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

KENJI NEMOTO[1], SHOGO YAMADA[1], MASAMICHI NISHIO[2], MASAHIKO AOKI[2], RYUJI NAKAMURA[2], YASUO MATSUMOTO[2], RYUTA SASAMOTO[2], YOSHIHIRO SAITOH[2], MAKOTO TAKAYAMA[2], NORIO MITSUHASHI[2], KOHTARO GOMI[2], NAOTO KANESAKA[2], MASAO KOBAYASHI[2], HIROSHI OHNISHI[2], SHIGERU SASAKI[2], HIROYASU TAMAMURA[2], MICHIHIDE MITSUMORI[2], YASUMASA NISHIMURA[2], KAYOKO TSUJINO[2], MITSUHIRO TAKEMOTO[2], NOBUE UCHIDA[2], MICHINORI YAMAMOTO[2], YOSHIYUKI SHIOYAMA[2], KOHICHI HIRAKAWA[2] and SEIJI ONO[2]

[1]Department of Radiation Oncology, Tohoku University School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai 980-8574;
[2]JASTRO Study Group for Radiation Therapy for Superficial Esophageal Cancer, 2-8-16, Yushima, Bunkyoku, Tokyo, 113-0034, Japan

Abstract. *Background: Superficial esophageal cancer (SEC) is defined as esophageal cancer limited to the submucosal layers, including mucosal cancer and submucosal cancer, and is squamous cell carcinoma in most patients. In 2000, the Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group for SEC published a consensus guideline of standard radiotherapy methods. In this study, the interim treatment outcomes of SEC patients, who had received radiation therapy following the standard radiotherapy methods, were investigated. Patients and Methods: From 2000 to 2003, a total of 141 SEC patients were treated in 24 institutions in Japan. Results: The 1-, 2- and 3-year survival rates were 95%, 90% and 90%, respectively, for patients with mucosal cancer and 90%, 81% and 70%, respectively, for patients with submucosal cancer. The overall survival was better in patients who had undergone chemotherapy than in patients who had received radiation therapy alone, though the difference was not statistically significant. The clinical target volume (CTV) did not influence overall survival and intracavitary irradiation did not influence the local control rate in either patients with mucosal or submucosal cancer. Radiation-induced esophageal ulcer was not observed in this series. Conclusion: The standard radiotherapy methods are safe and effective for treating SEC. However, the usefulness of chemotherapy and intracavitary irradiation and the optimal setting of the CTV should be clarified by future randomized trials.*

Correspondence to: Dr. Kenji Nemoto, Department of Radiation Oncology, Tohoku Graduate School of Medicine, 1-1, Seiryo-machi, Aobaku, Sendai 980-8574, Japan. Tel: +81/22/717/7312, Fax: +81/22/717/7316, e-mail: knemoto@rad.med.tohoku.ac.jp

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Superficial esophageal cancer (SEC) is defined as esophageal cancer limited to the submucosal layers, including mucosal cancer and submucosal cancer, and is squamous cell carcinoma in most patients (1). The number of SEC cases has been increasing recently due to advances in endoscopic and dye-scattering techniques and SEC cases now account for 20% of esophageal cancer cases in Japan (1). Approximately 60% of patients diagnosed with SEC are between the ages of 60 and 79 years (1). SEC is asymptomatic in most patients and is frequently found incidentally during endoscopic examination of the upper gastrointestinal tract.

Surgery (2-7), endoscopic mucosal resection (EMR) (6-8) and radiation therapy (9-12) have been used to treat SEC. Lymph node metastasis is very rare in mucosal cancer but is frequently found in cases in which there is infiltration of the submucosa (2, 4, 7). Therefore, the standard management of small mucosal esophageal cancer is generally endoscopic mucosal resection (EMR). For large mucosal cancer and submucosal cancer, definitive radiation therapy or surgery have been the most popular choices of treatment.

