Original Article

Safety And Effectiveness of Radical Esophagectomy After Neoadjuvant Chemotherapy For Resectable Locally Advanced Esophageal Cancer

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Abstract

Background: Patients with locally advanced esophageal cancer (LAEC) have a poor prognosis and require a multimodal treatment. However, there are still debates on the optimal strategy in the treatment of LAECs. This study was to evaluate short-term and oncological outcomes of radical esophagectomy after neoadjuvant chemotherapy (nCT) in patients with LAEC.

Methods: This retrospective study was performed between July 2019 and December 2020. A total of 69 patients with LAECs underwent thoraco-laparoscopic McKeown esophagectomy with three-field lymphadenectomy after a complete nCT with DCX (docetaxel-cisplatin-capecitabine, 67 patients) or DCF regimen (docetaxel-cisplatin-fluorouracil, two patients). Short-term outcomes included clinical and pathologic response according to the Response Evaluation Criteria in Solid Tumor version 1.1, treatment-related adverse events (TRAEs) assessed using the National Cancer Institute-Common Toxicity Criteria for Adverse Events, and postoperative complications graded by Clavien-Dindo classification. Oncological outcomes included overall survival (OS) and disease-free survival (DFS) during following up.

Results: All patients were male and had squamous cell carcinoma: 22 with stage III and 47 with stage IVa at baseline. There were 67 patients (97.1%) with clinical complete response and 65 patients (94.2%) with tumor downstaging after nCT. Grade 3-4 TRAEs occurred in five patients (7.2%). All patients received an R0 resection; 37 (53.6%) had postoperative complications but only three (4.3%) were classified as grade III according to Clavien-Dindo classification. Two-year OS and DFS (95% confidence interval) were 78% (67-92%) and 72% (61-86%) respectively.

Conclusions: Radical esophagectomy after nCT is safe and can improve oncological outcomes for patients with LAECs.

Keywords: Esophageal squamous cell carcinoma; Neoadjuvant chemotherapy; Esophagectomy; Survival

INTRODUCTION

Esophageal cancer (EC) is an aggressive cancer with poor prognosis, especially in the advanced stage. It has been the seventh most common cancer and the sixth leading cause of death from cancer worldwide.[1] Histologically, adenocarcinoma is more common in Western countries, whereas in Asia, squamous cell carcinoma is the most common type of EC.[2] This type of cancer is a highly aggressive malignancy with a high rate of lymph node metastasis.[3,4] Radical esophagectomy with extensive lymph node resection remains the mainstay of treatment for locally advanced EC (LAEC). However, without additional therapy, patients have poor survival with high rates of recurrence and metastasis.[5-7] Therefore, neoadjuvant therapy combined with radical surgery is the treatment of choice to improve survival of patients with LAEC. This combination strategy is recently recommended by the National Comprehensive Cancer Network (NCCN) guidelines.[8] Studies have demonstrated that neoadjuvant chemoradiotherapy (nCRT) and neoadjuvant chemotherapy (nCT) provide considerable survival benefits and have been adopted routinely for patients with LAEC.[9-12] However, whether nCRT or nCT is more effective for LAEC is still debated, and the optimal regimen for nCRT or nCT is still inconclusive. There is a discrepancy in the multimodal treatment strategy between Western and Asian countries depending on results from different clinical trials.[13,14]

Currently, minimally invasive esophagectomy (MIE) has become a standard surgical procedure for patients with EC because it provides substantial benefits over conventional open esophagectomy.[15-17] Studies showed that MIE has favorable short-term outcomes as well as comparable or even better long-term outcomes in comparison with conventional open esophagectomy.[15-19] With the development of endoscopic surgery, thoraco-laparoscopic McKeown esophagectomy has become a common approach of MIE. Recently, robot-assisted McKeown esophagectomy has shown

a promising result for MIE as it provides 3D vision, free articulation of the robotic arms, and stable operating field. The advantages of robotic surgery have been shown in the literature, but its high cost prevents its wide application, particularly in the low-to-middle income country (LMIC) settings.[20,21]

Although the evidence of radical esophagectomy in combination with neoadjuvant chemotherapy is strong in LAECs, the evidence in a new population is still needed to be strengthened. In Vietnam, the combined therapeutic strategy has been used in recent years. The safety and effectiveness of the combined treatment for LAECs are still questioned. Therefore, we conducted this study to evaluate short-term and oncological outcomes of radical esophagectomy after neoadjuvant chemotherapy in patients with LAEC.

