of 84 Gy is approximately equivalent to 45 Gy with EBRT and 6 Gy for five fractions or 7 Gy for four fractions of HDR.

Standardization of HDR brachytherapy on an international level will assist institutions in terms of comparing toxicities and outcomes in patients with cervical cancer, and will also allow for the exchange of information and uniformity in a multi-institutional international randomized clinical trial that permits HDR brachytherapy. A cumulative dose of 80 Gy should be considered an achievable goal for patients with locally advanced cervical cancer. Analysis of the outcomes in Japanese patients treated with a lower total dose is necessary. Future randomized trials in the era of chemoradiation may attempt radiation dose variation based on response and on improved sparing of normal tissues with 3D imaging, to determine the acceptable safe threshold level that results in equivalent eradication of disease while minimizing toxicities.

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Int J Clin Oncol
DOI 10.1007/s10147-011-0285-4

ORIGINAL ARTICLE

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

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Received: 23 February 2011 / Accepted: 24 June 2011

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

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Published online: 12 July 2011

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

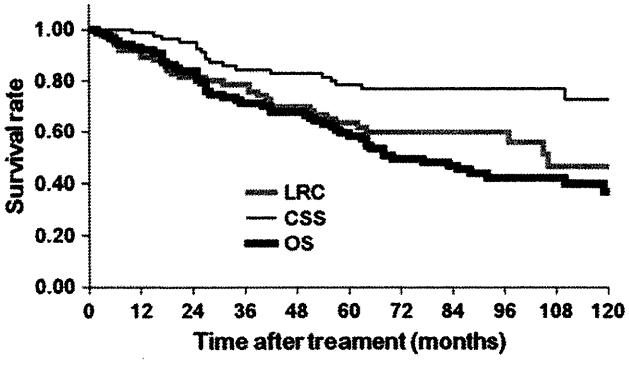

Fig. 1 Curves for overall survival (*OS*), cause-specific survival (*CSS*) and locoregional control (*LRC*) rates for all patients. The 5-year OS, CSS and LRC were 58% (95% CI 48–69%), 78% (95% CI 69–88%) and 63% (95% CI 52–75%), respectively

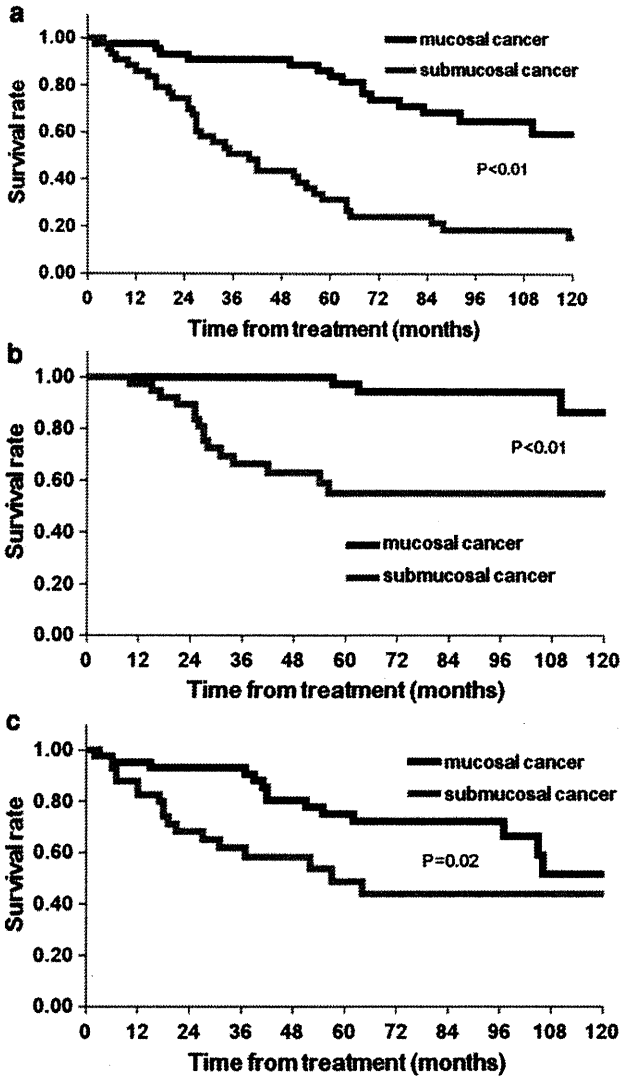

Fig. 2 **a** Curves for OS according to tumor depth. The 5-year OS for mucosal and submucosal cancer were 84% (95% CI 73–95%) and 31% (95% CI 17–46%), respectively ($p < 0.01$). **b** Curves for CSS according to tumor depth. The 5-year CSS for mucosal and submucosal cancer were 97% (95% CI 92–100%) and 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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Hepatology Research

Hepatology Research 2011; 41: 1046–1056 doi: 10.1111/j.1872-034X.2011.00857.x

Original Article

Clinical outcome of esophageal varices after hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with major portal vein tumor thrombus

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Aim: To analyze the clinical outcome of esophageal varices (EV) after hepatic arterial infusion chemotherapy (HAIC) in patients with advanced hepatocellular carcinoma (HCC) and major portal vein tumor thrombus (Vp3/4).

Methods: The study subjects were 45 consecutive patients who received HAIC for HCC with Vp3/4 between January 2005 and December 2009. HAIC comprised the combination therapy of intra-arterial 5-FU with interferon-α (5-FU/IFN) in 23 patients and low-dose cisplatin plus 5-FU (FP) in 22. Radiotherapy (RT) was also provided in 19 patients for portal vein tumor thrombosis. Aggravation rate for EV and overall survival rate were analyzed.

