Clinical Results of Preoperative CDDP/5-FU Chemotherapy Followed by Surgery for Patients with Clinical Stage II/III Thoracic Esophageal Cancer

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Clinical Results of Preoperative CDDP/5-FU Chemotherapy Followed by Surgery for Patients with Clinical Stage II/III Thoracic Esophageal Cancer

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Abstract

Purpose : The purpose of this study was to clarify the outcomes of preoperative CDDP/5-FU chemotherapy (FP therapy) followed by surgery for patients with clinical Stage II/III thoracic esophageal cancer.

Methods : Seventeen patients with clinical Stage II/III thoracic esophageal cancer who underwent FP therapy followed by esophagectomy were investigated with regard to the perioperative clinical results and postoperative outcomes.

Results : Grade 3 or 4 adverse effects associated with FP therapy were recognized in 2 of the 17 (11.8%) cases, and 16 patients completed 2 cycles of FP therapy (94.1%). Complications after surgery occurred in 7 cases (41.2%). There were 7 patients with postoperative recurrences (41.2%), 6 of whom had clinical Stage III disease. Similarly, 4 out of the 5 patients who died of cancer had clinical Stage III disease. All recurrences and cancer-related deaths were recognized in histological effectiveness of Grade 0/1 cases.

Conclusions : Preoperative FP therapy was found to be safe for patients with clinical Stage II/III thoracic esophageal cancer. However, the treatment seemed to be less beneficial for Stage III patients than for Stage II patients, thus suggesting that a more powerful preoperative treatment may be necessary for clinical Stage III patients.

Key words : Esophageal cancer・Standard CDDP/5-FU chemotherapy・Neoadjuvant chemotherapy・Complication, recurrence

Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide, and the sixth most common cause of death from cancer[1]. Although the incidence of early EC has been increasing, the majority of patients still have widespread disease at the time of symptom presentation[2]. The traditional management of patients with locally advanced EC has been by surgical resection, but the prognosis is generally poor. EC easily invades critical surrounding organs such as the aorta and tracheobronchus, and lymph node metastasis frequently occurs even in the early stages. However, various new treatment strategies are currently being investigated, and the patient prognosis has been improving[3].

The results of a randomized controlled trial (9907) in patients with Stage II/III thoracic EC performed by the Japan Clinical Oncology group (JCOG) established neoadjuvant chemotherapy (NAC) as a treatment strategy using with cisplatin plus 5-fluorouracil (FP therapy)[4]. The results demonstrated that preoperative FP therapy improved the overall survival, and showed better survival than previous randomized control-

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led trails. Consequently, the therapy has become a standard treatment for clinical Stage II/III EC in Japan. However, according to a stratification analysis of the JCOG 9907, chemotherapy-induced downstaging with subsequent complete resection was reported to be less beneficial in Stage III than in Stage II patients.

To confirm whether this was also the case at our institution, we conducted a retrospective study regarding the clinical results of preoperative FP therapy followed by surgery for patients with clinical Stage II/III thoracic EC treated at our institution.

Methods

Patients

The subjects evaluated in this study consisted of 17 patients with clinical Stage II/III thoracic EC who underwent esophagectomy after being treated with preoperative FP therapy between December 2009 and June 2013 in the Department of Surgery and Science (Department of Surgery II), Kyushu University Hospital Japan. All patients underwent subtotal thoracic esophagectomy and regional lymphadenectomy with curative intent. Table 1 shows the preoperative background characteristics of the patients. The mean age was 64.1 years old, and the male to female ratio was 2.4 to 1. There were 7 patients with clinical Stage II (41.2%), and 10 patients with Stage III (58.8%) disease. The survival data were updated in August 2013, and the follow-up term was 1.3 months to 31.1 months after the primary operation (median follow-up period of censored patients, 7.7 months). Clinical data were available for all patients.

