purpose of this study was to clarify the incidence, the clinical risk factors, and the dose–volume relationship of radiation-induced rib fracture (RIRF) after hypofractionated stereotactic body radiation therapy (SBRT).

Methods and Materials: One hundred sixteen patients treated with SBRT for primary or metastatic lung cancer at our institution, with at least 6 months of follow-up and no previous overlapping radiation exposure, were included in this study. To determine the clinical risk factors associated with RIRF, correlations between the incidence of RIRF and the variables, including age, sex, diagnosis, gross tumor volume diameter, rib–tumor distance, and use of steroid administration, were analyzed. Dose–volume histogram analysis was also conducted. Regarding the maximum dose, V10, V20, V30, and V40 of the rib, and the incidences of RIRF were compared between the two groups divided by the cutoff value determined by the receiver operating characteristic curves.

Results: One hundred sixteen patients and 374 ribs met the inclusion criteria. Among the 116 patients, 28 patients (46 ribs) experienced RIRF. The estimated incidence of rib fracture was 37.7% at 3 years. Limited distance from the rib to the tumor (<2.0 cm) was the only significant risk factor for RIRF ($p = 0.0001$). Among the dosimetric parameters used for receiver operating characteristic analysis, the maximum dose showed the highest area under the curve. The 3-year estimated risk of RIRF and the determined cutoff value were 45.8% vs. 1.4% (maximum dose, ≥42.4 Gy or less), 51.6% vs. 2.0% (V40, ≥0.29 cm^3 or less), 45.8% vs. 2.2% (V30, ≥1.35 cm^3 or less), 42.0% vs. 8.5% (V20, ≥3.62 cm^3 or less), or 25.9% vs. 10.5% (V10, ≥5.03 cm^3 or less).

Reprint requests to: Dr Yoshiyuki Shioyama, Department of Heavy Particle Therapy and Radiation Oncology, Kyushu University, Fukuoka, Japan. Tel: (+81) 92-642-5695; Fax: (+81) 92-642-5708; E-mail: shioyama@radiol.med.kyushu-u.ac.jp

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maximum dose and high-dose volume are strongly correlated with RIRF.

Conclusions: The incidence of RIRF after hypofractionated SBRT is relatively high. The maximum dose and high-dose volume are strongly correlated with RIRF. © 2012 Elsevier Inc.

Keywords: Stereotactic body radiation therapy, Rib fracture, Dose–volume histogram analysis

Introduction

Stereotactic body radiation therapy (SBRT) allows escalation of the fractional dose, which is important to improve the local control rate of tumors and overall survival. In general, therefore, SBRT is performed by using a large volume per fraction in fewer (from one to five) treatment sessions, a modality called hypofractionated SBRT. Because of its excellent local control and survival rates, hypofractionated SBRT is accepted as one of the best alternative treatments for medically inoperable patients with early-stage non-small-cell lung cancer (1). Recently, indications for SBRT have been extended to so-called oligometastases, with good potential for improved survival in patients with them (2).

Radiation-induced rib fracture (RIRF) is known to be a rare late adverse effect after conventional radiotherapy for thoracic lesions. Its incidence has been reported as 6% and 0.3% to 1.8% after mastectomy and breast-conservation surgery followed by chest wall irradiation (3–5). Recently, we have also observed patients who experienced RIRF after hypofractionated SBRT for lung tumors. Generally, in hypofractionated SBRT, the normal tissue adjacent to the planning target volume receives not only a high dose overall but also a high dose per fraction. Therefore, it is assumed that the predictive risk of normal tissue toxicity after hypofractionated SBRT is different from that after three-dimensional conformal radiotherapy with conventional fractionation. Our aim in this study was to assess the incidence, clinical features, risk factors, and dose–volume relationship of RIRF after hypofractionated SBRT for lung tumors.

