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Survival Comparison Between Open and Thoracoscopic Upfront Esophagectomy in Patients With Esophageal Squamous Cell Carcinoma

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Background: The survival outcomes of patients with esophageal squamous cell carcinoma (ESCC) after open or thoracoscopic upfront esophagectomy remained unclear.

Objective: The aim of this retrospective study was to compare overall survival between open and thoracoscopic esophagectomy for ESCC patients without neoadjuvant chemodatiotherapy (CRT).

Methods: The Taiwan Cancer Registry was investigated for ESCC cases from 2008 to 2016. We enrolled 2053 ESCC patients receiving open (n = 645) or thoracoscopic (n = 1408) upfront esophagectomy. One-to-two propensity score matching between the two groups was performed. Stage-specific survival was compared before and after propensity score matching. Univariate analysis and multivariate analysis were used to identify risk factors.

Results: After one-to-two propensity score matching, a total of 1299 ESCC patients with comparable clinic-pathologic features were identified. There were 433 patients in the open group and 866 patients in the thoracoscopic group. The 3-year overall survival of matched patients in the thoracoscopic group was better than that of matched patients in the open group (58.58% vs 47.62%, P = 0.0002). Stage-specific comparisons showed thoracoscopic esophagectomy is associated with better survival than open esophagectomy in patients with pathologic I/II ESCC. In multivariate analysis, surgical approach was still an independent prognostic factor before and after one-to-two propensity score matching.

Conclusion: This propensity-matched study revealed that thoracoscopic esophagectomy could provide better survival than open esophagectomy in ESCC patients without neoadjuvant CRT.

Keywords: esophageal squamous cell carcinoma, open, survival, thoracoscopic esophagectomy

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Esophageal cancer is one of the leading cancer-related causes of death worldwide. The 2 common histologic subtypes (squamous cell carcinoma and adenocarcinoma) are quite different in incidence, etiology, pathogenesis, staging systems, and treatment protocols.[1,2] In Taiwan, squamous cell carcinoma was the most common type of esophageal cancer and also the leading cancer-related cause of death.[3,4]

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Oncology for Esophageal and Esophagogastric Junction Cancers, patients with local esophageal squamous cell carcinoma (ESCC) are recommended to receive definitive chemodatiotherapy (CRT), neoadjuvant CRT followed by esophagectomy, or upfront esophagectomy with/without adjuvant CRT. Esophagectomy was considered a major curative treatment for local ESCC.[2] Including neoadjuvant CRT with esophagectomy significantly impacts perioperative outcome and long-term survival.[5-9]

Minimally invasive esophagectomy has developed rapidly in recent decades, and growing evidence has shown that it has short-term perioperative benefits compared to open esophagectomy.[10-14] Whether long-term survival is different depending on whether patients are treated with thoracoscopic esophagectomy or open esophagectomy is still inconclusive. Two randomized controlled trials had limited sample sizes, and both of them showed no survival difference between open esophagectomy and minimally invasive esophagectomy.[15,16] Single-center cohort studies have limited sample sizes.[17] Two meta-analyses[17,13] and 4 population-based analyses[18-21] have compared long-term survival after minimally invasive esophagectomy and open esophagectomy. All of these studies included both adenocarcinoma and squamous cell carcinoma into one analysis. Patients with and without neoadjuvant CRT before esophagectomy were also mixed in these studies. These heterogeneous patients with different cell types could contribute to inconstant results about survival difference between open and minimally invasive esophagectomy.

Therefore, we only included into analysis patients with ESCC undergoing upfront esophagectomy. Upfront esophagectomy means that esophagectomy was the first treatment modality applied to the patient regardless of subsequent treatments. We used the Taiwan Cancer Registry to select the patients. The patients were divided into 2 groups (thoracoscopic

esophagectomy vs open esophagectomy). Propensity score matching was used to balance basic demographics of the two groups, and overall stage-specific survival was compared. The aim of the study was to compare overall survival between open and thoracoscopic esophagectomy for ESCC patients without neoadjuvant CRT.

METHODS

The Internal Review Board in Changhua Christian Hospital approved this study. The Internal Review Board number is 171116. The Taiwan Cancer Registry was implemented in 1979. After the Cancer Control Act was promulgated in 2003, the completeness (97%) and data quality of the cancer registry database have been excellent.[22] The Taiwan Cancer Registry is organized and funded by the Ministry of Health and Welfare of Taiwan. To monitor the cancer care patterns and evaluate the cancer treatment outcomes, the central cancer registry has been reformed since 2002. The overall number of clinic-pathologic variables extended from 20 to 114 in 2011. The Taiwan Cancer Registry has run smoothly for > 30 years. The database of the Taiwan Cancer Registry was used to retrieve records for patients with ESCC. The Taiwan Cancer Registry was linked to National Health Insurance of Taiwan and Taiwanese death certificates. We only included patients with pathologic diagnoses in the database.

