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Adjuvant chemotherapy in node-positive patients after esophagectomy for esophageal squamous cell carcinoma

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Abstract

Background: The role of adjuvant chemotherapy in esophageal squamous cell carcinoma (ESCC) remains controversial. This study aimed to evaluate the impact of adjuvant chemotherapy on survival in patients with positive nodes after surgery for ESCC.

Methods: We retrospectively reviewed the survival outcomes of node-positive patients with ESCC who underwent curative resection with or without adjuvant chemotherapy between January 1994 and December 2015.

Results: We analyzed 460 patients (333 adjuvant chemotherapy, 127 surgery alone). The surgery-alone group was older (64 vs. 60 years, $p < 0.001$) and had more comorbidities ($p = 0.004$) than the adjuvant chemotherapy group. After propensity score matching, overall survival (OS) and recurrence-free survival (RFS) of the adjuvant chemotherapy group were better than those of the surgery-alone group: 5-year OS rate 62.7% (95% confidence interval [CI] 54.4–72.3%) vs. 46.8% (95% CI 38.5–57%, $p = 0.001$) and 5-year RFS rate 53.9% (95% CI 45.4–63.9%) vs. 36.2% (95% CI 28.3–46.3%, $p < 0.001$). Notably, in patients with pT3–4 stage, the adjuvant chemotherapy group had significantly better 5-year OS rate (41.3% [95% CI 29.3–58.3%] vs. 18% [95% CI 10–32.5%], $p = 0.01$) and 5-year RFS rate (37% [95% CI 25.3–53.9%] vs. 12% [95% CI 5.7–25.4%], $p < 0.001$) than in the surgery-alone group. In multivariable analysis, adjuvant chemotherapy had a favorable effect on both OS (hazard ratio [HR] 0.562, 95% CI 0.426–0.741, $p < 0.001$) and RFS (HR 0.702, 95% CI 0.514–0.959; $p = 0.026$).

Conclusion: Adjuvant chemotherapy may improve survival in node-positive patients with ESCC, especially in those with pT3–4 stage.

KEYWORDS
adjuvant chemotherapy, curative resection, esophageal cancer

INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is a highly aggressive disease with a poor prognosis. Although esophagectomy has been the mainstay of treatment for localized ESCC, surgery alone has limited efficacy in improving survival in patients with locally advanced esophageal cancer.[1–3] In recent decades, multimodal treatment strategies, which include preoperative or postoperative chemotherapy, radiotherapy, and chemoradiotherapy (CRT), have been studied for their effects on patient survival.[3–7] Randomized trials have shown that neoadjuvant CRT followed by surgery significantly improves survival in patients with locally advanced ESCC,[8,9] therefore neoadjuvant CRT before surgery has been widely adopted.

On the other hand, the optimal postoperative therapeutic strategy for locally advanced ESCC remains controversial.[10] The 2019 National Comprehensive Cancer Network guidelines for the diagnosis and treatment of esophageal cancer and gastroesophageal junction carcinoma recommended that regardless of the pT or pN staging, no additional treatment other than surveillance is needed for

patients with R0 resection.[11] In 2016, the updated European Society for Medical Oncology Clinical Practice Guidelines for esophageal cancer did not provide any clear recommendations for adjuvant treatment in patients after surgery.[12] Additionally, the Society of Thoracic Surgeons Practice Guidelines on the Role of Multimodality Treatment for Cancer of the Esophagus and Gastroesophageal Junction had no clear recommendations for adjuvant therapy for ESCC.[13] Meanwhile, the 2017 esophageal cancer practice guidelines edited by the Japan Esophageal Society recommended postoperative chemotherapy for patients with clinical stage II or III esophageal cancer who have undergone surgery without preoperative therapy.[14] This was based on weak evidence. So far, only a subgroup analysis of a randomized controlled trial and a prospective study have shown that postoperative chemotherapy could prolong disease-free survival in lymph node (LN)-positive patients with ESCC.[7,15]

In this study, we aimed to evaluate the impact of adjuvant chemotherapy, compared with surgery alone, on survival in patients with ESCC with positive nodes after surgery.

METHODS

Patient selection

We reviewed 2343 consecutive patients with ESCC who underwent esophagectomy for esophageal squamous cell carcinoma at our institution between January 1994 and December 2015. Patients were included in the present study if they met all the following criteria: (i) patients had undergone complete resection for esophageal cancer without neoadjuvant therapy prior to surgery and were pathologically confirmed with positive node; (ii) patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and (iii) patients who were supposed to be able to tolerate chemotherapy by physicians' judgment. Patients were excluded from the study for the following reasons: (i) patients who had other malignancies; (ii) patients with positive operative margins; (iii) patients who had received postoperative radiotherapy; (iv) patients who had poor performance status (ECOG 2–4); (v) patients who refuse chemotherapy; (vi) patients who had a severe postoperative complication or died within 60 days of operative complications; (vii) patients who were confirmed recurrence within postoperative 60 days; and (viii) patients with missing survival data.

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived with the approval of the Institutional Review Boards (IRB no. 2021-04-122).

Surgery

Stomach or colon mobilization was conducted through an upper midline laparotomy. Most patients underwent esophagectomy via a transthoracic approach. The anastomosis was conducted between the conduit and the esophagus on the left side of the neck or just below the thoracic inlet, using a stapling technique or a hand-sewn technique. For middle- to lower-thoracic ESCC, two-field LN dissection was conducted at the mediastinal and abdominal LN stations. For upper-thoracic ESCC, three-field LN dissection was conducted by resecting the LNs within the cervical LN station and the two LN stations mentioned above.

Postoperative adjuvant therapies

Adjuvant chemotherapy was started 4–8 weeks after surgery. The chemotherapy consisted of cisplatin (60 mg/m^2, intravenously) and 5-fluorouracil (5-FU; 1000 mg/m^2/day) in a continuous infusion for 4 days. From 2005 to 2010, patients who were enrolled in a clinical trial received capecitabine (1000 mg/m^2, twice a day, per oral, days 1–14) and cisplatin (75 mg/m^2/day, intravenously, day 1). Each cycle was repeated every 3 weeks (four cycles). From 2011 to 2015, patients who were enrolled in another clinical trial received leucovorin and 5-FU (LV5FU2) or LV5FU2 plus oxaliplatin (FOLFOX) combination chemotherapies.[16] The LV5FU2 regimen consisted of 2-week cycles of 200 mg/m^2 leucovorin and a bolus injection of 5-FU (400 mg/m^2, intravenously, day 1) followed by a 46-h continuous infusion of 5-FU (2,400 mg/m^2). The FOLFOX regimen consisted of 2-week cycles of oxaliplatin (85 mg/m^2, intravenously, day 1) before administering the LV5FU2 regimen. Other patients were observed without adjuvant chemotherapy because of the patients' poor general condition or refusal or on the basis of the physician's judgment.