METHODS

Study design and patients

This was a retrospective review of patients who underwent esophagectomy after nCT for LAEC between July 2019 and December 2020 in Cho Ray hospital, a tertiary medical center of Southern Vietnam. The study was approved by the institutional ethics committee. All patients provided written informed consent for all treatments beforehand. Inclusion criteria included (i) patients aged ≥18 years, (ii) histologically confirmed EC, (iii) locally advanced stage (i.e., tumor that invades regional lymph nodes [N1-3] or local structures [T3-4]) according to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system,[22] (iv) completed neoadjuvant therapy, and (v) undergoing radical esophagectomy. Patients with postoperative T4b staging were excluded.

Patient evaluation and staging

All patients underwent multidisciplinary consultations for staging and treatment planning. Upper gastrointestinal endoscopy and contrast-enhanced thoracoabdominal computed tomography (CT) scan were performed for clinical staging at baseline and every three weeks before surgery. After surgery, patients were followed up in the outpatient department at one month, every three months during the first two years, and then every six months. Endoscopy and CT scan were done every six months during the first two years, then every year. In some patients, 18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT fusion images were used when necessary. Clinical staging was based on the AJCC TNM staging system (8th edition). At each visit, patients were received physical examination and evaluations of complete blood count, routine blood chemistry, electrocardiogram and the Eastern Cooperative Oncology Group (ECOG) performance status.

Neoadjuvant chemotherapy

Before surgery, patients received 3-6 cycles of DCX regimen every three weeks. Each cycle included docetaxel (60-70 mg/m^2, intravenous [IV]) and cisplatin (60-70 mg/m^2, IV) on day 1 in combination with capecitabine (2000 mg/m^2 bid, PO) in 14 days (day 1 to 14). In cases of severe dysphagia and not being able to orally administer the drug, DCF regimen was used with 3-6 cycles every two weeks. Each cycle included docetaxel (40 mg/m^2, IV), leucovorin (400 mg/m^2, IV), and fluorouracil (400 mg/m^2, IV) on day 1, fluorouracil (1000 mg/m^2, IV) on day 2, and cisplatin (40 mg/m^2, IV) on day 3. Doses of docetaxel, cisplatin and capecitabine were reduced by 20% if grade-4 hematological toxicity occurred. Doses of docetaxel and capecitabine were reduced by 20% if grade-3 or 4 non-hematological toxicity occurred. Doses of cisplatin were reduced by 20% if creatinine clearance (CCr) decreased to 50-60 ml/min, 40% if CCr decreased to 40-50 ml/min, and were discontinued if CCr decreased to <40 ml/min. Granulocyte colony-stimulating factor (G-CSF) was used if grade-4 febrile neutropenia occurred.

Surgical technique

All patients underwent thoraco-laparoscopic McKeown esophagectomy with three-field lymphadenectomy. The surgical procedure had three phases: the thoracic, abdominal and cervical phases. In the thoracic phase, patients were in a left lateral position with single lung ventilation and five trocars were used including three operation trocars, one camera and one assistant trocar. The esophagus along with the surrounding fat tissue and lymph nodes (supradiaphragmatic, paraesophageal, subcarinal, right and left bronchial, and posterior mediastinal lymph nodes) were dissected. The esophagus was transected above the carina using an endoscopic linear stapler. The upper mediastinal lymphadenectomy including paratracheal and bilateral recurrent laryngeal nerves lymph nodes was also performed. The abdominal and cervical phases were performed simultaneously with patients in supine position. Five trocars were used for the abdominal phase including two operation trocars, one camera and two assistant trocars. Pericardial, proximal lesser curvature and peri-celiac lymph nodes were harvested. The esophagus was separated from the diaphragm and pulled to the abdominal cavity. A 4-5 cm mini-laparotomy was performed to make the gastric conduit. During the cervical phase, lymph nodes along the laryngeal nerves, around the common carotid arteries, below the omohyoid muscle, above the subclavian veins, and around the scalene muscles were harvested. An end-to-side anastomosis was performed with a circular stapler.