Patients with ESCC in Taiwan received staging workups, including upper gastrointestinal endoscopies with biopsies, bronchoscopic examinations, contrast-enhanced chest/abdominal computed tomography scans, and positron emission tomography/computed tomography scans. All costs were covered by National Health Insurance.

The records for patients with certain *International Classification of Diseases for Oncology (ICD-O-3)* site codes (C15.0, C15.1, C15.2, C15.3, C15.4, C15.5, C15.8 and C15.9) and morphology codes (8052, 8070, 8071, 8072, 8073, 8074, 8076, 8077, 8083, and 8084) were retrieved from the Taiwan Cancer Registry.

A total of 18,741 patients with ESCC in Taiwan between 2008 and 2016 were identified. The primary treatment strategies included definitive CRT (n = 8581, 45.8%); neoadjuvant CRT plus esophagectomy (n = 2680, 14.3%); esophagectomy alone (n = 2117, 11.3%); esophagectomy plus adjuvant CRT (n = 841, 4.5%); esophagectomy followed by adjuvant chemotherapy (n = 247, 1.3%); esophagectomy followed by adjuvant radiotherapy (n = 205, 1.1%); radiotherapy alone (n = 1381, 7.4%); chemotherapy alone (n = 1102, 5.9%); and others (n = 1588, 8.5%). For the purpose of this study, we selected patients undergoing upfront esophagectomy with/without adjuvant CRT into this study. The exclusion criteria consisted of clinical stage IV ESCC (n = 66), pathologic stage IV ESCC (n = 35), unknown clinical stage (n = 248), unknown pathologic stage (n = 17), and unknown surgical method (n = 537). The following clinic-pathologic variables were included: age, sex, Charlson score, tumor location, tumor length, grading, pathologic T stage, pathologic N stage, pathologic stage, margin status (longitudinal and circumferential margin), adjuvant CRT and surgical approach. The pathologic staging system was based on the 8th edition of the TNM classification staging system. Finally, a total of 2053 ESCC patients were enrolled into the analysis. Patients were divided into 2 groups. One was the open esophagectomy group, and the other was the thoracoscopic esophagectomy group.

Statistical Analysis

Categorical and continuous variables were compared between the 2 groups by using the chi-square test and Student 2-tailed *t* test, respectively. The duration of overall survival was defined as the interval in days between the date of surgery and either the date of death or the censoring date of December 31, 2017. The overall survival was calculated by the Kaplan-Meier method. One-to-two propensity score matching between the 2 groups was performed. The following variables were included into matching: age, sex, Charlson score, tumor location, tumor length, pathologic T stage, pathologic N stage, pathologic stage, margin status, and adjuvant CRT. Univariate and multivariate analyses were performed by means of the Cox proportional hazards model. To investigate the impact on overall survival, the following variables were included in univariate analyses: age, sex, Charlson score, tumor location, tumor length, grading, pathologic T stage, pathologic N stage, pathologic stage, margin status, adjuvant therapy, and surgical approach. The prognostic factors were all entered in multivariate analyses to identify independent predictors of survival. Survival analysis was analyzed using the Cox proportional hazards regression model, and the difference was determined by the log-rank test. Analysis was considered to be significant when the probability value was < 0.05.

The Charlson comorbidities score was used for risk adjustment in analysis of administrative data[23] to represent clinical physical status in the analysis. SPSS software (version 20, IBM, Armonk, NY) and SAS software (version 9.3; SAS Institute, Cary, NC) were used. All statistical calculations were performed by a biostatistician (H.-S.C.).

RESULTS

A total of 2053 ESCC patients were identified from the Taiwan Cancer Registry. Patients received upfront open esophagectomy (n = 645) or thoracoscopic esophagectomy (n = 1408) with/without adjuvant CRT. There were similar distributions of age, sex, Charlson score, and margin status between the two groups. Patients in the open group tended to have a lower tumor location, a longer tumor length (3.96 ± 2.34 cm vs 3.40 ± 2.17 cm, *P* < 0.0001), higher histology grading, a higher pathologic T stage, a higher pathologic N stage, a higher pathologic stage, and a higher adjuvant CRT rate (39.22% vs 28.84%, *P* < 0.0001) compared with the thoracoscopic esophagectomy group. One-to-two propensity score matching resulted in 1299 patients with comparable clinic-pathologic features. There were 433 patients in the open group and 866 patients in the thoracoscopic group. The basic characteristics are summarized in Table 1. The details of adjuvant CRT for each pathologic stage before and after propensity score matching were summarized in Supplement Table 1, http://link-s.lww.com/SLA/D155 and Supplement Table 2, http://links.lww.com/SLA/D155, respectively. With the increased pathologic stage, more patients received adjuvant CRT.

