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Original Article

The Role of Adjuvant Chemotherapy after Neoadjuvant Chemoradiotherapy Followed by Surgery in Patients with Esophageal Squamous Cell Carcinoma

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Purpose This study aimed to investigate the efficacy of adjuvant chemotherapy after neoadjuvant chemoradiotherapy (CCRTx) followed by surgery in patients with esophageal squamous cell carcinoma (ESCC).

Materials and Methods We retrospectively analyzed the data from 382 patients who received neoadjuvant CCRTx and esophagectomy for ESCC between 2003 and 2018.

Results This study included 357 (93.4%) men, and the years median patient age was 63 (range, 40 to 84 years). Overall, 69 patients (18.1%) received adjuvant chemotherapy, whereas 313 patients (81.9%) did not. The median follow-up period was 28.07 months (interquartile range, 15.50 to 62.59). The 5-year overall survival (OS) and disease-free survival were 47.1% and 42.6%, respectively. Adjuvant chemotherapy did not improve OS in all patients, but subgroup analysis revealed that adjuvant chemotherapy improved the 5-year OS in patients with ypT+N+ (24.8% vs. 29.9%, p=0.048), whereas the survival benefit of adjuvant chemotherapy was not observed in patients with ypT0N0, ypT+N0, or ypT0N+. Multivariable analysis revealed that ypStage and adjuvant chemotherapy (hazard ratio, 0.601; p=0.046) were associated with OS in patients with ypT+N+. Freedom from distant metastasis was marginally different according to the adjuvant chemotherapy (48.3% vs. 41.3%, p=0.141).

Conclusion Adjuvant chemotherapy after neoadjuvant therapy followed by surgery reduces the distant metastasis in ypT+N+ ESCC patients, thereby improving the OS. The consideration could be given to administration of adjuvant chemotherapy to ypT+N+ ESCC patients with tolerable conditions.

Key words Esophageal neoplasms, Esophagectomy, Adjuvant chemotherapy

Introduction

Esophageal cancer is the seventh most common cancer and the sixth most common cause of cancer-related deaths worldwide; it accounted for 1 in every 18 cancer-related deaths in 2020 [1,2]. The gold standard treatment modalities for locally advanced esophageal cancer include surgical treatment, chemotherapy, and radiotherapy; a multidisciplinary approach that combines these three modalities is considered the most effective therapy [3]. Despite the advances in surgical techniques and chemoradiation (CCRTx) strategies for esophageal cancer, survival in patients with esophageal cancer after receiving trimodality therapy remains unsatisfactory. The 5-year overall survival (OS) in patients with ypStage I and ypStage II was 50% and 30%, respectively, according to the Worldwide Esophageal Cancer Collaboration data for 8th staging system [4]. In particular, patients with pathologic residual lesion after neoadjuvant therapy followed by surgery have a high risk of recurrence. To improve survival, patients with residual disease after trimodality therapy should be administered a more appropriate adjuvant therapy.

However, no appropriate management has been reported, and adjuvant cytotoxic chemotherapy is not recommended for patients with residual disease after neoadjuvant therapy plus surgery. The European Society for Medical Oncology guideline and Japanese guidelines recommend surveillance as the only standard of care after neoadjuvant chemoradiotherapy and surgery [5,6] due to the lack of evidence on the effectiveness of adjuvant cytotoxic chemotherapy. Studies on the benefits of adjuvant chemotherapy are limited by either sample size or retrospective nature and mainly focus on esophageal adenocarcinoma [7-9]. Therefore, this retrospective study aimed to evaluate the efficacy of adjuvant chemotherapy after neoadjuvant CCRTx plus surgery in patients with esophageal squamous cell carcinoma (ESCC).

Materials and Methods

1. Patients

Data from a prospectively maintained institutional database of patients who underwent surgical resection for eso-

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phageal cancer between 2003 and 2018 at Samsung Medical Center were retrospectively analyzed. The inclusion criteria are presented in Fig. 1. The exclusion criteria were as follows: patients who received preoperative therapy with a palliative or definitive aim, operative mortality cases, patients enrolled in other clinical trials, and patients who received neoadjuvant chemotherapy or radiotherapy. Finally, 382 patients were included for analysis. Briefly, the mean percentage of patients who could not receive esophagectomy after neoadjuvant CCRTx over the study period was 15.8%.

The pathologic stages were reported according to the American Joint Committee on Cancer 7th TNM staging system. Prior to surgery, all patients were evaluated via contrast chest computed tomography (CT), abdominal CT, esophagogastroduodenoscopy, endoscopic ultrasound, and whole-body positron emission tomography CT. The neoadjuvant chemoradiotherapy regimen mainly comprised cisplatin and 5-fluorouracil (5-FU) with or without 4,000-4,400 cGY radiation. The adjuvant chemotherapy regimen also included cisplatin with either fluorouracil or capecitabine.

