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Adjuvant treatment efficacy in esophageal adenocarcinoma patients receiving neoadjuvant therapy and esophagectomy

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The application of adjuvant therapy following neoadjuvant treatment and subsequent esophagectomy remains a subject of debate due to the limited availability of comprehensive studies. This study aims to evaluate the role of adjuvant therapy in patients with esophageal adenocarcinoma (EAC) who have undergone neoadjuvant therapy and esophagectomy, thereby offering evidence-based guidance for clinical decision-making. Patients diagnosed with EAC and treated with neoadjuvant therapy followed by surgical intervention were enrolled in our study. The data for patients in the training cohort were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. To validate the findings, new patient cohorts were utilized. A total of 3,445 patients with EAC were identified from the SEER database based on the established eligibility criteria. The analysis revealed no significant differences between the adjuvant therapy group and the non-adjuvant therapy group in terms of 5-year overall survival, with rates of 35.7% and 37.2%, respectively (p=0.920), nor in 5-year cancer-specific survival, with rates of 39.5% and 43.2%, respectively (p=0.520). Additionally, 130 patients were identified from the Affiliated Jinling Hospital of Nanjing University's Medical School. In this cohort, findings indicated that patients receiving adjuvant therapy demonstrated improved overall survival compared to those not receiving such therapy (p=0.031). Leveraging the SEER database, our study demonstrated that adjuvant therapy did not confer a survival advantage for patients with EAC following neoadjuvant therapy and surgery. In contrast, data analysis from the Affiliated Jinling Hospital, Medical School of Nanjing University in China, indicated that EAC patients might indeed benefit from adjuvant therapy after undergoing neoadjuvant treatment and esophagectomy.

Key words: esophageal adenocarcinoma; esophagectomy; neoadjuvant therapy; adjuvant therapy; SEER

Esophageal cancer (EC) ranks as the sixth leading cause of mortality associated with cancer on a global scale [1]. Despite significant advancements in treatment, the majority of EC cases are diagnosed at an advanced stage, resulting in a five-year survival rate of less than 40% [2].

The current standardized treatment protocol for EC (excluding T4 stage) predominantly involves esophagectomy, either in conjunction with or without adjuvant and/or neoadjuvant chemotherapy or chemoradiotherapy [3]. Although surgery continues to serve as the primary approach in the treatment of EC, numerous studies have demonstrated that surgical resection following preoperative neoadjuvant therapy comprising chemotherapy, radiotherapy, or their combination can significantly enhance the prognosis for patients with early local invasion and metastatic dissemination [4–6]. The 2019 National Comprehensive Cancer Network (NCCN) Guidelines strongly advocated that patients diagnosed with locally advanced EC should undergo neoadjuvant therapy prior to esophagectomy [7].

Additional adjuvant therapy may be necessary for patients who present with residual disease and lymph node metastases following neoadjuvant treatment. The CheckMate 577 study had demonstrated that nivolumab significantly prolongs disease-free survival [8]. The 2019 NCCN guidelines advocated for the utilization of adjuvant therapy in patients who had undergone an incomplete esophagectomy [7]. However, several studies had indicated that postoperative radiotherapy might be inadequate for effectively controlling residual disease. Furthermore, patients were highly likely to face an increased risk of experiencing adverse events [9–12].

Previous research into the effectiveness of adjuvant therapy following surgery after neoadjuvant treatment was conducted at single institutions and produced inconsistent results. The Surveillance, Epidemiology, and End Results (SEER) database, maintained by the National Cancer Institute (NCI), provides demographic and clinical data that covers nearly one-third of the United States population. Our study assessed the prognostic significance of adjuvant therapy in patients with esophageal adenocarcinoma (EAC) who underwent surgery post-neoadjuvant therapy, utilizing data from the SEER database and the Affiliated Jinling Hospital, Medical School of Nanjing University. Propensity score matching (PSM) was employed to equilibrate baseline characteristics, taking into account the selection bias inherent in adjuvant treatments within the SEER database.

Patients and methods

Study population and outcomes. This study conducted a retrospective analysis of the SEER 18-Registry database, maintained by the NCI, encompassing data from 1975 to 2019 (dataset submitted in November 2021; www.seer.cancer.gov). Clinicopathological and survival information available within the database were extracted using SEER*Stat software (version 8.3.9; National Institutes of Health, Bethesda, MD, USA). Authorization to access the research data file in the SEER registry was granted by the NCI, USA (Reference No. 20059-Nov 2021).

We initially identified patients with a primary diagnosis involving the esophagus (C27.0) between 1975 and 2019. Those who met the following specified inclusion criteria were subsequently included in the study: 1) histologic types of EAC with the malignant behavior code (/3) according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3) [13]; 2) diagnosis between 2010 and 2019; 3) age older than 18 years; 4) survival time more than three months; 5) no distant metastasis (M0); 6) receipt of neoadjuvant therapy and cancer-directed surgery with lymph node dissection. The demographic and clinicopathological attributes, including gender, race, age at diagnosis, primary tumor site, histological differentiation, tumor-node-metastasis (TNM) staging, tumor size, and treatment modalities, were systematically collected.

