The phase I study consisted of escalating doses of weekly administration of DOC combined with continuous 5-FU (250 mg/m^2/day) and radiotherapy (2 Gy per fraction: total 60–66 Gy). Dose-limiting toxicity (DLT) was noted at DOC 10 mg/m^2 (level 2) with Grade 4 esophagitis, and the recommended dose (RD) of DOC was decided to be 7.5 mg/m^2.[12]

In this prospective phase II study, the primary endpoint was antitumor effect and the secondary endpoints were local control rate, time to progression, survival, and safety for inoperable locoregionally advanced esophageal cancer.

METHODS

Patient eligibility

Patients were regarded eligible according to the following criteria: a histologically proven malignant neoplasm of the esophagus; prior chemotherapy was permitted when it was completed more than 4 weeks earlier; no distant metastases except for supraclavicular lymph node metastases; no prior radiotherapy to the sites planned for irradiation in the present study; evaluable or measurable disease; 18–75 years of age; a performance status of 0 or 1 based on the World Health Organization scale; adequate bone marrow function (white blood cell [WBC] count between 3000 and 12 000/mm^3, neutrophil count > 2000/mm^3, platelet count > 100 000/mm^3, hemoglobin > 9.5 g/dL); adequate renal function (creatinine < 1.5 mg/dL); adequate liver function (bilirubin < 1.5 mg/dL, aspartate transaminase [AST] and alanine transaminase [ALT] within 1.5 times the upper limit of normal for the institution, alkaline phosphatase within 2.5 times the upper limit of normal). Written informed consent was obtained from all participants.

Patients were excluded if any of the following exclusion criteria were fulfilled: symptomatic infectious disease, pulmonary fibrosis, interstitial pneumonia, malignant hypertension, congestive heart failure, severe coronary artery disease, severe liver cirrhosis, uncontrolled diabetes mellitus, bleeding tendency, preexisting symptomatic peripheral neuropathy or edema of greater than grade 2 severity according to the common toxicity criteria of the National Cancer Institute (NCI-CTC) version 2.0, active double cancer, pleural effusion or pericardial effusion with symptom, history of allergic reaction to polysorbate 80, pregnancy, or breast-feeding.

The Simon two-stage minimax design was applied to determine sample size.[15] It was calculated on the basis of an expected response rate of 80% and a threshold response rate of 60%, with alpha error of 0.05 and beta error of 0.20, and 33 eligible patients were needed. Considering some deviant cases, the planned accrual number was set to 35 patients.

Evaluation

Pretreatment examination included a complete blood count, a biochemical screening profile, a urinalysis, and an electrocardiogram. Radiological examination included a chest radiography, barium esophagography, and computed tomography (CT) of the neck, thorax, and abdomen. Patients underwent endoscopy with biopsy of the primary tumor. Additional examinations were performed if there was a clinical indication. The clinical tumor staging was defined according to the 7th TNM classification of the International Union Against Cancer (UICC).[16]

All patients were examined weekly for symptoms and performance status, as well as a weekly blood test during the study period. At the end of CRT and 4 weeks after completion of CRT, upper endoscopy, barium esophagography, and CT were performed to assess the response. Toxicity was graded according to NCI-CTC version 2.0. An adverse event at more than 90 days after the beginning of CRT was defined as late toxicity.

Treatment plan

The treatment schedule is outlined in Figure 1. All treatments were performed in the inpatient setting. DOC 7.5 mg/m^2 was diluted in 100 mL of physiological saline and infused over 1 hour on days 1, 8, 22, and 29. DOC was also administrated on day 43 if possible. Premedication with dexamethasone (8 mg intravenously) was administered 30 minutes prior to infusion of DOC. 5-FU 250 mg/m^2/day was continuously infused for 24 hours on days 1–5, 8–12, 15–19, 22–26, 29–33, 36–40, and 43–45 as shown in Figure 1.

Treatment schedule of radiotherapy was also shown in Figure 1 with a total dose of 66 Gy delivered in 2 Gy per fraction. Radiotherapy was performed using 18-MV X-rays. For treatment planning, a three-dimensional CT simulator was employed. The target volume (TV) of radiotherapy was determined according to the distribution of lymph node metastasis due to tumor location.[17] TV for cervical and upper thoracic cancers included the supraclavicular, cervical, and upper mediastinal lymph nodes. TV for middle thoracic or lower thoracic cancers included the cervical, mediastinal, and upper perigastric lymph nodes. If the cervical nodes were positive by radiological imaging, the supraclavicular lymph nodes were also included. The primary tumor was included with a craniocaudal margin of 2–3 cm. After 40 Gy of irradiation, TV was shrunk to encircle the primary tumor with a margin of 2–3 cm and swollen nodes with a surrounding 0.5–1 cm margin.

Administration of DOC was suspended for 7 days when the white blood cell count decreased to <2000/mm^3, the neutrophil count decreased to <1000/mm^3, or the platelet count decreased to <100 000/mm^3.

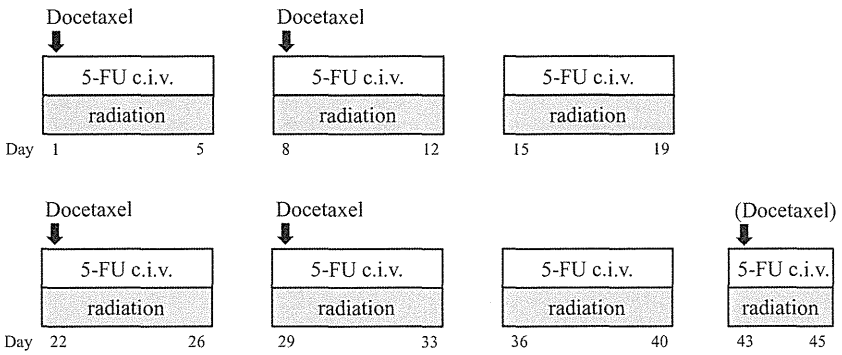

Fig. 1 Treatment schedule of docetaxel (DOC) and 5-fluorouracil (5-FU) with concurrent radiotherapy. DOC 7.5 mg/m^2 was administered on days 1, 8, 22, 29, and 43. DOC was also administrated on day 43 if possible. 5-FU 250 mg/m^2/day was administered by continuous infusion for 24 hours. Fractionated radiotherapy was performed with a total dose of 66 Gy delivered in 2 Gy per fraction. 5-FU, 5-fluorouracil; c.i.v., continuous intravenous infusion.

Administration of DOC and 5-FU was suspended for 7 days when serum bilirubin levels were >1.7 mg/dL, AST and ALT were >1.7 times the upper limit of normal, alkaline phosphatase was within 2.8 times the upper limit of normal, or creatinine was >1.7 mg/dL. CRT was suspended until the resolution of toxicity to Grade 1 or less except for esophagitis. CRT was cancelled when the therapy was delayed more than 2 weeks.

The study protocol was approved by the Institutional Review Board of Hiroshima University Hospital. The protocol was discontinued at any time the patient expressed the desire to discontinue it.

Assessment of response

The responses to CRT of the primary tumor and metastatic lymph nodes were assessed independently. Complete response (CR) was defined as the abolition of all signs of cancer. Partial response (PR) was defined as over 50% reduction in the sum of the products of the orthogonal diameters of target lesions. Progressive disease (PD) was defined as >25% increase in the sum of the products of the orthogonal diameters of target lesions or the occurrence of novel lesions. Stable disease (SD) was defined when CR, PR, or PD was not applicable. The evaluation of CR, PR, and SD was confirmed when the effect was maintained for at least 4 weeks. Treatment effect of the primary tumor was assessed by modified criteria of the Japanese Society for Esophageal Diseases.[18] Primary tumors were deemed CR when all visible tumors, including ulcerations, disappeared for a minimum of 4 weeks, and there was histologically cancer-negative status in the biopsy specimens. PR was defined as reduction in area of the primary tumor by at least 50% on esophagography. PD was defined as >25% increase in the tumor area.

Statistics

OS was calculated from the starting date of the CRT to the date of death or the last follow up. OS was calculated according to the Kaplan–Meier method and compared using the log-rank test. A P value < 0.05 was considered significant. Data analysis was performed using SPSS software (version 20.0).

RESULTS

Patients' characteristics

Patients were recruited from July 1, 2005 to February 29, 2008. It was planned to recruit 35 patients for this trial, but the trial was closed due to difficulties in patient recruitment. Eleven thoracic esophageal cancer patients and five cervical esophageal cancer patients were enrolled in this study. The patients' characteristics are shown in Table 1. There were 12 men and 4 women and the median age was 64 years. Patients' performance status was evaluated as 0 in 14

Table 1 Patients' background characteristics

	N (%)
Gender	
Male	12 (75)
Female	4 (25)
Age (range [median])	44–74 [64]
Performance status	
0	14 (87)
1	2 (13)
Location of primary tumor	
Cervical	5 (31)
Upper thoracic	6 (38)
Middle thoracic	5 (31)
Lower thoracic	0 (0)
Histology	
Squamous cell carcinoma	16 (100)
Others	0 (0)
UICC clinical TNM stage	
T3N1M0 cStage IIIA	2 (13)
T4bN0M0 cStage IIIC	2 (13)
T4bN1M0 cStage IIIC	7 (43)
T3N0M1 cStage IV	1 (6)
T4bN1M1 cStage IV	4 (25)
Target lesion	
Primary tumor	16 (100)
Lymph node	14 (88)

ISDE The International Society for Diseases of the Esophagus

Table 2 Summary of adverse effects

Item	Grade 1	2	3	4
Hematologic toxicities				
Leukopenia	1	0	0	0
Anemia	0	0	0	0
Thrombocytopenia	0	0	0	0
Nonhematologic toxicities				
Esophagitis	7	2	3	2
Fever	3	2	0	0
Anorexia	0	0	1	0
Dermatitis	1	1	0	0
Fistula	1	0	1	0
Liver dysfunction	0	0	0	0
Nausea	0	0	0	0
Pneumonitis	0	1	0	0
Mucositis	0	0	0	0
Pain	0	1	0	0
Fatigue	1	0	0	0

patients and 1 in 2 patients. All patients had squamous cell carcinoma on pathological examination. Two patients had clinical stage (cStage) IIIA, 9 cStage IIIC, and 5 cStage IV esophageal cancers. Target lesions were primary tumors in all patients and metastatic lymph nodes in 14 patients. Clinical decisions for CRT were made due to unresectable adjacent structure invasion (cT4b) in nine patients (56.3%) and refusal of surgery in seven (43.8%) including five patients with cervical esophageal cancer. There was no patient who received prior chemotherapy and/or radiotherapy, while two patients with airway invasion were performed prophylactic esophageal bypass surgery before CRT without resection of primary or metastatic lesions to minimize a symptom when an esophago-airway fistula was complicated during or after CRT.[19]

Toxicity and treatment compliance

The adverse events are summarized in Table 2. Hematologic toxicity was mild; only one patient had Grade 1 leukopenia. As for nonhematologic adverse effects, five patients (31%) had Grade 3 or 4 esophagitis. They all needed to be managed by total parenteral nutrition, and symptoms of esophagitis resolved in all patients after completion of CRT. Other nonhematologic Grade 3 or higher adverse effects were anorexia in one patient (6%) and esophago-bronchial fistula in one patient (6%). For the esophago-bronchial fistula, both esophageal and bronchial stents were inserted 3 weeks after completion of CRT. Although one patient (6%) developed Grade 2 pneumonitis at the end of CRT, it was cured by stopping chemotherapy and steroid administration. Grade 2 or less fever elevation was observed in five patients (31%). No treatment-related deaths occurred.

