



ORIGINAL RESEARCH PAPER

Cardiothoracis

OUTCOMES OF IVOR-LEWIS AND MINIMAL INVASIVE MCKEOWN ESOPHAGECTOMY FOR LOWER AND MIDDLE ESOPHAGEAL CANCER.

KEY WORDS: Esophageal Cancer; Esophagectomy; Ivor Lewis; Mckeown; Minimally Invasive.

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ABSTRACT

Background: Ivor-Lewis esophagectomy and Mckeown esophagectomy are used to treat esophageal cancer, and minimally invasive technique is increasingly adopted to lower morbidities and complications after operation. Surgical approaches to esophageal cancer are not standardized however. This study compares results of Mckeown esophagectomy as minimally invasive technique with the conventional Ivor-Lewis esophagectomy. **Methods:** Data of patients underwent Ivor-Lewis esophagectomy (ILE) or minimally invasive Mckeown esophagectomy (MIME) operation from January 2009 to December 2019 were retrospectively collected. Preoperative conditions, cancer characteristics, and operative outcomes were selected as variables for analysis. Total 125 patients undergone surgery for esophagus, 54 got ILE for esophageal cancer and 65 got MIME. **Results:** Despite minimally invasive approach, Mckeown esophagectomy tend to get more complications than Ivor-Lewis esophagectomy. Postoperative arrhythmias and vocal cord palsy occurred significantly higher in MIME group than ILE. Fatal complications like pneumonia, bronchoesophageal fistula, stenosis or leakage of anastomosis site also appeared more frequent in MIME group with low significance. Short term mortalities showed no difference. When comparing total survival and disease-free survival at middle to lower esophageal cancer, MIME group seemed better survival and lower cancer recurrence than ILE group, although significance was low. **Conclusions:** Surgical methods should be thoroughly considered in managing esophageal cancer due to possible postoperative morbidities. MIME tend to have higher postoperative complications than ILE, but short-term mortalities showed no differences. When managing middle and lower esophageal cancer MIME can be an option to lower cancer recurrence and better survival.

INTRODUCTION

Esophageal cancer is a fatal disease with high mortality and poor prognosis [1]. Primary treatment for the cancer is surgery, and due to the character of esophagus a surgeon has to radically process esophagectomy and lymph node dissection in order to avoid possible cancer recurrence. Since operative techniques include highly invasive approach, conventional open esophagectomies tend to have high mortality and morbidity after surgery [2]. To lower postoperative complications, minimally invasive approaches which perform endoscopic approach to either thoracic or abdominal area were introduced [3, 4]. Esophageal surgeries can be divided into two large groups – Ivor-Lewis esophagectomy (ILE) which approaches through chest and abdomen, and Mckeown esophagectomy (ME) by which through chest, abdomen, and neck. Several studies compared results of ILE and ME, proving similar results that ME has more reliable R0 resection and lower cancer recurrence with more perioperative complications than ILE. Regarding minimally invasive technique lowers the complication rate than conventional open form, a theory can be made that ME with minimally invasive approach (MIME) may have as lower complication rate as ILE, and similar R0 resection rate as conventional ME. This study targets this theory by comparing MIME and ILE in esophageal cancer.

MATERIALS AND METHODS

From January 2009 to December 2019, we retrospectively collected patient data who received surgical treatment for esophageal cancer. Hospital electro medical record was used to collect each patient's personal data which was approved by IRB and informed consent. Preoperative information includes patient age, sex, height, weight, underlying disease, smoking habits according to history taking. Additional underlying diseases not taken from patient's history were diagnosed by preoperative work-ups. ILE was performed as gastropasty through median laparotomy approach and gastroesophageal anastomosis formation through right thoracotomy. MIME in this study was performed as esophageal dissection through right thoracoscopic approach, gastropasty as median laparotomy, and gastroesophageal anastomosis through left cervical incision. Perioperative characteristics include

cancer stage, location, numbers of harvested lymph node or invaded lymph node, clearance of resection margin, adjuvant or neoadjuvant chemotherapy or radiotherapy. Pathology proven TNM stage was converted to esophageal cancer staging according to AJCC 8th edition, and pathology proven not as cancer, such as esophageal stricture after chemical burn, were excluded. Cancer location was defined as upper when the middle part of the tumor lies above upper incisor (UI) 25cm, lower if below UI 30cm, and middle between UI 25 to 30cm. Other values were directly collected through medical records. Intraoperative data consist of operation time, hospital days and intensive care unit (ICU) stay days, follow up duration and disease-free duration, and complications.

