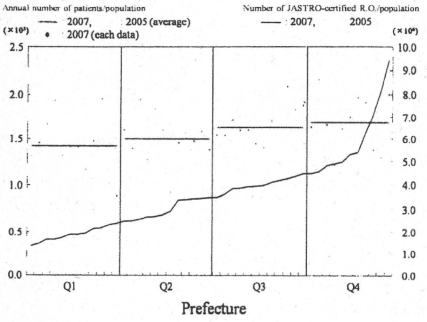

Fig. 3. Geographic distribution for 47 prefectures of annual numbers of patients (new plus repeat) per 1,000 population arranged in order of increasing number of Japanese Society of Therapeutic Radiology and Oncology (JASTRO)–certified radiation oncologists (ROs)/1,000,000 population by prefecture: Q1, 0–25%; Q2, 26–50%; Q3, 51–75%; and Q4, 76–100%. Horizontal lines show average annual number of patients (new plus repeat) per 1,000 prefectural population per quarter.

These findings may reflect the fact that more curative patients are referred to academic institutions and more palliative patients with lung cancer are treated at nonacademic institutions in Japan. However, the increase in the number of lung cancer patients in A1 institutions and that in prostate cancer patients in A1-, A2-, and B1-type institutions in 2007 were noteworthy. This suggests that the use of stereotactic body RT for lung cancer in A1 and of 3D CRT for prostate cancer in A1, A2, and B1 increased in 2007. The number of patients with brain metastasis increased significantly by 38.6% over 2005. This may also reflect dissemination of stereotactic RT for brain metastasis. The use of specific treatments and the number of patients treated with these modalities were significantly affected by institutional stratification, with more specific treatments being performed at academic institutions. These findings indicate that significant differences in patterns of care, as reflected in structure, process, and possibly outcome for cancer patients, continued to be prevalent in Japan in 2007. These differences point to opportunities for improvement. The Japanese PCS group published structural guidelines based on PCS data (20), and we are using the structural data obtained in 2007 to revise the Japanese structural guidelines for radiation oncology. The use of intraoperative RT and thermoradiotherapy decreased significantly, so these two modalities may not be considered as mainstay treatments anymore in Japan.

Geographic patterns showed that there were significant differences among prefectures in the use of RT, and the number of JASTRO-certified physicians per population was associated with the utilization of RT in both 2005 (5) and 2007, so a shortage of ROs or medical physicists on a regional basis will remain a major concern in Japan. However, the overall utilization rate of radiation in 2007 improved further compared with 2005 (5). The Japanese Society of Therapeutic Radiology and Oncology has been making every effort to recruit and educate ROs and medical physicists through public relations, to establish and conduct training courses at academic institutions, to become involved in the national examination for physicians, and to seek an increase in the reimbursement by the government-controlled insurance scheme and other actions.

In conclusion, the Japanese structure of radiation oncology has clearly and steadily improved over the past 17 years in terms of installation and use of equipment and its functions, although a shortage of personnel and differences in maturity by type of institution and by caseload still remain. Structural immaturity is an immediate target for improvement, whereas for improvements in process and outcome, the PCS and National Cancer Database, which are currently operational and the subject of close examination, can be expected to play an important role in the near future in Japan.

REFERENCES

1. Owen JB, Coia LR, Hanks GE. Recent patterns of growth in radiation therapy facilities in the United States: A Patterns of Care Study report. *Int J Radiat Oncol Biol Phys* 1992;24:983–986.
2. Tsunemoto H. Present status of Japanese radiation oncology: National survey of structure in 1990 [In Japanese]. Tokyo: Japanese Society of Therapeutic Radiology and Oncology (Special Report); 1992. p. 1–30.
3. Teshima T, Owen JB, Hanks GE, *et al.* A comparison of the structure of radiation oncology in the United States and Japan. *Int J Radiat Oncol Biol Phys* 1996;34:235–242.
4. Shibuya H, Tsujii H. The structural characteristics of radiation oncology in Japan in 2003. *Int J Radiat Oncol Biol Phys* 2005;62:1472–1476.
5. Teshima T, Numasaki H, Shibuya H, *et al.* Japanese structure survey of radiation oncology in 2005 based on institutional stratification of Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2008;72:144–152.
6. Tanisada K, Teshima T, Ikeda H, *et al.* A preliminary outcome analysis of the Patterns of Care Study in Japan for esophageal cancer patients with special reference to age: Non-surgery group. *Int J Radiat Oncol Biol Phys* 2000;46:1223–1233.
7. Tanisada K, Teshima T, Ohno Y, *et al.* Patterns of Care Study quantitative evaluation of the quality of radiotherapy in Japan. *Cancer* 2002;95:164–171.
8. Uno T, Sumi M, Sawa Y, *et al.* Process of care and preliminary outcome in limited-stage small-cell lung cancer: Results of the 1995-1997 Patterns of Care Study in Japan. *Int J Radiat Oncol Biol Phys* 2003;55:629–632.
9. Gomi K, Oguchi M, Hirokawa Y, *et al.* Process and preliminary outcome of a Patterns-of-Care Study of esophageal cancer in Japan: Patients treated with surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;56:813–822.
10. Sugiyama H, Teshima T, Ohno Y, *et al.* The Patterns of Care Study and regional cancer registry for non-small cell lung cancer in Japan. *Int J Radiat Oncol Biol Phys* 2003;56:1005–1012.
11. Mitsumori M, Hiraoka M, Negoro Y, *et al.* The Patterns of Care Study for breast-conserving therapy in Japan: Analysis of

process survey from 1995 to 1997. *Int J Radiat Oncol Biol Phys* 2005;62:1048–1054.
12. Teshima T. Japanese PCS Working Group. Patterns of Care Study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
13. Toita T, Kodaira T, Shinoda A, *et al.* Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): Patterns of Care Study in Japan. *Int J Radiat Oncol Biol Phys* 2008;70: 788–794.
14. Uno T, Sumi M, Ishihara Y, *et al.* Changes in patterns of care for limited –stage small cell lung cancer: Results of the 99-01 Patterns of Care Study—A nationwide survey in Japan. *Int J Radiat Oncol Biol Phys* 2008;71:414–419.
15. Ogawa K, Nakamura K, Sasaki T, *et al.* External beam radiotherapy for clinically localized hormone-refractory prostate cancer. Clinical significance of Nadir prostate-specific antigen value within 12 months. *Int J Radiat Oncol Biol Phys* 2009;74:759–765.
16. SAS Institute. SAS user's guide: Statistics. Cary, NC: SAS Institute; 1985.
17. Oshima A, Kuroishi T, Tajima K, editors. Cancer statistics—2004. Tokyo: Shinohara Shuppan Shinsha; 2004. p. 207.
18. Ministry of Internal Affairs and Communications, Statistics Bureau, Director-General for Policy Planning (Statistical Standards) & Statistical Research and Training Institute. Current population estimates as of October 1, 2007. Available from: URL: http://www.stat.go.jp/english/data/jinsui/2007np/index.htm. Accessed June 11, 2009.
19. Parker RG, Bogardus CR, Hanks GE, et al. Radiation oncology in integrated cancer management. Report of the Inter-Society Council for Radiation Oncology. Merrifield, VA: American College of Radiology Publications, ISCRO; 1991.
20. Japanese PCS Working Group. Radiation oncology in multidisciplinary cancer therapy—Basic structure requirement for quality assurance of radiotherapy based on Patterns of Care Study in Japan, 2005. Self-publication supported by the Ministry of Health, Welfare and Labor in Japan; 2005.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 452–459, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.029

CLINICAL INVESTIGATION **Esophagus**

USEFULNESS OF INTRALUMINAL BRACHYTHERAPY COMBINED WITH EXTERNAL BEAM RADIATION THERAPY FOR SUBMUCOSAL ESOPHAGEAL CANCER: LONG-TERM FOLLOW-UP RESULTS

HITOSHI ISHIKAWA, M.D., PH.D.,* TETSUO NONAKA, M.D., PH.D.,* HIDEYUKI SAKURAI, M.D., PH.D.,* YOSHIO TAMAKI, M.D., PH.D.,† YOSHIZUMI KITAMOTO, M.D., PH.D.,† TAKESHI EBARA, M.D., PH.D.,* MARIKO SHIOYA, M.D.,* SHIN-EI NODA, M.D., PH.D.,* KATSUYUKI SHIRAI, M.D.,† YOSHIYUKI SUZUKI, M.D., PH.D.,* TAKEO TAKAHASHI, M.D., PH.D.,* AND TAKASHI NAKANO, M.D., PH.D.*

*Department of Radiation Oncology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan; and †Department of Radiation Oncology, Gunma Cancer Center, 617-1 Takabayashi-nishi, Ota, Gunma 373-8550, Japan

Purpose: To assess the efficacy of radiation therapy (RT) by using intraluminal brachytherapy (IBT) combined with external beam RT (EBRT) for submucosal esophageal cancer.

Methods and Materials: Between 1991 and 2005, 59 consecutive patients received definitive RT without chemotherapy. IBT was performed after patients completed EBRT as a booster therapy for 17 patients, using low-dose-rate Cs-137 sources until 1997, and for 19 patients, using high-dose-rate Ir-192 sources thereafter. The long-term outcomes were investigated with a median follow-up time of 61 months.

Results: Logoregional recurrences and distant metastases were observed in 14 patients and in 2 patients in the lung, respectively, and 5 patients were rescued by salvage treatments. The 5-year logoregional control and cause-specific survival rates were 75% and 76%, respectively. The 5-year cause-specific survival rate in the EBRT group was 62%, whereas the corresponding rate in the IBT group was 86% ($p = 0.04$). Multivariate analysis revealed that IBT was the most powerful predictor of survival but did not reach a significant level ($p = 0.07$). There were five esophageal ulcers in the IBT group, but no ulcers developed with small fractions of 3 Gy. Grade 2 or higher cardiorespiratory complications developed in 2 patients (5.6%) in the IBT group and in 3 patients (13.0%) in the EBRT group.

Conclusions: Combining IBT with EBRT is suggested to be one of the preferable treatment modalities for medically inoperable submucosal esophageal cancer because of its preferable local control and survival probabilities, with appreciably less morbidity. © **2010 Elsevier Inc.**

Radiation therapy, Brachytherapy, Esophageal cancer, Survival, Prognostic factor.

INTRODUCTION

The incidence of superficial esophageal cancer (SEC), which is defined as esophageal cancer that has invaded to the lamina propria or submucosa, has increased in Japan, mainly due to advances in endoscopic examination using ultrasound and chromoendoscopy with an iodine solution (1, 2). In addition, very minute tumors have recently been detected by magnifying endoscopy and narrow-band imaging (3, 4). As a result, the prevalence of SEC now comprises approximately 30% of all esophageal cancers in Japan (2, 3), and the population of elderly patients with esophageal cancer is also increasing steadily. The proportion of esophageal cancer patients ≥75 years old was 25.6% ($n = 2,886$) in 1992, but the corresponding number in 2002 was 28.4% ($n = 4,603$) according to statistics of the Cancer Control and Information Services by the National Cancer Center (5), and the number of elderly patients is expected to increase further.

It is well known that the standard therapy for patients with submucosal esophageal cancer (SMEC) is esophagectomy with lymph node (LN) dissection (6–9), because the probability of LN metastasis in SMEC is about 20% to 50% (3, 6, 10, 11). However, the risk of severe complications in elderly patients remains considerably high, regardless of recent advances in postsurgical management (12–14).

Reprint requests to: Hitoshi Ishikawa, M.D., Ph.D., Department of Radiation Oncology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel: (+81) 27-220-8383; Fax: (+81) 27-220-8397; E-mail: hisikawa@med.gunma-u.ac.jp

Conflict of interest: none.

Acknowledgment—We thank Dr. Su K. Metcalfe for assistance with manuscript preparation.

Received Jan 9, 2009, and in revised form Feb 6, 2009. Accepted for publication Feb 7, 2009.

Furthermore, previous reports have proven that RT is a safe and effective treatment modality for SMEC patients (15–20). Therefore, RT may replace surgery as a curative and conservative treatment for medically inoperable or elderly SMEC patients.

