A retrospective study of postoperative chemoradiotherapy for locally advanced esophageal squamous cell carcinoma

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Summary
Objective: To investigate the role of postoperative chemoradiotherapy in locally advanced esophageal cancer after primary surgery.
Methods: Forty-one patients with locally advanced esophageal cancer (30/41 pathologic Stage IIIA-C, 73.2%) who underwent radical surgery and complete postoperative chemoradiotherapy between May 2004 and May 2010 were enrolled. The radiotherapy was delivered by the intensity-modulated radiotherapy technique. Concurrently, chemotherapy with cisplatin and 5-fluorouracil was given on the 1st week and the 5th week of radiotherapy. The overall survival, disease-free survival, and local recurrence rate were calculated to determine the role of postoperative radiotherapy in locally advanced esophageal cancer. Univariate analysis was used to elucidate the prognostic risk factors.
Results: After a median follow-up of 34.5 months (range, 3–87 months), the median overall survival was 13 months. The 1-year and 3-year overall survival rates were 61.0 % and 24.6%, respectively. The disease free survival after 1 year and 3 year was 42.8% and 28.1%, respectively. There was a significant difference in survival between the patients who had N0/1 and N2/3 disease by univariate analysis with 1-year survival and median survival rates of 66.7% versus 37.5% and 17 months versus 10.5 months, respectively ($p = 0.036$). The local recurrence rate was 17.1 % (7/41) at 3 years. Acute treatment-related toxicities were mild. Most of the patients died of distant metastasis.

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1. Introduction

Esophageal cancer is a notorious, insidious disease because over 50–60% of patients are diagnosed at the advanced, unresectable stage, and the 5-year overall survival rate improved only a little from 5% in the years 1975–1977 to 19% in 1999–2005. Since the prognosis is grave for the advanced stage of esophageal cancer, a single treatment mode such as surgery alone is reserved for early stage tumors only. The 3-year overall survival rate in squamous cell carcinoma treated by surgery alone is 6–35%. Postoperative radiotherapy was shown to improve mostly local control and a few studies also reported that this modality improved both local control and survival in thoracic esophageal squamous cell carcinoma. Distant metastasis accounts for most failures after surgical treatment as it occurs in over 60% of the patients with locally advanced esophageal cancer. Based on the recent clinical data, postoperative adjuvant therapy is a reasonable approach for the treatment of locally advanced esophageal cancer with or without positive regional lymph nodes after surgery. Postoperative chemoradiotherapy is now a standard treatment in the USA for patients with a node-positive adenocarcinoma of the stomach or gastroesophageal junction according to the results of the American Intergroup trials. However, the optimum postoperative adjuvant therapy for esophageal cancer, especially for squamous cell carcinoma of the thoracic esophagus, has not yet been established.

In our hospital, the treatment guideline for patients with T1–2N0M0 tumors (according to the 2010 AJCC staging system) is to perform surgery. Palliative treatment or best supportive care is given to those who already have distant metastasis on presentation. Patients with a T3–4N1–3M0 tumor are usually treated using one of our neoadjuvant chemoradiotherapy treatment protocols in our treatment guidelines. However, some patients who had clinically staged T1–2N0M0 were found to have unsuspected T3–4 or N1–3 disease during surgery. Some technically resectable but locally advanced esophageal cancers were also treated by surgery initially. For patients with a pathologic stage T3–4N0M0 tumor, our treatment guidelines suggest an additive of postoperative radiotherapy because of the benefit of local control. For a patient with a pathologically stage T3–4N1–3 tumor, our treatment guidelines suggest an additional of postoperative chemoradiotherapy 4–6 weeks after the operation in an attempt to improve overall survival. If the patient refuses chemotherapy, our recommended adjuvant therapy is postoperative radiotherapy. Some studies have shown survival benefits from postoperative adjuvant chemoradiotherapy for patients with locally advanced stage of disease, especially for tumors located at the lower thoracic esophagus or esophagogastric junction. This retrospective study was conducted to investigate the treatment outcomes of the patients who had technically resectable but locally advanced squamous cell carcinoma or unsuspected T3–4 or N1–3 squamous cell carcinoma discovered during surgery. These patients have subsequently been treated by postoperative chemoradiotherapy in our hospital since 2004.