Table 3 Summary of antitumor effects

Primary lesion		Metastatic LNs		Total	
CR	7 (44%)	CR	5 (36%)	CR	5 (31%)
PR	8 (50%)	PR	8 (57%)	PR	10 (63%)
SD	1 (6%)	SD	1 (7%)	SD	0 (0%)
PD	0 (0%)	PD	0 (0%)	PD	1 (6%)
RR	94%	RR	93%	RR	94%

CR, complete response; LN, lymph node; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

All patients completed the prescribed dose of radiotherapy. Twelve patients (75.0%) completed the planned cycles of DOC (more than 4) and 5-FU (more than 6 weeks), while one or two cycles of chemotherapy had to be reduced in the others mostly by esophagitis. Chemotherapy dose reduction was not performed.

Treatment response

The response status by CRT is summarized in Table 3. The evaluable lesions were 16 primary lesions and 14 metastatic lymph nodes. For the primary lesions, seven patients (44%) had a CR, eight (50%) had a PR, and one had SD (6%). For the metastatic lymph nodes, five (36%) had a CR, eight (57%) had a PR, and one had SD (7%). The response rate in total was 94%, with five CR (31%) and 10 PR (63%). PD was observed in only one patient with enlargement of lymph nodes (new lesions) within the TV of radiotherapy. Accordingly, the local control rate was 94%.

Survival

The median follow-up period was 71 months. Currently, four patients are alive without relapse, and eight patients have died of disease. The patterns of failure in the eight patients were as follows: four had lymph node recurrence; two had a relapse of primary tumor; one had multiple organ metastases; and one had recurrent disease affecting lymph nodes and lungs. No patient underwent salvage surgery for residual or recurrent disease. Two patients died of metachronous cancer at 46 and 64 months, and two patients died of intercurrent illnesses without evidence of relapse at 29 and 41 months. The median time to progression was 20 months. The 3-year and 5-year OS were 44% and 31%, respectively (Fig. 2). According to the main location of the tumor, no significant difference was seen in OS between cervical and thoracic esophageal cancers ($P = 0.927$).

Late toxicity

During follow up, one patient had Grade 2 radiation-induced pneumonitis 2 months after completion of

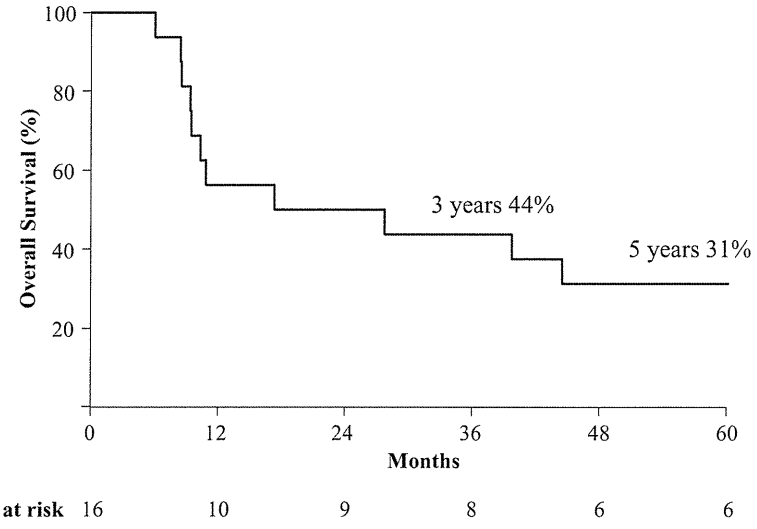

Fig. 2 Overall survival of all patients. The overall 3-year and 5-year survival rates are 43% and 31%, respectively.

CRT, which was cured by steroid therapy. No late toxicity-related deaths occurred.

DISCUSSION

For esophageal cancer, some CRT regimens including DOC have been reported, but a combination of DOC and 5-FU with radiation is rare, and only a few neoadjuvant studies have been reported.[13,14] Our previous phase I study was the first report of definitive CRT using the doublet of DOC and 5-FU.[12] The combination of DOC and 5-FU was based on the synergistic effect between them, which was explained by biochemical modulation,[9] and high antitumor activity was shown in a phase I/II study for advanced gastric cancer.[10,11]

CDDP and 5-FU have been the standard chemotherapeutic agents in combination with radiotherapy for unresectable locally advanced thoracic esophageal cancer. With two to four cycles of CDDP/5-FU and 45–60 Gy of radiation, a response rate (CR+PR) of 78–87% and 5-year survival of 7–26% have been reported in unresectable thoracic esophageal cancer patients with mainly T4 disease.[20–24] Major toxicities were leukopenia, anemia, thrombocytopenia, esophagitis, and fistula formation. On the other hand, the reports of definitive CRT for locally advanced cervical esophageal cancer are limited. Median survival time (MST) of 16–18 months and 3-year survival of 29–32% have been reported for CRT using CDDP and 5-FU.[25,26]

As for CRT regimens containing DOC, Font *et al.* reported weekly DOC in combination with 66 Gy of radiation for unresectable thoracic esophageal cancer, and MST, 1-year OS, and 3-year OS were 5 months, 22%, and 0%, respectively. Grade 3 or higher major adverse effects were esophagitis, leukocytopenia, and anemia.[27] Shim *et al.* used weekly DOC and CDDP with 54 Gy of radiation for unresectable esophageal cancer. Median time to progression and MST were 13.5 and 26.9 months, respectively, and 3-year survival was 27.8%. Grade 3 or higher major adverse effects were esophagitis, leukocytopenia, febrile neutropenia, and esophagotracheal fistula.[28] In addition, Higuchi *et al.* used DOC, CDDP, and 5-FU with 50.4–66 Gy of irradiation for unresectable thoracic esophageal cancer.[29,30] In their latest report, MST was 23 months, and Grade 3 or higher major toxicities comprised leukopenia (71%), neutropenia (57%), anemia (17%), febrile neutropenia (38%), anorexia (31%), and esophagitis (29%).[30]

Although the differences in study populations such as clinical stage or histology make it difficult to compare previous results with those of the current study, the present result with 3-year survival of 43.8% in unresectable advanced cancer of the cervical and thoracic esophagus compares favorably with previous studies. Hematologic toxicity was very mild, but esophagitis (Grade 3 or higher) occurred in 31.3% of cases. In addition to DOC, incorporation of 5-FU, which is also associated with mucosal damage, might be responsible for the high frequency of esophagitis.

The present study is limited by the number of patients included due to difficulties in patient recruitment. A large-scale study would be needed to truly evaluate the clinical outcome of this novel CRT regimen, but the number of patients with unresectable esophageal cancer receiving definitive CRT is limited, and a large trial is not expected. Another issue complicating comparisons of outcomes with other studies is the mixed population with cervical and thoracic esophageal cancers. However, there was no difference in survival between cervical and thoracic esophageal cancer patients in this study.

In addition, we had performed prophylactic esophageal bypass surgery in two patients with airway invasion before definitive CRT to minimize an adverse effect when an esophago-airway fistula was complicated. This strategy is unique and might affect the clinical results of CRT. As primary tumor and metastatic lesions were not resected in esophageal bypass surgery, an effect on clinical outcome of following CRT was considered to be minimal.[19]

In our phase I study, DLT was Grade 4 esophagitis and RD of DOC was determined to be 7.5 mg/m^2.[12] This dose is considerably lower than in other trials using DOC as part of CRT. We consider that DOC acts as a radiosensitizer and biochemical modulator of 5-FU, rather than as an anticancer agent in our regimen. A modest dose of DOC would preserve bone marrow function, and it resulted in a very low rate of hematologic toxicities. In addition, esophageal cancer patients sometimes have decreases in renal function, and CDDP is not applicable for them. This CRT protocol might be considered as an alternative to CDDP and 5-FU in patients with inadequate bone marrow or renal dysfunction.

In conclusion, a novel CRT using DOC and 5-FU with concurrent radiotherapy could be performed safely, and it appears to have a favorable antitumor effect for locally advanced ESCC.