Brachytherapy has been considered an effective dose escalation method for the treatment of various cancers including cervical, prostate, and breast cancers, with minimal complications. However, the advantage conferred by intraluminal brachytherapy (IBT) in the management of SEC is still controversial (15–17). A recent retrospective report by the Japanese Society of Therapeutic Radiology and Oncology Study Group did not validate the efficacy of IBT (16). Alternatively, our interim report demonstrated that both local control and survival rates for patients treated with external-beam radiotherapy (EBRT) combined with IBT were superior to those of patients treated with EBRT alone, but the difference did not reach a significance level (21). There were several shortcomings in the report, which would be addressed by (1) longer follow-up, (2) larger population size, and (3) adjustment of the difference in treatment periods between the group treated with EBRT alone and the group treated with EBRT plus IBT. Therefore, we updated patients' outcomes based on 3 additional years of follow-up examinations and analyzed only those patients treated after the implementation of IBT for SEC at our hospitals. In this report, treatment outcomes for SMEC are presented with an emphasis on the efficacy of IBT.

METHODS AND MATERIALS

Patients

The characteristics of patients in this study are summarized in Table 1. Among the 82 patients with SEC, this study evaluated 59 consecutive thoracic SMEC patients whose tumors had invaded to the submucosal layer of the esophagus, as found by endoscopic examination, and who were treated with definitive RT between 1991 and 2005 at either Gunma University Hospital or Gunma Cancer Center. The median age of patients was 72 years old (range, 49–86 years), and 45 patients were male and 14 were female. The tumors were located at the upper thoracic, middle thoracic, and lower thoracic esophagus in 7, 37, and 15 patients, respectively. Pathology examination of biopsy samples obtained with endoscopy proved that all patients had primary squamous cell carcinoma of the esophagus. The rationale for selecting RT for these patients is as follows. (1) Their condition was judged to be medically inoperable (n = 46) due to advanced age (n = 11) and other complications such as cardiovascular diseases and chronic pulmonary, renal, and liver dysfunctions (n = 25), and (2) they refused surgical resection (n = 13). Three patients received endoscopic mucosal resection

Table 1. Characteristics of patients with submucosal esophageal cancer

	Number of patients (%) receiving the treatment shown			
Patient characteristics	EBRT alone	EBRT plus IBT	Total	p value
Gender				
Male	17 (74)	28 (78)	45 (76)	0.97
Female	6 (26)	8 (22)	14 (24)	
Age (years)				
Median age (range)	74 years (61–86 years)	71 years (49–82 years)	72 years (49–86 years)	
≤74 years old	12 (52)	23 (64)	35 (59)	0.37
75≥ years old	11 (48)	13 (36)	24 (41)	
Performance status				
0	7 (30)	14 (39)	21 (36)	0.74
1	13 (57)	19 (53)	32 (54)	
2	3 (13)	3 (8)	6 (10)	
Site				
Upper thoracic	2 (9)	5 (14)	7 (12)	0.4
Middle thoracic	13 (57)	24 (67)	37 (63)	
Lower thoracic	8 (34)	7 (19)	15 (25)	
Tumor length				
Short (≤5 cm)	15 (65)	26 (72)	41 (69)	0.59
Long (≥5.1 cm)	8 (35)	10 (28)	18 (31)	
Total dose (Gy)				
Median dose (range, Gy)	64 (60–72)	69 (59–73)	69 (59–73)	
≤64 Gy	12 (52)	2 (6)	14 (24)	<0.01
65≥ Gy	11 (48)	34 (94)	45 (76)	
Reason				
Medically inoperable	20 (87)	26 (72)	46 (78)	0.18
Patient refused surgery	3 (13)	10 (28)	13 (22)	
Period				
1991–1996	9 (39)	17 (47)	26 (44)	0.73
1997–2004	14 (61)	19 (53)	33 (56)	

(EMR) prior to RT and pathology examination proved that the tumors removed had invaded to the submucosal layer of the esophagus and had positive margins. Furthermore, 14 patients had preexisting malignancies, and 7 patients had coexisting early-stage malignancies in this study; gastric cancer was found in 5 (2 patients in the EBRT group and 3 in the IBT group), laryngeal cancer was found in 1 (EBRT group), and hypopharyngeal cancer was found in 1 (EBRT group). Thus, more than 75% of patients in this study were unsuitable for curative surgery. Before patients started RT, staging evaluation was performed by using chest x-ray, esophagography, endoscopic ultrasound, ultrasound, and computed tomography (CT).

External beam radiation therapy

The RT treatment policy for the present study was previously described in detail (21, 22). In brief, RT was administered to all patients by using a 10-MV photon beam with anteroposterior-opposed fields at a total dose of 40 to 46 Gy, and then additional therapy was delivered using either bilateral oblique portals or more than three beam ports with shrunken fields. The median width of the initial field was 7 cm (range, 6–8 cm), with a 3- to 4-cm margin at both the cranial and the caudal aspects of the tumor. In order to visualize the tumor location on x-ray simulation, two to four surgical clips were placed while the patient underwent endoscopy at the tumor edges prior to the initial treatment planning. The radiation field for the boost therapy was set with a 1.5- to 2-cm margin relative to the location of these clips in the initial field. Treatment plans and doses to organs at risk were also evaluated based on CT planning.

For the group of patients treated with combined EBRT and IBT, EBRT was delivered at a median total dose of 60 Gy (range, 48–64 Gy) with a conventional daily dose of 2 Gy within 7 weeks and was followed by low-dose rate (LDR) using Cs-137 sources or high-dose-rate (HDR) IBT using Ir-192 sources. The median total dose of IBT plus EBRT in the IBT group was 69 Gy, ranging from 59 Gy to 73 Gy. For the patients who refused IBT or could not receive IBT, a boost using a EBRT shrinking technique was delivered, and the total doses were determined depending on the patient's condition, field size, and tumor response. The median total dose to the group treated with EBRT alone was 64 Gy, ranging from 60 Gy to 72 Gy. There were significant differences in the total dose but no differences in other parameters such as age, gender, length of tumor, and time period in which patients received RT between the groups (Table 1). Conversely, the total dose of EBRT to the IBT group was significantly smaller than that given to the group treated with EBRT alone (IBT group, 58.2 ± 3.9 Gy; EBRT group, 64.6 ± 4.4 Gy; $p < 0.01$).

IBT

The technique of IBT was introduced previously (21, 22). IBT was administered to 36 patients, and it was started 3 to 5 days after the completion of EBRT. LDR IBT was given to 17 patients between 1991 and 1996, and HDR IBT took its place since 1997 (n = 19). A 10-mm-diameter rubber gastric tube was used for LDR IBT, and a 15- or 20-mm outer-diameter commercial double-lumen-balloon applicator was used for HDR IBT. The reference point for dose calculation was a point at a distance of 5 mm from the applicator surface. LDR IBT was performed with a fractional dose of 5 Gy, given once per week at a total dose of 10 Gy, whereas HDR IBT was given with a fractional dose of 3 Gy, twice per week at a total dose of 9 Gy. However, 2 initial cases receiving HDR IBT were treated with the same treatment protocol as that used for LDR IBT (5 Gy × 2).

IBT was not performed for 23 patients due to their refusal ($n = 4$), to dementia (n = 3), and to acute esophagitis induced by EBRT ($n = 6$). In addition, 3 patients could not keep the applicator position, and 7 patients did not receive IBT because of renovations being made to the treatment room between September 2000 and April 2002.

Follow-up examination

The last follow-up was performed in June 2008, and the median follow-up time for survivors was 61 months (range, 25–145 months) or until death. The follow-up examination included a physical examination and the measurement of a serum tumor marker of squamous cell carcinoma antigen; measurements were taken at 1-month intervals during the first year after RT and then at 1- to 3-month intervals thereafter. Esophagography and endoscopy were performed for assessment of the tumor response at 1 month after completion of RT. These examinations were repeated every 3 months during the first year and every 6 months thereafter. When a local recurrence was suspected, pathology confirmation with a biopsy sample was performed. CT scans were also obtained for the evaluation of tumor recurrence in the LNs and distant organs at 6-month intervals during the first 3 years after RT, even if tumor recurrence was not suspected. Logoregional recurrence was documented for either tumor recurrence in the esophagus or regional LNs.

Toxicity assessment was performed according to the National Cancer Institute's Common Terminology Criteria of Adverse Effect, version 3, and the Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer late morbidity scoring schema (23).

Statistics

Comparison of data was analyzed by Fisher's exact t test or Yates' continuity-corrected chi-square test. The overall survival (OS), cause-specific survival (CSS), recurrence-free survival (RFS), and logoregional control (LRC) rates were calculated from the date of the start of RT to the patient's death or to the last follow-up examination, according to the Kaplan-Meier method (24). OS data included deaths due to any cause, and CSS included both cancer-related deaths and treatment-related deaths. Furthermore, RFS includes both the rate of all deaths and the rate of recurrences. The survival curves were compared by the log-rank test as a univariate analysis. The parameters were also analyzed by multivariate analysis using Cox's proportional hazard model when p was ≤0.10 with the univariate analysis.

RESULTS

Response and tumor recurrence

Table 2 summarizes the clinical outcomes according to the treatment method. All tumors showed definite reduction in the overall sizes. In this study, 52 (88%) of 59 tumors regressed completely, and the remaining 7 tumors (12%) showed minimal residual disease 1 month after RT. There was no difference in the initial tumor response according to the treatment method.

Tumor recurrences were observed in 16 patients (27%), and the 5-year LRC rate was 75% (95% confidence intervals [CI], 63%–88%) in this study. Of 23 patients treated with

Table 2. Differences of outcomes according to treatment method

Parameter	Number of patients (% of total) receiving the treatment shown: EBRT alone (n = 23)	EBRT plus IBT (n = 36)	All (n = 59)	p value
Initial response				
Complete	20 (87)	32 (89)	52 (88)	0.82
Partial	3 (13)	4 (11)	7 (12)	
All recurrences				
Yes	9 (39)	7 (19)	16 (27)	0.17
No	14 (61)	29 (81)	43 (73)	
Locoregional recurrence				
Yes	8 (35)	6 (17)	14 (24)	0.2
No	15 (65)	30 (83)	45 (76)	
Distant metastasis				
Yes	1 (4)	1 (3)	2 (3)	0.75
No	22 (96)	35 (97)	47 (97)	
Treatment related death				
Yes	1 (4)	2 (6)	3 (5)	0.84
No	22 (96)	34 (94)	56 (95)	
Survival				
Alive	6 (26)	20 (56)	26 (44)	0.03
Dead	17 (74)	16 (44)	33 (56)	
Disease-specific	9	5	14	0.18
Intercurrent-disease	8	11	19	

EBRT alone, 8 (35%) patients had logoregional recurrences, and 1 (2%) patient had lung metastasis as the initial recurrence site. In the 36 patients treated with IBT plus EBRT (IBT group), there were 6 (17%) logoregional recurrences and 1 (3%) lung metastasis. Logoregional recurrences were more frequently observed in the EBRT group than in the IBT group, but the difference did not reach a significant level.

In the 14 logoregional recurrence cases, 8 (73%) recurrances consisted of a superficial tumor at the esophagus. Two patients underwent salvage surgery; 2 patients underwent argon laser ablation; 1 patient received EMR; 1 patient received re-irradiation with concurrent chemotherapy; and 2 patients received no treatment because of advanced age (one patient was 91 years old and the other was 78 years old at the time of recurrence) and poor general condition;. Five of these 8 patients with superficial recurrences were successfully rescued by the salvage treatments. On the other hand, in the patients with advanced local recurrences (n = 3) or lymph node metastases (n = 3), palliative chemotherapy was administered for 2 patients, and re-irradiation was administered to 1 patient. However, these 3 patients had further progression of their recurrent tumors. No additional treatments were given to the remaining 3 patients due to their poor general condition, and they died of tumor progression.

Survival and prognostic factors

Of 59 patients, 14 (24%) had disease-specific deaths at the time of the last follow-up examination; 11 had progression of esophageal cancer; and 3 had treatment-related deaths (2 patients had fistulae, and 1 had heart failure). Nineteen (32%) patients died of intercurrent death, including 4 who died of other cancer-related causes without recurrences of esophageal cancer. Overall, deaths were frequently observed in the EBRT group, but there were no significant differences in disease-specific death rates between the EBRT group and the IBT group (Table 2). Median survival time for all patients was 39 months (6–145 months). The 5-year rates of OS, CSS, and RFS were 52% (95% CI, 38%–65%), 76% (95% CI, 64%–88%), and 46% (95% CI, 34%–59%), respectively (Fig. 1).