2. Materials and methods

2.1. Patient population, surgery and adjuvant chemotherapy

Between May 2004 and May 2010, 715 patients with esophageal cancer were admitted to our hospital for treatment. Surgery alone was performed for 10% of the patients; about 40% of the patients with locally advanced stage of esophageal cancer received definitive chemoradiotherapy, while palliative treatment was reserved for patients with Stage IV disease. The remaining patients received postoperative radiotherapy, postoperative chemoradiotherapy or neoadjuvant chemoradiotherapy (since 2007). In this study, we enrolled 41 patients who had technically resectable but locally advanced thoracic esophageal cancer or unsuspected T3–4 or N1–3 thoracic esophageal cancer discovered in surgery and who underwent complete postoperative chemoradiotherapy. Those patients who did not complete postoperative chemoradiotherapy were excluded from this study. Esophagectomy was performed through a three-phase incision with extensive two-field lymph node dissection in the mediastinum and abdomen. The stomach was mobilized to the neck via the retrosternal route and a cervical esophageal anastomosis was performed. Most patients in this study were males with a mean age of 54 years (range, 34–78 years) and a male-to-female ratio of 40:1. The pathological stages of these patients were assigned according to the recommendation of the American Joint Committee on Cancer’s tumor—lymph node—metastasis classification. Patient characteristics and tumor stages are shown in Table 1. Over 73% (30/41) of the patients were Stage IIIA-C by pathological staging (Table 1).

2.2. Chemotherapy

Adjuvant chemotherapy was carried out concurrently with radiotherapy. This consisted of two cycles of cisplatin and 5-fluorouracil (5-FU). Cisplatin was administered at a dose of 20 mg/m²/day i.v. within 60 minutes after adequate hydration for 4 days and 5-FU was administered via
2.3. Radiotherapy

Radiotherapy was administered 4–6 weeks postoperatively using an intensity-modulated radiation therapy (IMRT) treatment plan. All patients underwent computed tomography (CT) simulation in a supine position with their arms above their heads, and a customized vacuum bag was used for immobilization. The CT images were taken at a 5-mm thickness throughout the neck and the entire thorax for the upper and the middle thoracic tumors or the entire thorax and the abdomen for the lower thoracic tumors. Since the tumor was resected along with the esophagus during the operation, the gross tumor volume was not assessed. Clinical tumor volume (CTV), planning tumor volume (PTV), and the organs at risk were outlined on the CT images. CTV included the whole esophageal region, lymph nodes in the mediastinum and supraclavicular area (if the tumor was located in the upper or middle thoracic portion), and celiac trunk region (if the tumor was located in the lower thoracic portion). A margin of 0.5 cm was also added to the CTV as PTV to allow for the daily setup error and organ motion.

The IMRT plan was delivered to each patient by a linear accelerator (Varian 2100EX with a 120-leaf Millennium multileaf collimator; Varian Oncology Systems, Palo Alto, CA, USA) using 6 MV photons. Dose calculations were performed using the Varian Eclipse planning system (versions 6.5–7.2.24) based on the pencil beam model. A total dose of 45–50.4 Gy in 25–28 fractions within 5–6 weeks was administered to the PTV. For both lungs, the dose limit to the mean dose was set at 16 Gy, and the volume receiving more than 20 Gy ($V_{20}$) was limited to 30%. For the heart, as another organ at risk, the dose was set at the volume receiving 35 Gy less than a volume of 30%. For the spinal cord the maximum dose was set at 40 Gy. Six or seven beam portals were used to deliver the required doses to the targets. The beam direction was determined carefully according to the shape of CTV to reduce the possibility of normal lung tissue receiving more than the prescribed doses. The quality of the plan was evaluated by dose volume histogram, dose distribution curves, and a calculated conformity index.