The inclusion criteria for patients from the Affiliated Jinling Hospital of Nanjing University's Medical School were aligned with those of the SEER database, except for the time frame of diagnosis, which spanned from January 2016 to June 2021. All patients underwent neoadjuvant chemoradiotherapy in accordance with the NCCN guidelines [7]. Postoperative adjuvant treatment included radiotherapy, chemotherapy, or a combination of both.

Ethics statement. This study was approved by the Institutional Review Board of Affiliated Jinling Hospital, Medical School of Nanjing University (Approval No. 2018-024-02). The written consent of the study's participants and permission to use resected specimens were obtained preoperatively.

Propensity score matching. Propensity score matching (PSM) was employed to reduce selection bias arising from baseline characteristics in the SEER database. The baseline covariates considered included age, gender, race, year of diagnosis, primary tumor site, histological differentiation, TNM staging, tumor size, and treatment modalities. A 1:2 matching ratio with a caliper width of 0.1 was used to match patients between the adjuvant therapy and non-adjuvant therapy groups.

Statistical analysis. All statistical analyses were conducted utilizing R version 3.5.3 (R Development Core Team). Categorical variables were evaluated using either the Pearson Chi-square test or Fisher's exact test, while continuous variables were assessed via the Student's t-test. The Kaplan-Meier method was employed to compute overall survival (OS) and cancer-specific survival (CSS) curves, with statistical significance determined by the log-rank test. Univariate Cox regression analysis was used to identify variables associated with OS and CSS within the matched cohort. Variables yielding p-values less than 0.1 were incorporated into the multivariate Cox regression model. Statistical significance was defined as two-tailed tests with p-values less than 0.05.

Results

Patient characteristics. The schematic representation of the therapeutic strategy is illustrated in Figure 1. A total of 3,445 patients diagnosed with EAC were identified from the SEER database based on the specified eligibility criteria (Figure 2). The baseline demographic and clinical character-

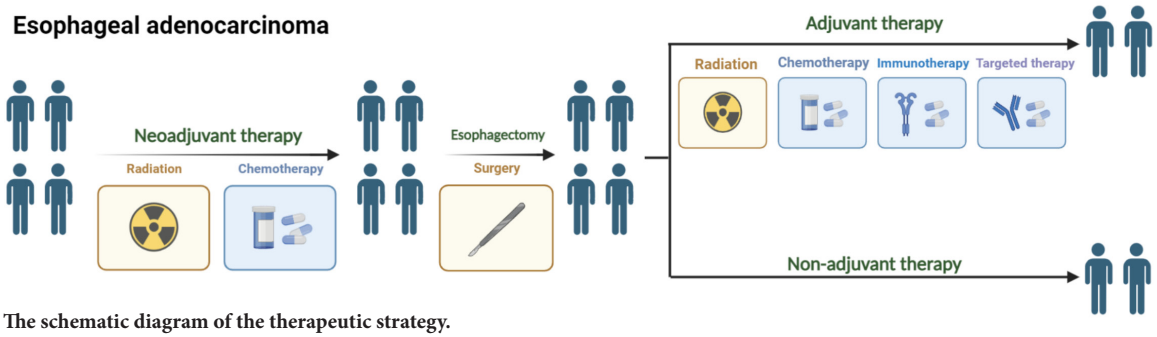

Figure 1. The schematic diagram of the therapeutic strategy.

istics of these patients are summarized in Table 1. Among them, 503 patients received postoperative adjuvant therapy, while 2,942 did not. Within this study population, the median age was 64 years (range: 23 to 87), and the median tumor length was 4.2 cm. The majority of the cohort (95.3%, 3,284/3,445) were white, and 89.3% (3,078/3,445) were male.

Additionally, 89.1% (3,070/3,445) presented with tumors located in the lower thoracic region. Regarding pathologic nodal status, 1,116 (32.4%), 1,617 (46.9%), 547 (15.9%), and 165 (4.8%) patients were classified as N0, N1, N2, and N3, respectively. Patients who were younger (p<0.001), female (p=0.034), or exhibited more advanced TNM staging

Table 1. Baseline characteristics of patients from the SEER database before and after propensity score matching.