Before the surgery, the American Society of Anesthesiology (ASA) scores of patients were evaluated by an anesthesiologist independently from the thoracic surgeons. Postoperative complications were defined according to the Clavien-Dindo classification [10]. Locoregional recurrence was defined as recurrence at the surgical margin (anastomotic site) or site of surgery. Distant metastases were defined as recurrence at locations outside the site of surgery, such as the lung, bone, and liver. Follow-up evaluations were performed using chest and abdomen CT at an interval of 4 months and endoscopic esophagogastroduodenoscopy every year. OS was calculated from the date of surgery to the last follow-up date (date of death or last contact). Disease-free survival (DFS) was estimated from the date of surgery to the date of death, recurrence, or last contact. The duration of freedom from recurrence was calculated from the date of surgery to the first date of radiologic evidence of recurrence. Patients who did not die or had recurrence on the last follow-up date were blinded.

2. Statistical analysis

Continuous variables were compared using the Student's t test, and categorical variables were compared using the chi-square or Fisher's exact tests. The median follow-up time was estimated using the Kaplan-Meier method. Patient survival was compared according to adjuvant chemotherapy using the log-rank test. A multivariable analysis of

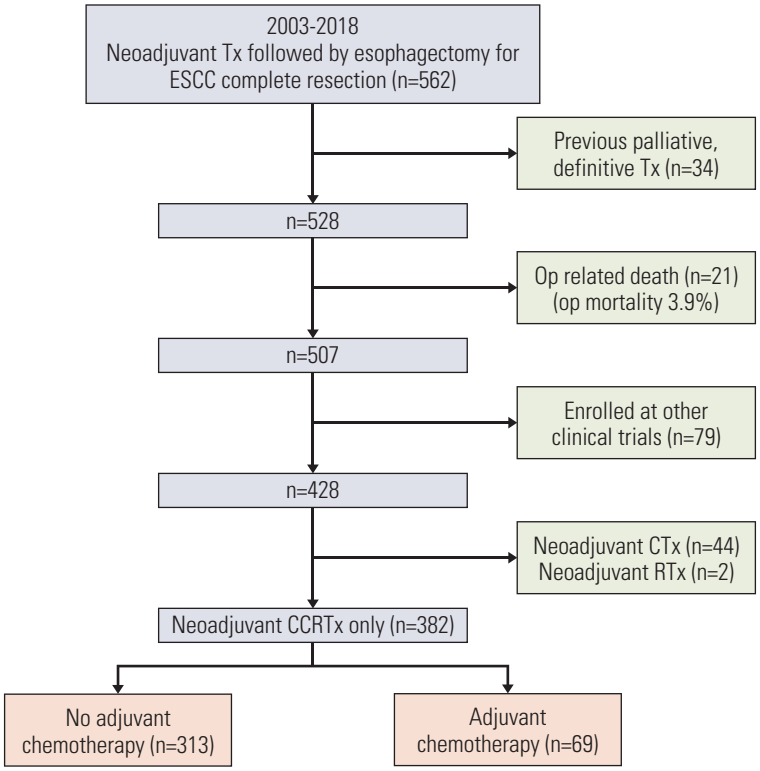

Fig. 1. Study patients. CCRTx, concurrent chemoradiotherapy; CTx, chemotherapy; ESCC, esophageal squamous cell carcinoma; Op, operation; RTx, radiotherapy; Tx, therapy.

Table 1. Baseline characteristics of patients

	No adjuvant CTx (n=313)	Adjuvant CTx (n=69)	p-value
Age (yr), median (range)	64 (41-84)	58 (40-74)	< 0.001
Male sex	293 (93.6)	64 (92.8)	0.789
FEV_1	2.9±3.0	3.0±0.6	0.040
DLCo (%)	86.3±17.0	82.3±17.2	0.138
ASA score			
1	48 (15.3)	26 (37.7)	< 0.001
2	242 (77.3)	38 (55.1)	
3	23 (7.3)	5 (7.2)	
cStage (AJCC 7th)			
II	62 (19.8)	14 (20.3)	0.893
III	250 (79.9)	55 (79.7)	
IV	1 (0.3)	0	
Location of lesion			
Cervical	4 (1.3)	0	0.499
Upper	100 (31.9)	24 (34.8)	
Mid	118 (37.7)	21 (30.4)	
Lower	88 (28.1)	24 (34.8)	
Esophagogastric junction	3 (1.0)	0	

