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ORIGINAL PAPER

Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience

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Abstract
Purpose To clarify the toxicity of palliative radiotherapy (RT) and its efficacy against bleeding of unresectable gastric cancer.
Methods Clinical data of 19 patients received palliative RT for bleeding from unresectable gastric cancer were reviewed. The median total dose and dose per fraction were 40 Gy (range 2–50 Gy) and 2.5 Gy (range 1.8–3 Gy).
Results The treatment success rate was 68.4%. By using a tumor alpha/beta ratio of 10, biological effective dose of 50 Gy_{10} or more was significantly correlated with treatment success ($P = 0.040$). The median event-free survival was 1.5 months after RT and the median overall survival from starting RT was 3.4 months. Grade 3 nausea and anorexia were recorded in 1 and 3 patients, respectively.
Conclusion Palliative RT was effective for hemostasis in patients with gastric cancer bleeding with minor adverse events.

Keywords Gastric cancer · Radiotherapy · Bleeding · Hemostasis

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Introduction

Gastric cancer is the fourth most common malignancy and is the second leading cause of death, accounting for 700,000 confirmed deaths annually with about 930,000 new cases in the world (Kamangar et al. 2006). In Japan, about 100,000 patients suffer from gastric cancer, and roughly half of them died in 2002. These patients were unfortunately not localized at the first diagnosis. Unresectable gastric cancer has poor prognosis, with the 5-year overall survival (OS) rate of 10%. Fluorouracil-based chemotherapy for patients with unresectable gastric cancer has shown some benefits in improving survival compared with the best supportive care (Glimelius et al. 1994; Murad et al. 1993; Pyrhönen et al. 1995). However, no international standard regimens have been established to date (Ohtsu et al. 2006).

Gastric cancer induces various local symptoms such as bleeding, obstruction, anorexia and pain. Chronic bleeding from gastric cancer can lead to anemia, anorexia, dehydration or hypoalbuminemia. Anemia, in particular, occasionally interrupts the continuity of chemotherapy, and thus control of bleeding is important to improve the quality of life (Pereira and Phan 2004).

Several modalities can be considered as the treatment of choice against bleeding from gastric cancer; nevertheless, which treatment is more effective remains a matter of debate. For example, palliative gastrectomy may be appropriate only for well-selected patients with severe hemorrhage refractory to conservative treatment. Endoscopic hemostasis achieved using thermal probes or by epinephrine injection is temporarily effective in limited cases (Savides et al. 1996). Endoscopic intervention including argon plasma coagulation (APC) has achieved hemostasis in 67% of patients with gastroduodenal tumor bleeding (Loftus et al. 1994).

However, APC sometimes causes severe complications such as perforation in 5–15% of patients, and recurrence of bleeding was frequently found (Loftus et al. 1994). Some investigators have applied gastrointestinal arterial embolization to stop bleeding from gastric cancer, and they have proven its safety and efficacy in limited cases (Encarnacion et al. 1992; Srivastava et al. 2000).

Radiation therapy (RT) has been shown to palliate bleeding from every type of malignant tumors, such as cervical, lung and bladder cancers (Ferris et al. 2001; Onsrud et al. 2001; Hoskin 1998). Recently, two retrospective analyses have been reported regarding the benefit of palliative RT for symptomatic advanced gastric cancer (Kim et al. 2007; Tey et al. 2007). In these reports, palliative RT successfully controlled tumor bleeding in 53–70% of patients without causing severe toxicity. As a clinical practice, we have applied RT for the palliation of bleeding from gastric cancer at our institution. We report here the results of our retrospective analysis of palliative RT for patients with bleeding from gastric cancer, particularly focusing on the dose–fractionation relationship and treatment outcome.

Methods

We retrospectively reviewed the clinical data from the database of our institution of patients with advanced gastric cancer receiving palliative RT between January 1994 and October 2007. Of these patients, those who received RT for a primary lesion for the purpose of palliating tumor bleeding were identified. This study was performed in accordance with Declaration of Helsinki in 1964.

The following clinical characteristics of the patients were reviewed: age, Eastern Cooperative Oncology Group performance status (PS), endoscopic findings, primary site, tumor histology, oral intake status, serum hemoglobin (Hb) level, chemotherapy regimens, dose fractionation of RT, adverse events and treatment outcome. The amount of transfused red blood cells (RBCs) within 1 month before RT was also recorded. Successful treatment was defined as a patient being alive with no need for blood transfusion after more than 1 month following RT. Even if endoscopy proved bleeding improvement, patients who did not meet the successful treatment criterion were considered as treatment failure.

All patients included in this study received external beam RT. They were treated with 6–25 MV X-ray beams from a linear accelerator or microtron. All patients were conformally treated based on CT planning. The typical irradiation technique applied was opposed anterior–posterior two fields. Oblique opposed two fields were sometimes used to avoid irradiation of the right kidney or spinal cord. The biological effective dose (BED) was calculated using a tumor alpha/beta ratio of 10 using the linear-quadratic formalism. Adverse events were retrospectively recorded according to the Common Terminology Criteria for Adverse Events version 3.0.

We defined event-free survival (EFS) as the interval from the last day of RT to the first day of an event including blood transfusion or any cause of death. OS was defined as the interval from the first day of RT to the day of death. Survival curve was estimated by the Kaplan–Meier method (Kaplan and Meier 1958). Univariate analysis was performed using the Fisher's exact test to determine the factors correlating with treatment success. Statistical analysis was performed using StatView version 5.0 (SAS Inc., USA).

Results

Patients' characteristics

Nineteen patients with advanced gastric cancer receiving RT for the palliation of bleeding from primary gastric cancer ($n = 18$) or with postoperative local recurrence

Table 1 Patients' characteristics at the time of starting radiation

$n = 19$	Number
Male/female	13/6
Median age (range)	61 (33–78)
Performance status	
1	5
2	10
3	3
4	1
Histopathology	
Adenocarcinoma	18
Interstitial	11
Diffuse	6
Unknown	1
Squamous cell carcinoma	1
Location	
Upper	7
Middle	5
Lower	6
Stamp	1
Macroscopic type classification	
Type1	2
Type2	4
Type3	11
Type4	2
Median quantity of transfusion one month prior to radiation (range) (ml)	2,400 (0–4,600)

Table 2 Dose, fractionations of radiation therapy, regimens of chemotherapy and clinical outcomes in each case

Patient no.	Age	Sex	Performance status	Total dose (Gy)	Fractions	BED (Gy)	Completion of RT	Prior chemotherapy	Concurrent chemotherapy	Post RT chemotherapy	Lowest Hb level prior to RT (g/dl)	Prior transfusion one month before RT (ml)	Hb level one month after RT (g/dl)	Oral intake before RT	Oral intake after treatment	Treatment outcome	OS (days)	EFS (days)	Status
1	70	M	2	5,000	25	60	Complete	1. CDDP/CPT 2. S1	None	None	4.7	1,700	9.5	Possible	Possible	Succeeded	248	56	Death
2	68	F	2	4,000	16	50	Complete	None	None	S1	7.1	1,000	10	Possible	Possible	Succeeded	1,157	1,136	Alive
3	60	M	4	4,000	16	50	Complete	5FU	None	1. PTX 2. CPT/MMC	6	3,400	10.1	Impossible	Possible	Succeeded	340	318	Death
4	68	M	2	4,000	16	50	Complete	1. 5FU 2. CDDP/CPT 3. PTX	None	None	4.3	1,200	8.3	Possible	Possible	Succeeded	275	254	Death
5	33	M	1	4,000	16	50	Complete	5FU	FP	1. S1 2. CDDP/CPT	6.6	500	8.6	Possible	Possible	Succeeded	194	173	Unknown
6	62	M	3	4,000	16	50	Complete	5FU	None	None	6.8	0	10.1	Impossible	Possible	Succeeded	191	66	Death
7	46	M	1	4,000	16	50	Complete	CDDP/CPT	None	S1	5	2,400	8.4	Possible	Possible	Succeeded	125	38	Death
8	69	M	2	4,000	16	50	Complete	CDDP/S1	None	PTX	5.1	1,700	9.2	Possible	Possible	Succeeded	101	56	Death
9	78	F	1	4,000	16	50	Complete	S1	None	None	5.3	700	7.6	Possible	Possible	Succeeded	88	66	Death
10	53	M	2	4,000	16	50	Complete	S1	S1	None	6.1	1,000	10.2	Possible	Possible	Succeeded	66	41	Death
11	62	M	3	4,000	16	50	Complete	CDDP/CPT	PTX	None	3.5	3,100	NE	Possible	Possible	Failed	29	7	Death
12	53	M	2	4,000	20	48	Discontinue[a]	1. FP 2. CDDP/CPT 3. DTX 4. MMC/CPT	None	None	4.9	1,900	10.2	Impossible	Possible	Succeeded	75	45	Death
13	61	F	3	3,500	14	44	Suspend[b]	1. S1 2. CDDP/CPT	None	None	7	1,000	NE	Possible	Possible	Failed	29	3	Death
14	57	M	1	2,700	9	35	Discontinue[a]	CDDP/CPT	None	PTX	5.4	4,600	8	Impossible	Possible	Succeeded	265	32	Death
15	51	M	2	2,000	10	24	Complete	None	MF	PTX	8.4	3,400	12.3	Impossible	Impossible	Succeeded	77	64	Death
16	51	F	2	2,000	10	24	Discontinue[a]	None	None	None	5.9	1,200	NE	Impossible	Impossible	Failed	30	3	Death
17	71	M	2	1,800	9	22	Suspend[b]	1. 5FU 2. CDDP/CPT	None	None	4.8	1,900	6.4	Possible	Possible	Failed	39	1	Death
18	71	F	2	720	4	8.5	Suspend[c]	S1	None	None	6.5	1,000	NE	Impossible	Impossible	Failed	30	21	Alive
19	33	F	3	200	1	2.4	Suspend[c]	CDDP/CPT	None	None	4.6	2,500	NE	Impossible	Impossible	Failed	3	2	Death

CDDP cisplatin, *CPT* irinotecan, *FP* 5FU/cisplatin, *DTX* docetaxel

MMC mitomycin C, *PTX* paclitaxel, *MF* methotrexate/5FU

RT radiation therapy, *BED* biological effective dose (α/β ratio of 10), *OS* overall survival, *EFS* event free survival, *NE* not examined

[a] Stopped because bleeding improved

[b] No clinical symptom improved

[c] General condition deteriorated

($n = 1$) were identified. The median age of the patients was 61 years (range 33–71) and the median PS was 2 (range 1–4). Table 1 shows the characteristics of the patients. All patients were classified as stage IV at the time of RT and ineligible for surgery because of tumor invasion to other organs. To confirm the bleeding site, all patients underwent endoscopy before RT.