Variable	Patients before PSM (n=3,445)					Patients after PSM (n=1,481)				
	Non-adjuvant		Adjuvant		p-value	Non-adjuvant		Adjuvant		p-value
	(n=2,942)	%	(n=503)	%		(n=984)	%	(n=497)	%	
Age (years)					<0.001					0.851
≤65	1,507	51.2	303	60.2		593	60.3	297	59.8	
>65	1,435	48.8	200	39.8		391	39.7	200	40.2	
Race					0.168					0.939
White	2,811	95.5	473	94.0		921	93.6	469	94.4	
Black	43	1.5	6	1.2		13	1.3	6	1.2	
Other	81	2.8	23	4.6		47	4.8	21	4.2	
Unknown	7	0.2	1	0.2		3	0.3	1	0.2	
Diagnosis year					0.163					0.494
2010–2014	1,409	47.9	224	44.5		458	46.5	222	44.7	
2015–2019	1,533	52.1	279	55.5		526	53.5	275	55.3	
Gender					0.034					0.989
Male	2,615	88.9	463	92.0		905	92.0	457	92.0	
Female	327	11.1	40	8.0		79	8.0	40	8.0	
Tumor site					0.823					0.965
Lower	2,623	89.2	447	88.9		874	88.8	441	88.8	
Middle	152	5.2	23	4.6		44	4.5	23	4.6	
Upper	6	0.2	1	0.2		1	0.1	1	0.2	
Unknown	161	5.4	32	6.3		65	6.6	32	6.4	
Differentiation					0.077					0.718
G1	105	3.6	20	4.0		45	4.6	20	4.0	
G2	925	31.4	129	25.6		275	27.9	128	25.8	
G3	1,068	36.3	196	39.0		380	38.6	195	39.2	
Gx	844	28.7	158	31.4		284	28.9	154	31.0	
Stage					<0.001					0.945
I	304	10.3	36	7.2		73	7.4	36	7.2	
II	935	31.8	118	23.5		244	24.8	118	23.7	
III	1,681	57.1	336	66.8		652	66.3	334	67.2	
IV	22	0.8	13	2.5		15	1.5	9	1.9	
Tumor status					0.427					0.992
T1	297	10.1	44	8.7		91	9.2	44	8.9	
T2	515	17.5	83	16.5		161	16.4	82	16.5	
T3	2,015	68.5	350	69.6		683	69.4	345	69.4	
T4	115	3.9	26	5.2		49	5.0	26	5.2	
Node status					<0.001					0.986
N0	1,004	34.1	112	22.3		230	23.4	112	22.5	
N1	1,382	47.0	235	46.7		463	47.1	235	47.3	
N2	437	14.9	110	21.9		213	21.6	110	22.1	
N3	119	4.0	46	9.1		78	7.9	40	8.1	
Tumor size (cm)					0.229					0.987
≤4.2	1,093	37.2	203	40.4		402	40.9	201	40.4	
>4.2	1,093	37.2	187	37.2		361	36.7	183	36.8	
Unknown	756	25.6	113	22.4		221	22.4	113	22.8	

(p<0.001) and higher nodal (N) staging (p<0.001) were more likely to receive adjuvant therapy.

In the matched cohort, 497 patients received postoperative adjuvant therapy while 984 patients did not. Following the matching process, all variables exhibited p-values greater than 0.05, indicating that propensity score matching effectively minimized potential selection bias in the administration of adjuvant therapy.

Table 2 provides a summary of the baseline characteristics of the validation cohort: 58 patients underwent postoperative adjuvant therapy, whereas 72 did not. Within this study population, 124 individuals (95.4%) were male, and 102 (78.5%) had esophagogastric junction cancer. All participants were of Asian descent. The p-values for all variables exceeded 0.05, confirming a baseline equilibrium between the two study groups.

Survival outcomes. In the overall cohort derived from the SEER database, the median follow-up time was 41.0 months (95% CI: 38.3–43.7 months), as estimated by the Kaplan-Meier method. No significant differences in OS were observed between the adjuvant and non-adjuvant therapy groups prior to matching, with 5-year survival rates of 35.6% and 40.3%, respectively (p=0.351, Figure 3A). Similarly, CSS demonstrated no statistically significant difference between the two groups, with 5-year CSS rates of 39.3% and 47.4%, respectively (p=0.055, Figure 3B). Even after propensity score matching, no statistically significant differences were identified between the adjuvant and non-adjuvant therapy groups. The 5-year OS rates were 35.7% and 37.2% (p=0.920, Figure 3C), while the 5-year CSS rates were 39.5% and 43.2% (p=0.520, Figure 3D). Furthermore, subgroup survival analyses for OS and CSS were conducted based on N stage

Table 2. Baseline characteristics of patients.

Variable	Patients (n=130)						p-value
	All patients		Non-adjuvant		Adjuvant		
	(n=130)	%	(n=72)	%	(n=58)	%	
Age (years)							0.822
≤64	88	67.7	49	68.1	40	69	
>64	42	32.3	24	33.3	18	31	
Gender							0.406
Male	124	95.4	70	97.2	54	93.1	
Female	6	4.6	2	2.8	4	6.9	
Tumor site							0.601
Upper	4	3.1	2	2.8	2	3.4	
Middle	8	6.2	6	8.3	2	3.4	
Lower	16	12.4	10	13.9	6	10.3	
Junction	102	78.5	54	75	48	82.8	
Differentiation							0.255
G1	6	4.6	4	5.5	2	3.4	
G2	56	43.1	26	36.1	30	51.7	
G3	56	43.1	36	50	20	34.5	
Gx	12	9.2	6	8.3	6	10.3	
Stage							0.103
I	48	36.9	22	30.6	26	44.8	
II	24	18.5	14	19.4	10	17.2	
III	40	30.8	28	38.9	12	20.7	
IV	18	13.8	8	11.1	10	17.2	
Tumor status							0.228
T0	12	9.2	5	6.9	7	12.1	
T1	20	15.4	8	11.1	12	20.7	
T2	26	0.2	14	19.4	12	20.7	
T3	72	55.4	45	62.5	27	46.6	
Node status							0.238
N0	74	56.9	36	50	38	65.5	
N1	22	16.9	16	22.2	6	10.3	
N2	20	15.4	12	16.7	8	13.8	
N3	14	10.8	8	11.1	6	10.3	
Tumor size (cm)							0.965
≤4.2	72	55.4	40	55.6	32	55.2	
>4.2	58	44.6	32	44.4	26	44.8	