Values are presented as median (range), number (%), or mean±SD. AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiology; CTx, chemotherapy; DLCo, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

survival was performed using the Cox proportional hazard model. All statistical tests were two-sided at a significance level of 0.05 and were performed using R ver. 4.03 (R Core Team (2022); R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Results

1. Patient characteristics

Baseline patient characteristics are summarized in Table 1. This study included 357 (93.4%) men, and the median patient age was 63 years (range, 40 to 84 years). Among 382 patients, 69 (18.1%) received adjuvant chemotherapy, whereas 313 (81.9%) did not. Regarding neoadjuvant therapy, 364 patients (95.3%) received cisplatin+5-FU with 4,400 cGY radiation, six (1.6%) received capecitabine+cisplatin with 4,400 cGY radiation, and 12 received another regimen. The age, forced expiratory volume in 1 second (FEV_1), and ASA scores were different between the two groups, whereas the clinical stage, operative methods, and postoperative complications were comparable. The number of dissected lymph nodes was not significantly different between two groups.

Among 69 patients who received the adjuvant chemotherapy, median duration from operation to the beginning of adjuvant chemotherapy was 6.43 weeks (range, 3.00 to 13.14 weeks). Sixty patients received the adjuvant chemotherapy with cisplatin+5-FU regimen, three patients received with leucovorin with 5-FU. In six patients, the regimen of adjuvant chemotherapy was unknown because they received the adjuvant chemotherapy at other hospital. Regarding the cycles of fluorouracil/cisplatin chemotherapy, 15 patients received the 2 cycles, one patient received the 4 cycles, and other received the 3 cycles. Even though the patients analyzed in the study received the R0 resection, the adjuvant radiotherapy was done in 15 patients according to the surgeon's decision and experience.

Table 2 summarizes the postoperative results and pathologic stages of patients; the rate of pathologic complete response (pCR) was higher in patients who did not receive adjuvant chemotherapy, whereas ypStage was higher in patients who received adjuvant chemotherapy. Moreover, patients in both groups received either sequential or concurrent adjuvant radiotherapy.

2. Patterns of recurrence and survival

In total, 177 patients (46.3%) had recurrence: 48 patients (12.6%) had locoregional recurrence only, 73 (19.1%) had distant recurrence only, and 56 (14.7%) had combined recurrence. The median follow-up period was 28.07 months (interquartile range, 15.50 to 62.59). The 5-year OS and DFS

Table 2. Postoperative pathologic outcomes of patients

	No adjuvant CTx (n=313)	Adjuvant CTx (n=69)	p-value
Level of anastomosis			
Intrathoracic anastomosis	177 (56.5)	35 (50.7)	0.423
Cervical anastomosis	136 (43.5)	34 (49.3)	
Neck dissection (3-field dissection)	145 (46.3)	36 (52.2)	0.425
No. of dissected LNs	38.2±14.4	39.6±14.4	0.471
No. of dissected LNs in neck	7.9±11.2	8.7±9.5	0.601
No. of dissected LNs in chest	17.5±7.3	17.8±8.7	0.695
No. of dissected LNs in abdomen	12.7±6.5	12.9±7.1	0.796
Postoperative complications	239 (76.4)	51 (73.9)	0.644
ypStage (AJCC 7th)			
0	112 (35.8)	6 (8.7)	< 0.001
I	23 (7.3)	2 (2.9)	
II	113 (36.1)	28 (40.6)	
III	64 (20.4)	31 (44.9)	
IV	1 (0.3)	2 (2.9)	
Complete response	109 (34.8)	4 (5.8)	< 0.001
ypT			
ypT0	158 (50.5)	24 (34.8)	0.067
ypTis	5 (1.6)	3 (4.3)	
ypT1	37 (11.8)	8 (11.6)	
ypT2	58 (18.5)	13 (18.8)	
ypT3	49 (15.7)	21 (30.4)	
ypT4	6 (1.9)	0	
ypN			
N0	186 (59.4)	1 (14.5)	< 0.001
N1	81 (25.9)	35 (50.7)	
N2	37 (11.8)	15 (21.7)	
N3	9 (2.9)	9 (13.0)	
ypT+N+	76 (24.3)	38 (55.1)	< 0.001
ypT+N0	74 (23.6)	4 (5.8)	< 0.001
ypT0N+	51 (16.3)	21 (30.4)	0.010
Adjuvant radiotherapy (either concurrent or sequential)	14 (4.5)	1 (1.5)	0.242

Values are presented as number (%) or mean±SD. AJCC, American Joint Committee on Cancer; CTx, chemotherapy; LN, lymph node; SD, standard deviation.

were 47.1% and 42.6% in all patients, respectively (Fig. 2A and B). The 5-year OS was not significantly different between patients with and without adjuvant chemotherapy (37.5% vs. 49.6%, p=0.248) (Fig. 2C) and the 5-year DFS was not also significantly different between patients with and without adjuvant chemotherapy (35.5% vs. 44.0%, p=0.288) (Fig. 2D).

