ORIGINAL ARTICLE

Neoadjuvant chemotherapy followed by minimally invasive esophagectomy is safe and feasible for treatment of esophageal squamous cell carcinoma

Shaohua Ma[1] 🆔, Tiansheng Yan[1], Dandan Liu[1], Keyi Wang[1], Jingdi Wang[1], Jintao Song[1], Tong Wang[1], Wei He[1], Jie Bai[1], Liang Jin[1] & Xiaoxin Chen[2]

1 Department of Thoracic Surgery, Peking University Third Hospital, Beijing, China
2 Cancer Research Program, Julius L. Chambers Biomedical Biotechnology Research Institute, North Carolina Central University, Durham, North Carolina, USA

Abstract

Background: The advantage of neoadjuvant chemotherapy (NAC) followed by open esophagectomy for treatment of esophageal squamous cell carcinoma has been widely recognized. However, the safety and feasibility of NAC for patients receiving minimally invasive esophagectomy (MIE) remain controversial. The purpose of this study was to evaluate the potential impact of prior neoadjuvant chemotherapy on the clinical outcome of MIE by comparing two groups of patients, MIE alone and NAC plus MIE.

Methods: From May 2013 to July 2017, 124 patients with esophageal squamous cell carcinoma underwent MIE in our department, with 57 cases receiving NAC plus MIE and 67 cases receiving MIE alone. Perioperative parameters and short-term postoperative survival were compared between these two groups to evaluate the safety and feasibility of NAC given before MIE.

Results: The group with NAC plus MIE had slightly longer operating time, more blood loss, higher morbidity, increased chance of surgical intensive care unit stay, and longer surgical intensive care unit stay time than the group with MIE alone. However, there was no statistically significant difference between these two groups ($P > 0.05$). The number of lymph nodes harvested was similar in the two groups without significant difference ($P > 0.05$). The overall survival was not significantly different between these two groups either ($P > 0.05$), although before surgery the clinical stage of the group with NAC plus MIE was more advanced than the group with MIE alone.

Conclusions: NAC followed by MIE is safe and feasible for treatment of esophageal squamous cell carcinoma. NAC does not negatively impact the therapeutic outcome of MIE.

Introduction

Esophageal squamous cell carcinoma (ESCC) is a common malignancy worldwide. The majority of patients with operable esophageal cancer present with locally advanced disease, for which surgical resection as a sole treatment modality has been historically associated with poor survival. Postoperative treatment with chemotherapy, radiotherapy, or chemoradiotherapy yields disappointing outcomes.[1,2] Therefore, efforts are required to develop new treatment strategies to improve survival of ESCC patients with resectable locally advanced lesions.

In the past 20 years, neoadjuvant chemotherapy (NAC), neoadjuvant radiotherapy, or combination chemoradiotherapy for resectable ESCC has been extensively studied. Randomized clinical trials and a subsequent meta-analysis have supported the practice of preoperative NAC for ESCC patients treated with open esophagectomy.[3–5]

NAC has been incorporated into the standard treatment strategy for resectable ESCC in Japan.[6,7] However, the safety and feasibility of NAC before minimally invasive esophagectomy (MIE) remains controversial because of the potential of additional complications during and after surgery. Here, we report our single-center experience with NAC followed by MIE, and compare the clinical outcomes between patients treated with NAC plus MIE with those treated with MIE alone.

Methods

Patients

From May 2013 to July 2017, 124 patients with ESCC were scheduled for MIE at the Department of Thoracic Surgery, Peking University Third Hospital, Beijing, China. The characteristics of these patients are shown in Table 1.

Table 1 Clinical characteristics of 124 patients with esophageal squamous cell carcinoma

	NAC plus MIE (*n* = 57)	MIE alone (*n* = 67)	*P*-value
Gender			0.630
Male	41 (71.9%)	52 (77.6%)	
Female	16 (28.1%)	15 (22.4%)	
Mean age (years)	62.2 ± 8.7	61.9 ± 8.7	0.915
Location			0.255
Cervical esophagus	1 (1.8%)	2 (3.0%)	
Upper esophagus	15 (26.3%)	11 (16.4%)	
Middle esophagus	28 (49.1%)	29 (43.3%)	
Lower esophagus	13 (22.8%)	25 (37.3%)	
Clinical T stage			<0.001
Tis	0 (0%)	4 (6.0%)	
T1	4 (7.0%)	25 (37.3%)	
T2	7 (12.3%)	20 (29.9%)	
T3	45 (78.9%)	18 (26.9%)	
T4	1 (1.8%)	0 (0%)	
Clinical N stage			0.082
N0	38 (66.7%)	56 (83.6%)	
N1	16 (28.1%)	10 (14.9%)	
N2	3 (5.3%)	1 (1.5%)	
Clinical stage			<0.001
0	0 (0%)	4 (6.0%)	
Ib	4 (7.0%)	22 (32.9%)	
IIa	7 (12.3%)	12 (17.9%)	
IIb	27 (47.4%)	24 (35.8%)	
IIIa	16 (28.1%)	4 (6.0%)	
IIIb	2 (3.5%)	1 (1.5%)	
IIIc	1 (1.8%)	0 (0%)	

MIE, minimally invasive esophagectomy; NAC, neoadjuvant chemotherapy.

