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Efficacy of Video-assisted Thoracoscopic Esophagectomy for Stage II/III Esophageal Cancer: Analysis Using the Propensity Scoring System

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Abstract. *Background/Aim: The purpose of this study was to evaluate the usefulness of minimally invasive esophagectomy (MIE) for stage II/III esophageal cancer (EC). Patients and Methods: We compared surgical outcomes between MIE and open esohagectomy in EC patients with pStage II/III using the propensity scoring system. Results: Fifty-seven patients were classified into the MIE group and 57 patients into the open esophagectomy (OE) group. The incidence of major complications was similar between the two groups. The 5-year OS was significantly better in the MIE group (69.0% vs. 35.5%; p=0.004) and no significant difference was observed in the 5-year recurrence-free survival (RFS, 52.2% vs. 29.2%; p=0.064). Multivariate analysis showed MIE was a prognostic factor of OS (p<0.001) and RFS (p=0.032). Conclusion: MIE was as safe and feasible as OE, and an independent prognostic factor for OS and RFS in patients with stage II/III EC.*

Esophageal cancer (EC) is the seventh most common malignancy in the world (1), and the overall 5 year survival rate is approximately 20% (2, 3). Various treatments including endoscopic resection, surgery, chemotherapy, and radiation therapy are required for EC because of its clinical diversity. In Japan, according to the Japanese guideline for the treatment of EC (4, 5), chemoradiotherapy (CRT) for early EC is also listed as a curable treatment as surgery. Furthermore, surgical esophagectomy is the main treatment for cStage II/III EC as it can be expected to result in radical cure. However, the optimal approach of esophagectomy remains unclear. Meanwhile, EC surgery sometimes causes life-threatening complications. Essential organs such as the trachea, recurrent nerve, and cardiopulmonary vessels nearby the esophagus are often injured by the esophagectomy with lymphadenectomy, which can lead to death. Several approaches have been reported to decrease postoperative complications and mortality (6-8). Minimally invasive esophagectomy (MIE) using a thoracoscope is widely performed worldwide, and several reports have suggested the safety and efficacy of MIE compared with open esophagectomy (OE) (9-13). Most of these have shown that MIE provided faster recovery and lower morbidity. However, it is uncertain which surgical approach (MIE or OE) provides an acceptable long-term outcome.

Therefore, this study aimed to reveal the long-term outcome of MIE for pStage II/III EC compared to that of OE using the propensity scoring system.

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Key Words: Esophageal cancer, minimally invasive esophagectomy, thoracoscope.

Patients and Methods

Ethics. This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the institutional review board, and written informed consent was obtained from study patients to use data from their medical records (B191200059).

Study subjects. All subjects selected from the hospital medical records were consecutive patients with EC at the Department of Surgery, Gastroenterological Center, Yokohama City University, between June 1992 and December 2015. The inclusion criteria were as follows: 1) patients with pStage II/III EC based on the Japanese Classification of Esophageal Cancer, 11th Edition (14, 15); 2) patients without cervical EC invasion; 3) patients who underwent surgery with R0 resection; 4) patients without other synchronous or metachronous malignancies. According to these criteria, the patients were retrospectively selected and divided into two groups (the MIE and OE groups) using the propensity scoring system.

Surgical procedures. All patients received epidural and general anesthesia during the operation. Patients were placed in the supine position for the abdominal procedure initially and then placed in a left lateral decubitus position to perform the chest cavity procedure. MIE and OE were performed by EC specialists who had achieved the learning curve of esophagectomy in all cases. The surgeon made the four thoracoscopic ports generally used in MIE. The operation procedures included three steps: 1) mobilization of the stomach with lymphadenectomy around the celiac artery. The left gastric artery was ligated, and the stomach was divided by linear stapler for narrow gastric tube reconstruction. This procedure was performed for hand-assisted laparoscopic surgery within approximately 5 cm abdominal incision in both groups; 2) mobilization of the intrathoracic esophagus and dissection of intrathoracic and mediastinal lymph nodes. Cervical lymphadenectomy was performed in the case of upper EC and cases which were preoperatively suspected to have metastatic lymph nodes; 3) tumor resection and anastomosis. The posterior mediastinal route was principally selected for reconstruction. The anastomosis was performed within the thoracic cavity or in the neck using the instrumental devices (DST-EEA 25 mm, Medronics, Tokyo, Japan).