References

1 Muto M, Minashi K, Yano T *et al.* Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010; 28: 1566–72.
2 Bains M S, Stojadinovic A, Minsky B *et al.* A phase II trial of preoperative combined-modality therapy for localized esophageal carcinoma: initial results. J Thorac Cardiovasc Surg 2002; 124: 270–7.
3 Dubecz A, Gall I, Solymosi N *et al.* Temporal trends in long-term survival and cure rates in esophageal cancer: a SEER database analysis. J Thorac Oncol 2012; 7: 443–7.
4 Kato H, Nakajima M. Treatments for esophageal cancer: a review. Gen Thorac Cardiovasc Surg 2013; 61: 330–5.
5 Ajani J A, Barthel J S, Bentrem D J *et al.* Esophageal and esophagogastric junction cancers. J Natl Compr Canc Netw 2011; 9: 830–87.
6 Minsky B D, Pajak T F, Ginsberg R J *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: 1167–74.
7 Kleinberg L, Gibson M K, Forastiere A A. Chemoradiotherapy for localized esophageal cancer: regimen selection and molecular mechanisms of radiosensitization. Nat Clin Pract Oncol 2007; 4: 282–94.
8 Yamasaki M, Miyata H, Miyazaki Y *et al.* Perioperative therapy for esophageal cancer. Gen Thorac Cardiovasc Surg 2014; 62: 531–40.
9 Wada Y, Yoshida K, Suzuki T *et al.* Synergistic effects of docetaxel and S-1 by modulating the expression of metabolic enzymes of 5-fluorouracil in human gastric cancer cell lines. Int J Cancer 2006; 119: 783–91.
10 Yoshida K, Hirabayashi N, Takiyama W *et al.* Phase I study of combination therapy with S-1 and docetaxel (TXT) for advanced or recurrent gastric cancer. Anticancer Res 2004; 24: 1843–51.
11 Yoshida K, Ninomiya M, Takakura N *et al.* Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 2006; 12: 3402–7.
12 Hihara J, Yoshida K, Hamai Y, Emi M, Yamaguchi Y, Wadasaki K. Phase I study of docetaxel (TXT) and 5-fluorouracil (5-FU) with concurrent radiotherapy in patients with advanced esophageal cancer. Anticancer Res 2007; 27: 2597–603.
13 Font A, Garcia-Alfonso P, Arellano A *et al.* Preoperative combined multimodal therapy with docetaxel plus 5-fluorouracil and concurrent hyperfractionated radiotherapy for locally advanced esophageal cancer. Proc Am Soc Clin Oncol 2002; 21: abstr 2326.
14 Wood M D, Zaki B I, Gordon S R *et al.* Trimodality therapy for stage II-III carcinoma of the esophagus: a dose-ranging study of concurrent capecitabine, docetaxel, and thoracic radiotherapy. J Thorac Oncol 2013; 8: 487–94.
15 Simon R. Design and conduct of clinical trials. In: DeVita V, Hellman S, Rosenberg S, (eds). Cancer-Principles and Practice of Oncology. Philadelphia, PA: Lippincott, 1993; 418–40.
16 Sobin L H, Gospodarowicz M, Wittekind C, (eds). UICC. Oesophagus including oesophagogastric junction. In: TNM Classification of Malignant Tumors, 7th edn. New York: Wiley, 2009; 66–72.
17 Akutsu Y, Matsubara H. Lymph node dissection for esophageal cancer. Gen Thorac Cardiovasc Surg 2013; 61: 397–401.
18 Japanese Society for Esophageal Diseases, (ed.). Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus, 9th edn. Tokyo: Kanehara Shuppan, 1999.
19 Hihara J, Hamai Y, Emi M *et al.* Esophageal bypass operation prior to definitive chemoradiotherapy in advanced esophageal cancer with tracheobronchial invasion. Ann Thorac Surg 2014; 97: 290–5.
20 Ohtsu A, Boku N, Muro K *et al.* Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 1999; 17: 2915–21.
21 Crosby T D, Brewster A E, Borley A *et al.* Definitive chemoradiation in patients with inoperable oesophageal carcinoma. Br J Cancer 2004; 90: 70–5.
22 Seto Y, Chin K, Gomi K *et al.* Treatment of thoracic esophageal carcinoma invading adjacent structures. Cancer Sci 2007; 98: 937–42.
23 Nishimura Y, Suzuki M, Nakamatsu K, Kanamori S, Yagyu Y, Shigeoka H. Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol 2002; 53: 134–9.
24 Itoh Y, Fuwa N, Matsumoto A, Asano A, Morita K. Outcomes of radiotherapy for inoperable locally advanced (T4) esophageal cancer-retrospective analysis. Radiat Med 2001; 19: 231–5.
25 Uno T, Isobe K, Kawakami H *et al.* Concurrent chemoradiation for patients with squamous cell carcinoma of the cervical esophagus. Dis Esophagus 2007; 20: 12–8.
26 Gkika E, Gauler T, Eberhardt W, Stahl M, Stuschke M, Pottgen C. Long-term results of definitive radiochemotherapy in locally advanced cancers of the cervical esophagus. Dis Esophagus 2014; 27: 678–84.
27 Font A, Arellano A, Fernandez-Llamazares J *et al.* Weekly docetaxel with concomitant radiotherapy in patients with inoperable oesophageal cancer. Clin Transl Oncol 2007; 9: 177–82.
28 Shim H J, Kim D E, Hwang J E *et al.* A phase II study of concurrent chemoradiotherapy with weekly docetaxel and cisplatin in advanced oesophageal cancer. Cancer Chemother Pharmacol 2012; 70: 683–90.
29 Higuchi K, Koizumi W, Tanabe S *et al.* A phase I trial of definitive chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) for advanced esophageal carcinoma: Kitasato digestive disease & oncology group trial (KDOG 0501). Radiother Oncol 2008; 87: 398–404.
30 Higuchi K, Komori S, Tanabe S *et al.* Definitive chemoradiation therapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) in advanced esophageal cancer: a phase 2 trial (KDOG 0501-P2). Int J Radiat Oncol Biol Phys 2014; 89: 872–9.

Int J Clin Oncol (2015) 20:897–904
DOI 10.1007/s10147-015-0819-2

ORIGINAL ARTICLE

Long-term results of definitive concurrent chemoradiotherapy for patients with esophageal submucosal cancer (T1bN0M0)

Yuji Murakami[1] · Ippei Takahashi[2] · Ikuno Nishibuchi[3] · Yoshiko Doi[1] · Tomoyuki Okabe[1] · Masahiro Kenjo[1] · Tomoki Kimura[1] · Yasushi Nagata[1]

Received: 18 November 2014 / Accepted: 12 March 2015 / Published online: 24 March 2015

Abstract
Background The long-term outcomes of definitive concurrent chemoradiotherapy for patients with esophageal submucosal cancer without regional and distant metastasis were retrospectively analyzed.
Methods Patients with histologically confirmed esophageal submucosal cancers without regional and distant metastasis who received definitive concurrent chemoradiotherapy from 2001 to 2011 were included. Radiation therapy of a median total dose of 60 Gy/30 fractions (range, 54–66 Gy) with elective nodal irradiation of 40 Gy was combined concurrently with 5-furuorouracil-based chemotherapy.
Results Thirty-six patients (33 men and 3 women) aged from 45 to 80 years (median, 67 years) were assessed. All patients had squamous cell carcinoma. With a median follow-up time of 61 months, the 5-year overall survival, disease-free survival, and locoregional failure-free survival rates were 86 % [95 % confidence interval (CI), 74–99 %], 59 % (95 % CI, 42–77 %), and 90 % (95 % CI, 79–100 %), respectively. Late toxicities of grade 3 pleural effusion in 2 patients, grade 4 pericardial effusion in 1 patient, and grade 5 pneumonitis in 1 patient were observed. Metachronous esophageal cancer was observed in 8 patients (22 %). Among them, 6 patients with mucosal legions were salvaged by endoscopic resection.
Conclusion Our long-term results of concurrent chemoradiotherapy (CCRT) for patients with esophageal submucosal cancer showed acceptable toxicities and favorable locoregional control and survivals while maintaining organ preservation.

Keywords Esophageal cancer · Submucosal cancer · Chemoradiotherapy

✉ Yuji Murakami
yujimura@hiroshima-u.ac.jp

Ippei Takahashi
ippei@hiroshima-u.ac.jp

Ikuno Nishibuchi
ikuno@hiroshima-u.ac.jp

Yoshiko Doi
yoshikod@hiroshima-u.ac.jp

Tomoyuki Okabe
t-okabe1115@hiroshima-u.ac.jp

Masahiro Kenjo
kenjom@hiroshima-u.ac.jp

Tomoki Kimura
tkimura@hiroshima-u.ac.jp

Yasushi Nagata
nagat@hiroshima-u.ac.jp

[1] Department of Radiation Oncology, Hiroshima University Graduate School of Biomedical Sciences, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

[2] Department of Radiation Oncology, Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, 1-9-6 Senda-machi, Naka-ku, Hiroshima 730-8619, Japan

[3] Department of Radiation Oncology, Hiroshima Prefectural Hospital, Ujinakanda Minami-ku, Hiroshima 734-8530, Japan

Introduction

Mucosal and submucosal cancers constitute two forms of superficial esophageal cancer. Most mucosal cancers are potentially curable by endoscopic resection alone. However, submucosal cancers have a high risk of lymph node (LN) metastasis, so treatments for primary tumors and occult regional LN metastasis, such as surgery or definitive radiotherapy, are needed.

Intraluminal brachytherapy (IBT) combined with external-beam radiotherapy (EBRT) was used as the radiotherapeutic method of choice for superficial esophageal cancer in Japan in the 1990s. The efficacy of this radiotherapeutic method has been reported by several authors [1–5], but its superiority to EBRT alone is controversial. On the other hand, recently, the effectiveness of concurrent chemoradiotherapy (CCRT) for early-stage esophageal cancer has been studied, and promising results have been reported [6, 7]. The survival rates from these studies were equivalent to those of surgery.

At our institution, IBT combined with EBRT was commonly used for treating superficial esophageal cancer in the 1990s. We previously reported long-term treatment results in patients with superficial esophageal cancer who received IBT combined with EBRT [8]. Those results showed a clear difference in clinical outcomes between mucosal and submucosal cancers, and we concluded that more intensive treatment should be considered for submucosal cancers. Thus, since 2001, we have performed CCRT to improve treatment results for patients with submucosal cancer. In the present study, we retrospectively analyzed the long-term treatment outcomes after a median follow-up period of more than 60 months in patients who received definitive CCRT for esophageal submucosal cancer.

Materials and methods

Eligibility criteria

In total, 36 patients were included in this study. Patients were considered eligible for this retrospective analysis on the basis of the following criteria: histologically confirmed esophageal cancer; submucosal cancer diagnosed by endoscopic ultrasonography; no regional or distant metastasis diagnosed by cervical, thoracic, and abdominal computed tomography (CT) scan; age $\leq$80 years; World Health Organization scale performance status of 0–2; radiotherapy with a dose $\geq$50 Gy performed with radical intent; administration of concurrent chemotherapy; and treatment performed from 2001 to 2011. A threshold of 5-mm short-axis diameter was used for determination of positive LN metastasis. Patients who had undergone previous treatment for malignancies in the past were included, excluding those who had undergone thoracic radiotherapy. Written and informed consent for CCRT was obtained from each patient before treatment. This retrospective analysis was approved by the institutional review board.

Treatment

Radiotherapy was performed by using a megavoltage photon beam (6–18 MV). The gross tumor volume (GTV) was defined as the total volume of the primary tumor. Before performing a planning CT, metallic clips were placed endoscopically to indicate the craniocaudal extent of the lesion. The clinical target volume for the primary lesion (CTV-p) was defined as a GTV with a 1.5- to 2-cm margin in the longitudinal direction. The clinical target volumes for subclinical regional LNs (CTV-s) according to primary tumor sites were cervical, supraclavicular, and upper mediastinal LNs for cervical tumors; supraclavicular, upper mediastinal, and middle mediastinal LNs for upper thoracic tumors; and upper to lower mediastinal and perigastric LNs for middle thoracic or lower thoracic tumors. The planning target volumes for primary tumor (PTV-p) and for subclinical regional LN area (PTV-s) were defined as clinical target volumes with a 0.8- to 1.5-cm margin. Three-dimensional radiotherapy treatment planning was performed for all patients. Multi-portal beams were used for reducing the dose to the heart, if possible. The planned dose prescription of EBRT was 60–66 Gy at 2.0 Gy per fraction for PTV-p and 40 Gy for PTV-s. The spinal cord never received >40 Gy in either plan.

Administration of chemotherapy was performed after pretreatment evaluation of blood cell count, liver function, renal function, and cardiac function. Selection of chemotherapeutic regimens and dosages was determined according to the protocol at that time, the patients' renal function, cardiac function, age, and general condition.