Because adjuvant chemotherapy was usually performed according to the pathologic status after operation, subgroup analysis of survival was performed according to the ypT and ypN status. The survival benefit of adjuvant therapy was significant in patients with ypT+N+ (24.8% vs. 29.9%, p=0.048) (Fig. 3B), but it was not significant in those with complete response (71.1% vs. 100%, p=0.264) (Fig. 3A), ypT+N0 (44.7% vs. 25.0%, p=0.759) (Fig. 3C), and ypT0N+ (47.8% vs. 50.9%, p=0.936) (Fig. 3D).

3. Prognostic factors for survival

Characteristics of patients with ypT+N+ are summarized in Table 3. Age and ASA scores were different between two groups, whereas other preoperative factors and postoperative complications and ypStages were not significantly different between the two groups. The risk factors for OS in patients with ypT+N+ were evaluated (Table 4). Univariable analysis revealed that age, diffusing capacity of the lungs for carbon monoxide, FEV_1, and ASA scores were not associated with OS. Multivariable analysis revealed that the ypStage

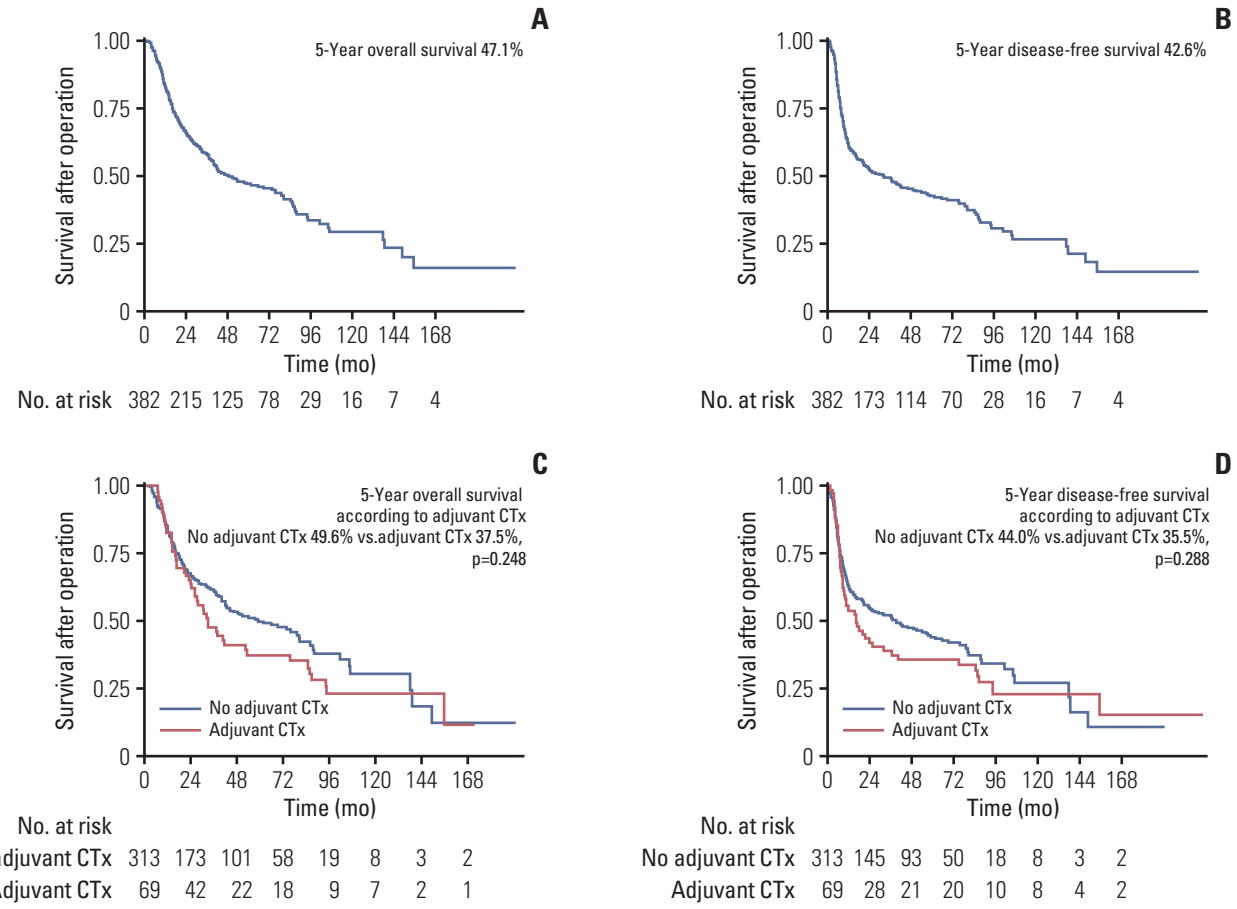

Fig. 2. Survival curves of all patients. Overall survival in all patients (A), disease-free survival in all patients (B), overall survival in patients who received adjuvant chemotherapy (CTx) (C), and disease-free survival in patients who received adjuvant CTx (D).

and adjuvant chemotherapy (hazard ratio, 0.601; p=0.046) were associated with survival after neoadjuvant therapy plus surgery in patients with ypT+N+ and ESCC. The results of multivariable analysis in ypT+N0 and ypT0N+ patients were documented in S1 and S2 Tables.

Fig. 4 shows DFS, freedom from locoregional recurrences and distant metastasis in ypT+N+ patients. In patients with ypT+N+, DFS was not different according to adjuvant chemotherapy (25.1% vs. 26.3%, p=0.317) (Fig. 4A). The freedom from locoregional recurrences (46.4% vs. 46.8%, p=0.505) (Fig. 4B) and distant metastasis (48.3% vs. 41.3%; log-rank test, p=0.141; Breslow test, p=0.071) (Fig. 4C) was marginally different after adjuvant chemotherapy.

Discussion

Neoadjuvant CCRTx followed by surgery is a well-established standard of care for patients with locally advanced esophageal or gastroesophageal junction cancer. In our study, survival in patients who showed pCR after induction therapy was acceptable; the 5-year OS in patients with pCR was 72.1%, and follow-up without additional treatment was possible. Unfortunately, pCR is often not achieved, and most patients with residual pathologic viable lesion have a poor prognosis [5,11]. The effectiveness of adjuvant therapy in patients who have received neoadjuvant therapy and undergone surgery remains to be sufficiently verified. Recently, Checkmate 577 study reported improved DFS using adjuvant immunotherapy in patients who underwent neoadjuvant therapy and surgical resection for esophageal cancer [12], but its application in Korea is limited because of economic problems; adjuvant immunotherapy is not reimbursed by the insurance system even though its use is permitted. Current guidelines do not recommend the administration of adjuvant cytotoxic chemotherapy. According to the esophageal cancer practice guidelines published by the Japan Esophageal Society in 2017, there is weak evidence

