Radical Radiotherapy for Superficial Esophageal Cancer: Impact of Clinical N Stage on Survival

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Abstract. Aim: To retrospectively analyze the results of radical radiotherapy for patients with superficial esophageal cancer (SEC). Patients and Methods: Forty-eight patients with SEC were reviewed. The median dose of external beam radiotherapy was 66 Gy (range, 30 to 70 Gy). Intraluminal brachytherapy was used in 10 patients, and 15 patients (31%) underwent chemotherapy. The median follow-up period was 28 months (range, 4 to 116 months). Results: Sixteen patients had recurrence (11 patients: in-field local recurrence; 3 patients: regional lymph node recurrence; 2 patients: distant metastasis), and the 5-year local control (LC) rate was 74.2%. The 5-year overall survival and disease-free survival (DFS) rates were 44.5% and 48.6%, respectively. Patients with clinical N1 disease (5-year DFS: 0%) had significantly poorer DFS than patients with clinical N0 disease (5-year DFS: 51%, p=0.019). Conclusion: Radical radiotherapy yielded relatively favorable LC rates in patients with SEC, and clinical N stage was a significant prognostic factor for DFS.

Superficial esophageal cancer (SEC) is defined as esophageal cancer limited to the submucosal layer. New developments in endoscopy techniques have led to an increased detection rate of SEC and to revised treatment strategies. The rate of lymph node metastases (LNM) has been reported to be low (0-1.4%) in mucosal cancer with confined lesions, therefore, endoscopic mucosal resection (EMR) is now considered to be a curative treatment for such patients. EMR is currently the standard treatment for patients with mucosal esophageal cancer in Japan (1).

On the contrary, submucosal cancer has an LNM rate of about 50% (2-6), and patients with submucosal cancer are generally treated by esophagectomy plus lymph-node dissection (7, 8). The presence of LNM has been demonstrated to be one of the most important prognostic factors in surgical studies (9-14). Although surgery is the standard treatment for patients with submucosal cancer, radical surgery has had a relatively high morbidity rate (7, 8), therefore less invasive treatment strategies are needed. Radical radiotherapy is currently considered to be an effective alternative. Several studies have indicated that radiotherapy is an acceptable treatment option (4, 20, 22, 24, 26). However, the effect of LNM on survival after radiotherapy has not been clarified.

In the current study, we retrospectively analyzed the results of radical radiotherapy for patients with SEC to evaluate its clinical efficacy in our institution, and analyzed the impact of LNM on prognosis.

Patients and Methods

A retrospective review of medical records identified 48 consecutive patients with histologically-confirmed SEC, treated at the Department of Radiology, University of the Ryukyus Hospital between 1986 and 2008. Table I summarizes the patient characteristics for all 48 patients. All patients were histologically diagnosed with squamous cell carcinoma. Patient ages ranged from 45 to 87 years (median, 72 years), and Eastern Cooperative Oncology Group performance status (PS) ranged from 0 to 2 (median, 0). The tumors were staged according to the system devised by the Union Internationale Contre le Cancer (15), and staging was based on physical examination, chest radiography, barium swallow, esophageal endoscopy and computed tomography (CT). The depth of tumor invasion was usually determined by endoscopic ultrasonography.

Table II lists the treatments for all 48 patients. External beam radiotherapy (EBRT) was administered with 4 to 18 MV x-ray linear accelerators. Forty-seven patients underwent EBRT with daily fractional doses of 1.8 to 2 Gy (median, 2 Gy), initially using the anterior-posterior/posterior-anterior technique. In 16 patients, the radiation field included the primary tumor plus regional lymph nodes, and in the remaining 32 patients, the radiation field consisted of...
primary tumor only plus minimum margins of 3-5 cm both caudally and cranially. After 40 to 45 Gy of initial irradiation, the radiation portals were changed to oblique portals to shield the spinal cord. The median total dose of EBRT was 66 Gy (range=30 to 70 Gy). For 10 patients, after 40 to 46 Gy in 20 to 25 fractions of ERBT, intraluminal brachytherapy (ICBT) was performed using a high-dose-rate remote afterloader (Buchler Facts, Braunschweig, Germany). The source was 192iridium, and a single catheter was used. A silicon balloon applicator (Dokiya applicator), consisting of an outer balloon and a triple inner balloon, was used (29). When it was optimally expanded with 15 ml of water, the balloon was 15 mm in diameter. The treatment usually consisted of 5 Gy in one fraction at 5 mm below the mucosal surface. Two patients, each received 6 Gy in one fraction. One patient was treated with ICBT only (25 Gy/5 fractions).