Analysis

Treatment response was evaluated at 10–260 days (median, 42 days) after completion of CCRT. Complete response (CR) was defined as the disappearance of malignant cells in the primary site on endoscopic biopsy. Follow-up examinations were performed at 4-month intervals for the first year typically and at 6-month intervals thereafter. Follow-up examinations included physical examinations; complete blood cell count; blood chemistry profiles; endoscopy; and CT of the neck, chest, and abdomen. Overall survival (OS) was defined as the time period from initiation of CCRT to death from any cause. Disease-free survival (DFS) was defined as the time from initiation of CCRT to progression of disease, death for any reason, diagnosis of new double

cancer, progression of known double cancer, or diagnosis of esophageal metachronous cancer. Locoregional failure-free survival (LFS) was defined as the time period from initiation of CCRT to locoregional failure of esophageal cancer. Esophageal metachronous cancer was defined as the secondary cancer detected in different site from the primary lesion after CCRT by endoscopy and was not included in local failure in this analysis. The Kaplan–Meier method was used to calculate survival rates. The log-rank test was used to compare survival curves in univariate analysis. Multivariate analysis was performed using Cox's proportional hazards model. A p value <0.05 was considered to indicate statistical significance. The Common Terminology Criteria for Adverse Events (version 3.0) were used to assess toxicities. Acute toxicity was defined as the events that occurred within 3 months from initiation of CCRT and late toxicity as the events that occurred after 3 month from initiation of CCRT.

Table 1 Patient and tumor characteristics

Characteristics	
Gender	
Male	33 (92 %)
Female	3 (8 %)
Age (years)	
Range	45–80
Median	67
Performance status	
0–1	32 (89 %)
2	4 (11 %)
Operability	
Inoperable	17 (43 %)
Operable	19 (57 %)
CVD history	
Yes	4 (11 %)
No	32 (89 %)
Double cancer history	
Yes	18 (50 %)
No	18 (50 %)
Histology	
Squamous cell	36 (100 %)
Tumor location	
Cervical	5 (14 %)
Upper thoracic	3 (8 %)
Middle thoracic	20 (56 %)
Lower thoracic	8 (22 %)
Tumor length (cm)	
Range	1–8
Median	4

CVD cardiovascular disease

Results

Patient and tumor characteristics

The patient and tumor characteristics are summarized in Table 1. Seventeen patients were judged medically inoperable, and 19 operative patients declined surgery. Previous double cancers were observed in 18 patients with 21 malignancies. These malignancies were distributed as follows: gastric cancer in 6 patients, head and neck cancer in 5 patients, colorectal cancer in 4 patients, hepatocellular carcinoma in 3 patients, esophageal metachronous cancer in 2 patients, and renal cell carcinoma in 1 patient. All previous double cancers were treated before CCRT, and there was no active lesion at the beginning of CCRT. Patients were judged medically inoperable according to the following factors: main factors were concurrent illnesses including heart disease in 3, pulmonary disease in 2, and liver disease in 1, advanced age of 76 years or older in 7, and history of surgery for double cancer, hepatocellular carcinoma in 2 and gastric cancer in 2.

Treatment

The median total dose of irradiation was 60 Gy in 30 fractions (range, 54–66 Gy). Elective nodal irradiation was performed in 30 patients, and another 6 patients received irradiation only for PTV-p in consideration of their general condition, past history, and other factors. Two patients who needed reduction of chemotherapeutic intensity because of toxicity received a late-course accelerated hyper-fractionated schedule, 40 Gy at 2.0 Gy per fraction for PTV-s followed by 21–24 Gy at 1.5 Gy/fraction (twice a day) for PTV-p.

Selection of chemotherapeutic regimens was determined according to the protocol at that time including fluorouracil (5-FU)/nedaplatin ($n = 16$), 5-FU/docetaxel ($n = 3$), and 5-FU/cisplatin ($n = 15$). For the combination of 5-FU and cisplatin/nedaplatin, 700 mg/m^2/day of 5-FU on days 1–4 and days 29–32 and 70 mg/m^2/day of cisplatin/nedaplatin on days 1 and 29 were administered. For the combination of 5-FU and docetaxel, 250 mg/m^2/day of 5-FU on the first 5 days of 4 consecutive weeks and 7.5 mg/m^2/day of docetaxel on days 1, 8, and 22 were administered. Dosages of chemotherapeutic agents were reduced by 30–50 % according to the patients' renal function, cardiac function, age, and general condition, when necessary. Two patients who were judged unsuitable for use of protocol regimens were administered 5FU/carboplatin (in 1) and oral TS1 (in 1).

Survival and failure pattern

The clinical data were updated in March 2014. The median follow-up times were 61 months (range, 5–127 months) for all patients and 67 months (range, 18–127 months) for survivors.

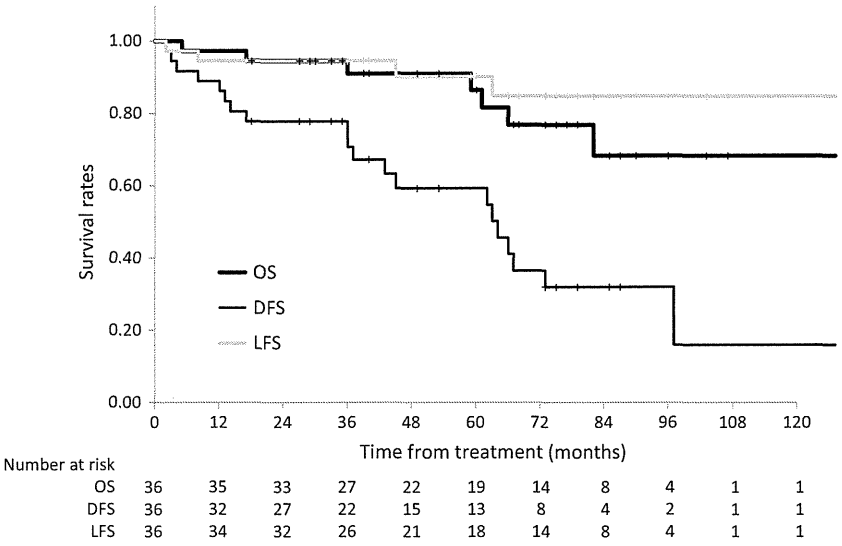

Fig. 1 The 5-year OS, DFS, and LFS rates were 86 % (95 % CI, 74–99 %), 59 % (95 % CI, 42–77 %), and 90 % (95 % CI, 79–100 %), respectively. *OS* overall survival, *DFS* disease-free survival, *LFS* locoregional recurrence-free survival for all patients

Table 2 Prognostic factors

Factors	5-year OS (%)	*p* value	
		UVA	MVA
Age (years)			
<67	92	0.20	0.52
≥67	81		
Performance status			
0–1	89	0.46	–
2	67		
Gender			
Male	85	0.37	–
Female	100		
Operability			
Yes	95	0.13	0.12
No	87		
Double cancer history			
Yes	86	0.56	–
No	87		
Tumor location			
Ce-Ut	100	0.09	0.09
Mt-Lt	81		
Tumor length			
<4 cm	84	0.53	–
≥4 cm	89		

OS overall survival, *Ce* cervical esophagus, *Ut* upper thoracic esophagus, *Mt* middle thoracic esophagus, *Lt* lower thoracic esophagus, *UVA* univariate analysis, *MVA* multivariate analysis

The 5-year OS, DFS, and LFS rates were 86 % (95 % CI, 74–99 %), 59 % (95 % CI, 42–77 %), and 90 % (95 % CI, 79–100 %), respectively (Fig. 1). The prognostic factors are summarized in Table 2. The univariate and multivariate analyses did not show any significant factor associated with OS.

Of the 36 patients, 35 (97 %) achieved CR. Failures were observed in 3 patients (8 %): local failure in 1 (3 %), distant failure in 1 (3 %), and regional and distant failure in 1 (3 %). In the patient with local failure, a mucosal lesion was detected at the primary site 8 months after CCRT and was salvaged by endoscopic resection. The patient who suffered concurrent distant LN metastases in the supraclavicular fossa and abdominal paraaortic region (both sites were outside the RT field) at 45 months after CCRT also underwent salvage surgery and postoperative CCRT. The patient who suffered regional and distant metastasis 63 months after CCRT received best supportive care and was alive with disease at the last follow-up of 67 months after the initial treatment.

Metachronous esophageal cancer

Metachronous esophageal cancer was observed in eight patients (22 %). The median duration from the end of treatment to diagnosis of the metachronous tumor was 52.5 months (3–97 months). The tumor depth level was mucosal in six patients, submucosal in one patient, and muscularis propria in one patient. All six patients with mucosal lesions were salvaged by endoscopic resection. The patient who had a submucosal lesion concurrently suffered leukemia and received the best supportive care because of low performance status and older age. The patient who had a muscularis propria lesion in the cervical esophagus outside the irradiated field was salvaged by performing definitive CCRT.

Toxicity

The toxicities are summarized in Table 3. Grade 3 acute toxicities of esophagitis, leucopenia, and thrombocytopenia occurred in 5 (14 %) patients, 11 (31 %) patients,

Table 3 Toxicities

	No. of patients (%)			
	Grade 2	Grade 3	Grade 4	Grade 5
Acute				
Esophagitis	15 (42)	5 (14)	0 (0)	0 (0)
Leucopenia	14 (39)	11 (31)	0 (0)	0 (0)
Thrombocytopenia	3 (8)	1 (3)	0 (0)	0 (0)
Renal function	3 (8)	0 (0)	0 (0)	0 (0)
Liver function	1 (3)	0 (0)	0 (0)	0 (0)
Late				
Esophageal stenosis	4 (11)	0 (0)	0 (0)	0 (0)
Pleural effusion	3 (8)	2 (6)	0 (0)	0 (0)
Pericardial effusion	0 (0)	0 (0)	1 (3)	0 (0)
Pneumonitis	0 (0)	0 (0)	0 (0)	1 (3)

and 1 (3 %) patient, respectively. Grade 4 or higher acute toxicities were not observed. Grade 3 or higher late toxicities of pleural effusion, pericardial effusion, and radiation pneumonitis were observed in 2 (6 %) patients, 1 (3 %) patient, and 1 (3 %) patient, respectively. Among them, pericardial effusion was grade 4, and pneumonitis was grade 5. One patient with grade 3 pleural effusion had a history of myocardial infarction before receiving CCRT and did not select surgery because of older age and cardiac dysfunction. In this patient, a local remnant tumor was detected by endoscopic biopsy at 3 months after CCRT, and he received salvage surgery on request. However, no cancer was detected in the surgical specimen. After surgery, this patient suffered symptomatic pleural effusion. The other patient with grade 3 pleural effusion received CCRT for cervical esophageal cancer and suffered from pleural effusion resulting from hypothyroidism; he received thyroid hormone and pleurodesis therapy at 37 months after CCRT and was still alive at 87 months. The patient with grade 4 pericardial effusion was inoperable because of low pulmonary function caused by severe emphysema at the diagnosis of esophageal cancer; he received pericardial fenestration to treat the pericardial effusion at 31 months after CCRT and was still alive at 68 months. Although the patient who suffered pneumonitis at 3 months after CCRT received steroid pulse therapy, he died of pneumonitis (grade 5).

There was one patient who possibly developed a treatment-related second malignancy. As already mentioned, the patient who had a metachronous submucosal lesion concurrently suffered leukemia at 67 months from CCRT and received the best supportive care because of low performance status and older age. There was no other second malignancy in the irradiated volume.