The 3-year overall survival rates for the open group and thoracoscopic group were 42.48% and 56.26% (*P* < 0.0001), respectively. The overall survival was also compared after stratifying by pathologic stage. For pathologic I/II ESCC, the patients in the thoracoscopic group had better survival than the patients in the open group, but the survival was similar for pathologic 0 and pathologic III ESCC. After propensity score matching, the overall survival of patients in the thoracoscopic group was better than that of patients in the open group (58.58% vs 47.62%, *P* = 0.0002). Stage-specific comparison showed thoracoscopic esophagectomy is associated with better survival than open esophagectomy in patients with pathologic I/II ESCC.

TABLE 1. Characteristics of Patients Treated With Upfront Open or Thoracoscopic Esophagectomy

| | All Patients (N = 2053) | | | | | Propensity-Matched Patients 1:2 (N = 1299) | | | | |
| | Open (N = 645) | | Thoracoscopy (N = 1408) | | | Open (N = 433) | | Thoracoscopy (N = 866) | | |
Characteristics	n	%	n	%	*P*	n	%	n	%	*P*
Age, y	55.9 ± 10.1		56.3 ± 9.8		0.4013	57.2 ± 10.1		56.5 ± 10.0		0.2838
Female sex	40	6.20	105	7.46	0.3026	400	92.38	803	92.73	0.8220
Charlson score (mean ± SD)	0.7 ± 1.1		0.8 ± 1.2		0.0940	0.7 ± 1.1		0.7 ± 1.1		0.6540
Tumor location					0.0009					0.9131
L	218	33.80	390	27.70		121	27.94	233	26.91	
M	211	32.71	576	40.91		182	42.03	361	41.69	
U	70	10.85	171	12.14		51	11.78	100	11.55	
X	146	22.64	271	19.25		79	18.24	172	19.86	
Tumor length, cm	3.96 ± 2.34		3.40 ± 2.17		< 0.0001	3.46 ± 2.14		3.39 ± 2.06		0.5545
Grading					0.0045					0.8547
G1	20	3.10	39	2.77		10	2.31	21	2.42	
G2	398	61.71	895	63.57		299	69.05	577	66.63	
G3/4	187	28.99	332	23.58		100	23.09	216	24.94	
Unknown	40	6.20	142	10.09		24	5.54	52	6.00	
Pathologic T stage					< 0.0001					0.8823
Tis	11	1.71	45	3.20		6	1.39	16	1.85	
0	16	2.48	30	2.13		6	1.39	9	1.04	
1	180	27.91	571	40.55		165	38.11	349	40.30	
2	90	13.95	239	16.97		81	18.71	162	18.71	
3	313	48.53	490	34.80		175	40.41	324	37.41	
4	35	5.43	33	2.34				6	0.69	
Pathologic N stage					< 0.0001					0.5550
0	339	52.56	900	63.92		276	63.74	578	66.74	
1	161	24.96	293	20.81		91	21.02	173	19.98	
2	94	14.57	156	11.08		57	13.16	104	12.01	
3	27	4.19	33	2.34		9	2.08	11	1.27	
Unknown	24	3.72	26	1.85						
Pathologic stage					< 0.0001					0.4353
0	24	3.72	69	4.90		11	2.54	24	2.77	
1	157	24.34	491	34.87		137	31.64	291	33.60	
2	214	33.18	484	34.38		168	38.80	353	40.76	
3	250	38.76	364	25.85		117	27.02	198	22.86	
Margin status					0.2241					0.7051
Negative	563	87.29	1238	87.93		384	88.68	774	89.38	
Positive	79	12.25	145	10.30		49	11.32	92	10.62	
Unknown	3	0.47	25	1.78						
Adjuvant therapy					< 0.0001					0.6401
No (surgery alone)	392	60.78	1002	71.16		296	68.36	603	69.63	
Yes (surgery + CRT)	253	39.22	406	28.84		137	31.64	263	30.37	

There was no survival difference in pathologic 0 and pathologic III ESCC. The overall survival comparison was summarized in Table 2.