Prognostic factors relating to LRC and CSS are summarized in Table 3. The possible predictive parameters for univariate analysis for LRC were tumor length (p = 0.01), RT method (p = 0.10), and total dose (p = 0.07). The prognostic factors for CSS were gender (p = 0.09), tumor length (p = 0.06), and RT method (p = 0.04). Furthermore, multivariate analysis revealed that tumor length was the most important factor for LRC (p = 0.01) and that the RT method had the strongest effect on the CSS rate, but the difference did not reach a significant level (hazard ratio, 2.79 [95% CI, 0.92–8.51]; p = 0.07).

The differences in clinical outcomes between the EBRT group and the IBT group are summarized in Table 4. The 5-year CSS rates of the EBRT group and those of the IBT group were 62% (95% CI, 39%–85%) and 86% (95% CI, 75%–96%), respectively (Fig. 2), and the difference between these groups was statistically significant (p = 0.04). Regarding LRC, the 5-year rate of the IBT group was better than that of the EBRT group, but the difference did not reach the significance level (Fig. 3). Similarly, the differences in OS and RFS between the two groups were not statistically significant (Table 4).

Late morbidity

Late complications according to the treatment method are shown in Table 5. The Grade 2 or higher complications of

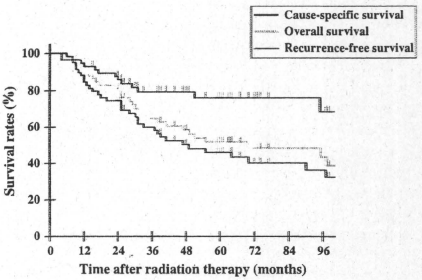

Fig. 1. Curves for OS, CSS, and RFS rates of submucosal esophageal cancer are shown. The 5-year rates of OS, CSS, and RFS were 52% (95% CI, 38%–65%), 76% (95% CI, 64%–88%), and 46% (95% CI, 34%–59%), respectively.

Table 3. Prognostic factors of the loco-regional control and cause-specific survival rates for submucosal esophageal cancer

Patient characteristics	LRC 5-year rate	*p*-value UVA	*p*-value MVA	CSS 5-year rate	*p*-value UVA	*p*-value MVA
Gender						
Male ($n = 45$)	72%	0.26	NA	71%	0.09	0.12
Female ($n = 14$)	85%			92%		
Age (years)						
−74 ($n = 35$)	70%	0.49	NA	73%	0.74	NA
75+ ($n = 24$)	82%			82%		
Performance Status						
0 ($n = 21$)	82%	0.5	NA	89%	0.19	NA
1-2 ($n = 38$)	71%			68%		
Tumor length (cm)						
−5.0 ($n = 41$)	87%	0.01	0.01	86%	0.06	0.14
5.1+ ($n = 18$)	48%			57%		
Total dose (Gy)						
−64 ($n = 14$)	56%	0.07	0.25	60%	0.32	NA
65+ ($n = 45$)	82%			81%		
RT method						
EBRT alone ($n = 23$)	66%	0.1	0.75	62%	0.04	0.07
EBRT + IBT ($n = 36$)	81%			86%		
Reason						
Inoperable ($n = 46$)	73%	0.7	NA	78%	0.45	NA
Operable ($n = 13$)	84%			69%		

Abbreviations: EBRT = external beam radiation therapy; IBT = intraluminal brachytherapy; LRC = loco-regional control; CSS = cause-specific survival; UVA = univariate analysis; MVA = multivariate analysis; NA = no assessment.

pericarditis, heart failure, pleural effusion, pneumonitis, bone, and esophagus were observed in 1 (2%), 1 (2%), 2 (3%), 1 (2%), 1 (2%), and 5 (8%) patients in both treatment groups, respectively.

Three (5%) treatment-related deaths were seen in this study. Severe pneumonia, resulting from esophageal fistula at 8 and 11 months after RT, occurred in 2 patients who received boost treatments with IBT. A patient in the EBRT group, who was 86 years old at the diagnosis of the esophageal cancer, died of heart failure 12 months after the start of RT. Given that the patient had neither cardiac symptoms nor abnormal signs on electrocardiograms before RT, the death was attributed to cancer treatment.

Grade 2 or severe toxicity affecting the cardiorespiratory system was observed in 3 (13%) of 23 patients in the EBRT group and in 2 (6%) of 36 patients in the IBT group. Esophageal ulcer was observed in 5 (14%) patients of the IBT group (4 after receiving LDR IBT and 1 after receving HDR IBT). The patient with an esophageal ulcer after HDR IBT was treated with a large fractional dose of 5 Gy (22), but no further incidence of esophageal ulcer developed for patients treated with a modified fractional HDR IBT dose of 3 Gy.

DISCUSSION

The 5-year CSS rate for all patients in this study was 76%, and the rate for the IBT group was statistically higher than that of the EBRT group (86% vs. 62%, $p = 0.04$). These are the first long-term results that indicate a survival benefit of IBT combined with EBRT in the treatment of SMEC patients, although the therapy still has some limitations which may be addressed by a prospective multi-institutional study. The treatment-related complications were also acceptable in comparison with those of previous studies (15–20).

The role of RT for patients diagnosed with SMEC has increased in Japan (16), given not only the rising incidence of SMEC but also the large number of elderly and inoperable patients with this disease. EMR is recognized as a suitable treatment for MEC because of its high curability without severe morbidity (3, 6, 25, 26). On the other hand, the utility of EMR for treating SMEC patients remains contested, because these patients have a higher potential for regional LN metastasis than MEC patients (3, 6, 10, 11, 27). Therefore, it is thought that more aggressive treatments such as surgery with LN dissection and chemoradiotherapy (CRT) are necessary for most patients with SMEC. However, many elderly patients who present with SMEC are not only inoperable but are also intoleraant of systemic chemotherapy because of their multiple comorbidities, unfortunately (20, 21). Taking these conditions into consideration, it is necessary for elderly SMEC patients to explore alternative curative treatment modality with minimal toxicity.

The advantages of chemotherapy given concurrently with RT have been tested for locally advanced esophageal cancer (28–31). However, the role of chemotherapy is controversial in cases of SMEC patients, as some previous reports showed RT alone provided a high control rate in these patients (15–20). Our study also demonstrates that the 5-year CSS and LRC rates were high at 76% and 75%, respectively. Furthermore, while chemotherapy enhances the efficacy of RT for tumors, it may cause toxicity in surrounding healthy tissues. Long-term results of the Radiation Therapy Oncology Group 85-01 study showed that 10% of patients who received CRT had life-threatening toxic effects, but only 2% of patients had those effects in the group treated with RT alone (28). Another study also assessed long-term toxicity after definitive CRT was given to 139 patients with thoracic esophageal cancer (32). In that study, Grade 2 or higher pericarditis, heart failure, pleural effusion, and pneumonitis occurred in 16 (12%), 2, (1%), 15 (11%), and 4 (3%) patients, respectively, and the corresponding incidence rates in our study were less than that as shown in Table 4. With special regard to Grade 3 or higher cardiorespiratory complications, our study showed only 1 (2%) case, which is remarkably smaller than the 15 (11%) cases in that study, although the median age of patients in our study was 10 years older (72 years old vs. 62 years old) and the median follow-up time in our study was longer than that study's (61 months vs. 53 months). The high rate of severe complications in that study may be affected by CRT as well as by a large RT field (32). Therefore, RT alone is suggested to be one of the important curative treatment choices, especially for elderly patients and those with inoperable SMEC.

Brachytherapy is a useful dose escalation method because of its physical characteristics of dose concentration, which

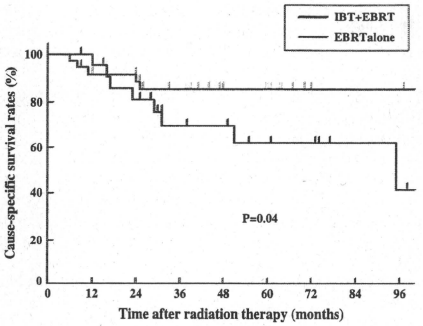

Fig. 2. The CSS curves for patients with submucosal esophageal cancer according to treatment methods are shown. The 5-year CSS rate for the IBT group was significantly superior to that of the group treated with EBRT alone (86% vs. 62%, $p = 0.04$).

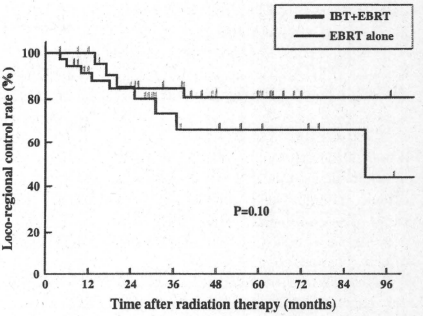

Fig. 3. Curves LRC for patients with submucosal esophageal cancer according to treatment methods are shown. The 5-year LRC rate of the IBT group was better than that of the group treated with EBRT alone, but the difference did not reach a significance level (81% vs. 66%, $p = 0.10$).

provides a higher dose to the target without increasing the damage to healthy tissue. Although high-dose irradiation is one strategy for improving outcomes of various cancer treatments that utilize RT, a previous randomized trial revealed that dose escalation of EBRT combined with chemotherapy produced no benefits for treating esophageal cancer (33). However, the advantage of dose escalation with RT alone for SMEC is still controversial, because that trial included many advanced diseases and used concurrent chemotherapy (33). As all but 1 patient received a total dose of ≥60 Gy in our study, the effect of high-dose irradiation on local control may be masked. Nevertheless, the present study demonstrated that the 5-year local control rate in the high-dose group (≥65 Gy) was better than that in the low-dose group (82% vs. 56%), although it did not reach a significant level ($p = 0.07$), mainly due to small sample size. In addition, tumor length was a significant factor of local control (short tumor, 87%; long tumor, 48%; $p < 0.01$). Eighteen patients had tumors more than 5 cm in length. Among them, 5 received a total dose <65 Gy, and 3 (60%) of these patients had locoregional recurrence, whereas recurrences were observed in only 5 (38%) of 13 patients who received a total dose of ≥65 Gy. Considering these results, the better CSS rate seen with IBT in this study was possibly produced by a higher LRC rate in the IBT group (IBT group, 81%; EBRT group, 66%) given high-dose irradiation. In fact, the total dose of RT given to the IBT group was significantly higher than that in the group treated with EBRT alone (IBT group, 68.1 ± 2.8 Gy; EBRT group, 64.6 ± 4.4 Gy; $p < 0.01$). Therefore, dose escalation using safe techniques such as IBT may be effective for definitive RT, even for esophageal cancer as well as other cancers.

Another advantage of IBT is the reduction in the occurrence of cardiopulmonary toxicity, because previous reports revealed the dose-volume effects on pericardial effusion and pneumonitis in thoracic RT (34,35). In this study, the occurrence of Grade 2 or severe morbidity in the IBT group was observed in only 2 (6%) patients, which was smaller than that for the 3 (13%) patients in the EBRT group, although the total dose in the IBT group was significantly higher

Table 4. Clinical outcomes of submucosal esophageal cancer according to RT method

Survival variable	% of patients with 5-year rate (95% CI) EBRT group	IBT group	*p* value (log-rank test)
Overall survival	32 (13–52)	67 (50–83)	0.07
Cause-specific survival	62 (39–85)	86 (75–96)	0.04
Recurrence-free survival	28 (10–47)	59 (42–75)	0.1
Locoregional control	66 (48–84)	81 (67–95)	0.1

Table 5. Incidence of Grade 2 or higher late morbidities according to treatment method

Characteristic	No. of patients (% of total) EBRT alone ($n = 23$)	EBRT plus IBT ($n = 36$)	Total ($n = 59$)
Grade ≥2			
Pericarditis	0 (0)	1 (3)	1 (2)
Heart failure	1 (4)	0 (0)	1 (2)
Pleural effusion	1 (4)	1 (3)	2 (3)
Pneumonitis	1 (4)	0 (0)	1 (2)
Bone	1 (4)	0 (0)	1 (2)
Esophagus	0 (0)	5 (14)	5 (8)
Grade ≥3			
Pericarditis	0 (0)	0 (0)	0 (0)
Heart failure	1 (4)	0 (0)	1 (2)
Pleural effusion	0 (0)	0 (0)	0 (0)
Pneumonitis	0 (0)	0 (0)	0 (0)
Bone	1 (4)	0 (0)	1 (2)
Esophagus	0 (0)	2 (6)	2 (3)

than that in the EBRT group. In addition, radiation-induced pneumonitis was observed only in the EBRT group. One explanation for this observation is that radiation doses to the lung in the IBT group may be much lower than that in the EBRT group, because there were significant differences in the EBRT doses between these groups (IBT group, 58.2 ± 3.9 Gy; EBRT group, 64.6 ± 4.4 Gy; $p < 0.01$). The actual dose and volume effects of EBRT, however, were undetermined because the assessments of respiratory and cardiac function were not completely performed in this study. Therefore, prospective studies may be needed to determine the impact of IBT on the incidence and severity of complications.