Chemotherapy was administered to 15 patients (31%). Fourteen patients underwent concurrent chemoradiotherapy with or without adjuvant chemotherapy, and the remaining patient received adjuvant chemotherapy alone. Six patients received cisplatin with 5-fluorouracil (5-FU). One course of chemotherapy consisted of cisplatin (80 mg/m² on day 1) and 5-fluorouracil (800 mg/m² on days 2-6) at intervals of 3 to 4 weeks, for a total of one to two courses. One patient was treated with cisplatin together with 5-FU as adjuvant chemotherapy, because of the need to treat synchronous cancer of the glottis. Six patients received nedaplatin and 5-FU. One course of chemotherapy consisted of nedaplatin (90 mg/m² on day 1) and 5-FU (800 mg/m² on days 2-6) at intervals of 3 to 4 weeks for a total of one to two courses. One patient was treated with docetaxel only (12 mg/m² weekly). Oral administration of TS-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium) was administered to one patient. These regimens were decided by the treating physicians with regard to the condition of the patient.

After radical radiotherapy, patients were monitored at regular intervals, usually every 1 to 3 months, using chest radiography and esophagoscopy. Computed tomography (CT) scans were also performed at 3- to 6-month intervals, or when failure was suspected. The median follow-up period was 28 months (range=4 to 116 months).

### Results

At the time of this analysis, disease in 16 patients had recurred: 11 patients (23%) had in-field local recurrence, three patients had regional lymph node recurrence outside of the irradiated field, and two patients had distant metastasis (Table III). The 5-year LC rate was 74.2% (Figure 1). On univariate analysis, there were no significant prognostic factors associated with LC.

After their recurrences, four patients underwent salvage surgery, five patients underwent chemotherapy, two patients received argon plasma coagulation, three patients underwent repeated radiotherapy, and four patients received palliative treatment (Table III). After salvage treatment, 1 patient achieved complete response, and 2 patients were alive with disease at the time of analysis.

At the time of analysis, 22 patients had died: 11 patients from esophageal carcinoma, one patient from brain infarction with clinical signs of esophageal cancer recurrence, and 10 patients died from other diseases without clinical signs of recurrence. The 5-year OS and DFS rates considering all 48 patients were 44.5% and 48.6%, respectively.

Patients with clinical N1 disease (5-year DFS: 0%) had significantly poorer DFS than patients with clinical N0 disease (5-year DFS: 51%, \( p=0.019 \); Figure 2). On univariate analysis, the clinical N stage alone had a significant impact on DFS.
Table III. Summary of patients with recurrence.

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<th>No.</th>
<th>Age</th>
<th>Gender</th>
<th>PS</th>
<th>T</th>
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<th>Location</th>
<th>OTT</th>
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<th>ICBT dose</th>
<th>Field</th>
<th>Chemo regimen</th>
<th>Response</th>
<th>DFS time</th>
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<td>Local</td>
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<td>5Gy*3</td>
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<td>CR</td>
<td>41</td>
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<td>BSC</td>
<td>DWD</td>
<td>47</td>
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</table>

PS: Performance status; OTT: over-all treatment time; DFS: disease-free survival; OS: over-all survival; Ut: upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; LN: lymph node; unk: unknown; CDDP: cisplatin; 5-FU: 5-fluourouracil; CR: complete response; OTT: over-all treatment time; BSC: best supportive care; APC: argon plasma coagulation; NED: no evidence of disease; AWD: alive with disease; DWD: died with disease; DWOD: died with other disease.
whereas other variables, such as total radiation dose and chemotherapy administration, were not significant prognostic factors. On multivariate analysis, no factors attained statistical significance. Chemotherapy tended to reduce local recurrence compared with radiotherapy alone (Figure 3).

