A Case of Esophageal Cancer with Multiple Lymph Node Metastases which Responded to Neoadjuvant Chemotherapy (DCF therapy)

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Abstract. It is difficult to perform radical surgery for esophageal cancer with multiple lymph node metastases. Therefore, effective neoadjuvant adjuvant treatment is necessary to achieve successful radical resection. The use of neoadjuvant chemotherapy of docetaxel, cisplatin (CDOP) and 5-fluorouracil (5-FU) (DCF) in an advanced case is reported. The patient (a 67-year-old female) was diagnosed with esophageal cancer, T3, N4, M0, stage IVa with a large number of lymph node metastases in the mediastinum and in the abdominal cavity. Neoadjuvant DCF chemotherapy was initiated in August 2006. Adverse events were mild. A complete response of the lymph node metastases in the abdominal cavity and a partial response of the esophageal lesion were achieved. The surgical procedure included a right thoracolaparotomy followed by a subtotal excision of the esophagus and two-field lymph node dissection. The cancer was diagnosed to be moderately differentiated squamous cell cancer, pT2, pN4(3c) and pstage IVa. The histological efficacy of the chemotherapy was determined to be grade 1a. Two additional courses of DCF therapy were administered followed by postoperative adjuvant chemotherapy.

Surgical treatment for advanced esophageal cancer with three-field lymph node dissection has contributed to an improvement in the survival rates (1-3), however, it is not sufficient for very advanced cancer cases, where the tumor is likely to recur even when surgically resected. Therefore, effective neoadjuvant adjuvant treatment is necessary in order to achieve successful radical resection. Combination chemotherapy such as FP therapy using cisplatin (CDDP) and 5-fluorouracil (5-FU) has been used as neoadjuvant chemotherapy in this department for advanced esophageal cancer since 1994, resulting in a favorable prognosis in responsive cases (4, 5). In recent years, Adriamycin has been added to this FP therapy regimen (FAP therapy) to treat very advanced esophageal cancer (stage III or above) with favorable results (6, 7). This report describes a case of very advanced esophageal cancer with multiple lymph node metastases, present in the mediastinum and the abdominal cavity which was treated with combined with docetaxel.

Case Report

A 67-year-old female patient presented with dysphagia. The patient had no history of smoking or alcohol consumption. Difficult swallowing was first noted about 1 year earlier, which was left untreated. The symptoms become aggravated and the patient saw a physician and was diagnosed with esophageal cancer based on esophageal endoscopy. In July 2006, the patient was referred to this hospital. The initial examination showed nothing remarkable with regard to the patient’s clinical symptoms. Blood tests revealed that a tumor marker, cytokeratin 19 fragment (CYFRA), was increased to 9.4 ng/ml, with no other abnormal findings.

Esophagography revealed an irregular stenosing lesion accompanied by low elevation with a major axis of 40 mm in the lower thoracic esophagus, thus leading to a diagnosis of type 4 esophageal cancer (Figure 1a). Esophageal endoscopy showed a stenosing lesion, which bled easily, low elevation and irregular erosion in the lower thoracic esophagus, which was consistent with the diagnosis of type 4 esophageal cancer (Figure 1b). A biopsy and histopathological examination revealed either highly or moderately differentiated squamous cell cancer.
Chest computed tomography (CT) revealed a large number of enlarged lymph nodes, including the bilateral trachea bronchial lymph nodes (Nos. 106tbR and 106tbL) in the mediastinum (Figure 2a); thus, the patient was diagnosed with lymph node metastasis. Wall thickening was observed in the lower thoracic esophagus (Figure 2b), thus leading to a diagnosis of esophageal cancer. The depth of the tumor in the esophageal wall was determined to be T3.

Abdominal CT demonstrated a large number of enlarged lymph nodes both in the lesser curvature of the stomach (no. 3) and in the area surrounding the aorta abdominalis (no. 16a, b) (Figure 2c, d); thus, also indicating a diagnosis of lymph node metastases.

Positron-emission computed tomography (PET-CT) showed accumulation in the lower esophagus and the mediastinal lymph nodes (Figure 3). No accumulation was found in lymph nodes of the abdominal cavity.