Results: The aggravation rates for EV were 47% and 64% at 12 and 24 months, respectively. The survival rates were 47% and 33% at 12 and 24 months, respectively. The response rates to 5-FU/IFN and FP were 35% and 41%, while the disease control rates in these two groups were 57% and 50%, respectively. There were no significant differences in the objective response and disease control between 5-FU/IFN and FP. Multivariate analysis identified size of EV (F2/F3) ($HR = 7.554$, $P = 0.006$) and HCC disease control ($HR = 5.948$, $P = 0.015$) as significant and independent determinants of aggravation of EV, and HCC disease control ($HR = 12.233$, $P < 0.001$), metastasis from HCC ($HR = 11.469$, $P = 0.001$), ascites ($HR = 8.825$, $P = 0.003$) and low serum albumin ($HR = 4.953$, $P = 0.026$) as determinants of overall survival. RT for portal vein tumor thrombosis tended to reduce the aggravation rate for EV in patients with these risk factors.

Conclusions: Hepatocellular carcinoma disease control was the most significant and independent factor for aggravation of EV and overall survival in HCC patients with major portal vein tumor thrombosis treated with HAIC.

Key words: esophageal varices, hepatic arterial infusion chemotherapy, hepatocellular carcinoma, portal vein tumor thrombosis, radiotherapy

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the commonest malignancies worldwide.[1–3] The causes of death in patients with HCC are cancer-related; including hepatic failure and massive bleeding from esophageal varices (EV). Development of new diagnostic techniques and advancements in therapeutic modalities have gradually improved the prognosis of HCC patients.[4–8] However, the prognosis of patients with advanced HCC and portal vein tumor thrombosis (PVTT) is still poor.[9–13] PVTT is associated with widespread intrahepatic and extrahepatic dissemination by the spread of tumor cells through the portal tract. Recent advances in implantable drug delivery systems have facilitated repeated arterial infusion of chemotherapeutic agents. Because hepatic arterial infusion

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Received 23 February 2011; revision 8 June 2011; accepted 13 June 2011.

chemotherapy (HAIC) increases local tissue drug concentrations and consequently reduces the side effects of anticancer agents, this modality is suitable for HCC patients with PVTT and poor hepatic reserve. Several groups[14,15] reported favorable results with low-dose cisplatin plus 5-FU (FP) for advanced HCC, especially those with PVTT in the first branch (Vp3) or in the main trunk (Vp4), though the prognosis of HCC patients with Vp3/4 is poor. Recent studies[16–19] have also reported the survival benefits of the combination therapy of intra-arterial 5-FU with interferon-α (IFN-α) (5-FU/IFN) for advanced HCC with Vp3/4; the response rate to the latter therapy in HCC with Vp3/4 is about 30–50%.[16–19] However, portal hypertension, which is commonly present in HCC with Vp3/4, is associated with aggravation of the condition, due to bleeding from EV,[20] and poor prognosis of these patients. Moreover, the mortality rate in association with the first episode of variceal bleeding remains high (20–35%), and bleeding from EV is extremely traumatic.[21–24] It is reported that PVTT and large HCC are independent risk factors for bleeding from EV in patients with HCC,[20] and that the EV-aggravation rate in patients with HCC was higher than in those without HCC. Thus, the combination of portal hypertension and EV in HCC patients with Vp3/4 potentially increases the aggravation rate. To date, there is no standardized treatment for EV in HCC patients with Vp3/4. Prophylactic therapy for EV may be needed to reduce death from variceal bleeding and add survival benefits to patients with HCC. Before one can determine the most appropriate type and timing of prophylactic therapy, the factors related to variceal bleeding should be evaluated and defined. The aims of the present study were (i) retrospective analysis of the clinical outcome of EV during HAIC for HCC with Vp3/4; (ii) identification of the factors associated with aggravation and survival rates for EV in HCC patients with Vp3/4; and (iii) set up a strategy for treatment of these patients.

METHODS

Patients

FORTY-FIVE CONSECUTIVE PATIENTS who underwent HAIC for HCC with Vp3/4 at Hiroshima University Hospital between January 2005 and December 2009 were enrolled in this cohort study. We analyzed retrospectively the clinical course of EV in these patients. Endoscopic findings of the EV were evaluated according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices.[25] The form of EV was classified as complete eradication after treatment (F0), small straight (F1), enlarged tortuous (F2), or large coiled-shaped (F3) varices. The positive red color (RC) sign represented the presence of dark red spots on the mucosa of the lower esophagus detected on endoscopy. RC was classified into four grades in order to evaluate the risk of hemorrhage and provide a rough estimate of intravascular pressure within the EV: RC0: no mucosal coloring (negative RC sign); RC1: a few localized red spots; RC2: between RC1 and RC3; and RC3: several mucosal red spots throughout the circumference of the lower esophagus. HCCs were classified according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer by Liver Cancer Study Group of Japan.[26] The institutional review board approved this study, which was based on the Declaration of Helsinki as declared by the World Health Organization. Each patient gave informed consent before the study.

Treatment protocol

Hepatic arterial infusion chemotherapy

Patients with advanced HCC received repeated arterial infusions of anticancer agents via the injection port. One course of chemotherapy represented 2 weeks and comprised either 5-FU/IFN or FP. In both regimens, 5-FU (300 mg/m^2/day; Kyowa Hakko, Tokyo) was administered within 5 h using a mechanical infusion pump on days 1–5 of the first and second weeks (5 g per course). Recombinant IFN α-2b (Intron A, Schering-Plough Pharmaceuticals, Osaka, Japan) at 3×10^6 U (3MU), or natural IFN-α (OIF, Otsuka Pharmaceuticals, Tokyo) at 5×10^6 U (5 MU), was administered intramuscularly on days 1, 3 and 5 of each week (total dose, 18 and 30 MU, respectively). Alternatively, low-dose CDDP (6 mg/m^2/day; Randa, Nippon Kayaku, Tokyo) was administered first followed by 5-FU at the above dose and schedule. In principle, treatment was repeated several times unless PS changed to three or four during the treatment. A 2- to 4-week rest period of no treatment was allowed after each treatment course. The regimen of HAIC varied according to the study period; the 5-FU/IFN was used between January 2005 and December 2007, and FP was used between January 2008 and December 2009.