Follow-up and toxicity

All patients were followed up every 3 months for the first 2 years and every 6 months thereafter. The median follow-up time was 4.1 years (range 0.02–23.36 years). Recurrences were detected with chest or abdominal computed tomography, endoscopy with or without biopsy, positron emission tomography, or bone scintigraphy. Toxicity was assessed for each cycle of chemotherapy and was classified according to the World Health Organization toxicity criteria.

Statistical analyses

The primary end point of the study was overall survival (OS), and the secondary end point was recurrence-free survival (RFS). OS was defined as the interval between the date of surgery and the date of death or the last follow-up. RFS was calculated from the date of surgery to the date of recurrence, death, or the last follow-up. OS and RFS were analyzed using the Kaplan–Meier method, and the groups were compared using the log-rank test. A p value of <0.05 was

considered statistically significant. The baseline characteristics were compared between the two groups using Student's *t*-test or the Mann–Whitney U test for continuous variables, depending on the normality of distribution. Pearson's χ^2 and Fisher's exact tests were used for categorical variables, as appropriate. To minimize selection bias between the groups, propensity score matching was performed. The variables for matching included age, gender, comorbidity, body weight index (BMI), American Society of Anesthesiologists (ASA) physical status classification, forced expiratory volume in 1 s (FEV1), and pathologic stage. Matched pairs were created by performing 1:1 optimal pair matching. After propensity score matching, 113 patients in each group were selected for analysis. Prognostic factors were determined using Cox logistic regression analysis. Multicollinearity was assessed using variance inflation factor, which measures the inflation in the variances of the parameter estimates due to multicollinearity potentially caused by the correlated predictors. Statistical analysis was conducted using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

RESULTS

Patient characteristics

A total of 699 patients had positive nodes on postoperative pathology during the study period. Patients with medically compromised conditions, including old age ($n = 50$), poor general condition or underlying comorbidities ($n = 60$), postoperative complications or mortality ($n = 27$), or early relapse ($n = 10$), were excluded. Additionally, patients who refused chemotherapy ($n = 55$) or had radiotherapy ($n = 21$) and patients with missing survival data ($n = 10$) were excluded. Finally, 333 patients who received the adjuvant chemotherapy and 127 patients who underwent surgery alone were included in the analysis (Figure 1).

Patients in the surgery-alone group were older (64 vs. 60 years, $p < 0.001$) and had more comorbidities ($p = 0.004$) or higher ASA class ($p = 0.035$) than those in the adjuvant chemotherapy group. There were no differences in lung function and BMI between the groups.