The survival curve was assessed according to all patients and for each pathologic stage. The survival curve of all patients stratified by esophagectomy approach is shown in Figure 1A. Patients treated with thoracoscopic esophagectomy had a significantly superior 3-year overall survival rate (p < 0.0001). The overall survival curve was also assessed based on pathologic I stage (Fig. 1B), pathologic II stage (Fig. 1C), and pathologic III stage (Fig. 1D), respectively. After one-to-two propensity score matching, the overall survival curve was also compared between the two groups according to each pathologic stage. Matched patients undergoing thoracoscopic esophagectomy had

TABLE 2. Three-Year Overall Survival of Patients Treated With Upfront Open or Thoracoscopic Esophagectomy

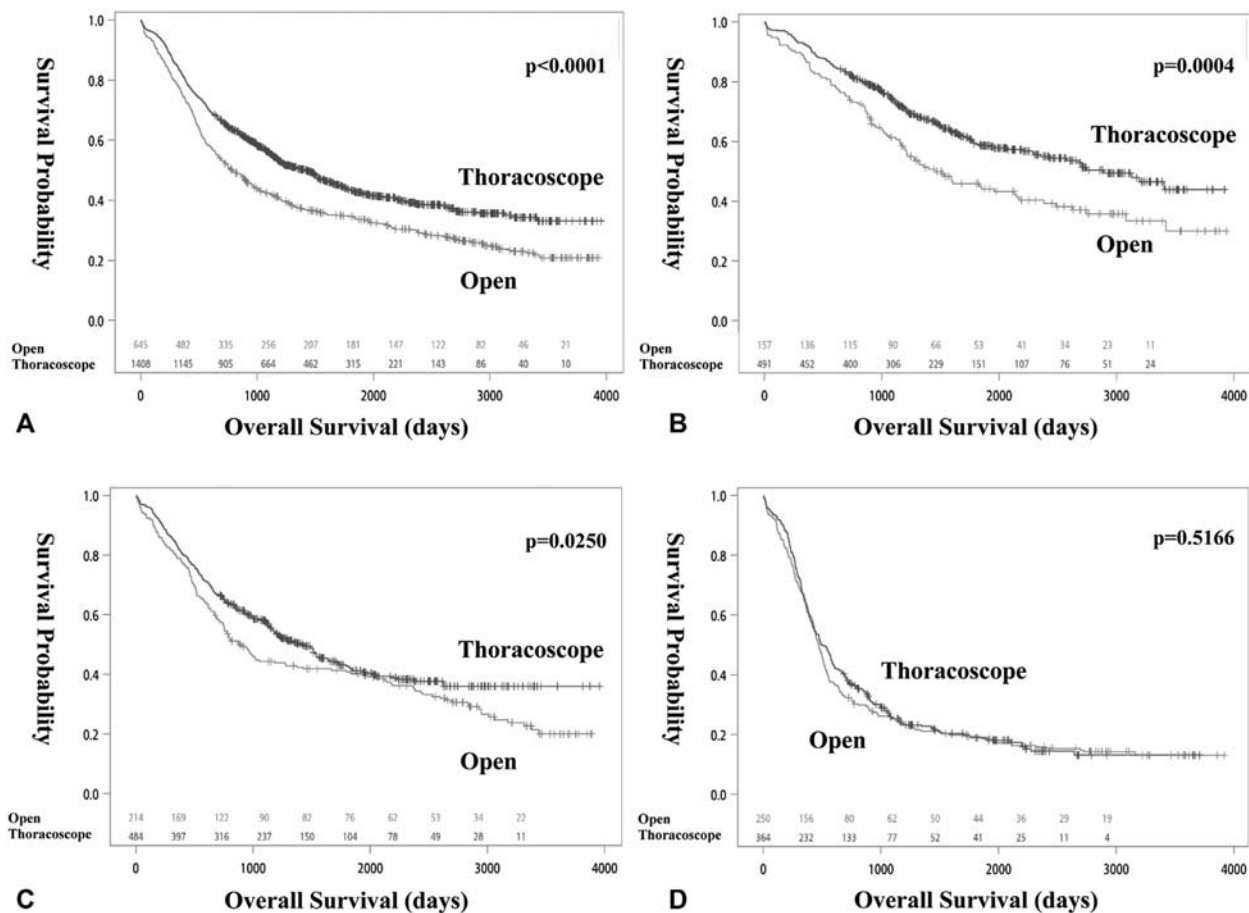| | All Patients | | | Propensity-Matched Patients | | |
	Open (n = 645)	Thoracoscopy (n = 1408)	*P*	Open (n = 433)	Thoracoscopy (n = 866)	*P*
All	42.48%	56.26%	< 0.0001	47.62%	58.58%	0.0002
Pathologic stage						
0	75.00%	76.26%	0.8138	90.91%	83.33%	0.5928
1	61.38%	74.33%	0.0015	62.32%	76.25%	0.0032
2	44.44%	57.94%	0.0014	46.00%	58.76%	0.0111
3	25.83%	25.66%	0.4721	28.74%	28.94%	0.5746

