Thoracic Cancer

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Postoperative Adjuvant Therapy Benefits Non-pCR Patients Rather Than pCR Patients for Locally Advanced ESCC: A Multicenter Real-World Study

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Received: 10 January 2025 | **Revised:** 4 February 2025 | **Accepted:** 8 February 2025

Funding: This work was supported by National Natural Science Foundation of China, 82172677.

Keywords: adjuvant therapy | disease-free survival | esophageal squamous cell carcinoma | immunotherapy | overall survival

ABSTRACT

Background: There is no unified standard in adjuvant therapy (AT) for patients with esophageal squamous cell carcinoma (ESCC) after neoadjuvant therapy and surgery. We evaluated the significance of AT for these patients and explored its influencing factors.

Methods: ESCC patients who underwent neoadjuvant therapy and surgery from 2019 to 2022 at three centers were divided into AT ($n = 227$) and non-AT groups ($n = 435$). Baseline characteristics were balanced using propensity score matching (PSM). Primary endpoints were disease-free survival (DFS) and overall survival (OS), assessed using the Kaplan–Meier method. Subgroup analyses and univariate and multivariate Cox regression analyses were conducted to identify the prognostic factors.

Results: The median follow-up period is 36 (2–72) months. After PSM, the total population had 1-, 2-, and 3-year OS rates of 71.3%, 66.0%, and 64.1%, respectively. There were no statistically significant differences in DFS (HR: 0.79; 95% CI: 0.55–1.14, $p = 0.21$) or OS (HR: 0.75; 95% CI: 0.49–1.13, $p = 0.17$) between AT and non-AT groups. Subgroup analysis revealed that non-pCR patients benefited from AT in DFS ($p = 0.042$) and OS ($p = 0.033$). Moreover, in non-pCR patients who received AT, BMI $\geq 21.5\,kg/m^2$ and ypN0 were independent protective factors of DFS. ypN0 was an independent protective factor of OS. In terms of AT regimens, the Kaplan–Meier analysis revealed that adjuvant immunochemotherapy (AICT) provided superior survival benefits than adjuvant radiotherapy and adjuvant chemotherapy.

Conclusions: Postoperative AT benefited ESCC patients with non-pCR, while AICT may be a relatively better AT regimen in real-world data, which deserves further exploration.

1 | Introduction

Esophageal cancer ranks the seventh leading cause of cancer-related mortality worldwide, and esophageal squamous cell carcinoma (ESCC) is the most common pathological type, especially in Asia [1, 2]. Due to the lack of obvious early symptoms, many patients with ESCC are diagnosed at a locally advanced stage, where surgical treatment alone shows limited efficacy [3].

For locally advanced resectable or potentially resectable cases, multidisciplinary approaches should be actively explored to extend survival, minimize side effects, and enhance the quality of life [4–6].

Based on the data of the landmark clinical trials CROSS study and NEOCRTEC5010 study, the current standard treatment for operable locally advanced ESCC is neoadjuvant chemoradiotherapy (nCRT) [7, 8]. Additionally, neoadjuvant chemotherapy (nCT), chemotherapy combined with immunotherapy (nICT), and chemoradiotherapy combined with immunotherapy (nICRT) have been investigated, supported by emerging clinical evidence [9–11]. However, limited research exists on postoperative management following neoadjuvant therapy and surgery. The CheckMate577 study [12] showed that in patients with resected esophageal or gastroesophageal junction cancer who received nCRT, adjuvant nivolumab treatment significantly improved disease-free survival (DFS) compared to placebo. This finding established nivolumab as a primary adjuvant therapy (AT) option in the National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO) guidelines for esophageal cancer patients following neoadjuvant therapy [5]. However, this study primarily included patients with pathological residual disease after neoadjuvant therapy and did not report whether patients achieving pathological complete response (pCR) could benefit from adjuvant treatment. Additionally, in real-world settings, postoperative treatment options are highly variable, highlighting the need for studies on optimizing treatment selection.

In recent years, some small retrospective studies have explored feasible AT strategies for esophageal cancer [13–17], but the choice of postoperative AT remains controversial. For patients with the ypT3 N+ stage, adjuvant radiotherapy (ART) has the potential to reduce recurrence and enhance survival outcomes [18]. Conversely, another study has shown that postoperative adjuvant chemotherapy (ACT) might act as a detrimental factor, negatively affecting both DFS and overall survival (OS) [19]. In ypT+ N+ ESCC patients, adjuvant immunotherapy after nICT and surgery improves survival [20]. Xie et al. show that the combination of adjuvant chemotherapy and immunotherapy (AICT) does not result in better DFS compared to ACT.

pCR is one of the key indicators of neoadjuvant therapy [21]. Studies have shown that patients achieving pCR after neoadjuvant therapy tend to have longer DFS and OS [22, 23]. Several ongoing clinical trials have set inclusion and exclusion criteria based on the specific postoperative pathological outcome [12, 24, 25]. However, it still remains unclear whether AT is necessary for pCR patients. Studies that include different postoperative pathological outcomes are necessary. Furthermore, the association between other clinicopathological factors and postoperative treatment benefit remains uncertain.

Therefore, we conducted this study to explore the effect of AT following neoadjuvant therapy in locally advanced ESCC and identify the patient populations that benefit from postoperative treatment. In addition, we aim to analyze the prognostic factors and compare different AT regimes.

2 | Methods

2.1 | Study Population

Clinical data of patients who were newly diagnosed with ESCC and received neoadjuvant therapy plus radical surgery at three large clinical centers in China including the Shandong Cancer Hospital, the Shandong Provincial Hospital affiliated to Shandong First Medical University, and the Second Hospital of Shandong University from January 2019 to December 2022 were retrospectively reviewed.

2.2 | Ethics Statement

This study adhered to the fundamental principles of the Declaration of Helsinki and was approved by the ethics committees of all participating clinical centers, with the ethical approval number SDTHEC202410067. Informed consent was obtained in writing from all patients, and their personal privacy was strictly protected.

2.3 | Inclusion and Exclusion Criteria

Patients with any of the following conditions will be excluded/included in the trial. Inclusion criteria were as follows: 1. ESCC that was confirmed by pathological diagnosis; 2. clinical stage were defined as II-IVA; 3. received radical resection of esophageal cancer and achieved R0 resection; and 4. received complete neoadjuvant therapy followed by surgery. The exclusion criteria are listed below: 1. incomplete neoadjuvant therapy; 2. history of thoracic surgery; 3. incomplete perioperative clinical data; 4. combined with other types of malignant tumors; 5. death due to severe perioperative complications; 6. patients lost to follow-up; and 7. combined with other systemic diseases affecting prognosis.