Although it is generally thought that HDR brachytherapy may have a higher risk of side effects than LDR brachytherapy, esophageal ulcers were observed in 4 (24%) of 17 patients treated with LDR IBT and in 1 (5%) of 19 patients treated with HDR IBT. This result may have been caused by the use of a 10-mm-outer-diameter rubber gastric tube during LDR IBT, at which time no appropriately designed applicator was available. Regarding dose fractionation in IBT, a consensus guideline published by the Japanese Society of Therapeutic Radiology and Oncology Study Group in 2000 recommended a fractional HDR IBT dose of ≤4 Gy (36). When our institution started giving HDR IBT, we used a large-dose fractionation schedule (5 Gy × 2) for the initial 2 patients, and one of them died of esophageal fistula due to an overdose to the esophageal mucosa. After our IBT protocol was modified (3 Gy × 3), no esophageal ulcer has developed for more than 8 years. Therefore, HDR IBT using our refined treatment method is considered safe and effective for treating SMEC patients.

Recurrences were initially observed as a superficial cancer at the esophagus in 8 (50%) of 16 recurrences in this study, and 5 patients were rescued by salvage therapies such as surgery, EMR, and argon laser ablation. On the other hand, no patient was cured if the recurrent tumors were detected at advanced local recurrence stages, lymph node metastases, and distant metastases. One probable reason for why the IBT group had a better survival rate than the group treated with EBRT alone is that 4 (57%) of 7 recurrences were detected as superficial esophageal cancer and were successfully rescued by salvage therapy in the IBT group. Conversely, one (11%) of nine recurrences was cured in the EBRT group. Therefore, as more than 70% of failures occurred within 3 years after the initial treatment in this study, periodic examination using endoscopy is recommended during this period, even if tumors have a complete response after treatment.

CONCLUSIONS

Definitive RT is a curative and tolerable treatment method for medically inoperable SMEC patients. The addition of IBT to deliver higher RT doses after initial treatment with EBRT confers preferable outcomes with respect to local tumor control, patient survival, and morbidity when we used appropriate IBT methods with a small-fraction dose and a large-diameter applicator. In addition, the early detection of recurrences by repeated endoscopy after RT is crucial for improving treatment outcomes, as superficial recurrent tumors may be cured with salvage therapy. Finally, these results indicate the need for a prospective study to validate the efficacy of IBT combined with EBRT for the curative treatment of SMEC.

REFERENCES

1. Mori M, Adachi Y, Matsushima T, *et al.* Lugol staining pattern and histology of esophageal lesions. *Am J Gastroenterol* 1993; 88:701–705.
2. Comprehensive Registry of Esophageal Cancer in Japan (1998, 1999) & Long Term Results of Esophagectomy in Japan (1988-1997). 3rd edition. The Japanese Society for Esophageal Disease; 2002.
3. Takubo K, Aida J, Sawabe M, *et al.* Early squamous cell carcinoma of the oesophagus: The Japanese viewpoint. *Histopathology* 2007;51:733–742.
4. Inoue H, Honda T, Nagai K, *et al.* Ultrahigh magnification endoscopic observation of carcinoma in situ of the edophagus. *Dig Endosc* 1997;9:16–18.
5. Matsuda T, Marugame T, Kamo K, *et al.* Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. *Jpn J Clin Oncol* 2008;38: 641–648.
6. Tajima Y, Naknishi Y, Ochiai, *et al.* Histopathologic findings predicting lymph node metastasis and prognosis of patients with superficial esophageal carcinoma: Analysis of 240 surgically resected tumors. *Cancer* 2000;88:1285–1293.
7. Holscher AH, Bollschweiler E, Schneider PM, *et al.* Prognosis of early esophageal cancer. *Cancer* 1995;76:178–186.
8. Igaki H, Kato H, Tachimori Y, *et al.* Clinicopathological characteristics and survival of patients with clinical Stage I squamous cell carcinomas of the thoracic esophagus treated with three-field lymph node dissection. *Eur J Cardiothorac Surg* 2001;20:1089–1094.
9. Sugimachi K, Watanabe M, Sadanaga N, *et al.* Recent advances in the diagnosis and surgical treatment of patients with carcinoma of the esophagus. *J Am Coll Surg* 1994;178:363–368.
10. Shimada H, Nabeya Y, Matsubara H, *et al.* Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. *Am J Surg* 2006; 191:250–254.
11. Kim DU, Lee JH, Min BH, *et al.* Risk factors of lymph node metastasis in T1 esophageal squamous cell carcinoma. *J Gastroenterol Hepatol* 2008;23:619–625.
12. Moskovitz AH, Rizk NP, Venkatraman E, *et al.* Mortality increases for octogenarians undergoing esophagogastrectomy for esophageal cancer. *Ann Thorac Surg* 2006;82:2031–2036.
13. Kinugasa S, Tachibana M, Yoshimura H, *et al.* Esophageal resection in elderly esophageal carcinoma patients: improvement in postoperative complications. *Ann Thorac Surg* 2001;71:414–418.
14. Ferguson MK, Martin TR, Reeder LB, *et al.* Mortality after esophagectomy: risk factor analysis. *World J Surg* 1997;21: 599–603.
15. Okawa T, Dokiya T, Nishio M, *et al.* Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. *Int J Radiat Oncol Biol Phys* 1999;45:623–628.

16. Nemoto K, Yamada S, Nishio M, *et al.* Results of radiation therapy for superficial esophageal cancer using the standard radiotherapy method recommended by the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. *Anticancer Res* 2006;26:1507–1512.
17. Nishimura Y, Okuno Y, Ono K, Mitsumori M, Nagata Y, Hiraoka M. External beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for patients with superficial esophageal carcinoma. *Cancer* 1999;86:220–228.
18. Sai H, Mitsumori M, Araki N, *et al.* Long-term results of definitive radiotherapy for stage I esophageal cancer. *Int J Radiat Oncol Biol Phys* 2005;62:1339–1344.
19. Sasaki T, Nakamura K, Shioyama Y, *et al.* Treatment outcomes of radiotherapy for patients with stage I esophageal cancer: a single institute experience. *Am J Clin Oncol* 2007 Oct;30(5): 514–519.
20. Nemoto K, Matsumoto Y, Yamakawa M, *et al.* Treatment of superficial esophageal cancer by external radiation therapy alone: results of a multi-institutional experience. *Int J Radiat Oncol Biol Phys* 2000;46:921–925.
21. Ishikawa H, Sakurai H, Tamaki Y, *et al.* Radiation therapy alone for stage I (UICC T1N0M0) squamous cell carcinoma of the esophagus: Indications for surgery or combined chemoradiotherapy. *J Gastroenterol Hepatol* 2006;21:1290–1296.
22. Ishikawa H, Sakurai H, Yamakawa M, *et al.* Clinical outcomes and prognostic factors for patients with early esophageal squamous cell carcinoma treated with definitive radiation therapy alone. *J Clin Gastroenterol* 2005;39:495–500.
23. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–1346.
24. Kaplan E, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53:457–481.
25. Kodama M, Kakegawa T. Treatment of superficial cancer of the esophagus: A summary of response to a questionnaire on superficial cancer of the esophagus in Japan. *Surgery* 1998;123: 432–439.
26. Fujita H, Sueyoshi S, Yamana H, *et al.* Optimum treatment strategy for superficial esophageal cancer: Endoscopic mucosal resection vs. radical esophagectomy. *World J Surg* 2001;25: 424–431.
27. Eguchi T, Nakanishi Y, Shimada T, *et al.* Histopathological criteria for additional treatment after endoscopic mucosal resection for esophageal cancer: analysis of 464 surgically resected cases. *Modern Pathol* 2006;19:475–480.
28. Cooper JS, Guo MD, Herskovic A, *et al.* Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01)-Radiation Therapy Oncology Group. *JAMA* 1999;281:1623–1627.
29. Smith TJ, Ryan LM, Douglass HO Jr., *et al.* Combined chmoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: A study of the Eastern Cooperative Oncology Group. *Int J Radiat Oncol Biol Phys* 1998;42: 269–276.
30. Stockeld D, Tennvall J, Wagenius G, *et al.* A Swedish study of chemoradiation in squamous cell carcinoma of the esophagus. *Acta Oncol* 2001;40:566–573.
31. Hironaka S, Ohtsu A, Boku N, *et al.* Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2-3)/N(any)/M(0) squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003;57: 425–433.
32. Ishikura S, Nihei K, Ohtsu A, *et al.* Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–2702.
33. Minsky BD, Pajak TF, Ginsberg RJ, *et al.* INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002; 20:1167–1174.
34. Wei X, Liu HH, Tucker SL, *et al.* Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2008;70:707–714.
35. Liao Z, Cox JD, Komaki R. Radiochemotherapy of esophageal cancer. *J Thorac Oncol* 2007;2:553–568.
36. Yamada S, Nemoto K, Takai Y, *et al.* Standard radiotherapy methods for superficial esophageal cancer. *J Jpn Soc Ther Radiol Oncol* 2000;12:169–176.

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–6, 2010

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.03.046

CLINICAL INVESTIGATION

DOSE–VOLUME HISTOGRAM PARAMETERS AND CLINICAL FACTORS ASSOCIATED WITH PLEURAL EFFUSION AFTER CHEMORADIOTHERAPY IN ESOPHAGEAL CANCER PATIENTS

KATSUYUKI SHIRAI, M.D., PH.D.,*† YOSHIO TAMAKI, M.D., PH.D.,* YOSHIZUMI KITAMOTO, M.D., PH.D.,* KAZUTOSHI MURATA, M.D.,† YUMI SATOH, M.D.,† KEIKO HIGUCHI, M.D., PH.D.,* TETSUO NONAKA, M.D., PH.D.,† HITOSHI ISHIKAWA, M.D., PH.D.,† HIROYUKI KATOH, M.D.,† TAKEO TAKAHASHI, M.D., PH.D.,† AND TAKASHI NAKANO, M.D., PH.D.†

*Department of Radiation Oncology, Gunma Prefectural Cancer Center, Ota; and †Department of Radiation Oncology, Gunma University Graduate School of Medicine, Maebashi, Japan

Purpose: To investigate the dose–volume histogram parameters and clinical factors as predictors of pleural effusion in esophageal cancer patients treated with concurrent chemoradiotherapy (CRT).
Methods and Materials: Forty-three esophageal cancer patients treated with definitive CRT from January 2001 to March 2007 were reviewed retrospectively on the basis of the following criteria: pathologically confirmed esophageal cancer, available computed tomography scan for treatment planning, 6-month follow-up after CRT, and radiation dose ≥50 Gy. Exclusion criteria were lung metastasis, malignant pleural effusion, and surgery. Mean heart dose, mean total lung dose, and percentages of heart or total lung volume receiving ≥10–60 Gy (Heart-V_{10} to V_{60} and Lung-V_{10} to V_{60}, respectively) were analyzed in relation to pleural effusion.
Results: The median follow-up time was 26.9 months (range, 6.7–70.2) after CRT. Of the 43 patients, 15 (35%) developed pleural effusion. By univariate analysis, mean heart dose, Heart-V_{10} to V_{60}, and Lung-V_{50} to V_{60} were significantly associated with pleural effusion. Poor performance status, primary tumor of the distal esophagus, and age ≥65 years were significantly related with pleural effusion. Multivariate analysis identified Heart-V_{50} as the strongest predictive factor for pleural effusion ($p = 0.01$). Patients with Heart-V_{50} <20%, 20%≤ Heart-V_{50} <40%, and Heart-V_{50} ≥40% had 6%, 44%, and 64% of pleural effusion, respectively ($p < 0.01$).
Conclusion: Heart-V_{50} is a useful parameter for assessing the risk of pleural effusion and should be reduced to avoid pleural effusion. © 2010 Elsevier Inc.