We examined the adverse effects associated with FP therapy, as well as the postoperative complications, short-term morbidity, mortality, and prognosis after esophagectomy. The clinical stage was evaluated according to the guidelines for clinical and pathological studies on carcinoma of the esophagus[5]. The depth of invasion and presence of lymph node metastasis were defined based on the preoperative upper gastrointestinal endoscopy, computed tomography and positron emission tomography findings.

Table 1 The preoperative background characteristics

Factors	n=17
Age (years)	
Mean ± SD	64.1 ± 7.6
Sex	
Male/Female	12 (70.6)/5 (29.4)
Location of the thoracic tumor	
Upper esophagus	3 (17.6)
Mid-esophagus	10 (58.8)
Lower esophagus	4 (23.5)
Histological type of squamous cell carcinoma	
Well differentiated	7 (41.2)
Moderately differentiated	6 (35.3)
Poorly differentiated	4 (23.5)
cT	
cT1b	5 (29.4)
cT2	3 (17.4)
cT3	9 (52.9)
cN	
Positive	14 (82.3)
Negative	3 (17.6)
Clinical Stage	
cStage II	7 (41.2)
cStage III	10 (58.8)

The numbers in parentheses are percentages.

Chemotherapy

Chemotherapy with cisplatin plus 5-fluorouracil was repeated twice according to the JCOG 9907[4]. A dose of 60-80 mg/m^2 cisplatin was given by intravenous drip infusion, and 5-fluorouracil was administered at a dose of 600-800 mg/m^2 by continuous infusion. All cases underwent esophagectomy within 4 to 10 weeks after FP therapy.

Pathological efficacy of NAC

The effects of NAC were assessed based on the criteria outlined in the *Guidelines for the Clinical and Pathologic Studies on Carcinoma of the Esophagus by the Japan Esophageal Society*[5]. A Grade 3 response (markedly effective), meant that all cancer cells were destroyed and no evidence of viable cancer cells remained ; Grade 2 (moderately effective), meant that more than two-thirds of the

cancer cells were damaged, despite the continued presence of viable cancer cells. In this study, slightly effective (Grade 1) and ineffective results (Grade 0) were classified together as ineffective. The grading was determined by the presence of both viable cancer cells and the scar tissue created by NAC.

Results

The factors associated with the operation

Table 2 shows the factors associated with the operation. All cases underwent subtotal esophagectomy and were reconstructed with a gastric tube. The retro-sternal route was chosen for 9 of 10 cases of clinical Stage III patients. The median length of the operation was 619 minutes, and the median blood loss was 340 ml. The median length of the operation in Stage II and Stage III cases was 592 minutes and 669 minutes, and the median blood losses were 200 ml and 410 ml, respectively.

Table 2 The factors associated with the operation

Factors	n=17
Organ used for reconstruction	
Gastric tube	17 (100)
Route of reconstruction	
Retro-sternal	12 (70.6)
Posterior mediastinum	5 (29.4)
Median length of operation (range, min)	619 (484-753)
Median blood loss (range, ml)	340 (56-1447)

The numbers in parentheses are percentages.

Table 3 The morbidity and mortality

Factors	n=17
NAC associated adverse effects	
All complications	11 (64.7)
Mild (Grade 1, 2)	9 (52.9)
Anorexia	3
Nausea	4
Renal dysfunction	2
Severe (Grade 3, 4)	2 (11.8)
Hyponatremia	2
Death	0
Postoperative complications	
All complications	7 (41.2)
Pulmonary complications	1
Anastomotic leakage	6
Death	0

NAC : neoadjuvant chemotherapy
The numbers in parentheses are percentages.

The mortality and morbidity

Table 3 shows the morbidity and mortality rates. NAC-associated adverse effects were found in 11 cases (64.7%), including 2 cases (11.8%) with Grade 4 of hyponatremia. Grade 4 hyponatremia was observed in 1 patient after the first cycle of FP therapy, NAC was discontinued and the hyponatremia was recovered after the intravenous administration of supplemental sodium. All patients were able to undergo surgery after FP therapy, and there were no cases of NAC-associated death or surgery-related death. Postoperative complications were found in 7 cases (41.2%), as listed in Table. 3.