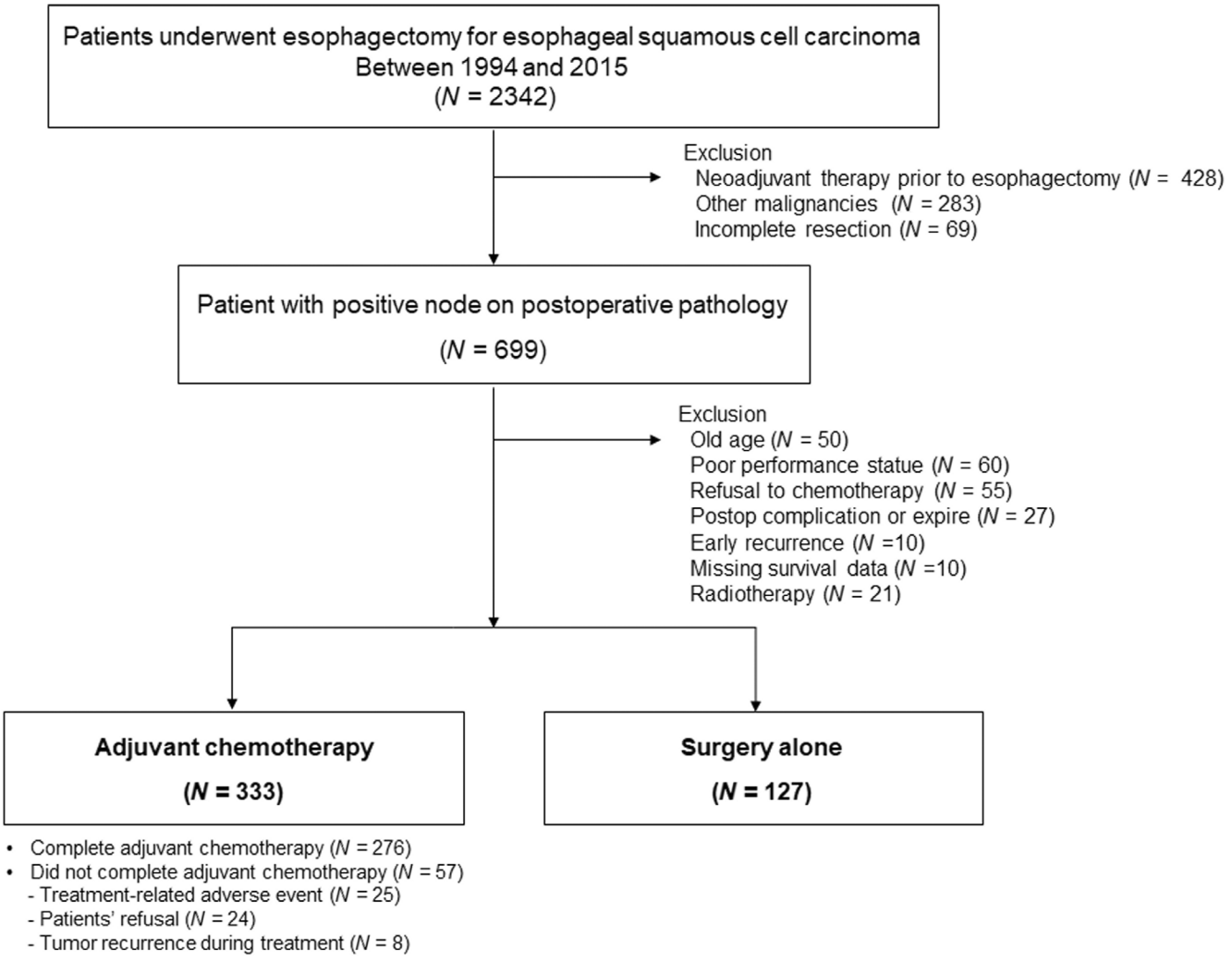

FIGURE 1 Flowchart of patient selection

TABLE 1 Baseline characteristics

	Before PSM				After PSM			
	Total ($n = 460$)	**Surgery alone ($n = 127$)**	**Adjuvant CT ($n = 333$)**	***p* value**	**Surgery alone ($n = 113$)**	**Adjuvant CT ($n = 113$)**	***p* value**	**SMD**
Sex				0.395			1.000	**0.038**
Female	21 (4.6)	8 (6.3)	13 (3.9)		6 (5.3)	9 (7.1)		
Male	439 (95.4)	119 (93.7)	320 (96.1)		107 (94.7)	106 (93.8)		
Age, years	61 (57, 66)	64 (59, 69)	60 (56, 65)	**<0.001**	63.12 ± 7.63	62.92 ± 5.46	0.818	**0.031**
CCI				**0.004**			0.927	**0.143**
0	19 (4.1)	1 (0.8)	18 (5.4)		1 (0.9)	0		
1	130 (28.3)	28 (22.1)	102 (30.6)		26 (23.0)	26 (23.0)		
2	183 (39.8)	50 (39.4)	133 (39.9)		46 (40.7)	49 (43.4)		
3+	128 (27.8)	48 (37.8)	80 (24)		40 (35.4)	38 (33.6)		
ASA class				**0.035**			0.847	**0.102**
1	52 (11.3)	7 (5.5)	45 (13.5)		7 (6.2)	9 (8)		
2	400 (87)	118 (92.9)	282 (84.7)		104 (92)	103 (91.2)		
3	8 (1.7)	2 (1.6)	6 (1.8)		2 (1.8)	1 (0.9)		
FEV_1				0.28			1.000	**0.028**
≥80%	408 (88.7)	108 (85)	300 (90.1)		97 (85.8)	98 (86.7)		
60%–79%	42 (9.1)	15 (11.8)	27 (8.1)		13 (11.5)	12 (10.6)		
<60%	10 (2.2)	4 (3.2)	6 (1.8)		3 (2.7)	3 (2.7)		
BMI	22.3 (20.4, 24.2)	22.2 (20.4, 24)	22.5 (20.3, 24.2)	0.512	22.2 (20.4, 24)	22.3 (20.3, 24.2)	0.956	**0.034**
Smoking history				0.954			0.66	
No	42 (9.1)	12 (9.5)	30 (9)		12 (9.45%)	16 (12.6%)		
Yes	411 (89.4)	113 (89)	298 (89.5)		113 (88.98%)	110 (86.61%)		
Tumor location				0.294			0.164	
Upper 1/3	48 (10.4)	16 (12.6)	32 (9.6)		14 (12.4)	10 (8.9)		
Middle 1/3	85 (18.5)	28 (22.1)	57 (17.1)		51 (45.1)	43 (38.1)		
Lower 1/3	321 (69.7)	82 (64.6)	239 (71.8)		47 (41.6)	57 (50.4)		
Pathologic stage				**<0.001**			0.975	**0.062**
IIB	165 (35.9)	67(52.8)	98(29.4)		55 (48.7)	52 (46)		
IIIA	142 (30.9)	35(27.6)	107(32.1)		33 (29.2)	36 (31.9)		
IIIB	86 (18.7)	17(13.4)	69(20.7)		17 (15)	17 (15)		
IIIC	61 (13.3)	8(6.3)	53(15.9)		8 (7.1)	8 (7.1)		
IV	6 (1)	0	6 (1.8)					
No. of positive LN dissected	2 (1, 4)	1 (1, 2)	2 (1, 4)	**<0.001**	1 (1, 3)	2 (1, 4)	**0.009**	
No. of LN dissected	41 (31.5, 52)	38 (30, 46)	41 (32, 52)	0.078	39 (31, 47)	40 (30, 52)	0.626	

(Continues)

TABLE 1 (Continued)

	Before PSM				After PSM			
	Total ($n = 460$)	Surgery alone ($n = 127$)	Adjuvant CT ($n = 333$)	p value	Surgery alone ($n = 113$)	Adjuvant CT ($n = 113$)	p value	SMD
Extent of LN dissection				0.314			0.941	
1 Field	6 (1.3)	3 (2.4)	3 (0.9)		2 (1.8)	2 (1.8)		
2 Fields	385 (83.7)	108 (85)	277 (83.2)		97 (85.8)	95 (84.1)		
3 Fields	69 (15)	16 (12.6)	53 (15.9)		14 (12.4)	16 (14.2)		
Histologic grade				0.809			0.687	
G1	64 (13.9)	18 (14.2)	46 (13.8)		17 (15)	12 (10.6)		
G2	312 (67.8)	84 (66.1)	228 (68.5)		75 (66.4)	82 (72.6)		
G3	76 (16.5)	22 (17.3)	54 (16.2)		18 (15.9)	15 (13.3)		

Abbreviations: ASA, American Society of Anesthesiologis; BMI, body weight index; CCI, Charlson Comorbidity Index; CTx, chemotherapy; FEV_1, forced expiratory volume in 1 s; LN, lymph node.

Additionally, patients in the adjuvant chemotherapy group had more advanced stages ($p < 0.001$).

In matched group, there were no differences in age, sex, Charlson Comorbidity Index (CCI), ASA class, FEV1, BMI, and pathologic stage between the groups. The patients' baseline characteristics details are described in Table 1.