Radiotherapy and patient condition

The dose fractionation of RT, prior chemotherapy, previous blood transfusion and treatment outcomes are shown in Table 2. All but one patient received blood transfusion to improve serum Hb level within 1 month prior to RT. The lowest serum Hb level before RT ranged from 3.5 to 8.4 g/dl (median 5.4 g/dl; Table 2). RBCs corresponding to a median of 1,700 ml of total blood (range 700–4,600 ml) were transfused prior to RT.

The prescribed dose–fractionation regimen ranged from 20 Gy in 10 fractions to 50 Gy in 25 fractions. The median BED was 50 Gy_{10}, which corresponds to a dose of 40 Gy in 16 fractions. Thirteen of 19 (68%) patients completed the total prescribed dose. Three discontinued the prescribed irradiation course because they were clinically judged as treatment success, while another three did not complete the planned irradiation course because of deterioration of general condition.

Treatment outcomes

Treatment success was observed in 13 of 19 patients (68%). The typical endoscopic findings of patients successfully treated are shown in Fig. 1. Complete hemostasis was confirmed in six of seven patients who underwent endoscopy after RT. The median BED was 50 Gy_{10}. Of those who completed the total prescribed dose, successful hemostasis was observed in 11 (92%) of 12 patients. In contrast, of those who were unable to complete the planned irradiation course, successful hemostasis was seen in only two of seven (29%) patients. Treatment success group received significantly higher dose than failure group (median total dose 40 Gy vs. 19 Gy, $P = 0.026$; Fig. 2). The causes of treatment failure ($n = 6$) were deterioration of general condition ($n = 2$), poor treatment effect ($n = 2$) and re-bleeding ($n = 2$). A BED of 50 Gy_{10} or more was significantly correlated with treatment success compared with a BED of <50 Gy_{10} ($P = 0.040$). Other factors considered to affect treatment success such as good PS (1 or 2) and Hb level before RT were not correlated with outcome ($P = 0.26$ and $P > 0.99$, respectively).

After completion of RT, two of three patients without prior chemotherapy could switch to chemotherapy, whereas seven of ten patients with one previous chemotherapy regimen could shift to second-line chemotherapy. Only one of six patients with two prior chemotherapy regimens could continue chemotherapy. Of eight patients in whom oral

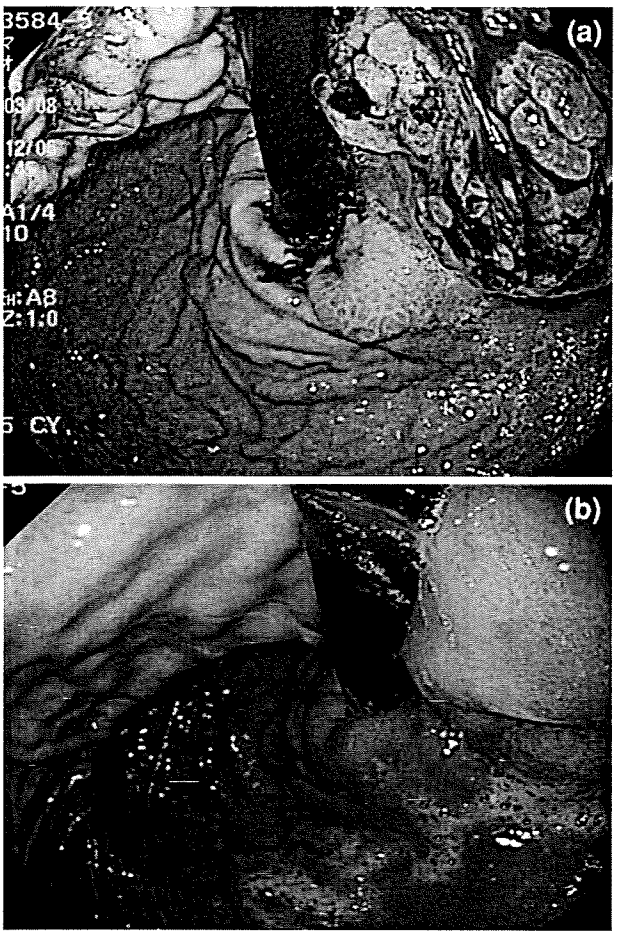

Fig. 1 Typical endoscopic findings. **a** Hemorrhagic gastric cancer of stomach body before radiation therapy. **b** Complete hemostasis following radiation therapy (40 Gy) of the same site

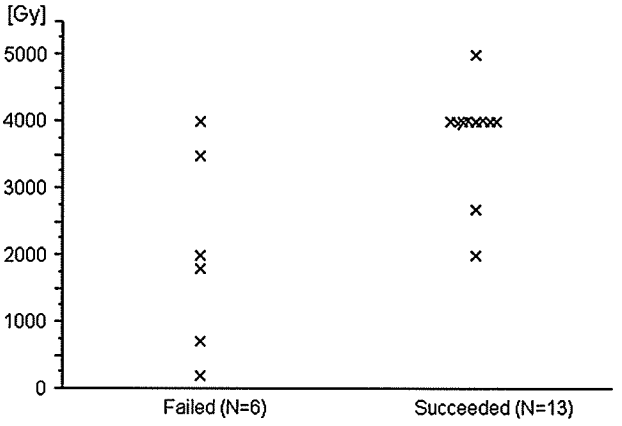

Fig. 2 Dose–effect relationship

intake was prohibited due to gastric bleeding before RT, four (50%) resumed oral intake after RT.

Survival analysis and adverse events

As shown in Figs. 3 and 4, the median EFS from the end of RT and the OS from the first day of RT were 1.5 and 3.4 months, respectively. For EFS, one patient underwent blood transfusion after RT because of anemia, which was supposed to be caused by the subsequent chemotherapy following RT. The median survival time of all patients from the first diagnosis was 12.7 months.

The observed adverse events presented in Table 3 show the frequent occurrence of hematological adverse events. However, most of the patients with grade 3–4 hypohemoglobinemia showed the same grade before, during and after RT. One patient who received chemoradiotherapy developed grade 3 leukocytopenia with no sign of infection. Although there were three patients with grade 3 anorexia (one patient underwent chemoradiation), all of them recovered immediately after completion of RT.

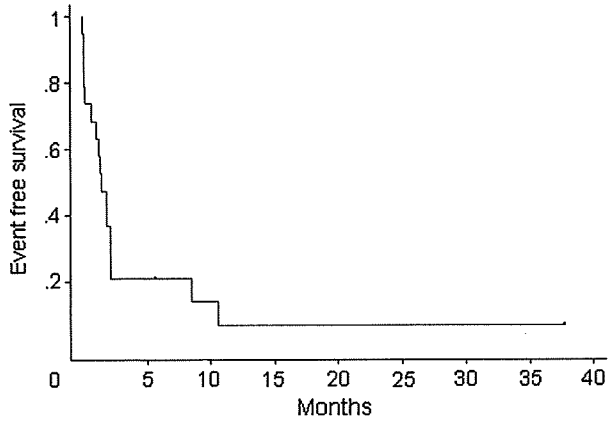

Fig. 3 Event-free survival from the day of completing radiation

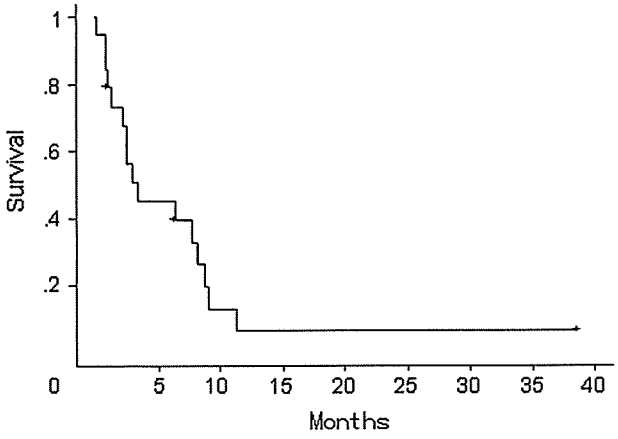

Fig. 4 Survival from the day of starting radiation

Table 3 Toxicity in patients receiving radiation

	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte	0	2	2[a]	0
Hemoglobin	0	4	9[b]	6[c]
Platelet	0	0	0	0
Anorexia	3	4	3	0
Nausea	3	1	1	0
Lethergy	3	2	0	0
Diarrhea	1	0	0	0
Dysphagia	0	1	0	0

[a] One patient received chemoradiation

[b] Ten patients had grade 3 hemoglobin at start of radiation

[c] Two patinets had grade 4 hemoglobin at start of radiation

Discussion

We confirmed here the efficacy of palliative RT in achieving hemostasis in patients with bleeding from gastric cancer. In our clinical experience, successful hemostasis was observed in 13 of 19 patients (68%), without severe adverse effects.

Several reports of palliative RT for local symptom control in patients with unresectable or metastatic gastric cancer are found in the literature. Moreover, several investigators have applied RT for the palliation of obstructive symptoms. Mantell (1982) reported that palliative RT improved dysphasia in 13 of 17 patients (76%). Coia et al. (1998) showed that a combination of RT, fluorouracil and mitomycin successfully relieved dysphasia in six of nine patients (67%). More recently, Kim et al. (2007) have reported that 13 (81%) of 16 patients with dysphasia/obstruction positively responded to RT.

For bleeding control, Tey et al. (2007) reported that 13 of 24 patients (54%) with bleeding from gastric cancer were responsive to RT. However, they simply defined a positive response as improvement or stabilization of the Hb level without providing any discussion on blood transfusion. Kim et al. (2007) have also reported that palliative RT was successful in achieving hemostasis in 14 (70%) of 20 patients. Bleeding was controlled for a median of 11.4 months, which corresponded to 81% of the patients' remaining life (Kim et al. 2007).

In the present analysis, we defined treatment success as absence of the need for blood transfusion for more than 1 month after RT without any other cause of death. Our results are comparable with those of previous reports. We also demonstrated the median duration of sustained

efficacy; however, the median EFS of 1.5 months here was shorter than that of Kim's report. This can be explained by the difference in the definition of treatment success and cohort differences. We believe that the cohort of this study has limited survival when RT was conducted. Interestingly, Kim et al. simply defined treatment success as the absence of the need for coagulation, or no compliant of symptoms during follow up; however, they made no mention about blood transfusion. Here, the median OS was 3.4 months, also shorter than those reported by Tey et al. (2007) and Kim et al. (2007). Most patients analyzed here had poor PS with severe bleeding, and all of them were classified as stage IV and thus ineligible for operation. Moreover, heterogeneous patients who presented with not only bleeding but also stenosis or pain were included in the analysis in previous reports (Kim et al. 2007; Tey et al. 2007).