2.4 | Treatment

2.4.1 | Neoadjuvant Therapy

Neoadjuvant therapy includes nCT, nICT, nCRT, and nICRT, all of which are strictly carried out according to the protocols outlined below to ensure the homogeneity of treatment. The treatment regimen for enrolled patients was based on established guidelines and reached a consensus across the three centers.

nCT and nICT: The nCT regimen was a platinum-based doublet-drug chemotherapy, including paclitaxel-based (paclitaxel, 175 mg/m^2, albumin-bound paclitaxel, 260 mg/m^2, or docetaxel, 70 mg/m^2) or fluoropyrimidine-based (5-fluorouracil, 800 mg/m^2) combined with platinum (cisplatin, 80 mg/m^2 or carboplatin: AUC = 5). The number of chemotherapy cycles was 2–4. The nICT regimen was platinum-based doublet-drug chemotherapy combined with a single-agent immune checkpoint inhibitor (ICI), which was performed simultaneously with nCT.

nCRT and nICRT: nCRT requires the start of a three-dimensional conformal radiotherapy on the first day of chemotherapy. The

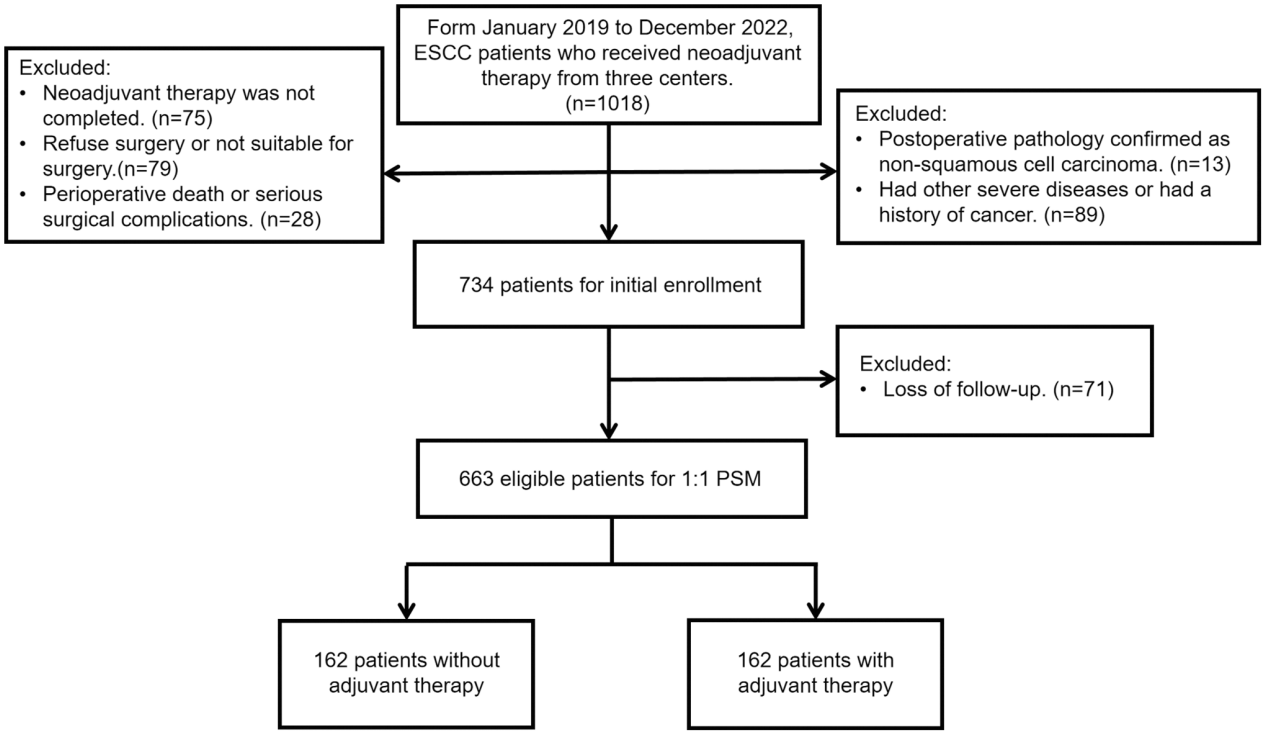

FIGURE 1 | The screening flowchart.

total radiation dose is 40 Gy, given in 20 fractions over 4 weeks, or 41.4 Gy, given in 23 fractions, each 1.8 Gy. nICRT requires the start of radiotherapy on the first day of chemotherapy combined with ICI. The regimen of chemotherapy combined with immunotherapy has been described above.

2.4.2 | Surgery and Adjuvant Therapy

Surgery is scheduled 4–8 weeks after neoadjuvant therapy. All patients underwent radical esophagectomy and confirmed R0 reaction. The postoperative treatment plan mirrors the preoperative systemic treatment strategy. Patients receiving nCT or nCRT before surgery will undergo ACT postoperatively. Some patients with extensive preoperative lymph node metastasis who did not receive preoperative radiotherapy underwent ART. The radiation field included the tumor bed and the lymphatic drainage areas corresponding to the pre-treatment sites. Patients receiving nICT or nICRT before surgery will receive AICT for the initial 2–4 cycles, followed by immunotherapy alone for subsequent cycles. Postoperative treatments also followed a standardized protocol, tailored based on the initial treatment regimen, to ensure consistency across the centers.

2.5 | Evaluation and Follow-Up

2.5.1 | Evaluation

Baseline clinical information and examination results, including gender, age, body mass index (BMI), group performance status (ECOG-PS) score, upper gastrointestinal X-ray, endoscopy, pathology, and contrast-enhanced CT findings, were collected from all patients before neoadjuvant therapy. Clinical stage was primarily determined using the 8th edition of the AJCC TNM staging criteria for esophageal cancer. After completion of neoadjuvant therapy, follow-up is conducted according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), which classifies clinical responses into complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD) [26].

Postoperative pathological findings were reviewed by experienced pathologists. pCR was defined as the absence of viable tumor cells in the surgical specimen, including the primary tumor site and lymph nodes. The status of pathological specimens after neoadjuvant therapy was evaluated according to the tumor regression grading (TRG) classification of the American College of Pathology [27].

2.5.2 | Follow-Up

Upper gastrointestinal radiography, contrast-enhanced CT, and related blood tests were conducted every 3 months during the first 2 years after surgery. Follow-up was performed every 6 months after 2 years. OS was defined as the time from the start of treatment to death from any cause or loss to follow-up. DFS was defined as the time from radical surgery to the first occurrence of tumor recurrence, metastasis, or death from any cause.

2.6 | Statistical Analysis

We used Pearson's chi-square test to compare baseline clinical characteristics between the groups. A 1:1 propensity score matching (PSM) was employed to balance the baseline characteristics (including gender, age, BMI, ECOG-PS, tumor location,

TABLE 1 | Baseline demographic and clinical characteristics.