Radiotherapy

Among the 45 patients, 19 received three-dimensional (3D) conformal radiotherapy (3D-CRT), high-energy photon beam irradiation using 18, 10 or 6 MV, deliv-

ered by a 3D conformal technique (CLINAC 2300 C/D or CLINAC iX linear accelerators, Varian Medical Systems Inc., Palo Alto, CA, USA), at the Division of Radiation Oncology at our hospital. The planning computed tomography (CT) determined the gross tumor volume (GTV) representing the PVTT only. The clinical target volume (CTV) represented the GTV plus intrahepatic tumor forming the basal part of PVTT. 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 volume, total liver tissue and at risk structures, including the spinal cord, both kidneys and 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, in accordance with the dose-volume constraint of normal tissue and liver function. At least 95% of the prescribed dose targeted 95% of the PTV. The decision to use or not to use 3D-CRT was left to the attending physician. Indeed, the use of radiotherapy (RT) varied according to the study period; HAIC alone was used between January 2005 and June 2007, whereas HAIC combined with RT was used between July 2007 and December 2009.

Evaluation of response to HAIC and RT

Follow-up endoscopy after the start of HAIC for HCC was performed every 3–6 months. The EV-related endoscopic findings were evaluated according to the classification system of the Japanese Society for Portal Hypertension and Esophageal Varices[25] and were compared with the findings before the start of HAIC (baseline). Worsening of the F and RC sign relative to baseline or bleeding on follow-up endoscopy was regarded as aggravation of EV. We defined aggravation of EV as the primary endpoint and survival as the secondary endpoint. Data were analyzed in October 2010.

The response to HCC therapy was assessed with contrast-enhanced CT and tumor markers, such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), at 1–2 months after completion of the first course of the treatment, and then every 2–3 months. The response was defined according to the response evaluation criteria for solid tumors (RECIST version 1.1).[27] We evaluated the response to the therapies for PVTT and intrahepatic tumor as well as the overall response. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Table 1 Clinical characteristics of patients

Gender (male/female)	38/7
Age (≤65/>65) (years)†	64 (35–79)
Varices size (F0/F1/F2/F3)‡	13/22/8/2
Red color sign (RC0/RC1/RC2/RC3)‡	34/9/2/0
Platelet count ($\leq 12 \times 10^4 / > 12 \times 10^4$) (/μL)	18/27
T. bilirubin (≤1.0/>1.0) (mg/dL)	25/20
Albumin (≤3.5/>3.5) (g/dL)	18/27
Prothrombin time activity (≤70/>70) (%)	6/39
Ascites (yes/no)	9/36
Tumor size (mm)†	75 (18–140)
Size of HCC relative to whole liver (≤50/>50) (%)	28/17
Vp (3/4)§	29/16
Vv (yes/no)	34/11
Metastasis from HCC (yes/no)	13/32
Etiology (HBV/HCV/NBNC)	16/19/10
HAIC regimen (low-dose FP/5-FU-IFN)	22/23
RT for PVTT (yes/no)	19/26

†Data are median values (range). ‡Classification of esophageal varices: F0 no varices, F1 small straight, F2 enlarged tortuous, F3 large coiled-shaped, RC0 negative red color sign, RC1 a few localized red spots, RC2 between RC1 and RC3, RC3 several mucosal spots throughout the circumference. §PVTT grade: Vp3, tumor thrombus in the first branch of the portal vein; Vp4, tumor thrombus in the trunk of the portal vein.
HAIC, hepatic arterial infusion chemotherapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NBNC, infection without HBV or HCV; PVTT, portal vein tumor thrombus; RT, radiotherapy; Vv, tumor thrombus in the hepatic vein.

Statistical analysis

The cumulative aggravation and survival rates were determined using the Kaplan–Meier method with The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA). Significance was tested using a generalized log-rank test and *t*-test. The independent determinants of the cumulative aggravation and survival rates were compared using a Cox proportional hazards model. A P-value < 0.05 was regarded as statistically significant.

RESULTS

Clinical and endoscopic findings

TABLE 1 LISTS THE clinical characteristics of patients. Based on the endoscopic findings of EV, 13 patients were classified as F0, 22 as F1, 8 as F2, and 2 patients as F3. Furthermore, the RC sign findings were classified as RC0 in 34 patients, RC1 in nine, and RC2 in two patients. The median tumor size for the entire group was

Table 2 Response and disease control rates of hepatocellular carcinoma (HCC) to hepatic arterial infusion chemotherapy (HAIC) with or without radiotherapy (RT)

	Response of PVTT			Response of intrahepatic HCC		
	HAIC combined with RT	HAIC alone	*P*-value	HAIC combined with RT	HAIC alone	*P*-value
CR	2	4		1	4	
PR	10	4		8	4	
SD	7	3		4	3	
PD	0	15		6	15	
CR + PR	63%	31%	0.03	47%	31%	0.25
CR + PR + SD	100%	42%	<0.0001	68%	42%	0.08

CR, complete response; PD, progressive disease; PR, partial response; PVTT, portal vein tumor thrombus; SD, stable disease.

75 mm. The size of the HCC tumor relative to the whole liver was ≤50% in 28 patients and >50% in 17 patients. The severity of portal vein tumor thrombosis was Vp3 in 29 patients and Vp4 in 16.

