Proton Beam Therapy Combined with Concurrent Chemotherapy for Esophageal Cancer

HITOSHI ISHIKAWA[1], TAKAYUKI HASHIMOTO[1], TOSHIKAZU MORIWAKI[2], ICHINOSUKE HYODO[2], KATSUJI HISAKURA[3], HIDEO TERASHIMA[3], NOBUHIRO OHKOHCHI[3], TOSHIKI OHNO[1], HIROKAZU MAKISHIMA[1], MASASHI MIZUMOTO[1], KAYOKO OHNISHI[1], TOSHIYUKI OKUMURA[1] and HIDEYUKI SAKURAI[1]

Departments of [1]Radiation Oncology, [2]Gastroenterology, and [3]Gastroenterological and Hepatobiliary Surgery, University of Tsukuba, Faculty of Medicine, Ibaraki, Japan

Abstract. *Background/Aim: The aim of the present study was to evaluate the outcomes of proton beam therapy (PBT) concurrently combined with chemotherapy consisting of cisplatin and 5-fluorouracil for esophageal cancer. Patients and Methods: Forty consecutive patients (stage I in 16 patients, II in 9 and III in 15) treated between 2008 and 2012 were evaluated. A total dose of 60 Gray equivalents (GyE) in 30 fractions was delivered, and an additional boost of 4-10 GyE was given when residual tumors were suspected. The median follow-up time was 24 months (range=7-66 months). Results: No cardio-pulmonary toxicities of grade 3 or higher were observed. Recurrences were observed in 16 patients, and the 2-year rates of disease-specific survival and locoregional control were 77% and 66%, respectively. Conclusion: Irrespective of the small sample size and short follow-up time of the study, proton beam therapy combined with chemotherapy seems to be feasible for esophageal cancer.*

Although the standard therapy for esophageal cancer is definitive esophagectomy with lymph node dissection, a significant proportion of patients are unsuitable for surgery due to confounding factors, such as advanced age and co-existing medical issues (1-3). Hence, radiation therapy (RT) has played a more important role in the management of esophageal cancer for patients with inoperable disease.

Previous clinical trials have revealed that definitive RT combined with concurrent chemotherapy has yielded significantly better outcomes in patients with esophageal cancer compared to RT-alone (4-6). However, certain studies with long-term follow-up periods showed relatively high rates of cardio-pulmonary dysfunction after concurrent chemoradiotherapy (CCRT) for esophageal cancer, mainly due to large irradiated volumes of the lung and heart (7-9). Therefore, three-dimensional conformal RT with multiple portals or intensity-modulated RT instead of a traditional two-dimensional treatment technique has been recently used to reduce the incidence of cardio-pulmonary morbidities, although long-term follow-up results are awaited (10, 11).

Proton beam therapy (PBT) offers advantageous physical properties for the treatment of various types of cancer when compared to conventional RT using photon beams because proton beams exhibit a spread-out Bragg peak and use specified beam modulations to achieve a desirable dose distribution to the target volume (12-14). Hence, PBT can deliver a large irradiation dose to the tumor using a limited number of portals, thus sparing the surrounding normal tissues. With RT for esophageal cancer especially, it is anticipated that PBT can reduce cardio-pulmonary toxicity by limiting the irradiation dose to the lung and heart. In fact, preliminary results from the MD Anderson Cancer Center showed that PBT using a total dose of 50.4 Gray equivalents (GyE) was promising with regard to cardio-pulmonary morbidity (15).

In a previous randomized trial on CCRT for esophageal cancer, dose escalation did not improve the survival of patients, probably due to increased treatment-related morbidity of grade 3 or higher, and the standard dose of CCRT has been widely recognized as 50.4 Gy delivered in 28 fractions (16). However, the most frequent site of tumor recurrence after definitive RT for esophageal cancer is the primary site (*i.e.* the esophagus) irrespective of concurrent chemotherapy use (9, 16-18). Therefore, if a dose escalation can be performed safely for esophageal cancer treatment, the probability of tumor control will possibly be improved.