Evaluation of surgical outcomes. We retrospectively compared the patient characteristics, including age, sex, tumor location, macroscopic appearance, and pathological findings. The histological type was classified according to the Japanese guidelines for EC (14, 15). Pathological staging was carried out according to the Union for International Cancer Control EC tumor–node–metastasis staging system eighth edition (16). Tumor locations were divided into four groups: upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus, and abdominal esophagus. The surgical outcome was evaluated according to the type of surgical procedures, the extent of lymph node dissection, the number of metastatic lymph nodes, operating time, the volume of blood loss, and complications. All of the postoperative complications were defined according to the Clavien–Dindo classification, and we evaluated grade II or higher as major complications (17). The postoperative outcome included pathological findings, recurrence rate, and overall survival (OS) and recurrence-free survival (RFS). The prognostic factors for survival were examined in the univariate and the Cox proportional regression analyses.

Follow-up. All patients were followed up regularly at our institution. Blood examination including squamous cell carcinoma antigen, cytokeratin-19 fragments, and carcinoembryonic acid assays were performed every 3 to 6 months, computed tomography was conducted every 6 to 12 months, and upper gastrointestinal endoscopy was performed annually at least for 5 years.

Statistical analysis. To minimize the potential differences in the baseline characteristics of patients who underwent OE and MIE, the propensity-score matching system was used. The propensity score

Table I. *Patient characteristics in the MIE and OE groups*.

	MIE (n=57)	OE (n=57)	*p*-Value
Age (years)			0.57
<65	31	27	
≥65	26	30	
Gender			1.00
Male	42	41	
Female	15	16	
Location			0.40
Ut	4	4	
Mt	29	25	
Lt	22	28	
Ae	2	0	
Macroscopic appearance			0.41
Superficial	11	9	
Well-defined	20	27	
Ill-defined	26	21	
Tumor diameter (mm)			0.57
<50	30	34	
≥50	27	23	
Histological type			0.16
Well diff. sq	19	15	
Mod diff. sq	28	20	
Por diff. sq	7	16	
Adenocarcinoma	1	1	
Others	2	5	
pT stage			0.48
pT1	10	6	
pT2	15	19	
pT3	31	32	
pT4	1	0	
pN stage			0.98
pN0	24	22	
pN1	9	10	
pN2	19	20	
pN3	5	5	
Number of metastatic lymph nodes			0.79
0	24	22	
1-3	24	28	
4-7	5	5	
8-	4	2	
Lymphatic invasion			0.85
Absent	26	28	
Present	31	29	
Venous invasion			0.35
Absent	30	24	
Present	27	33	
Intraepithelial spread			0.62
Absent	46	49	
Present	11	8	
pStage			0.71
II	34	31	
III	23	26	
Preoperative treatment			0.53
Absent	46	41	
Chemotherapy	10	14	
Chemoradiotherapy	1	2	

Ut: Upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus; Well diff. sq: well-differentiated squamous cell carcinoma; Mod diff. sq: moderately-differentiated squamous cell carcinoma; Por diff. sq: poorly-differentiated squamous cell carcinoma; MIE: minimally invasive esophagectomy; OE: open esophagectomy.

Table II. *Surgical procedure and outcomes between the groups.*

		MIE (n=57)	OE (n=57)	*p*-Value
Operation time (min)	Median (range)	512 (312-710)	515 (256-775)	0.91
Thoracoscopic time (min)		230 (93-435)	-	
Bleeding (ml)	Median (range)	540 (150-1500)	700 (50-2800)	<0.01
Extent of lymphadenectomy				1.00
Two-field		51	52	
Three-field		6	5	
Number of harvested lymph nodes	Median (range)	40 (12-80)	31 (6-73)	<0.01
Major complications (C-D classification≥II)				0.93
Anastomotic leakage		4	7	
Cardiopulmonary complication		5	10	
Recurrent laryngeal nerve injury		10	13	
Post-operative death		1	2	1.0

C-D classification: Clavien-Dindo classification; MIE: minimally invasive esophagectomy; OE: open esophagectomy.

was estimated by logistic regression using age, gender, and pStage between the two groups as explanatory variables, and a case-matched control study was conducted. One-to-one matched groups were created using the nearest-neighbor matching algorithm without replacement. The caliper of 0.20 times the standard deviation of the logic of the propensity score was used to prevent poor matches. Statistical analysis was performed using Student's *t*-test for continuous variables with parametric distribution and Mann–Whitney *U*-test for variables with the non-parametric distribution. The chi-square and Fisher's exact probability tests were used for the analysis of proportion. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. A *p*-value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics. A total of 156 patients with pStage II/III EC who underwent R0 esophagectomy at the Department of Surgery Gastroenterological Center, Yokohama City University, between June 1992 and December 2015, were enrolled in this study. Of those, 95 patients (60.9%) underwent MIE, and the remaining 61 patients (39.1%) underwent OE. Of those, 114 cases were matched by the propensity scoring system estimated by using age, sex, and pStage between the two groups. As a result, 57 patients were classified into the MIE group, and 57 patients were classified into the OE group.