	Before PSM			After PSM		
	Without adjuvant therapy ($n=435$)	**Adjuvant therapy ($n=227$)**	***p***	**Without adjuvant therapy ($n=162$)**	**Adjuvant therapy ($n=162$)**	***p***
Total	435	227		162	162	
Gender						
Female	76 (17.47)	27 (11.89)	0.0774	22 (13.58)	20 (12.35)	0.8686
Male	359 (82.53)	200 (88.11)		140 (86.42)	142 (87.65)	
Age (years)						
< 62	198 (45.52)	112 (49.34)	0.3934	70 (43.21)	75 (46.30)	0.6549
≥ 62	237 (54.48)	115 (50.66)		92 (56.79)	87 (53.70)	
ECOG—PS						
0	163 (37.47)	99 (43.61)	0.1471	60 (37.04)	71 (43.83)	0.2576
1	272 (62.53)	128 (56.39)		102 (62.96)	91 (56.17)	
BMI (kg/m2)						
< 21.5	151 (34.71)	86 (37.89)	0.4697	57 (35.19)	72 (44.44)	0.1121
≥ 21.5	284 (65.29)	141 (62.11)		105 (64.81)	90 (55.56)	
Location						
Down	221 (50.80)	124 (54.63)	0.5807	88 (54.32)	85 (52.47)	0.5966
Middle	153 (35.17)	71 (31.28)		57 (35.19)	54 (33.33)	
Up	61 (14.02)	32 (14.10)		17 (10.49)	23 (14.20)	
Primary T stage						
T2	31 (7.13)	10 (4.41)	0.0198	11 (6.79)	10 (6.17)	0.9748
T3	389 (89.43)	199 (87.67)		145 (89.51)	146 (90.12)	
T4	15 (3.45)	18 (7.93)		6 (3.70)	6 (3.70)	
Primary N stage						
N+	310 (71.26)	160 (70.48)	0.9048	113 (69.75)	120 (74.07)	0.4583
N0	125 (28.74)	67 (29.52)		49 (30.25)	42 (25.93)	
Clinical stage						
II	120 (27.59)	60 (26.43)	0.908	48 (29.63)	37 (22.84)	0.2164
III	282 (64.83)	148 (65.20)		98 (60.49)	113 (69.75)	
IV	33 (7.59)	19 (8.37)		16 (9.88)	12 (7.41)	
Primary tumor length (cm)						
< 5	122 (28.05)	49 (21.59)	0.0874	41 (25.31)	34 (20.99)	0.4294
≥ 5	313 (71.95)	178 (78.41)		121 (74.69)	128 (79.01)	
Neoadjuvant therapy regimen						
nCT	46 (10.57)	58 (25.55)	< 0.0001	37 (22.84)	41 (25.31)	0.9244
nCRT	130 (29.89)	112 (49.34)		70 (43.21)	65 (40.12)	
nICT	182 (41.84)	44 (19.38)		41 (25.31)	43 (26.54)	
Others	77 (17.70)	13 (5.73)		14 (8.64)	13 (8.02)	

(Continues)

TABLE 1 | (Continued)

	Before PSM			After PSM		
	Without adjuvant therapy ($n=435$)	**Adjuvant therapy ($n=227$)**	***p***	**Without adjuvant therapy ($n=162$)**	**Adjuvant therapy ($n=162$)**	***p***
ypT stage						
T0	171 (39.31)	53 (23.35)	0.0004	44 (27.16)	47 (29.01)	0.8417
T1	60 (13.79)	39 (17.18)		24 (14.81)	24 (14.81)	
T2	57 (13.10)	29 (12.78)		23 (14.20)	22 (13.58)	
T3	138 (31.72)	103 (45.37)		66 (40.74)	67 (41.36)	
T4	9 (2.07)	3 (1.32)		5 (3.09)	2 (1.23)	
ypN stage						
N+	135 (31.03)	95 (41.85)	0.0072	64 (39.51)	68 (41.98)	0.7345
N0	300 (68.97)	132 (58.15)		98 (60.49)	94 (58.02)	
Resected lymph nodes (*n*)						
<30	377 (86.67)	197 (86.78)	1	141 (87.04)	138 (85.19)	0.748
≥ 30	58 (13.33)	30 (13.22)		21 (12.96)	24 (14.81)	
TRG stage						
0	169 (38.85)	50 (22.03)	0.0002	43 (26.54)	45 (27.78)	0.7196
1	69 (15.86)	47 (20.70)		30 (18.52)	29 (17.90)	
2	104 (23.91)	75 (33.04)		41 (25.31)	48 (29.63)	
3	93 (21.38)	55 (24.23)		48 (29.63)	40 (24.69)	
pCR						
No	277 (63.68)	189 (83.26)	<0.0001	126 (77.78)	124 (76.54)	0.8947
Yes	158 (36.32)	38 (16.74)		36 (22.22)	38 (23.46)	
Adjuvant therapy regimen						
ACT	—	144		—	96	—
AICT	—	50		—	40	
ART	—	33		—	26	

Abbreviations: ACT, adjuvant chemotherapy; AICT, adjuvant immunochemotherapy; ART, adjuvant radiotherapy; BMI, body mass index; ECOG-PS, eastern cooperative oncology group performance status; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; nICT, neoadjuvant immunochemotherapy; pCR, pathological complete response; pCR, pathological complete response; PSM, propensity score matching; TRG, tumor regression grade; ypN, postoperative pathological N stage; ypT, postoperative pathological T stage.

primary T stage, primary N stage, neoadjuvant treatment regimen, ypT stage, ypN stage) [28]. Patients in two groups were matched 1:1 by the nearest neighbor algorithm (the caliper was calculated as 0.05 times the standard deviation of the logit of the propensity score, which was random matching order and no replacement was done). The Kaplan–Meier curves were used to plot DFS and OS in different groups, with survival differences analyzed using the log-rank test. Subgroup analysis was performed based on the univariate Cox regression with results visualized using forest plots. Univariate and multivariate Cox regression analyses for DFS and OS were conducted on subgroups stratified by survival-related variables. Statistical analyses were conducted using SPSS 27.0 and R version 4.4.0. A two-sided p value <0.05 was considered statistically significant.