Correspondence to: Hitoshi Ishikawa, MD, Ph.D., Department of Radiation Oncology, University of Tsukuba, Faculty of Medicine, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. Tel: +81 298537100, Fax: +81 298537102, e-mail: hishikawa@pmrc.tsukuba.ac.jp

Key Words: Proton beam therapy, esophageal cancer, concurrent chemoradiotherapy, survival, late toxicity.

Hence, we herein report the clinical outcomes of PBT, used at ≥60 GyE total dose, with concurrent chemotherapy in patients with esophageal cancer.

Patients and Methods

Patients. Between November 2008 and February 2013, definitive PBT was performed for 64 patients with esophageal cancer. Among them, a total of 40 patients received PBT concurrently combined with chemotherapy [cisplatin, 70 mg/m^2 on day 1, and 5-fluorouracil (5-FU), 700 mg/m^2/24 h on days 1-4, every 28 days, 2-4 cycles]. The characteristics of the patients in the present study are summarized in Table I. The study patients consisted of 38 men and two women whose median age was 69 years, ranging from 52 to 79 years. Twenty-four patients (60%) were regarded as having inoperable disease due to deep tumor invasion to adjacent organs (n=4) or co-existing diseases (n=20), whereas the remaining 16 patients (40%) refused surgical resection. The tumors were located at the cervical, upper thoracic, middle thoracic, or lower thoracic esophagus in 2, 10, 21, and 7 patients, respectively. The median primary tumor length was 5 cm, ranging from 2 to 12 cm. According to the 2009 TNM Classification of the International Union Against Cancer (UICC) (19), the patients were stratified as having disease T1 in 16, T2 in 9, T3 in 11, and T4 in four, or as stage I, II, and III in 16, 9, and 15, respectively. Written informed consent for concurrent chemo-proton therapy (CCPT), *i.e.* PBT with concurrent chemotherapy, was obtained from all patients. Each treatment was approved by the Committee of Proton Medical Research Center and the institutional conference routinely checked all treatment plans before carrying out the actual treatment.

Proton therapy. PBT was performed using a respiration-gated technique with 155-, 200-, 230-, or 250-MV protons (14). In principle, the total irradiation dose of 60 GyE in 30 fractions (2 GyE/fraction, five fractions per week) was delivered without planned interruption. Two to four metallic markers or surgical clips were placed at the tumor edges while the patients underwent endoscopy prior to the initial treatment planning; this allowed identification of the tumor location during the treatment planning and confirmation of the position for each treatment.

In principle, the initial clinical target volume (CTV) for patients with N0 disease was defined as the gross tumor volume plus 3.0- to 4.0-cm margins from both the cranial and caudal edges of the tumor and 1.5- to 2.0-cm margins from the other directions. After delivery of 40-50 GyE via anteroposterior (AP)-opposed fields, boost therapy was delivered using AP-opposed fields or anterior and lateral oblique fields with reduced margins (cranial and caudal margins of 2.0 cm and other margins of 1.0 cm), and the irradiation dose to the spinal cord was completely restricted to up to 46 GyE of the biologically equivalent dose in 2 GyE per fraction. For patients with lymph node (LN) metastases, the AP irradiation fields included the primary and regional LNs. Since August 2010, the designed-seamless irradiation technique (D-SLIT) has been used to include the bilateral supraclavicular and mediastinal regions (20). In this method, the junction between the two fields is shifted after delivery of 20 GyE to avoid over- or under-dosage. The planning target volume (PTV) was defined by adding 5 mm margins around the perimeter of the CTV to compensate for any variabilities in treatment set-up or internal organ motion. A PBT dose distribution using D-SLIT is shown in Figure 1.

The early treatment effects in all patients at a total dose of 50 GyE were evaluated by endoscopic examination and computed tomographic (CT) scans, and an additional boost of 4-10 GyE was given for 21 patients (52%) because residual tumors were suspected. Irradiation doses for boost therapy were determined after measuring the irradiation field size and any acute reactions of the esophagus.

Chemotherapy. Two courses of chemotherapy consisting of cisplatin at 70 mg/m^2 on day 1, and continuous infusion of 5-fluorouracil (5-FU) at 700 mg/m^2 per 24 h on days 1 to 4, were administered during PBT and repeated every four weeks. For those with stage II-III disease, two additional courses of adjuvant chemotherapy were administered after CCPT, if possible.