In cases of SEC not suitable for EMR, surgery has been the main treatment method with 5-year survival rates ranging from 40 to 80% (2-6). On the other hand, good outcomes

Table I. *Standard treatment methods (arms) according to the JASTRO Study Group for Superficial Esophageal Cancer and number of treated patients.*

Treatment arm	EXRT	HDR	LDR	Mucosal cancer	Submucosal cancer
A1	60-66 Gy			32	–
A2		28-35 Gy/8-10 fractions		1	–
B1	60-70 Gy			–	85
B2	50-60 Gy	8-12 Gy/2-6 fractions		7	7
B3	60 Gy		12 Gy/3 fractions	2	7

EXRT: external radiation therapy (2 Gy/fraction, 5 times a week); HDR: high-dose-rate intracavitary irradiation group (once or twice a week); LDR: low-dose-rate intracavitary irradiation group (once a week).

after radiation therapy for SEC comparable with those of surgery have been reported (9-12) and radiation therapy may become a standard therapy for SEC not suitable for EMR.

However, there has been great variation in the radiotherapy methods used for SEC and standardization was considered to be necessary (12). The Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group for Superficial Esophageal Cancer published a consensus guideline of standard radiotherapy methods (JASTRO guideline (13)) and 24 institutions in Japan have started to use the guideline. In this study, the interim treatment outcomes of SEC patients, who had received radiation therapy following the JASTRO guideline, were investigated to evaluate the effectiveness and safety of the guideline.

Patients and Methods

The JASTRO guideline defines total doses and fractional doses of external radiation therapy (EXRT) and intracavitary radiation therapy (ICRT) and consists of 2 treatment methods (arms) for mucosal cancer and 3 arms for submucosal cancer (13). The contents of each arm and the number of patients treated are listed Table I.

From July 2000 to June 2003, a total of 141 SEC patients were treated following the JASTRO guideline in 24 institutions in Japan. Appropriate treatment methods within the JASTRO guideline were determined in each institution. Endoscopy, endoscopic ultrasonography (EUS) and barium esophagography were performed to determine the depth of invasion. Forty-one patients were diagnosed with mucosal cancer and 100 patients were diagnosed with submucosal cancer. Patients with lymph node metastasis and patients with active cancers other than those of the esophagus were excluded from the analysis. The patient characteristics are listed in Table II and the treatment characteristics are listed in Table III. Chemotherapy with cisplatin (CDDP) and/or 5-Fuorouracil (5-FU) was used in 82 patients. The dose per fraction of ICRT was less than 4 Gy following the

Table II. *Patient characteristics.*

	No. of patients
Age (y.o.)	
Median (range)	68 (46-92)
Sex	
Male	123
Female	18
Stage (UICC)	
T1aN0M0	41
T1bN0M0	100
Histology	
SCC	141

SCC: squamous cell carcinoma.

Table III. *Treatment characteristics.*

Treatment	No. of patients
Chemotherapy	
Yes	59
No	82
Intracavitary irradiation	
Low-dose rate	9
High-dose rate	15
No	117
Initial CTV	
Local	81
More than 2 lymph node regions	60

CTV: clinical target volume.

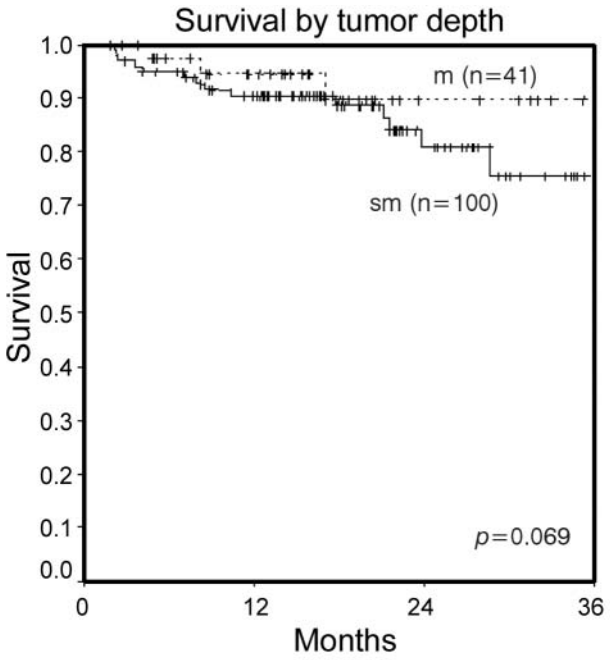

Figure 1. *Overall survival by tumor depth. m: mucosal cancer patients; sm: submucosal cancer patients.*