Practice pattern

Most patients who underwent surgery before 2005 and were found to have positive nodes after surgery received adjuvant chemotherapy (106/126, 84%). From 2005 to 2009, we conducted a randomized clinical trial of surgery alone versus surgery followed by adjuvant chemotherapy in patients who underwent curative resection of esophageal cancer, in which only 53% (57/107) of the patients received adjuvant chemotherapy.[15] From 2010 to 2015, 75% (170/227) of the patients who underwent surgery received adjuvant chemotherapy. Figure 2 illustrates the practice pattern for each year.

Survival outcomes

In the intention-to-treat analysis, the 5-year OS rate was not different between the adjuvant treatment and surgery-alone groups: 49.5 (95% confidence interval [CI] 41.5–59.1%) vs. 51.5 (95% CI 46.4–57.2%, $p = 0.2$). The 5-year RFS rate also did not differ between the two groups: 44.4% (95% CI 39.3–50.1%) vs. 38.5% (95% CI 30.9–48%, $p = 0.1$). In matched patients, OS and RFS of the adjuvant chemotherapy group were better than those of the surgery-alone group: 5-year OS rate 62.7% (95% CI 54.4–72.3%) vs. 46.8% (95% CI 38.5–57%, $p = 0.001$) and 5-year RFS rate 53.9% (95% CI 45.4–63.9%) vs. 36.2% (95% CI 28.3–46.3%, $p < 0.001$). Figure 3 shows the survival curves. In the per-protocol analysis excluding 56 patients who did not complete treatment, the survival outcomes of the adjuvant chemotherapy group were much better than those of the surgery-alone group: 5-year OS rate 65.2% (95% CI 56.2–75.5%) vs. 46.8% (95% CI 38.5–57%, $p < 0.001$) and 5-year RFS rate 56.7% (95% CI 47.5–67.6%) vs. 36.2% (95% CI 28.3–46.3%, $p < 0.001$). The survival curves in the per-protocol analysis are shown in Supporting Information Figure S1.

We carried out subgroup analysis based on the pathologic T stage for matched patients. No significant differences in OS and RFS rates were observed in matched patients with pT1 or pT2 stage. For pT1 patients, the 5-year OS was 77.3% (95% CI 66.4–90.1%) for the adjuvant treatment group and 79.4% (95% CI 68.4–92.4%) for the surgery alone group respectively ($p = 0.945$), and the 5-year RFS was 69.2% (95% CI 57.4–83.5%) for the adjuvant treatment group and 61.2% (95% CI 48.3–77.5%), for the surgery alone group respectively ($p = 0.297$). For pT2 patients, the 5-year OS was 77.8% (95% CI 60.8–99.6%) for the adjuvant treatment group and 47.4% (95% CI 29.5–76.1%), for the surgery alone group respectively ($p = 0.015$), and the 5-year RFS

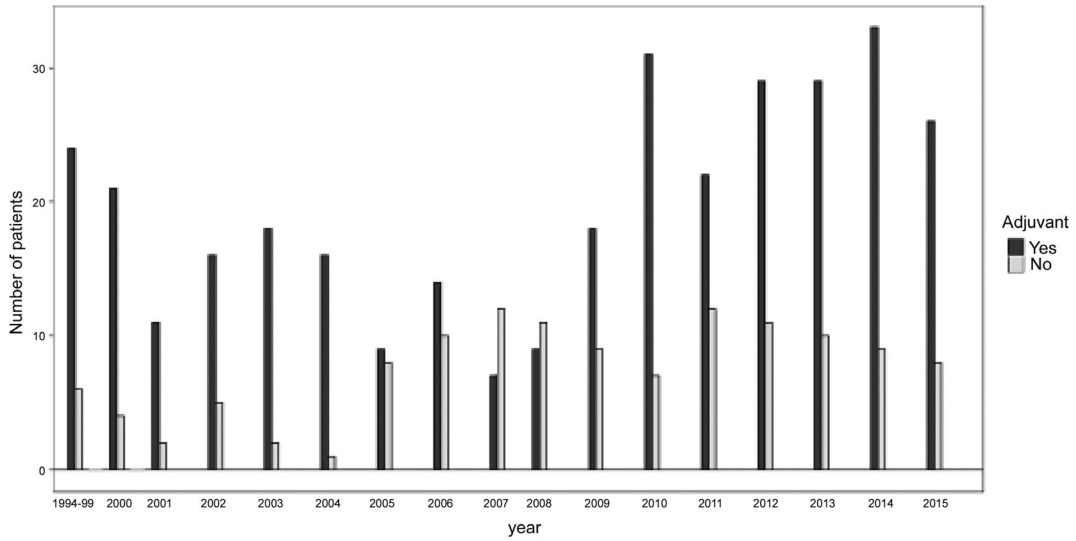

FIGURE 2 Practice pattern over time

was 55.6% (95% CI 36.8–84%) for the adjuvant treatment group and 42.1% (95% CI 24.9–71.3%), for the surgery alone group respectively ($p = 0.101$). Notably, in patients with pT3 or higher stage, both the 5-year OS rate (41.3% [95% CI 29.3–58.3%] vs. 18% [95% CI 10–32.5%], $p = 0.01$) and the 5-year RFS rate (37% [95% CI 25.3–53.9%] vs. 12% [95% CI 5.7–25.4%], $p < 0.001$) were significantly higher in the adjuvant treatment group than in the surgery-alone group. Figure 4 shows the survival curves based on the pathologic T stage in matched patients.

In terms of the chemotherapy agent, the 5-year OS of the adjuvant chemotherapy group was consistently better than that of the surgery-alone group regardless of the agent of chemotherapy, except for FOLFOX (Supporting Information Figure S2).

In univariable analysis of factors affecting OS, male sex, old age (≥65 years), higher CCI (score ≥ 3), advanced T stage (pT3–4), and higher N stage (pN2–3) had an unfavorable effect on OS. In multivariable analysis, old age (≥65 years), advanced T stage (pT3–4), and higher N stage (pN2–3) were associated with worse OS. Notably, adjuvant chemotherapy had a favorable effect on OS (hazard ratio [HR] 0.56, 95% CI 0.43–0.74, $p < 0.001$). The details are provided in Table 2.

With respect to prognostic factors for RFS, male sex, advanced T stage (pT3–4), and higher N stage (pN2–3) had an unfavorable effect on RFS in univariable analysis. In multivariable analysis, male sex, advanced T stage (pT3–4), and higher N stage (pN2–3) had an unfavorable effect on RFS. Notably, adjuvant chemotherapy was a good prognostic factor for RFS (HR 0.7, 95% CI 0.51–0.96, $p = 0.026$). The details are shown in Table 2.