2.4. Toxicity assessment

Acute toxicities such as radiation pneumonitis and hematologic toxicity (leukopenia, anemia, and thrombocytopenia) were evaluated each week during the treatment and every 2 weeks after radiotherapy for 3 months. All treatment-related toxicities were assessed according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG).

2.5. Follow-up evaluation

Follow-up evaluations were performed every 2 weeks after radiotherapy for the first 3 months and then every month for 2 years. The diagnosis for recurrence or metastasis was aided by clinical examinations including physical examination, CT, esophagoscopy plus biopsy, and/or positron emission tomography scan. Survival analysis by the Kaplan–Meier Method was performed using SPSS statistical software. Differences were considered significant if the two-tailed $p$ value was less than 0.05.

3. Results

### 3.1. Clinical results

After a median follow-up of 34.5 months (range, 15–94 months), the median overall survival was 13 months. The 1-year and 3-year overall survival rates were 61.0% and 24.6%, respectively (Fig. 1). The disease-free survival rates at 1 year and 3 years were 42.8% and 28.1%, respectively. There was a significant difference in survival between the patients who had N0/1 disease and those having N2/3 disease by univariate analysis with 1-year survival and median survival rates of 66.7% versus 37.5% and 17 months versus 10.5 months, respectively ($p = 0.036$; Fig. 2).
The local recurrence rate was 17.1% (7/41) at 3 years. In seven patients who had local recurrence, three had tumor local recurrence at the anastomotic site, which was discovered by a CT scan first, and proved by an endoscopic biopsy. The other four had recurrence at the tumor bed, which was detected by the abnormal soft tissue mass found by a CT scan of the chest only. Most deaths during follow-up were due to distant metastases. There were five patients who showed distant metastasis to the lungs only during follow-up; two patients had distant metastasis to the liver only; one patient had brain metastasis; most patients with distant metastasis showed multiple sites of distant metastases. The percentage of patients with distant metastasis was 58.5% (24/41). Acute toxicity during treatment was mild with 9 of 41 patients exhibiting Grade 3 leukopenia and none had Grade 3 or above lung toxicity (Table 2). Six patients needed periodic esophageal balloon dilatation for the stenosed anastomosis shortly after the operation, which was not considered a side effect of postoperative chemoradiotherapy. Constrictive pericarditis was found in one patient 4 months after postoperative chemoradiotherapy. That patient expired 2 months after the appearance of the constrictive pericarditis in spite of medical treatment. Another patient with pericardial effusion, which occurred 3 months after postoperative chemoradiotherapy was insufficiently controlled by nonsteroidal anti-inflammatory drugs and he finally died of local recurrence 12 months after the operation.

3.2. Dosimetric results

In this study, six beam arrangements were used with beam angles of 0°, 60°, 140°, 155°, 205°, 305°. One more beam with beam angle 220° will be added if the PTV is mainly situated in the central to right thoracic area to spare most of the heart and lungs in the treatment fields. The dose delivery was administrated smoothly in all cases. The dose data for CTV and organs at risk are shown. PTV cover of the CTV in the supraclavicular region may be too close to the skin, thus resulting in inhomogeneity appearing at the skin surface. For the spinal cord, the average maximum dose was 27.74 Gy, which is relatively low for the spinal cord. The mean dose for the lungs was 13.19 Gy. The average volume receiving radiation doses more than 5 Gy (V5) and V20 for the lungs was 70.9% and 22% respectively, which is lower than the dose limit known to increase the risk of radiation pneumonitis. A typical isodose distribution of IMRT plan is presented in Fig. 3. The average treatment time was around 15 minutes for each plan.