The clinicopathological characteristics of patients are summarized in Table I. Tumor location, tumor size, histology, tumor depth, number of metastatic lymph nodes, and other pathological data did not differ between the two groups. Moreover, the number of patients who received preoperative chemotherapy or CRT was 19.3% in the MIE group and 28.1% in the OE group (p=0.27).

Short-term surgical outcomes

The surgical outcomes are summarized in Table II. The volume of bleeding was significantly reduced (p<0.01), and the number of harvested lymph nodes was greater in the MIE group (p<0.01). However, there were no significant differences in operation time and the extent of lymph node dissection between the two groups. Moreover, there were no

Table III. *Recurrence pattern, post-recurrence therapy and prognosis between the groups.*

	MIE (n=57)	OE (n=57)	*p*-Value
Recurrence			
Total	24	29	0.45
Recurrence site			0.19
Loco-regional	9	18	
Distant	5	4	
Combined	10	7	
Treatments for recurrence			0.16
Chemoradiotherapy	8	6	
FP+RT	5	5	
DOC+CDDP+RT	3	0	
5FU+CDGP+RT	0	1	
Chemotherapy	6	17	
FP	4	9	
DOC+CDDP	2	7	
5FU+CDGP	0	1	
Radiotherapy	4	5	
Prognosis			<0.001
Alive/Dead	43/14	18/39	
Cause of death			0.11
Esophageal cancer	7	29	
Other cancer	0	0	
Other disease	7	10	
Recurrence site of patients with esophageal cancer death			0.028
Loco-regional	1	19	
Distant	2	3	
Combined	4	7	

RT: Radiation therapy; FP: 5-fluorouracil+cisplatin; DOC+CDDP: docetaxel + cisplatin; 5FU+CDGP: 5-fluorouracil+nedaplatin; MIE: minimally invasive esophagectomy; OE: open esophagectomy.

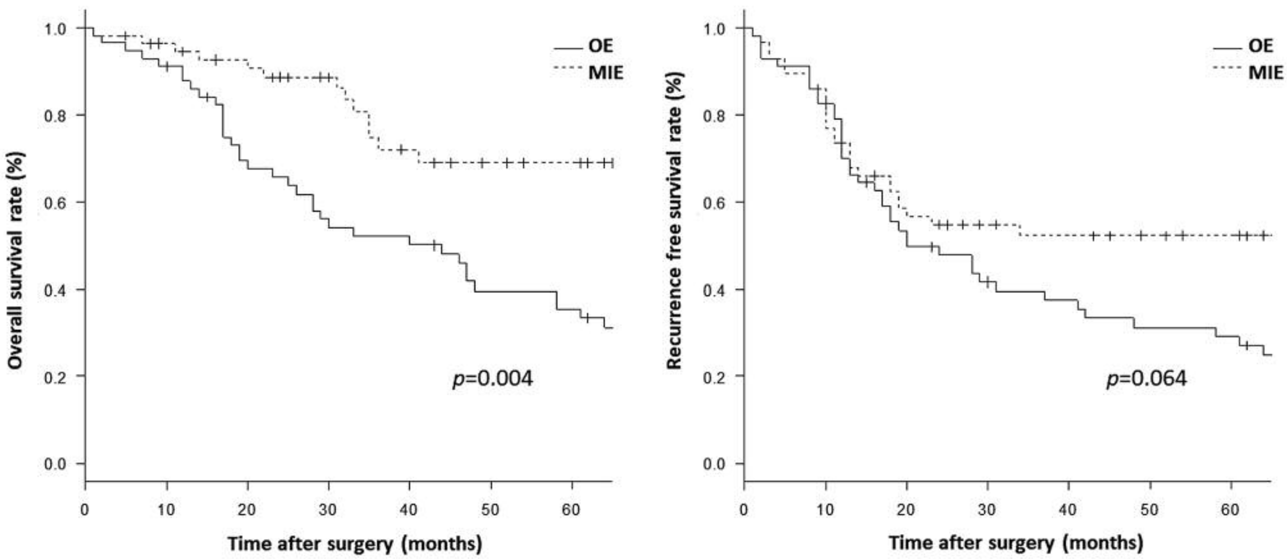

Figure 1. *Comparison of overall survival and disease-free survival between the two groups.*