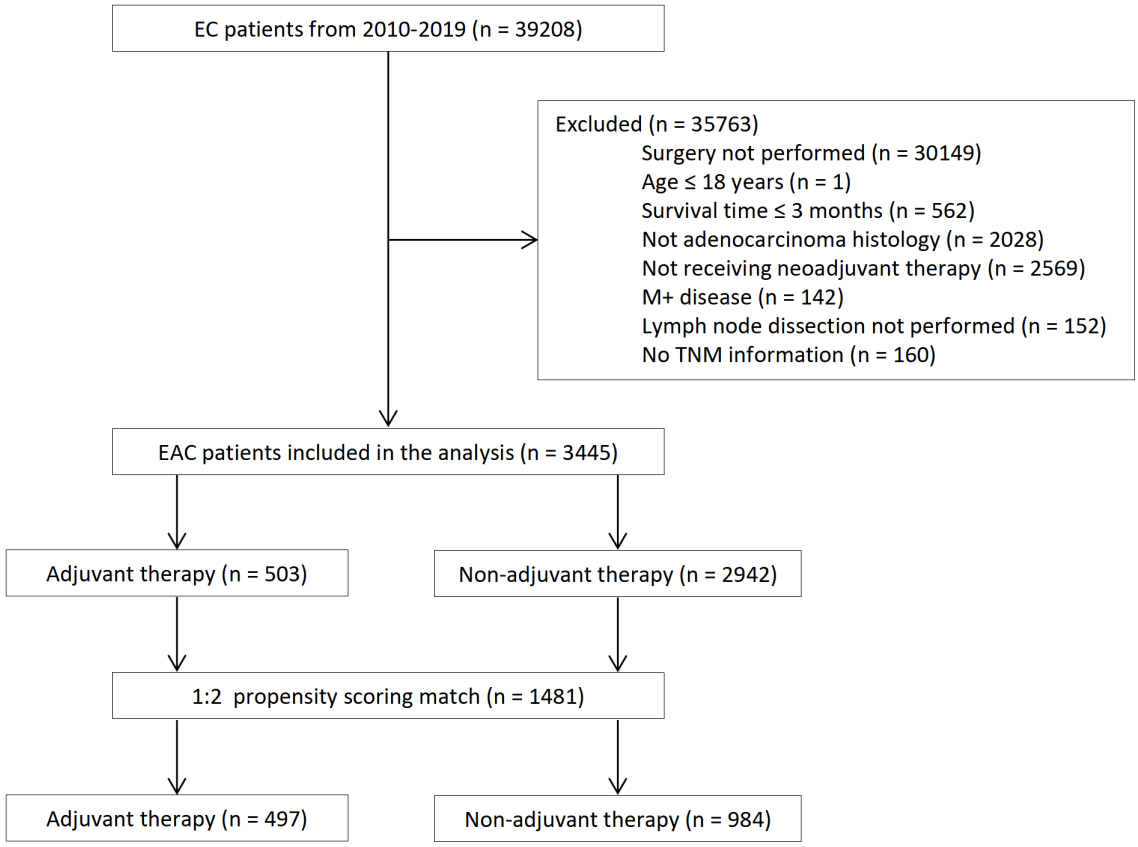

Figure 2. CONSORT diagram.

(N0, N1, N2, and N3). Regardless of N stage, no significant differences in either OS or CSS were detected between the adjuvant and non-adjuvant therapy groups ($p>0.05$, Figures 4A–4H).

The median follow-up duration (interquartile range, IQR) for the validation cohort was 15 months (IQR: 9.00–21.9 months). The adjuvant therapy group demonstrated significantly better OS compared to the non-adjuvant therapy group ($p=0.031$, Figure 5A). Additionally, adjuvant therapy appeared to show a trend toward improving CSS. Although this improvement did not reach statistical significance, there was an observable tendency for adjuvant therapy to enhance CSS ($p=0.057$, Figure 5B).