The reported palliative RT doses for unresectable gastric cancer range widely from 8 to 60 Gy. Tey et al. found no dose–response relationship between responders and non-responders ($P = 0.078$), whereas Kim et al. suggested that a BED of 41 Gy_{10} or more was correlated with better local symptom control ($P = 0.05$). Our data demonstrated a significant dose–response relationship between BEDs of 50 Gy_{10} or more and <50 Gy_{10} ($P = 0.040$). These results are based on the fact that only patients with bleeding were analyzed, and our definition of hemostasis was a clearer objective endpoint than that of other reports. In our experience, successful hemostasis was observed in as high as 91% of patients who completed an initial planned dose (mostly 40 Gy in 16 fractions: BED of 50 Gy_{10}). Despite this relatively high dose, toxicities were tolerable in most patients similarly to other reports (Kim et al. 2007; Tey et al. 2007).

Kim et al. suggested that a lower RT dose (BED <41 Gy) correlated with poor local control (56 and 70%), while Tey et al. found no evidence suggestive of a dose–response relationship. Most patients received a BED of 39 Gy_{10}, which corresponds to a dose of 30 Gy in ten fractions. Thus, different cut-off points may produce different result from ours.

It remains a matter of debate whether gastrectomy for preventing mortality from local progression can improve survival of patients with metastatic gastric cancer. A previous cohort study has shown that only 7% of gastric cancer patients with metastases not undergoing gastrectomy needed intervention due to bleeding (Sarela et al. 2007). Their median survival time was similar to those of a previous series of patients undergoing gastrectomy. A clinical trial is now underway in Japan and Korea to compare the effects of chemotherapy following gastrectomy with the effects of chemotherapy without gastrectomy in patients with metastatic gastric cancer.

Because of the retrospective nature of the present analysis, there are a number of study limitations that may have affected the interpretation of our findings. The dose used in our facility may not always be valid in other facilities because the best available dose has not yet been established. Also, patient population was not homogenous because palliative RT was not used for initial treatment in most cases. Moreover, patients with gastric cancer who presented with bleeding after the failure of several chemotherapeutic regimens might be more resistant to palliative RT. Additionally, those showing good PS with less bleeding could easily complete the total planned dose, and thus may easily be considered as treatment success. On the other hand, those with pronounced bleeding could hardly complete the planned dose. In the present study, the treatment failure group included patients who discontinued the irradiation course because of deterioration of general condition. The dose–response relationships in our study might also be biased. Further studies in large number of patients are warranted to elucidate the appropriate dose for the palliation of bleeding from gastric cancer.

In conclusion, palliative RT was shown to be a powerful treatment of choice for achieving hemostasis in patients with bleeding from gastric cancer. Successful hemostasis was achieved in as high as 91% of patients who completed the initial planned dose (mostly 40 Gy in 16 fractions). A BED of 50 Gy_{10} or more was significantly correlated with treatment success compared with a BED of <50 Gy_{10} ($P = 0.040$). We recommend 40 Gy in 16 fractions for palliating bleeding from gastric cancer according to our analysis. Palliative RT is considered to be helpful not only in rendering transfusion unnecessary but also in re-starting oral nutrition, as well as in potentiating a positive response to other chemotherapy regimens.

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5TH JUCTS AND THE 5TH S. TAKAHASHI MEMORIAL INTERNATIONAL JOINT SYMPOSIUM

SURVEY OF STEREOTACTIC BODY RADIATION THERAPY IN JAPAN BY THE JAPAN 3-D CONFORMAL EXTERNAL BEAM RADIOTHERAPY GROUP

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Purpose: To recognize the current status of stereotactic body radiotherapy (SBRT) in Japan, using a nationwide survey conducted by the Japan 3-D Conformal External Beam Radiotherapy Group.

Methods and Materials: The questionnaire was sent by mail to 117 institutions. Ninety-four institutions (80%) responded by the end of November 2005. Fifty-three institutions indicated that they have already started SBRT, and 38 institutions had been reimbursed by insurance.

Results: A total of 1111 patients with histologically confirmed lung cancer were treated. Among these patients, 637 had T1N0M0 and 272 had T2N0M0 lung cancer. Metastatic lung cancer was found in 702 and histologically unconfirmed lung tumor in 291 patients. Primary liver cancer was found in 207 and metastatic liver cancer in 76 patients. The most frequent schedule used for primary lung cancer was 48Gy in 4 fractions at 22 institutions (52%), followed by 50Gy in 5 fractions at 11 institutions (26%) and 60Gy in 8 fractions at 4 institutions (10%). The tendency was the same for metastatic lung cancer. The average number of personnel involved in SBRT was 1.8 radiation oncologists, including 1.1 certified radiation oncologists, 2.8 technologists, 0.7 nurses, and 0.6 certified quality assurance personnel and 0.3 physicists. The most frequent amount of time for treatment planning was 61–120min, for quality assurance was 50–60min, and for treatment was 30min. There were 14 (0.6% of all cases) reported Grade 5 complications: 11 cases of radiation pneumonitis, 2 cases of hemoptysis, and 1 case of radiation esophagitis.

Conclusion: The current status of SBRT in Japan was surveyed. © **2009 Elsevier Inc.**

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The following institutes in Japan participated in this survey: National Defense Medical College, Yamanashi University, Tohoku University, Keio University, Osaka Rosai Hospital, Hokkaido University, Yamagata Saiseikan Hospital, Hiroshima University, Tokyo Metropolitan Hiroo Hospital, Oita National Hospital, Asahikawa Municipal Hospital, Kitazato University, Tokyo University, Nara Medical College, Kagoshima Satunan Hospital, Kobe IBRI Hospital, Saitama Medical College, NTT East Sapporo Hospital, Gifu University, Hakodate Municipal Hospital, Ibaraki Prefectural Central Hospital, Obihiro Kosei Hospital, Mie University, Chiba Cancer Center, Showa University, Kyushu University, Hyogo Medical Center for Adults, Nagasaki Prefectural Shimabara Hospital, Sapporo Municipal Hospital, Fukui Red Cross Hospital, Kameda General Hospital, Yamaguchi University, Daiyukai General Hospital, Musashino Red Cross Hospital, Hokkaido Cancer Center, Sapporo Medical College, Nihon University, Handa Municipal Hospital, Tenri Hospital, Saitama Cancer Center, Tokyo Medical College Hachioji Center, Aichi Cancer Center, Hiroshima Red Cross Hospital, Kobe University, Kashiwabara General Hospital, Hitachi General Hospital, Hirosaki University, Iwate Tanzawa Hospital, Sendai Kosei Hospital, Furukawa Municipal Hospital, Takeda General Hospital, Tokyo Metropolitan Komagome Hospital, Nagaoka Red Cross Hospital, Fukui University, Hiroshima Prefectural Hospital, Tokushima University, Kagawa University, Kumamoto University, West Kobe Medical Center, Jyuntendo University Hospital, Osaka Medical College, Asahikawa Kohsei Hospital, Gunma University, Japan Defense Structure Central Hospital, St. Luke's International Hospital, Maebashi Red Cross Hospital, Sagamihara Kyodo Hospital, Toyama Municipal Hospital, Shizuoka Saiseikai Hospital, Shiga University, Rinku Central Medical Center, Kurume University, Niigata Cancer Center, Aichi Medical College, Asanokawa General Hospital, Ehime University, Osaka University, Osaka City University, Osaka Red Cross Hospital, Osaka Medical Center for Cancer, Okayama University, Nagoya Second Red Cross Hospital, Kanazawa University, Kawasaki Medical College, Nagoya City University, Nagoya University, The Cancer Institute Hospital, Gifu Prefectural Hospital, Yokohama Municipal Hospital, Kyushu Cardiovascular Center, Kinki University, Konan St. Hill Hospital, National Cancer Center Hospital, National Cancer Center Hospital East, National Kure Hospital, Saga University, Shikoku Cancer Center, Shizuoka Cancer Center, Yokohama Rosai Hospital, Shizuoka General Hospital, Jichi University, JA Hiroshima General Hospital, Yamagata University, St. Marianna University, Seirei Hamamatsu General Hospital, Teikyo University, Tokai University, Tokyo Medical University, Tokyo Women's Medical University, Toyohashi Municipal Hospital, Nagasaki University, Nagoya National Hospital, and Kyoto University.

Conflict of interest: none.

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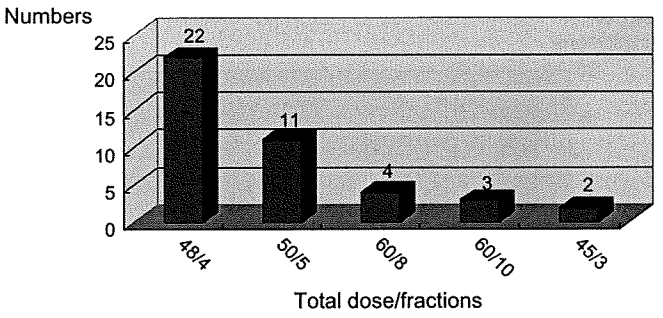

Fig. 1. Fractionation schedules of stereotactic body radiotherapy used in primary T1N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

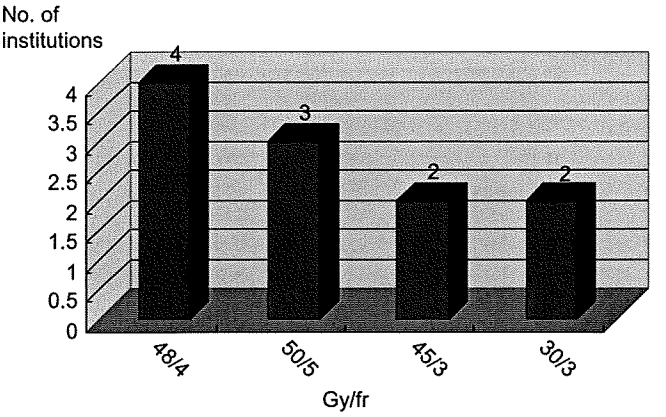

Fig. 3. Fractionation schedules of stereotactic body radiotherapy used in primary liver cancer. The most common schedule was 48 Gy in 4 fractions.

SBRT, Survey, Stereotactic radiotherapy, Lung cancer, Liver cancer.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a new technique to treat early lung or liver cancer. This technique uses a hypofractionation schedule and was introduced in the late 1990s (1–5). Recently, many articles have been published from Japan, the European Union, and the United States describing promising clinical results, especially for early-stage lung cancer (6–31). However, a few complications, including death, have also been reported. Because reimbursement for this treatment was approved by the Japanese governmental health insurance in 2004, a rapid increase has been seen in the number of institutions providing SBRT. Therefore, to appraise the present status of SBRT in Japan, a nationwide survey was conducted by the Japan 3-D Conformal External Beam Radiotherapy Group.

METHODS AND MATERIALS

To review the current status of SBRT in Japan, this study was conducted to evaluate the number of institutions, number of patients, quality assurance (QA), technique, and complications of SBRT.