Follow-up and outcomes

Clinical response to the neoadjuvant chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 [23] which was classified into four categories: complete response, partial response, stable disease, and progressive disease. Pathologic response was evaluated after surgery. Pathologic complete response (pCR)

was defined as absence of residual tumor cells in the tumor specimen and all resected lymph nodes. Pathologic partial response (pPR) was defined as <10% vital residual tumor cells at the primary site. T downstaging was a reduction in the T descriptor, N downstaging was a reduction in the N descriptor, and tumor downstaging was defined as either T or N downstaging. Neoadjuvant treatment-related adverse events (TRAEs) were assessed according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0. Postoperative complications were graded according to the Clavien-Dindo classification based on the type of therapy required to treat the complication.[24] Overall survival (OS) was defined as the time since the first dose of the neoadjuvant chemotherapy until death from any cause. Disease-free survival (DFS) was the time since the first treatment dose until the detection of recurrence or metastasis, or death from any cause.

Statistical analysis

Baseline characteristics and outcomes were summarized using the number of patients and percentage for categorical variables and mean and standard deviation (SD) for continuous variables. Oncological outcomes including OS and DFS were analyzed using Kaplan-Meier method to estimate 1-year and 2-year OS and DFS with 95% confidence interval (CI) and were visualized by Kaplan-Meier curves. All statistical analyses were performed with the statistical software R version 4.1.0.

RESULTS

Baseline characteristics

A total of 69 patients with esophageal cancer underwent radical esophagectomy after neoadjuvant chemotherapy in our hospital from July 2019 to December 2020. All were male with a mean age of 60.8 years; the youngest was 43 years old. Forty-two (60.9%) were former or current smoker. Majority of the tumors were located in the middle (35 patients, 50.7%) or lower esophagus (31 patients, 44.9%). All tumors were squamous cell carcinoma. Most were moderately differentiated (58 patients, 84.1%). There were 22 patients (31.9%) with stage III and 47 patients (68.1%) with stage IVa prior to any treatment (Table 1).

Neoadjuvant response and treatment-related adverse event

Most patients (67 patients, 97.1%) received the DCX regimen. Clinical complete response was observed in 67 patients (97.1%). There were 65 patients (94.2%) with tumor downstaging, including 63 patients (91.3%) with T downstaging and 25 patients (78.1%) with N downstaging. Before surgery, most patients (55 patients, 79.7%) were at stage II (Table 2).
Grade 3-4 TRAEs were rare including three patients (4.3%) with neutropenia and two patients (2.9%) with anemia. The most common grade 1-2 TRAE was alopecia (100%), followed by hand-foot syndrome (88.4%), nausea (85.5%), anemia (76.8%), stomatitis (72.5%), and vomiting (68.1%). Other grade 1-2 TRAEs occurred in <50% of the patients (Table 3).

Surgical indices and complications

Mean operating time was 420.5 mins and mean postoperative hospital length of stay was 12.4 days. All patients received an R0 resection. After surgery, 14 patients (20.3%) received a chemotherapy and three patients (4.3%) received a radiation. Based on pathological findings, 18 patients (26.1%) had pCR and 51 patients (73.9%) had pPR.
The most common postoperative complication was temporary hoarseness (22 patients, 31.9%), followed by anastomotic leak (9 patients, 13%), surgical site fluid collection (6 patients, 8.7%), pneumonia (5 patients, 7.2%), and subcutaneous emphysema (4 patients, 5.8%). Other complications were infrequent. There were 37 patients (53.6%) with any complication but only three (4.3%) were classified as grade III according to Clavien-Dindo classification, including a case with chyle leak required reoperation (grade IIIb) and two cases with anastomotic stenosis required endoscopic dilatation (grade IIIa). All cases with anastomotic leak recovered after medical treatment (Table 4).

Survival outcomes

All patients were followed up with a mean length of 17.3 months. Disease progression occurred in 10 patients with five lymph node metastases, three liver metastases, one bone and one lung metastasis. There were 11 deaths during the follow-up period. Two-year OS and DFS (95% CI) were 78% (67-92%) and 72% (61-86%) respectively (Table 5, Figure 1).

DISCUSSION

The study showed good safety and effectiveness of radical esophagectomy after nCT in the treatment of patients with resectable LAEC. The neoadjuvant therapy resulted in a clinical complete response and tumor downstaging in most of the patients with a pCR of 26.1%. Most TRAEs were mild to moderate. The surgery was safe without severe complications. Two-year OS and DFS were more than 70%.