Discussion

In this study, we retrospectively analyzed the long-term treatment outcomes in patients who received definitive CCRT for esophageal submucosal cancer without regional and distant metastasis. With a median follow-up of more than 60 months, the 5-year OS and LFS rates were 86 % (95 % CI, 74–99 %) and 90 % (95 % CI, 79–100 %), respectively. We suggest that CCRT for esophageal submucosal cancer can achieve a high rate of locoregional control and provide favorable OS while preserving organs.

With advances in endoscopic techniques, there has been an increase in the number of early-stage esophageal cancers being treated. According to a report by the Registry of Esophageal Carcinomas in Japan, stage I cancers accounted for 27 % of all esophageal cancers in 2004 [9]. Stage I cancers are divided into mucosal and submucosal cancers, and pathological analyses have shown significant differences in the rates of LN metastasis between them (0–6 % vs. 38–53 %, respectively) [10–15]. Endoscopic resection is now widely used as the standard treatment for mucosal cancer. Recently, endoscopic submucosal dissection (ESD) has been developed and increasingly performed as an alternative technique to conventional endoscopic mucosal resection (EMR). ESD achieved a higher rate of complete en bloc resection and lower recurrence rates than those of EMR, irrespective of tumor size or shape [16]. Thus, most mucosal cancers are potentially curable by endoscopic resection alone, and no additional treatment is needed. On the other hand, for submucosal cancer with a greater risk of LN metastasis, treatments for local esophageal tumors and occult regional LN metastasis are needed. Moreover, once LN metastasis is developed macroscopically, the treatment results become remarkably worse [9]. The standard treatment for patients with submucosal disease is

esophagectomy with extended lymphadenectomy. Several reports have shown that the 5-year OS rates of esophagectomy were approximately 64–74 % with acceptable morbidity [12, 16, 17]. However, organ and functional impairments of varying severity are inevitable for patients who undergo esophagectomy. Therefore, patients with concurrent illness or of older age often receive radical RT.

IBT combined with EBRT is an optional RT method for treatment of esophageal submucosal cancer in Japan. Although its efficacy has been reported by several authors [1–5], the study group of the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) reported no advantage when a combination of IBT and EBRT was compared with EBRT alone [19]. Moreover, according to the Japanese Patterns of Care Study of RT for esophageal cancer, the performance rate of IBT in the treatment of esophageal cancer has decreased [20]. In our previous report of long-term results of this RT method [8], the 5-year locoregional control and OS rates for mucosal cancer were 75 % and 84 %, respectively, and those for submucosal cancer were 49 % and 31 %, respectively. We concluded that more intensive treatment should be considered for submucosal cancer.

CCRT has become the standard nonsurgical treatment for locally advanced esophageal cancer because randomized controlled trials have demonstrated the efficacy of CCRT [21–23]. Recently, the efficacy of CCRT for treating early-stage esophageal cancer has been studied. Yamada et al. [6] reported that the 5-year OS rate of CCRT for stage I esophageal cancer was 66.4 %. Kato et al. [7] reported the outcome of a phase II trial of CCRT in patients with stage I esophageal cancer that was conducted by the Japan Clinical Oncology Group (JCOG9708). In their study, the 4-year OS rate was reported to be 80.5 %. In our present study, the 5-year OS was 86 % (95 % CI, 74–99 %), and the LFS was 90 % (95 % CI, 79–100 %). These results were much better than our previous results for IBT combined with EBRT in patients with submucosal cancer (5-year OS, 31 %; 5-year locoregional control rate, 49 %) [8]. We believe that CCRT is able to achieve a high locoregional control rate and provide favorable OS for patients with submucosal cancer. Moreover, the survival rates in this study were comparable to those of surgery while preserving organs. For the combination of CCRT and IBT boost, the Radiation Therapy Oncology Group Study (RTOG 9207) has reported its association with a high incidence of esophageal fistula and absence of clear benefits of IBT boost in terms of tumor response, local control, or patient survival rates [24]. The standard chemotherapeutic regimen in CCRT is a combination of 5-FU and cisplatin. However, patients who receive CCRT are sometimes judged unsuitable for this regimen for reasons of comorbidities, poor organ function, older age, and so on. We mainly used 5-FU/cisplatin and 5-FU/nedaplatin per protocol during the period of this study, but we did not compare between these protocols because of the small number of patients.

Metachronous esophageal cancer is an important issue in patients who have received organ preservation treatment for esophageal cancer. The occurrence rates of metachronous cancer after endoscopic resection have been reported to be 13–14.6 % [25, 26]. In the present study, the metachronous esophageal cancer rate was 22 %, and six of these cancers were detected as mucosal lesions and successfully salvaged by endoscopic resection. We consider that detection of metachronous cancers as superficial lesions by using close endoscopic observation is very important.

RT induces effects on various portions of the heart, such as the pericardium, myocardium, and coronary artery [27]. Serious cardiopulmonary toxicities have been reported when using CCRT to treat esophageal cancer [28]. In our study, grade 3 pleural effusion was observed in two patients (5 %), and grade 4 pericardial effusion was observed in one patient (3 %). Two of these three patients had a history of cardiopulmonary disease at the beginning of CCRT and were, therefore, inoperable. We think that the occurrence rate of cardiopulmonary toxicities in this study was acceptable; however, it is important to decrease the irradiation dose to the heart as much as possible. When using three-dimensional conformal RT, plans using multiportal beams should be followed to try and lower the irradiation dose to the heart to a safe level. Regarding modern RT techniques, image-guided radiation therapy (IGRT), breath-control techniques such as breath-hold or respiratory-gated RT, and intensity-modulated radiotherapy (IMRT) can potentially reduce cardiopulmonary toxicities. Lin et al. [29] reported the efficacy of IMRT for esophageal cancer patients. They observed a significantly greater cumulative incidence of cardiac-related deaths in the 3D-CRT group than in the IMRT group. Currently, we are investigating the efficacy of IMRT with IGRT and breath-control techniques for thoracic esophageal cancer. Moreover, in recent years, the number of proton therapy centers has been increasing worldwide. Proton beams can localize the radiation dose more precisely than X-ray beams. In the treatment of esophageal cancer, proton therapy should have a significant role in achieving high locoregional control and reducing RT-induced toxicity. Further investigations to establish the efficacies of these new high-precision RTs are needed.

The optimal RT field in CCRT for submucosal cancer is controversial. Because submucosal cancer has a high risk of LN metastasis, we have adopted prophylactic nodal irradiation. LN recurrence in the RT field was observed in only one patient (3 %) in this study. We think that the use of prophylactic nodal irradiation contributed to this high regional control rate. However, a large irradiation field can possibly

lead to severe cardiopulmonary toxicities. Further investigation for the optimal RT field for treatment of esophageal submucosal cancer is needed.

Our study was limited by its retrospective nature, the small numbers of patients, and the variety of chemotherapeutic regimens. However, as there are few reports on long-term results of CCRT for esophageal submucosal cancer patients at a single institution, we think that the results of this study are of great significance. Our results suggest that CCRT for submucosal cancer can contribute to favorable local control and long-term survival while preserving organs.

Conclusion

We reported the outcomes of CCRT for patients with esophageal submucosal cancer without metastasis at a single institution. Our long-term results showed acceptable toxicities, favorable locoregional control, and survival rates associated with CCRT while preserving organs.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Hareyama M, Nishio M, Kagami Y et al (1992) Intracavitary brachytherapy combined with external-beam irradiation for squamous cell carcinoma of the thoracic esophagus. Int J Radiat Oncol Biol Phys 24:235–240
2. Okawa T, Dokiya T, Nishio M et al (1999) Multi-institutional randomized trial of external radiotherapy with or without intraluminal brachytherapy for esophageal cancer in Japan. Int J Radiat Oncol Biol Phys 45:623–628
3. Yorozu A, Dokiya T, Oki Y (1999) High-dose-rate brachytherapy boost following concurrent chemoradiotherapy for esophageal carcinoma. Int J Radiat Oncol Biol Phys 45:271–275
4. Maingon P, Hombres A, Truc G et al (2000) High dose rate brachytherapy for superficial cancer of the esophagus. Int J Radiat Oncol Biol Phys 46:71–76
5. Ishikawa H, Nonaka T, Sakurai H et al (2010) 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
6. Yamada K, Murakami M, Okamoto Y et al (2006) Treatment results of chemoradiotherapy for clinical stage I (T1N0M0) esophageal cancer. Int J Radiat Oncol Biol Phys 64:1106–1111
7. Kato H, Sato A, Fukuda H et al (2009) A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group study (JCOG9708). Jpn J Clin Oncol 39:638–643
8. Murakami Y, Nagata Y, Nishibuchi I et al (2012) Long-term outcomes of intraluminal brachytherapy in combination with external beam radiotherapy for superficial esophageal cancer. Int J Clin Oncol 17:263–271
9. Ozawa S, Tachimori Y, Baba H et al (2012) Comprehensive Registry of Esophageal Cancer in Japan, 2004. Esophagus 9:75–98
10. Nishimaki T, Tanaka O, Suzuki T et al (1993) Tumor spread in superficial esophageal cancer: histopathologic basis for rational surgical treatment. World J Surg 17:766–772
11. Makuuchi H, Shimada H, Mizutani K et al (1997) Clinical pathological analysis of surgically resected superficial esophageal carcinoma to determine criteria for deciding on treatment strategy. Diagn Ther Endosc 3:211–220
12. Tachibana M, Yoshimura H, Kinugasa S et al (1997) Clinicopathological features of superficial squamous cell carcinoma of the esophagus. Am J Surg 174:49–53
13. Kodama M, Kakegawa T (1998) Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. Surgery (St. Louis) 123:432–439
14. Endo M, Yoshino K, Kawano T et al (2000) Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus 13:125–129
15. Bollschweiler E, Baldus SE, Schröder W et al (2006) High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy 38:149–156
16. Takahashi H, Arimura Y, Hosokawa M et al (2010) Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus (with video). Gastrointest Endosc 72:255–264
17. Altorki NK, Lee PC, Liss Y, Meherally D et al (2008) Multifocal neoplasia and nodal metastases in T1 esophageal carcinoma: implications for endoscopic treatment. Ann Surg 247:434–439
18. Tachibana T, Matono S, Nagano T et al (2012) Esophagectomy with extended lymphadenectomy for submucosal esophageal cancer: long-term outcomes and prognostic factors. Ann Surg Oncol 19:750–756
19. Nemoto K, Yamada S, Nishio M et al (2006) 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 26:1507–1512
20. Murakami Y, Kenjo M, Uno T et al (2007) Results of the 1999–2001 Japanese Patterns of Care Study for patients receiving definitive radiation therapy without surgery for esophageal cancer. Jpn J Clin Oncol 37:493–500
21. Herskovic A, Martz K, Al-Sarraf M et al (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 326:1593–1598
22. Al-Sarraf M, Martz K, Herskovic A et al (1997) Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 15:277–284
23. Cooper JS, Guo MD, Herskovic A et al (1999) 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
24. Gasper L, Winter K, Kocha W et al (2000) A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207). Cancer (Phila) 88:988–995
25. Shimizu Y, Tukagoshi H, Fujita M et al (2001) Metachronous squamous cell carcinoma of the esophagus arising after endoscopic mucosal resection. Gastrointest Endosc 54:190–194
26. Urabe Y, Hiyama T, Tanaka S et al (2009) Metachronous multiple esophageal squamous cell carcinomas and Lugol-voiding lesions after endoscopic mucosal resection. Endoscopy 41:304–309

