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Influence of Neoadjuvant Chemotherapy on Short-term Outcomes After Minimally Invasive Esophagectomy for Esophageal Cancer

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Abstract. *Background/Aim: The safety of minimally invasive esophagectomy (MIE) after neoadjuvant chemotherapy (NAC) for esophageal cancer has not been adequately confirmed. Patients and Methods: Two hundred and twelve patients who underwent MIE for esophageal cancer at the Kumamoto University Hospital between May 2011 and June 2018 were enrolled. A total of 46 patients received NAC and underwent subsequent MIE. The control group comprised 166 patients who underwent MIE without any preoperative treatments. We retrospectively investigated the patient-related, tumor-related, and surgery-related factors, as well as the short-term outcomes, between the two groups. Results: Preoperative lymphocyte counts and hemoglobin and albumin levels were significantly lower in the NAC plus MIE group than in the MIE alone group. Preoperative nutritional status, as measured by the prognostic nutrition index and controlling nutritional status, was also poorer in the NAC plus MIE group ($p<0.001$). However, short-term outcomes such as operation time, intraoperative blood loss, and incidence of postoperative complications were statistically equivalent between the groups. Conclusion: Although administration of NAC was associated with a poorer preoperative condition, it did not worsen the short-term outcomes after MIE.*

Esophagectomy, the main treatment for esophageal cancer, is highly invasive, and the incidences of postoperative morbidity and mortality of esophagectomy are higher than those of surgery for other gastrointestinal cancers. Minimally invasive esophagectomy (MIE) is considered less invasive than open esophagectomy. Hence, MIE is increasingly being performed, and is expected to improve short-term outcomes after surgery.

However, it is not clear whether MIE can truly reduce postoperative morbidity and mortality. Thus far, one randomized controlled trial suggested that MIE can contribute to reducing postoperative pulmonary infections (1). However, several retrospective studies with large real-world cohorts showed no advantages of MIE in terms of short-term outcomes (2-5).

Neoadjuvant therapy followed by esophagectomy has become a standard therapy for locally advanced esophageal cancer. In Japan, neoadjuvant chemotherapy (NAC) is commonly administered as neoadjuvant therapy since the results of the JCOG9907 were published in 2012 (6). Although MIE after NAC is increasingly performed, the safety of MIE in this situation has not been adequately verified. Therefore, this study aimed to clarify whether MIE can be safely performed after NAC.

Patients and Methods

Patients. Between May 2011 and June 2018, 232 patients underwent three-incisional MIE accompanying two- or three-field lymphadenectomy for esophageal squamous cell carcinoma (ESCC) at Kumamoto University (Kumamoto, Japan). Sixteen patients who underwent preoperative chemoradiotherapy and 4 patients who underwent two-stage MIE without digestive reconstruction were excluded. Consequently, 46 patients who received NAC and subsequent MIE and 166 patients who underwent MIE alone without any preoperative treatment were suitable for this study.

The patient-, tumor-, and surgery-related factors, and short-term outcomes between the groups were retrospectively investigated. In this study, we classified the clinical tumor stage according to the Union for International Cancer Control (UICC) TNM classification of malignant tumors, 7th edition (7).

The Institutional Ethics Committee at Kumamoto University approved this study.

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Treatment strategy. Esophagectomy alone was performed for patients with clinical stage 0 and IA. NAC was administered to patients with clinical stage IB, II, and III. MIE was defined as complete thoracoscopic esophagectomy, irrespective of laparoscopy use. The extent of lymphadenectomy was determined according to the 2012 guidelines of the Japan Esophageal Society (8). Three-field lymphadenectomy was mainly conducted for the upper-thoracic and middle-thoracic ESCC. Cervical lymphadenectomy was excluded for T1 ESCC in the lower-thoracic.

Neoadjuvant chemotherapy. We adopted two regimens of NAC during this study period. The FP regimen consisted of cisplatin (80 mg/m^2, day 1) and 5-fluorouracil (5-FU) (800 mg/m^2, days 1-5) delivered intravenously. The DCF regimen consisted of docetaxel (60 mg/m^2, day 1), cisplatin (6 mg/m^2, days 1-5), and 5-FU (350 mg/m^2, days 1-5) delivered intravenously. Selection of the two current regimens was determined chiefly owing to a historical reason: the DCF regimen was predominantly administered between 2011 and 2015 and the FP regimen was dominant between 2016 and 2018. Each regimen was administered every 3 to 4 weeks and principally repeated for two cycles. MIE was performed 4 weeks after the last cycle of NAC was completed.

Definition of morbidities. Postoperative morbidities were defined according to the definitions advocated by the Society of Thoracic Surgeons (9). Morbidity details are also available elsewhere. Any complication and any severe complication were defined as a state where the Clavien-Dindo classification was ≥II and ≥IV, respectively (10).