The prognosis after surgery

Table 4 shows the prognosis of the patients who received FP therapy followed by surgery. There were 7 patients with postoperative recurrences (41.2%), 6 of whom had clinical Stage III disease. The median term of recurrence after surgery was 3 months. There were 5 cases that died of the cancer death (29.4%) ; similarly, 4 of those were clinical Stage III cases.

Table 4 The prognosis after surgery

Factors	n=17
Recurrence	7 (41.2)
cStage II / III	1/6
Pattern of recurrence	
Local	1
Lymph node	4
Lung	2
Pleural dissemination	1
Liver	1
Brain	1
Median term to recurrence after surgery (range, months)	3 (1.8-10.8)
Cancer death	5 (29.4)
cStage II /III	1/4
Alive	12 (70.6)
cStage II /III	6/6

The numbers in parentheses are percentages.

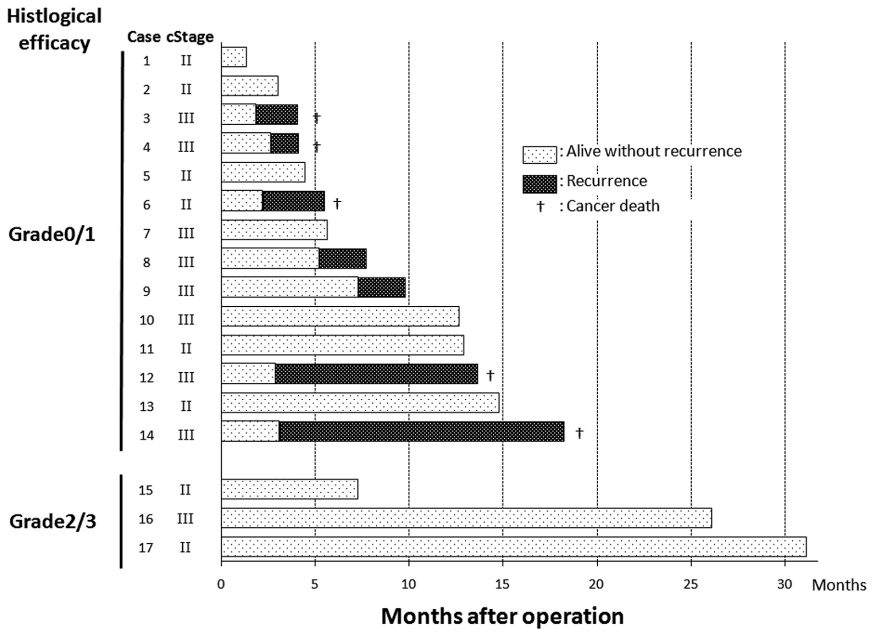

Fig. 1 The outcomes after surgery according to the histological efficacy of the treatment. Grade 3 indicated that the treatment was markedly effective, and Grade 2 meant moderately effective, while slightly effective (Grade 1) and ineffective results (Grade 0) were classified together as ineffective. The grading was determined by the presence of both viable cancer cells and the scar tissue created by the NAC. All recurrences and cancer death were recognized in the patients with a Grade 0/1 response.

The outcomes after surgery according to the histological efficacy of the treatment

Figure1 shows the outcomes after surgery according to the histological efficacy of the treatment. There was 1 case of Grade 0, 13 cases of Grade 1, 2cases of Grade 2, and 1 case with a Grade 3 response. All recurrences and cancer deaths occurred in Grade 0/1 patients.

Discussion

NAC has been tested in numerous randomized trials in patients with locoregional and locally advanced EC. Some previous randomized controlled studies had demonstrated that NAC was superior to surgery alone in terms of the overall survival of patients with EC[6], while another study showed no survival benefit[7]. Thus, it has been controversial whether NAC can improve the survival of patients with potentially resectable advanced EC. The results of the JCOG 9907 trial demonstrated that preoperative FP therapy improved the overall patient survival, and this treatment thus became the standard treatment for patients with potentially resectable Stage II/III thoracic esophageal squamous cell carcinoma in Japan[4]. This study was also intended for clinical stage II/III thoracic esophageal squamous cell carcinoma. However, a stratification analysis of the JCOG 9907 showed that this treatment was less beneficial in Stage III patients than in Stage II patients. Consistent with the findings of the JCOG 9907 trial, in the present study, the Stage III patients had more recurrence and cancer-related death cases than did the Stage II patients.