These findings led to a final diagnosis of type 4 esophageal cancer, T3, N4, M0, stage IVa, with a major axis of 40 mm, occupying the lower thoracic esophagus with a large number of lymph node metastases in the mediastinum and in the abdominal cavity (i.e., in the lesser curvature of stomach and the area surrounding the aorta abdominalis). Neoadjuvant DCF chemotherapy using docetaxel, CDDP and 5-FU was initiated in August 2006, since it was impossible to perform a radical excision. One course of the treatment included an intravenous infusion of 90 mg docetaxel on Day 1 together with an intravenous infusion of 20 mg/day CDDP and 750 mg/day 5-FU from day 1 to day 5, followed by a withdrawal period of two weeks (Table I). The efficacy evaluation conducted after the completion of one course of treatment revealed reduction of both the lymph node metastases and the esophageal lesion; thus, a total of five courses of chemotherapy was administered until down-staging was achieved. Grade 3 leukocytopenia was observed twice, but all other events were mild in severity. The results of the efficacy evaluation performed after the completion of five courses of treatment are shown below.

Esophagography revealed that the lesion was markedly contracted, the mucosal surface flattened and only induration was observed (Figure 4a). Esophageal endoscopy showed that the lesion was flattened and was stained by Lugol’s solution (Figure 4b). A biopsy and histopathological examination showed only slightly thickened stratified squamous epithelia with no malignancy. A chest CT demonstrated that the right-sided trachea bronchial lymph node (no. 106tbR) persisted, but was markedly reduced (Figure 5a). The wall thickening in the lower thoracic esophagus had almost disappeared (Figure 5b).

An abdominal CT showed that the lymph nodes both in the lesser curvature of the stomach and in the surrounding area of the aorta abdominalis (no. 3 and 16) had disappeared (Figure 5c, d).

These findings indicated that a complete response of the lymph node metastases in the abdominal cavity and a partial response of the esophageal lesion had been achieved; thus indicating successful down-staging. The serum CYFRA level was also normalized; thus, it was thought that the patient would be able to tolerate radical surgery, and an esophageal resection was performed in April 2007. The surgical procedure included a right thoracolaparotomy followed by a subtotal excision of the esophagus, two-field lymph node dissection, and anastomosis of the stomach to the cervical esophagus via a posterior mediastinal route (R0, the degree of radical cure B). Macroscopically, the lesion was flattened (Figure 6a). A histopathological examination of the excised specimen revealed that the esophageal lesion contained moderately differentiated squamous cell cancer.

Table I. Treatment schedule (total: 5 courses).

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<th>1st course</th>
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<th>2nd course</th>
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<tr>
<td>Day 1</td>
<td></td>
<td>5</td>
<td>Evaluation</td>
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<tr>
<td>5-FU</td>
<td>750 mg/day</td>
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<tr>
<td>CDDP</td>
<td>20 mg/day</td>
<td>Evaluation</td>
<td>20 mg/day</td>
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<td>Docetaxel</td>
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12×5 mm in size from the submucosa to the center of the muscularis propria (Figure 6b, c). The cancer was diagnosed to be pT2, pN4(3c), i.e. (−), lyo, v0, and pstage IVa (the number of metastases was corrected). The histological efficacy of the chemotherapy was determined to be Grade 1a. There were no complications associated with the chemotherapy during or after surgery. The patient was discharged from hospital about 3 weeks after the surgery. Two additional courses of DCF therapy were administered followed by postoperative adjuvant chemotherapy using TS-1 (Tegafur • Gimeracil • Oteracil potassium combination granule) and docetaxel on an outpatient basis. Metastasis to the left axillary lymph node developed. After 20 months of chemotherapy the lymph node was finally removed and found to harbour squamous cell cancer. The patient continued outpatient chemotherapy.
The clinical findings, histopathological findings and histological efficacy evaluation of chemotherapy were based on the criteria established by the Japanese Society for Esophageal Diseases, ninth edition (8). Adverse events reported during treatment were coded according to the Common Terminology Criteria for Adverse Events v3.0 (9).