27. Adams MJ, Hardenbergh PH, Constine LS et al (2003) Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol 45:55–75
28. Ishikura S, Nihei K, Ohtsu A et al (2003) Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:2697–2702
29. Lin SH, Wang L, Myles B et al (2012) Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys 84:1078–1085

Journal of Radiation Research, Vol. 56, No. 5, 2015, pp. 830–834
doi: 10.1093/jrr/rrv034
Advance Access Publication: 20 June 2015

Final results from a multicenter prospective study (JROSG 05-5) on postoperative radiotherapy for patients with ductal carcinoma *in situ* with an involved surgical margin or close margin widths of 1 mm or less

Naoto Shikama[1]*, Kenji Sekiguchi[2], Naoki Nakamura[3], Hiroshi Sekine[4], Yuko Nakayama[5], Kazufumi Imanaka[6], Takeshi Akiba[7], Masahiko Aoki[8], Yoshiomi Hatayama[8], Etsuyo Ogo[9], Yoshikazu Kagami[10], Miho Kawashima[11] and Kumiko Karasawa[12]

[1]Department of Radiation Oncology, Saitama Medical University, International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama, 350-1298 Japan
[2]Department of Radiation Oncology, St Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo, 104-8560, Japan
[3]Department of Radiation Oncology, National Cancer Center East, 6-5-1 Kashiwanoha, Kashiwa-shi, Chiba, 277-8577, Japan
[4]Department of Radiology, The Jikei University Third Hospital, 4-11-1 Izumihonmachi, Komae-shi, Tokyo, 201-8601, Japan
[5]Department of Radiation Oncology, Kanagawa Cancer Center, 2-3-2 Nakao, Asahi-ku, Yokohama, Kanagawa, 241-8515, Japan
[6]Department of Radiology, Nishikobe Medical Center, 5-7-1 Kojidai, Nishi-ku, Kobe, Shogo, 651-2273, Japan
[7]Department of Radiation Oncology, Tokai University, 143 Shimokasuya, Isehara, Kanagawa, 259-1193, Japan
[8]Department of Radiology, Hirosaki University School of Medicine and Hospital, 53 Honmachi, Hirosaki, Aomori, 036-8563, Japan
[9]Department of Radiation Oncology, Kurume University Hospital, 67 Asahimachi, Kurume-shi, Fukuoka, 830-0011, Japan
[10]Department of Radiation Oncology, Showa University Hospital, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142-8666, Japan
[11]Department of Radiology, Dokkyo Medical University, Koshigaya Hospital, 2-1-50 Mimamikoshigaya, Koshigaya-shi, Saitama, 343-8555, Japan
[12]Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba-shi, Chiba, 263-8555, Japan
*Corresponding author: Department of Radiology Oncology, Saitama Medical University, International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan. Tel: +81-42-984-4111; Fax: +81-42-984-4136; Email: nshikama0525@gmail.com
Received February 24, 2015; Revised April 15, 2015; Accepted May 20, 2015

ABSTRACT

This multicenter prospective study (Japanese Radiation Oncology Study Group: JROSG 05-5) aimed to evaluate the effectiveness of postoperative radiotherapy (PORT) in patients with ductal carcinoma *in situ* (DCIS) with an involved surgical margin or close margin widths of ≤1 mm or less. PORT consisted of whole-breast irradiation (50 Gy in 25 fractions) followed by boost irradiation (10 Gy in 5 fractions). Eligibility criteria were as follows: (i) DCIS without an invasive carcinoma component, (ii) age between 20 and 80 years old, (iii) involved margin or close margin widths of ≤1 mm, (iv) refusal of re-resection, (v) performance status of 0–2, and (vi) written informed consent. The primary endpoint was ipsilateral breast tumor recurrence (IBTR), and secondary endpoints were overall survival (OS), relapse-free survival (RFS), recurrence patterns, and adverse events. A total of 37 patients from 12 institutions were enrolled from January 2007 to May 2009. The median follow-up time was 62 months (range, 28–85 months). The median pathological tumor size was 2.5 cm (range, 0.3–8.5 cm). Of the 37 patients, 21 had involved margins, and 16 had close margins. The 5-year IBTR, OS and RFS rates were 6% (95% confidence interval [CI]: 2–21), 97% (95% CI: 83–99) and 91% (95% CI: 77–97), respectively. Two patients developed local recurrence at the original site after 39 and 58 months. No severe adverse events were found. Our study suggests that this PORT regimen could be a treatment option for patients with DCIS with involved margin or close margin who don't desire re-resection.

KEYWORDS: ductal carcinoma *in situ*, breast cancer, margin width, radiotherapy, breast conservation

INTRODUCTION

Ductal carcinoma *in situ* (DCIS) arising from the breast represents an intraductal epithelial proliferation of malignant cells and is considered to be a non-obligate precursor of invasive cancer [1, 2] Mammography screening programs and high-resolution magnetic resonance imaging have changed the clinical presentation of DCIS [3, 4]. Approximately one-fifth of all screen-detected breast cancers are now DCIS [4, 5]. Several randomized clinical trials have demonstrated that postoperative radiotherapy (PORT) after partial resection decreases the risk of ipsilateral breast tumor recurrence (IBTR) [6–9]. Breast-conserving therapy, including partial resection followed by PORT, has been one of the current standards of care for DCIS [2, 10, 11]. However, these randomized trials have mainly included low-risk patients who underwent partial resection and achieved negative surgical margins. There has been little evidence supporting the use of breast-conserving therapy for patients with high-risk DCIS such as those with a positive surgical margin or a narrow distance between surgical margins and tumor cells.

An involved surgical margin has been thought as one of the adverse prognostic factors for IBTR after breast-conserving therapy [12, 13]. It was reported that patients with surgical margin widths of <1 mm could benefit from PORT; however, an 8-year IBTR rate after partial resection followed by PORT was ~30% [14]. The previous retrospective studies included various PORT regimens such as whole-breast irradiation alone and in combination with boost irradiation. Few prospective studies have evaluated the effectiveness of PORT exclusively for the patients with DCIS with an involved surgical margin or close margin, and a standard PORT regimen hasn't been established yet. This multicenter prospective study (Japanese Radiation Oncology Study Group: JROSG 05-5) aimed to evaluate the effectiveness of PORT in patients with DCIS with an involved surgical margin or close margin widths of ≤1 mm.

MATERIALS AND METHODS

This multicenter prospective study was conducted to evaluate the effectiveness of PORT consisting of tangential whole-breast irradiation (50 Gy in 25 fractions) using photon beams followed by boost irradiation (10 Gy in 5 fractions) of the tumor bed using electron beams for patients with DCIS with an involved surgical margin or close margin widths of ≤1 mm. Patients were eligible for inclusion in the study if they: (i) had DCIS without an invasive carcinoma component, (ii) were between 20 and 80 years of age, (iii) were diagnosed as having an involved margin or close margin widths of ≤1 mm after pathological evaluation using 5-mm thick specimens, (iv) refused re-resection, (v) had a performance status of 0–2, and (vi) provided written informed consent. Exclusion criteria were: (i) bilateral breast cancers, (ii) diffuse calcification on the pre-treatment images, (iii) multiple tumors, (iv) macroscopic residual tumor, (v) axillary lymph node metastases, (vi) past history of chest irradiation, (vii) collagen vascular disease, (viii) pregnancy, (ix) active double cancer, (x) mental disorders, (xi) uncontrolled diabetes, (xii) uncontrolled hypertension, and (xiii) cardiovascular disease.

Surgical resection and pathological evaluation

All patients were treated with breast-conserving surgery. The partial breast resection was performed with the appropriate surgical margin of 1 or 2 cm from the macroscopic tumor extension. Thirty-two patients received the axillary sentinel lymph node biopsy, and five patients did not receive axillary dissention and/or biopsy. The pathological evaluation of resection samples was conducted using 5-mm thick slices. A specimen mammogram was not performed; nor was a central pathological review. An involved surgical margin was defined as tumor cells on the surgical edge, and a close surgical margin was defined as the distance between the tumor cells and surgical edge being ≤1 mm. A number of surgical clips, which were useful guides for the boost irradiation, were located at each edge of the resection cavity. The routine application of surgical clips was not used in all cases.

Radiotherapy

All patients underwent computed tomography (CT) for data acquisition for the radiation treatment planning. CT scanning was performed in the supine position, and no respiratory control was used. Three-dimensional conformal radiotherapy (3D-CRT) treatment-planning software was used for all patients. Whole-breast irradiation was conducted using the tangential field technique with 4- or 6-MV photon beams. Simulation planning was performed to minimize radiation doses to the organs at risk, and to modify homogeneous dose distribution to fit target volumes using a wedge filter. Beam weights, beam angles, and wedge angles were manually optimized. A total dose of 50 Gy in 25 fractions for whole-breast irradiation was defined at the reference point. The reference point was placed in the center of the radiation field or vicinity. The electron beam field size for boost irradiation of the tumor bed was determined according to surgical clips, the surgical cavity, pathological findings and/or the surgical scar. The boost irradiation was mainly planned using the radiation treatment-planning system, and appropriate electron beam energy was selected according to the depth of the tumor bed. The boost irradiation field was decided according to the pre-surgical images, surgical findings, final pathological reports, and/or surgical clips.

Statistical analysis

The primary endpoint was the IBTR, and secondary endpoints were overall survival (OS), relapse-free survival (RFS), recurrence patterns, and adverse events. IBTR was defined as any recurrence including invasive carcinoma type and DCIS type in the ipsilateral irradiated breast. OS time was defined as the time from registration to death due to any causes. RFS time was defined as the time from registration to treatment failure (such as recurrence in the ipsilateral breast, axillary node, or at a distant site) or death due to any causes. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 3.0. The 5-year estimated IBTR rate was projected as 20%, and the lower threshold of the 5-year IBTR rate was set at 45%. It was estimated that a sample of 36 patients was required, with a one-sided alpha of 0.05 and a statistical power of 90%. Kaplan–Meier methods were used to estimate IBTR, OS and RFS. All enrolled patients were included in the primary endpoint assessment. The last follow-up date was 27 October 2014. Patients were followed up every 6 months for 5 years, then once per year by clinical examination with or without annually mammography. Statistical analyses were performed with JMP software version 10 (SAS Institute, Cary, NC).