Follow-up examination and statistical analysis. The follow-up examination included a physical examination, a blood test, and measurement of the squamous cell carcinoma antigen, a serum tumor marker, and was performed one month after completion of CCPT and at 3-month intervals thereafter. Endoscopy and CT scans were routinely performed one month after CCPT for assessment of the tumor response and for evaluation of tumor recurrence at LNs and distant organs at 3-month intervals during the first year and at 6-month intervals thereafter. When a local recurrence was suspected, biopsy was performed for pathological examination. Complications were assessed in each subject after CCPT according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4 (21).

The rates of overall survival (OS), cause-specific survival (CSS) and locoregional control (LRC) were calculated from the time of initiation of CCPT to that of the patient's death or the last follow-up using the Kaplan-Meier method (22). The survival curves were compared using the log-rank test for univariate analysis. The last follow-up was performed in May, 2014, and the median follow-up time was 24 months (range=7-66 months).

Results

Outcomes. PBT was successfully completed in all patents, and two or more cycles of chemotherapy were also administered in all but one. All tumors except two showed a definite reduction in overall size; 30 (75%) showed a complete response (CR), and the remaining eight tumors (20%) regressed partially 1-2 months after PBT according to endoscopy, esophagography, and chest CT. With regard to tumor stage, the CR rates for patients with stage I, II, and III tumors were 88% (14/16), 89% (8/9), and 56% (9/16), respectively.

Tumor recurrences were observed in 16 (40%) patients, their details are shown in Table II. Overall, 8 cases of recurrence developed solely in the esophagus, 4 solely in the mediastinal LN (within (n=1) and outside (n=3) of the irradiation field), 1 in both of the esophagus and mediastinal LN and 3 in distant organs (2 in the lung and 1 in the liver). The 2-year LRC rate after CCPT was 66.4% [95% confidence interval (CI)=50.4-82.4%) (Figure 2).

By the time of the last follow-up examination, 8 patients had died due to progression of their disease and another had died of intercurrent disease without recurrence. The 2- and 3-year OS rates for the whole patient group were 75.1% (95% CI=59.6-90.6%) and 70.4% (95% CI=53.4-87.4%), respectively (Figure 2). For 5 (56%) out of the 9 patients

Table I. *Characteristics of patients with esophageal cancer.*

Characteristic	No. of patients (%)
Age (years)	52-79 (median, 69)
Gender	
Male	38 (95%)
Female	2 (5%)
T-Stage	
T1	16 (40%)
T2	9 (22%)
T3	11 (18%)
T4	4 (10%)
N-Stage	
N0	19 (47%)
N1	11 (28%)
N2	7 (18%)
N3	3 (7%)
Clinical stage	
I	16 (40%)
II	9 (22%)
III	15 (38%)
Location of primary tumor site	
Cervical	2 (5%)
Upper thoracic	10 (40%)
Middle thoracic	21 (53%)
Lower thoracic	7 (12%)
Reasons of ineligibility for surgery	
Medically inoperable	24 (60%)
Patients refused surgery	16 (40%)

Table II. P*attern of tumor recurrences after proton beam therapy (PBT) combined with concurrent chemotherapy for patients with esophageal cancer.*

Site	No. of patients (%)
Recurrence	
No	24
Yes	16
Primary alone	8 (50%)
Primary and lymph nodes	1 (6%)
Lymph nodes alone	
Within the PBT field	1 (6)
Out of the PBT field	3 (19%)
Distant organs	3 (19%)

with local recurrences, local salvage therapies including endoscopic submucosal dissection (n=2), photodynamic therapy (n=1), and surgery (n=2) were successfully performed with no further recurrence observed, whereas the remaining 4 patients did not receive salvage therapy because of poor general condition (n=2) or refusal of patients (n=2). The 2-year CSS rate for the whole patient group was 77.4% (95% CI=62.1-92.7%), and those for patients with stage I-II and stage III disease were 100% and 30.1% (95% CI=0-62.7%), respectively, with a statistically significant difference between the two groups ($p<0.001$) (Figure 3).