Methods and Materials

Patient eligibility

We retrospectively reviewed all cases treated with SBRT for primary lung cancer or metastatic lesions to the lung (including histologically unproven lesions) at Kyusyu University between April 2003 and May 2007. The indications for SBRT at our institution are as follows: (*1*) early-stage (cT1 or T2N0M0) primary lung cancer or small (<5 cm, in principle) oligometastatic lesions in the lung; (*2*) medical inoperability, generally due to complications and age, or refusal of operation; and (*3*) lesions not adjacent to the hilar area. Inclusion criteria for this study were as follows: (*1*) prescribed dose of 48 Gy in four fractions for the isocenter; (*2*) availability of follow-up computed tomography (CT) images at least 6 months after SBRT; (*3*) no previous overlapping radiation exposure; and (*4*) no overlapping surgical procedures. The patients who received radiation therapy with overlap to initial treatment site after SBRT were handled as censored cases at the time the radiation therapy started. Surgical procedures are known to be a risk factor for osteoradionecrosis (ORN), and we therefore excluded patients with overlapping surgical procedures within the radiation fields. After these adjustments, a total of 116 patients met our criteria. A summary of patient and tumor characteristics is shown in Table 1. No patients were receiving steroid therapy in our series.

Treatment

All patients were immobilized in a stereotactic body frame (Engineering System Co., Matsumoto, Japan), which uses a rigid frame, vacuum pillow, and thermoplastic body shell (6). No respiratory gating techniques were used, and all patients were under shallow breathing during simulation and treatment. Tumors and adjacent structures were screened with fluoroscopy on the anterior–posterior view and the lateral view to measure respiratory tumor motion. Treatment planning was performed with multidetector (four-row) CT with a slice thickness of 2 mm with the patient under free breathing. Treatment planning was conducted using an Eclipse system, ver. 6.5 (Varian Medical Services, Palo Alto, CA). The gross tumor volume (GTV) was contoured on each axial CT slice with the use of a pulmonary window setting (window level, -700 HU; window width, 2000 HU). The clinical target volume was defined as being the same volume as the GTV. The internal target volume, including the internal margin, was defined on the basis of three-dimensional tumor motion measured on fluoroscopy. The planning target volume, including the setup margin, was created by adding 5 mm to the internal target volume in all directions. The beam arrangement consisted of six to eight coplanar and noncoplanar photon beams accelerated to 4 to 10 MV. In all cases, the prescribed dose was 48 Gy in four fractions for the isocenter. In this study, the pencil beam convolution algorithm with Batho Power Law for tissue heterogeneity was used for dose calculation.

Follow-up and clinical assessment

To evaluate the clinical features of RIRF, we assessed the crude and estimated cumulative incidence, the time to onset, and the symptoms. We adopted follow-up chest CT scans after SBRT to identify RIRFs. The follow-up CT was initially performed 1 or 2 months after the completion of SBRT and then every 3 months during the first 2 years and every 4 to 6 months thereafter. All

Table 1 Patient, tumor, and radiotherapy characteristics

Characteristic	No. of patients (range)
Age, y (median)	36–92 (75)
Sex	
M	66
F	50
Diagnosis	
Primary lung cancer	97
Metastatic lung tumor	19
Tumor size, cm (median)	1.0–5.1 (2.4)
Rib–tumor distance, cm (median)	0.3–6.2 (2.0)

follow-up chest CT images were re-evaluated by one of the authors (A.K.) to determine the exact number and location of the rib fractures. The diagnosis of rib fracture was made by the findings of cortical discontinuity or linear sclerotic change across the rib. We defined an RIRF as a newly appearing fracture located within the irradiated volume of SBRT and with no obvious history of trauma. Clinical symptoms associated with rib fracture were estimated by reviewing the clinical records and were graded using the National Cancer Institute Common Toxicity Criteria version 3.0. To clarify the predictive factor of RIRF, we assessed the following clinical factors: age, sex, diagnosis, tumor size, and rib–tumor distance. Tumor size was defined as the maximum diameter of GTV measured on the axial plane. We defined the rib–tumor distance as the minimum distance from the radiation isocenter to the rib on the three orthogonal planes.