In our study, most patients received the DCX regimen (docetaxel-cisplatin-capecitabine) for neoadjuvant therapy; only two patients received the DCF regimen (docetaxel-cisplatin-fluorouracil) because of severe dysphagia. Several studies demonstrated favorable outcomes of nCRT when compared to nCT with respect to the rate of pCR,[25-30] however, survival outcomes seemed to be comparable between them. In addition, the efficacy of nCRT showed in clinical trials could not be reproduced in real-world situations.[31-33] Moreover, histological characteristic of the cancer is an important factor to select an appropriate neoadjuvant therapy. The histology of EC in our country is similar to other Asian nations, of which the majority are squamous cell carcinoma. We followed guidelines for the treatment of EC in Japan and used nCT as the first choice for neoadjuvant therapy. We achieved a pCR of 26.1%, which is quite high compared to other

reports. This might be because we selected only patients with resectable tumor who underwent a radical surgery. The overall pCR of all patients with EC who received nCT would be lower since some patients never undergo surgery because the tumors are not resectable.

The safety of the whole treatment strategy (including nCT and surgery) in our study is acceptable. No new safety profile was detected in our study population. Grade-3 and -4 TRAEs were infrequent, which showed that patients could well absorb the neoadjuvant regimen. Perioperative complications were also uncommon and mostly mild. Currently, radical esophagectomy with lymphadenectomy is the cornerstone in the multimodal treatment of EC.[34] The lymph nodes along bilateral RLNs are important locations for cancer metastasis,[3] thus, a complete mediastinal lymphadenectomy for EC requires lymph nodes dissection along bilateral recurrent laryngeal nerves.[35,36] It is not easy to achieve complete removal of lymph nodes in these areas because the limited operating field which might lead to surgical complications. However, our surgical team had already reached the learning curve of thoraco-laparoscopic McKeown esophagectomy and could perform the surgery safely.

Patients with EC have a poor prognosis, although receiving advanced therapies. In our study, 2-year OS and DFS of resectable LAEC patients were less than 80% even with adequate nCT and radical surgery. However, adding nCT or nCRT before surgery significantly increases survival chance for EC patients with an increase of 13% to 15% in the 5-year OS, which has been shown in the literature.[14] Currently, many studies have been conducted to find better neoadjuvant therapies to improve survival and quality of life of EC patients. There are still debates on the comparison between nCT and nCRT, and the optimal regimens of nCT and nCRT are still questioned.[14,13] Meanwhile, immunotherapy has emerged as a hot direction in the treatment of EC and other cancers. However, targeted therapy is under investigation, so nCT and nCRT are still the mainstay of neoadjuvant therapy for patients with LAECs. In line with current knowledges in the world, our study provides an evidence of the safety and effectiveness of the multimodal treatment for patients with resectable LAECs in our country.

The study has several limitations. First, a retrospective design at a single center without a comparison group would limit the generalizability of the findings. Second, the study had a relatively small sample size along with a limited follow-up period. Third, as mentioned before, we included only patients with resectable EC, thus, the response results of the nCT could not be applied for all EC patients.

In conclusion, our study provided a real-world evidence of the multimodal treatment including radical esophagectomy and neoadjuvant chemotherapy for resectable LAECs. This multimodal treatment is safe and can improve clinical outcomes of the patients. However, patients with EC still have poor prognosis and there is an urgent requirement to explore novel treatments for this cancer.

Conflict of interest statement
All authors declare that they have no conflict of interest.

Ethical standards statement
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.

Statement of informed consent
Informed consent was obtained from all patients for being included in the study.

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Table 1. Baseline characteristics

	All patients(N=69)
Age (years)	60.8 ± 6.3
Sex	
Male	69 (100.0)
Female	0 (0.0)
BMI (kg/m^2)	20.9 ± 3.1
Nutritional status	
Underweight (BMI<18.5)	16 (23.2)
Normal weight (BMI:18.5-24.9)	47 (68.1)
Overweight/obese (BMI≥25)	6 (8.7)
ECOG PS score	
0	29 (42.0)
1	40 (58.0)
Former/current smoker	42 (60.9)
Alcohol drinking	19 (27.5)
Hypertension	12 (17.4)
Chronic hepatic disease	4 (5.8)
Diabetes	4 (5.8)
Chronic renal disease	2 (2.9)
Tumor location	
Upper esophagus	3 (4.3)
Middle esophagus	35 (50.7)
Lower esophagus	31 (44.9)
Histopathological subtype	
Squamous cell carcinoma	69 (100.0)
Differentiation status	
Well differentiated	4 (5.8)
Moderately differentiated	58 (84.1)
Poorly differentiated	7 (10.1)
Clinical TNM stage	
III	22 (31.9)
IVa	47 (68.1)
Clinical T stage	
T3	22 (31.9)
T4a	47 (68.1)
Clinical N stage	
N0	37 (53.6)
N1	25 (36.2)
N2	7 (10.1)