FIGURE 1. A, Overall survival curves for all patients treated via upfront open or thoracoscopic esophagectomy ($P < 0.0001$). B, Overall survival curves for pathologic stage I patients stratified based on surgical approach ($P = 0.0004$). C, Overall survival curves for pathologic stage II patients stratified based on surgical approach ($P = 0.025$). D, Overall survival curves for pathologic stage III patients stratified based on surgical approach ($P = 0.5166$).

a significantly better overall survival than patients undergoing open esophagectomy ($P = 0.0008$) (Fig. 2A). Further stage-specific analysis showed that only for the pathologic I stage did the thoracoscopic group have a significantly superior survival rate (Fig. 2B); patients with pathologic II/III ESCC had similar survival across the 2 groups (Fig. 2C–D).

Before propensity score matching, univariate survival analysis showed that sex, Charlson score, tumor location, tumor length, grading, pathologic T stage, pathologic N stage, pathologic stage, margin status, adjuvant CRT, and surgical approach were prognostic factors. After one-to-two propensity score matching, the univariate survival analysis indicated that age, sex, Charlson score, tumor location, tumor length, pathologic T stage, pathologic N stage, pathologic stage, margin status, adjuvant CRT, and surgical approach were prognostic factors (Table 3).

Multivariate analysis was summarized in Table 4. Before propensity score matching, sex, Charlson score, tumor location, tumor length, grading, pathologic N stage, margin status, adjuvant CRT, and surgical approach were identified as independent prognostic factors in multivariable analysis. After propensity score matching, sex, Charlson score, tumor location, grading, pathologic N stage, margin status, adjuvant

CRT, and surgical approach remained the independent prognostic factors.

DISCUSSION

This study investigated the overall survival of ESCC patients undergoing upfront esophagectomy either by an open approach or a thoracoscopic approach. The results showed thoracoscopic esophagectomy is associated with better survival than open esophagectomy. After stage-specific survival comparisons, only patients with pathologic stage I/II ESCC have better survival.

Two randomized controlled trials[15,16] showed similar survival between open esophagectomy and minimally invasive esophagectomy. Mariette et al[15] included 207 patients with esophageal cancer (41% ESCC) into analysis. In that study, there were 152 patients (74%) receiving neoadjuvant therapy (42% chemotherapy, 32% CRT). Another randomized trial[16] enrolled 115 patients, and 43 of the patients (37.4%) had ESCC. There were 106 patients (92.2%) undergoing neoadjuvant CRT, and the other 9 patients (7.8%) underwent neoadjuvant chemotherapy. The 2 randomized controlled trials had limited patient numbers, mixed cell types, and divergent treatment protocols.
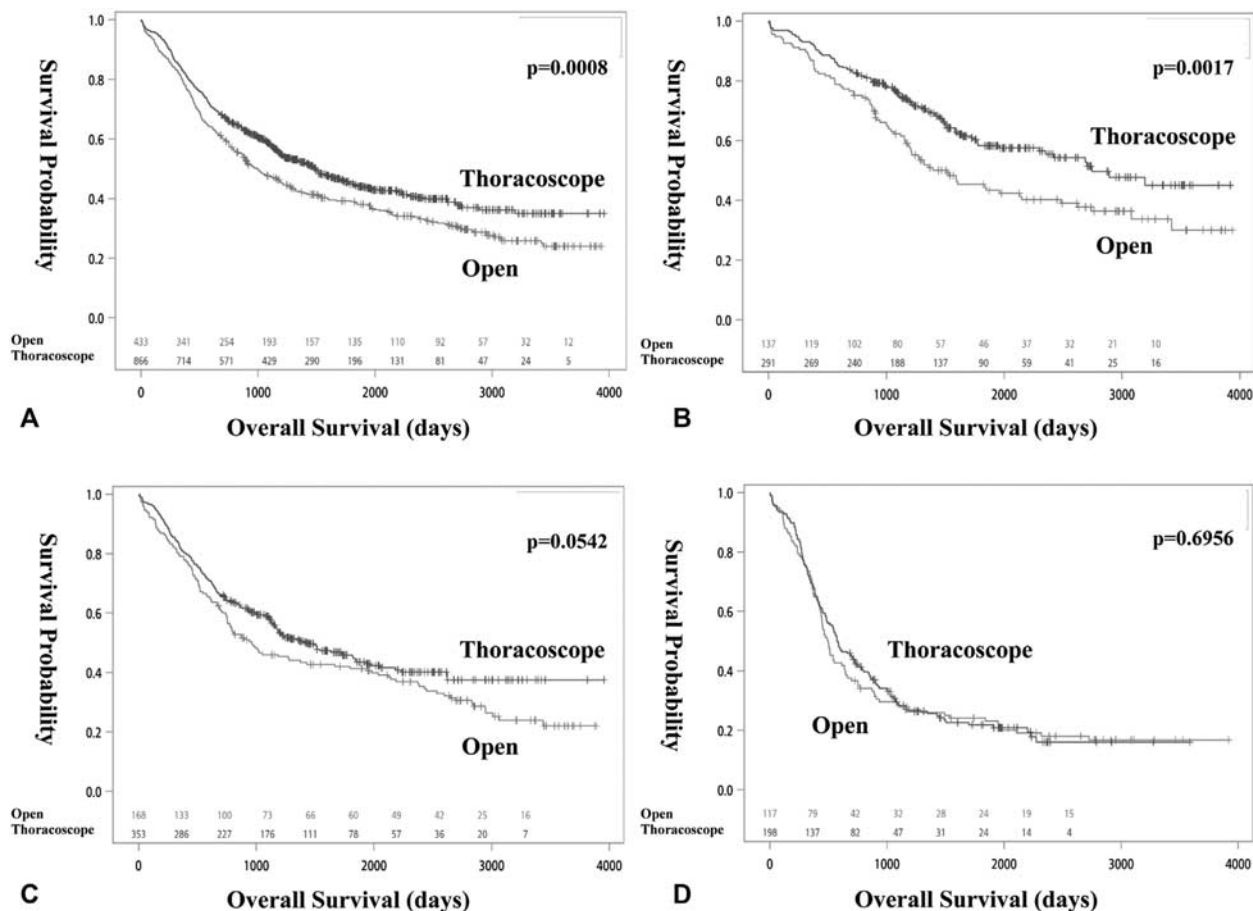
FIGURE 2. A, Overall survival curves for all matched patients treated via upfront open or thoracoscopic esophagectomy (*P* = 0.0008). B, Overall survival curves for matched pathologic stage I patients stratified based on surgical approach (*P* = 0.0017). C, Overall survival curves for matched pathologic stage II patients stratified based on surgical approach (*P* = 0.0542). D, Overall survival curves for matched pathologic stage III patients stratified based on surgical approach (*P* = 0.6956).