Dose–volume relationship analysis

All ribs receiving doses of 20 Gy or more, even to a small area, were subject to the dose–volume relationship analysis. This threshold was chosen because there were no fractures in the ribs that received a maximum dose of less than 20 Gy. After examination of the isodose distribution in all 116 cases, 374 ribs met our criteria. We contoured just on the rim of the ribs but did not include the cartilage, under the bone window setting (window level, 400; window width, 2000), on the radiation treatment planning system, and calculated the irradiated dose (Fig. 1). The following dosimetric parameters were calculated for each rib: maximum dose (Dmax) and the absolute volume receiving $\geq$10 Gy (V10), $\geq$20 Gy (V20), $\geq$30 Gy (V30), and $\geq$40 Gy (V40).

Statistics

The cumulative incidence of rib fracture was estimated by the Kaplan-Meier method. For the risk factor analysis, each factor (age, sex, diameter of GTV, and chest wall–tumor distance) was divided into two groups by using the median value as a cutoff, and the statistical significance was calculated with the log-rank test for univariate analysis. The irradiated doses to the ribs were compared between fractured ribs and unfractured ribs, and the statistical significance of the differences was evaluated by Student's t test. The receiver operating characteristic (ROC) curve was also generated to assess the predictability of dosimetric parameters related to rib fracture and to determine the optimal cutoff value for each dosimetric parameter. The curve was defined as the plot of the sensitivity vs. the false-positive rate (1-specificity). Each dosimetric parameter was divided into two groups by using the optimal cutoff value obtained from ROC analysis, and the estimated incidence of rib fractures was compared between the two groups with the log-rank test. Statistical significance was defined as a p value <0.05. Analyses were performed with the JMP8.0 software (SAS Institute, Inc., Cary, NC).

Results

Incidence of rib fracture and clinical risk factors

Among the 116 cases included in this study, RIRF developed in 28 patients (24.1%). Twenty-four patients had primary lung cancer, and 4 patients had oligometastatic lesions. The median time to onset of RIRF was 22 months (range, 9–42 months) after the completion of SBRT. The estimated cumulative incidence of RIRF was 37.7% at 3 years (Fig. 2). Among the 28 cases of fracture, 12 cases (42.9%) were symptomatic. The symptoms associated with rib fracture were localized pain (12 cases) and neurologic pain (2 cases). The symptomatic severity was grade 1 in 4 patients, grade 2 in 7 patients, and grade 3 in 1 patient. In most of the cases, the duration of symptoms was short (only a few months). However, 1 patient with grade 3 pain required oral administration of a narcotic agent for 9 months. As for radiologic findings of RIRF at the point of diagnosis, 15 cases showed cortical discontinuity (7 cases were symptomatic), 8 cases showed linear sclerotic change (4 cases were symptomatic) and 5 cases showed boss findings (2 cases were symptomatic).

In univariate analysis to estimate the clinical risk factors related to RIRF, shortness of rib–tumor distance was the only significant factor: the 3-year cumulative incidence of RIRF was 58.1% in those with a distance of $<$2.0 cm and 24.4% in those with a distance of $\geq$2.0 cm ($p = 0.0001$). All other clinical factors, including age ($\geq$75 years vs. $<$75 years), sex, diagnosis,