Hospital days were defined as from admission, or transfer in day to discharge, expire, or transfer out day since there were cases that patient kept admission for other conditions. ICU stay days were counted as from surgery date to general ward transfer out date, or transfer out date. If patient was readmitted to ICU for complications after surgery, ICU days were counted. In cases of transferred to other department with ICU kept state, or readmitted for other cause, ICU days were not counted. Days from surgery to each patient's death, or research endpoint was defined as follow up duration, and to the date of last normal CT findings – recorded as no evidence of tumor recurrence of metastasis – was defined as disease free duration. Mortality was largely based-on postoperative outpatient medical records, if there is no record after discharge, validity of national health care insurance was used. Complications after surgery include leakage or stenosis of anastomosis site, pneumonia, bronchoesophageal fistula (BEF), arrhythmia, and vocal palsy. Esophagography or endoscopic findings were used to decide anastomosis site problem and BEF. Reference of pulmonary haziness in chest x-ray findings within 1 month after surgery or record of consulting to pulmonary department for antibiotics use were defined as postoperative pneumonia. Electrocardiogram (EKG) recording after surgery was used to diagnose arrhythmia and reference of voice change or consult to otolaryngology department after surgery were defined as vocal cord palsy. Statistical data used means and standard deviation. Student t-test was used comparing

continuous variables and *chi square test* for percentage difference. Overall survival and cancer recurrence (or metastasis) rate comparison among time were compared through Kaplan-Meier curve using R. Significance was defined as *p* value less than 0.05.

RESULTS

Those who received esophageal surgery were 125 with 58 ILE and 67 MIME. Among them, ILE for esophageal cancer were 56 and 2 got minimally invasive ILE. MIME for esophageal cancer were 65, so total 119 patients (54 for ILE, 65 for MIME) were enrolled. All of patient's medical record did not lost follow-ups until death, or December 2019 (data closure time). Mean age of patient was 71.5 and 71.8, with no significance. male to female ratio was approximately 8:1 in both groups. Body weight, height, and comorbidity conditions were not significantly different between two groups (Table 1). Stage I cancer was most frequent in both group (24 in ILE and 25 in MIME), and the number of patients decreased in higher stage. There was no significant difference in cancer stage distribution, but when comparing cancer location MIME group got more upper esophageal cancer cases than ILE ($p=0.02$). ME is known to apply mostly on upper esophageal cancer [5], but in this study lower esophageal cancer case was most frequent in whether ILE or MIME. Most of cancers were squamous cell carcinoma in both groups. ME is previously known to dissect more lymph nodes than ILE [6] and MIME group got actually slightly more lymph node dissection, but there was no significant difference between the number of dissected lymph nodes or invaded lymph nodes, which both methods got about 25 dissection of lymph nodes in each surgery. ME does more radical resection and thus is known to get clearer resection margins than ILE [7]. But in this study both ILE and MIME had similar R0 resection rate around 90%, and the exact ratio was high in ILE. Preoperative or postoperative chemoradiotherapy case were not so different in both groups, although MIME had smaller preoperative chemoradiotherapy numbers (Table 2). ILE was not performed after 2016 and MIME started from 2015. Mean operation time was 278 minutes in ILE and 319 in MIME, with *p* value less than 0.01. Mean ICU stay period was about 5 days, and total hospital days were about 1 month, showing similar results in both groups. Short term mortalities, both 30 days and 90 days, showed no significant difference comparing to other studies presenting ME tend to have larger short-term mortality than ILE [8, 9]. Mean follow up duration was significantly longer in ILE group as 43.2 months, comparing MIME group as 20 months. When comparing postoperative complications, MIME group got significantly more arrhythmia, and vocal cord palsy. Chances of leakage or stenosis at anastomosis site, pneumonia, chylothorax were also higher in MIME group with no significance, which are different to previous studies [10]. Bronchoesophageal fistula occurred more in ILE group with no clear difference, which is different to other studies presenting the complication occur more on ME [9] (Table 3). Overall survival and disease-free survival after surgery showed different conclusions according to cancer location. When comparing survival and cancer recurrence rate regardless of cancer location, both groups showed similar results. Although Kaplan-Meier curve showed MIME group got slightly better survival than ILE after 1 year of surgery, *p* value was 0.76, meaning no difference. And this survival gap inverted after about 3 years of surgery (Fig. 1A). Chances of disease-free survival were slightly better in MIME group, showing that after 10 months of surgery MIME group got lesser cancer recurrence or metastasis, but the *p* value was 0.68. Median survival period was 17.7 months in MIME and in 29.9 months in ILE (Fig. 1B). But concerning cancer location distribution was different especially on upper esophagus, this comparison may not reflect exact results. When comparing middle to lower esophageal cancer management, Kaplan-Meier curve was drawn differently. Although *p* values were still over 0.05, MIME group tend to get better survival (Fig. 2A) and lesser tumor recurrence than ILE