Summary statistics are mean ± SD for continuous variables and count (%) for categorical variables BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Response assessment after neoadjuvant chemotherapy and staging before surgery

	N	All patients (N=69)
Neoadjuvant therapy	69	
Docetaxel-cisplatin-capecitabine		67 (97.1)
Docetaxel-cisplatin-fluorouracil		2 (2.9)
Response after neoadjuvant therapy	69	
Complete response		67 (97.1)
Partial response		2 (2.9)
Progressive/stable disease		0 (0.0)
Tumor downstaging	69	65 (94.2)
Downstaging in T category	69	63 (91.3)
Downstaging in N category	32	25 (78.1)
TNM stage before surgery	69	
I		3 (4.3)
II		55 (79.7)
III		3 (4.3)
IVa		8 (11.6)
T stage before surgery	69	
T1		3 (4.3)
T2		22 (31.9)
T3		36 (52.2)
T4a		8 (11.6)
N stage before surgery	69	
N0		61 (88.4)
N1		8 (11.6)

Summary statistics are count (%)

Table 3. Neoadjuvant treatment-related adverse event

	None	Grade 1-2	Grade 3-4
Leukopenia	66 (95.7)	3 (4.3)	0 (0.0)
Neutropenia	57 (82.6)	9 (13.0)	3 (4.3)
Anemia	14 (20.3)	53 (76.8)	2 (2.9)
Thrombocytopenia	69 (100.0)	0 (0.0)	0 (0.0)
Liver abnormalities	68 (98.6)	1 (1.4)	0 (0.0)
Hand-foot syndrome	8 (11.6)	61 (88.4)	0 (0.0)
Nausea	10 (14.5)	59 (85.5)	0 (0.0)
Vomiting	22 (31.9)	47 (68.1)	0 (0.0)
Stomatitis	19 (27.5)	50 (72.5)	0 (0.0)
Diarrhea	38 (55.1)	31 (44.9)	0 (0.0)
Alopecia	0 (0.0)	69 (100.0)	0 (0.0)

Summary statistics are count (%)

Table 4. Surgical characteristics and complications

	All patients (N=69)
Operating time (mins)	420.5 ± 56.6
Operating time for the thoracic phase (mins)	174.5 ± 39.5
Postoperative hospital length of stay (days)	12.4 ± 4.7
R0 resection	69 (100)
Chemotherapy after surgery	14 (20.3)
Radiation after surgery	3 (4.3)
Postoperative complication	
Temporary hoarseness	22 (31.9)
Anastomotic leak	9 (13.0)
Surgical site fluid collection	6 (8.7)
Pneumonia	5 (7.2)
Subcutaneous emphysema	4 (5.8)
Anastomotic stenosis	2 (2.9)
Atrial fibrillation	1 (1.4)
Surgical site infection	1 (1.4)
Chyle leak	1 (1.4)
Any complication*	37 (53.6)
Clavien-Dindo classification	
Grade I	17 (24.6)
Grade II	17 (24.6)
Grade IIIa	2 (2.9)
Grade IIIb	1 (1.4)
Grade IVa	0 (0)
Grade IVb	0 (0)
Grade V	0 (0)
Pathologic response	
Complete response (pCR)	18 (26.1)
Partial response (pPR)	51 (73.9)

Summary statistics are mean ± SD for continuous variables and count (%) for categorical variables
*A patient can have more than 1 complication

Table 5. Long-term outcomes

	N	All patients (N=69)
Length of follow-up (months)	69	17.3 ± 5.2
Recurrence/metastasis	69	10 (14.5)
Location of recurrence/metastasis	10	
Local recurrence		0 (0.0)
Bone		1 (10.0)
Liver		3 (30.0)
Lung		1 (10.0)
Lymph node		5 (50.0)
Mortality	69	11 (15.9)
Survival probability (95% CI) (%)		
1-year OS		91 (84 – 98)
2-year OS		78 (67 – 92)
1-year DFS		88 (81 – 96)
2-year DFS		72 (61 – 86)

Summary statistics are mean ± SD for continuous variables, count (%) for categorical variables, and Kaplan-Meier probability (95% CI) for survival probability CI, confidence interval; DFS, disease-free survival; OS, overall survival

Figure 1. Kaplan-Meier curves of overall survival and disease-free survival