Table III. *Treatment-related morbidities after proton therapy combined with chemotherapy*

	No. of patients (%)			
Grade	0-1	2	3	4
Acute				
Bone marrow	7 (17%)	23 (58%)	8 (20%)	2 (5%)
Esophagus	10 (25%)	21 (53%)	9 (22%)	0 (0%)
Skin	27 (67%)	11 (28%)	2 (5%)	0 (0%)
Late				
Heart	37 (92%)	3 (8%)	0 (0%)	0 (0%)
Lung	39 (98%)	1 (2%)	0 (0%)	0 (0%)
Esophagus	34 (85%)	4 (10%)	2 (5%)	0 (0%)

Table IV. *Grade 3 or severe late toxicities after definitive chemoradiotherapy for esophageal cancer.*

	JROSG021 Ref. (18)	JCOG9906 Ref. (6)	Present
Pericardial effusion	9%	16%	0%
Pleural effusion	7%	9%	0%
Pneumonitis	1%	4%	0%
Treatment-related death	1%	5%	0%

Acute and late morbidities. Table III summarizes the details of toxicities; no treatment-related deaths occurred in the present study. With regard to acute treatment-related morbidity, grade 3 and 4 hematological toxicities developed in eight (20%) and two (5%) patients, respectively. As for non-hematological toxicity, grade 3 esophagitis and dermatitis occurred in nine (22%) and two (5%) patients, respectively. In addition, a 66-year-old man temporarily had grade 3 encephalopathy probably due to 5-FU. His symptom was completely resolved by medication within 10 days, and he completed a total dose of 60-GyE of PBT.

Regarding the late adverse effects of CCPT, a small amount of asymptomatic pleural and pericardial effusion (grade 2) was observed in one (2%) and three (8%) patients respectively, but cardio-pulmonary morbidities of grade 3 or higher had not developed up to the time of the last follow-up. Esophageal stricture developed in a 70-year-old man with T3 disease 4 months after completion of PBT. Since he developed grade 3 acute esophagitis two weeks after the start of PBT, no further chemotherapy was administered, but a total dose of 60 GyE was delivered. His symptoms

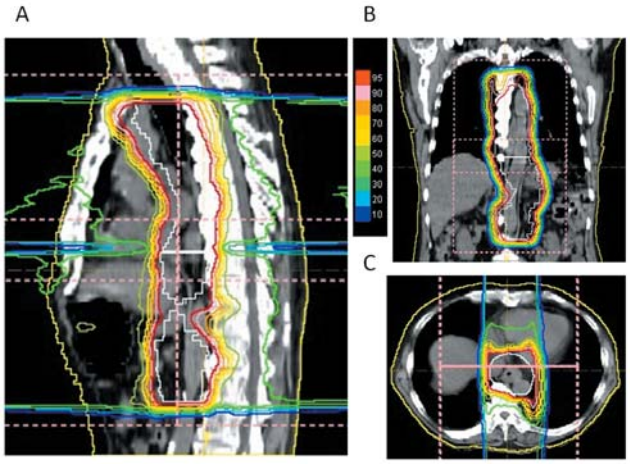

Figure 1. *Dose distribution of proton beam therapy using our designed-seamless irradiation technique: sagittal view (A), coronal view (B) , and axial view (C).*

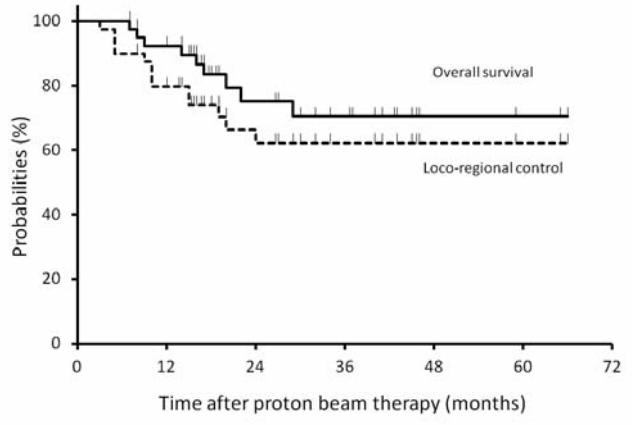

Figure 2. *The curves of locoregional control and overall survival after proton beam therapy combined with concurrent chemotherapy for esophageal cancer.*