That could cause limited power to examine survival difference after esophagectomy between open and minimally invasive esophagectomy.

Meta-analysis and population-based studies have contradictory conclusions. The first meta-analysis[13] (n = 1212) showed no statistically significant survival difference between open and minimally invasive esophagectomy. The latest meta-analysis[17] included 14,592 patients and revealed long-term survival benefits after minimally invasive esophagectomy compared with open esophagectomy. There were another four population-based studies[13,18-20] that compared survival between open and minimally invasive esophagectomy. All of these studies also included analysis patients with and without neoadjuvant treatment before esophagectomy. Adenocarcinoma and squamous cell carcinoma were also mixed into one analysis. A heterogeneous patient distribution could confound a study and contribute to inconsistent conclusions.

The NCCN TNM staging system of esophageal cancer was used widely.[24] Accurate tumor staging plays a crucial role in cancer treatment, especially concerning optimal treatment modality selection and outcome prediction. With the increased use of preoperative CRT for esophageal cancer, the TNM staging system also included the prefix "y." The pathologic stage and y-pathologic stage have totally different clinical outcomes.

The 8th staging system separated classifications for pathologic (pTNM) and post-neoadjuvant pathologic (ypTNM) groups. Discrepancies in outcomes between the pathologic and the y-pathologic stages of ESCC existed.[7,25] Pathologic and y-pathologic stages should not be mixed into one system in a study. Adenocarcinoma and squamous cell carcinoma were also designated different staging systems in the 8th TNM staging system. Because of these classification changes, we only included ESCC patients with upfront esophagectomy into analysis.

There are possible negative effects of neoadjuvant CRT. It could increase mediastinal inflammation and fibrosis. The toxicity of neoadjuvant CRT also deteriorates patients' performance status before operation. Neoadjuvant CRT has a crucial influence on perioperative complications, surgical margin, and mortality.[8] The presence or absence of neoadjuvant CRT could affect whether surgeons perform open or thoracoscopic esophagectomy. To avoid the confounding effect of neoadjuvant CRT on the operation method, we only included patients without neoadjuvant CRT into analysis.