group about 10 months after surgery (Fig. 2B). Median survival period in this plot was 17 months in MIME and 27.5 months in ILE group.

DISCUSSION

This study compares outcomes of esophageal cancer between MIME and ILE. Previous studies have shown McKeown esophagectomy had disadvantages of higher morbidity and postoperative complication than Ivor-lewis esophagectomy [7], and this gap might be overcome by minimally invasive approach, as MIME has lesser complications than conventional ME [4, 11]. Results were consistent to previous studies. What was different to other studies were short term mortalities and occurrence rate of chylothorax and BEF. Previous studies got results ME has higher perioperative mortality and complications than ILE [6], whereas there was no significant difference in this study. This suggests that MIME may serve as an option for lowering these complications while having similar mortality. Operational results appeared different as cancer location, since there is a trend to apply ME on upper esophageal cancer due to the operation method [12]. According to this study MIME might also be an option for middle and lower esophageal cancer for better survival and lower cancer recurrence, although there is a risk of more complications. Distribution of cancer location showed different result comparing to other research [5], but it is not clear that this was due to general trend shift, or especially unique patient pool at this center. Comparing other centers' results is needed for further analysis. Precise stage workup is needed in esophageal cancer in order to predict prognosis and thus dissection of lymph node is committed during the surgery [13, 14]. Both ILE and MIME turned out dissecting similar number of nodes in this study. Generally, postoperative complications occur in about 50% of the patients after esophagectomy, and the most common complications are anastomosis site problem, pneumonia, and arrhythmias [10]. Researches comparing long term results between ME and ILE concludes ME tend to lower quality of life than ILE after long term survival due to high postoperative complication, but there are few papers comparing ILE with minimally invasive ME. In this study ILE cases had longer follow up duration than MIME cases, which mainly started after 2009 and 2015, suggesting long term comparison may not be valid. Comparing ILE with MIME as tumor recurrence and patient's life quality for longer duration demands longer follow up.