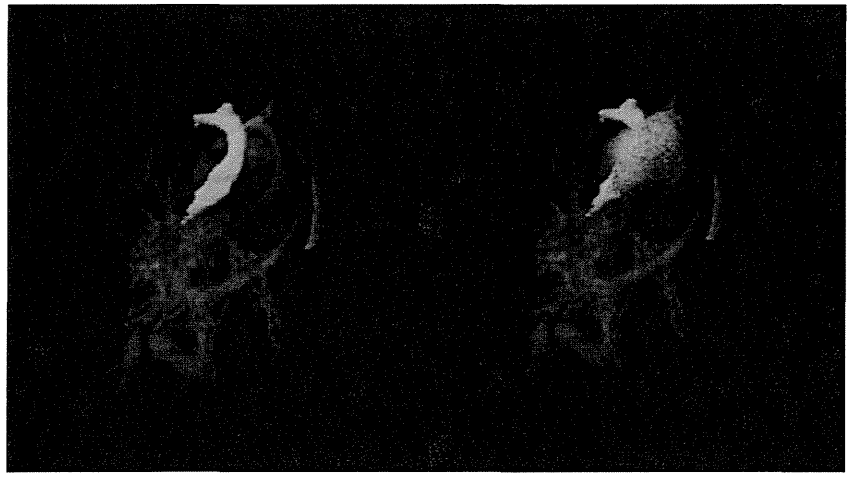

Fig. 1. Delineation of ribs for dose–volume histogram analysis. (Left) All parts of the rib that received more than 20 Gy, even in a small region, were delineated. (Right) Overlap image of delineated ribs and dose–volume more than 20 Gy.

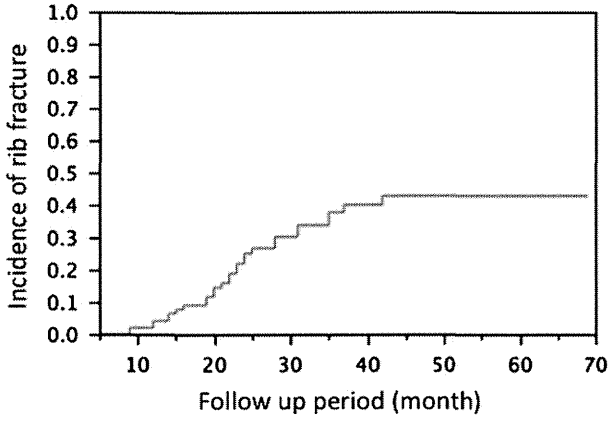

Fig. 2. Cumulative incidence of radiation-induced rib fracture.

and GTV diameter (≥2.4 cm vs. <2.4 cm) were not significantly correlated with the RIRF (Table 2).

Dose–volume relationship

Among the 374 ribs, RIRF was observed in 46 ribs. Table 3 lists the values of the Dmax and V40, V30, V20, and V10 doses for the ribs with or without rib fracture. The Dmax, V40, V30, and V20 were significantly higher in fractured ribs than in unfractured ribs. Among the fractured ribs, the minimum value of Dmax was 34.1 Gy. The approximate AUC results from the ROC plots for Dmax, V40, V30, V20, and V10 were 0.83, 0.82, 0.81, 0.71, and 0.56, respectively. This result revealed that the best predictor of rib fracture was Dmax, and the high dose irradiated volume was more strongly correlated with rib fracture than the low dose irradiated volume. As shown in Table 4, the 3-year estimated risk of RIRF when a division was made into two groups with the cutoff value determined by ROC analysis was 45.8% vs. 1.4% (Dmax, ≥42.4 Gy or less), 51.6% vs. 2.0% (V40, ≥0.29 cm^3 or less), 45.8% vs. 2.2% (V30, ≥1.35 cm^3 or less), 42.0% vs. 8.5% (V20, ≥3.62 cm^3 or less), or 25.9% vs. 10.5% (V10, ≥5.03 cm^3 or less). In each parameter, the difference in the incidence of RIRF between the two groups was statistically significant. However, the difference was greater for Dmax, V40, and V30 than for V20 and V10.