3 | Results

3.1 | Screening Process

A total of 1018 patients with ESCC who underwent neoadjuvant therapy followed by surgery across three centers between January 2019 and December 2022 were screened. Patients were excluded for the following reasons: postoperative pathology confirmed non-squamous cell carcinoma ($n=13$), presence of other severe diseases or a history of cancer ($n=89$), failure to complete neoadjuvant therapy ($n=75$), refusal or ineligibility for surgery ($n=79$), perioperative death or severe surgical complications ($n=28$), and loss to follow-up ($n=71$). A total of 663 patients were ultimately included and subjected to a 1:1 propensity score

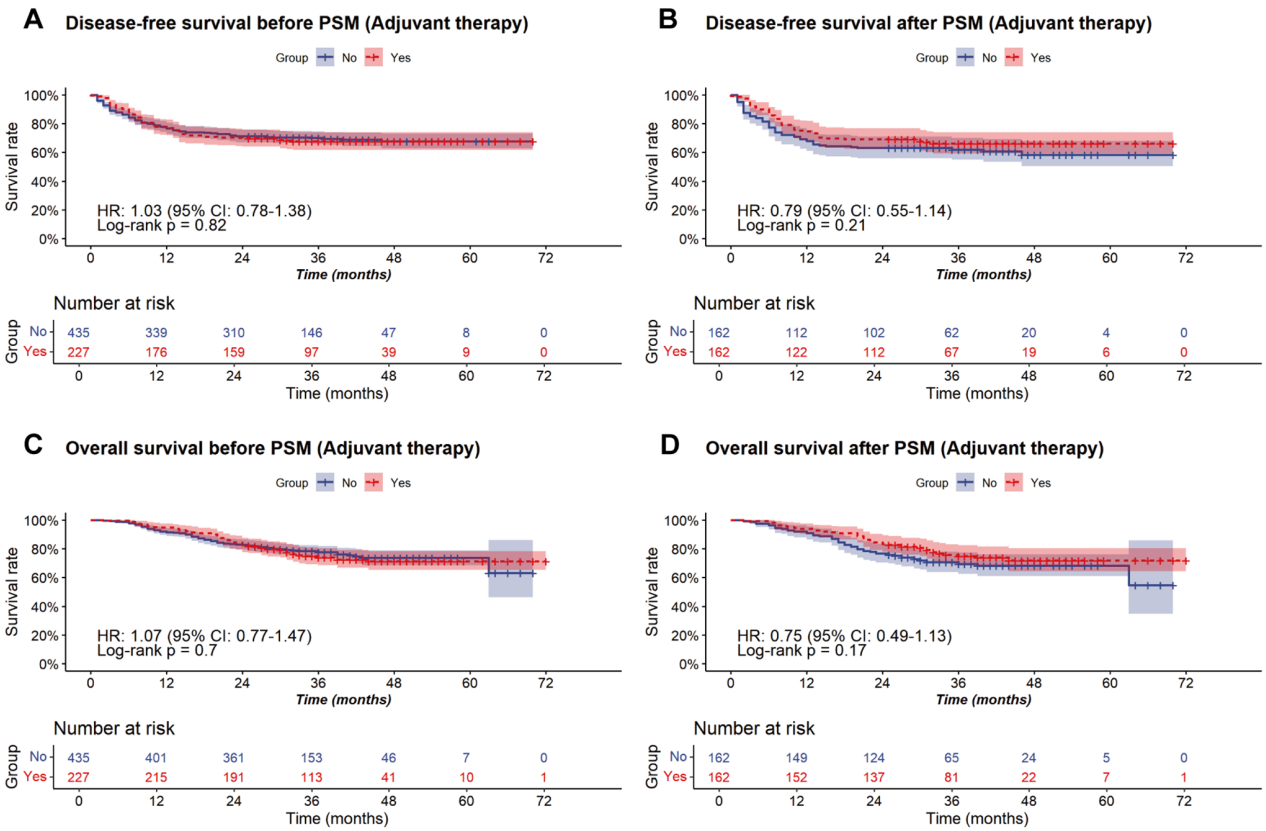

FIGURE 2 | The Kaplan–Meier analysis of disease-free survival and overall survival in total population. PSM, propensity score matching.

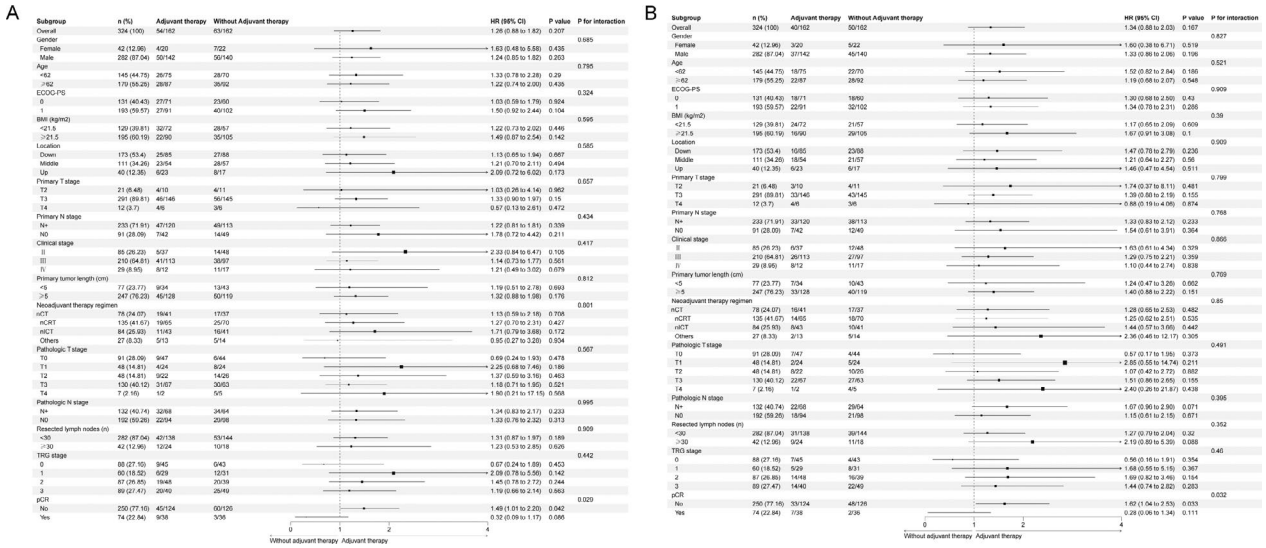

FIGURE 3 | Subgroup analysis. (A) Disease-free survival; (B) overall survival. BMI, body mass index; CI, confidence interval; ECOG-PS, eastern cooperative oncology group performance status; HR, hazard ratio; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; nICT, neoadjuvant immunochemotherapy; pCR, pathological complete response; TRG, tumor regression grade.

matching, resulting in two groups: the AT group ($n = 162$) and the non-AT group ($n = 162$) (Figure 1).