Cox regression analysis. Table 3 presents the 11 variables from the SEER database that were incorporated into the univariate Cox regression analysis following propensity score matching. Variables with a p-value of <0.1 in the univariate analysis were subsequently included in the multivariate Cox regression model. However, the TNM stage was excluded from the multivariate models due to its statistical correlation with T and N stages. The results of the multivariate Cox regression analysis indicated that age and N stage were independent prognostic factors for both OS and CSS, with statistical significance ($p<0.05$). (Table 4).

Discussion

The efficacy of preoperative neoadjuvant therapy in enhancing oncologic outcomes for EAC has been substantiated through several randomized controlled trials. Consequently, it was strongly endorsed by the NCCN guidelines for patients with locally advanced EAC [5–7, 14]. The question of whether patients undergoing esophagectomy following neoadjuvant therapy should receive postoperative adjuvant therapy remains a subject of ongoing debate. In this study, we performed an analysis of survival outcomes in patients with EAC over the past decade, utilizing data derived from the SEER database as well as clinical records from the Affiliated Jinling Hospital, Medical School of Nanjing University.

In prior research, Schreiber et al. utilized the SEER database and concluded that only patients diagnosed with clinical stage III EC derived significant benefit from postoperative radiotherapy [15]. Similarly, Mokdad et al., through an analysis of the NCDB database, demonstrated that the integration of adjuvant chemotherapy for patients with gastroesophageal adenocarcinoma who had undergone neoadjuvant therapy and surgical resection was associated with markedly improved prognosis [16]. Further supporting these findings, Drake et al. [17] examined the impact of