Table 2 Univariate analysis of clinical factors

Parameter	Fractured	Unfractured	Cumulative 3-year incidence, %	*p* value
Age, y				
≥75	12	46	38.3	0.94
<75	16	42	37.2	
Sex				
M	13	54	31.7	0.2
F	15	34	46.5	
Diagnosis				
Primary lung tumor	24	73	38.3	0.62
Oligometastasis	4	15	34.0	
Tumor size (cm)				
≥2.4	15	44	49.3	0.72
<2.4	13	44	27.8	
Rib–tumor distance (cm)				
≥2.0	9	50	24.4	0.0001
<2.0	19	38	58.1	

Table 3 Comparison of dosimetric factors between fractured and unfractured ribs

Parameter	Fractured	Unfractured	*p* value
Dmax (Gy)	47.02 ± 2.77	36.31 ± 9.42	<0.0001
V40 (cm^3)	1.81 ± 1.19	0.67 ± 1.35	<0.0001
V30 (cm^3)	3.10 ± 1.30	1.3 ± 2.01	<0.0001
V20 (cm^3)	4.48 ± 1.53	3.31 ± 3.57	0.0283
V10 (cm^3)	6.74 ± 2.35	6.51 ± 3.45	0.6573

Discussion

Adverse effects to the chest wall after hypofractionated SBRT have been known to include chest wall pain, fibrosis of soft tissue, and rib fracture (7). RIRF is often found as a result of pain, but it is sometimes asymptomatic and is found incidentally. In several previous reports, dosimetric analysis was performed to determine the radiation dose to the chest wall or ribs to predict the risk of RIRF after SBRT (8–12). However, in most of these studies, the radiation dose to the chest wall was the object of the analysis, because chest wall toxicity, including both chest wall pain and rib fracture, was the main interest. In this study, we focused on dose to the ribs to clarify the precise dose–volume relationship with respect to RIRF. In previous studies focusing on the rib dose, Voroney *et al.* (10) and Andolino *et al.* (12) analyzed the maximum dose to the rib fracture sites in patients treated with SBRT for liver and lung lesions. Pettersson *et al.* performed a dose–volume relationship analysis for 81 ribs of 33 patients who received SBRT for non-small-cell lung cancer (8). Our dosimetric study included 374 ribs (113 cases), making it the largest study in this field so far, to our knowledge.

Adverse effects on mature bone after radiotherapy include radiation osteitis, ORN, pathologic fracture, and, in rare cases,

Table 4 Comparison of the provability of radiation-induced rib fracture (RIRF) for each dosimetric parameter

Parameter	Cutoff value	3-year cumulative incidence of RIRF (%)	*p* value
Dmax	≥42.4 Gy	45.8	<0.0001
	<42.4 Gy	1.43	
V40	≥0.29 cm^3	51.6	<0.0001
	<0.29 cm^3	2.01	
V30	≥1.35 cm^3	45.8	<0.0001
	<1.35 cm^3	2.16	
V20	≥3.62 cm^3	42.0	<0.0001
	<3.62 cm^3	8.53	
V10	≥5.03 cm^3	25.9	0.03
	<5.03 cm^3	10.5	

radiation-induced neoplasm. Radiation-induced fractures have been considered to occur in a bone structurally weakened by irradiation and are characterized by high rates of nonunion or delayed union. The biologic effect of ionizing radiation on bone has been considered to be a combination of direct cell injury and radiation-induced vascular injury that can lead to radiation osteitis, atrophy, osteopenia, ORN, and resultant bone fragility (13).

In conventional radiotherapy, the known risk factors of osteoradionecrosis are previous surgery, abuse of alcohol and tobacco, and no use of steroids (14). In the present study, the only risk factor significantly correlated with rib fracture was a short rib–tumor distance. When the rib–tumor distance was less than 2.0 cm, the predictive risk of rib fracture was about 60% over 3 years. However, the distance of the rib to the tumor has been strongly correlated with the dosimetric distribution to the ribs, so the relationship between the fracture rate and the rib–tumor distance must change with the prescribed dose and number of fractions. Considering that there were no significant correlative clinical factors except for the rib–tumor distance, it may rather be assumed that the fracture rate was more strongly influenced by the dosimetric distribution than by the patients' clinical factors in hypofractionated SBRT because of its higher biologically effective dose.