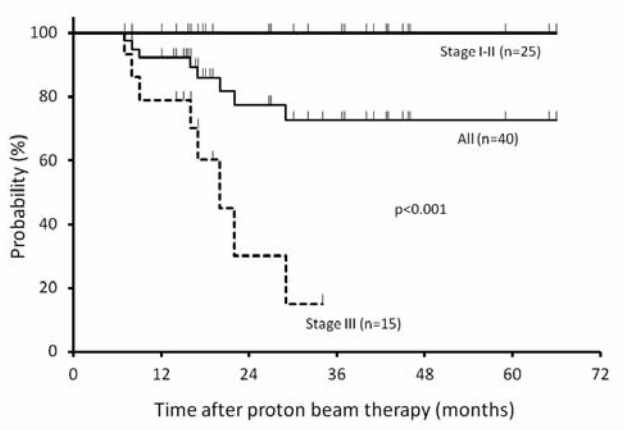

Figure 3. *Cause-specific survival curves according to clinical tumor stage. The 2-year cause-specific survival rate of 25 patients with stage I-II disease was 100% and the corresponding rate of 15 with stage III disease was 30.1%. A statistically significant difference between the survival curves of patients with stage I-II and those with stage III disease was found (p<0.001).*

Table V. *The effects of an additional boost therapy after 60 Gy on local tumor control according to tumor stage in patients with oesophageal cancer.*

	Boost therapy			
	No (n=19)		Yes (n=21)	
	Non-recurrent	Recurrence	Non-recurrent	Recurrence
Stage I	10 (91%)	1 (9%)	4 (80%)	1 (20%)
Stage II	5 (100%)	0	3 (75%)	1 (25%)
Stage III	3 (100%)	0	6 (50%)	6 (50%)
All	18 (95%)	1 (5%)	13 (62%)	8 (38%)

progressed gradually and he died of tumor recurrence seven months after the treatment. Esophageal ulcer was observed in a 55-year-old man with T3 disease four months after completion of PBT. For this case, a total dose of 68 GyE was given because endoscopic evaluation at 50 GyE revealed that his esophageal tumor (6 cm in length) had grossly remained.

Discussion

In the present study, PBT was performed successfully in all patients, and 98% of them received two or more cycles of concurrent chemotherapy. Furthermore, grade 3 or higher late cardio-pulmonary toxicities were not observed. In addition, no disease-specific death had occurred in any of the 25 patients with stage I-II esophageal cancer up to the time of the last follow-up. Although the number of study participants was small, our use of CCPT seemed to be feasible in this study.

PBT has a well-known physical advantage of reducing the irradiation dose to surrounding normal tissues during administration of the curative dose (12-15). Traditionally, a two-dimensional treatment technique using AP and posterior-anterior (PA)-opposing beams is typically used in RT for esophageal cancer, but previous long-term follow-up results showed that grade 3 or higher cardio-pulmonary morbidities after CCRT occurred in 10-20% of study subjects, likely due to the large volumes irradiated at low to middle doses in the lung and at middle to high doses in the heart (7, 9, 23). On the other hand, PBT can provide curative doses to the target volumes within the tolerance dose of the spinal cord, using only opposing AP and PA

fields (Figure 1). The lower incidence of late cardio-pulmonary morbidities in the present study than those in other studies using similar treatment protocols regarding irradiation doses and chemotherapy use was possibly achieved by PBT (Table IV), since a close relationship between the morbidities and the irradiated heart and lung doses in CCRT for esophageal cancer was reported (24, 25).

To achieve an improved CR rate and survival, escalation of the irradiated dose appears to be effective for RT in various types of cancer, but the results of a previous randomized trial revealed that a dose escalation from 50.4 to 64.8 Gy in CCRT was not advantageous with respect to survival, mainly due to a higher rate of toxicity with 64.8 Gy compared with the standard dose (50.4 Gy) (16). However, many of the grade 5 morbidities in the high-dose group developed at a total dose of less than 50.4 Gy and the most likely site for recurrence after CCRT was the primary site (*i.e.* esophagus) in the study. Hence, if the dose escalation is safely achieved, the LCR may be improved, and an increase in the survival rate will be anticipated. In the present study, irradiated doses were further escalated from 60 to 64-70 GyE in 21 patients whose tumors remained according to the endoscopic evaluation after using a 50-GyE dose, but local recurrences developed in 8 (38 %) of them (Table V). On the other hand, local recurrence developed in only one (5%) out of 19 intuits whose tumors were considered to have disappeared by the evaluation at 50 GyE. The findings suggested that our criterion for dose escalation seems to be reasonable, but we were unable to determine whether or not dose escalation could inhibit tumor recurrences.