Standard preoperative evaluation included clinical symptoms, barium esophagogram, flexible endoscopy with biopsy, enhanced computed tomography of the thoracic and abdominal cavities, ultrasonography of supraclavicular lymph nodes, and deep venous ultrasonography of the lower extremities. According to the seventh TNM classification, tumors were in the cervical area in three cases, the upper esophagus in 26 cases, middle esophagus in 57 cases, and the lower esophagus in 38 cases. Clinical T stages were Tis in four cases, T1 in 29 cases, T2 in 27 cases, T3 in 63 cases, and T4 in one case, respectively. Clinical N stages were N0 in 94 cases, N1 in 26 cases, and N2 in four cases, respectively. Clinical stages were stage 0 in four cases, Ib in 26 cases, IIa in 19 cases, IIb in 51 cases, IIIa in 20 cases, IIIb in three cases, and IIIc in one case, respectively.

NAC

In principle, patients with early cancer were referred directly to MIE, whereas patients with locally advanced cancer (T2 and up, or N1 and up) underwent NAC before MIE. However, some patients with locally advanced cancer had MIE alone for two reasons: (i) patients refused to take NAC and requested surgery as soon as possible; and (ii) preoperative clinical staging in this study was based on a computed tomography scan, which is not always accurate.[8,9] Patients who received NAC were operated approximately 3–4 weeks after chemotherapy. After one to four cycles of NAC (docetaxel plus cisplatin [TP regimen] for NAC at the doses of 75 mg/m^2 docetaxel i.v. on day 1 and 25 mg/m^2 cisplatin i.v. on days 1, 2, and 3), the tumor was restaged with a computed tomography scan. The indication of MIE was the presence of a resectable lesion after staging and restaging.

Surgical procedure

In MIE, the combined thoracoscopic and laparoscopic approach was performed for complete esophageal resection and gastric mobilization. Two-field lymph nodes were dissected routinely for clearance of lymph nodes, especially those close to bilateral recurrent laryngeal nerves. Cervical lymph nodes clearance was accomplished if they were reported positive by ultrasonography or core needle biopsy. Gastric conduit was used as the substitute through the esophageal bed for anastomosis with remnant cervical esophagus in all cases.

Clinical outcome

The entire retrospective data of all esophageal surgeries were linked with the prospective database with institutional review board approval. Perioperative outcomes and

postoperative survival were reviewed. Operative data-points included the operation time, the amount of blood loss, intensive care unit stay and the intensive care unit stay time, length of postoperative hospitalization, and chest tube indwelling time. Short-term postoperative outcomes referred to complications within 30 days after surgery, such as anastomotic leakage or gastric conduit leakage, chyle leakage, recurrent nerve palsy, and pulmonary complications. Clinical follow-up was finally accomplished in July 2017. The median duration of follow-up was 19.5 months (range 1–51 months). During the follow-up period, postoperative patients were scheduled for regular visits to our outpatient clinic once every 3 months for the first 2 years, once every 6 months from the third to the fifth year, and annually thereafter. A total of 80% of patients were followed up according to the above protocol, and the remaining 20% through telephone interview or mail. Eight patients (6.5%, 8/124) were lost during follow-up.

Statistical analysis

SPSS 19.0 software (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Fisher's exact test and Student's t-test were used to evaluate any differences in the preoperative characteristics, as well as perioperative outcomes between two groups. Univariate analysis of overall survival (OS) was carried out with the Kaplan–Meier method and subjected to a log–rank test to analyze statistical significance. A P-value <0.05 was considered statistically significant.

Results

Before treatment, patients in the NAC plus MIE group were similar to the MIE alone group in gender distribution, age, and cancer location. However, the NAC plus MIE group had significantly more patients in the latter stages than the MIE alone group ($P < 0.001$ for both clinical T stage and clinical state) (Table 1).