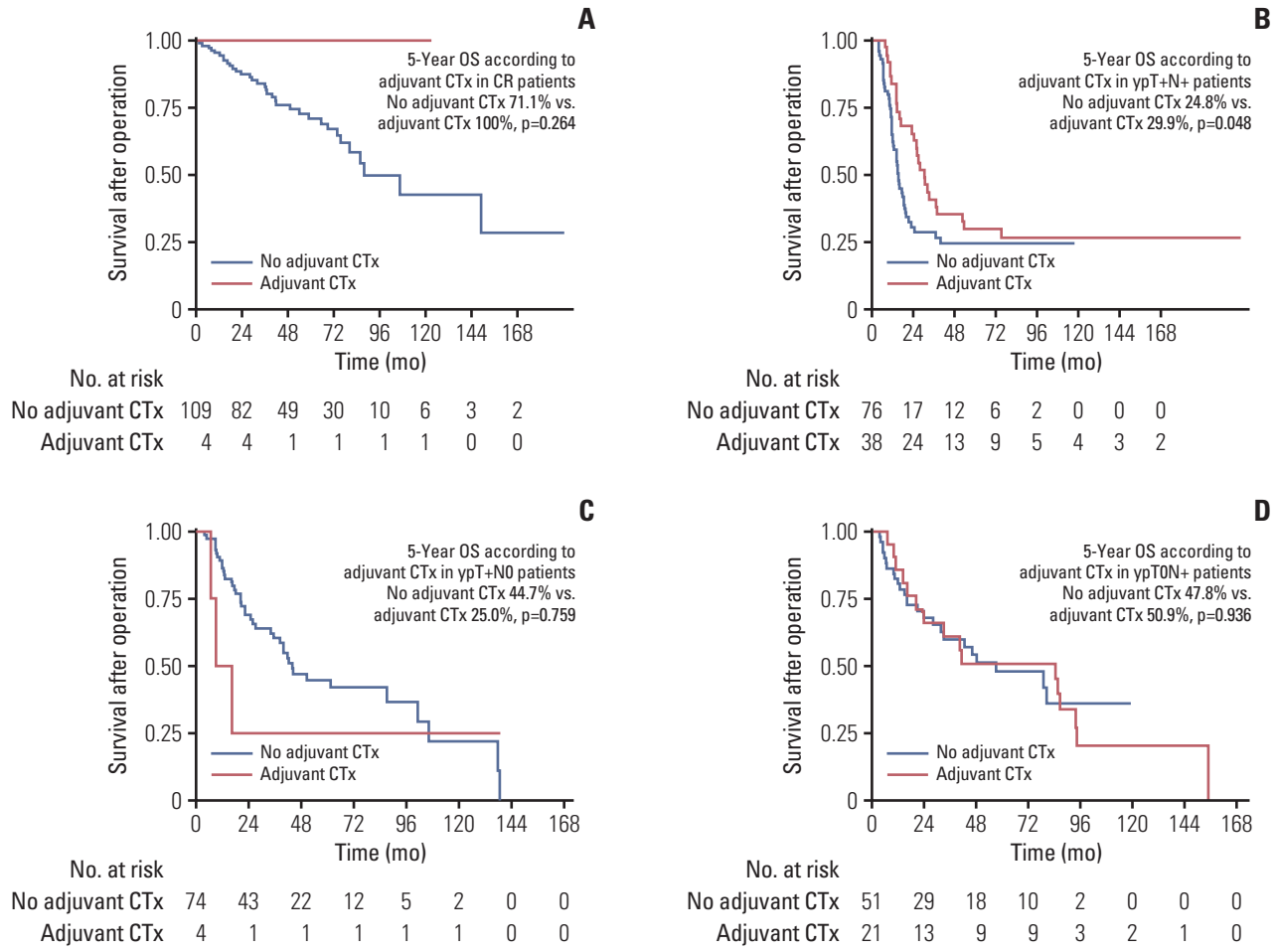

Fig. 3. Survival curves according to the ypStatus. Overall survival (OS) in patients with complete response (CR) according to adjuvant chemotherapy (CTx) (A) and in patients with ypT+N+ (B), ypT+N0 (C), and ypT0N+ (D).

regarding the administration of postoperative chemotherapy in patients with stage II or III ESCC who have undergone neoadjuvant therapy plus surgery [6]. Furthermore, the Society for Thoracic Surgeons guidelines on multimodality treatment for esophageal cancer do not suggest optimal treatment for node-positive patients who have already received multimodality therapy [13]. Although adjuvant therapy is not recommended in these guidelines, 18.1% of patients received adjuvant chemotherapy in our study. Moreover, a multi-institutional study from North America reported that the rate of adjuvant therapy was 3.2%-50% in real-world clinical practice [7], indicating that the administration of adjuvant therapy is on a case-by-case basis and at the discretion of each physician and institution for many patients.

Several retrospective studies have examined the effects of adjuvant chemotherapy after neoadjuvant therapy and complete (R0) resection. Samson et al. [14] analyzed 3,100 patients with pathologic positive lymph nodes from the National Cancer Database who underwent induction therapy plus esophagectomy from 2006 to 2012. In this cohort, adjuvant cytotoxic chemotherapy