Some previous randomized studies and meta-analyses have emphasized the superiority of the clinical results of neoadjuvant chemoradiotherapy (NACRT) plus surgery over surgery alone[8]. However, they have been unable to demonstrate a significant survival difference in the patients with potentially resectable EC[9]. Another trial showed that patients with squamous cell carcinoma who received NACRT had better progression-free survival than those

with nonsquamous carcinomas[10]. It is also controversial whether NACRT increases the long-term survival in patients with surgically resectable EC. Some authors have reported that NACRT increases the incidence of postoperative complications[11] and high mortality associated with the operation in patients with EC[12]. In this study, all NAC-related adverse effects were manageable, and neither NAC-related death nor surgery-related death was observed. This suggests that preoperative FP therapy is safe and relatively well tolerated by patients.

As shown in our previous reports, a response to NACRT is the most important factor predicting the long-term survival after surgery[13][14]. In the present study, the recurrences and cancer-related deaths tended to be observed more often in histological Grade 0/1 cases than Grade 2/3 cases. This suggests that patients with a good response to preoperative FP therapy also had a better long-term survival. The response to this treatment seems to be an important factor for determining the prognosis after surgery. We previously reported some biomarkers that predicted the response to NACRT in EC[15][16]. Another recent retrospective study demonstrated that breast cancer susceptibility gene 1 (BRCA1) mRNA expression could be used as a predictive and prognostic marker in EC patients who received cisplatin based chemotherapy[17]. It is considered to be essential to improve the accuracy of the pretreatment diagnosis in order to identify the patients who will obtain a benefit from preoperative therapy, and considering such predictive markers for the response would likely be helpful.

Recently, there were some clinical trials of docetaxel plus cisplatin and 5-fluorouracil (DCF) therapy for advanced EC. The therapeutic efficacy was demonstrated with a good response rate and pathological complete response rate[18]. A randomized controlled trial is now ongoing which is comparing preoperative FP therapy, DCF therapy and NACRT for advanced EC (JCOG 1109)[19]. The trial results are expected to identify a more powerful treatment strategy for Stage III EC.

In conclusion, preoperative FP therapy for the patients with clinical Stage II/III thoracic EC seems to be a safe and efficient therapy, especially for Stage II patients. However, the benefits of this treatment were lower for clinical Stage III patients. It is therefore necessary to develop a more powerful multimodal treatment strategy for patients with potentially resectable locally advanced EC.

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（和文抄録）

CDDP/5-FU を用いた術前化学療法後に手術を施行した cStage II/III 胸部食道癌症例の当院における臨床転帰の検討

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【目的】CDDP/5-FU（FP 療法）を用いた術前化学療法（NAC）後，手術を施行した cStageII/III 胸部食道癌症例の転帰について明らかにすることである．

【方法】当科で FP 療法後に食道切除術が施行された胸部食道癌症例 17 例の周術期治療成績および術後転帰について調査した．

【結果】Grade3/4 の NAC 関連副作用を 2 例（11.8%）に認めたが，16 例（94.1%）で 2 サイクルの NAC を完遂出来た．術後合併症は 7 例（41.2%）に認めた．術後 7 例（41.2%）に再発を認め，その内 6 例が cStageIII であり，5 例認めた癌死の内 4 例が cStageIII であった．また，すべての再発・癌死例は，術後病理所見による治療効果判定が Grade0/1 症例であった．

【考察】FP 療法は安全な治療法であるが，その効果は cStageII 症例に比べ cStageIII 症例では弱いように思われ，cStageIII 症例はより強力な術前治療が必要と考えられた．