Response to treatment

The median number of HAIC treatment courses was four in 23 patients of the 5-FU/IFN group and four courses in 22 patients of the FP group. With regard to the response to HAIC among patients of the 5-FU/IFN group, 3, 5, 5, and 10 were classified as complete response, partial response, stable disease, and progressive disease, respectively. The respective patients for the FP group were 2, 7, 2, and 11. Thus, the response rates of the 5-FU/IFN and FP groups were 35% and 41%, respectively, while the disease control rates of these groups were 57% and 50%, respectively. The response and disease control rates were not significantly different between the two regimens. The response and disease control rates for all patients were 38% and 53%, respectively. The response and disease control rates of PVTT were 63% and 100%, respectively, for those treated with HAIC plus RT and 31% and 42%, respectively, for those treated with HAIC alone (Table 2). There were significant differences in these rates between the two groups ($P = 0.03$, <0.0001).

The response and disease control rates of intrahepatic HCC were 47% and 68%, for those who received HAIC plus RT and 31% and 42%, respectively, for those who received HAIC alone (Table 2). There were no differences in these rates between the two groups ($P = 0.25$, 0.08).

Aggravation rates for esophageal varices

Aggravation was recognized in 26 patients. Aggravation according to the F factor and RC sign was noted in 13 patients, and according to variceal bleeding in 13 patients. The median follow-up period was 18 months. The cumulative aggravation rates for EV were 39%, 47%, and 64% at 6, 12, and 24 months, respectively, for all patients (Fig. 1a). The cumulative bleeding rates for EV were 25%, 29%, and 39% at 6, 12, and 24 months, respectively, for all patients. Table 3 shows the factors that correlated with the cumulative aggravation rate by univariate analysis. The overall aggravation rate correlated significantly with varices size ($P < 0.0001$), RC sign ($P < 0.0001$), serum albumin ($P = 0.0333$), ascites ($P = 0.0041$), size of HCC relative to the whole liver ($P = 0.0210$), metastasis from HCC ($P = 0.0018$), and disease control of HCC ($P < 0.0001$).

The above factors were entered into multivariate analysis, which identified varices size ($P = 0.006$) and disease control of HCC ($P = 0.015$) as significant and independent factors of overall aggravation (Table 4). The cumulative aggravation rates at 12 and 24 months were 90% and 90%, for patients with F2/F3, and 33, and 55%, respectively, for patients with F0/F1 (Fig. 1b). There was a significant difference in cumulative aggravation rate between the two groups ($P < 0.0001$). The cumulative aggravation rates at 12 and 24 months were 21% and 46%, respectively, for patients of the disease control group, and 77% and 77%, respectively, for patients of the non-disease control group (Fig. 1c). There was a significant difference in the cumulative aggravation rate between the two groups ($P < 0.0001$).

Effect of radiotherapy in patients at risk for aggravation of esophageal varices

Radiotherapy did not correlate with aggravation of EV on univariate analysis for all patients. However, analysis

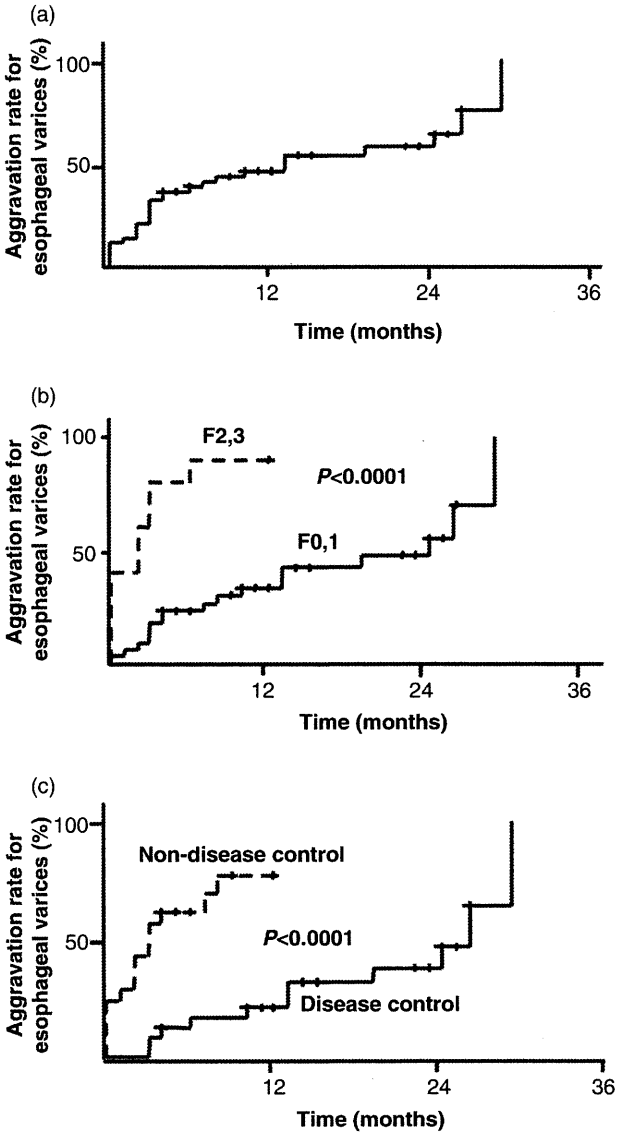

Figure 1 Cumulative aggravation rates for esophageal varices in patients with Vp3/4 hepatocellular carcinoma (HCC). (a) Cumulative aggravation rates for esophageal varices using data of all patients. (b) Cumulative aggravation rate according to the size of esophageal varices (F grade). (c) Cumulative aggravation rate according to HCC disease control with hepatic arterial infusion chemotherapy (HAIC). Disease control: patients who responded to HAIC, non-disease control: patients who did not respond to HAIC.

of data of 32 patients with EV according to the F classification showed a significant difference in cumulative aggravation rate between the RT ($n = 14$) group and non-RT ($n = 18$) group ($P = 0.0044$, Fig. 2a). Moreover, for 28 patients who showed no response to HAIC, the cumulative aggravation rate was significantly different between the RT ($n = 10$) and non-RT ($n = 18$) groups ($P = 0.0465$, Fig. 2b).