To simplify the issue, we only included ESCC patients undergoing upfront esophagectomy to investigate the long-term survival between thoracoscopic and open esophagectomy. We should not mix patients with different esophageal cell types and treatment protocols (with/without neoadjuvant CRT) into one

TABLE 3. Univariate Analysis for Patients With Upfront Open or Thoracoscopic Esophagectomy

Variables	All Patients (N = 2053)				Propensity-Matched Patients (N = 1299)			
	HR	95% CI		*P*	HR	95% CI		*P*
Age, y	1.00	1.00	1.01	0.3798	1.01	1.00	1.02	0.0473
Sex (ref: female)								
Male	1.73	1.33	2.23	<0.0001	1.67	1.21	2.29	0.0017
Charlson Score	1.11	1.05	1.16	<0.0001	1.07	1.01	1.14	0.0304
Tumor location (ref: L)								
M	0.96	0.84	1.10	0.5487	1.20	1.00	1.43	0.0503
U	1.23	1.02	1.48	0.0309	1.41	1.10	1.79	0.0058
X	1.14	0.98	1.34	0.0990	1.19	0.95	1.47	0.1267
Tumor length, cm	1.13	1.11	1.16	<0.0001	1.11	1.08	1.15	<0.0001
Grading (ref: G1/G2)								
G3/4	1.24	1.09	1.40	0.0011	1.15	0.97	1.36	0.1034
Unknown	0.87	0.71	1.07	0.1948	0.88	0.64	1.21	0.4363
Pathologic T stage (ref:0/Tis)								
1	1.19	0.86	1.66	0.2988	1.71	0.94	3.13	0.0813
2	1.84	1.31	2.59	0.0005	2.42	1.31	4.47	0.0047
3/4	2.91	2.11	4.03	<0.0001	3.61	1.98	6.59	<0.0001
Pathologic N stage (ref: 0)								
1	1.83	1.60	2.10	<0.0001	1.61	1.35	1.91	<0.0001
2	2.70	2.31	3.16	<0.0001	2.48	2.04	3.02	<0.0001
3	4.46	3.37	5.91	<0.0001	3.63	2.23	5.91	<0.0001
Pathologic stage (ref: 0)								
1	1.33	0.92	1.93	0.1295	1.86	0.95	3.62	0.0699
2	2.14	1.48	3.08	<0.0001	2.85	1.47	5.53	0.0020
3	4.33	3.01	6.22	<0.0001	5.30	2.72	10.31	<0.0001
Margin status (ref: negative)								
Positive	2.74	2.34	3.20	<0.0001	2.82	2.31	3.43	<0.0001
Adjuvant therapy (ref: yes)								
No	0.70	0.63	0.79	<0.0001	0.69	0.60	0.81	<0.0001
Surgery approach (ref: thoracoscopic)								
Open	1.40	1.25	1.57	<0.0001	1.29	1.11	1.49	0.0008

HR indicates hazard ratio.

study. On the contrary, if the pTNM and ypTNM staging systems were considered into the same study, that could severely confound the result and analysis.

Whether the open or thoracoscopic approach was chosen depended on the surgeons' experience, patient's preference, hospital facility, neoadjuvant therapy, and tumor stage. The long-term survival influence of open or thoracoscopic esophagectomy could vary based on the tumor stage and neoadjuvant therapy. We only enrolled patients receiving upfront esophagectomy. We also compared survival according to different pathologic stages (I, II, and III).

Records for 2053 patients with ESCC were retrieved from the Taiwan Cancer Registry, and one-to-two propensity score matching was used to find 1289 well-matched patients. The matched results showed that thoracoscopic esophagectomy resulted in better 3-year overall survival compared to open esophagectomy. Furthermore, we compared stage-specific survival between the 2 groups. For pathologic I and II ESCC, we found thoracoscopic esophagectomy is still associated with better survival than open esophagectomy. Overall survival was similar for open versus thoracoscopic esophagectomy in patients with pathologic III ESCC. We found that the survival influence of open esophagectomy and thoracoscopic esophagectomy varied in different tumor stages in patients undergoing upfront esophagectomy.

According to the NCCN Clinical Practice Guidelines, neoadjuvant CRT following by esophagectomy was recommended for local advanced ESCC.[2] The ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) clinical trial, which enrolled 366 patients (cT3 81.1%, cN1 64.5%), concluded that preoperative CRT improved survival.[5] In contrast, the Francophone de Cancerologie Digestive (FFCD) 9901 trials (cT1/2 72.3%, cN0 72.3%), which included 195 patients with esophageal cancer concluded that preoperative CRT not only does not improve survival compared with surgery alone, but also is associated with increased morbidity in clinical I/II patients.[6] Patients with early stages, such as clinical I/II, could not have survival benefits from neoadjuvant CRT. We have investigated the influence of treatment modalities on overall survival of clinical II/III ESCC.[26] Upfront esopahgectomy was associated with significantly poorer overall survival than neoadjuvant CRT followed by esophagectomy for patients with clinical stage III ESCC, but not in clinical stage II ESCC.[26] If ESCC patients have bulky tumor or metastatic lymph nodes, upfront esophagectomy was not suggested. Neoadjuvant CRT should be applied for tumor down-staging. Furthermore, thoracoscopic esophagectomy could not provide survival benefit compared with open esophagectomy in clinical stage III patients. Upfront esophagectomy was not recommended in clinical stage III ESCC. We suggested that upfront thoracoscopic esophagectomy is indicated for clinical I/II disease. Further randomized controlled trial designs should be considered according to clinical stages.