Limitations

There are several limitations in this study. First, this was a retrospective study performed in a single center with single surgeon, which had relatively small number of patients and lack of matching results to other performers. Second, from 2009 to 2019 there was surgeon's preference and skill change. In this study, change from conventional to minimal invasive approach technique was found, and ME was more applied than ILE as time lapses, but these were not reflected. Formation of gastroesophageal anastomosis at cervical level is easier than thoracic level, meaning duration of learning curve may different for single person. In this study the surgeon started ILE at younger age, suggesting there might be a lot more time-consuming period for esophageal surgery. Patients with upper esophageal cancer largely got MIME, and there is a chance that upper esophageal cancer itself may cause vocal cord palsy regardless of the surgical approach. Also, there was a trend shift from ILE to MIME in 2015-2016, which means MIME case may not be valid in long term survival. Third, there is a chance of selection bias. As the operator continues surgery, it is likely that one gathers patient data to decide which to go on or not. Finally, this study relies on data about Korean patients, which will have difficulty to apply on other countries. The histology of esophageal cancer and location distribution differs world widely, where lower part adenocarcinoma dominant in west and upper part squamous cell carcinoma in east [15]. In this study patient

pool was largely consistent to eastern type, meaning there would be different result if applied to other pool of patients.

CONCLUSION

Surgical approach to esophageal cancer is still controversial. Further trials and researches are needed to compare long term results, and to decide the most appropriate surgical methods. When managing middle and lower esophageal cancer, MIME approach might be an option for expecting lowering tumor recurrence or metastasis.

Conflicts of Interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript, or any other conflicts of interest to disclose.

Table 1. Baseline Characteristics Of Patients In Study (n=119)

	ILE (n=54)	MIME (n=65)	P value
Age, year	71.5±9.8	71.8±10.0	0.43
Sex	male 47, female 7	male 58, female 7	0.71
Weight, Kg	62.2±11.2	61.1±10.7	0.29
Height, cm	165.4±7.8	165.0±6.8	0.39
BMI, Kg/cm²	22.7±3.3	22.4±3.4	0.32
Comorbidities			
smoking	27 (50%)	26 (40%)	0.27
HTN	29 (54%)	28 (43%)	0.25
DM	11 (20%)	17 (26%)	0.46
COPD	6 (11%)	11 (17%)	0.37
CAD	6 (11%)	8 (12%)	0.84
CKD	1 (2%)	2 (3%)	0.67

Values are presented as mean±standard deviation, or number (%)

ILE: Ivor-lewis esophagectomy, MIME: minimally invasive McKeown esophagectomy, BMI: body mass index, HTN: hypertension, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, CKD: chronic kidney disease

Table 2. Pathologic Features Of Esophageal Cancer After Surgery

Stage	ILE (n=54)	MIME (n=65)	P value
I	24 (44.4%)	25 (38.5%)	0.51
II	13 (24.1%)	19 (29.2%)	0.53
III	11 (20.4%)	13 (20.0%)	0.96
IV	6 (11.1%)	8 (12.3%)	0.84
Cancer location			
upper	4 (7.4%)	15 (23.1%)	0.02
middle	15 (2.8%)	15 (23.1%)	0.56
lower	35 (64.8%)	35 (53.8%)	0.23
Cancer pathology			
SqCC	48 (88.9%)	58 (89.2%)	0.95
Adenoca	4 (7.4%)	6 (9.2%)	0.72
other	2 (3.7%)	1 (1.5%)	0.45
Harvested LN	25±11	27±12	0.11
Invaded LN	2±3	1±2	0.07
Free resection margin	50 (92.6%)	57 (87.7%)	0.38
preop chemo/RT	10 (18.5%)	5 (7.7%)	0.08
postop chemo/RT	24 (44.4%)	31 (47.7%)	0.72

SqCC: squamous cell carcinoma, adenoca: adenocarcinoma, LN: lymph node, chemo: chemotherapy, RT: radiotherapy

Table 3. Outcomes and complications of ILE and MIME

	ILE (n=54)	MIME (n=65)	P value
Operation time, min	278±47	319±81	<0.01
ICU stay day	5.2±8.4	5.4±7.8	0.28
Total hospital day	30.8±17.4	30.2±17.4	0.28
30 days mortality	2 (3.7%)	3 (4.6%)	0.66
90 days mortality	5 (9.3%)	7 (10.8%)	0.57