This questionnaire was mailed to 117 institutions. Ninety-four institutions (80%) responded by the end of November 2005. Fifty-three institutions indicated having already started SBRT, and 38 institutions had already received reimbursement from the government.

RESULTS

A total of 1111 patients with histologically confirmed lung cancer were treated. Stagewise among these patients, 637 had T1N0M0, 272 had T2N0M0, and 202 had T3–4N0M0 lung cancer. Metastatic lung cancer was found in 702 patients and histologically unconfirmed but radiologically diagnosed lung tumor in 291. Primary liver cancer was found in 207 patients and metastatic liver cancer in 76.

The most frequent schedules used for primary lung cancer were 48 Gy in 4 fractions at 22 institutions (52%), followed by 50 Gy in 5 fractions at 11 institutions (26%) and 60 Gy in 8 fractions at 4 institutions (10%), as shown in Fig. 1. The schedule tended to be the same for metastatic lung cancer, as shown in Fig. 2.

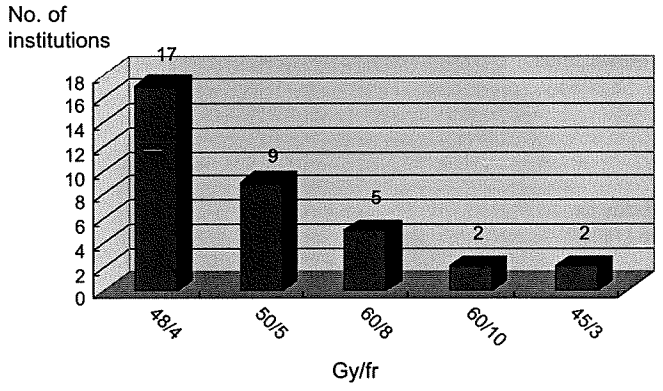

Fig. 2. Fractionation schedules of stereotactic body radiotherapy used in primary T2N0M0 lung cancer. The most common schedule was 48 Gy in 4 fractions.

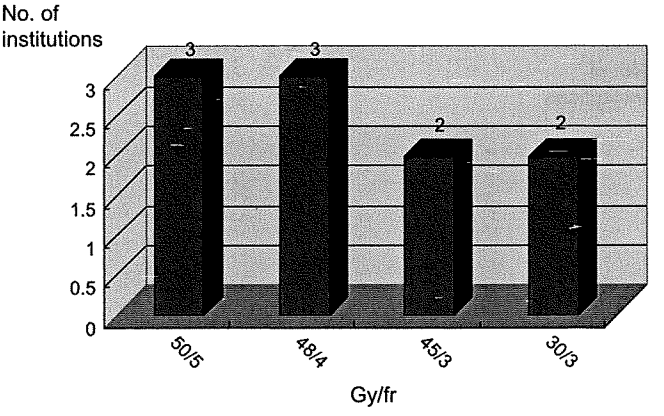

Fig. 4. Fractionation schedules of stereotactic body radiotherapy used in secondary liver cancer. The most common schedules were 50 Gy in 5 fractions and 48 Gy in 4 fractions.

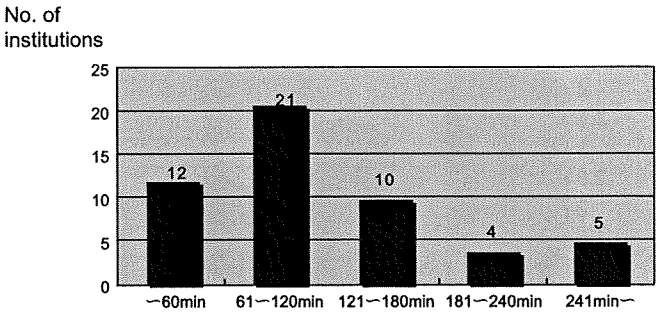

Fig. 5. Amount of time used for treatment planning (RTP) of stereotactic body radiotherapy. The most common time was 61–120 min.

The most frequent schedules used for primary liver cancer were 48 Gy in 4 fractions at four institutions, followed by 50 Gy in 5 fractions at three institutions and 45 Gy or 30 Gy in 3 fractions at two institutions, as shown in Fig. 3. The schedule tended to be the same for metastatic liver cancer, as shown in Fig. 4.

The average number of personnel involved in SBRT was 1.8 radiation oncologists, which included 1.1 certified radiation oncologists, 2.8 technologists, 0.7 nurses, and 0.6 certified QA personnel and 0.3 physicists.

The most frequent time consumed for treatment planning was 61–120 min, as shown in Fig. 5. For QA it was 50–60 min, as shown in Fig. 6, and for single daily treatment it was <30 min, as shown in Fig. 7.

The most frequently used fixing apparatus was a body frame at 30 institutions (68%), followed body fix system, plastic shell, and others, as shown in Fig. 8.

The most frequent verification method before each treatment was portal film at 41 institutions (62%), followed by 9 institutions (13%) with CT on rails and 8 (12%) with an image-guided radiotherapy system, as shown in Fig. 9.

The most common respiratory state was free breathing at 40 institutions (77%), followed by breath-holding at 7 (13%) and respiratory-gated irradiation at 5 (10%). Thirty-two institutions (74%) used abdominal compression, followed by 6 (14%) using voluntary breath holding and 5 (12%) using compulsory holding, as shown in Fig. 10.

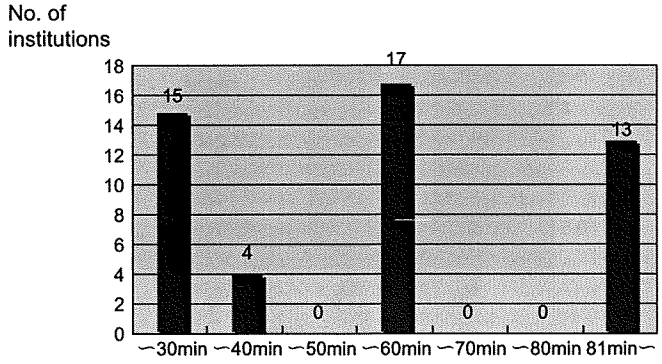

Fig. 6. Amount of time used for the single quality assurance (QA) of stereotactic body radiotherapy. The most common time was 50–60 min.

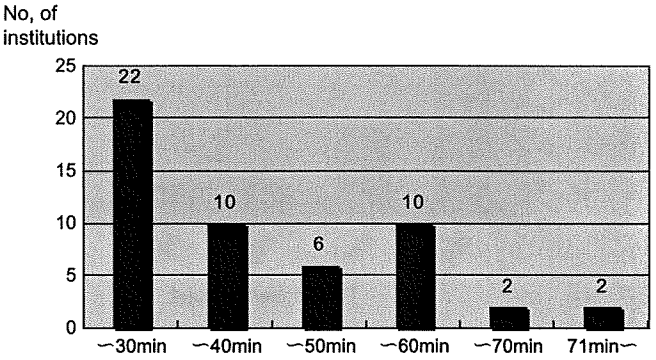

Fig. 7. Amount of time used for single daily treatment of stereotactic body radiotherapy. The most common time was <30 min.

Eighteen institutions (34%) used Focus-Xio (CMS, St. Louis, MO), followed by Eclipse (Varian Medical Systems, Palo Alto, CA) in 15 (28%), the Pinacle system (Philips, Milpitas, CA) in 11 (20%), and the RPS-700 system (Mitsubishi, Tokyo, Japan) in 5 (9%). Forty-three institutions (79%) used fixed noncoplanar beams, nine used dynamic arc therapy, and three used both rotational and dynamic therapy. Forty-eight institutions (94%) used lung heterogenous corrections.

There were 14 (0.6% of all cases) reported cases of Grade 5 complications: 11 cases of radiation pneumonitis, 2 cases of hemoptysis, and 1 case of radiation esophagitis.

DISCUSSION

In Japan, SBRT has been approved as a new method for the treatment of early lung cancer and oligometastatic lung tumors, early liver cancer, oligometastatic liver tumors, and spinal arteriovenous malformation.

However, to limit abuse of this high-technology treatment, the government set up several requirements for radiotherapy institutes to obtain reimbursement. The first requirement is to have a minimum of one full-time experienced radiation oncologist, one radiation physicist, and one experienced technician. The second requirement is for the apparatus for

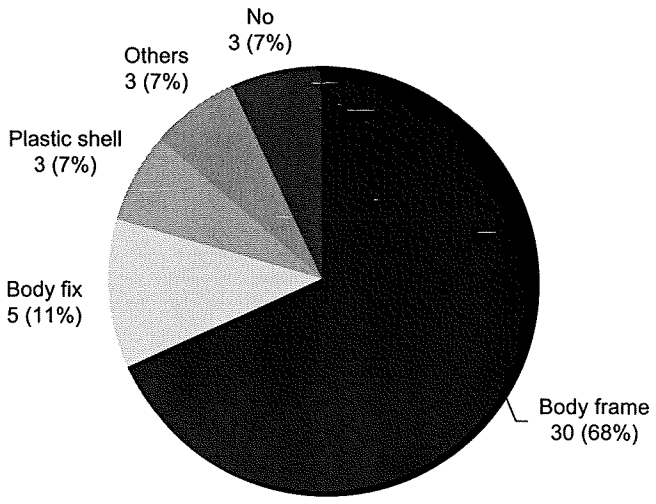

Fig. 8. Fixing apparatus used for stereotactic body radiotherapy. Body frame was most frequently used.

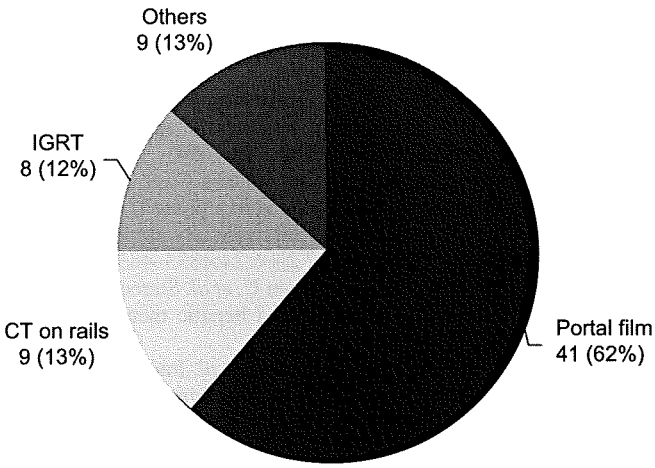

Fig. 9. Verification methods used for stereotactic body radiotherapy. Portal film was most frequently used. IGRT = image-guided radiotherapy; CT = computed tomography.