Strengths and Weaknesses

The strengths of our study include the restriction to a single cancer cell type and the consideration of only 2 upfront treatment modalities. We only included patients with ESCC. We

TABLE 4. Multivariate Analysis for Patients With Upfront Open or Thoracoscopic Esophagectomy

Variables	All Patients				Propensity-Matched Patients			
	HR	95% CI		*P*	HR	95% CI		*P*
Age, y	1.00	1.00	1.01	0.3600	1.00	1.00	1.01	0.2466
Sex (ref: female)								
Male	1.73	1.32	2.28	< 0.0001	1.84	1.33	2.54	0.0003
Charlson score	1.16	1.10	1.22	< 0.0001	1.17	1.10	1.25	< 0.0001
Tumor location (ref: L)								
M	1.10	0.95	1.28	0.1966	1.17	0.97	1.40	0.0990
U	1.36	1.11	1.66	0.0034	1.39	1.09	1.79	0.0086
X	1.06	0.89	1.25	0.5460	1.15	0.92	1.43	0.2202
Tumor length, cm	1.06	1.03	1.09	0.0001	1.03	0.99	1.08	0.1175
Grading (ref: G1/G2)								
G3/4	1.17	1.02	1.35	0.0212	1.23	1.04	1.47	0.0180
Unknown	1.05	0.78	1.40	0.7684	1.13	0.79	1.61	0.5003
Pathologic T stage (ref: 0/Tis)								
1	1.41	0.43	4.68	0.5730	1.42	0.32	6.25	0.6436
2	1.67	0.52	5.40	0.3934	1.69	0.40	7.18	0.4780
3/4	1.99	0.62	6.36	0.2469	2.26	0.54	9.48	0.2656
Pathologic N stage (ref: 0)								
1	1.35	1.03	1.76	0.0270	1.42	1.03	1.97	0.0348
2	1.81	1.29	2.54	0.0006	1.99	1.27	3.12	0.0027
3	2.77	1.85	4.14	< 0.0001	2.71	1.44	5.11	0.0020
Pathologic stage (ref: 0)								
1	1.42	0.37	5.39	0.6080	1.45	0.28	7.45	0.6580
2	1.78	0.48	6.59	0.3893	1.73	0.35	8.61	0.5049
3	2.35	0.61	9.01	0.2120	1.86	0.36	9.67	0.4589
Margin status (ref: negative)								
Positive	2.13	1.79	2.53	< 0.0001	2.05	1.65	2.54	< 0.0001
Adjuvant therapy (ref: yes)								
No	1.74	1.49	2.04	< 0.0001	1.49	1.22	1.82	< 0.0001
Surgery approach (ref: thoracoscopic)								
Open	1.20	1.06	1.36	0.0042	1.24	1.07	1.44	0.0041

HR indicates hazard ratio.

used a large national cancer database to explore the stage-specific survival differences between open and thoracoscopic esophagectomy. One-to-two propensity score matching was used to decrease selection bias.

This retrospective study had unavoidable bias. The radiotherapy protocols, chemotherapy regimens, surgical skill, staging work-up, and surgical volume varied in different hospitals in Taiwan. Open esophagectomy was replaced with thoracoscopic esophagectomy gradually and overall survival will improve mildly over time. Diagnostic year might be a potential bias. The heterogeneous surgical skills may influence the analysis. The thoracoscopic esophagectomies in this study included instances of the Iver-Lewis procedure and the McKeown procedure. McKweon procedure is the most common procedure in Taiwan. Details of the extent of lymph node dissection is unavailable in this database. The abdominal phase of a thoracoscopic esophagectomy involves a laparoscope, laparostomy, or hand-assisted techniques. Since we only considered ESCC and upfront esophagectomy, the results may not extend to adenocarcinoma or ESCC with neoadjuvant therapy.

CONCLUSIONS

This study revealed that thoracoscopic esophagectomy could provide better survival than open esophagectomy in ESCC patients without neoadjuvant CRT. Stage-specific survival comparisons showed thoracoscopic esophagectomy is associated with better survival than open esophagectomy in patients with pathologic I/II ESCC.

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