RESULTS

The protocol concept was accepted in October 2005, and the full protocol was accepted in August 2006 by the Japanese Radiation Oncology Study Group (JROSG) Executive Committee (Institutional Review Board of Saitama Medical University: No. 06-077-1). A total of 37 patients from 12 institutions were enrolled from January 2007 to May 2009. Two patients were enrolled simultaneously at the end of the enrollment, and total of 37 patients were enrolled in this study. The median follow-up time was 62 months (range, 28–85 months). The median age was 52 years (range, 33–78 years), and the median pathological tumor size was 2.5 cm (range, 0.3–8.5 cm). Patient characteristics are shown in Table 1. Sixteen patients had close margins, and 21 had involved margins. All patients received PORT per-protocol, and no patient interrupted PORT. Fourteen (38%) patients received adjuvant hormonal therapy.

The 5-year IBTR, OS and RFS rates were 6% (95% confidence interval [CI]: 2–21), 97% (95% CI: 83–99) and 91% (95% CI: 77–97), respectively (Figs 1, 2). Two patients developed IBTR after PORT. One patient with an involved margin, who was 55 years old, developed IBTR at the original site after 39 months. The maximum diameter of the pathological tumor extension at the initial treatment was 8 cm. That patient underwent a salvage mastectomy, and the pathological diagnosis of IBTR was DCIS without an invasive carcinoma component. The other patient with IBTR was 45 years old, and she had a margin width <1 mm. She developed IBTR at the original site after 58 months. The maximum diameter of the pathological tumor extension at the initial treatment was 2.1 cm. She received salvage partial resection and axillary resection, and the pathological diagnosis of IBTR was DCIS. Although these two patients with IBTR had a positive estrogen receptor status, they didn't receive adjuvant hormonal therapy. They live without evidence of any more recurrence as at the time of the last follow-up. One patient died of colon cancer 28 months after registration, without experiencing breast cancer recurrence. No recurrence events were identified in regional lymph nodes or distant sites, and no severe adverse events (Grade 3 or 4) were reported as at the last follow-up.

Table 1. Patient characteristics

	n (%)	
Age (years)		Median 52 (33–78)
30–39	3 (8)	
40–49	11 (30)	
50–59	14 (38)	
60–70	6 (16)	
>70	3 (8)	
Pathological diameter (cm)		Median 2.5 (0.3–8.5)
<1.9	15 (41)	
2–3.9	6 (16)	
4–5.9	7 (19)	
>6	9 (24)	
Estrogen receptor		
Positive	26 (70)	
Negative	7 (19)	
Unknown	4 (11)	
Progesterone receptor		
Positive	22 (59)	
Negative	11 (30)	
Unknown	4 (11)	
Margin status		
Close margin	16 (43)	
Involved margin	21 (57)	
Axillary surgery		
Sentinel biopsy	32 (86)	
None	5 (14)	

DISCUSSION

The current standard of care for patients with DCIS has consisted of mastectomy and breast-conserving therapy [1, 10]. A randomized controlled trial comparing mastectomy with breast-conserving therapy has not been performed, but current data demonstrate similar long-term survival times with either approach. Mastectomy has been mainly applied for patients with diffuse infiltrative disease, large tumors, or involved surgical margins after repeated resection [4]. Breast-conserving surgery followed by PORT is an acceptable treatment for a small and unifocal area of DCIS, and there is not enough evidence to omit PORT routinely. Several randomized control trials indicated that the administration of PORT after breast-conserving surgery reduced the IBTR rate by ~60% [11, 15, 16]. The main goals of DCIS management are to reduce the risk of progression to invasive carcinoma, optimize breast cosmesis and prevent local recurrence [2, 17]. DCIS has a variable biological behavior, and there remains room for discussion regarding whether all patients with DCIS should be treated intensively. The impact of higher doses of radiotherapy in DCIS has been less clear, and Rakouitch *et al.* analyzed the data for 1895 patients from the population-based Ontario Cancer Registry and reported that the administration of boost irradiation after whole-breast irradiation was not associated with a lower IBTR [17]. On the other hand, the Rare Cancer Network conducted a multicenter retrospective study to evaluate the role of the administration of boost irradiation in patients 45 years or younger, and reported that compared with whole-breast irradiation alone, the administration of boost irradiation had a significant advantage (hazard ratio 0.45) [18]. There hasn't been enough evidence to confirm the role of administration of boost irradiation after whole-breast irradiation for DCIS, and the BONBIS trial in France has been now in ongoing.

Silverstein *et al.* developed a prognosis predictive model that included tumor size, margin width, and pathological classification (the Van Nuys Prognostic Index; VNPI) [12]. The patients with high

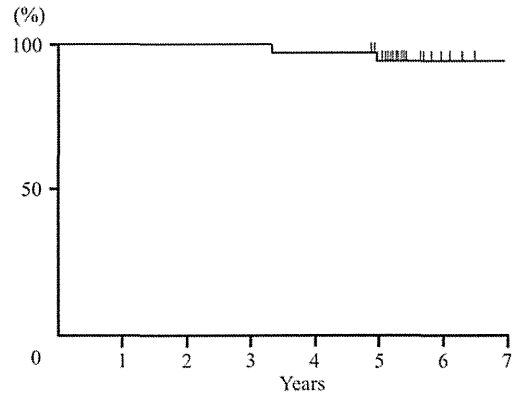

Fig. 1. The ipsilateral breast tumor recurrence-free rate of all patients.

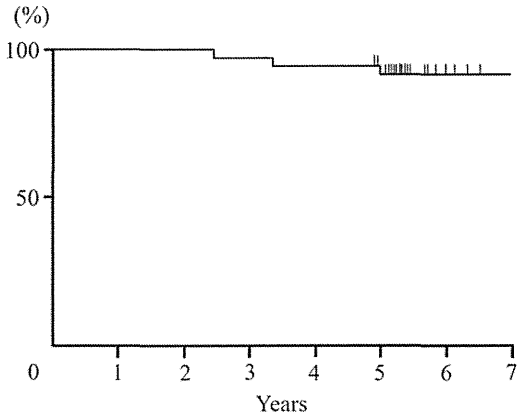

Fig. 2. The relapse-free survival rate of all patients.

VNPI scores showed high rates of IBTR after breast-conserving surgery followed by PORT. Investigators in the Memorial Sloan-Kettering Cancer Center developed a nomogram for predicting IBTR after breast-conserving surgery for DCIS using the data for 1868 consecutive patients [19]. Predictive factors consist of age, margin status, adjuvant endocrine therapy, PORT, and treatment period. The margin status was categorized as involved/close margin (≤2 mm), or negative margin. Dunne *et al.* conducted a systematic review and reported that a margin threshold of 2 mm seemed to be as good as a larger margin when breast-conserving surgery for DCIS was combined with PORT [20]. Wang *et al.* conducted a meta-analysis of the margin threshold for 7564 patients with DCIS [21]. This study demonstrated that the 10-mm threshold had the lowest odds ratio [OR] (patients with positive margins being the reference group) of IBTR (OR = 0.17) compared with the OR of IBTR for a 2-mm threshold (OR = 0.38), and that for a 5-mm threshold (OR = 0.55). On the other hand, Sahoo *et al.* analyzed the 103 consecutive patients with DCIS, and reported that involved margin status had a strong association with IBTR compared with close or negative margin status [22]. They reported that the 5-year IBTR was 7% in patients with a negative or close surgical margin as compared with 31% in patients with an involved margin.

Silverstein *et al.* reported that patients with tumor margin widths <1 mm could benefit from PORT, and an 8-year IBTR probability after breast-conserving surgery combined with PORT was 30% in comparison with 58% after breast-conserving surgery alone [14]. Approximately 80% of recurrence after breast-conserving surgery followed by PORT occurred within the first three years. Cutuli *et al.* conducted the multicenter retrospective analyses using 705 patients with DCIS treated between 1985 and 1995 in nine French regional cancer centers [23]. They reported that patients with negative, involved or uncertain margins had a 7-year crude IBTR rate of 9.7%, 25.2% and 12.2%, respectively. IBTR occurred within 5 years in 63.6% and 81.3% of patients receiving breast-conserving therapy combined with PORT versus breast-conserving surgery alone. They emphasized that the IBTR risk was higher in patients ≤40 years of age among those with incomplete excision. These retrospective studies included various radiotherapy regimens consisting of whole-breast irradiation (40–50 Gy) combined with/without boost irradiation (10–20 Gy) to the tumor bed via brachytherapy or electron beam therapy. We conducted the prospective study for high-risk DCIS using whole-breast irradiation (50 Gy in 25 fractions) followed by boost irradiation (10 Gy in 5 fractions) via electron beam therapy, and decided that the primary endpoint was the 5-year IBTR rate. Our prospective study showed that the 5-year IBTR rate was only 6% after PORT, and it was indicated that this PORT regimen was a promising schedule for patients with a single DCIS lesion with an involved surgical margin or close margin widths of ≤1 mm.

Tamoxifen may be considered as an adjuvant endocrine treatment in patients with estrogen receptor–positive disease [1, 13]. Although the relative benefit of tamoxifen is ~30–50%, the absolute reduction is only ~2–4%, which may not justify the clinical benefits of endocrine treatment. There was no differential impact of Tamoxifen for patients with or without adverse pathological characteristics. The role of systemic treatments of DCIS needs further investigation [10, 13]. A number of ongoing studies are evaluating the effects of aromatase inhibitor and human-epithelial receptor-2 antibody. Further research focused on molecular and biological profiling is likely to enable personalized treatment strategies in order to minimize treatment harm [1, 10]. We did not evaluate the role of hormonal therapy because of the small sample size and unplanned subgroup analysis.

The limitations of this study are its small sample size and relatively short follow-up time. Silverstein *et al.* reported that ~80% of recurrence after breast-conserving surgery followed by PORT occurred within the first three years [14], and then we decided the primary endpoint was the 5-year IBTR rate. However, our experience demonstrated that IBTR occurred after 3 years, and 5-year or longer follow-up duration is desirable. In addition, a central pathological review wasn't conducted. Although a central pathological review system was not established at the start of this trial, we determined that the pathological evaluation of resection samples would be conducted using 5-mm thick slices. We believed that this evaluation method provided accurate pathological evaluation of the tumor extension and margin width. Furthermore, symptomatic DCIS is associated with higher rates of IBTR compared with screen-detected disease [4, 10]. We did not collect the data concerning detection methods from the case report forms. We did not decide the post-surgical images including

magnetic resonance images and mammograms, and did not collect the pathological data for focally surgical margin–positive versus diffuse surgical margin–positive.

CONCLUSIONS

This prospective study suggests that this radiotherapy schedule (whole-breast irradiation followed by boost irradiation) could be a treatment option for patients with DCIS with an involved margin or a close margin who don't desire repeated surgery. A large-scale randomized trial is required, however, to make any definitive conclusions.

ACKNOWLEDGEMENTS

This study was presented in part at the 55th Annual Meeting of the American Society for Radiology Oncology, Atlanta, GA, in October 2013. The authors are grateful to Mrs K. Saito for technical assistance. This study was supported by a Grant-in-Aid for Cancer Research (26-A-1) and a Grant-in-Aid for Cancer Research (H26–Cancer Control Policy–General–014) from the Ministry of Health, Labor and Welfare of Japan.