4. Discussion

Based on historical studies, the primary treatment of esophageal cancer is either surgical or nonsurgical. Surgery is the standard treatment for early stage esophageal cancer, although only 30–40% of patients have potentially operable disease at presentation. For patients with inoperable esophageal cancer, or who have a complicated medical problem, and are therefore not suitable to undergo an operation, the combined modality therapy using both chemotherapy and radiotherapy concurrently was recorded in many nonrandomized and randomized clinical studies in the past. Among these previous studies, the RTOG 85-01 trial reported by Herskovic et al showed the superiority of chemoradiotherapy over radiation therapy alone. The patients in the chemoradiotherapy arm received radiotherapy (50 Gy in 25 fractions) and two cycles of intravenous infusion of cisplatin (75 mg/m² on Day 1) and 5-FU (1000 mg/m² every 24 hours for 4 days) on the 1st and 5th weeks of radiotherapy and then every 3 weeks for two more cycles after radiotherapy. The control arm received radiotherapy alone with higher radiation doses (64 Gy) than the chemoradiotherapy arm. The 5-year overall survival rates (27% vs. 0%, p < 0.0001) and the median survival rate (14 months vs. 9 months) were significantly improved in the
chemoradiotherapy arm. Based on the positive results from the RTOG 85-01, the conventional nonsurgical treatment for esophageal cancer is now chemoradiotherapy.

Patients who are found to have advanced esophageal cancer after primary surgery may need adjuvant therapy. Distant metastasis is the most important factor for the treatment failure in advanced esophageal cancer. In order to cope with distant metastasis, systemic therapy such as chemotherapy is a reasonable adjuvant therapy for advanced esophageal cancer. A nonrandomized Phase II study\(^5\) in 2003 in a single institute compared the result of postoperative chemoradiotherapy in 31 patients with advanced esophageal cancer (26 cases of adenocarcinoma and 5 cases of squamous cell carcinoma) and esophagectomy alone in 52 patients (43 cases of adenocarcinoma and 9 cases of squamous cell carcinoma) in 2003. Chemotherapy was given by two 4-day cycles of intravenous infusion of cisplatin (20 mg/m\(^2\)/day) and 5-FU (1000 mg/m\(^2\)/day) in the 1\(^{\text{st}}\) and 4\(^{\text{th}}\) weeks of adjuvant therapy in patients who received postoperative chemoradiotherapy. Radiotherapy with 50.4–59.4 Gy in 1.8 daily fractions was given to the tumor bed. The addition of postoperative chemoradiotherapy to esophagectomy in patients who had locally advanced esophageal cancer doubled the survival time, time to recurrence, and recurrence-free survival.\(^5\)

However, in a prospective randomized study of postoperative chemotherapy versus chemoradiotherapy reported, Tachibana et al expressed an opposing opinion.\(^11\) Forty-five patients with advanced squamous cell carcinoma of the esophagus were randomized to receive either postoperative chemotherapy or postoperative chemoradiotherapy. The chemotherapeutic regimen was the same in both groups, and cisplatin (50 mg/m\(^2\)) was given by intravenous infusion on Days 1 and 15, and the 5-FU (300 mg/m\(^2\)) was given daily by continuous intravenous infusion for 5 weeks. In the postoperative chemoradiotherapy group, 50 Gy of radiotherapy was given to the mediastinum over 5 weeks. There was no improvement in the survival rate by adding radiotherapy to postoperative chemotherapy.\(^11\) Whether postoperative chemoradiotherapy has survival benefits for the patients who are found to have advanced-stage esophageal cancer during the operation is a controversial issue.

In our retrospective study, the role of adjuvant chemoradiotherapy in advanced esophageal squamous cell carcinoma after primary surgery was assessed. The median overall survival was 13 months with a projected 3-year overall survival of 24.6%. Most of the patients who were entered into this study had a pathologic Stage IIIA-C tumor (73.2%), and only six (14.6%) patients had Stage II A esophageal cancer. Therefore a poor prognosis would be expected. Our results are inferior to the 3-year projected overall survival of 27% and the freedom-from-recurrence rate of 31% reported in a study of multimodality therapy at the Cleveland Clinic.\(^12\) However, the population in the Cleveland study had a lower proportion of advanced stage (50% of Stage III or above) cancer and so it may not be meaningful to compare the results with ours. The local recurrence rate in the current study was 17.1%, which is better than the local-regional failure rates reported in the surgical arms of recent randomized trials.\(^13\) The local-regional failure sites in the current study were found within the treatment field in three cases, and in the other four cases local recurrence was found at the anastomotic site. Further research is needed to improve the local control by augmented the radiation doses.