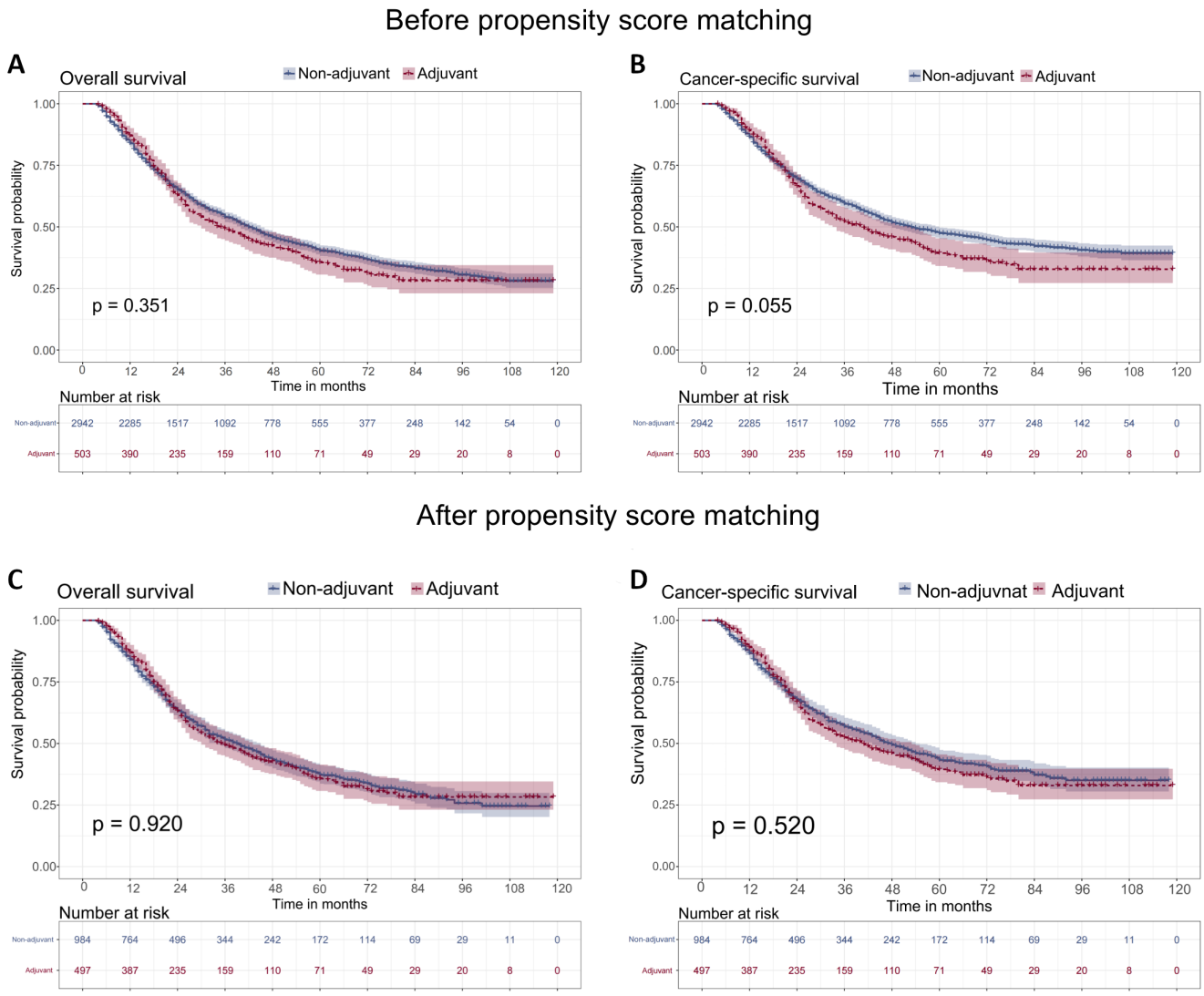

Figure 3. Kaplan-Meier curves were utilized to compare OS and CSS, with the log-rank test employed to assess statistical significance between the two groups. A) Prior to matching, there was no significant difference in OS between the adjuvant therapy and non-adjuvant therapy groups (p=0.351); B) Prior to matching, CSS did not significantly differ between the adjuvant and non-adjuvant therapy groups (p=0.055); C) Following matching, no significant difference in OS was observed between the two groups (p=0.920); D) Following matching, CSS remained statistically similar between the two groups (p=0.520).

neoadjuvant therapy followed by adjuvant chemotherapy in EAC patients with lymph node metastasis, reporting results consistent with those of Mokdad et al. [16]. Additionally, Semenkovich et al. [18] conducted a multicenter retrospective cohort study, which indicated that EC patients presenting with positive pathological lymph nodes benefited significantly from adjuvant therapy following neoadjuvant treatment and surgical intervention. In a recent 2022 study analyzing the SEER database, Zheng et al. [19] observed that postoperative radiotherapy did not confer a survival advantage for EC patients who underwent surgery after receiving neoadjuvant treatment. Furthermore, a meta-analysis performed by Lee et al. in 2021 concluded that the administration of adjuvant therapy subsequent to neoadjuvant therapy and margin-negative resection resulted in prolonged OS [20].

After performing PSM, our analysis revealed that adjuvant therapy was not associated with OS or CSS in the SEER population. However, results from our study demonstrated that adjuvant therapy significantly improved OS. These contradictory conclusions could be attributed to several potential reasons. First, the level of evidence provided by our retrospective study was limited due to its small sample size and shorter follow-up period. Second, variations in treatment strategies might have played a role.

Table 3. Univariate Cox regression for patients from the SEER database.

Univariate analysis	OS	p–value	CSS	p–value
	HR (95% CI)		HR (95% CI)	
Age (years)		0.004		0.072
≤64	Ref.		Ref.	
>64	0.811 (0.703–0.936)		1.155 (0.987–1.351)	
Race		0.401		0.430
White	Ref.		Ref.	
Black	0.714 (0.370–1.378)	0.316	0.649 (0.308–1.367)	0.255
Other	0.859 (0.603–1.225)	0.402	0.863 (0.587–1.268)	0.452
Unknown	0.321 (0.045–2.282)	0.256	0.375 (0.053–2.668)	0.327
Diagnosis year		0.818		0.563
2010-2014	Ref.		Ref.	
2015-2019	0.982 (0.843–1.144)		0.952 (0.808–1.123)	
Gender		0.266		0.635
Male	Ref.		Ref.	
Female	0.852 (0.643–1.129)		0.931 (0.694–1.250)	
Tumor site		0.205		0.282
Lower	Ref.		Ref.	
Upper/Middle	1.235 (0.891–1.713)		1.184 (0.825–1.700)	
Differentiation		0.065		0.071
G1	Ref.		Ref.	
G2	1.083 (0.768–1.526)	0.651	1.032 (0.713–1.493)	0.869
G3	1.305 (0.935–1.822)	0.118	1.277 (0.892–1.827)	0.181
Gx	1.097 (0.761–1.579)	0.620	1.067 (0.721–1.580)	0.746
Stage		<0.001		<0.001
I	Ref.		Ref.	
II	1.210 (0.869–1.687)	0.259	1.410 (0.955–2.082)	0.084
III	1.731 (1.273–2.354)	<0.001	2.126 (1.478–3.058)	<0.001
IV	3.634 (1.820–7.256)	<0.001	5.242 (2.556–10.75)	<0.001
Tumor status		0.002		<0.001
T1	Ref.		Ref.	
T2	1.021 (0.736–1.417)	0.899	1.037 (0.716–1.501)	0.849
T3	1.418 (1.072–1.876)	0.014	1.565 (1.141–2.145)	0.005
T4	1.501 (1.01–2.229)	0.044	1.668 (1.079–2.580)	0.021
Node status		<0.001		<0.001
N0	Ref.		Ref.	
N1	1.259 (1.039–1.526)	0.019	1.312 (1.061–1.623)	0.012
N2	1.663 (1.341–2.062)	<0.001	1.763 (1.391–2.233)	<0.001
N3	2.559 (1.954–3.352)	<0.001	3.017 (2.268–4.013)	<0.001
Tumor size (cm)		0.484		0.848
≤4.2	Ref.		Ref.	
>4.2	1.097 (0.935–1.287)	0.257	1.052 (0.885–1.250)	0.566
Unknown	1.085 (0.898–1.310)	0.400	1.028 (0.836–1.263)	0.793
Adjuvant therapy				
Yes	Ref.		Ref.	
No	0.992 (0.853–1.154)	0.921	1.055 (0.897–1.240)	0.520