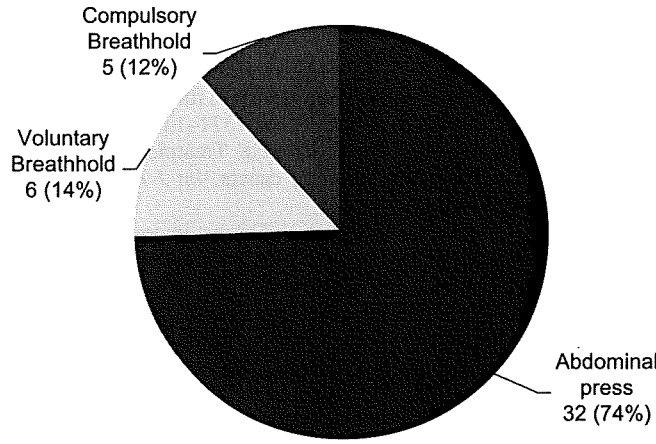

Fig. 10. Respiratory regulation method used for stereotactic body radiotherapy. Abdominal press was most frequently used.

SBRT to include a CT simulator, a three-dimensional radiation treatment-planning system, a microdosimeter, and a water phantom. The third requirement is to perform SBRT under institutional QA guidelines and to limit the setup error of the isocenter to within 5 mm.

In 2005, of the more than 700 radiation oncologic departments, 53 institutions had started SBRT.

The most frequent indication for SBRT was primary lung cancer, followed by secondary lung cancer, primary liver cancer, secondary liver cancer, and spinal arteriovenous malformation. One of the most important points of this survey was to recognize serious complications of SBRT. In total, 11 serious pulmonary Grade 5 complications, 2 bronchial bleedings, and an esophageal ulceration were encountered. Our retrospective analysis revealed that most of these pulmonary Grade 5 patients also had interstitial pneumonitis, although 2 had no underlying pulmonary disease. These 2 patients are suspected to have had underlying interstitial pulmonary disease without manifestation in chest X-rays. Inasmuch as SBRT is known to be basically harmless, rare Grade 5 complications should be carefully studied.

This survey will continue to be performed to recognize current trends and results.

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5TH JUCTS AND THE 5TH S. TAKAHASHI MEMORIAL INTERNATIONAL JOINT SYMPOSIUM

PROSPECTIVE COMPARISON OF SURGERY ALONE AND CHEMORADIOTHERAPY WITH SELECTIVE SURGERY IN RESECTABLE SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

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Purpose: Esophagectomy remains the mainstay treatment for esophageal cancer, although retrospective studies have suggested that chemoradiotherapy (CRT) is as effective as surgery. To determine whether CRT can substitute for surgery as the primary treatment modality, we performed a prospective direct comparison of outcomes after treatment in patients with resectable esophageal cancer who had received CRT and those who had undergone surgery.

Methods and Materials: Eligible patients had resectable T1–3N0–1M0 thoracic esophageal cancer. After the surgeon explained the treatments in detail, the patients selected either CRT (CRT group) or surgery (OP group). The CRT course consisted of two cycles of cisplatin and fluorouracil with split-course concurrent radiotherapy of 60Gy in 30 fractions. Patients with progressive disease during CRT and/or with persistent or recurrent disease after CRT underwent salvage resection.

Results: Of 99 eligible patients with squamous cell carcinoma registered between January 2001 and December 2005, 51 selected CRT and 48 selected surgery. Of the patients in the CRT group, 13 (25.5%) underwent esophagectomy as salvage therapy. The 3- and 5-year survival rates were 78.3% and 75.7%, respectively, in the CRT group compared with 56.9% and 50.9%, respectively, in the OP group ($p = 0.0169$). Patients in the OP group had significantly more metastatic recurrence than those in the CRT group.

Conclusions: Treatment outcomes among patients with resectable thoracic esophageal squamous cell carcinoma were comparable or superior after CRT (with salvage therapy if needed) to outcomes after surgery alone. © 2009 Elsevier Inc.

Esophageal cancer, Chemoradiotherapy, Surgery, Salvage resection, Metastatic relapse.

INTRODUCTION

Surgery has been the mainstay of treatment for resectable esophageal cancer for many years. Since the reports from the Radiation Therapy Oncology Group (1, 2), the number of patients receiving chemoradiotherapy (CRT) has increased worldwide (3). Although definitive CRT without planned resection has become a potentially curative option for esophageal squamous cell carcinoma (4, 5), the outcomes of surgery and CRT have not yet been directly compared.

The absence of a direct comparison causes difficulties with drawing definitive conclusions about whether CRT can truly achieve comparable treatment outcomes to surgery. Moreover, outcomes other than survival, such as causes of failure and quality of life (QOL), cannot be compared at all. Ishikura *et al.* (6) reported that radiation-induced heart and/or pleural diseases seemed to be substantial long-term toxicities.

A randomized controlled trial would provide the data needed to determine various aspects of clinical outcomes after CRT or surgery. However, because of the differing

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Conflict of interest: none.

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treatment characteristics (7), many patients cannot cope with random assignment to surgery or CRT. We decided to ask patients to choose either surgery or CRT, and then we performed a prospective direct comparison of the outcomes.

METHODS AND MATERIALS

Study design

This prospective, nonrandomized study directly compared the outcomes of CRT and surgery for esophageal cancer. All eligible patients were registered and provided written informed consent before entry into the trial. After receiving a detailed explanation of both treatments from the surgeon, the patients themselves decided on either CRT (CRT group) or surgery (OP group). To eliminate disadvantages caused by selecting CRT from the viewpoint that surgery is the standard treatment for resectable esophageal cancer, tumor response to CRT was assessed at the end of each treatment cycle, and patients with unchanged or progressive disease discontinued CRT and underwent immediate salvage surgery (Fig. 1).

The primary study endpoint was overall survival, and secondary endpoints were sources of failure, tolerability of treatment, acute and late toxicities of CRT, and QOL. Baseline characteristics of the treatment groups were compared by use of the *t* test or Mann-Whitney *U* test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Survival was analyzed by the actuarial Kaplan-Meier method, and differences between curves were analyzed with the log-rank test. The time to each outcome was calculated from the date of treatment initiation, and the cutoff date was January 1, 2007. The following variables were assessed as potential prognostic factors with respect to overall survival in the multivariate analysis (stepwise Cox regression model): age, gender, tumor length, site and clinical stage, and patient's choice of treatment. Quality of life was compared between the two groups by the Mann-Whitney *U* test.

Our institutional review board approved the study, which proceeded according to the Declaration of Helsinki.

Eligibility criteria

Eligible patients were aged 20 to 80 years with previously untreated, T1–3N0–1M0 (International Union Against Cancer criteria, 1987), (8) histologically confirmed squamous cell carcinoma of the thoracic esophagus. Candidates for endoscopic mucosal resection (EMR) were not included in this study. The Eastern Cooperative Oncology Group performance status had to be 0 or 1, and patients had to be good surgical candidates. Baseline laboratory requirements were

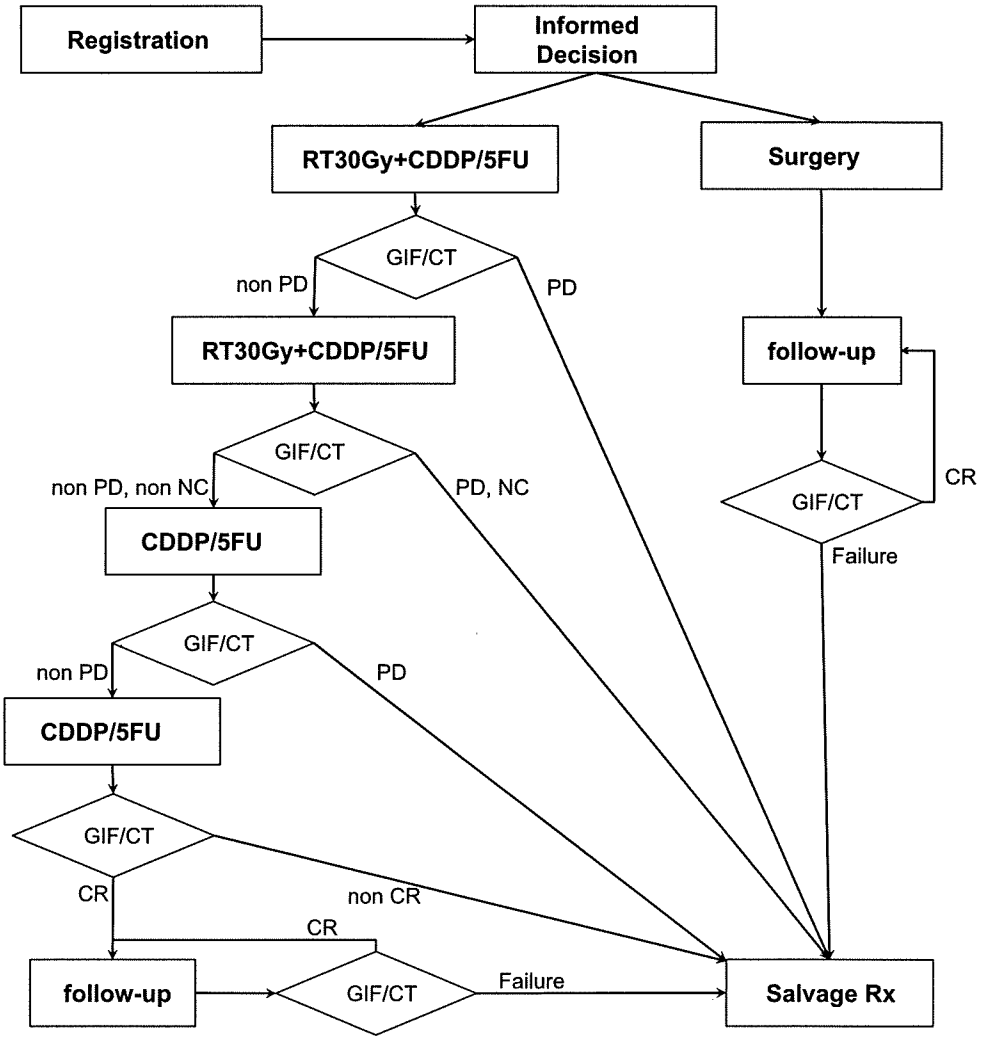

Fig. 1. Treatment design. RT = radiotherapy; CDDP = cisplatin; 5FU = 5-fluorouracil; GIF = gastrointestinal endoscopy; CT = computed tomography; PD = progressive disease; NC = no change; CR = complete response; non CR = not complete response; Rx = treatment.

as follows: white blood cell count, 3,000/mm^3 or greater; hemoglobin level, 10 g/dL or greater; platelet count, 100,000/mm^3 or greater; aspartate transaminase/alanine aminotransferase level, less than or equal to two times the upper limit of normal; total bilirubin level, 1.5 mg/dL or lower; serum creatinine concentration, 1.2 mg/dL or lower; creatinine clearance, 50 mL/min or greater; partial pressure of oxygen (arterial), 70 mm Hg or greater; and no severe electrocardiographic abnormalities. Exclusion criteria included patients with other concurrent malignancies; prior radiation; prior chemotherapy; serious underlying medical conditions such as coronary heart disease, liver cirrhosis, infection, and diabetes that were difficult to control; and concurrent pregnancy or lactation.