Discussion

Several randomized controlled trials in Western countries have compared surgery with neoadjuvant chemotherapy and surgery alone (10-13). Although some of these studies showed the effectiveness of neoadjuvant chemotherapy, a meta-analysis conducted on these studies was controversial, and to date there have been no data to directly prove the efficacy of neoadjuvant chemotherapy (14-16). Therefore, the Japanese guidelines for the treatment of esophageal cancer indicate a grade C recommendation for neoadjuvant chemotherapy regimen because there is insufficient evidence to support the neoadjuvant chemotherapy regimen for cases in which a tumor resection is feasible (17). However, surgery for esophageal cancer has been associated with less favorable results in Western countries in comparison to that performed in Japan. Because of the coexistence of squamous cell cancer and adenocarcinoma as well as different surgical procedures such as resection of the esophagus with a thoracotomy and removal of the esophagus without a thoracotomy, rigorously planned comparative studies are necessary to assess the usefulness of neoadjuvant chemotherapy.

In order to resolve this problem, the Japan Clinical Oncology Group (JCOG) conducted a phase III study, JCOG 9907, and the results of the intermediate analysis showed that neoadjuvant FP therapy improved the overall survival in patients with Stage II/III esophageal squamous cell cancer in comparison to postoperative FP therapy, with no serious adverse events (18). This favorable result was attributed to the fact that down-staging and R0 resection were possible in patients receiving neoadjuvant FP therapy. Therefore, neoadjuvant chemotherapy should become a standard treatment for stage II/III esophageal cancer in the future. At the same time, British researchers reported that patients with resectable stomach cancer and lower esophageal cancer who received neoadjuvant and postoperative chemotherapy had a markedly prolonged survival in comparison to those who underwent surgery alone (19).

The Australasian Gastro-Intestinal Trials Group (AGITG) also reported the results of a meta-analysis on 10 randomized controlled trials in which patients with operable localized esophageal cancer who received neoadjuvant chemoradio-therapy or neoadjuvant chemotherapy were compared with those who underwent surgery alone. They concluded that neoadjuvant chemotherapy reduced the overall mortality by 10%, and the 2-year survival rate was improved by 7%, thus indicating the benefit of neoadjuvant treatment (20).

However, the recent introduction of taxane anticancer drugs has allowed the use of DCF therapy, in which docetaxel is added to FP therapy for the treatment of cancer in the head/neck, stomach, and other organs (21). In addition, there have been some cases of esophageal cancer which were responsive (complete response) to DCF therapy (22-24), possibly because the mechanism of action of docetaxel differs from other anticancer drugs, resulting in less cross-resistance and higher therapeutic effects (25). A study conducted to verify this hypothesis showed that human esophageal cancer xenografts which did not respond to 5FU/CDDP therapy were successfully treated with the DCF regimen (26). In addition, the mechanism of action of DCF therapy can be explained by the fact that taxane anticancer drugs inhibit dihydropyrimidine dehydrogenase (OPD)-related genes, responsible for an enzyme required for the decomposition of 5-FU (21). Ajani et al. conducted a study comparing DCF therapy and FP therapy for cancer of the esophagogastric junction and reported DCF therapy to be superior to FP therapy in terms of the progression-free survival, survival rates and response rates (27).

Since the present case was stage IVa esophageal cancer with multiple lymph node metastases, DCF therapy was performed in anticipation of the greater antitumor effect on the basis of the above findings. Down-staging was attained after chemotherapy, thereby enabling the radical surgery. The
adverse events reported during treatment were mild in severity except bone-marrow suppression, and there was no problem during the perioperative period with a favorable postoperative course, thereby indicating the higher safety profile associated with this therapy.

Neoadjuvant DCF chemotherapy is effective and can be safely conducted for the treatment of very advanced esophageal cancer; therefore, it is expected to be widely used as a standard treatment for very advanced esophageal cancer in the future.

Figure 5. Chest (a, b) and abdominal (c, d) CT. after 5 courses of treatment a: The right-sided tracheal lymph node persisted, but was markedly reduced. b: Wall thickening in the lower thoracic esophagus had almost disappeared. c, d: The lymph nodes both in the lesser curvature of the stomach and in the surrounding area of the aorta abdominalis had disappeared.

Figure 6. The resected esophagus. a: Macroscopically, the lesion was flattened. b, c: Histopathologically the esophageal lesion contained moderately differentiated squamous cell cancer from the submucosa to the center of the muscularis propria.

References