FUNDING

Funding to pay the Open Access publication charges for this article was provided by the Japanese Radiation Oncology Study Group.

REFERENCES

1. Choy C, Mokbel K. Towards optimal treatment of ductal carcinoma *in situ*. *World J Clin Oncol* 2014;5:194–6.
2. Punglia RS, Schnitt SJ, Weeks JC. Treatment of ductal carcinoma *in situ* after excision: would a prophylactic paradigm be more appropriate? *J Natl Cancer Inst* 2013;105:1527–33.
3. Ernster VL, Barclay J, Kerlikowske K, et al. Incidence of and treatment for ductal carcinoma *in situ* of the breast. *JAMA* 1996;275:913–8.
4. Lambert K, Patani N, Mokbel K. Ductal carcinoma *in situ*: recent advances and future prospects. *Int J Surg Oncol* 2012;2012: 347385.
5. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11–30.
6. Fisher B, Costantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med* 1993;328:1581–6.
7. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 1998;16:441–52.
8. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma *in situ* of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet* 2003;362:95–102.
9. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma *in situ*: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet* 2000;355:528–33.
10. Patani N, Khaled Y, Al Reefy S, et al. Ductal carcinoma *in situ*: an update for clinical practice. *Surg Oncol* 2011;20:e23–31.
11. Warnberg F, Garmo H, Emdin S, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma *in situ*: 20 years follow-up in the randomized SweDCIS trial. *J Clin Oncol* 2014;32:3613–8.
12. Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma *in situ* of the breast. *Cancer* 1996;77: 2267–74.
13. Kane RL, Virnig BA, Shamliyan T, et al. The impact of surgery, radiation, and systemic treatment on outcomes in patients with ductal carcinoma *in situ*. *J Natl Cancer Inst Monogr* 2010;2010: 130–3.
14. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma *in situ* of the breast. *N Engl J Med* 1999;340:1455–61.
15. Kuerer HM, Albarracin CT, Yang WT, et al. Ductal carcinoma *in situ*: state of the science and roadmap to advance the field. *J Clin Oncol* 2009;27:279–88.
16. Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma *in situ*: an update of the National Surgical Adjuvant Breast and Bowel Project experience. *Semin Oncol* 2001;28:400–18.
17. Rakovitch E, Narod SA, Nofech-Moses S, et al. Impact of boost radiation in the treatment of ductal carcinoma *in situ*: a population-based analysis. *Int J Radiat Oncol Biol Phys* 2013;86:491–7.
18. Omlin A, Amichetti M, Azria D, et al. Boost radiotherapy in young women with ductal carcinoma *in situ*: a multicentre, retrospective study of the Rare Cancer Network. *Lancet Oncol* 2006;7:652–6.
19. Rudloff U, Jacks LM, Goldberg JI, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma *in situ*. *J Clin Oncol* 2010;28:3762–9.
20. Dunne C, Burke JP, Morrow M, et al. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma *in situ*. *J Clin Oncol* 2009;27:1615–20.
21. Wang SY, Chu H, Shamliyan T, et al. Network meta-analysis of margin threshold for women with ductal carcinoma *in situ*. *J Natl Cancer Inst* 2012;104:507–16.
22. Sahoo S, Recant WM, Jaskowiak N, et al. Defining negative margins in DCIS patients treated with breast conservation therapy: the University of Chicago experience. *Breast J* 2005;11:242–7.
23. Cutuli B, Cohen-Solal-le Nir C, de Lafontan B, et al. Breast-conserving therapy for ductal carcinoma *in situ* of the breast: the French Cancer Centers' experience. *Int J Radiat Oncol Biol Phys* 2002;53:868–79.

Journal of Radiation Research, Vol. 56, No. 3, 2015, pp. 561–567
doi: 10.1093/jrr/rru130
Advance Access Publication: 16 February 2015

Survival outcomes after stereotactic body radiotherapy for 79 Japanese patients with hepatocellular carcinoma

Hideomi Yamashita[1]*, Hiroshi Onishi[2], Naoya Murakami[3], Yasuo Matsumoto[4], Yukinori Matsuo[5], Takuma Nomiya[6] and Keiichi Nakagawa[1], Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG)

[1]Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan
[2]Department of Radiology, Yamanashi University
[3]Department of Radiology, National Cancer Center Hospital
[4]Department of Radiology, Niigata University School of Medicine
[5]Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[6]Department of Radiology, Yamagata University Hospital
*Corresponding author. Department of Radiology, University of Tokyo Hospital, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan. Tel: +81-3-5800-8667; Fax: +81-3-5800-8935; Email: yamachan07291973@yahoo.co.jp
Received September 13, 2014; Revised November 24, 2014; Accepted December 24, 2014

ABSTRACT

Stereotactic body radiotherapy (SBRT) is a relatively new treatment for liver tumor. Outcomes of SBRT for liver tumors unsuitable for ablation or surgical resection were evaluated.

A total of 79 patients treated with SBRT for primary hepatocellular carcinoma (HCC) between 2004 and 2012 in six Japanese institutions were studied retrospectively. Patients treated with SBRT preceded by trans-arterial chemoembolization were eligible. Their median age was 73 years, 76% were males, and their Child–Pugh scores were Grades A (85%) and B (11%) before SBRT. The median biologically effective dose ($\alpha/\beta = 10$ Gy) was 96.3 Gy.

The median follow-up time was 21.0 months for surviving patients. The 2-year overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival were 53%, 40% and 76%, respectively. Sex and serum PIVKA-II values were significant predictive factors for OS. Hypovascular or hypervascular types of HCC, sex and clinical stage were significant predictive factors for PFS. The 2-year PFS was 66% in Stage I vs 18% in Stages II–III. Multivariate analysis indicated that clinical stage was the only significant predictive factor for PFS. No Grade 3 laboratory toxicities in the acute, sub-acute, and chronic phases were observed.

PFS after SBRT for liver tumor was satisfactory, especially for Stage I HCC, even though these patients were unsuitable for resection and ablation. SBRT is safe and might be an alternative to resection and ablation.

KEYWORDS: hepatocellular carcinoma, stereotactic body radiotherapy, SBRT

INTRODUCTION

In Japan, the infection rate of hepatitis C is high, with many cases of hepatocellular carcinoma (HCC) [1]. According to clinical practice guidelines from Japan, resection, radiofrequency ablation (RFA), and liver transplantation are the curative options available for HCC [2]. Recently, stereotactic body radiotherapy (SBRT) has become a treatment option for patients with liver tumors who are not eligible for surgery, RFA, or liver transplantation [3]. HCC has good radiation sensitivity [4]. However, currently SBRT of the liver is not frequently performed. This is because radiotherapy (RT) for liver tumors has been limited due to the risk of radiation-induced liver disease (RILD) [5]. However, technological advances have made it possible for radiation to be delivered to small liver tumors, while reducing the risk of RILD [6]. Resection, RFA, or transcatheter arterial chemoembolization (TACE) are often performed for HCC in Japan. However, only 10–20% of HCC patients have

resectable disease [7]. A drawback for RFA is that the procedure is difficult to perform in some anatomic areas [8]. Patients who are introduced to SBRT consist only of those with a central lesion of the liver, with direct invasion into the vessels, and/or with an insufficient outcome from TACE. In patients with centrally located HCC with chronic hepatitis or cirrhosis, major resection is often contraindicated due to insufficient residual liver volume [9]. RFA is therefore often contraindicated for HCC in those areas that are located in and near the hepatic portal vein or the central bile duct [10] and abutting the diaphragm [8]. Additionally, the risk of neoplastic seeding along the needle track after RFA has been reported [11].

The purpose of this study was to retrospectively evaluate the outcomes, mainly concerning survival, for patients treated at various dose levels in several Japanese institutions, although the local control rate has been reported elsewhere [12]. Because of the small number of cases of liver SBRT performed in each institution, it was necessary to gather results and data on side effects from many institutions in order to obtain meaningful information.

MATERIALS AND METHODS

Patients

This retrospective study reviewed data extracted from the database of the Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG) for 79 patients with HCC treated at six institutions (27, 19, 14, 9, 5 and 5 cases). The investigation period was from May 2004 to November 2012.

The diagnosis of HCC depended primarily on imaging studies, because pathological confirmation was not feasible in the candidates for SBRT. During follow-up of patients with liver disease, nodules ≥1 cm were diagnosed as HCC based on the typical hallmarks. These included being hypervascular in the arterial phase, with washout in the portal, venous or delayed phases about hypervascular HCC and, on the other hand, less-than-subtle density area in delayed phases and showing enlargement, plethoric change, and/or MRI signal change during long-time follow-up about hypovascular HCC from imaging studies. The imaging techniques included a combination of contrast-enhanced ultrasonography, 4-phase multi-detector computed tomography (CT), dynamic contrast-enhanced magnetic resonance imaging (MRI), and CT during hepatic arteriography and arterio-portography studies. The diagnosis was established according to a review of the imaging studies [13] and clinical practice guidelines [14–15]. The eligibility for SBRT for HCC was a single lesion. The version of staging classification used in this paper was the UICC classification version 7.

Patient and tumor characteristics are shown in Table 1. With regard to Child–Pugh scores before liver SBRT, 84.8% of patients had Grade A, 11.4% had Grade B, and 1.3% had Grade C. Hypovascular HCC was found in 16/79 cases (20%) and hypervascular HCC was found in 55/79 cases (70%). The feature of vascularity for the remaining eight patients was not evaluable in five patients, was unclear in one patient, and was not detectable by CT in two patients. The median alpha-fetoprotein (AFP) (ng/ml) and des-gamma carboxy prothrombin (PIVKA-II) (AU/ml) values before liver SBRT for 73 evaluable patients were 12.7 ng/ml (range, 0.8–8004) and 35 AU/ml (range, 3.1–16 900), respectively. The median indocyanine green retention rate at 15 min (ICG15) before liver SBRT for 25 evaluable patients was 21.2% (range; 3.0–56.2%). Liver SBRT was the first treatment in 26/79 cases (33%) and was also the first treatment for ectopic recurrences of liver SBRT in an additional seven cases.

Table 1. Patient and tumor characteristics of SBRT

Factors	*n*	Rate
All patients	79	100%
Stage		
I	29	37%
II	21	27%
III	7	9%
Recurrence	11	14%
NE	11	14%
Chilid–Pugh before SBRT		
A	67	85%
B	9	11%
C	1	1%
NE	2	3%
Sex		
Female	19	24%
Male	60	76%
Tumor maximum diameter (mm)		
Range	6–70	
Median	27	
Performance status (ECOG)		
0	34	43%
1	39	49%
2	4	5%
3	1	1%
Age (years old)		
Range	38–95	
Median	73	
SRT total dose (Gy)		
Range	40–60	
Median	48	
BED-10 (Gy)		
Range	75–106	
Median	96.3	