Staging modality

Pretreatment evaluation included a physical examination, chest radiograph, barium meal, endoscopy with biopsy, and neck, chest, and abdominal computed tomography (CT). Esophageal ultrasound, bronchoscopy, bone scintigraphy, chest magnetic resonance imaging, or brain magnetic resonance imaging were optional. The T factor was determined basically from endoscopy and CT scans, whereas the N factor was determined from CT scans. We also obtained optional positron emission tomography (PET) images of some patients in the late period using ^{18}F-2-deoxy-D-glucose (FDG).

Treatment

Chemoradiotherapy. The CRT schedule basically followed the protocol of Ohtsu *et al.* (9). In brief, we delivered two cisplatin cycles of 40 mg/m^2 on Days 1 and 8 and a continuous infusion of 5-fluorouracil at 400 mg/m^2 over a 24-hour period on Days 1 to 5 and 8 to 12 every 5 weeks, with concurrent radiotherapy of 60 Gy in 30 fractions over a period of 8 weeks, including a 2-week break. Radiation therapy was delivered with 10- or 15-megavoltage equipment via a multiple leaf collimator. All patients underwent three-dimensional radiation therapy. Gross tumor volume (GTV) was defined as the primary tumor and pathologic lymph nodes based on pretreatment staging examinations. The initial target volume included the GTV and the supraclavicular, mediastinal, and celiac axis lymph node regions; however, the celiac axis lymph nodes were excluded from the initial field when tumors were located in the upper third of the esophagus. This volume received 40 Gy in 2-Gy fractions with a 2-week pause after the 30-Gy dose. Reduced target volume with an approximate 3-cm margin superior and inferior on the GTV and spinal blockage then received an additional 20 Gy, usually by an oblique approach. The planning target volumes were determined by adding 0.5 to 1.5 cm to these volumes to compensate for setup variation and internal organ motion. Two additional cycles of 80 mg/m^2 of cisplatin on Day 1 and a continuous infusion of 800 mg/m^2 of 5-fluorouracil over a 24-hour period on Days 1 to 5 every 4 weeks were administered as adjuvant chemotherapy (Fig. 1).

Surgery. Esophagectomy was performed with a thoracoscopy procedure with basically two-field lymph node dissection. When tumors were located in the upper third of the esophagus, three-field lymph node dissection was performed. We inserted six ports into the thoracic cavity, and esophagectomy proceeded with the assistance of a video monitor. The stomach was usually used as an esophageal substitute through either the posterior mediastinal or the retrosternal route, with a cervical esophagogastric anastomosis. Salvage esophagectomy for persistent or recurrent tumors after definitive CRT was also performed by thoracoscopy in essentially the same manner (10).

Endpoint assessment and follow-up

A complete response (CR) for the primary tumor was defined in the CRT group by endoscopy when all visible tumors, including ulcerations, disappeared and the result of the biopsy proved negative. Responses of metastatic lymph nodes were assessed by CT scans by use of the World Health Organization response criteria for measureable diseases. The CRT group was evaluated at the end of each treatment cycle (Fig. 1), every 3 months for 2 years, and every 6 months for the next 3 years. These patients were also assessed by FDG-PET imaging if necessary. Medically fit patients with persistent or recurrent disease underwent salvage strategies such as esophagectomy or EMR. Acute and late toxicities of CRT were assessed at every hospital visit and graded by use of CTCAE (Common Terminology Criteria for Adverse Events) version 3.0. The amount of bleeding, days in the hospital after surgery, death within 30 days, anastomotic leakage, and cardiac and pulmonary complications were recorded for the OP group. To detect recurrence or metastases, we performed endoscopy and CT scans every 4 months for 1 year and then every 6 months for the next 4 years. Patients with recurrence or metastasis after surgery underwent salvage treatment if indicated. Quality of life after treatment was assessed by a cross-sectional survey with the European Organisation for Research and Treatment of Cancer QOL questionnaire (QLQ-C30 [core questionnaire] and OES18 [esophageal cancer module]) version 3.0 (11) when all candidates had survived for at least 2 years after treatment (October 2006).

RESULTS

Patients

Of 104 patients who registered for the study between October 2001 and November 2004, 56 chose CRT and 48 chose surgery. All patients underwent CT scanning and endoscopy as pretreatment staging modalities. Pretreatment esophageal ultrasound was performed in 15 patients mainly to exclude EMR candidates (Stage T1, T2, and T3 tumors in 17 patients, 1 patient, and 4 patients, respectively), and only 10 patients underwent FDG-PET. Of 56 patients who received CRT, 5 were excluded from analysis because of M1 lymph node metastasis (3 patients), T4 tumors, or medically inoperable status. Table 1 shows the tumor characteristics of the 99 eligible patients in the CRT and OP groups ($n = 51$ and $n = 48$, respectively). The groups were well balanced in terms of age, gender, tumor site and length, clinical T stage, and clinical N stage, and no significant differences were evident between them. The median follow-up duration was 49.7 and 36.4 months in the CRT and OP groups, respectively (55.7 and 50.0 months, respectively, for patients who remained alive).

Treatment characteristics

Compliance with the CRT protocol was quite satisfactory. Of 51 patients, 50 completed 60 Gy of planned radiotherapy without interruption. One patient underwent esophagectomy at a dose of 30 Gy because the tumor response was assessed as progressive. Of the 50 patients, 4 did not complete concurrent chemotherapy because of renal dysfunction ($n = 3$) and poor overall condition ($n = 1$). Before adjuvant chemotherapy, 3 patients underwent esophagectomy. Planned adjuvant chemotherapy was not completed by 4 patients because of renal dysfunction ($n = 2$), bone marrow suppression ($n = 1$), and refusal to continue ($n = 1$). At the end of the course of treatment, persistent disease was identified in 5 more patients

Table 1. Patient characteristics

Characteristic	CRT group (n = 51)	OP group (n = 48)	p Value
Gender			0.263
Male	43 (84)	44 (92)	
Female	8 (16)	4 (8)	
Age (y)			0.179
Median	63	65.5	
Range	42–79	46–78	
T category*			0.631
T1	22 (43)	17 (36)	
T2	5 (10)	5 (10)	
T3	24 (47)	26 (54)	
N category*			0.231
N0	23 (45)	16 (33)	
N1	28 (55)	32 (67)	
Stage*			0.665
I	15 (29)	10 (21)	
IIA	8 (16)	6 (13)	
IIB	9 (18)	9 (19)	
III	19 (37)	23 (48)	
Tumor location			0.204
Upper thoracic portion	5 (10)	5 (10)	
Mid thoracic portion	33 (65)	23 (48)	
Lower thoracic portion	13 (25)	20 (42)	
Tumor length (cm)			0.078
Median	5	4	
Range	1–20	1–8	

Abbreviations: CRT = chemoradiotherapy; OP = surgery.
Values are expressed as n (%), unless otherwise indicated.
* Numbers correspond to the tumor-node-metastasis system of classification (International Union Against Cancer criteria, 1987).

(non–CR) (Fig. 1), and 4 underwent esophagectomy (1 patient refused to undergo surgery). Thus 94% (47 of 50) of the enrolled patients completed CRT, and 83% (39 of 47) completed the treatment protocol (excluding those who underwent salvage surgery according to the protocol). Progressive or persistent disease was detected in 9 patients (CR rate, 82.4%), and 8 patients underwent esophagectomy by the end of the entire treatment course. During the follow-up period, disease recurred in some of the patients who had once achieved CR, and a total of 18 patients underwent salvage therapies as described later.

Of the 48 patients in the OP group, 46 (95.8%) underwent curative resection. One patient had a positive margin at a lymph node metastasis, and another had para-aortic lymph node dissemination. These two patients and another with many lymph node metastases in the mediastinum underwent postoperative CRT (40–60 Gy in 2-Gy fractions). None of the other patients received adjuvant treatment as an initial therapy.

Toxicity of treatment

In the OP group 1 patient (2.1%) died of acute myocardial infarction at 1.6 months after surgery, whereas none in the CRT group died. Death did not seem to be related to treatment in either group. Table 2 shows the incidence of acute and late toxicities graded based on CTCAE criteria in the CRT group. Although Grade 3 or higher acute toxicity developed in several patients—with leucopenia, anemia, thrombocytopenia,

Table 2. Summary of toxicity in chemoradiotherapy group

Toxicity	Grade 3	Grade 4	Grade 5
Acute			
Leukocyte	45	0	0
Hemoglobin	14	4	0
Platelets	8	2	0
Creatinine	0	0	0
Bilirubin	0	0	0
Aspartate transaminase	2	0	0
Alanine transaminase	2	2	0
Nausea	16	0	0
Esophagitis	2	0	0
Dermatitis	2	0	0
Late			
Radiation pneumonitis	0	2	0
Pleural effusion	0	0	0
Pericardial effusion	0	0	0
Skin	0	0	0
Esophagus	0	0	0
Spinal cord	0	0	0

Values are expressed as %.

and nausea in 45%, 18%, 10%, and 16% of patients, respectively—most of them satisfactorily complied with treatment. In terms of late toxicity, 1 patient with radiation pneumonitis required mechanical ventilator support (Grade 4) at 6 months after treatment. Other late toxicities remain negligible. Follow-up CT images were obtained from 32 (91.4%) of 35 recurrence-free patients in the CRT group (including 5 who underwent salvage therapy by EMR). Transient and long-lasting pleural effusions occurred in 12 and 3 patients (46.9%), respectively, whereas 9 and 2 patients (34.4%) had transient and long-lasting pericardial effusions, respectively; however, none were symptomatic or required therapeutic intervention (Grade 1). Univariate analysis by use of clinical factors showed that more advanced age was correlated with the onset of pleural (p = 0.002) and pericardial (p = 0.028) effusion. Surgical complications of the OP group comprised the following: mean amount of bleeding, 717 mL; duration of hospital stay after surgery, 36.7 days; deaths within 30 days, 0; anastomotic leakage, 9 (18%); cardiac complications, 9 (18%); and pulmonary complications, 7 (14%).