Follow up duration, month	43.2±36.8	20.0±15.2	<0.01
Complications			
Anastomosis site leakage	3 (5.6%)	10 (15.4%)	0.06
Anastomosis site stenosis	7 (13.0%)	15 (23.1%)	0.09
Pneumonia	11 (20.4%)	21 (32.3%)	0.08
Chylothorax	2 (3.7%)	3 (4.6%)	0.66
BEF	4 (7.4%)	3 (4.6%)	0.70
Arrhythmia	2 (3.7%)	10 (15.4%)	0.02
Vocal cord palsy	3 (5.6%)	29 (44.6%)	<0.01

ICU: intensive care unit, BEF: bronchosophageal fistula

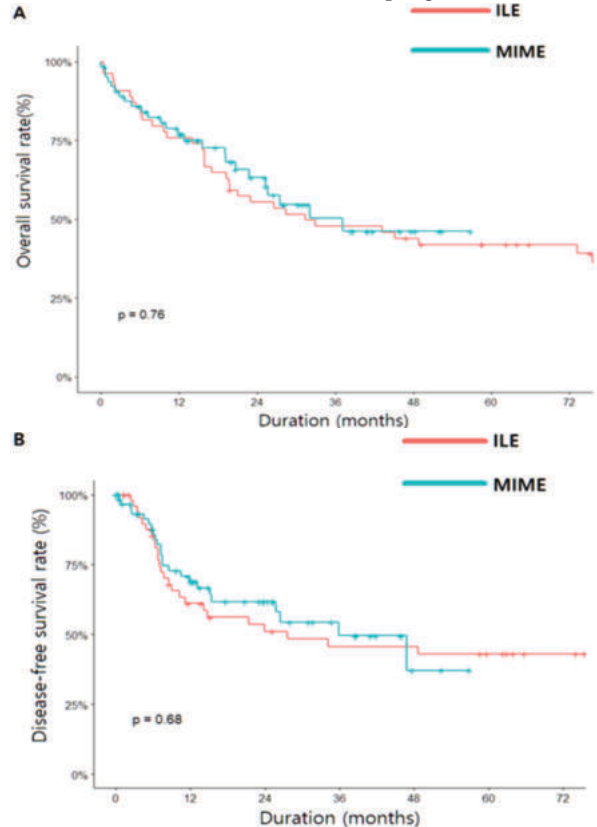


Fig. 1. (A) Kaplan-Meier curve for comparing ILE and MIME as overall survival rate and (B) disease-free survival rate.

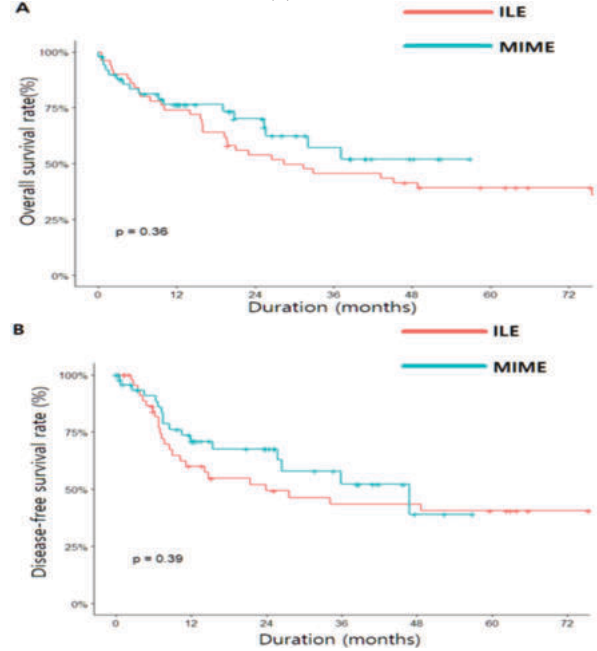


Fig. 2. (A) Kaplan-Meier curve for comparing ILE and MIME in lower and middle esophageal cancer as overall survival

rate and (B) disease-free survival rate.

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