Discontinuation of adjuvant chemotherapy

A total of 57 (17.1%) patients did not complete adjuvant chemotherapy. Treatment-related adverse events (AEs) led to the discontinuation of adjuvant chemotherapy in 25 (7.5%) patients (Supporting Information Table S1). The most common cause of discontinuation was fatigue ($n = 9$). Four (1.2%) patients experienced grade 3–4 treatment-related AEs. No grade 5 treatment-related AEs occurred in the adjuvant chemotherapy group. Additionally, 24 (7.2%) patients refused additional chemotherapy during treatment. Eight (2.4%) patients did not complete adjuvant chemotherapy because of tumor recurrence during treatment.

DISCUSSION

Surgery is the standard treatment for ESCC, but survival remains poor. Attempts have been made to improve the survival of patients with ESCC, including the use of chemotherapy, radiotherapy, or CRT before or after surgery.

The evidence for the role of induction therapy in patients with advanced ESCC is well established, and this treatment strategy is generally applied in clinical practice. The randomized prospective trial OEO2, conducted by the Medical Research Council Esophageal Cancer Working Party, demonstrated that induction chemotherapy followed by esophageal resection improved survival, with a 5-year survival rate of 23% in patients who received preoperative chemotherapy before surgery versus 17.1% in patients who underwent surgery alone (HR 0.84, 95% CI 0.72–0.98, $p = 0.03$).[6,8] Additionally, the large randomized trial CROSS also showed that induction chemotherapy (carboplatin and paclitaxel) and concurrent radiotherapy resulted in significantly better OS and RFS than surgery alone, with a median OS of 49.4 months in the CRT group versus 24.0 months in the surgery-alone group (HR 0.66, 95% CI 0.5–0.87, $p = 0.003$).[17]

By contrast, the role of adjuvant chemotherapy is not well established. In a retrospective study by Brescia et al.

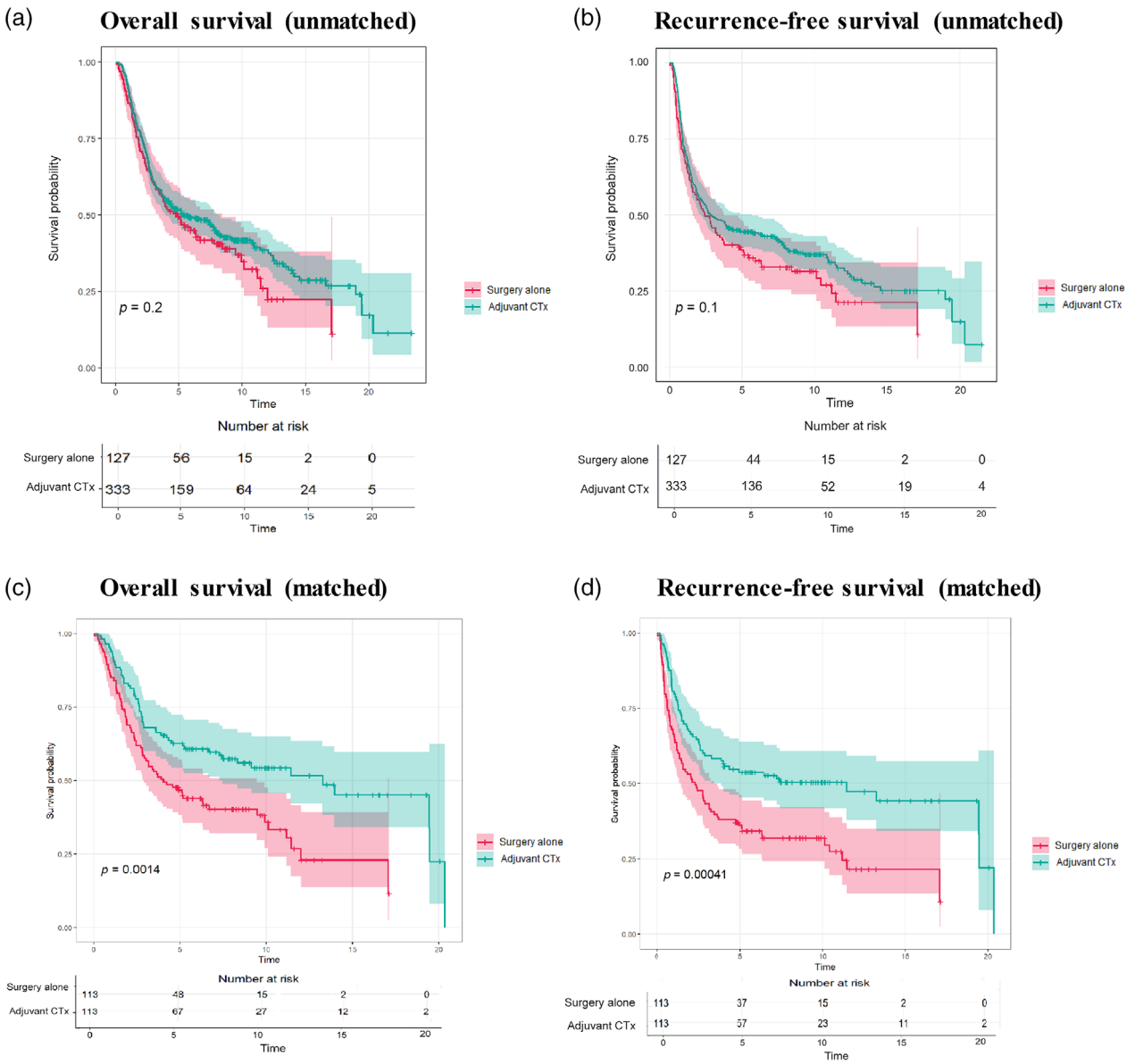

FIGURE 3 Overall survival and recurrence-free survival of matched patients in the intention-to-treat analysis

on adjuvant chemotherapy for node-positive patients after induction therapy and resection of esophageal cancer, the adjuvant treatment group had a better median survival (24.0 months [95% CI 16.6–32.2 months] vs. 18.0 months [95% CI 11.1–25.0 months], $p = 0.033$).[18] In a meta-analysis conducted by Zhang et al. in 2014, which included 11 studies published between 1995 and 2012, the 3-year OS did not differ between the postoperative chemotherapy and surgery-alone groups (relative risk [RR] 0.89, $p = 0.25$) and the 3-year RFS was not significantly different between the two groups (RR 0.97, $p = 0.84$). Subgroup analysis showed that adjuvant chemotherapy improved the 5-year RFS of node-positive patients (RR 0.97, $p = 0.04$).[19] In another meta-analysis conducted by Zhao et al. in 2018, which included nine articles published between 1996 and 2016, patients with ESCC who received postoperative chemotherapy had improved OS (HR 0.78, 95% CI 0.66–0.91, $p = 0.002$) and RFS (HR 0.72, 95% CI 0.6–0.86, $p < 0.001$).[20] Table 3 summarizes the literature reports on adjuvant chemotherapy for esophageal cancer.