Statistical analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienne, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (11). The chi-squared test was performed for statistical analyses of categorical variables between the two groups. The Mann-Whitney *U*-test or the Student's *t*-test was performed for analysis of continuous variables of the two groups. When the number of events was less than 5, Fisher's exact test was performed. A *p*-values of <0.05 were considered statistically significant.

Results

The baseline patient characteristics are shown in Table I. Most patient-related factors did not differ significantly between the two groups. However, the MIE after NAC group contained significantly more patients with advanced ESCC ($p<0.001$).

Table II shows the preoperative blood biochemistry and nutritional parameters in the two groups. Preoperative lymphocyte counts, hemoglobin, and albumin were lower in the MIE after NAC group compared with the MIE group. The prognostic nutritional index was also lower in the MIE after NAC group compared with the MIE group ($p<0.001$). Moreover, malnutrition, as measured by controlling nutritional status, was more frequently observed in the MIE after NAC group ($p<0.001$).

Table I. *Characteristics of patients*.

Variables	MIE (n=166)	NAC+MIE (n=46)	*p*-Value
Mean age±SD	66.1±7.9	64.1±6.6	0.127
Gender male	147 (89%)	40 (87%)	0.797
BMI	22.6±3.0	22.6±2.9	0.876
Brinkman index±SD	720±520	750±510	0.758
Performance status			>0.999
0	158 (95%)	44 (96%)	
1	7 (4%)	2 (4%)	
2	1 (1%)	0	
Comorbidity			
Cardiovascular	94 (56.6%)	24 (37.5%)	0.618
Respiratory	51 (30.7%)	9 (14.1%)	0.195
DM	35 (21.1%)	14 (21.9%)	0.235
Clinical stage			<0.001
0, I	154 (93%)	6 (13%)	
II	12 (7%)	17 (37%)	
III	0	18 (39%)	
IV	0	5 (11%)	

Data are expressed as mean±standard deviation or the number of cases (%). BMI: Body mass index; DM: diabetes mellitus; MIE: minimum invasive esophagectomy; NAC: neoadjuvant chemotherapy; SD: standard deviation.

The surgery-related factors between the two groups are shown in Table III. The extent of lymphadenectomy was significantly wider in the MIE after NAC group than in the MIE group ($p<0.001$). However, the use of laparoscopy, operation time, and intraoperative bleeding were statistically equivalent in the two groups.

The incidence of postoperative morbidities is depicted in Table IV. The incidence of each morbidity was statistically equivalent between the groups. In the MIE group, one patient died of progression of chronic myelomonocytic leukemia. In the MIE after NAC group, one patient died of respiratory failure. The length of hospital stay was also equivalent between the two groups.

Discussion

Neoadjuvant therapy followed by esophagectomy has become a standard therapy for locally advanced ESCC. Although MIE after NAC is being increasingly performed in Japan, the safety of MIE in this situation has not been well established. In this study, we found that preoperative nutritional status and hemoglobin levels were significantly worse in the MIE after NAC group. However, NAC did not adversely affect short-term outcomes after MIE.

There are several reasons why patients who underwent NAC had worse nutritional status and lower hemoglobin levels. First, the NAC plus MIE group had more patients with advanced cancer, which is often associated with disorders of

Table II. *Preoperative blood chemistries and nutritional parameters.*

	MIE (n=166)	NAC+MIE (n=46)	*p*-Value
WBC ($\times 10^3$)	5.83±1.73	5.33±1.57	0.081
Neutrophil ($\times 10^3$)	3.45±1.50	3.13±1.31	0.179
Lymphocyte ($\times 10^3$)	1.79±0.57	1.60±0.57	0.047
Hemoglobin (g/dl)	13.6±1.6	11.9±1.2	<0.001
Platelet ($\times 10^3$)	22.0±6.0	21.7±6.3	0.781
CRP (mg/dl)	0.19±0.34	0.23±0.36	0.517
Albumin (g/dl)	4.1±0.4	3.9±0.3	0.011
Creatinine (mg/dl)	0.8±0.2	0.8±0.1	0.690
Total cholesterol (mg/dl)	200±36	202±40	0.778
PNI	49.6±4.7	47.1±4.8	<0.001
CONUT			<0.001
Normal	118 (71%)	10 (22%)	
Malnutrition	46 (28%)	22 (48%)	
Missing data	2 (1%)	14 (30%)	

Data are expressed as mean±standard deviation or the number of cases (%). WBC: White blood cell; CRP: C-reactive protein; PNI: prognostic nutritional index; CONUT: controlling nutritional status.