Figures 3a and b are representative figures showing improvement of PVTT and EV, respectively. Figures 4a and b are representative figures showing aggravation of PVTT and EV, respectively.

Table 3 Results of univariate analysis for the relationship between cumulative aggravation rate and various clinicopathological variables

Gender (male/female)	0.4449
Age (≤65/>65) (years)	0.0969
Varices size (F0, 1/F2, 3)†	<0.0001
Red color sign (0/1–3)†	<0.0001
Platelet count (≤15 × 10^4/>15 × 10^4) (/μL)	0.1987
T. bilirubin (≤1.0/>1.0) (mg/dL)	0.5258
Albumin (≤3.5/>3.5) (g/dL)	0.0333
Prothrombin time activity (≤70/>70) (%)	0.3468
Ascites (yes/no)	0.0041
Tumor size (≤70/>70) (mm)	0.3936
Size of HCC relative to whole liver (≤50/>50) (%)	0.0210
Vp (3/4)†	0.4542
Vv (yes/no)	0.7653
Metastasis from HCC (yes/no)	0.0018
HCC treatment protocol (low-dose FP/5-FU-IFN)	0.3591
Radiotherapy (yes/no)	0.0892
Disease control of HCC (yes/no)	<0.0001

†See Table 1 for classification of endoscopic findings and of portal vein tumor thrombus (PVTT) grade and abbreviations.

Overall survival

The cumulative survival rates were 69%, 47%, and 33% at 6, 12, and 24 months, respectively, for all patients (Fig. 5a). The median follow-up period was 19 months. Univariate analysis showed that survival rate correlated

Table 4 Determinants of cumulative aggravation rate for esophageal varices by multivariate analysis

	Factor	Hazard ratio	95% confidence interval	*P*-value
Varices size	F2/3	7.554	1.571–14.155	0.006
	F0/1	1		
Disease control of HCC	Non-disease control	5.948	1.282–9.795	0.015
	Disease control	1		

HCC, hepatocellular carcinoma.

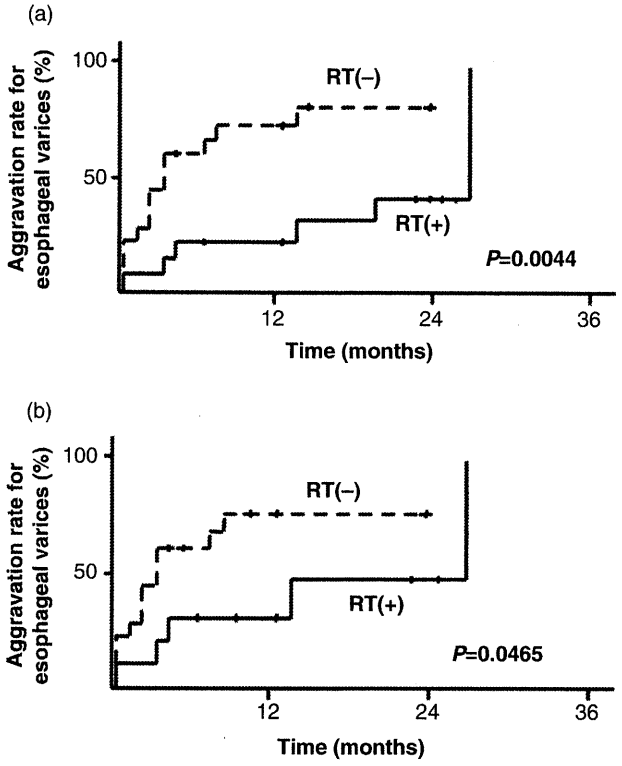

Figure 2 Cumulative aggravation rates for esophageal varices in patients with Vp3/4 hepatocellular carcinoma (HCC) treated with or without irradiation. (a) Cumulative aggravation rates in patients with F factor > F0. (b) Cumulative aggravation rates in non-responders to hepatic arterial infusion chemotherapy (HAIC), according to radiotherapy. RT(+): patients who received radiotherapy, RT(–): patients who did not receive radiotherapy.

significantly with varices size ($P = 0.0004$), RC sign ($P = 0.0001$), serum albumin ($P = 0.0061$), ascites ($P < 0.0001$), size of HCC relative to the whole liver ($P = 0.0003$), metastasis from HCC ($P < 0.0001$), and disease control of HCC ($P < 0.0001$) (Table 5). The above factors were entered in multivariate analysis, which identified disease control of HCC ($P < 0.001$), metastasis from HCC ($P = 0.001$), ascites ($P = 0.003$) and serum albumin ($P = 0.026$) as significant and independent factors of overall survival (Table 6), but not factors related to esophageal varices. The survival rates at 12 and 24 months were 82% and 61%, respectively, for patients of the disease control group, and 6% and 0%, respectively, for patients of the non-disease control group. There were significant differences in cumulative survival rates between two groups ($P < 0.0001$) (Fig. 5b).

Further analysis showed that the survival rates at 12 and 24 months were 26% and 13%, respectively, for patients of the EV rupture group, and 55% and 40%, respectively, for patients of the non-EV rupture group (Fig. 5c). There was a significant difference in the cumulative survival rate between the latter two groups ($P = 0.004$).

Effect of radiotherapy on overall survival in patients with poor prognostic factors

Univariate analysis showed no significant relationship between RT and overall survival, whereas multivariate analysis identified disease control of HCC, metastasis from HCC, ascites and serum albumin to be significant and independent factors of overall survival. However, the cumulative survival rate was different between the RT group and non-RT group ($P = 0.048$), for 35 patients with non-responders to HAIC, those with metastasis from HCC, ascites or serum albumin below 3.5 g/dL (Fig. 6).