Acute toxicity occurred in 17 patients (35%). Esophagitis occurred in nine patients, hepatotoxicities in five patients, pneumonitis in three patients, and hematotoxicities in five patients. All acute toxicities were manageable, and all patients recovered. Late toxicities occurred in six patients (12.5%). Grade 1 or 2 mild pericarditis occurred in four patients, and grade 1 radiation pneumonitis occurred in one patient. Grade 5 esophageal perforation and mediastinitis were observed in two patients. Both patients had been treated with ICBT, 6 Gy/fraction, with total doses ranging from 12 to 18 Gy; the ERBT doses for these patients were 45-50 Gy/22-25 fractions.

Discussion

The results of this study suggest that radical radiotherapy yields relatively favorable LC rates in patients with SEC, with a 5-year LC rate of 74.2%. Several other reports have also demonstrated favorable LC in patients with these
tumors. Nishimura et al. (20) treated 21 patients using EBRT, with a median dose of 66 Gy (range=60 to 69 Gy) and achieved a 3-year LC rate of 85%. Ishikawa et al. (21) treated 68 patients using EBRT, with or without ICBT, with a median dose of 66 Gy (range=60 to 72 Gy), and achieved a 3-year LC rate of 82.1%. Nemoto et al. (22) reported on a multi-institutional study of 78 patients treated using EBRT without ICBT, with a mean dose of 65.5 Gy (range=44 to 84 Gy), and achieved a 5-year LC rate of 66%. These results indicate that radical radiotherapy was effective in achieving LC in SEC patients.

With regard to prognosis after radiotherapy, several reports have indicated that ICBT (20), chemotherapy (23), tumor length (21), and depth of invasion (24) were important predictors of survival in patients with esophageal cancer. In the current study, clinical N stage alone was a prognostic factor for patients with SEC, treated using radical radiotherapy.

Results of studies on patients with advanced esophageal cancer who were treated using radiotherapy have indicated that clinical N stage was a significant prognostic factor for survival. Pomp et al. treated 69 patients with T2-4 esophageal cancer using EBRT with ICBT, and found on multivariate analysis that clinical N stage was a significant factor for OS (27). Rades et al. treated 124 patients with stage 2 or 3 esophageal cancer using radiotherapy with or without chemotherapy, and found on univariate analysis that clinical N stage was a significant factor for DFS (28). Taken together with our results, these findings in patients with advanced cancer, suggest that clinical N stage has a significant impact on survival in patients with SEC.

This study found late complications consisting of grade 5 esophageal perforation (one patient) and grade 5 mediastinitis (one patient). Both patients were treated using ICBT (6 Gy/fraction). Although the optimal use of ICBT has not been established, several authors have recommended a reduced dose per fraction for ICBT. Nemoto et al. (24) recommended that to prevent esophageal ulcers, the ICBT fractional dose should not exceed 5 Gy. Akagi et al. (25) also recommended a small fractional dose (2.0 or 2.5 Gy) for ICBT to minimize the risk of late complications. Since 1989, we have used a reduced dose of 5 Gy per fraction, and no other patients have developed grade 4/5 complications. Based on these results, a dose of 5 Gy or less per fraction appears to be appropriate for ICBT. Additional studies investigating the optimal fractional doses for ICBT are needed.

In conclusion, our results indicate that radical radiotherapy yielded relatively favorable LC rates in patients with superficial esophageal squamous cell carcinoma. Furthermore, the clinical N stage appeared to be a significant prognostic factor for DFS. These findings are useful for predicting outcomes of radical radiotherapy. However, this was a retrospective study, and additional studies with larger numbers of patients are needed to confirm our results.

Conflict of Interests
There is no conflict of interests regarding the manuscript.

References

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