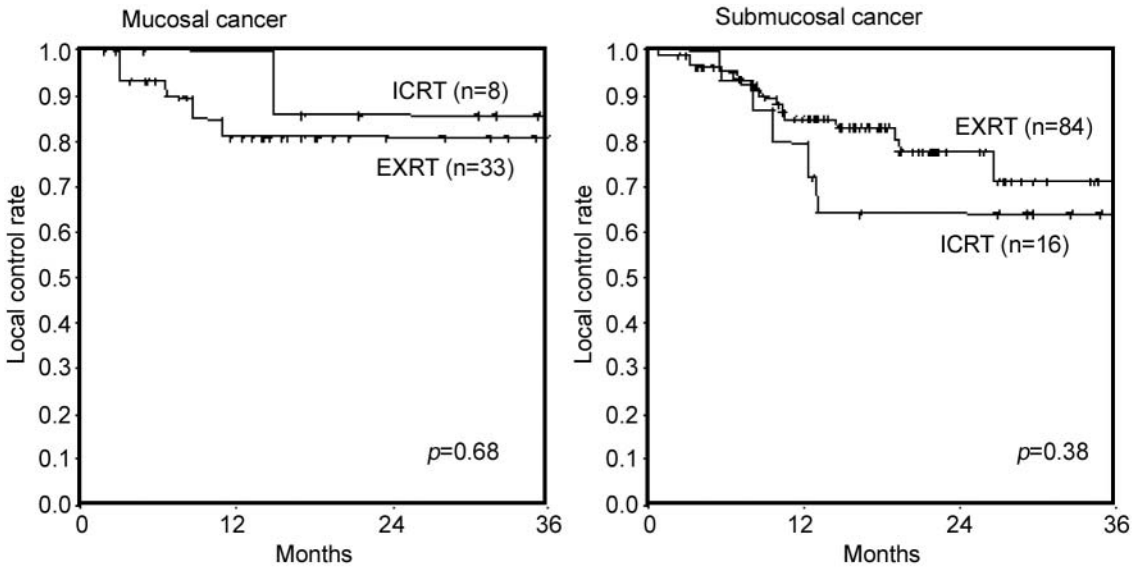

Figure 2. *Local control rate by use of intracavitary irradiation. ICRT: intracavitary radiation therapy; EXRT: external beam radiation therapy alone.*

JASTRO guideline and the minimum fractional dose was 2 Gy. For the high-dose-rate ICRT, an ^{192}Ir source in a balloon applicator 2 cm in diameter was used. For the low-dose-rate ICRT, a ^{226}Ra source in a solid applicator tube 1 cm in diameter or in a balloon applicator of 1.5 cm in diameter was used. The ICRT dose was evaluated at a point 5 mm outside the mucosa.

The cumulative survival rates, local control rates, and toxicity of treatment were used as end-points. The last follow-up was performed in October 2004. The observation period ranged from 14 months to 48 months (median: 28 months). The survival curves were generated using the Kaplan-Meier method and the logrank test was used to test differences in survival. Toxicities were graded according to the Common Toxicity Criteria of Adverse Effect (CTCAE) ver. 3.0.

Results

The overall survival curves according to tumor depth are shown in Figure 1. The overall survival rates for mucosal and submucosal cancer patients at 1, 2 and 3 years were 95%, 90% and 90% and 90%, 81%, and 70%, respectively. The survival of the mucosal cancer patients was better than that of the submucosal cancer patients, though the difference was not statistically significant ($p=0.069$).

The local control rates with the use of ICRT are shown in Figure 2. There was no difference in local control rate with the use of ICRT in either mucosal or submucosal cancer patients.

The effects of chemotherapy on the survival of patients with mucosal and submucosal cancer are shown in Figure 3. The survival of those mucosal and submucosal cancer patients who had received chemotherapy was better than that of patients who had not, although the differences were not statistically significant.

The survival curves for patients with mucosal and submucosal cancer according to the clinical target volume (CTV) are shown in Figure 4. There was no difference between the survival of patients who had received radiation therapy to the primary lesion alone and that of patients who had received radiation therapy to the primary lesion and regional lymph nodes.

Salvage therapy was performed for 9 patients with local recurrence. Surgery was indicated for 4 patients, EMR was indicated for 4 patients and laser therapy was indicated for 1 patient. Although the median observation period for those patients was only 9 months, no re-recurrence was observed.

The toxicity of treatment is shown in Table IV. Esophageal ulcer after ICRT was not observed. Grade 5 pneumonitis developed in 2 patients, 1 of whom had had severe pulmonary dysfunction before radiation therapy.