NAC plus MIE had a safety profile similar to MIE alone

Safety parameters are shown in Table 2. There was no death within 90 days of surgery in the two groups. Although, the operation time, the amount of blood loss, postoperative morbidity, and surgical intensive care unit stay time were slightly higher for the NAC plus MIE group than those of the MIE alone group. However, no statistically significant difference was present between these two groups. Other parameters of the safety profile were not different either.

NAC plus MIE had a feasibility profile similar to MIE alone

In both the thoracic and abdominal cavities, the numbers of lymph nodes harvested were similar in the NAC plus MIE group and the MIE alone group. The NAC plus MIE group tended to have slightly more metastatic lymph nodes than the MIE alone group. However, no statistical significance was found. In addition, for the 57 cases in the NAC plus MIE group, NAC resulted in downstaging of clinical T stage ($P < 0.001$), but not clinical N stage (Table 3).

NAC plus MIE yielded satisfactory survival outcome similar to MIE alone

The median follow-up time was 19.5 months (range 1–51 months). The 1-year OS, 2-year OS, and 3-year OS of all patients were 89.1%, 81.5%, and 70.3%, respectively. No significant difference was found in OS within 24 months between those receiving NAC plus MIE and those receiving MIE alone ($P = 0.451$) (Fig 1). These data suggest that NAC before MIE prolonged survival, even though the NAC plus MIE group had a higher clinical stage than the MIE alone group.

Discussion

Open esophagectomy is a complex and technically challenging procedure associated with high mortality and morbidity, especially after induction chemotherapy. Although open esophagectomy after NAC has been proven to be a feasible approach, there are not many reports about the safety and feasibility of NAC followed by MIE.[6,7] Although our cohort was not randomized and controlled, our data proved that NAC followed by MIE is safe and feasible for treatment of locally advanced ESCC. NAC does not negatively impact the therapeutic outcome of MIE, instead, it may benefit long-term OS due to its downstaging effect.

As compared with open esophagectomy, MIE significantly reduces postoperative morbidity and mortality.[10,11] However, for locally advanced ESCC, there are still concerns about the use of NAC before MIE. Although NAC may result in downstaging, which is beneficial, NAC may also lead to necrosis and fibrosis, especially around the tumor, and thus complicate the surgical procedure. As a result of an unclear tumor boundary, separation of major blood vessels and nerves from the tumor may become difficult; the chance of structural damage may increase, and the operation time may be prolonged. In our patients, the operation time and the amount of blood loss of the NAC plus MIE group cases were in fact slightly more than those of the MIE alone group.

Table 2 Comparison of safety and feasibility parameters of patients receiving neoadjuvant chemotherapy plus minimally invasive esophagectomy and those receiving minimally invasive esophagectomy alone

	NAC plus MIE (*n* = 57)	MIE alone (*n* = 67)	*P*-value
Safety profile			
Operation time (min)	376 ± 105	347 ± 160	0.240
Blood loss (mL)	179 ± 213	137 ± 181	0.244
Three-field dissection	4 (7.0%)	6 (9.0%)	0.693
Mortality within 90 days	0	0	–
Postoperative morbidity	18 (31.6%)	20 (29.9%)	0.835
Respiratory complications	5 (8.8%)	6 (9.0%)	0.971
Anastomotic leakage	3 (5.3%)	8 (11.9%)	0.192
Chyle leakage	1 (1.8%)	0 (0%)	0.276
Vocal cord paralysis	8 (14.0%)	4 (6.0%)	0.130
Other complications	3 (5.3%)	5 (7.5%)	0.619
No. of SICU stay cases	18 (31.6%)	22 (32.8%)	0.881
SICU stay time (days)	3.7 ± 2.7	2.3 ± 2.0	0.080
Postoperative hospitalization (days)	15.9 + 9.6	17.0 ± 14.3	0.108
Chest tube indwelling time (days)	5.4 ± 2.5	6.5 ± 4.4	0.091
Feasibility profile			
No. of thoracic lymph nodes harvested	13.4 ± 5.5	12.5 ± 3.8	0.295
No. of thoracic lymph nodes with metastasis	0.58 ± 1.5	0.28 ± 0.91	0.181
No. of abdominal lymph nodes harvested	5.6 ± 5.2	6.3 ± 5.2	0.306
No. of abdominal lymph nodes with metastasis	0.33 ± 0.93	0.12 ± 0.86	0.187
No. of cases with residual cancer			
R0	56 (98.2%)	65 (97.0%)	0.657
R1	0	0	–
R2	1 (1.8%)	2 (3.0%)	0.657

MIE, minimally invasive esophagectomy; NAC, neoadjuvant chemotherapy; SICU, surgical intensive care unit.