Adverse events

The two major adverse events during HAIC were leukopenia in 17 patients (38%) and thrombocytopenia in 13 (29%). These complications were mostly CTCAE grade 1 or 2. Other less common side effects were vomiting in one patient (2%), abdominal pain in one (2%), and appetite loss in one (2%). These were all CTCAE grade 1 or 2. On the other hand, the 19 patients who received RT were classified according to liver functional reserve as no change in 16 patients, deterioration in two patients, and improvement in one patient. In other words, RT was not associated with worsening of liver function in this cohort.

DISCUSSION

THE MAIN FINDINGS of the present study were the following: (i) an extremely high aggravation rate for EV in HCC patients with Vp3/4; (ii) large size varices and lack of response to HAIC were two significant and independent factors that influenced the aggravation rate for EV; and (iii) factors related to EV such as the F factor did not influence overall survival, while HCC disease control was categorized as a significant factor for overall survival.

Analysis of data of all patients showed that the cumulative aggravation rates for EV were 47% and 64% at 12 and 24 months, respectively. Previous study showed

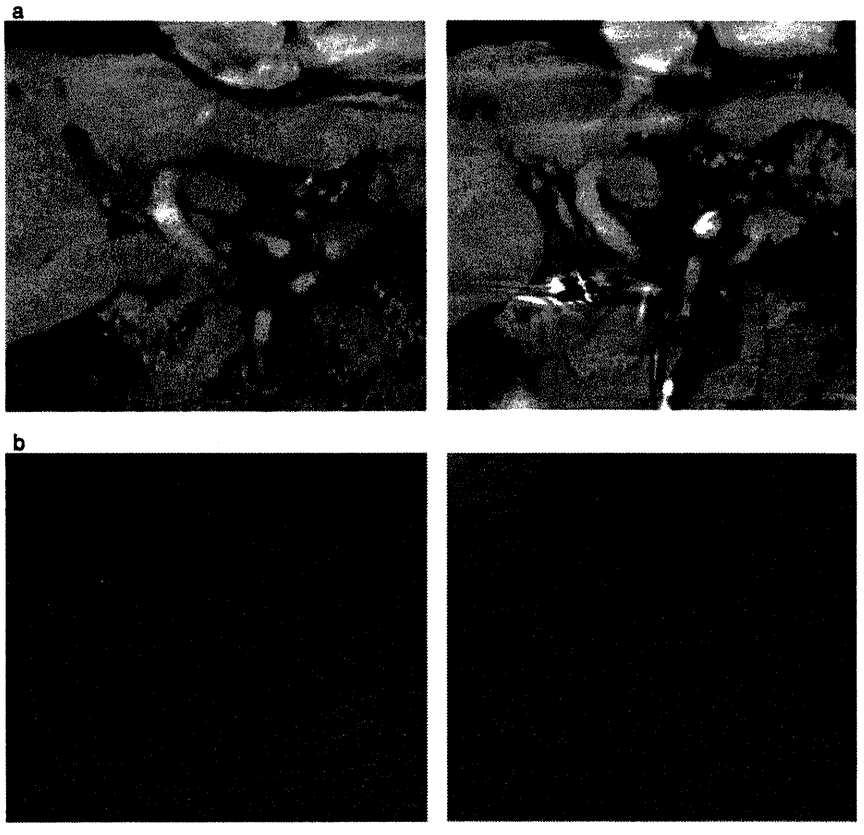

Figure 3 Representative figures showing improvement after the combination therapy of hepatic arterial infusion chemotherapy (HAIC) and radiotherapy (RT). The improvement from Vp3 to Vp2 in portal vein tumor thrombosis (PVTT) provided the reduction from F1 to F0 for varices size. (a) Improvement of PVTT. (b) Improvement of esophageal varices (EV). *Left:* before the combination therapy, *right:* after the combination therapy.

Table 5 Results of univariate analysis for the relationship between cumulative survival rate and various clinicopathological variables

Gender (male/female)	0.1914
Age (≤65/>65) (years)	0.8363
Varices size (F0, 1/F2, 3)†	0.0004
Red color sign (0/1–3)†	0.0001
Platelet count ($\leq 15 \times 10^4 / > 15 \times 10^4$) (/μL)	0.2844
T. bilirubin (≤1.0/>1.0) (mg/dL)	0.8501
Albumin (≤3.5/>3.5) (g/dL)	0.0061
Prothrombin time activity (≤70/>70) (%)	0.8449
Ascites (yes/no)	<0.0001
Tumor size (≤70/>70) (mm)	0.5367
Size of HCC relative to whole liver (≤50/>50) (%)	0.0003
Vp (3/4)†	0.4228
Vv (yes/no)	0.2654
Metastasis from HCC (yes/no)	<0.0001
HCC treatment protocol (low-dose FP/5-FU-IFN)	0.4816
Radiotherapy (yes/no)	0.2871
Disease control of HCC (yes/no)	<0.0001

†See Table 1 for classification of endoscopic findings and of portal vein tumor thrombus (PVTT) grade and abbreviations.

Table 6 Determinants of cumulative survival rate of esophageal varices by multivariate analysis

	Factor	Hazard ratio	95% confidence interval	*P*-value
Disease control of HCC	Non-disease control Disease control	12.233 1	2.215–16.811	<0.001
Metastasis from HCC	Yes No	11.469 1	1.894–10.948	0.001
Ascites	Yes No	8.825 1	1.796–17.390	0.003
Albumin (g/dL)	>3.5 ≤3.5	4.953 1	1.132–7.008	0.026

HCC, hepatocellular carcinoma.