significant differences in the incidence of postoperative complications (Clavien–Dindo classification ≥II) between the two groups (p=0.93). Operative mortality was 2.6% (three patients); of those, one patient in the MIE group died because of acute heart failure, and two patients in the OE group died because of pneumonia.

Recurrence after esophagectomy. Recurrence pattern, treatments for recurrence, and cause of death are summarized in Table III. There were 24 patients (42.1%) with recurrence in the MIE group and 29 patients (50.9%) in the OE group. The incidence of recurrence in the locoregional areas was lower in the MIE group than that in the OP group, although no statistically significant difference was observed (MIE, 37.5% *vs*. OE, 62.1%; p=0.19). EC death was observed in 7 patients in the MIE group and 29 patients in the OE group (p=0.11). Among these patients, the locoregional recurrence rate was significantly lower in the MIE group than that in the OE group (MIE, 14.3% *vs*. OE, 65.5%; p=0.028). Treatments for recurrence were performed in 88% and 96.6% of cases in the MIE and OE groups, respectively. Two patients had brain metastasis and underwent brain surgery in the MIE group. In the MIE group, 8 patients received CRT, 6 received chemotherapy, and 4 received radiotherapy after relapse. In the OE group, 6 patients received CRT, 17 received chemotherapy, and 5 received radiotherapy after relapse.

Long-term surgical outcomes. The observation period of both groups was similar (MIE, median 43 months *vs*. OE, 52 months; p=0.25). The OS was significantly better in the MIE group than that in the OE group (the 5-year rate: MIE, 69.0% *vs*. OE, 35.5%; p=0.004), whereas no significant difference was observed in the RFS (the 5-year rate: MIE, 52.1% *vs*. OE, 29.2%; p=0.064, Figure 1).

Prognostic factors for survival for stage II/III esophageal cancer. Table IV shows analytic outcomes of the prognostic factors for OS and RFS. Univariate analysis revealed that MIE, lymph node metastasis, intraepithelial spread, and pathological stage were prognostic factors for OS although no significant difference was observed regarding age, tumor location, tumor depth, the extent of lymph node dissection, postoperative complications, and preoperative therapy. Cox proportional regression analysis showed the type of surgical procedure [hazard ratio (HR)=3.64, 95%CI=1.87-7.08, p<0.001[and lymph node metastasis (HR=4.81, 95%CI=1.75-13.20, p=0.002) were independent prognostic factors (Table V). In contrast, univariate analysis showed that tumor diameter, lymph node metastasis, intraepithelial spread, and pathological stage were significant factors for RFS. MIE was not a significant factor of RFS in univariate analysis (p=0.064). However, multivariate analysis showed MIE was an independent prognostic factor for RFS (HR=1.75, 95%CI=1.05-2.91, p=0.032).

Discussion

This investigation showed the impact of MIE as a prognostic factor for pStage II/III EC. The major findings of this study were that MIE had equal postoperative morbidity as OE and MIE was an independent prognostic factor for OS and RFS. Esophagectomy is a morbid surgical procedure, and previous

Table IV. *Univariate analysis of prognostic factors for stage II/III esophageal cancer.*