3.2 | Baseline Characteristics

Baseline characteristics of enrolled patients are summarized in Table 1. Significant differences between the two groups were identified before matching, including primary T stage, neoadjuvant treatment regimens, ypT stage, ypN stage, TRG, and pCR. After PSM matching, demographic and disease characteristics were well balanced. The median age was 62 years (range: 39–80). Most patients were male (without vs. with AT: 86.42% vs. 87.65%). Most tumors were located in the lower esophagus (54.32% vs. 52.47%), and predominantly T stage was T3 (89.51% vs. 90.12%). Clinical staging was primarily

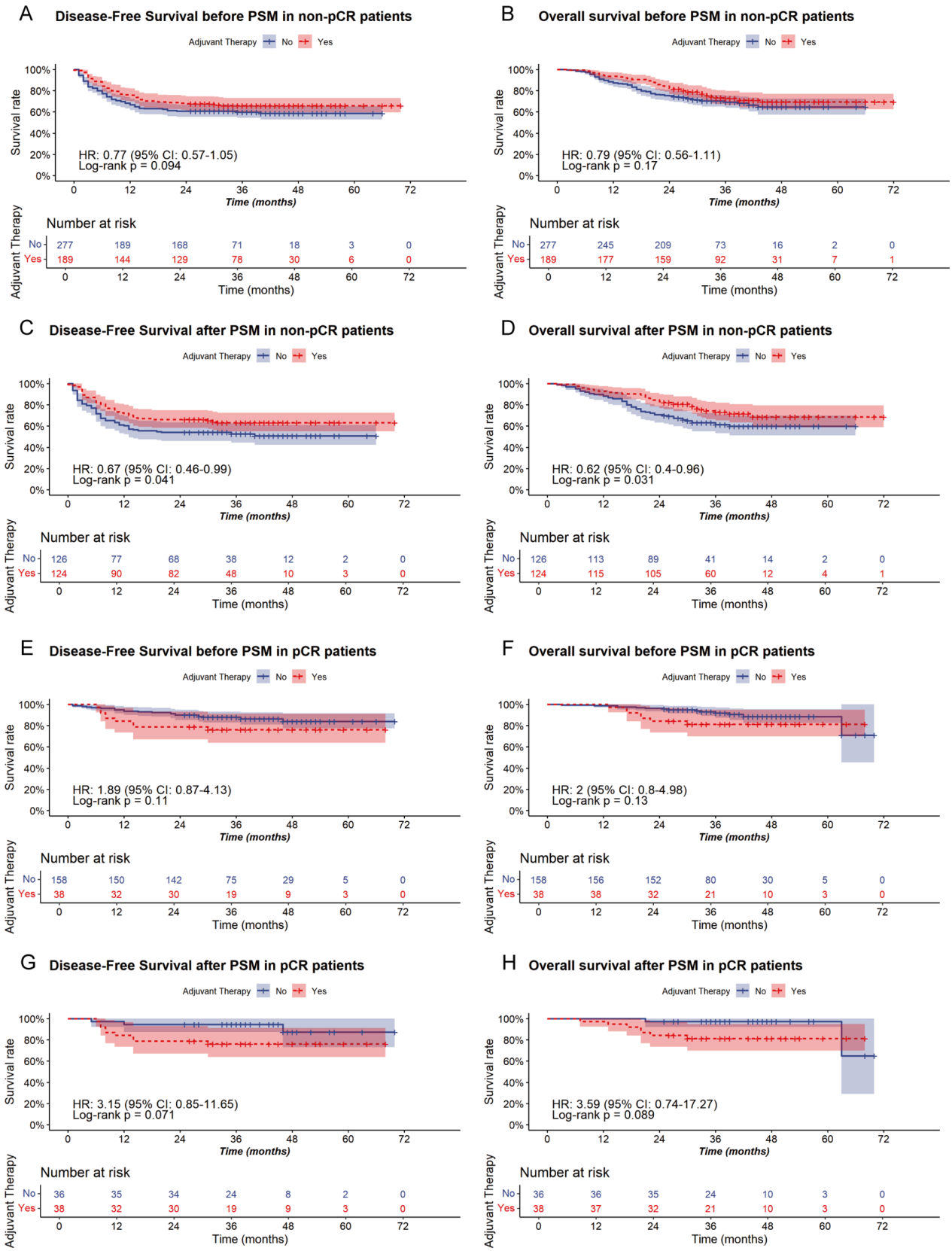

FIGURE 4 | The Kaplan–Meier analysis of disease-free survival and overall survival in pCR and non-pCR subgroups. pCR, pathological complete response; PSM, propensity score matching.

stage III (60.49% vs. 69.75%). Neoadjuvant regimens mainly comprised nCT (43.21% vs. 40.12%) and nICT (25.31% vs. 26.54%). The pCR rate was 22.22% vs. 23.46%. The ypN0 rate was 60.49% vs. 58.02%. In the AT group, the majority of patients received AICT ($n = 96$), while 40 patients received ART and 26 patients received ACT.

TABLE 2 | Univariable and multivariable cox regression analyses of factors associated with disease-free survival in non-pCR patients.

		Univariate		Multivariate	
		HR (95% CI)	***p***	**HR (95% CI)**	***p***
Gender	Male versus female	1.91 (0.77–4.77)	0.1633		
Age	≥62 versus <62	0.69 (0.42–1.13)	0.1371		
ECOG-PS	1 versus 0	0.64 (0.39–1.05)	0.0764		
BMI (kg/m2)	≥21.5 versus <21.5	**0.51 (0.31–0.83)**	**0.0067**	**0.51 (0.31–0.86)**	**0.0108**
Location	Middle versus down	1.18 (0.69–2.02)	0.5356		
	Up versus down	0.82 (0.38–1.78)	0.6205		
Primary T stage	T3 versus T2	0.74 (0.23–2.36)	0.6066		
	T4 versus T2	0.77 (0.19–3.09)	0.715		
Primary N stage	N0 versus N+	**0.52 (0.28–0.98)**	**0.0433**	0.54 (0.07–3.99)	0.5472
Clinical stage	III versus II	1.71 (0.88–3.31)	0.1114	0.79 (0.1–6.23)	0.8232
	IV versus II	**2.58 (1.07–6.23)**	**0.0351**	1.17 (0.12–11.06)	0.8919
Primary tumor length (cm)	≥5 versus <5	1.61 (0.82–3.16)	0.1683		
Neoadjuvant therapy regimen	nCRT versus nCT	**0.49 (0.28–0.86)**	**0.0135**	0.58 (0.31–1.08)	0.0843
	nICT versus nCT	**0.49 (0.24–0.99)**	**0.0483**	0.57 (0.27–1.2)	0.1364
	Others versus nCT	0.73 (0.26–2.09)	0.5611	1.16 (0.39–3.46)	0.7891
ypT stage	T1 versus T0	35249321.81 (0—Inf)	0.996		
	T2 versus T0	70502331.51 (0—Inf)	0.9959		
	T3 versus T0	110713696.46 (0—Inf)	0.9958		
	T4 versus T0	85808780.93 (0—Inf)	0.9958		
ypN stage	N0 versus N+	**0.37 (0.21–0.63)**	**<0.001**	**0.44 (0.25–0.78)**	**0.0046**
Resected lymph nodes (*n*)	≥30 versus <30	1.79 (0.97–3.3)	0.0604		
Adjuvant therapy	ACT versus AICT	**2.58 (1.16–5.72)**	**0.0202**	2.02 (0.87–4.67)	0.1011
	ART versus AICT	**2.81 (1.12–7.06)**	**0.0274**	1.6 (0.56–4.54)	0.3814

Abbreviations: ACT, adjuvant chemotherapy; AICT, adjuvant immunochemotherapy; ART, adjuvant radiotherapy; BMI, body mass index; CI, confidence interval; ECOG-PS, eastern cooperative oncology group performance status; HR, hazard ratio; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; nICT, neoadjuvant immunochemotherapy; pCR, pathological complete response; ypN, postoperative pathological stage N; ypT, postoperative pathological stage T.
Note: The *p*-values less than 0.05 are indicated in bold.