Survival

The mean duration of survival of the 51 patients in the CRT group and 48 patients in the OP group from starting treatment was 52.9 (95% confidence interval [CI], 47.7–58.1) and 41.2 (95% CI, 35.1–47.2) months, respectively, and the survival rates were 78.3 ± 5.8% and 75.7 ± 6.2%, respectively, at 3 years and 56.9 ± 7.4% and 50.9 ± 7.7% (p = 0.0169), respectively, at 5 years (Fig. 2A). Subgroup analysis showed 2- and 4-year survival rates of 100% and 100%, respectively, for the 15 CRT patients in Stage I and 90% and 75%, respectively, for the 10 OP patients in Stage I (p = 0.062) (Fig. 2B). Three patients in the CRT group had local recurrence at 9.4, 11.2, and 26.5 months, respectively; two underwent salvage therapy by EMR, and one underwent esophagectomy. Four patients in the OP group had

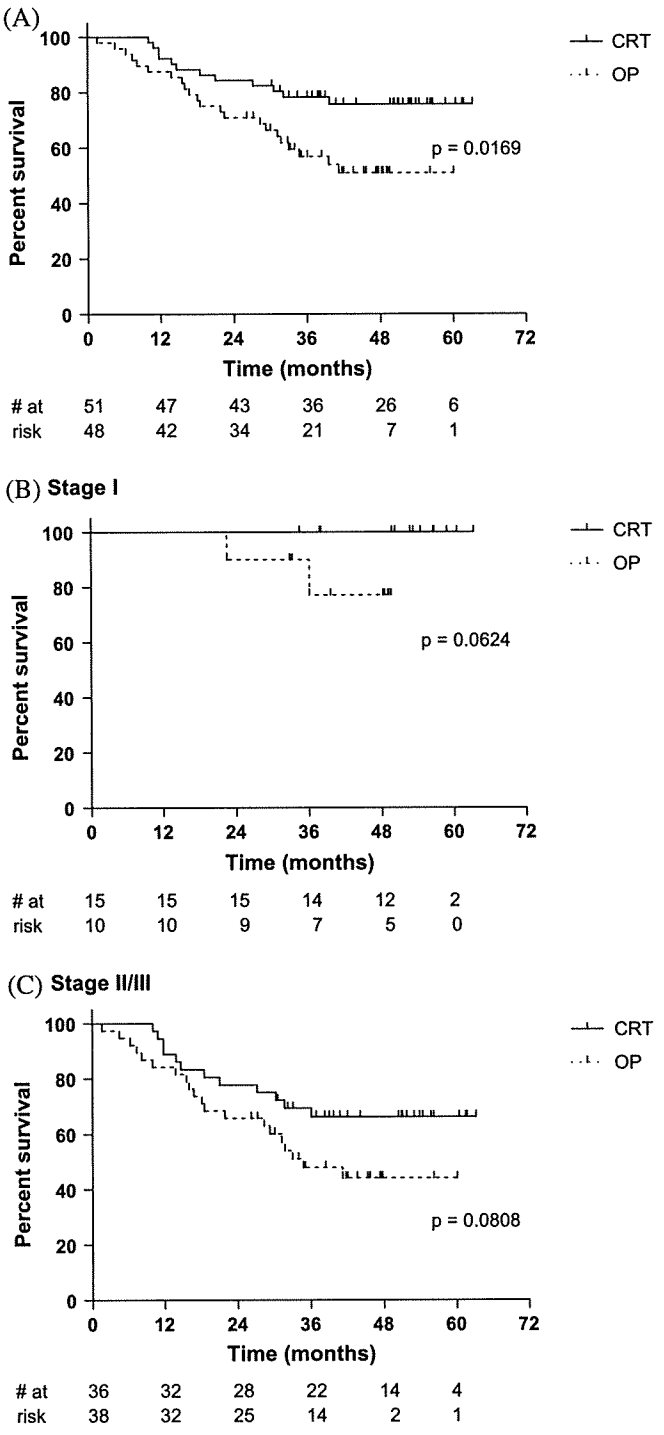

Fig. 2. Overall survival of patients with resectable esophageal cancer after either chemoradiotherapy (CRT) or surgery (OP). (A) Overall survival (p = 0.0169). (B) Survival of patients in Stage I. (C) Survival of patients in Stage II or III.

recurrence at 3.3, 10.1, 38.3, and 38.6 months, respectively; two with locoregional lymph node metastases underwent salvage therapy by CRT with and without surgery, and one with lung metastasis underwent surgery followed by CRT. Those 3 remained alive at the last follow-up, but the other patient, with para-aortic lymph node metastases, had only best supportive care. Another patient died at 22.5 months with no evidence of cancer recurrence. The 3- and 5-year survival rates were 69.1% and 65.3%, respectively, for the 36 CRT patients in Stage II or III and 47.9% and 44.2%, respectively, for 38 OP patients in Stage II or III (p = 0.083) (Fig. 2C). Multivariate analysis showed only clinical stage (p = 0.00045) and treatment modality (p = 0.081) as independent predictors of overall survival.

Table 3. Incidence and site of persistent/recurrent disease

	CRT group		OP group		
Site	No.	%	No.	%	p Value
Total failure	23	45.1	23	47.9	0.8415
First failure					
Locoregional	20	39.2	5	10.4	0.0011
Local only	18	35.3	—	—	0.0001
Distant	2	3.9	15	31.3	0.0003
Locoregional and distant	1	2.0	3	6.3	0.3524
Cumulative failure					
Distant failure	7	13.7	19	39.6	0.0056

Abbreviations: CRT = chemoradiotherapy; OP = surgery.

Causes of failure

Table 3 shows crude profiles of initial and cumulative failure. The recurrence probabilities were 45.1% (23 of 51) in the CRT group and 45.8% (22 of 48) in the OP group (p = not significant) (Fig. 3A). However, the failure sites significantly differed. Patients in the CRT group had more locoregional relapses (odds ratio for CRT vs. OP, 3.50; 95% CI, 1.36–8.979) (Fig. 3B), whereas those in the OP group had more distant metastases (odds ratio, 0.0184; 95% CI, 0.00396–0.0853) (Fig. 3C). The initial site of distant metastasis in the OP group was the lung and distant lymph node in 5, liver in 3, pleura and bone in 2, and peritoneum in 1, whereas the site in the CRT group was the brain in 1, adrenal gland in 1, and chest wall in 1, respectively.

Salvage treatment outcomes

Figure 4 shows a brief treatment scheme for all of the patients. In the CRT group 18 patients underwent salvage treatment (esophagectomy in 13 and EMR in 5). Thirteen patients underwent esophagectomy at a median of 3.6 months (range, 0.9–24.7 months) after CRT. Of these 13 patients, 2 had no evidence of carcinoma in the excised specimen, and curative resection was achieved in 12 patients (92.3%). Surgical complications were as follows: mean bleeding, 717 mL; mean hospital stay after surgery, 63.6 days; deaths within 30 days, 0; anastomotic leakage, 5 (38.5%), and tracheal necrosis, 1. Two patients died of intercurrent disease at 17 and 28.8 months, respectively, after salvage surgery, and four died of cancer. Mean survival was 33.6 months (95% CI, 23.7–43.6), and the 1- and 3-year survival rates calculated from salvage esophagectomy were 76.9% and 52.8%, respectively. All 6 patients who died after salvage esophagectomy were in pretreatment Stage III, whereas 5 patients in

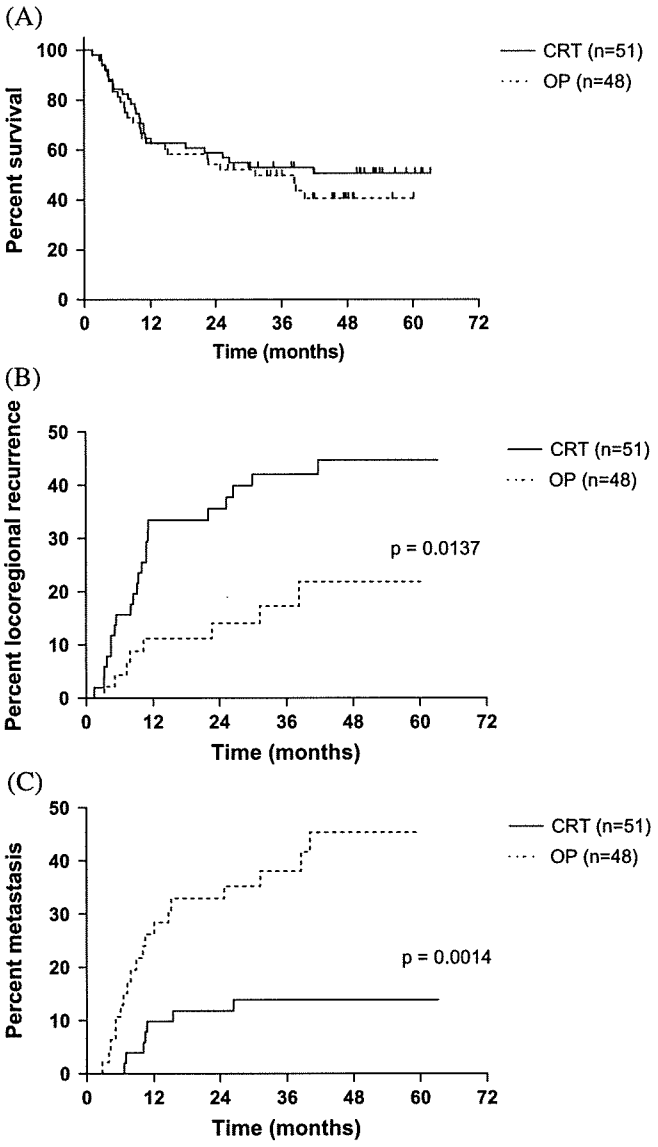

Fig. 3. (A) Disease-free survival of patients with resectable esophageal cancer after either chemoradiotherapy (CRT) or surgery (OP). (B) Time to locoregional failure according to treatment ($p = 0.0137$) (C) Time to distant metastasis according to treatment ($p = 0.0014$).

Stage I or II remained alive without evidence of disease. Five patients who received EMR at the median time of 9.2 months (range, 7.4–41.7 months) were all alive and disease-free at the last follow-up. Of these EMR patients, 2 were in Stage I, 2 were in Stage IIB, and 1 was in Stage III.

A total of 23 patients in the OP group had persistent or recurrent disease. Of the 17 patients who underwent salvage treatment, 8 were treated with curative intent (surgery in 3 and CRT in 5) and 9 received palliative therapy. At the last follow-up, 2 with locoregional lymph node recurrence alone remained disease free, 3 were alive with disease, and the others died of cancer.

Quality of life

The QOL was assessed by use of a cross-sectional approach when all candidates had survived for at least 2 years after treatment. Among 66 patients (39 in CRT group and 27 in OP group) who remained alive at the time of the survey (October 2006), 62 completed the questionnaires (37 in CRT group [response rate, 94.9%] and 25 in OP group [response rate, 92.6%]). The median intervals between starting treatment and the QOL evaluation were 49.7 months (range, 28.2–61.1 months) and 43.5 months (range, 24.1–58.0 months) in the CRT and OP groups, respectively. The mean values of almost all QOL scores (Table 4) were more favorable in the CRT group than in the OP group, and the differences reached statistical significance for appetite loss, diarrhea, and eating problems. Esophageal preservation was the only independent predictor ($p < 0.05$) of global QOL, and the time from treatment to survey completion was not significant.