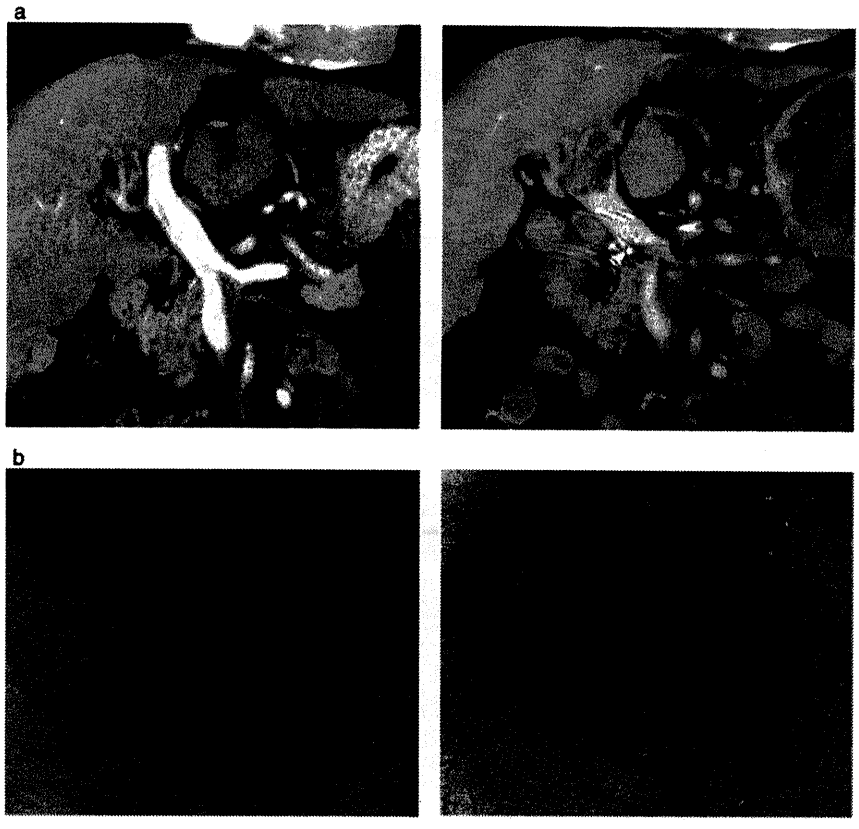

Figure 4 Representative figures showing aggravation after the combination therapy of hepatic arterial infusion chemotherapy (HAIC) and radiotherapy (RT). The aggravation from Vp3 to Vp4 in portal vein tumor thrombosis (PVTT) provided the increase from F1 to F2 for varices size. (a) Aggravation of PVTT. (b) Aggravation of esophageal varices (EV). *Left:* before the combination therapy, *right:* after the combination therapy.

that the proportions of LC patients free of HCC who were positive for the RC sign were 5%, 24% and 43%, at 1, 3, and 5 years, respectively.[20] The data showed that the aggravation rates for EV in HCC patients with Vp3/4 HCC were much higher than those in patients without HCC. In this study, varices size and the HCC disease control were significant and independent factors of overall aggravation for EV during the treatment (Table 4). These results suggest that disease control of HCC by HAIC reduced the aggravation of EV and the portal vein pressure. We analyzed retrospectively the clinical outcome of EV in HCC patients who received HAIC (low-dose FP therapy and 5-FU/IFN therapy). Previous studies reported that the response rate to those therapies in Vp3/4 HCC was less than ~50%.[23,24,28,29] Reduction of aggravation of EV is difficult without improvement in the response to HAIC in Vp3/4 HCC. Wu *et al.*[30] reported that Sorafenib, an oral multikinase inhibitor, could improve the outcome of variceal bleeding in patients with advanced Vp3/4 HCC. This new drug might provide better disease control and improve the aggravation of EV. However, Sorafenib might also increase the likelihood of hemorrhage from EV.

Our analysis showed that RT is not a serious factor in aggravation of EV and survival. However, Katamura *et al.*[31] showed that 5-FU/IFN-α combined with 3D-CRT for PVTT improved the response rate for PVTT and reduced the incidence of portal hypertension-related events. Our study also showed a significant difference in the cumulative aggravation rate between the RT and non-RT groups in patients non-responsive to HAIC or the F factor. Thus, patients who do not respond to HAIC should receive RT as complementary therapy. Moreover, our study showed a significant difference in the cumulative survival rate between the RT and non-RT groups in non-responders to HAIC or those with metastasis from HCC, ascites, or serum albumin below 3.5 g/dL. Thus, patients with these poor prognostic factors for overall survival (according to the results of multivariate analysis) might also benefit from RT as an additional therapy.

In addition to HCC disease control, varices size (F2/F3) was identified as an independent factor for aggravation of EV. Figure 2b shows that the cumulative aggravation rates at both 12 and 24 months were significantly higher in patients with large varices (F2/F3)

compared to those with small varices (F0/F1), suggesting the need for endoscopic treatment such as endoscopic injection sclerotherapy (EIS) or endscopic variceal legation (EVL) in patients with F-positive EV.