Pleural effusion, Esophageal cancer, Chemoradiotherapy, Dose–volume histogram, Heart.

INTRODUCTION

The prognosis in patients with esophageal cancer has been poor. Surgical resection is a potentially curative treatment for esophageal cancer. However, the mortality is high, and patients are often inoperable because of advanced tumor presentation at diagnosis, cardiopulmonary complications, or poor performance status (1). Radiotherapy (RT) alone was performed for inoperable esophageal cancer, but the 5-year survival rate was less than 10% (2). During the past decade, definitive chemoradiotherapy (CRT) has been considered a curative treatment option and has improved the prognosis for esophageal cancer, with 5-year survival of 26–46% (3–6).

Chemoradiotherapy has been considered a tolerable treatment as compared to surgical resection, even for patients who had poor performance status or cardiopulmonary complications. As the number of long-term survivors treated with CRT is increasing, treatment-related toxicities have recently been reported, such as radiation pneumonitis, heart failure, pericardial effusion, myocardial infarction, and pleural effusion (7). These late toxicities significantly impair patients' quality of life. Radiation pneumonitis and pericardial effusion have been analyzed to identify risk factors using dose–volume histogram (DVH) parameters in esophageal cancer (8, 9). Pleural effusion often occurs in esophageal cancer after CRT. Most pleural effusion is asymptomatic, whereas a few patients develop symptomatic pleural effusion that requires medical treatment, such as diuretics, thoracentesis, and pleurodesis. However, little has been known about the

Reprint requests to: Katsuyuki Shirai, M.D., Ph.D., Department of Radiation Oncology, Gunma Prefectural Cancer Center, 617-1 Takabayashinishi-machi, Ota, Gunma 373-8550, Japan. Tel: (+81) 276-38-0771; Fax: (+81) 276-38-0614; E-mail: katu.shirai@gmail.com

Presented at the 50th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO), Boston, MA, Sept 21–25, 2008.

Conflict of interest: none.

Received Jan 11, 2010, and in revised form March 18, 2010. Accepted for publication March 23, 2010.

effect of CRT on pleural effusion in esophageal cancer. Furthermore, to our knowledge there have been no reports to investigate the relationship between DVH parameters and pleural effusion.

Therefore, in this study, we evaluated pleural effusion in esophageal cancer patients treated with concurrent CRT. The DVH parameters and clinical factors were analyzed in relation to pleural effusion.

METHODS AND MATERIALS

Patient population

The institutional review board of our hospital approved this analysis. Esophageal cancer patients treated with definitive CRT between January 2001 and March 2007 at Gunma Prefectural Cancer Center were reviewed retrospectively on the basis of the following criteria: pathologically confirmed esophageal cancer, available computed tomography (CT) scan for treatment planning, 6-month follow-up after CRT, and radiation dose ≥50 Gy. Exclusion criteria were lung metastasis, malignant pleural effusion, treatment involving surgery, previous chest RT, and previous chemotherapy.

Pretreatment evaluation

Before treatment planning, each patient underwent physical examination, complete blood cell count, serum chemistry profile, chest X-ray, enhanced CT, barium esophagography, esophageal endoscopy with biopsy, and ^{18}F-fluorodeoxyglucose positron emission tomography. In most patients, tumor depth was assessed using endoscopic ultrasonography. Clinical staging was defined by the criteria of the International Union Against Cancer.

Treatment planning

All patients were treated with CRT, and induction chemotherapy was not performed in any patient. Simulation CT was performed with 5-mm slices with normal quiet breathing. The heart surface was delineated manually on each axial CT slice, which was defined from the inferior border of the right pulmonary artery through to the apex of the heart (**9**). Total lung excluding the bronchus was delineated. To detect the tumor location in treatment planning, two surgical clips were placed at the upper and lower tumor edges when the patients were undergoing endoscopy before treatment (**10**). Primary tumor length was defined as the distance between upper and lower clips. A commercial treatment planning system (XiO; CMS) was used to design radiation field. Patients were irradiated in 1.8- to 2.0Gy/fraction using 10-MV photons from a linear accelerator. The RT was initially performed using anterior-posterior opposing fields up to 40 Gy. The initial radiation field involved the 5-cm margin with primary tumor in the craniocaudal direction and lymph node region with metastasis. Prophylactic RT to the entire regional lymph node was not performed. A boost dose of 20 Gy was then given, using oblique opposing fields or multiple fields to avoid the spinal cord. The radiation field for boost therapy involved a 3-cm margin with primary tumor in the craniocaudal direction and a 1.5-cm margin with metastatic lymph nodes. Most patients were treated with 60 Gy in 30 fractions over 8 weeks, including a 2-week break (**7**). Patients received chemotherapy consisting of nedaplatin (cis-diammine-glycoplatinum) and 5-fluorouracil. Nedaplatin, a derivate of cisplatin, shows antitumor activity similar to that of cisplatin and has less renal and gastrointestinal toxicity (**11**); it is used to treat cancer in Japan (**12**). This regimen of concurrent CRT was two cycles of nedaplatin (45 mg/m^2) on Days 1 and 8, and continuous infusion of 5-fluorouracil (400 mg/m^2) on Days 1–5 and 8–12, repeated every 5 weeks with a 2-week break.

Evaluation of pleural effusion

Pleural effusion was assessed by CT 1 month after CRT, every 3 months for the first year, and every 6 months thereafter. The diagnosis of pleural effusion was independently assessed by a radiologist. Toxicity assessments were performed using Common Terminology Criteria for Adverse Events version 3.0. The following clinical factors were investigated in relation to pleural effusion: gender, age, Eastern Cooperative Oncology Group performance status, location of primary tumor, clinical stage, histology, cardiopulmonary complications, and radiation dose. The DVH parameters analyzed were mean heart dose, mean total lung dose, and volumes of heart and total lung receiving ≥10–60 Gy (Heart-V_{10} to V_{60} and Lung-V_{10} to V_{60}, respectively).

Statistical analysis

Time to pleural effusion was calculated from the last day of RT to the date at which pleural effusion was observed. Patients without pleural effusion were censored at the last follow-up or death. The Kaplan-Meier method was used for the probability of pleural effusion, and differences were statistically analyzed using the log-rank test. Multivariate analysis was applied using the Cox proportional hazard model with 95.0% confidence interval. All analyses were two-sided and differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed with SPSS software package, version 11.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Forty-three patients (39 males and 4 females) were enrolled with median follow-up of 27 months after CRT (range, 6–70 months). The median age was 64 years (range, 40–80 years). The Eastern Cooperative Oncology Group performance status of 0, 1, and 2 were 6, 32, and 5 patients, respectively. Squamous cell carcinoma was observed in 40 patients, adenocarcinoma in 2, and basaloid carcinoma in 1. The numbers of patients with Stage I, II, III, IVa, and IVb disease were 9, 7, 16, 3, and 8, respectively. Stage IVb patients has disease involving the supraclavicular or celiac lymph nodes, and there were no patients with distant metastasis. Primary tumor was observed at the proximal esophagus (cervical, upper thoracic, and midthoracic esophagus) in 27 patients, and at the distal esophagus (lower thoracic and abdominal esophagus) in 16. The median tumor length was 6.5 cm (range, 2.0–15.0 cm). Seventeen patients (40%) developed cardiopulmonary complications, such as 11 cases of hypertension, 5 of arrhythmia, 2 of angina pectoris, 2 of hypertrophic cardiomyopathy, 2 of emphysema, and 1 of mitral regurgitation. The mean and median doses were 60 Gy (range, 52–70 Gy). All patients were treated with concurrent CRT consisting of nedaplatin and 5-fluorouracil.

Of the 43 patients, 15 (35%) developed pleural effusion, and actuarial incidence at 3 years was 35% (**Fig. 1**). The median time to the occurrence of pleural effusion was 4 months (range, 1–6 months). Of the 15 patients with pleural effusion, 11 were asymptomatic and were classified as having Grade 1 pleural effusion. Most Grade 1 cases showed

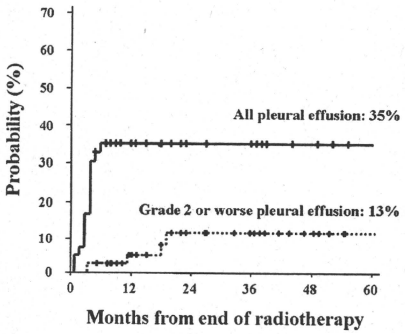

Fig. 1. Cumulative incidence of all pleural effusion and Grade 2 or worse pleural effusion.

either no change or a slight increase in pleural effusion without symptom until last follow-up. Two patients showed a decrease in pleural effusion, and in 1 patient the pleural effusion had completely vanished 20 months after CRT. Grade 2 or worse pleural effusion was 9% (4 of 43 patients) and actuarial incidence at 3 years was 13% (Fig. 1). Symptomatic patients were treated with diuretics, whereas asymptomatic patients were not treated prophylactically. In 3 patients with Grade 2 pleural effusion, thoracentesis was performed at 11, 18, and 19 months after CRT. Grade 3 pleural effusion was observed in 1 patient, and pleurodesis was performed at 3 months after CRT. In these patients, pleural effusions were transudative without malignant cells. No patients developed Grade 4 or worse pleural effusion.

The correlation between clinical factors and the crude rate of pleural effusion is shown in **Table 1**. Patients aged ≥65 years had a significantly higher rate of pleural effusion than those aged <65 years (52% vs. 15%, $p = 0.02$). Patients with performance status 2 had a significantly higher rate of pleural effusion than did those with performance status 0 to 1 (80% vs. 29%, $p = 0.02$). Primary tumor of the distal esophagus was a significant higher risk factor for pleural effusion than was primary tumor of the proximal esophagus (57% vs. 22%, $p = 0.04$). Higher clinical stage tended to increase the risk of pleural effusion ($p = 0.09$). Gender, histology, cardiopulmonary complications, and radiation dose were not associated with pleural effusion ($p = 0.67$, $p = 0.24$, $p = 0.18$, and $p = 0.24$, respectively).

The mean DVH parameters of the heart and total lung compared between the groups with and without plural effusion are shown in Table 2. Patients with pleural effusion had significantly higher Heart-V_{10} to V_{60} and Lung-V_{50} to V_{60} than did those without pleural effusion by univariate analysis. Mean heart dose was a significant difference between the groups with and without pleural effusion (40.6 Gy vs. 28.9 Gy, $p = 0.007$), whereas mean total lung dose was not (8.3 Gy vs. 7.3 Gy, $p = 0.312$). Among the DVH parameters,

Table 1. Univariate analysis of clinical factors influencing the risk of pleural effusion

Characteristic	*n*	Plural effusion (%)	*p* value
Total number of patients	43	35	
Gender			
Male	39	36	0.67
Female	4	25	
Age (y)			
≥65	23	52	0.01
<65	20	15	
ECOG performance status			
0/1	38	29	0.03
2	5	80	
UICC clinical stage			
I + II	16	19	0.09
III + IV	27	44	
Histology			
SCC	40	33	0.24
Others	3	67	
Location of primary tumor			
Proximal esophagus	27	22	0.03
Distal esophagus	16	56	
Cardiopulmonary complications			
Yes	17	47	0.18
No	26	27	
Radiation dose (Gy)			
≤60	27	26	0.24
>60	16	50	

Abbreviations: SCC = Squamous cell carcinoma; ECOG = Eastern Cooperative Oncology Group; UICC = International Union Against Cancer.