Abbreviations: OS-overall survival; CSS-cancer-specific survival; HR-hazard ratio

Historically, commonly used chemotherapeutic agents included cisplatin and fluorouracil. However, after the publication of the CROSS trial in 2012, treatment protocols underwent significant changes [5], and carboplatin and paclitaxel were the most frequently used chemotherapeutic agents. Historically, conventional radiation therapy was predominantly utilized; however, advancements in technology have led to the growing adoption of intensity-modulated radiation therapy and proton therapy. Thirdly, the neoadjuvant treatment approach at both of our centers

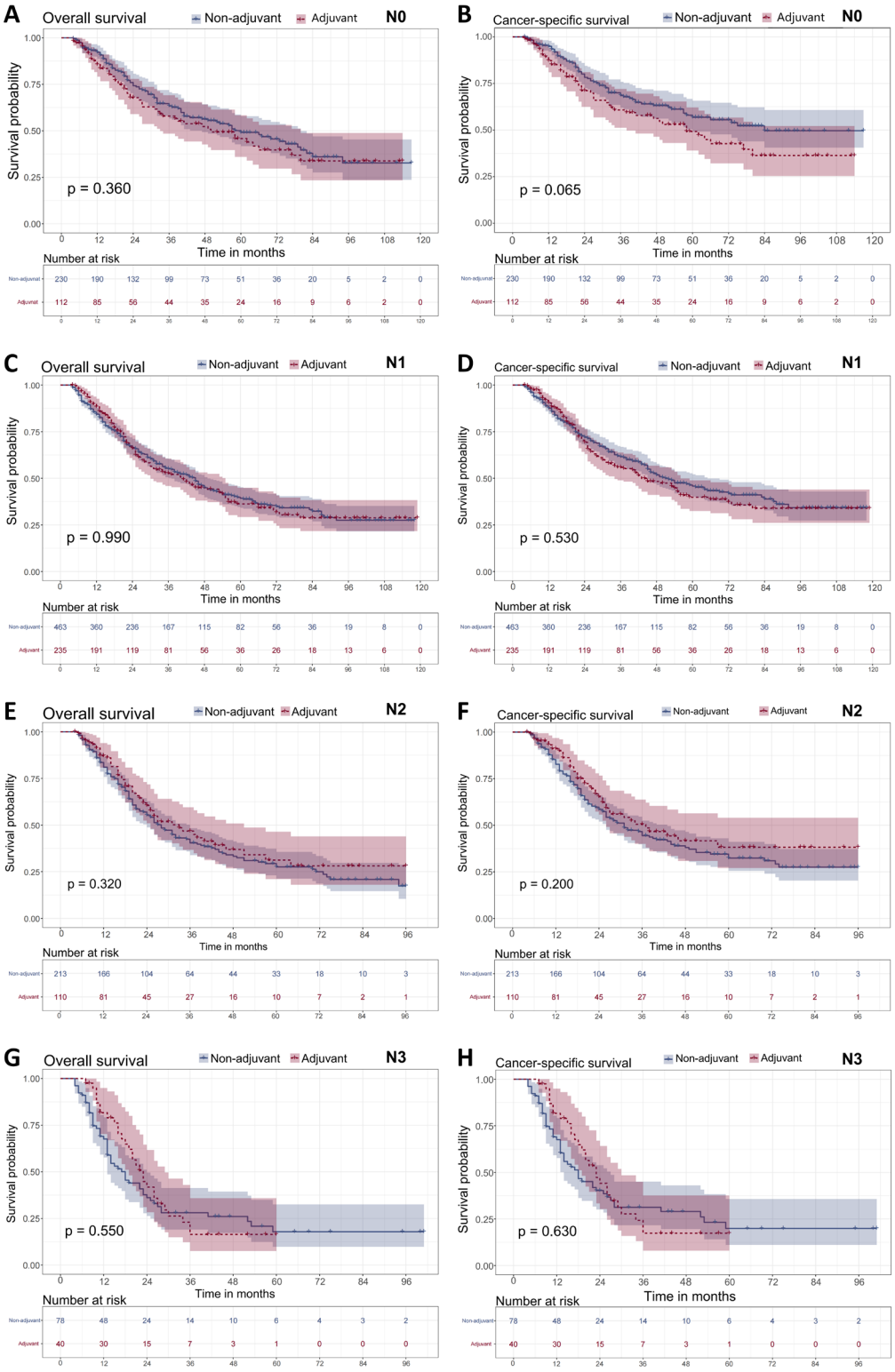

Figure 4. The comparison of OS and CSS was conducted using Kaplan-Meier curves, with the log-rank test employed to assess statistical significance between the two groups. Subgroup survival analyses for OS and CSS were carried out, stratified by N stage. There were no significant differences found between the two groups in terms of OS A) or CSS B) for patients with N0 status. Similarly, no significant differences were observed in OS C) or CSS D) for patients with N1 status. For patients with N2 status, there were again no significant differences in OS E) or CSS F). Lastly, analysis revealed no significant differences in OS G) or CSS H) for patients with N3 status.