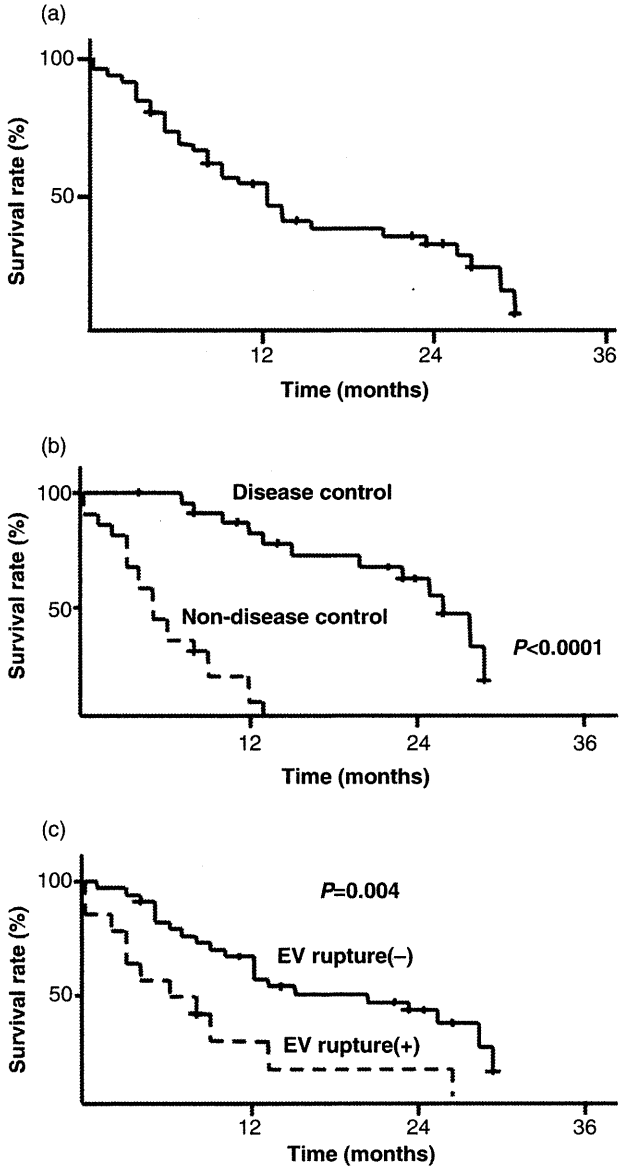

Figure 5 Cumulative survival rates for all patients with Vp3/4 hepatocellular carcinoma (HCC). (a) Cumulative survival rate of all patients. (b) Cumulative survival rate according to HCC disease control. Disease control with hepatic arterial infusion chemotherapy (HAIC): patients who responded to HAIC, non-disease control: patients who did not respond to HAIC. (c) Cumulative survival rate according to rupture of esophageal varices (EV). EV rupture(+): patients with rupture of esophageal varices, EV(–): patients with intact esophageal varices.

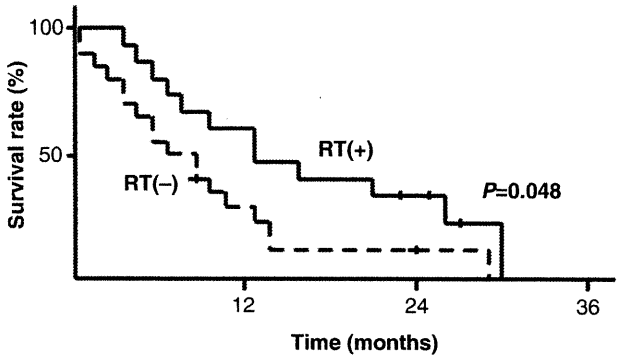

Figure 6 Cumulative survival rates of 35 patients with Vp3/4 hepatocellular carcinoma (HCC) who did not respond to hepatic arterial infusion chemotherapy (HAIC), or those with metastasis from HCC, ascites, or serum albumin below 3.5 g/dL according to radiotherapy (RT). RT(+): patients who received radiotherapy, RT(–): patients who did not receive radiotherapy.

EVL, which is less invasive than EIS, though it does not offer radical treatment, might be favorable for reduction of EV, considering the poor prognosis of HCC patients with Vp3/4. In this regard, radical treatment of EV might be considered after assessment of the response to HAIC. While treatment for EV is recommended for good responders to HAIC, it is not for poor responders. Taken together, we recommend the use of EVL for large EV (F2/F3) before HAIC in patients with Vp3/4 HCC to reduce varices size, followed by HAIC, although HCC disease control should be the most important in the treatment strategy for EV in these patients. On the other hand, HAIC should be provided for advanced HCC at first, while EV should not necessarily be treated since the bleeding rates of F0/F1 and RC0 in HCC patients with Vp3/4 are considered low. When HAIC produces an effective outcome, patients could undergo radical treatment for EV, especially those with F2/F3 and RC1/2/3. However, patients of the non-disease control could receive RT as an additional treatment without the need for treatment of EV (Fig. 7).

In conclusion, the present study demonstrated an extremely high aggravation rate of EV in HCC patients with Vp3/4. The results indicated that large-size varices and lack of response to HAIC are significant determinants of the aggravation rate of EV. In addition, the overall survival was significantly influenced by HCC disease control rather than by factors related to EV such as the F factor. These results emphasize the need for newer and more effective therapeutic modalities for the control of Vp3/4 HCC, and highlight the usefulness of

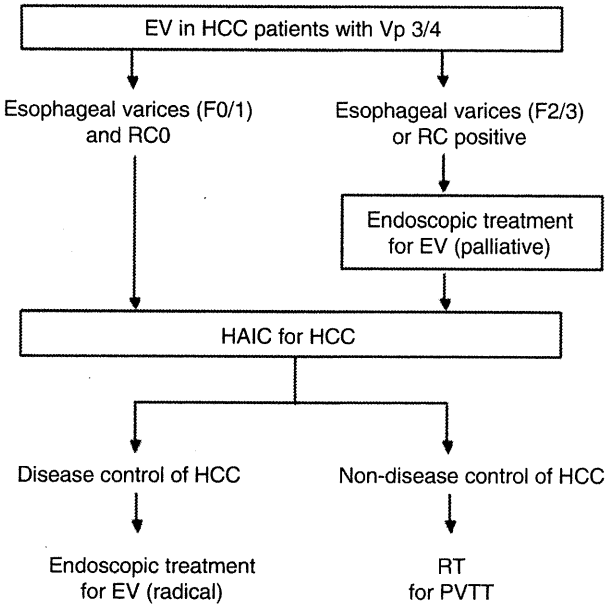

Figure 7 Treatment strategy for esophageal varices (EV) in hepatocellular carcinoma (HCC) patients with Vp3/4.

RT for poor responders to HAIC in the prevention of aggravation and bleeding of EV.

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