In conventional radiotherapy, it is known that biologic changes are dose dependent. The threshold for radiation-induced changes in bone has been reported to be 30 Gy, with cell death and devascularization of bone occurring at doses over 50 Gy (15). Another report described that ORN occurs after conventionally fractionated radiotherapy up to a total target dose of 66 Gy and higher (16). According to these previous studies, the threshold dose of radiation-induced fracture is considered to be 50 to 60 Gy in conventional radiotherapy.

The dose distributions of hypofractionated SBRT are steeper and more complex than those of conventional radiotherapy because the lower-dose region tends to become large and irregular, whereas the higher-dose region can be concentrated uniformly around the tumor. In addition, less is known about the dose–volume relationship of normal tissue toxicity when a large dose per fraction is used. Fenner *et al.* reported that histologic changes attributed to ORN could be reproducibly obtained in rat mandibular bones by stereotactic irradiation with a total dose of 60 Gy in four fractions at 6 weeks after the completion of irradiation (17). The metabolic rates in rodents have been known to be four to six times higher than those in humans. Therefore, it is possible that ORN develops 6 to 9 months after the completion of irradiation in humans. In fact, the earliest case of rib fracture was found 9 months after SBRT in the present study.

In a previous study using a normal tissue complication probability model, Pettersson *et al.* evaluated the dose administered to 81 ribs and reported a fracture rate of 50% and 5% for patients when the D_{2cc} was above 50 Gy and 27 Gy in three fractions, respectively (8). In our study, we determined optimal cutoff value using ROC curves for dosimetric parameters including Dmax, V40, V30, V20, and V10 of the ribs. The results showed that the highest AUC was in Dmax, and the AUC for V10 to V40 was higher in the order V40 to V10. In addition, the estimated fracture rate in 3 years was approximately 50% when Dmax, V40, or V30 was higher than the respective cutoff value. Our results are consistent with the results of Pettersson *et al.* in that a high dose in a small volume was more important to predict the risk of rib fracture than a lower dose in a larger volume in hypofractionated SBRT (8). In addition, our results suggested that the rib volume receiving ≥30 Gy (V30) or ≥40 Gy (V40) may also be important in predicting the risk of rib fractures. Dunlap *et al.* evaluated the dose to the chest wall in 60 patients after SBRT and reported that the chest wall volume receiving ≥30 Gy (V30) best predicted the risk of severe chest wall pain and/or rib fracture, among V20, V30, V40, V50, and V60 (9). Welsh *et al.* also reported that the risks of both skin changes and chest wall pain were correlated with the volume of the chest wall receiving ≥30 Gy (18). Therefore, when we predict the risk of chest wall toxicity, including chest wall pain, rib fracture, and skin toxicity, V30 and V40 may be a better parameter to use than Dmax.

It is known that RIRF is often painless and is discovered incidentally, unlike traumatic fracture (3). In our study, approximately half of the patients with fracture experienced pain that was transient and not severe, a finding compatible with previous reports. By contrast, Welsh *et al.* also reported that 67 of 265 patients (25.3%) experienced chest wall pain after hypofractionated SBRT (18). Among the patients with chest wall pain, only 8 patients had rib fractures. They found that body mass index and diabetes were strong predictors for the development of chest pain (18). At our institution, only a few patients described having chest wall pain after SBRT. The low obesity rate in Japan might be a cause of the difference in symptom presentation between the two nationalities.

There is a limitation to our study. In this study, we use a pencil beam convolution algorithm to calculate dose, which is known to be suboptimal for dose calculation for SBRT.

In conclusion, RIRF was a not uncommon but relatively tolerable late adverse effect after hypofractionated SBRT. A high dose volume was more strongly correlated with rib fractures than a low dose volume. To reduce the risk of RIRF, a restriction of the high dose volume of the rib should be considered, provided that coverage of the tumor will not be compromised.

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