DISCUSSION

Despite the increase in the number of patients undergoing definitive CRT as primary treatment for esophageal cancer (3), this modality has not been directly and prospectively compared with surgery. The patients selected their treatment strategy in this nonrandomized study. Although potential prognostic factors did not significantly differ (Table 1), the possibility of selection bias might remain. However, to our knowledge, this was the first study to enroll patients with esophageal squamous cell carcinoma who met the same eligibility criteria and assign them to surgery or CRT. Surgery and CRT should be directly compared from various aspects of clinical outcomes such as survival, patterns of failure, and QOL.

Our results suggest that CRT is not inferior to surgery in terms of long-term survival in patients with resectable esophageal squamous cell carcinoma. Although 13 patients (25.5%) required salvage esophagectomy after CRT, the overall survival of the CRT group was consistently and significantly better than that of the OP group ($p = 0.0156$). Multivariate analysis showed that clinical stage ($p = 0.00045$) and treatment group ($p = 0.081$) were the best independent predictors of outcome.

The 3- and 5-year survival rates of the CRT group were 78.3% and 75.7%, respectively, which are better than those previously reported (1, 2, 7, 12, 13). This might have been because of the following factors. First, the patient population of this study comprised candidates for esophagectomy, so they were in better physical condition than the usual radiotherapy candidates. Second, low treatment-related mortality rates and high rates of compliance with the CRT protocol might have improved survival. Acute toxicities, especially hematologic toxicities, were considerable but manageable. Although 94% of our patients completed the CRT part of the treatment and 83% completed an additional two courses of chemotherapy, none of them died of treatment-related causes. Third, salvage treatments (14) increased local control and improved the overall survival.

Up to 25% of our patients underwent salvage esophagectomy. Although all but 1 received 60 Gy of CRT, the 3-year survival rate after salvage was 56.8%. Larger studies of salvage surgery have found 5-year survival rates of 25% to

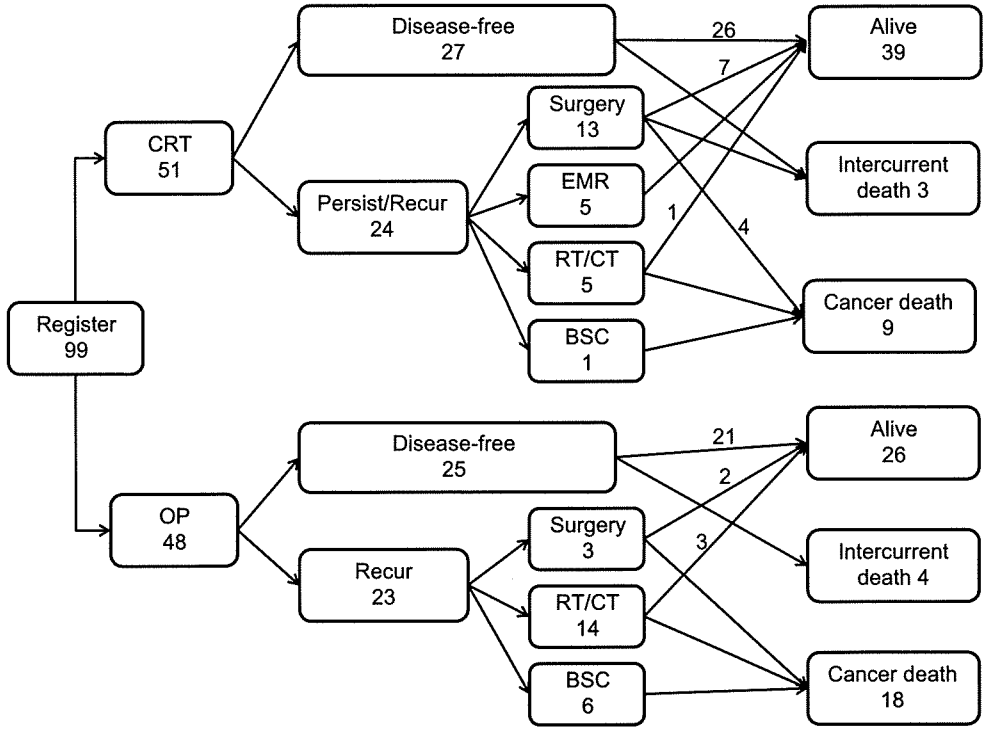

Fig. 4. Patient treatment scheme. CRT = chemoradiotherapy; OP = surgery; Persist = persistent disease; Recur = recurrence; EMR = endoscopic mucosal resection; RT/CT = radiotherapy and/or chemotherapy; BSC = best supportive care.

35% and that the most important prognostic factor affecting survival after salvage surgery is R0 resection (15, 16). The R0 resection rate in our study was 90.9%, and we believe that our intensive follow-up protocol enabled detection of early recurrence. The duration of hospital stay after surgery (63.6 days vs. 36.7 days) and anastomotic leakage rate (38.5% vs. 18%) were increased in the CRT group compared with the OP group. Because all 5 patients in pretreatment Stage I or II remained alive without evidence of disease, they may be good candidates for salvage surgery. Despite increased risks of morbidity and death, salvage esophagectomy is considered to be a feasible therapeutic option for CRT patients.

The enhanced survival of the CRT group compared with the OP group mainly arose from a decrease in distant metastasis. Although the increased lifespan of patients receiving CRT after salvage therapy placed them at a higher risk of distant metastases developing, the rate of such metastases was decreased in this group not only at the time of the first relapse but also cumulatively (Fig. 3C). One of the limitations of our study was that a modern diagnostic modality such as FDG-PET was not used in cancer staging. The significantly higher rate of metastatic relapse in the OP group compared with the CRT group appeared to be because of the misdiagnosis of tumor spread and the absence of upfront systemic therapy. Under these circumstances, CRT—which could have impacted both local and distant disease recurrence—had a great advantage. A recent meta-analysis has shown a significant survival benefit of neoadjuvant CRT or, to a lesser extent, chemotherapy compared with surgery alone (17). Another limitation of our study is that we selected patients who underwent surgery alone as the control group. Because our results support the ability of CRT to eradicate micrometastatic lesions of esophageal squamous cell carcinoma, definitive CRT with selective surgery should be compared with surgery plus neoadjuvant systemic therapy in the future.

In the context of neoadjuvant CRT as a standard treatment, the necessity of surgery is controversial. Two European randomized studies of patient populations with predominantly squamous cell carcinoma found no survival benefit of additional surgery among those who responded to neoadjuvant CRT (4, 5). Our results support the notion that a population can survive without esophagectomy but that local recurrence still develops in many responders and some of these should be cured with salvage resection. The European studies examined only patients with advanced disease (Stage III or higher), and the median survival was between 15 and 20 months. The patients in our study had an earlier stage of disease, and some were long-term survivors. Our data suggest that some populations with early-stage disease with long-term life expectancy do not need surgery.

Late toxicity is an important issue that could impair QOL after CRT. Ishikura *et al.* (6) found that pericarditis and pleural effusion of Grade 3 or higher developed in 10% of patients and 2 patients died of acute myocardial infarction. Our CRT protocol is basically identical to theirs and was characterized by an extended radiation target volume covering a three-field lymph node area. However, life-threatening late toxicities did not develop in any of our patients except for 1 patient with Grade 4 radiation pneumonitis. The difference between the series of Ishikura *et al.* and ours is thought to be the patients'

Table 4. Health-related quality of life in 2-year survivors

	CRT group (n = 30) [mean (range)]	OP group (n = 20) [mean (range)]	p Value
QLQ-C30			
Global health status	82.5 (50.0–100)	72.3 (50.0–100)	0.184
Functioning scales			
Physiologic functioning	94.0 (66.7–100)	88.8 (66.7–100)	0.085
Role functioning	95.0 (50.0–100)	87.1 (33.3–66.7)	0.133
Emotional functioning	93.1 (50.0–100)	89.4 (41.7–100)	0.584
Cognitive functioning	86.1 (66.7–100)	81.1 (33.3–100)	0.819
Social functioning	95.6 (50.0–100)	86.4 (50.0–100)	0.054
Symptom scales			
Fatigue	18.5 (0–55.6)	25.3 (0–77.8)	0.232
Nausea and vomiting	1.7 (0–33.3)	6.1 (0–33.3)	0.138
Pain	1.1 (0–16.7)	5.3 (0–33.3)	0.057
Dyspnea	13.3 (0–66.7)	16.7 (0–33.3)	0.134
Insomnia	4.4 (0–33.3)	12.1 (0–66.7)	0.183
Appetite loss	6.7 (0–33.3)	22.7 (0–100)	0.003*
Constipation	10.0 (0–66.7)	15.2 (0–66.7)	0.111
Diarrhea	10.0 (0–66.7)	28.8 (0–66.7)	0.002*
Financial difficulties	10.0 (0–66.7)	18.2 (0–100)	0.508
QLQ-OES18 (symptom scales)			
Dysphagia	3.0 (0–22.2)	9.1 (0–44.4)	0.351
Deglutition	3.9 (0–33.3)	9.1 (0–33.3)	0.174
Eating problems	8.1 (0–41.7)	22.0 (0–66.7)	0.004*
GI symptoms	6.7 (0–33.3)	15.2 (0–50.0)	0.163
Pain	1.9 (0–33.3)	5.1 (0–33.3)	0.111
Single item	7.2 (0–33.3)	11.0 (0–25.0)	0.488

Abbreviations: CRT = chemoradiotherapy; OP = surgery; QLQ = European Organisation for Research and Treatment of Cancer quality-of-life questionnaire; C30 = core questionnaire; OES18 = esophageal cancer module; GI = gastrointestinal.

Scores range from 0 to 100; a higher score represents a higher ("better") level of functioning or a higher ("worse") level of symptoms (10).

* The difference was statistically significant.

background, because more of our patients were in better physical condition. Our study showed that late toxicities of CRT would not always be considerable at least in patients who are good surgical candidates. However, the follow-up period of this study was not long enough to evaluate late toxicity, and further observation is needed to determine this outcome (18). To compare late toxicity between the CRT and OP groups, the QOL was surveyed among patients who survived for more than 2 years by use of a cross-sectional approach. Previous studies showed that the negative impact of esophagectomy on the QOL was transient for patients who survive for at least 2 years and that the QOL of the 2-year survivors was significantly better than that of other patients (19, 20). The percentage of patients responding among 2-year survivors was 86.0% (37 of 43) and 73.5% (25 of 34) in the CRT and OP groups, respectively. We found that the QOL of the CRT and OP groups was similar and that the QOL of the CRT group regarding symptoms such as diarrhea, appetite loss, and eating problems was significantly superior to that of the OP group (Table 4).

In conclusion, our prospective direct comparison showed that CRT accompanied by salvage therapy, if required, is comparable or superior to surgery alone in terms of treatment outcomes among patients with resectable thoracic esophageal squamous cell carcinoma.

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