3.3 | Survival Outcome

The final follow-up was conducted in December 31, 2024, with a median duration of 36 months (range: 2–72 months). Before PSM, the 1-, 2-, and 3-year DFS rates for the total population were 76.7%, 70.7%, and 69.2%, respectively. In the AT group, the corresponding DFS rates were 77.1%, 69.6%, and 67.5%. For the non-AT group, the 1-, 2-, and 3-year DFS rates were 76.6%, 71.3%, and 70.1%, respectively. No significant difference in DFS was observed between the two groups (HR: 1.03; 95% CI: 0.78–1.38, $p=0.82$; Figure 2a). Before PSM, the OS rates for the total population at 1, 2, and 3 years were 92.6%, 82.6%, and 76.2%, respectively. In the AT group, the OS rates were 94.7%, 82.4%, and 74.1% at 1, 2, and 3 years, respectively. The non-AT group showed OS rates of 91.5%, 82.8%, and 77.5% at the same time points. No significant difference in OS was observed (HR: 1.07; 95% CI: 0.77–1.47, $p=0.7$; Figure 2c).

After PSM, the 1-, 2-, and 3-year DFS rates for the total population were 71.3%, 66.0%, and 64.1%, respectively. In the AT group, the DFS rates were 74.7%, 69.1%, and 66.1%. In the non-AT group, the DFS rates were 67.9%, 63.0%, and 62.0% at the same time points. No significant difference in DFS was found between the two groups (HR: 0.79; 95% CI: 0.55–1.14, $p=0.21$; Figure 2b). After PSM, the total population had 1-, 2-, and 3-year OS rates of 92.3%, 79.9%, and 72.2%, respectively. In the AT group, the OS rates were 92.6%, 83.3%, and 75.0%. In the non-AT group, the OS rates were 90.7%, 76.5%, and 69.5%. No significant difference in OS was observed between the two groups (HR: 0.75; 95% CI: 0.49–1.13, $p=0.17$; Figure 2d).

3.4 | Subgroup Analysis

In the subgroup analysis of DFS, pCR showed significant statistical associations. Those who did not achieve

TABLE 3 | Univariable and multivariable cox regression analyses of factors associated with overall survival in non-pCR patients.

		Univariate		Multivariate	
		HR (95% CI)	***p***	**HR (95% CI)**	***p***
Gender	Male versus female	2.56 (0.8–8.22)	0.114		
Age	≥62 versus <62	0.73 (0.42–1.26)	0.2574		
ECOG-PS	1 versus 0	0.84 (0.49–1.44)	0.5244		
BMI (kg/m2)	≥21.5 versus <21.5	**0.55 (0.32–0.95)**	**0.0331**	0.6 (0.34–1.06)	0.0809
Location	Middle versus down	1.15 (0.64–2.08)	0.639		
	Up versus down	0.88 (0.38–2.02)	0.7584		
Primary T stage	T3 versus T2	1.12 (0.27–4.63)	0.8734		
	T4 versus T2	1.56 (0.31–7.71)	0.5889		
Primary N stage	N0 versus N+	0.7 (0.37–1.33)	0.2773		
Clinical stage	III versus II	1.17 (0.59–2.32)	0.6575	0.93 (0.45–1.93)	0.8474
	IV versus II	**2.55 (1.06–6.16)**	**0.0373**	1.58 (0.58–4.3)	0.3681
Primary tumor length (cm)	≥5 versus <5	1.42 (0.69–2.92)	0.3346		
Neoadjuvant therapy regimen	nCRT versus nCT	**0.49 (0.27–0.9)**	**0.0221**	0.68 (0.35–1.33)	0.2601
	nICT versus nCT	0.45 (0.2–1.01)	0.0526	0.49 (0.21–1.13)	0.0952
	Others versus nCT	0.42 (0.1–1.78)	0.2379	0.8 (0.18–3.54)	0.7657
ypT stage	T1 versus T0	1.02 (0.2–5.28)	0.9766		
	T2 versus T0	2.27 (0.48–10.67)	0.3011		
	T3 versus T0	3.15 (0.76–13.09)	0.1143		
	T4 versus T0	3.29 (0.3–36.4)	0.331		
ypN stage	N0 versus N+	**0.41 (0.23–0.74)**	**0.0033**	**0.46 (0.25–0.86)**	**0.0156**
Resected lymph nodes (*n*)	≥30 versus <30	1.33 (0.65–2.72)	0.4392		
Adjuvant therapy	ACT versus AICT	**3.15 (1.12–8.87)**	**0.0297**	2.25 (0.77–6.56)	0.1388
	ART versus AICT	**5.08 (1.65–15.58)**	**0.0045**	2.84 (0.79–10.19)	0.1092

Abbreviations: ACT, adjuvant chemotherapy; AICT, adjuvant immunochemotherapy; ART, adjuvant radiotherapy; BMI, body mass index; CI, confidence interval; ECOG-PS, eastern cooperative oncology group performance status; HR, hazard ratio; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; nICT, neoadjuvant immunochemotherapy; pCR, pathological complete response; ypN, postoperative pathological stage N; ypT, postoperative pathological stage T.
Note: The *p*-values less than 0.05 are indicated in bold.

pCR (HR = 1.49; 95% CI: 1.01–2.20, $p = 0.042$) tended to benefit from AT (Figure 3a). The interaction p value is 0.0029. The subgroup analysis of OS also demonstrated statistical significance for pCR. Patients without pCR (HR = 1.62; 95% CI: 1.04–2.53, $p = 0.033$) were more likely to benefit from AT, with an interaction p value of 0.032 (Figure 3b). Other clinical characteristics in the analysis did not show statistical significance.

The Kaplan–Meier survival analyses were then performed (Figure 4). In non-pCR patients, the AT group had significantly better DFS than those without AT after PSM (HR = 0.67; 95% CI: 0.46–0.99, $p = 0.0041$). Similarly, the AT group had significantly better OS after PSM (HR = 0.62; 95% CI: 0.4–0.96, $p = 0.031$). In pCR patients, there is no difference in DFS and OS between the two groups before and after PSM.