Heart-V_{50} was the one most significantly associated with pleural effusion ($p = 0.003$).

Furthermore, significant clinical characteristics and DVH parameters identified by univariate analysis were assessed using multivariate analysis. Among the variables, Heart-V_{50} was the strongest independent factor for pleural effusion ($p = 0.01$). Age was also a significant independent factor ($p = 0.04$). Other factors, such as location of primary tumor ($p = 0.56$), performance status ($p = 0.93$), Lung-V_{60} ($p = 0.73$), and mean heart dose ($p = 0.29$), were not significantly independent factors.

Patients were classified into three groups based on Heart-V_{50}, such as Heart-V_{50} <20%, 20% ≤Heart-V_{50} <40%, and Heart-V_{50} ≥40%. The actuarial incidences of pleural effusion at 3 years for the groups were 6%, 44%, and 64%, respectively (**Fig. 2**), which was statistically significant ($p < 0.01$).

Inasmuch as Heart-V_{50} was found to be the most significant predictive factor for pleural effusion, we investigated further to detect the clinical factors associated with Heart-V_{50}. Primary tumors of the distal esophagus were 35.1% of Heart-V_{50} and of the proximal esophagus were 20.3%, suggesting that distal esophageal tumors were significantly associated with higher Heart-V_{50} ($p < 0.01$). There was not a significant difference of Heart-V_{50} between Grade 1 and Grade 2 or worse cases of pleural effusion (39.3% vs. 29.0%, $p = 0.20$). Other factors were not associated with Heart-V_{50}.

Table 2. Univariate analysis for mean DVH parameters associated with pleural effusion

DVH parameters	With pleural effusion	Without pleural effusion	*p* value
Mean heart dose	40.6 ± 4.3 Gy	28.9 ± 5.3 Gy	0.007
Heart-V_{10}	77.4 ± 7.7 %	63.2 ± 11.3 %	0.044
Heart-V_{20}	70.3 ± 7.9 %	55.9 ± 10.5 %	0.035
Heart-V_{30}	64.5 ± 7.8 %	49.4 ± 9.9 %	0.021
Heart-V_{40}	56.2 ± 7.8 %	37.1 ± 9.6 %	0.004
Heart-V_{50}	36.5 ± 7.0 %	20.0 ± 6.7 %	0.003
Heart-V_{60}	16.1 ± 6.8 %	5.2 ± 3.1 %	0.009
Mean total lung dose	8.3 ± 1.6 Gy	7.3 ± 1.1 Gy	0.312
Lung-V_{10}	22.0 ± 5.2 %	21.8 ± 3.4 %	0.950
Lung-V_{20}	15.1 ± 3.3 %	13.7 ± 1.9 %	0.443
Lung-V_{30}	9.7 ± 1.8 %	9.2 ± 1.5 %	0.671
Lung-V_{40}	7.1 ± 2.1 %	5.7 ± 1.2 %	0.251
Lung-V_{50}	3.8 ± 1.1 %	2.4 ± 0.6 %	0.034
Lung-V_{60}	1.1 ± 0.4 %	0.5 ± 0.3%	0.014

Abbreviation: DVH = dose–volume histogram.

DISCUSSION

We showed the incidence of pleural effusion and the risk factors in esophageal cancer patients treated with concurrent CRT. Although this was a retrospective study, patients were treated with a homogeneous CRT regimen involving nedaplatin and 5-fluorouracil, with a median follow-up of 27 months. Table 3 shows the rate of pleural effusion by several studies of esophageal cancer patients treated with definitive CRT (7, 13, 14). In these studies, Grade 2 or worse pleural effusion was 9–19%, and Grade 3 or worse was 1–10%, respectively. The present study showed a relatively lower rate of severe pleural effusion (Grade 2 or worse was 9%, and Grade 3 was 2%, respectively) compared with other studies. This may be due to the lack of a prophylactic irradiation field for nodal areas in the present study, because the other studies used a prophylactic irradiation field from the supraclavicular fossa to the area of the celiac lymph nodes regardless of the primary site (13, 14). To our knowledge, there have been no reports to investigate the risk factors for pleural effusion. This is the first report, as far as we are aware, to identify the risk factors for pleural effusion in esophageal cancer patients treated with CRT.

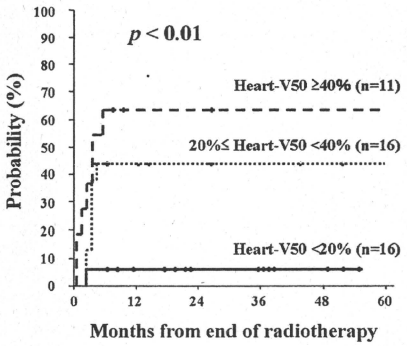

Fig. 2. Cumulative incidence of pleural effusion with respect to Heart-V_{50}. Patients were divided into three groups based on Heart-V_{50}: Heart-V50 <20%, 20% ≤Heart-V_{50} <40%, and Heart-V_{50} ≥40%. Heart-V_{50} is the percentage of the heart receiving ≥50 Gy.

Table 3. Published results of pleural effusion after definitive CRT

Study	*n*	Pleural effusion G 1	≥G 2	≥G 3
Ishikura *et al.* (7)	78	—	19%	10%
Kumekawa *et al.* (13)	34	—	15%	9%
Morota *et al.* (14)	69	—	14%	1%
Shirai *et al.* (present)	43	35%	9%	2%

Abbreviations: CRT = chemoradiotherapy; G = Grade.

We observed a strong association between heart irradiation and pleural effusion using DVH analysis. In particular, Heart-V_{50} was the strongest independent factor for pleural effusion by multivariate analysis ($p = 0.01$). However, the pathologic mechanisms could not be shown in the present study because invasive pathologic approaches such as thoracoscopy or pleural biopsy were not performed. Previously, we have been able to find only two case reports of Hodgkin's lymphoma that show the relationship between mediastinal RT and benign pleural effusion, and the pathologic findings (15, 16). These patients developed pleural effusion 8 and 20 years after RT without recurrence. The authors suggested that pleural effusion was induced by pleural fibrosis or lymphatic obstruction. However, the different causes are required to explain pleural effusion in the present study, because all our patients developed pleural effusion several months after CRT. Recent evidence has shown that RT strongly influences heart damage in esophageal cancer patients. Jingu *et al.* demonstrated that brain natriuretic peptide, an index of heart failure, was significantly increased several months after RT for patients with thoracic esophageal cancer (17). Furthermore, they showed that ^{18}F-fluorodeoxyglucose positron emission tomography detects focal uptake in the myocardium after RT for esophageal cancer, indicating the possibility of radiation-induced cardiac damage (18). Mukherjee *et al.* showed that CRT significantly reduced cardiac ejection fraction from the baseline in esophageal cancer patients (19). These studies indicate that irradiation decreases heart function in esophageal cancer patients treated with CRT. Generally, pleural effusion can be classified into transudative and exudative pleural effusions, and heart failure is the commonest cause of transudative pleural effusion (20, 21). In our study, pleural effusions induced by irradiation were transudative. Taken together, pleural effusion after CRT may be associated with radiation-

induced heart damage. Further studies to investigate the association between pleural effusion and heart irradiation are warranted.

Lung-V_{50} and -V_{60} were observed to be associated with pleural effusion by univariate analysis. However, these were not significant independent factors by multivariate analysis. Parapneumonic effusion by radiation pneumonia is possible, although the potential clinical impact of the slight increase, such as 1.4% of Lung-V_{50} or 0.6% of Lung-V_{60}, is not known. To date, we are unaware of any reports that radiation pneumonia is associated with pleural effusion (22, 23). The association between total lung dose and pleural effusion has been unclear.

Patients aged ≥65 years had a significantly higher risk of pleural effusion ($p = 0.02$), and age was an independent predictor ($p = 0.04$). Morota *et al.* also demonstrated that older esophageal cancer patients treated with CRT were significantly associated with late cardiopulmonary toxicities (14). In their report, the 2-year cumulative incidence of Grade 3 or worse cardiopulmonary toxicities for older patients was 29%, compared with 3% for younger patients ($p < 0.01$) (14). These results suggest that careful selection of treatment strategy and consideration of the risk for late toxicity are required in elderly patients. Primary tumor of the distal esophagus was a significant risk factor for pleural effusion ($p = 0.02$). The heart is located near the distal esophagus, and the present study shows that primary tumor of the distal esophagus is related to higher Heart-V_{50} ($p < 0.01$). These results suggest that the heart dose was higher when primary tumor was at the distal esophagus, which caused the pleural effusion.

All patients received chemotherapy consisted of nedaplatin and 5-fluorouracil with RT concurrently. Therefore, it is difficult to elucidate the individual contribution of cardiotoxicity between RT and chemotherapy. Platinum agents, including nedaplatin and cisplatin, rarely induce cardiotoxicity, whereas 5-fluorouracil is reported to induce cardiotoxicity (24). Radiosensitization has been reported in connect with platinum agents and 5-fluorouracil, and these agents may demonstrate an additive or synergistic effect on normal heart tissue with RT (25). Further study to evaluate the individual effect of chemotherapy and RT on the heart is warranted.

Decreased radiation dose to the heart is expected to avoid pleural effusion in esophageal cancer patients treated with CRT. In our study, patients were treated with a two-phase technique. Therefore, a single-phase conformal technique can be a better method to significantly reduce the heart dose. Recently, several studies have shown that intensity-modulated radiotherapy (IMRT) reduces the heart dose in esophageal cancer patients. Wu *et al.* showed that IMRT planning reduces the mean heart dose compared to three-dimensional conformal RT in thoracic esophageal cancer patients (26). Furthermore, Mayo *et al.* observed that IMRT planning compared to non-IMRT planning significantly reduced V30 of the heart dose in esophageal cancer patients (27). Such RT techniques are expected to refine DVH parameters and decrease heart complications irrespective of the accuracy of the target dose. We suggest that Heart-V_{50} will be a useful dose constraint to avoid pleural effusion in IMRT planning.

Heart-V_{50} is a useful marker to predict pleural effusion in esophageal cancer patients treated with CRT consisting of platinum agent and 5-fluorouracil. However, several CRT regimens with or without surgery have been widely performed for esophageal cancer patients. The limitation of our study is that it remains unknown whether Heart-V_{50} is a predictor of pleural effusion in different treatment strategies. Other investigations are warranted to validate our findings.

CONCLUSIONS

Our results suggest that Heart-V_{50} is a useful DVH parameter as a risk factor for pleural effusion in esophageal cancer patients treated with CRT. The heart should be delineated and be reduced to avoid pleural effusion during radiation treatment planning.

REFERENCES

1. Ando N, Ozawa S, Kitagawa Y, *et al.* Improvement in the results of surgical treatment of advanced squamous cell carcinoma during 15 consecutive years. *Ann Surg* 2000;232: 225–232.
2. Okawa T, Kita M, Tanaka M, *et al.* Results of radiotherapy for inoperable locally advanced esophageal cancer. *Int J Radiat Oncol Biol Phys* 1989;17:49–54.
3. Herskovic A, Martz K, al-Sarraf M, *et al.* Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N Engl J Med* 1992;326: 1593–1598.
4. Cooper JS, Guo MD, Herskovic A, *et al.* Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA* 1999;281:1623–1627.
5. Hironaka S, Ohtsu A, Boku N, *et al.* Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T2-3NanyM0 squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 2003;57:425–433.
6. Ohtsu A, Boku K, Muto K, *et al.* Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999;17:2915–2921.
7. Ishikura S, Nihei K, Ohtsu A, *et al.* Long-term toxicity after definitive chemotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–2702.
8. Tucker SL, Liu HH, Wang S, *et al.* Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. *Int J Radiat Oncol Biol Phys* 2006; 66:754–761.
9. Wei X, Liu HH, Tucker SL, *et al.* Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2008;70:707–714.