Whether preoperative NAC may increase postoperative complications is another major concern. An international survey found that the postoperative mortality rate of esophagectomy was as high as 7–9%, and the overall complication rate was >50%.[12] The overall complication rate of MIE was 30.6% in our study, which was similar to the reports in the literature.[13,14] Furthermore, the overall complication rate of the NAC plus MIE group was similar to the MIE alone group. The incidence of recurrent laryngeal nerve palsy was slightly higher for those with NAC, probably due to the fact that most cases in the NAC plus MIE group were locally advanced ESCC.[15] Tissue fibrosis after NAC resulted in difficulty in the mobilization of recurrent laryngeal nerve.[16,17] It is worth mentioning that MIE had lower incidences of chylothorax and pneumonia than open esophagectomy.[18,19] From these data, we found that NAC did not increase the incidences of postoperative complications and was safe for ESCC treated with MIE.

Lymph node dissection is essential for long-term survival of patients with ESCC.[20,21] In this study, the number of thoracic lymph nodes harvested was similar in both groups: 13.4 in the NAC plus MIE group and 12.5 in the MIE alone group. However, many surgeons believed that the location of lymph nodes was more important than the number of lymph nodes harvested, especially in the case of bilateral recurrent laryngeal nerve lymph nodes.[22] This would explain why laryngeal recurrent nerve paralysis occurred at a high rate in the NAC plus MIE group, as locally advanced ESCC is more likely to have lymph node metastasis near bilateral recurrent laryngeal nerves. In our cohort, the number of lymph nodes harvested was lower than what was reported in the literature.[20,22]

In this study, NAC resulted in downstaging in clinical T stage, but not in clinical N stage, which is consistent with the literature.[23] Although whether NAC improves the long-term survival in patients with ESCC is still

Table 3 Downstaging of esophageal squamous cell carcinoma by neoadjuvant chemotherapy for patients receiving neoadjuvant chemotherapy followed by minimally invasive esophagectomy (*n* = 57)

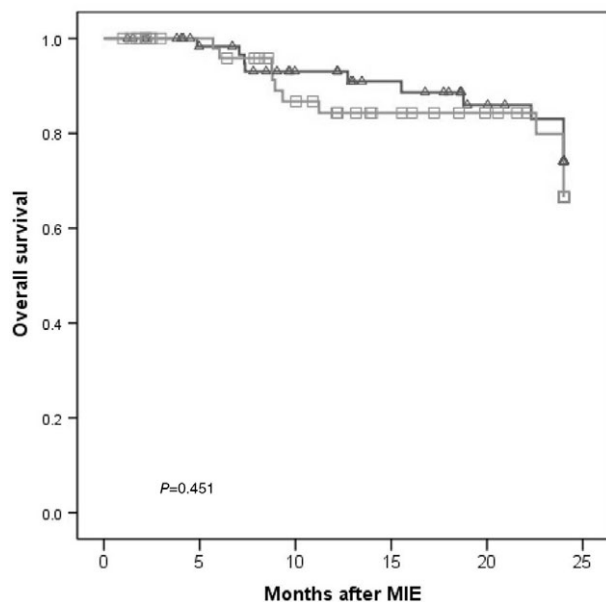|	Before NAC	After MIE	*P*-value
Clinical T stage: No. of cases (%)			<0.001
T1	4 (7.0%)	12 (21.1%)	
T2	7 (12.3%)	19 (33.3%)	
T3	45 (78.9%)	24 (42.1%)	
T4	1 (1.8%)	2 (3.5%)	
Clinical N stage: No. of cases (%)			0.788
N0	38 (66.7%)	37 (64.9%)	
N1	16 (28.1%)	14 (24.6%)	
N2	3 (5.3%)	5 (8.8%)	
N3	0 (0%)	1 (1.8%)	

Figure 1 Overall survival of patients (□) receiving neoadjuvant chemotherapy plus minimally invasive esophagectomy and those (△) receiving minimally invasive esophagectomy alone.

controversial, several randomized controlled trials and meta-analyses supported the survival benefits of NAC for ESCC treated with open esophagectomy or MIE.[3–5] According to our data, although the NAC plus MIE group had a higher stage than the MIE alone group, the 2-year OS was similar in these two groups. It is suggested that NAC may have a long-term survival benefit for locally advanced ESCC, yet a randomized well-controlled study will be required. Furthermore, patients with ESCC often have poor tolerance to chemotherapy after surgery due to the reconstruction of the digestive tract, and preoperative NAC can be better tolerated.[24,25] Therefore, NAC is better given before surgery than after if it is warranted anyway.

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Disclosure

No authors report any conflict of interest.

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