Table III. *Surgery between the groups.*

	MIE (n=166)	NAC+MIE (n=46)	*p*-Value
Fields of lymph node dissection			<0.001
≤2	62 (37%)	4 (9%)	
3	104 (63%)	42 (91%)	
Conduit			>0.999
Stomach	160 (96%)	45 (98%)	
Colon	6 (4%)	1 (2%)	
Use of a laparoscopy	140 (84%)	34 (74%)	0.134
Mean operation time±SD	610±100	600±70	0.603
Operation time in the chest	206±68	218±55	0.271
Mean blood loss±SD	285±353	331±315	0.422

Table IV. *Postoperative complications.*

	MIE (n=166)	NAC+MIE (n=46)	*p*-Value
Any complication (CDc ≥II)	51 (30.7%)	17 (26.6%)	0.476
Severe complication (CDc ≥IV)	11 (6.6%)	4 (6.3%)	0.745
Pneumonia	15 (9.0%)	4 (6.3%)	>0.999
Any pulmonary complication	22 (13.3%)	9 (14.1%)	0.345
Surgical site infection	41 (24.7%)	9 (14.1%)	0.559
Anastomotic leakage	27 (16.3%)	4 (6.3%)	0.244
Cardiovascular complication	9 (5.4%)	4 (6.3%)	0.486
Reoperation	11 (6.6%)	4 (6.3%)	0.745
Median hospital stays	22.5 (19.0-28.5)	24.5 (19.25-32.75)	0.391
In-hospital mortality	1 (0.6%)	1 (1.6%)	0.388

Data are expressed as median (interquartile range) or the number of cases (%). CDc: Clavien-Dindo classification.

dietary passage. Secondly, appetite loss and nausea can occur during NAC that can also induce malnutrition during preoperative treatment. In addition, hemorrhage from advanced primary cancer and myelosuppression induced by the anticancer therapy might reduce the hemoglobin levels. Previous studies suggested that preoperative low nutritional status is a significant risk factor for postoperative complications after esophagectomy (12-14). Therefore, it is important to maintain nutritional status during NAC. Enteral nutrition *via* nasogastric feeding tube and total parenteral nutrition may contribute to maintaining nutritional status during NAC. Mazaki *et al*. found that immunoenhancing the enteral and parenteral nutrition can reduce the incidence of various morbidities after gastrointestinal surgery (15). Patients with dysphagia due to advanced esophageal cancer should pay careful attention to nutrition during NAC. For such patients, esophageal stenting during preoperative chemotherapy for patients with stenosis may be effective to maintain preoperative nutrition (16, 17).

In this study, out of 46 patients who received NAC, 26 received the FP regimen and 20 received the DCF regimen. DCF is associated with more frequent and stronger myelosuppression than FP. In contrast, FP is correlated with a frequent incidence of nausea and appetite loss. It is necessary to determine whether the differences in adverse events affect preoperative nutritional status and short-term outcomes after MIE. However, preoperative nutritional status and surgical outcomes did not differ significantly between patients receiving the two regimens, in our study (data not shown). A phase III randomized controlled trial comparing the FP and DCF regimens as neoadjuvant treatments for locally advanced esophageal cancer (JCOG1109) is ongoing (18), that may elucidate the influence of the type of regimen on short-term outcomes after esophagectomy.

This study showed that MIE can be safely performed even after NAC. However, it is arguable whether the current result is applicable to every clinical situation. This study included only two T4 patients who received NAC. T4 tumors often require more invasive surgery and simultaneous resection of the invaded organ. In such situations, open esophagectomy may be useful to perform resection more safely and avoid the need for emergency surgery. Accumulation of data is necessary to elucidate whether MIE after NAC can be safely performed in T4 cases.

Furthermore, the indication of MIE after NAC for patients with high-risk comorbidity must be determined. Previous

study suggested that patients who are current smokers at surgery are more likely to have complications after MIE (19). Impaired respiratory function and worse performance status is also associated with increased postoperative morbidities (20, 21). Such patients may have anemia and malnutrition more frequently, which can be risks of postoperative morbidity, so they must be closely monitored. Marker *et al*. have shown that the ERAS program leads to an improvement in postoperative outcomes. Preoperative respiratory rehabilitation programs are effective at preventing postoperative pulmonary complications (22). In addition, sufficient preoperative smoking cessation may decrease postoperative morbidities after MIE (23). We adopted these prophylaxes during treatment, which may be associated with the current favorable results in the NAC plus MIE group.

This study has several limitations. It was performed at a single institution, and the number of patients was not large. In addition, it was a retrospective study that related to a significant difference in patient background between the two groups. Notably, MIE was primarily conducted in patients with early-stage cancer that required no preoperative treatment. Thus, the MIE after NAC group contained more recent cases than the MIE alone group, and is therefore associated with a historical bias regarding perioperative management.

In conclusion, NAC did not worsen the short-term outcomes after MIE. However, it is important to address methods of minimizing preoperative risks during NAC to reduce postoperative morbidity.

Conflicts of Interest

All Authors have no conflict of interests in relation to this article.

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