resulted in improved median OS compared with postoperative treatment (30.8 vs. 23.0 months) (hazard ratio [HR], 0.71; $p < 0.001$) in all patients, consistent with the results of propensity-matched cohort (median OS, 33.1 vs. 26.2 months; p=0.03). In a multicenter retrospective study of nine institutions, Semenkovich et al. [7] analyzed 1,082 patients with residual lymph nodes who underwent induction therapy plus esophagectomy and revealed that patients who received adjuvant chemotherapy had longer median OS than those who did not (2.6 vs. 2.3 years, p=0.02), thereby indicating the association between adjuvant treatment and improved survival (HR, 0.76; p=0.005). In these two retrospective studies, approximately 90% of patients were diagnosed with esophageal adenocarcinoma, and only 10% of them had ESCC. Considering the different pathophysiology and prognosis of esophageal

Table 3. Characteristics of patients with ypT+N+

	No adjuvant CTx (n=76)	Adjuvant CTx (n=38)	p-value
Age (yr)	62 (42-84)	58 (45-72)	0.018
Male sex	72 (94.7)	36 (94.7)	> 0.99
FEV_1 (L)	3.0±0.6	3.0±0.6	0.867
DLCo (%)	85.1±17.1	84.5±15.1	0.868
Postoperative complications	56 (73.7)	27 (71.1)	0.825
ASA			
1	13 (17.1)	15 (39.5)	0.027
2	60 (78.9)	21 (55.3)	
3	3 (3.9)	2 (5.3)	
cStage (AJCC 7th)			
II	9 (11.8)	6 (15.8)	0.664
III	66 (86.9)	32 (84.2)	
IV	1 (1.3)	0	
ypStage (AJCC 7th)			
II	21 (27.6)	11 (28.9)	0.865
III	54 (71.1)	26 (68.4)	
IV	1 (1.3)	1 (2.6)	