10. Ishikawa H, Nonaka T, Sakurai H, *et al.* Usefulness of intraluminal brachytherapy combined with external beam radiation therapy for submucosal esophageal cancer: Long-term follow-up results. *Int J Radiat Oncol Biol Phys* 2010;76:452–459.
11. Sasaki Y, Amanot T, Morita M, *et al.* Phase I study and pharmacological analysis of cis-diammine(glycolato)platinum (254-S; NSC 375101D) administered by 5-day continuous intravenous infusion. *Cancer Res* 1991;51:1472–1477.
12. Jingu K, Nemoto K, Matsushita H, *et al.* Results of radiation therapy combined with nedaplatin (cis-diammine-glycoplatinum) and 5-fluorouracil for postoperative locoregional recurrent esophageal cancer. *BMC Cancer* 2006;6:50.
13. Kumekawa Y, Kaneko K, Ito H, *et al.* Late toxicity in complete response cases after definitive chemoradiotherapy for esophageal squamous cell carcinoma. *J Gastroenterol* 2006;41:425–432.
14. Morota M, Gomi K, Kozuka T, *et al.* Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 2009;75:122–128.
15. Rodriguez-Garcia JL, Fraile G, Moreno MA, *et al.* Recurrent massive pleural effusion as a late complication of radiotherapy in Hodgkin's disease. *Chest* 1991;100:1165–1166.
16. Morrone N, Game e Silva Volpe VL, Dourad AM, *et al.* Bilateral pleural effusion due to mediastinal fibrosis induced by radiotherapy. *Chest* 1993;104:1276–1278.
17. Jingu K, Nemoto K, Kaneta T, *et al.* Temporal change in brain natriuretic peptide after radiotherapy for thoracic esophageal cancer. *Int J Radiat Oncol Biol Phys* 2007;69:1417–1423.
18. Jingu K, Kaneta T, Nemoto K, *et al.* The utility of 18F-fluorodeoxyglucose positron emission tomography for early diagnosis of radiation-induced myocardial damage. *Int J Radiat Oncol Biol Phys* 2006;66:845–851.
19. Mukherjee S, Aston D, Minett M, *et al.* The significance of cardiac doses received during chemoradiation of oesophageal and gastro-oesophageal junctional cancers. *Clin Oncol* 2003;15: 115–120.
20. Light RW. Clinical practice. Pleural effusion. *New Engl J Med* 2002;346:1971–1977.
21. Kataoka H. Pericardial and pleural effusions in decompensated chronic heart failure. *Am Heart J* 2000;139:918–923.
22. Graham MV, Purdy JA, Emami B, *et al.* Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323–329.
23. Tsoutsou PG, Koukourakis M. Radiation pneumonitis and fibrosis: Mechanisms underlying its pathogenesis and implications for future research. *Int J Radiat Oncol Biol Phys* 2006; 66:1281–1293.
24. Schimmel KJ, Richel DJ, van den Brink RB, *et al.* Cardiotoxicity of cytotoxic drugs. *Cancer Treat Rev* 2004;30:181–191.
25. Wilson GD, Bentzen SM, Harari PM. Biological basis for combining drugs with radiation. *Semin Radiat Oncol* 2006;1:2–9.
26. Wu VW, Sham JS, Kwong DL. Inverse planning in three-dimensional conformal and intensity-modulated radiotherapy of mid-thoracic oesophageal cancer. *Br J Radiol* 2004;77: 568–572.
27. Mayo CS, Urie MM, Fitzgerald TJ, *et al.* Hybrid IMRT for treatment of cancers of the lung and esophagus. *Int J Radiat Oncol Biol Phys* 2008;71:1408–1418.

Cancer Science
The official journal of the Japanese Cancer Association

Cost-effectiveness of carbon ion radiation therapy for locally recurrent rectal cancer

Abdulelah Mobaraki,[1] Tatsuya Ohno,[1,3] Shigeru Yamada,[2] Hideyuki Sakurai[1] and Takashi Nakano[1]

[1]Department of Radiation Oncology, Graduate School of Medicine, Gunma University, Maebashi; [2]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan

(Received January 17, 2010/Revised April 7, 2010/Accepted April 8, 2010/Accepted manuscript online April 28, 2010/Article first published online May 25, 2010)

The aim of this study was to evaluate the cost-effectiveness of carbon ion radiotherapy compared with conventional multimodality therapy in the treatment of patients with locally recurrent rectal cancer. Direct costs for diagnosis, recurrent treatment, follow-up, visits, supportive therapy, complications, and admission were computed for each individual using a sample of 25 patients presenting with local recurrent rectal cancer at the National Institute of Radiological Science (NIRS) and Gunma University Hospital (GUH). Patients received only radical surgery for primary rectal adenocarcinoma and had isolated unresectable pelvic recurrence. Fourteen and 11 patients receiving treatment for the local recurrence between 2003 and 2005 were followed retrospectively at NIRS and GUH, respectively. Treatment was carried out with carbon ion radiotherapy (CIRT) alone at NIRS, while multimodality therapy including three-dimensional conformal radiotherapy, chemotherapy, and hyperthermia was performed at GUH. The 2-year overall survival rate was 85% and 55% for CIRT and multimodality treatment, respectively. The mean cost was ¥4 803 946 for the CIRT group and ¥4 611 100 for the multimodality treatment group. The incremental cost-effectiveness ratio for CIRT was ¥6428 per 1% increase in survival. The median duration of total hospitalization was 37 days for CIRT and 66 days for the multimodality treatment group. In conclusion, by calculating all direct costs, CIRT was found to be a potential cost effective treatment modality as compared to multimodality treatment for locally recurrent rectal cancer. (*Cancer Sci* 2010; 101: 1834–1839)

Colorectal cancer is the fourth most common cancer worldwide and accounted for about 1 million new cases in 2002. In a low-risk population, colon and rectal cancer rates are generally of the same magnitude.[1] In 2002, 34 889 and 41 000 cases of rectal cancer were registered in the UK and USA, respectively.[2] In Japan, where rectal cancer comprises 14.6% of all lethal cancers, 31 990 cases were reported and it is predicted that cases will increase to 51 206 by 2020, with a 2.91% annual growth of newly diagnosed cases.[3] After radical surgery for primary rectal cancer, the incidence of local recurrence is up to 33%. Although surgery is the mainstay of treatment for locally recurrent rectal cancer (LRRC), 70% of the patients die within 5 years following its diagnosis. Unfortunately, as a result of pelvic wall involvement, the local recurrence is often unresectable, which generally leads to a poorer outcome than resectable lesions.[4]

Due to the high recurrence rate and the high annual growth rate, the treatment strategy for LRRC is expected to become a major burden for health care systems. In developed countries, cancer-related costs and public medical expenditures are increasing steadily owing to both increases in life expectancy and improved diagnostic and treatment options. For instance, preliminary data from the UK showed that spending on cancer treatment increased by 52% from 1990–1991 to 2000–2001, while total health spending increased by 12%.[5] Total health costs were announced by the Japanese Ministry of Health, Labour and Welfare as amounting to roughly ¥21.87 trillion in 1995, rising to approximately ¥24.4 trillion in 2001 and 8.5% and 9.02%, respectively, were cancer-related.[6] Moreover, in the USA, the cost of colorectal cancer treatment alone represents 13.1% of total national expenditure on cancer treatment.[5]

Recently published data from the National Institute of Radiological Science (NIRS) in Chiba, Japan, showed that carbon ion radiotherapy (CIRT) for LRRC has 3- and 5-year survival rates of 60% and 42.8%, respectively, and that it could be a promising alternative treatment modality next to surgery.[7] However, although the increased development of advanced technologies such as CIRT usually results in higher health care expenses,[8] cost-effectiveness of CIRT is rarely discussed. To date, only one cost-effectiveness study of CIRT has recently been published based on 10 patients with skull base chordoma. Although this published study showed a cost-effectiveness ratio of carbon ion of €2539 per 1% increase in survival, the study suffered from large uncertainty because direct costs were only estimated by a standard reimbursement system.[9] In the present study, actual direct costs for diagnosis, treatment, follow-up, supportive therapy, complications, and admission were retrospectively analyzed in 25 patients treated with CIRT at NIRS or multimodality therapy at Gunma University Hospital (GUH), Japan.

Materials and Methods

Inclusion criteria. Between 2003 and 2005, medical records of all patients with unresectable recurrent tumors in the pelvis after radical surgery alone for primary rectal adenocarcinoma and no distant metastasis at the time of recurrence at NIRS and GUH, were studied. Locally recurrent rectal cancer (LRRC) without distance metastasis was confirmed by computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) findings. Patients with recurrence in the colon were not included in the study due to the fact that the involvement of the colon could probably allow for reduced radiation doses to be applied. Furthermore, patients with another primary tumor, and infection at the tumor site and digestive tract adjacent to the clinical target volume, were excluded. The location, stage, and surgery of primary rectal cancer were considered in the inclusion criteria. These strict inclusion criteria, which allowed only 25 patients to be recruited in the study, were chosen to guarantee that the patients treated at GUH would have been equally suited for CIRT (Table 1). The period between 2003 and 2005 was selected because in 2003 a lump-sum payment system based on diagnosis procedure combinations (DPC) was introduced in 82 Japanese university hospitals including GUH.

[3]To whom correspondence should be addressed.
E-mail: tohno@gunma-u.ac.jp

doi: 10.1111/j.1349-7006.2010.01604.x

Table 1. Patients' characteristics

	Multimodality treatment (n = 11)	Carbon ion beam RT (n = 14)
Number of patients		
Male	8	13
Female	3	1
Age		
Mean	59	66
Median	60	65
Primary tumor site		
Rectal ampulla	9	13
Rectosigmoid junction	2	1
Primary tumor operation		
Abdominoperineal excision	4	7
Low anterior resection	6	6
High anterior resection	1	0
Hartmann's resection	0	1
Primary tumor stage (UICC/6th)		
I	1	1
IIa	3	3
IIIa	4	5
IIIb	3	5
Interval between primary surgery and recurrence/month		
Median	30	35
Mean	32	34
Treatment for recurrence		
Radiation	11	14
Chemotherapy	11	0
Hyperthermia	11	0
Additional treatment		
Secondary surgery	3	0
Total dose/Gy of radiation		
Mean	51.5	73.4
Median	50.0	73.6
Range	50–58	70.4–73.6
Radiation treatment duration (days)		
Median	35	29
Mean	34	28
Range	25–45	25–30

RT, radiotherapy; UICC/6th, International Union Against Cancer tumor-node-metastasis (TNM) classification, sixth edition.

Diagnosis procedure combination (DPC). Diagnosis procedure combination (DPC) payment in brief contains two parts, prospective and fee-for-service payment. Prospective payment, approximately corresponding to the total payments for admission, is the sum of hospitalization, 38.9%; injections, 11.0%; laboratory tests, 10.4%; diagnostic imaging, 6.6%; medication, 2.9%; procedures priced less than 1000 points (1 point = ¥10), 1.9%.

Fee-for-service payment, corresponding to the payment for the doctor's fee and covering the remaining 28.3% of the fee, is the sum of surgery and its material costs, 18.2%; and additional services and treatments (procedures priced at 1000 points or higher, cardiac catheterization, endoscopy, radiotherapy, rehabilitation, etc.), 10.1%.[10]

Fee-for-service payment depends on the national health insurance fee schedule. Prospective payment is paid per diem with a three-level step down based on the average length of stay for each diagnosis group. Furthermore, the prospective payment is adjusted by hospital coefficient, securing the previous year's payment in each hospital.[10,11]

Conventional treatment at GUH. All patients were treated by multimodality treatment including three-dimensional conformal radiotherapy (3D-CRT), chemotherapy, and hyperthermia, which is a standard treatment for unresectable LRRC at GUH. External beam radiation therapy at a total dose of 50 Gy (n = 9) or 58 Gy (n = 2) was delivered to the whole pelvis. The radiation treatments consisted of 25–29 fractions of 2.0 Gy, delivered 5 days a week with a Lineac of 10 MV. Chemotherapy consisted of 5-fluorouracil (5-FU) (250 mg/m^2 per day) and leucovorin (LV) (25 mg/m^2 per day) administered by continuous infusion during the night for 5 days a week in the second and fourth weeks of radiation therapy. Hyperthermia (mean, 40.4°C) once a week during the radiation therapy for 1 h was performed with radiofrequency devices (Thermotron-RF 8; Yamamoto Vinita, Osaka, Japan).[12] Consequently, all patients at GUH received chemo-thermo-radiation therapy as indicated by the standard treatment protocol. After being treated with chemo-thermo-radiation therapy, local resection for tumors was performed for three patients according to the treatment protocol at GUH. Therefore, only three patients received local resection for the recurrent tumors at GUH (two abdminoperineal resection and one stapled lower anterior resection).