Variables	n	5-year OS (%)	5-year RFS (%)	*p*-Value (OS/RFS)
Age (year)				0.63/0.35
<65/≥65	58/56	50.7/49.4	43.3/36.4	
Gender				0.27/0.63
Male/Female	83/31	46.1/60.2	36.7/46.9	
Location				0.41/0.61
Ut/Mt/Lt/Ae	8/54/50/2	72.9/53.0/42.1/0	62.5/35.7/39.3/0	
Macroscopic appearance				0.32/0.45
Superficial	20	59.4	58.5	
Well-defined	47	43.0	31.3	
Ill-defined	47	53.2	40.1	
Tumor diameter (mm)				0.16/0.036
<50/≥50	64/50	58.7/39.4	46.5/27.6	
Histological type				0.51/0.32
Well diff. sq	34	54.0	45.4	
Mod diff. sq	48	57.3	48.5	
Por diff. sq	23	40.4	21.3	
Adenocarcinoma	2	0	0	
Others	7	38.1	14.3	
pT stage				0.45/0.26
pT1/pT2/pT3/pT4	16/34/63/1	54.4/58.4/44.3/0	36.5/49.1/34.3/0	
pN stage				0.040/0.0032
pN0/pN1/pN2/pN3	46/19/39/10	63.6/62.0/36.2/40.0	55.3/39.3/30.3/20.0	
Lymphatic invasion				0.15/0.045
Absent/present	54/60	58.4/43.1	48.5/31.9	
pStage				0.038/0.035
pStage II/pStage III	65/49	61.0/37.3	48.1/29.5	
Venous invasion				0.11/0.11
Absent/present	54/60	62.2/39.7	48.5/32.2	
Intraepithelial spread				0.037/0.004
Absent/present	95/19	52.3/39.9	43.7/19.7	
Approach				0.004/0.064
MIE/OE	57/57	69.0/35.5	52.1/29.2	
Type of lymphadenectomy				0.14/0.20
Two-field/three-field	103/11	45.6/100	43.7/19.7	
Major complications				
(C-D classification≥II)				0.60/0.47
Yes/No	49/65	50.7/51.6	42.2/33.0	
Preoperative treatment				0.18/0.31
Absent	87	54.5	43.0	
Chemotherapy	24	37.2	27.3	
Chemoradiotherapy	3	0	0	

Ut: Upper thoracic esophagus; Mt: middle thoracic esophagus; Lt: lower thoracic esophagus; Ae: abdominal esophagus; Well diff. sq: well-differentiated squamous cell carcinoma; Mod diff. sq: moderately-differentiated squamous cell carcinoma; Por diff. sq: poorly-differentiated squamous cell carcinoma; MIE: minimally invasive esophagectomy; OE: open esophagectomy; C-D classification: Clavien-Dindo classification; OS: overall survival; RFS: recurrence-free survival.

studies have shown that its mortality was greater than 10% (18, 19). MIE has been first described in the 1990s (19-21). It has been reported that MIE was less invasive compared with OE, and had lower postoperative morbidity (22, 23). Moon *et al*. have reported that postoperative pulmonary complications occurred in 9.5% in the MIE group and 40.5% in the OE group (p=0.004) (24). A large multicenter study has also revealed that MIE was associated with less bleeding, lesser complication rate, and shorter hospital stay (25, 26). However, it is unclear whether a better long-term outcome is achieved by MIE for patients with pStage II/III advanced EC. Wang *et al*. have conducted a case-matched study and have reported the outcomes following MIE (n=444) *vs*. OE (n=444). They analyzed survival rates by stage of EC and found that 5 year OS was similar between two groups: stages 0 and I, 78% *vs*. 78% (p=0.864); stage II, 50% *vs*. 48% (p=0.725); stage III: 33% *vs*. 34% (p=0.592); and stage IV, 26% *vs*. 25% (p=0.802) (11). Yamashita *et al*. have also

Table V. *Multivariate analysis of prognostic factors for stage II and III esophageal cancer.*

	Overall survival				Recurrence-free survival		
Variables	Hazard ratio	95% confidence interval	*p*-Value	Variables	Hazard ratio	95% confidence interval	*p*-Value
pN stage				pN stage			
pN0 *vs*. pN1	0.93	0.37-2.31	0.87	pN0 *vs*. pN1	1.49	1.05-2.91	0.032
pN0 *vs*. pN2	1.50	0.76-2.97	0.24	pN0 *vs*. pN2	1.98	1.08-3.65	0.028
pN0 *vs*. pN3	4.81	1.75-13.20	0.002	pN0 *vs*. pN3	4.92	2.03-11.91	0.004
Intraepithelial spread				Intraepithelial spread			
Absent *vs*. Present	2.11	1.00-4.46	0.051	Absent *vs*. Present	2.25	1.18-4.29	0.014
Approach				Approach			
MIE *vs*. OE	3.64	1.87-7.08	<0.001	MIE *vs*. OE	1.75	1.05-2.91	0.032
				Tumor diameter (mm)			
				<50/≥50	2.22	1.33-3.70	0.002

MIE: Minimally invasive esophagectomy; OE: open esophagectomy.

compared long-term oncological outcomes between 121 patients who underwent MIE and 121 patients who underwent OE using propensity-score matching and revealed that patients in the MIE group had significantly better DFS and OS rates than those in the OE group (3 year DFS rate, 81.7% *vs*. 69.3%, p=0.021; 3 year OS rate, 89.9% *vs*. 79.2%, p=0.007) (6). In this study, all pathological stages were analyzed without distinction. Also, these previous studies did not mention the surgeon's technique and level of experience.