Values are presented as median (range), number (%), or mean±SD. AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiology; CTx, chemotherapy; DLCo, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

Table 4. Univariable and multivariable analyses for the risk factors for overall survival in patients with ypT+N+

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male sex	0.707 (0.258-1.938)	0.501	1.195 (0.412-3.461)	0.742
Age	0.986 (0.957-1.016)	0.361	0.987 (0.956-1.018)	0.427
ypStage (vs. II)				
III	2.511 (1.419-4.444)	0.002	2.526 (1.411-4.520)	0.002
IV	1.269 (0.167-9.626)	0.818	1.950 (0.135-7.891)	0.594
FEV_1	0.969 (0.625-1.502)	0.889	-	-
DLCo	0.994 (0.978-1.010)	0.451	-	-
ASA (vs. I)				
II	1.258 (0.755-2.097)	0.377	1.260 (0.723-2.201)	0.413
III	0.673 (0.157-2.884)	0.594	1.030 (0.135-7.891)	0.975
Adjuvant chemotherapy	0.653 (0.437-0.978)	0.039	0.601 (0.361-0.989)	0.046

ASA, American Society of Anesthesiology; CI, confidence interval; DLCo, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio.

adenocarcinoma and squamous cell carcinoma, the findings of these retrospective studies are not applicable to patients with ESCC. Zhao et al. [8] compared a group of patients with resectable ESCC who underwent postoperative adjuvant chemotherapy after preoperative chemotherapy plus radical surgery (175 patients) with a matched group of patients who did not receive postoperative adjuvant therapy (171 patients). Although adjuvant chemotherapy improved the 5-year recurrence-free survival rate (35.0% vs. 19.1%; HR, 0.62, $p < 0.001$), data on preoperative staging of the disease and surgical procedures were lacking [8].

Compared with previous studies, our study analyzed a uniform pathology (ESCC only) and provided detailed information on the operation, thereby highlighting the merits of our study. Another strength of this study was the analysis of the recurrence pattern. Although retrospective studies have shown that adjuvant chemotherapy can improve OS, the patterns of recurrences and possible reasons for improved sur-