Discussion

It is well established that EMR alone is the least invasive and most effective treatment method for small mucosal SEC (2, 4, 6, 7) and additional treatment is not used if the resection is complete, since the control rate after complete resection by EMR is usually very high (close to 100%) and lymph node metastasis is very rare in mucosal cancer. In cases of SEC not suitable for EMR, surgery has been the main treatment method with 5-year survival rates ranging from 40 to 80% (2-6). However, good outcomes of radiation therapy for SEC comparable with those of surgery have been reported (9-12) and radiation therapy may become a standard therapy for SEC not suitable for EMR. According

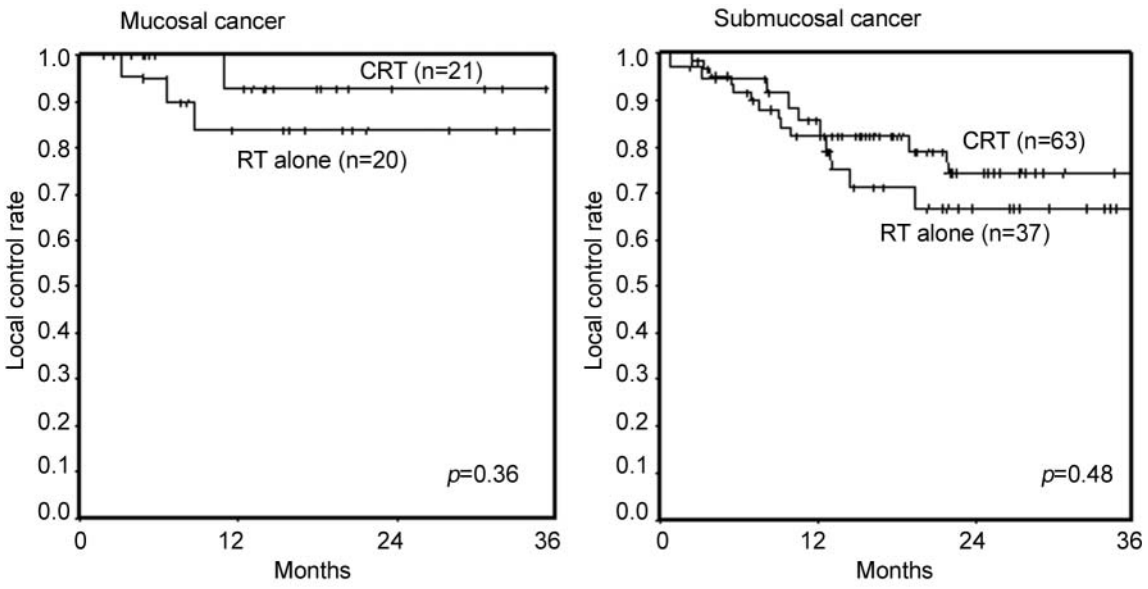

Figure 3. *Overall survival by use of chemotherapy. CRT: chemoradiotherapy; RT alone: radiation therapy alone.*