Meanwhile, only a few randomized prospective studies for adjuvant chemotherapy after curative resection have been conducted. This is because most patients undergoing esophagectomy have decreased performance status after surgery. Some patients experience postoperative complications such as pneumonia, acute lung injury, and anastomotic leakage. Furthermore, many patients experience postoperative discomfort, including postoperative pain, poor oral intake, and fatigue. In the JCOG9204 study, in which the outcomes were compared between patients who received two cycles of postoperative chemotherapy (cisplatin and 5-FU) and

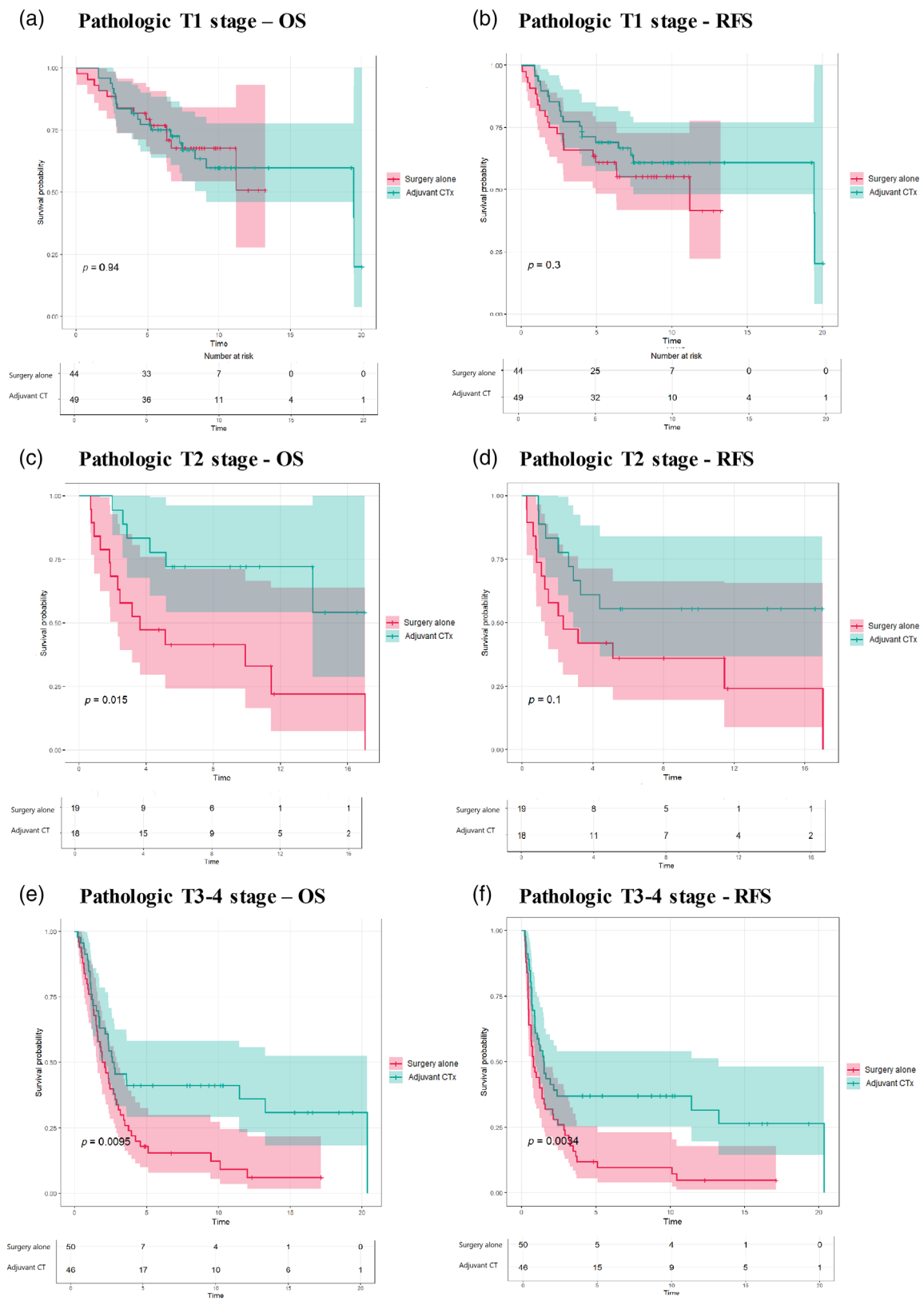

FIGURE 4 Overall survival and recurrence-free survival according to pathologic T stage in matched patients

patients who underwent surgery alone, a significant improvement in the 5-year RFS was observed in the adjuvant chemotherapy group, but there was no significant difference in OS between the two groups. The benefit of adjuvant chemotherapy for RFS was particularly evident in patients with positive LNs after surgery and was not found

TABLE 2 Univariable and multivariable analyses of factors associated with overall survival and recurrence-free survival