In the present study, the 30% 2-year CSS rate in patients with stage III disease seems to be disappointing. In addition to a small sampling of patients with stage III disease in this study (n=15), the limited PBT irradiation field that was delivered, even in those with advanced tumors, may have affected the poor survival. Recently, we reported the D-SLIT method to extend the field for prophylactic irradiation of LN for esophageal cancer, and this technique has been used in patients with stage II-III since April 2010 (19). Among 15 patients with stage III esophageal cancer in the present study, tumor recurrences were observed in all seven of the non-D-SLIT group but in five out of eight of the D-SLIT group. Moreover, there were also no grade 3 or higher late morbidities after introduction of the technique. Hence, CCPT using extended fields may reduce recurrence without causing a significant increase in late toxicity; however, a larger number of study patients and longer follow-up times are required.

In conclusion, irrespective of the small patient number and short follow-up time of the present study, PBT with concurrent chemotherapy consisting of cisplatin (70 mg/m^2 on day 1) and 5-FU (700 mg/m^2 on days 1-4) seems to be a promising CCRT method for patients with esophageal cancer, especially with regard to late cardio-pulmonary toxicity. The efficacy of dose escalation and prophylactic nodal irradiation using PBT needs to be further investigated.

Acknowledgements

This work was supported by Grants-in-Aid for scientific research from the Ministry of Education, Culture, Sports, Science, and Technology (24591832) of Japan.

Conflicts of Interest

There are no potential conflicts to disclose.

References

1 Moskovitz AH, Rizk NP, Venkatraman E, Bains MS, Flores RM, Park BJ and Rusch VW: Mortality increases for octogenarians undergoing esophagogastrectomy for esophageal cancer. Ann Thorac Surg *82*: 2031-2036, 2006.

2 Recht A: The role of radiation therapy in treating patients with potentially resectable carcinoma of the esophagus. Chest *107*: 233S-240S, 1995.

3 Ishikawa H, Sakurai H, Tamaki Y, Nonaka T, Yamakawa M, Saito Y, Kitamoto Y, Higuchi K, Hasegawa M and Nakano T: Radiation therapy alone for stage I (UICC T1N0M0) squamous cell carcinoma of the esophagus: indications for surgery or combined chemoradiotherapy. J Gastroenterol Hepatol *21*: 1290-1296, 2006.

4 Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, Byhardt R, Russell AH, Beitler JJ, Spencer S, Asbell SO, Graham MV and Leichman LL: Chemoradiotherapy of locally advanced esophageal cancer: Long-term follow-up of a prospective randomized trial (RTOG 85-01)-Radiation Therapy Oncology Group. JAMA *281*: 1623-1627, 1999.

5 Smith TJ, Ryan LM, Douglass HO Jr., Haller DG, Dayal Y, Kirkwood J, Tormey DC, Schutt AJ, Hinson J and Sischy B: 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 *42*: 269-276, 1998.

6 Stockeld D, Tennvall J, Wagenius G, Albertsson M, Backman L, Brodin O, Cwikiel M, Granström L, Gustafsson G, Gustavsson S, Hambraeus G, Lewensohn R, Sjöstedt S, Strander H, Aberg B and Fagerberg J: A Swedish study of chemoradiation in squamous cell carcinoma of the esophagus. Acta Oncol *40*: 566-573, 2001.

7 Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, Muto M, Ogino T and Yoshida S: Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol *21*: 2697-2702, 2003.

8 Morota M, Gomi K, Kozuka T, Chin K, Matsuura M, Oguchi M, Ito H and Yamashita T: Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. Int J Radiat Oncol Biol Phys *75*: 122-128, 2009.