Carbon ion radiotherapy at NIRS. The patients were treated with carbon ion radiotherapy alone which is the standard treatment for LRRC at NIRS. A total radiation dose of 73.6 Gy (n = 13) or 70.4 Gy (n = 1) in 16 fractions over 4 weeks was delivered to the tumors.

Treatment cost of recurrence. All patients in both treatment arms had undergone primary surgery alone, but calculation of the primary cost of the rectal cancer treatment is out of the scope of the present study. In order to assess the direct cost of recurrence; hospitalization (including in the intensive care unit), radiation therapy, chemotherapy, hyperthermia, surgical treatment, medical laboratory and imagining investigations, visits, follow-up, medications, supportive therapy (physical, nutritional, and medical), and consequential costs (medical reports, images copies, and health education) were thoroughly calculated using the medical records.

However, indirect costs and costs of intangibles could not be evaluated in the current retrospective study. The indirect costs are lost resources, due illness effects on sick people, and their support system, such as lost production, days off work, sickness pay, invalidity, or premature death. Intangible costs are the psychological aspects of disease as pain and suffering.[13] Therefore, since the present study is retrospective, only the direct cost of 2 years of follow-up from the time of recurrence was computed individually for each patient; afterwards an average cost of for patients in each group was calculated. The mean cost for each treatment group CIRT (A) and for multimodality treatment (B) was calculated. Subsequently, the incremental cost-effective ratio (ICER) which is expressed as the additional treatment costs of the new technique weighted by gain in outcome was analyzed.

$$\text{ICER} = \text{Cost (A)} - \text{Cost (B)}/\text{effectiveness (A)} - \text{effectiveness (B)}$$

The ICER can be based either on the gain in local control rates (ICER in terms of disease-free survival) which can be used as a measure of disease-free survival or on the overall survival rates (ICER per 1% increase in survival). Therefore, the 5-year overall survival rate and 5-year local control rate from literature review were analyzed for both groups using the calculated mean costs for CIRT (A) and multimodality treatment (B). Re-recurrence cost was also estimated by multiplying the mean costs of CIRT (A) or multimodality treatment (B) by their re-recurrence probability in each group.

It is worth mentioning that the multimodality treatment cost at GUH refers to real total costs paid by both the National Health Insurance System of Japan and the patient, while it refers to the real total costs paid by patient alone in case of carbon ion treatment since CIRT is still not covered by the National Health Insurance System.[14]

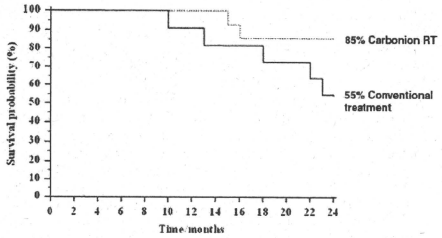

Fig. 1. Two-year overall survival curve for the carbon ion radiotherapy (RT) and conventional multimodality treatment groups for locally recurrent rectal cancer.

Results

After initiation of local recurrence treatment, the 2-year overall survival rate was 85% for CIRT and 55% for multimodality treatment, as shown by Kaplan–Meier curve (Fig. 1). According to the hazard ratio, the risk of dying in the multimodality treatment group was 1.4 of that in the carbon ion group. The 2-year local control rate was 100% in patients treated with CIRT at NIRS, while the local control rate could not be evaluated due to incomplete documentation of exact date of distant metastasis at GUH. However, all cost details related to the metastasis were well documented. The absolute values of the direct cost of recurrence for all patients in both groups are summarized in Table 2.

The ICER for CIRT based on the calculated survival rate was ¥6428 per 1% increase in survival. The percentage of mean cost showed that 65% of the cost in the carbon ion group belonged to the carbon ion beams cost, which was almost seven times more than the photon radiation cost at GUH. On the other hand, the cost of prospective payment of DPC at GUH represented 74% of the total cost (Table 3). The median hospitalization duration was 66 days for the multimodality treatment group and 37 days for the CIRT group. Additionally, by using 5-year survival and 5-year local control rates from literature review (Table 4), the mean estimated re-recurrence cost was ¥1 706 107 and ¥936 770 for multimodality treatment and CIRT, respectively. The average ICER for CIRT in terms of disease-free survival was ¥13 454/year of disease-free survival, while the average ICER due to CIRT per 1% increase in survival rate was ¥13 221. Given the age of the patients in the analysis (60 years), a remaining lifespan of at least 20 years could be estimated (Table 1); the ICER in terms of additional life year was

Table 2. Days of hospitalization and absolute total cost for each patient treated with carbon ion radiotherapy and multimodality treatment

Carbon ion radiotherapy			Multimodality treatment		
Patient	Days of admission	Overall treatment cost/¥	Patient	Days of admission	Overall treatment cost/¥
1	37	3 975 810	1	186	8 218 177
2	44	4 371 820	2	123	8 137 957
3	79	4 730 760	3	76	2 768 777
4	36	4 397 980	4	80	3 337 060
5	36	5 388 630	5	61	4 443 295
6	37	4 121 600	6	44	7 058 167
7	47	4 326 490	7	66	3 780 787
8	116	7 646 510	8	75	5 284 419
9	33	3 976 610	9	38	1 801 837
10	32	4 059 100	10	51	1 843 487
11	36	4 945 020	11	64	4 048 137
12	70	5 786 900			
13	51	5 33 8210			
14	35	4 189 800			

Table 3. Mean of direct costs for both groups and percentage

	Carbon ion RT		Multimodality treatment	
	Mean cost (¥)	Percentage (%)	Mean cost (¥)	Percentage (%)
Hospitalization cost (including DPC)	1 038 885	21.6	3 394 066	74.0
Food	66 154	01.4	114 795	02.5
Laboratory investigations	79 510	01.7	86 110	01.9
Imaging investigations	266 238	05.5	191 366	04.2
Radiotherapy	3 140 000	65.4	444 273	09.6
Chemotherapy	0	00.0	125 666	02.7
Hyperthermia	0	00.0	19 495	00.4
Surgery	0	00.0	24 384	00.5
Medication	57 435	01.2	186 584	04.0
Visit fee	14 028	00.3	13 063	00.3
Health education	48 297	01.0	11 298	00.2
Reports and image copies	93 399	01.9	0	0.00
Total (mean) (¥)	4 803 946		4 611 100	

DPC, diagnosis procedure combinations; RT, radiotherapy.

doi: 10.1111/j.1349-7006.2010.01604.x

Table 4. Overview of total costs of therapy for different local control and survival rates for locally recurrent rectal cancer

Treatment modality	Author	Year	No. of cases	5-year survival (%)	5-year local re-recurrence (%)	Estimated cost of re-recurrence (¥)	ICER (¥) in terms of disease-free survival	ICER (¥) per 1% increase in survival
Multimodality	Willet *et al.* (30)	1991	30	27	38	1 752 218	10 424	12 205
	Bussierses *et al.* (31)	1996	73	31	29	1 337 219	20 300	16 343
	Valentini *et al.* (32)	1999	47	22	31	1 429 441	16 769	9271
	Wiig *et al.* (33)	2000	107	30	50	2 305 550	6323	15 066
Mean			64	27.5	37	1 706 107	13 454	13 221
Carbon ion	Tsujii *et al.* (7)	2008	90	42.8	19.5	936 770		

ICER, incremental cost-effective ratio.

Table 5. Acute and late toxicity by NCI-CTC and RTOG/EORTC

	Carbon ion radiotherapy		Multimodality treatment	
	Acute (NCI-CTC)	Late (RTOG/EORTC)	Acute (NCI-CTC)	Late (RTOG/EORTC)
Skin				
Grade 0	0	4	0	0
Grade 1	13	10	0	0
Grade 2	1	0	0	0
Grade 3	0	0	0	0
Gastrointestinal				
Grade 0	0	0	5	8
Grade 1	0	0	2	1
Grade 2	0	0	1	2
Grade 3	0	0	3	0

NCI-CTC, National Cancer Institute – Common Toxicity Criteria, version 2; RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

¥4397/year. Although all patients in both groups tolerated and completed their treatment courses, grade 3 toxicities were observed (Table 5). In brief, a grade 3 early toxicity (gastrointestinal tract) developed in three patients (27%) treated with multimodality treatment. In contrast, no severe toxicity was observed in the CIRT group and 93% of the patients developed only grade 1 early toxicity (skin). No severe late toxicity was detected and no urinary or hematological toxicities were recorded in any group.

Discussion

Carbon ion beams allow uniquely precise delivery of a high dose to the target volume, while sparing the surrounding normal tissue. Carbon ion beams deliver a large mean energy per unit length of their trajectory in the body (linear energy transfer, LET). In contrast to neutron beams whose LET remains uniform at any depth, the LET of carbon ion beams increases steadily from the point of entrance into the body with increasing depth, reaching a maximum in the peak region (Bragg peak). The ratio of the Bragg peak dose to the dose at the entrance region is larger for carbon ions than for protons. Carbon ion beams might therefore be used effectively in the treatment of cancers resistant to conventional radiation.[14,15]

At present, carbon ion radiotherapy is available at three facilities: two hospital-based facilities in Japan (Chiba and Hyogo), and the Heidelberg Ion Therapy facility in Germany.

Although little cost information is available, carbon ion facilities are anticipated to be costly. The proton/carbon ion facility in Hyogo, Japan, which opened in 2001, was estimated to cost ¥28 billion (approximately $US253 million).[16] Even though this expenditure may suggest a significant cost issue, a cost-benefit analysis by Nakagawa *et al.* showed that good financial balance can be achieved as 600 patients are treated annually with a CIRT cost of ¥3.14 million per patient. They analyzed carbon ion facilities in Hyogo and NIRS and the estimated lifespan of the accelerator, building, and equipment was 20, 30 and 6 years respectively. The total depreciation cost, which includes the accelerator, building, equipment, and operating costs as well as maintenance fee, was ¥1.826 billion per year.[17] However, both models were installed over a decade ago and were not dedicated for CIRT alone but also for proton radiotherapy (Hyogo) and for research purposes (NIRS). Therefore, commercial vendors are currently offering fixed and compacted CIRT facilities that are expected to be less costly. For instance, a compact carbon ion beam accelerator was installed in 2008 at Gunma University, Japan.[18] The facility size and construction costs of the Gunma University accelerator were about one-third of those at NIRS.[19] With such reduction in size and cost, spread of CIRT seems feasible. Germany has already had a second facility in operation since 2009 and two others are expected in 2010 and 2012.[20,21] Italy,[21] the USA,[22] and Austria[23] are anticipating their first facilities in 2010, 2013, and 2014 respectively. France is expecting to open two facilities, one in 2012 and another in 2014.[21] Generally, about 20 CIRT centers are anticipated over the next decade.[20] However, in respect to these centers, questions about the cost-effectiveness of carbon ion radiotherapy compared to conventional treatment modalities remain unanswered.

The current average estimated cost of proton therapy is €25 000 and the cost ratio between proton treatment and intensity modulated photon irradiation is approximately 2.4.[24] Based on the French ETOILE project, the cost of carbon ion treatment per patient varied widely from €12 000 to €28 000 as a result of variation in fraction number and session duration.[25] However, our analysis showed that CIRT alone, which is paid per treatment not per fraction, could be a cost-effective treatment modality for certain tumors that are typically treated by the multimodality approach including three-dimensional conformal radiotherapy, such as LRRC. This cost effectiveness is related to costs of hospitalization and treatment-related morbidity which generally was found to be much lower in cases where CIRT was used.[26] Our findings also showed significantly less days of admission (Table 2) and less toxicity (Table 5) for CIRT than multimodality treatment. Compared to conventional radiotherapy, the superior physical property of CIRT allowing high-precision delivery to the target volume, while sparing the surrounding normal tissue,[7,14,26] explains the low rate of gastrointestinal tract (GIT) toxicity in the CIRT group in our study (Table 5).

In fact, when treating LRRC, photon radiotherapy alone has not been shown to achieve significant survival benefit.[27,28] For this reason, the combination of conventional