		Univariable analysis				Multivariable analysis			
Overall survival	**No. of patients**	**Hazard ratio (95% CI)**			***p* value**	**Hazard ratio (95% CI)**			***p* value**
Sex									
Male	439 (95.43%)	2.532	1.127	5.687	**0.025**	2.261	0.998	5.121	0.051
Age									
≥65 y	145 (30.85%)	1.294	1.014	1.652	**0.039**	1.349	1.048	1.736	**0.020**
CCI									
1	130 (28.26%)	1.611	0.778	3.339	0.200				
2	183 (39.78%)	1.610	0.785	3.305	0.194				
3	128 (27.83%)	2.409	1.169	4.965	**0.017**				
Pathologic T stage									
T2	66 (14.35%)	1.468	0.975	2.211	0.066	1.265	0.830	1.928	0.274
T3–4	239 (50.85%)	3.018	2.257	4.037	**<0.001**	2.452	1.790	3.359	**<0.001**
Pathologic N stage									
N2–3	190 (40.43%)	2.254	1.783	2.849	**<0.001**	1.485	1.103	1.999	**0.009**
No. of positive LNs dissected		1.128	1.099	1.159	**<0.001**	1.094	1.054	1.136	**<0.001**
No. of LNs dissected		1.006	0.999	1.013	0.089				
Adjuvant chemotherapy	127 (27.02%)	3.161	0.788	12.677	0.104	0.562	0.426	0.741	**<0.001**
		Univariable analysis				**Multivariable analysis**			
Recurrence-free survival	**No. of patients**	**Hazard ratio (95% CI)**			***p* value**	**Hazard ratio (95% CI)**			***p* value**
Sex									
Male	439 (95.43%)	3.585	1.334	9.635	**0.011**	2.945	1.089	7.959	**0.033**
Age									
≥65 y	145 (30.85%)	0.982	0.743	1.297	0.898				
CCI									
1	130 (28.26%)	1.619	0.744	3.522	0.224				
2	183 (39.78%)	1.461	0.678	3.151	0.333				
3	128 (27.83%)	1.704	0.782	3.715	0.180				
Pathologic T stage									
T2	66 (14.35%)	1.471	0.934	2.317	0.096	1.314	0.832	2.076	0.242
T3–4	239 (50.85%)	2.988	2.179	4.098	**<0.001**	2.521	1.797	3.537	**<0.001**

(Continues)

TABLE 2 (Continued)

Recurrence-free survival	No. of patients	Univariable analysis				Multivariable analysis			
		Hazard ratio (95% CI)			*p* value	Hazard ratio (95% CI)			*p* value
Pathologic N stage									
N2–3	190 (40.43%)	2.609	2.012	3.383	**<0.001**	1.729	1.252	2.388	**0.001**
No. of positive LNs dissected		1.118	1.088	1.149	**<0.001**	1.067	1.027	1.109	**0.001**
No. of LNs dissected		1.004	0.997	1.011	0.289	0.992	0.985	1.000	0.050
Adjuvant chemotherapy	127 (27.02%)	1.084	0.805	1.458	0.596	0.702	0.514	0.959	**0.026**

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; LN, lymph node.

in patients with negative LNs.[7] In a prospective study conducted in South Korea on postoperative chemotherapy in node-positive patients with ESCC who underwent curative resection, postoperative chemotherapy prolonged the 3-year RFS; the 3 year disease-free survival rate was 47.6% in the adjuvant group and 35.6% in the surgery-alone group ($p = 0.049$).[15] Although prospective controlled studies provide strong evidence, patients in clinical trials do not reflect real-world populations because clinical trials restrict patient enrollment to those with good performance status. In addition, esophagectomy which requires high technical procedures may have inter-institutional heterogeneity with respect to postoperative complication and survival rate, and should be interpreted with caution.[21]

The optimal chemotherapy agents for node-positive ESCC have not been established so far. In this study, more than 60% of patients in the adjuvant treatment group ($n = 206$) received the combination of 5-FU and cisplatin (FP) regimens. This is the most commonly used regimen as a first-line chemotherapy in metastatic esophageal cancer. However, this frequently resulted in severe diarrhea and vomiting as well as discomfort caused by a chemoport insertion. On the other hand, capecitabine, an oral medication used in 36 patients (11.5%) in this study, could improve such problems. Capecitabine is an oral fluoropyrimidine that is preferentially metabolized in tumor tissues via an enzymatic pathway to fluorouracil and thus has a lower incidence of high-grade adverse events.

Meanwhile, leucovorin and 5-FU (LV5FU2) or LV5FU2 plus oxaliplatin (FOLFOX) combination chemotherapy were introduced for use in patients with advanced or metastatic esophageal cancer in 2000. FOLFOX chemotherapy in the definitive concurrent CRT (CCRT) was also recently shown to be more convenient and less toxic than a FP regimen. We found that the survival rate of the adjuvant chemotherapy group was consistently better than that of the surgery-alone group regardless of the agent of chemotherapy, except for FOLFOX. There was no difference between the surgery group and the FOLFOX group because this may be attributed to a small number of patients in the FOLFOX group.

In this study, we evaluated the impact of adjuvant chemotherapy on improving survival in node-positive patients with ESCC using prospectively collected information at single large-volume institution. We found that the OS and RFS of the adjuvant chemotherapy group were better than those of the surgery-alone group on propensity-score matching analysis. Of note, in patients with pT3–4N + ESCC, adjuvant chemotherapy after esophagectomy was associated with significantly improved survival. Additionally, multivariable analysis demonstrated that adjuvant chemotherapy had a favorable effect on both OS and RFS.

This study had several limitations. First, it was limited by its relatively small sample size and retrospective nature. Second, selection bias was present because only patients who were clearly suitable to receive adjuvant therapy were included. The criteria for administering adjuvant therapy are unclear. Among patients who underwent surgery alone,

TABLE 3 Summary of literature reports on adjuvant chemotherapy for esophageal cancer