9 Kato K, Muro K, Minashi K, Ohtsu A, Ishikura S, Boku N, Takiuchi H, Komatsu Y, Miyata Y, Fukuda H and Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (JCOG): Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys *81*: 684-690, 2011.

10 Zhao KL, Ma JB, Liu G, Wu KL, Shi XH and Jiang GL: Three-dimensional conformal radiation therapy for esophageal squamous cell carcinoma: is elective nodal irradiation necessary? Int J Radiat Oncol Biol Phys *76*: 446-451, 2010.

11 Gerber N, Ilson DH, Wu AJ, Janjigian YY, Kelsen DP, Zheng J, Zhang Z, Bains MS, Rizk N, Rusch VW and Goodman KA: Outcomes of induction chemotherapy followed by chemo-radiation using intensity-modulated radiation therapy for esophageal adenocarcinoma. Dis Esophagus *27*: 235-241, 2014.

12 Terasawa T, Dvorak T, Ip S, Raman G, Lau J and Trikalinos TA: Systematic review: Charged-particle radiation therapy for cancer. Ann Intern Med *151*: 556-565, 2009.

13 Oshiro Y and Sakurai H: The use of proton-beam therapy in the treatment of non-small cell lung cancer. Expert Rev Med Devices *10*: 239-245, 2013.

14 Mizumoto M, Sugahara S, Nakayama H, Hashii H, Nakahara A, Terashima H, Okumura T, Tsuboi K, Tokuuye K and Sakurai H: Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer. Strahlenther Onkol *186*: 482-488, 2010.

15 Lin SH, Komaki R, Liao Z, Wei C, Myles B, Guo X, Palmer M, Mohan R, Swisher SG, Hofstetter WL, Ajani JA and Cox JD: Proton beam therapy and concurrent chemotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys *83*: e345-351, 2012.

16 Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, Okawara G, Rosenthal SA and Kelsen DP: 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 *20*: 1167-1174, 2002.

17 Nishimura Y, Hiraoka M, Koike R, Nakamatsu K, Itasaka S, Kawamura M, Negoro Y, Araki N, Ishikawa H, Fujii T and Mitsuhashi N: Long-term follow-up of a randomized Phase II study of cisplatin/5-FU concurrent chemoradiotherapy for esophageal cancer (KROSG0101/JROSG021). Jpn J Clin Oncol *42*: 807-812, 2012.

18 Ishikawa H, Nonaka T, Sakurai H, Tamaki Y, Kitamoto Y, Ebara T, Shioya M, Noda SE, Shirai K, Suzuki Y, Takahashi T and Nakano T: 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 *76*: 452-459, 2010.

19 Okonogi N, Hashimoto T, Ishida M, Ohno T, Terunuma T, Okumura T, Sakae T and Sakurai H: Designed-seamless irradiation technique for extended whole mediastinal proton-beam irradiation for esophageal cancer. Radiat Oncol *7*: 173, 2012.

20 Sobin LH, Gospodarowicz MK, Wittekind C: TNM classification of malignant tumors. 7th ed. Oxford, Wiley-Blackwell, pp. 66-72, 2010.

21 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v4.0 2010. Avaiable at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. [Last accessed Nov 3, 2014]

22 Kaplan E and Meier P: Non-parametric estimation from incomplete observation. J Am Stat Assoc *53*: 457-481, 1958.

23 Hironaka S, Ohtsu A, Boku N, Muto M, Nagashima F, Saito H, Yoshida S, Nishimura M, Haruno M, Ishikura S, Ogino T, Yamamoto S and Ochiai A: 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 *57*: 425-433, 2003.

24 Wei X, Liu HH, Tucker SL, Wang S, Mohan R, Cox JD, Komaki R and Liao Z: Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. Int J Radiat Oncol Biol Phys *70*: 707-714, 2008.

25 Shirai K, Tamaki Y, Kitamoto Y, Murata K, Satoh Y, Higuchi K, Nonaka T, Ishikawa H, Katoh H, Takahashi T and Nakano T: Dose-volume histogram parameters and clinical factors associated with pleural effusion after chemoradiotherapy in esophageal cancer patients. Int J Radiat Oncol Biol Phys *80*: 1002-1007, 2011.

Received November 4, 2014
Revised November 12, 2014
Accepted November 17, 2014