In our series, RFS was similar between the MIE and OE groups and OS was significantly higher in the MIE group. Furthermore, the number of the harvested lymph nodes was significant larger, and the incidence of recurrences in the locoregional areas was lower in the MIE group than that in the OE group. Optimal lymph node dissection around vital organs could be achieved under the fine optical view using the thoracoscope by skilled surgeons. The single and multicenter cohort studies showed that MIE was a safe and feasible procedure as concerns surgical and oncological aspects (12, 13, 27). These previous reports and the present study revealed that MIE may lead to favorable long-term prognosis. Also, considering that there was no significant difference in recurrence rate and treatments after recurrence, the favorable OS despite the equal RFS means that the low invasiveness of high-quality MIE may improve the postoperative immune function to avoid tumor growth and multidisciplinary treatments for recurrence were more effective compared with OE.

Large population-based comparative studies of MIE and OE reported from the Netherlands, the UK, and the USA, have revealed equivalent morbidity and mortality between MIE and OE (28-30). Seesing *et al*. have pointed out the learning curve of surgeons. These population studies and large cohort studies have been reported from high-volume centers because esophagectomy is a challenging surgery and was often performed by experienced surgeons (28). Therefore, the surgeon's technique and experience should be considered when conducting such a study. Guo *et al*. have evaluated the surgical learning curve in 89 patients receiving thoracoscopic esophagectomies and reported that the overall morbidity rate was 53% in the first 20 cases although the rate decreased to 7% in the last 29 cases (p=0.005) (31). Osugi *et al*. have also reported the learning curve of video-assisted thoracoscopic esophagectomy (32). Eighty patients were divided into two groups: one group included the first 34 patients, and the other group included the last 46 patients. They found less blood loss (p<0.0001) and low incidence of pulmonary infection in the last 46 patients compared with those in the initial group. These studies show that the outcome may be influenced the surgeon's skill.

According to recent studies, MIE varies depending on the facility and the country. For example, Palanivelu *et al*. have analyzed the efficacy of prone position (33), and Weksler *et al*. have reported the long-term outcome of patients receiving esophagectomy with robotic-assisted minimally invasive esophagectomy (RAMIE) and standard MIE (34). Therefore, it is important to establish the optimal minimally invasive surgical approach for EC.

In the present investigation, there was no difference in the incidence of complications, and it is considered to be the cause of performing esophagectomy by skilled surgeons in all cases. Therefore, it is necessary to consider the experience of the operator to judge whether EC surgery is minimally invasive. Although the sample size was small, all surgeries were performed by an experienced surgeon who may reach the surgical learning curve in our series. Therefore, surgical quality was the same between the two groups.

The limitations of this study include the small sample size, its retrospective nature and single-institution design. Moreover, MIE was introduced since 2002 in our institute. Thus, there may be some differences in the multidisciplinary treatments between the two periods. The transition time of the therapeutic strategy may affect survival time. Therefore, selection bias was inevitable in spite of the propensity scoring system. So, it is necessary to conduct randomized controlled trials (RCT) with a large sample size, in multiple institutions and in different countries to confirm the validity of MIE for EC. A randomized trial (JCOG1409) comparing MIE with OE is going on, and the result of the trial may clarify the validity of MIE for EC (35).

In conclusion, this retrospective study showed that MIE was as safe and feasible as OE and was an independent prognostic factor for OS and RFS in patients with stage II/III EC. We can anticipate the results of a randomized trial (JCOG1409) comparing MIE with OE.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

All Authors contributed equally to this study. Details of contributions by each author are as follows: Concept and study design were conducted by K. Iguchi, C. Kunisaki, S. Sato, Y. Tanaka, K. Sato, H. Miyamoto, T. Kosaka and H. Akiyama. Data collection and literature search were done by K. Iguchi. Data analysis and interpretation were done by K. Iguchi, C. Kunisaki, T. Yamanaka, I. Endo, N. Yukawa, Y. Rino and M. Masuda; Interpretation of data was done by investigators. Drafting the article was done by K. Iguchi and C. Kunisaki. Finally, this article was revised and approved by all Authors.

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