Authors	Year	Study design	No. of patients	Histologic type	Regimen	OS	DFS	Remarks
Ando et al.[7]	2003	RCT	242	SCC	Cisplatin + 5-fluorouracil	5-year OS, AC 61% vs. S 52% ($p = 0.13$)	5-year DFS, AC 55% vs. S 45% ($p = 0.037$)	Risk reduction by AC was remarkable in the subgroup with lymph node metastasis
Lee et al.[10]	2005	Prospective, historical control	92	SCC	Cisplatin + 5-fluorouracil	5-year OS, AC 50.7% vs. S 43.7% ($p = 0.228$)	3-year DFS, AC 47.6% vs. S 35.6% ($p = 0.049$)	Patients with positive lymph nodes were included
Heroor et al.[21]	2003	Retrospective	211	SCC	Cisplatin + 5-fluorouracil or vindesine	5-year OS, AC 63% vs. S 47% ($p = 0.012$)		OS in patients with metastasis in 8+ lymph nodes was significant
Shiozaki et al.[22]	2005	Retrospective	167	SCC	Cisplatin + 5-fluorouracil	3-year OS, AC 83.7% vs. S 62.2% ($p < 0.05$)		AC had significantly better outcome in patients with pStage III, pN1 tumor
Zhang et al.[23]	2008	Retrospective, matched	226	SCC (97%), ADC (3%)	Cisplatin + 5-fluorouracil + leucovorin	3-year OS, AC 61.9% vs. S 57.4% ($p = 0.83$)	3-year DFS, AC 41.3% vs. S 51.2% ($p = 0.29$)	AC was most effective for patients who had cervical or celiac lymph node metastasis
Speicher et al.[24]	2015	Retrospective	1694	ADC	Various	5-year OS, AC 24.2% vs. S 14.9% ($p < 0.001$)		Patients with positive lymph nodes and negative margins were included
Saeed et al.[12]	2017	Retrospective, PSM	138	ADC (89%), SCC (8%)	5-Fluorouracil ± cisplatin or leucovorin	No difference	No difference	Patients who received neoadjuvant CRT were included
Zhang et al.[19]	2014	Meta-analysis	2047	SCC	Various	No difference	No difference	Patients with stages III–IV or positive lymph nodes could benefit from AC in terms of survival
Zhao et al.[20]	2018	Meta-analysis	1684	SCC	Various	AC could improve OS (HR 0.78, 95% CI 0.66–0.91, $p = 0.002$)	AC could improve DFS (HR 0.72, 95% CI 0.6–0.86, $p < 0.001$)	

Abbreviations: AC, adjuvant chemotherapy; ADC, adenocarcinoma; CI, confidence interval; CRT, chemoradiation; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; PSM, propensity score matching; RCT, randomized control trial; S, surgery alone; SCC, squamous cell carcinoma.

60% were included according to the physician's preference. To control for selection bias, we excluded patients who did not undergo adjuvant chemotherapy because of medically compromised conditions, including old age, poor general condition, comorbidities, patient refusal, and postoperative complications or mortality. Additionally, we included patients who were eligible for the randomized study (surgery alone vs. surgery followed by adjuvant chemotherapy) in the analysis. In fact, 40% of patients in the surgery-alone group were included according to a randomization protocol. Third, the chemotherapy regimen varied (cisplatin plus 5-FU, capecitabine plus cisplatin, leucovorin plus 5-FU, or LV5FU2 plus oxaliplatin). The effect of the adjuvant chemotherapy was consistently found regardless of the agent of chemotherapy.

In conclusion, adjuvant chemotherapy may improve survival in node-positive patients with ESCC who did not receive induction therapy before surgery. We recommend considering postoperative chemotherapy for patients with pT3–4N + ESCC who underwent upfront surgery without induction therapy. Future prospective studies on adjuvant treatment are needed.

AUTHOR CONTRIBUTIONS

Conceptualization, H.K.K. and Y.M.S.; Methodology, H.K.K. and J.-M.S.; Software, Y.J.J. and J.H.C.; Validation, Y.J.J. and J.H.C.; Formal Analysis, Y.J.J.; Investigation, Y.S.C and Y.J.J.; Resources, Y.S.C.; Data Curation, Y.J.J.; Writing—Original Draft Preparation, Y.J.J.; Writing—Review and Editing, Y.M.S. and J.-M.S.; Visualization, Y.J.J.; Supervision, J.H.C. and Y.M.S.; Project Administration, J.H.C. and H.K.K. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no competing interests.

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REFERENCES

1. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349:2241–52.
2. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet. 2013;381:400–12.
3. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359:1727–33.
4. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6:659–68.
5. Lee JL, Park SI, Kim SB, et al. A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma. Ann Oncol. 2004;15:947–54.
6. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27:5062–7.
7. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan clinical oncology group study – JCOG9204. J Clin Oncol. 2003;21:4592–6.
8. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074–84.
9. Yang H, Liu H, Chen Y, et al. Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial. J Clin Oncol. 2018;36:2796–803.
10. Atay SM, Blum M, Sepesi B. Adjuvant chemotherapy following trimodality therapy for esophageal carcinoma-is the evidence sufficient? J Thorac Dis. 2017;9:3626–9.
11. Ajani JA, D'Amico TA, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17:855–83.
12. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. ESMO guidelines committee. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50–v7.
13. Little AG, Lerut AE, Harpole DH, et al. The Society of Thoracic Surgeons practice guidelines on the role of multimodality treatment for cancer of the esophagus and gastroesophageal junction. Ann Thorac Surg. 2014;98:1880–5.
14. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 1. Esophagus. 2019;16:1–24.
15. Lee J, Lee KE, Im YH, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. Ann Thorac Surg. 2005;80:1170–5.
16. Lim SH, Shim YM, Park SH, et al. A randomized phase II study of leucovorin/5-fluorouracil with or without oxaliplatin (LV5FU2 vs. FOLFOX) for curatively-resected, node-positive esophageal squamous cell carcinoma. Cancer Res Treat. 2017;49:816–23.
17. Saeed NA, Mellon EA, Meredith KL, et al. Adjuvant chemotherapy and outcomes in esophageal carcinoma. J Gastrointest Oncol. 2017;8:816–24.
18. Brescia AA, Broderick SR, Crabtree TD, et al. Adjuvant therapy for positive nodes after induction therapy and resection of esophageal cancer. Ann Thorac Surg. 2016;101:200–10.
19. Zhang SS, Yang H, Xie X, et al. Adjuvant chemotherapy versus surgery alone for esophageal squamous cell carcinoma: a meta-analysis of randomized controlled trials and nonrandomized studies. Dis Esophagus. 2014;27:574–84.
20. Zhao P, Yan W, Fu H, Lin Y, Chen KN. Efficacy of postoperative adjuvant chemotherapy for esophageal squamous cell carcinoma: a meta-analysis. Thorac Cancer. 2018;9:1048–55.
21. Kataoka K, Nakamura K, Mizusawa J, et al. Variations in survival and perioperative complications between hospitals based on data from two phase III clinical trials for oesophageal cancer. Br J Surg. 2015;102:1088–96.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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