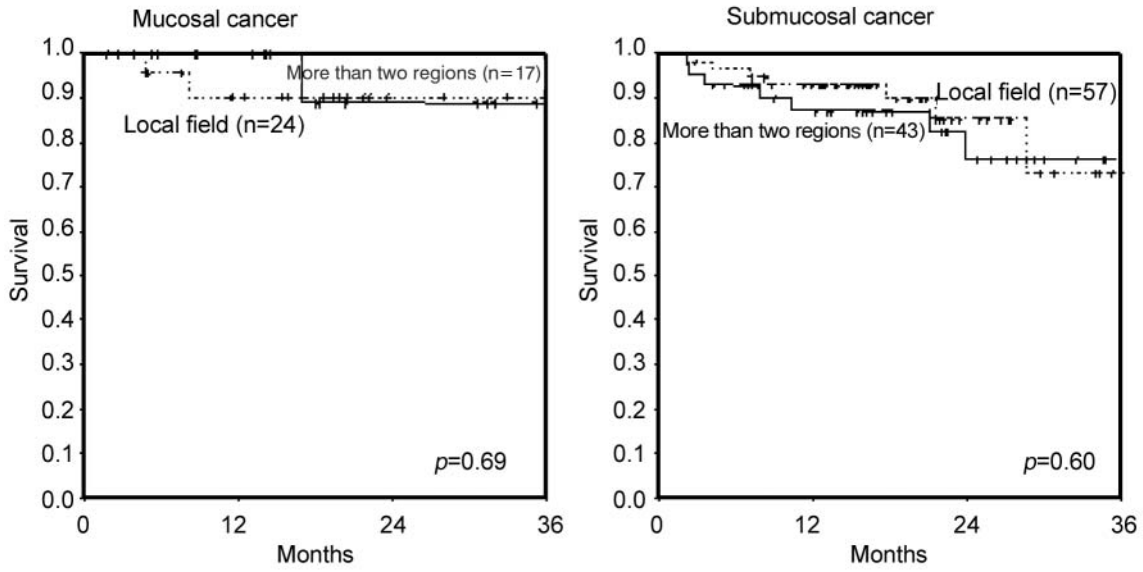

Figure 4. *Overall survival by CTV (clinical target volume).*

to a Japanese nationwide study, the 50-month survival rates of mucosal cancer patients and submucosal cancer patients were 75.8% and 60.4%, respectively (1). In the present study, the 3-year survival rates of mucosal cancer patients and submucosal cancer patients were 90% and 70%, respectively. These data suggest that the survival of patients who had received radiation therapy was comparable with the survival of patients after surgery; however, care must be taken in drawing conclusions since the observation period in our series was short.

The JASTRO guideline defines total doses and fractional doses of external radiation therapy and intracavitary radiation therapy. However, standardization of CTV and determination of the usefulness of ICRT and chemotherapy are necessary to optimize treatment methods.

Table IV. *Toxicity of treatment according to the Common Toxicity Criteria of Adverse Effect v3.0.*

Grade	1	2	3	4	5
Mucositis (Esophagitis)	115(88%)	7 (5%)	9 (7%)	–	–
Pneumonitis	106 (95%)	0 (0%)	3 (3%)	–	2 (2%)
Nausea	112 (88%)	12 (10%)	2 (2%)	–	–
AST,SGOT	104 (96%)	4 (4%)	-	–	–
WBC	73 (64%)	28 (24%)	14 (12%)	–	–
Platelet	105 (93%)	7 (6%)	1 (1%)	–	–

Okawa *et al.* performed a randomized study and reported that ICRT significantly improved local control and survival for T1-T2 esophageal cancer patients (9). On the other hand, in a retrospective study of a large number of patients, it was shown that ICRT had no effect on local control or survival of SEC patients (12). In the present study, ICRT did not improve the local control of SEC. The usefulness of ICRT should be tested in a randomized trial in the future.

In SEC patients treated with ICRT, esophageal ulcer is one of the most dangerous complications. The rate of esophageal ulcer has been demonstrated to depend on the fractional dose and total dose of ICRT (14, 15). The recommended fractional ICRT doses in the JASTRO guideline are less than 4 Gy. In the present series, esophageal ulcer did not develop in any of the 24 patients who had been treated with ICRT. ICRT following the JASTRO guideline therefore seems to be a safe treatment method.

Several randomized trials have shown that chemoradiotherapy (CRT) is superior to radiotherapy alone for the treatment of esophageal cancer (16-19) and good outcomes of CRT for advanced esophageal cancer patients have been reported (20, 21). However, for SEC CRT has not been compared with radiotherapy alone in randomized clinical trials. In the present study, there was no statistically significant difference between the survival of patients who had received CRT and that of patients who had received radiation therapy alone for both mucosal and submucosal cancer patients. The outcomes of radiation therapy alone for SEC are much better than those of radiation therapy alone for advanced esophageal cancer and the survival benefit of CRT compared with radiation therapy alone may be small.

The standard CTV for mucosal cancer is a primary tumor with a longitudinal margin of 2-4 cm, because lymph node metastasis is very rare in this cancer (6, 7). On the other hand, lymph node metastasis is frequently found in cases in which there is infiltration of the submucosa (6, 7). Therefore, as shown in Table III, CTVs including 2 or 3 of the neck, mediastinum and the abdominal region are frequently used. However, lung, cardiac and hematologic complications increase when a large radiation field is used (22, 23) and this must be considered.

Radiation therapy within the JASTRO guideline is a safe and effective treatment for SEC patients and can be one of the standard treatment methods for SEC not suitable for EMR, since the treatment outcome seems to be the same as that of surgery. However, long-term outcomes should be evaluated. In addition, further standardization of CTV and the use of ICRT is necessary.

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