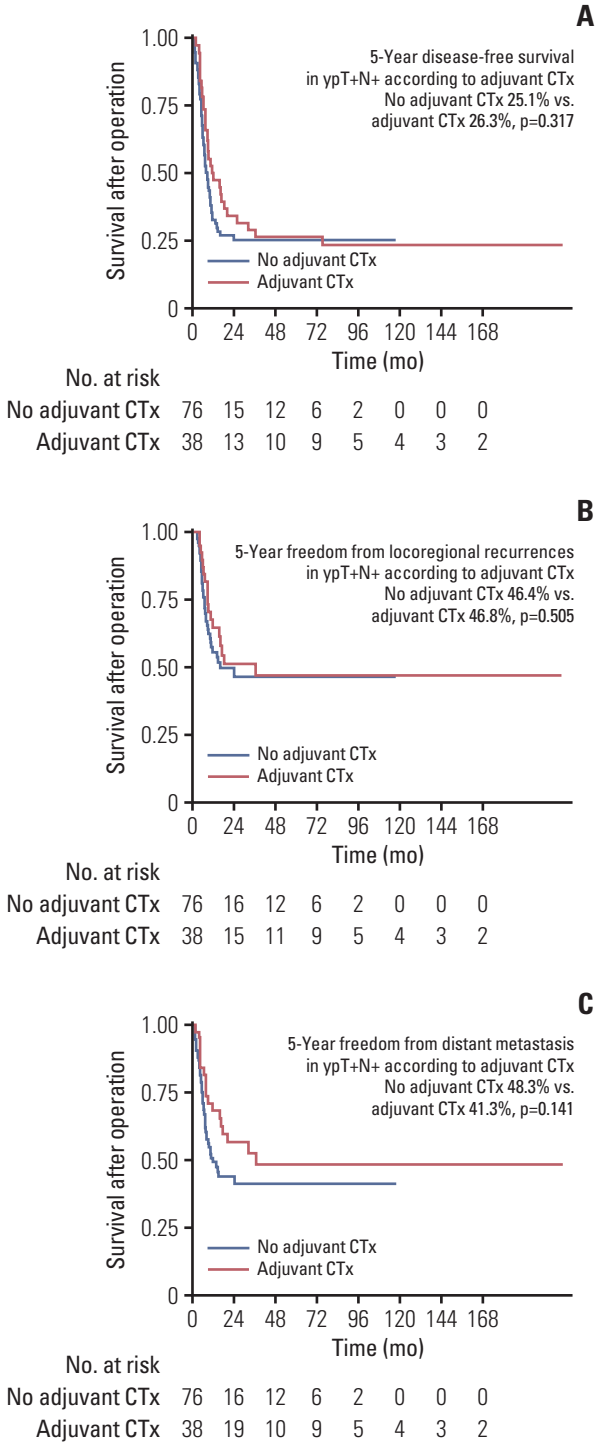

Fig. 4. Survival curves in ypT+N+ patients. Disease-free survival (A), freedom from locoregional recurrences (B), and freedom from distant metastasis (C). CTx, chemotherapy.

vival have not yet been reported. Our study revealed that adjuvant chemotherapy marginally reduced distant metastasis, possibly due to the effects of systemic cytotoxic chemotherapy. Previous studies have reported that the benefit of adjuvant chemotherapy is prominent in patients with pathologic node-positive (ypN+). In contrast, our study showed that the benefit of adjuvant chemotherapy is prominent in patients with ypT+N+, whereas patients with ypT0N+ or ypT+N0 did not show any survival benefit. Theoretically, since ypT+N+ patients have worse survival than ypT+N0 or ypT0N+ patients, the effect of additional chemotherapy could be more prominent in ypT+N+ patients. Alternatively, there may be insufficient numbers of ypT+N0 and ypT0N+ patients to produce statistically significant results in this analysis. The appropriate indications for adjuvant cytotoxic chemotherapy in terms of the yp-status should be investigated in the future. Compared with the Checkmate study, patients with ypT+N+ showed survival benefits in our study, whereas those with ypT0 showed the best survival benefits after adjuvant immunotherapy [13]. These findings indicate that the patient group who can benefit from adjuvant therapy varies according to the modality of adjuvant therapy.

Even though the main finding of this study is that the adjuvant chemotherapy improves OS in patients with ypT+N+ after neoadjuvant therapy and surgery, we believe that adjuvant chemotherapy cannot be administered in all ypT+N+ ESCC patients uniformly. The survival benefit of patients with ypT+N+ according to the adjuvant chemotherapy over 5 years was 5.1% in our study. Esophagectomy and reconstruction with gastric conduit or colon is a highly invasive procedure with high morbidity and mortality rates, and some patients cannot endure adjuvant chemotherapy after esophagectomy, particularly due to postoperative morbidities and poor general conditions related to malnutrition. Patient condition after neoadjuvant therapy and esophagectomy needs to be assessed carefully and the balance between the risk of recurrence and survival benefits of adjuvant chemotherapy should be evaluated. Furthermore, physicians have to search for appropriate patients who have tolerance status to endure chemotherapy, and the criteria for screening candidates need to be studied in the future. In addition, early postoperative morbidity and mortality are obstacles in adjuvant chemotherapy, efforts need to be made to reduce postoperative complications and improve long-term survival.

This study has some limitations. First, patients who received adjuvant therapy may have more favorable overall medical conditions, which may lead to a selection bias in this study. To overcome this limitation, we performed multivariable analysis using the Cox model, but overall medical conditions were not related to OS in ypT+N+. Second, the study period (17 years) was relatively long, and treatment

strategies might have changed over time. Third, this was a single institutional study, and the quality of surgery, skills in the radiation field design, and other factors were largely different between centers. Further randomized controlled clinical trials are warranted to investigate the appropriate timing, indications, and regimen for adjuvant chemotherapy.

In conclusion, adjuvant chemotherapy improved OS in patients with ypT+N+ after neoadjuvant therapy plus surgery for treating ESCC. The findings of this retrospective study should be further evaluated in randomized controlled trials. Adjuvant chemotherapy can be a treatment option for these patients as they can tolerate the additional treatment.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study was approved by the institutional review boards (Samsung Medical Center 2022-09-050), and the requirement of patient consent was waived due to the retrospective nature of the study.

Author Contributions

Conceived and designed the analysis: Park SY, Kim HK.
Collected the data: Park SY.
Contributed data or analysis tools: Kim HK, Jeon YJ, Lee J, Cho JH, Choi YS, Shim YM, Zo JI.
Performed the analysis: Park SY.
Wrote the paper: Park SY, Kim HK.

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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