Univariate analysis shows a significant difference in survival between the patients who had no lymph node involvement (N0) or only one or two lymph node metastases (N1) and patients who had metastases to more than two lymph nodes (N2/N3). The 1-year survival and median survival rate for N0/N1 and N2/N3 were 66.7% versus 37.5% and 17 months versus 10.5 months, respectively (\(p = 0.036\)). There were no significant differences in survival based on age, T stage, tumor grade, tumor sites, angiolymphatic invasion, or perineural invasion by univariate analysis. The number of lymph nodes involved in metastases found in the pathologic specimen played an important role in the prediction of prognosis. This result reconfirmed our previous assertion from demonstrating the prognostic importance of the extent of nodal involvement in squamous cell carcinoma of the thoracic esophagus.\(^14\)
Kofoed et al compared adjuvant chemoradiotherapy or surgery alone in resectable adenocarcinoma at the gastroesophageal junction in a retrospective study with 211 patients, also showing that the positive node status in the resected specimen had a significant partial effect on survival. The combined modalities for the detection of lymph node involvement during clinical staging by endoscopic ultrasonography, a CT scan of the chest and abdomen and a 2-fluoro-2-deoxy-D-glucose positron emission tomographic scan, should be used.

Pulmonary toxicity is a challenging issue in the radiation therapy of esophageal cancer with or without chemotherapy in a postoperative setting. By using IMRT, we can reduce the doses to the lungs as low as possible without compromising the total doses to the treatment target (esophageal bed). In this study, our mean V20 and V5 were 20% and 70.9%, respectively, both lower than those in the RTOG criteria for minimizing the risk of radiation pneumonitis. None of our patients suffered from Grade 3 or above radiation pulmonary toxicity during the postoperative chemoradiotherapy. A reported correlation between V20 and severity of radiation pneumonitis showed 0% of radiation pneumonitis when V20 was controlled below 22%, and the risk increased to more than 19% when V20 was more than 40%. Our results agree with those in that report, and a further large-scale study to confirm the role of V20 in the relationship to the risk of radiation pneumonitis in thoracic radiation therapy is suggested.

For patients who are found to have node-positive disease during the operation, adjuvant therapy is a reasonable approach to improve clinical outcomes. MacDonald et al conducted a large randomized intergroup trial of postoperative chemoradiotherapy for patients with adenocarcinoma in the stomach and at the esophagogastric junction in 2001. The 3-year overall survival rate was 41% in patients who had surgery alone as compared with 50% in patients who had both surgery and postoperative chemoradiotherapy. Postoperative chemoradiotherapy is now a standard approach in the USA for patients who have node-positive adenocarcinoma of the stomach or gastroesophageal junction. For patients who had primary advanced squamous cell carcinoma of the esophagus, some retrospective studies suggested a potential benefit in survival after postoperative chemoradiotherapy. A mature Phase II clinical trial reported by the Cleveland Clinic in 2009 supported the benefit in survival from postoperative chemoradiotherapy in poor-prognosis cancer of the esophagus and gastroesophageal junction. However, data from Japan did not demonstrate any survival benefit by adding chemotherapy to chemoradiotherapy in adjuvant setting. To date, no large randomized clinical trials have shown that the use of postoperative chemoradiotherapy in advanced esophageal cancer as compared with surgery alone improves survival, and thus the therapeutic benefit remains unclear.

5. Conclusions

Multimodality treatment in advanced esophageal cancer is attractive theoretically but the optimal mode of treatment has not yet been established. Our study showed a relatively good local control of the disease by the addition of postoperative chemoradiotherapy to locally advanced esophageal squamous cell carcinoma with a mild, acute treatment-related toxicity, but this did not contribute a higher survival rate for this group of patients.

References