3.5 | Prognostic Factors of Non-pCR Patients Who Received AT

We conducted univariate and multivariate Cox regression analyses to identify factors associated with OS and DFS. Variables with a p value <0.05 in the univariate analysis were included in the multivariate analysis. For non-pCR patients, univariate analysis identified that BMI, primary N0 stage, clinical stage, neoadjuvant therapy regimen, ypN stage, and adjuvant therapy were associated with DFS. Further multivariate analysis confirmed that BMI ≥21.5 kg/m^2 (HR = 0.51, 95% CI: 0.31–0.86, $p = 0.0108$) and ypN0 stage (HR = 0.44, 95% CI: 0.25–0.78, $p = 0.0046$) were independent protective factors (Table 2). OS analysis revealed that BMI, clinical stage, neoadjuvant therapy regimen, ypN stage, and adjuvant therapy were associated with OS. Multivariate analysis identified the ypN0 stage (HR = 0.46, 95% CI: 0.25–0.86, $p = 0.0156$) as independent prognostic factors (Table 3).

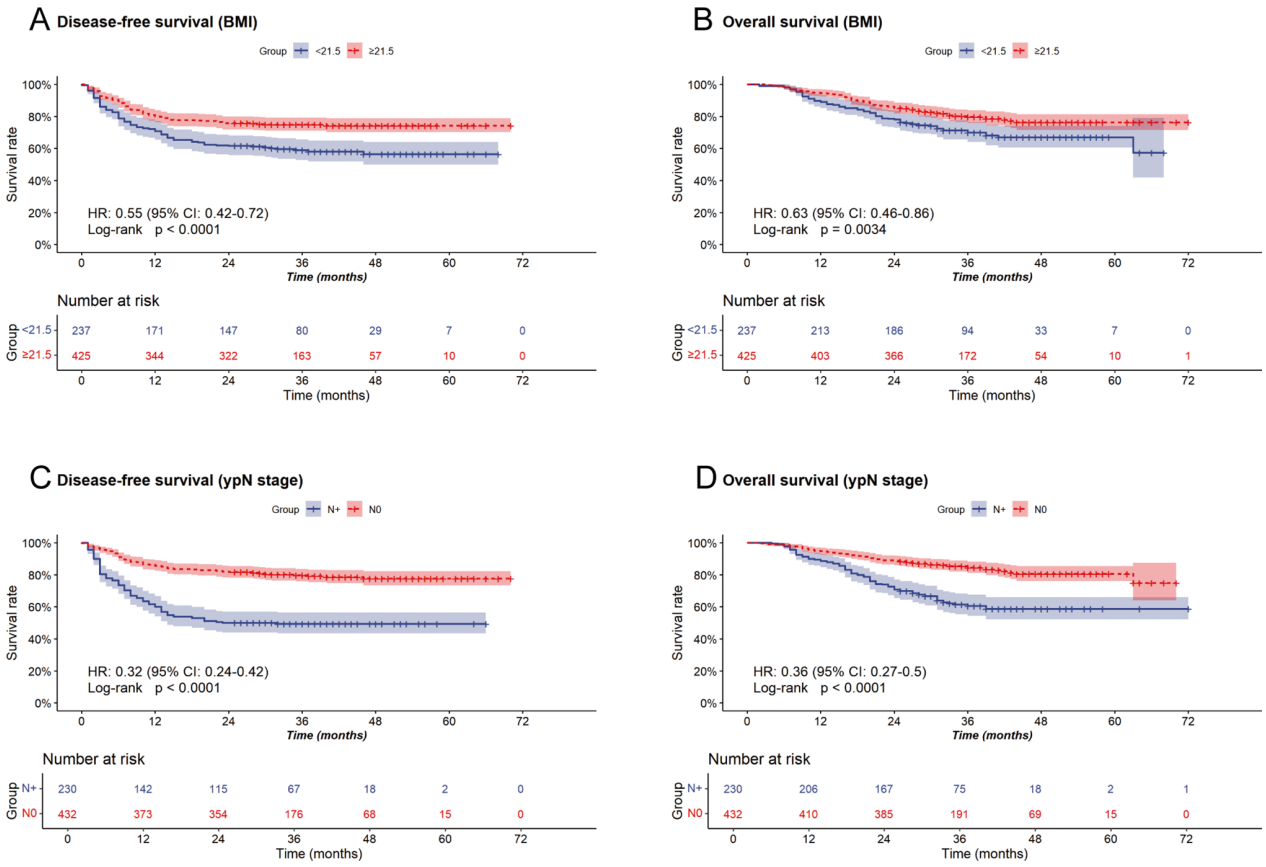

FIGURE 5 | The Kaplan–Meier analysis of BMI and ypN stage in non-pCR patients with adjuvant therapy. BMI, body mass index; pCR, pathological complete response; ypN, postoperative pathological stage N.

The Kaplan–Meier survival analyses were then performed. Patients with BMI ≥21.5 kg/m^2 had significantly better DFS (HR = 0.55, 95% CI: 0.42–0.72, $p < 0.0001$; Figure 5a) and OS (HR = 0.63, 95% CI: 0.46–0.86, $p = 0.0034$; Figure 5b) compared to those with lower BMI. In addition, ypN0 patients had significantly better DFS (HR = 0.32, 95% CI: 0.24–0.42, $p < 0.0001$; Figure 5c) and OS (HR = 0.36, 95% CI: 0.27–0.5, $p < 0.0001$; Figure 5d) compared to ypN+ patients.

3.6 | Comparison of AT Regimens

We then compared the survival of different AT regimens in non-pCR patients (Figure 6). AICT demonstrated a significant benefit over ACT in DFS (HR = 0.39, 95% CI: 0.18–0.87, $p = 0.0212$) and OS (HR = 0.32, 95% CI: 0.11–0.9, $p = 0.0305$). In addition, AICT also demonstrated a significant benefit over ART in DFS (HR = 0.35, 95% CI: 0.14–0.88, $p = 0.0252$) and OS (HR = 0.21, 95% CI: 0.07–0.63, $p = 0.0057$). There was no survival difference between ACT and ART.

4 | Discussion

Neoadjuvant therapy combined with radical surgery is currently the first-line standard treatment for locally advanced ESCC [29]. Clinically, a significant proportion of locally advanced ESCC patients undergoing neoadjuvant therapy and surgery receive postoperative AT based on the initial treatment plan. However, there is still insufficient evidence to support its efficacy and value. In this multicenter, real-world study, we evaluated the impact of postoperative AT on patients with locally advanced ESCC who had previously received neoadjuvant therapy followed by surgery. Our findings show that, for the overall population, there were no significant differences in DFS or OS between patients who received AT and those who did not. The subgroup analysis demonstrated that patients with non-pCR may benefit from AT. Furthermore, in non-pCR patients, BMI ≥21.5 kg/m^{2}and ypN0 were identified as independent protective factors for DFS. ypN0 was an independent protective factor for OS. To our knowledge, this is the largest real-world clinical study to date, evaluating the role of AT in ESCC patients who have received neoadjuvant therapy and surgery.

The achievement of pCR is traditionally viewed as a favorable prognostic indicator [30], often associated with improved survival outcomes [31, 32]. Saichun Qi et al. reported a median survival of 68.2 months in pCR patients, which was significantly higher than the 30.8 months observed in non-pCR patients [33]. Similarly, M. Caro et al. demonstrated that the median survival for pCR patients could reach 132 months, with a 5-year survival rate of 67%, substantially exceeding that of non-pCR patients [34]. The favorable prognosis of pCR patients may explain why the additional benefit of AT is limited. This suggests that for patients who achieve pCR, an observation strategy may be more appropriate than routine AT, as it can avoid unnecessary treatment-related toxicity and reduce the economic burden on patients.

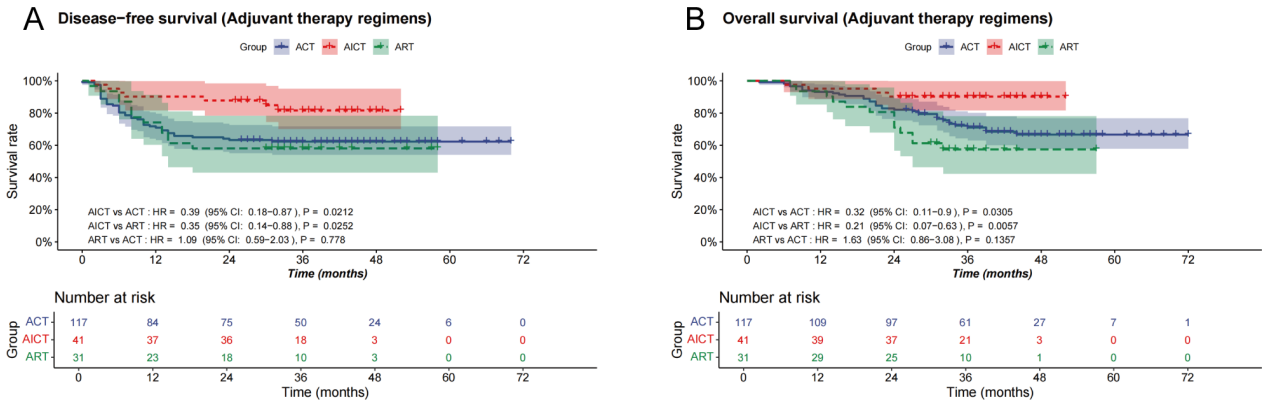

FIGURE 6 | The Kaplan–Meier analysis for non-pCR patients with different adjuvant therapy regimens. (A) Disease-free survival; (B) overall survival. ACT, adjuvant chemotherapy; AICT, adjuvant immunochemotherapy; ART, adjuvant radiotherapy; pCR, pathological complete response.

However, the reported pCR rate for neoadjuvant therapy in locally advanced ESCC is low [10, 35–37], and most patients still have residual tumors, facing a high risk of recurrence. Our study indicates that for the non-pCR population, postoperative AT is appropriate. This is consistent with the findings from the Checkmate 577 trial [12]. Univariate and multivariate analyses highlighted the prognostic significance of postoperative N stage. Our study identified that ypN0 was an independent protective factor for both DFS and OS. These findings align with previous studies confirming the prognostic relevance of postoperative pathological staging [16, 38]. Additionally, some retrospective studies have supported the potential benefit of lymph node N staging from AT [39], although this benefit was not observed in the study by Arnaud Pasquer et al. [40]. Furthermore, BMI $\geq 21.5\,kg/m^2$ was identified as an independent protective factor of DFS, suggesting that maintaining adequate nutritional status may be critical for optimizing treatment outcomes and improving the tolerability of AT. Collectively, these findings underscore the need for individualized postoperative AT strategies in ESCC patients.

In the comparison of different postoperative adjuvant regimens, our study suggests that AICT may be more beneficial for patients in achieving the best prognosis. This is consistent with emerging evidence suggesting that immunotherapy can enhance the efficacy of traditional chemotherapy in neoadjuvant or first-line therapy [41–46] as well as have fewer adverse effects and greater safety compared to treatment regimens involving radiotherapy [47]. Chemotherapy combined with immunotherapy helps eliminate residual lesions and reduce recurrence in patients with high-risk pathological factors [48]. These results advocate for the integration of immunotherapeutic agents into postoperative treatment regimens, especially for patients who do not achieve pCR, to maximize survival outcomes. However, the results of prospective randomized controlled clinical trials remain lacking and reports of retrospective studies are controversial [49].

Although immunotherapy has shown promise in improving survival outcomes, the potential toxicities associated with AICT are of critical importance. It has been reported that the combination of immunotherapy with chemotherapy is generally well tolerated in most cases [50, 51]. However, combination strategies involving immunotherapy and other treatment modalities may increase the risk of immune-related adverse events (irAEs), such as dermatitis, colitis, hepatitis, and pneumonitis, which can be severe in some cases [52–54]. Additionally, chemotherapy itself can cause gastrointestinal disturbances, hematologic toxicity, and neurotoxicity [55]. These toxicities can significantly impact the patient's quality of life, and their management requires close monitoring. Thus, the potential for enhanced survival outcomes must be weighed against the risk of these toxicities. Investigations into biomarkers that can predict treatment tolerability, as well as prospective trials that assess the long-term safety and side effect profile of different adjuvant therapies, will be critical in optimizing treatment selection.

One strength of our research is its real-world, multicenter design, which enhances the generalizability of the findings. However, as a retrospective study, inherent limitations, such as selection bias and heterogeneity in treatment protocols, must be acknowledged. To address this, we employed PSM to balance the baseline differences between the two groups and reduce the potential for bias. Furthermore, detailed toxicity and quality-of-life data were not collected, which are important when recommending additional therapies. Future prospective trials are needed to clarify the optimal patient selection for postoperative adjuvant therapy. Investigations into biomarkers, immune microenvironment features, and genetic signatures may further refine patient stratification. Moreover, understanding the mechanisms behind the lack of benefit in pCR patients could guide more rational adjuvant therapy use.

5 | Conclusion

In summary, our study showed that postoperative adjuvant therapy benefits ESCC patients with non-pCR but not those with pCR. AICT showed a trend of superiority over other treatment options, and its potential role in adjuvant therapy deserves further exploration.

Author Contributions

Defeng Liu contributed to the study design, data collection, statistical analysis, and manuscript writing. Ao Liu was involved in the study design and manuscript writing. Longxiang Guo, Yi Li, and Yuanlin Li contributed to data analysis and proofreading. Yuxiang Chi and Haiqun Lin were responsible for data collection from different centers. Minghuan Li and Jinming Yu made critical revisions to the manuscript

for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

This study was supported by the National Natural Science Foundation of China [Grant Number 82172677].

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are available from the corresponding author on reasonable request.

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