Table 4. Multivariate Cox regression for patients from the SEER database.

Characteristics	OS		CSS	
	Multivariate analysis	p-value	Multivariate analysis	p-value
Age (years)		<0.001		0.004
≤64	Ref.		Ref.	
>64	1.328 (1.149–1.535)		1.259 (1.075–1.475)	
Tumor status		0.052		0.017
T1	Ref.		Ref.	
T2	0.937 (0.674–1.302)	0.698	0.942 (0.649–1.365)	0.751
T3	1.215 (0.913–1.617)	0.181	1.308 (0.948–1.806)	0.102
T4	1.324 (0.887–1.976)	0.17	1.432 (0.921–2.226)	0.111
Node status		<0.001		<0.001
N0	Ref.		Ref.	
N1	1.231 (1.013–1.497)	0.037	1.264 (1.019–1.569)	0.033
N2	1.648 (1.322–2.055)	<0.001	1.705 (1.338–2.172)	<0.001
N3	2.524 (1.914–3.328)	<0.001	2.89 (2.156–3.873)	<0.001

Abbreviations: OS-overall survival; CSS-cancer-specific survival

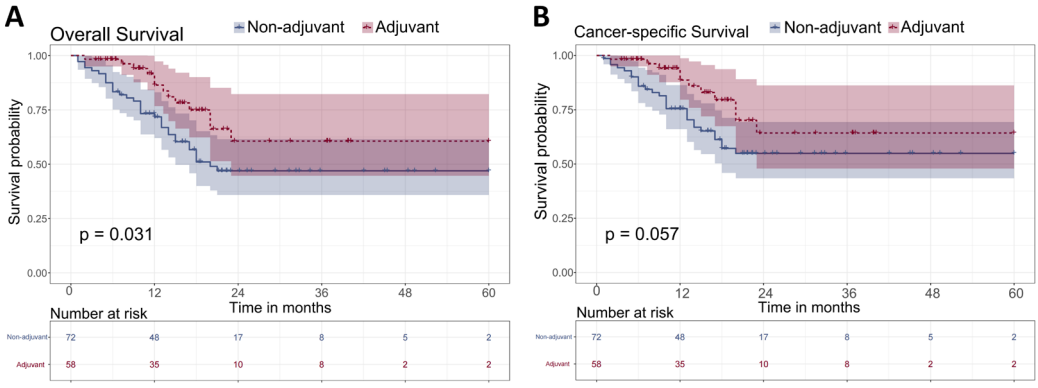

Figure 5. OS and CSS were compared using Kaplan-Meier curves. The statistical significance between the two groups was determined using the log-rank test. A) Patients undergoing the adjuvant therapy group had a better OS compared with patients not (p=0.031); B) Patients undergoing the adjuvant therapy intended to have a better CSS compared with patients not (p=0.057).

involved neoadjuvant chemoradiotherapy. Additionally, adjuvant immunotherapy was incorporated into the treatment framework for patients included in the SEER database population. Lastly, EC demonstrated significant geographical variations. The majority of patients treated at our retrospective study were of East Asian descent, and most cases of EAC were located at the esophagogastric junction.

Age and N stage were identified as independent prognostic factors for both OS and CSS, consistent with findings from multiple prior studies. While adjuvant therapy was generally anticipated to yield favorable outcomes and extend survival, it did not demonstrate a survival benefit for patients with EAC who had already undergone neoadjuvant therapy and surgery. A potential explanation for this observation could be that patients receiving neoadjuvant chemoradiotherapy might exhibit decreased sensitivity to subsequent adjuvant therapy [21, 22]. Moreover, all forms of adjuvant therapy could potentially induce systemic adverse effects in patients [23]. Adverse effects on the immune system might compromise the patient's ability to resist tumors and elevate the risk of tumor recurrence following adjuvant therapy. This could potentially represent one of the underlying contributing factors [24].

Several prior studies utilizing the SEER database had explored the prognostic significance of adjuvant and neoadjuvant therapies in patients with EC. However, our study distinguished itself in several critical aspects: 1) PSM was employed to minimize selection bias, 2) the analysis incorporates the most recent data spanning from 2010 to 2019, 3) additional independent datasets were utilized to validate the findings, and 4) the study specifically evaluated the prognostic value of adjuvant therapy in patients with EAC following neoadju-

vant therapy and esophagectomy. These advancements might provide valuable insights to guide clinical decision-making regarding adjuvant therapy for EAC.

This study is subject to several limitations. First, the SEER database does not provide detailed information regarding adjuvant therapy regimens or surgical margins. Second, despite the application of the PSM method, the inherent nature of this retrospective study makes it impossible to entirely eliminate selection bias. Third, the findings obtained from the SEER database may not be generalizable to populations in other regions.

In conclusion, this study, utilizing data from the SEER database, demonstrated no survival benefit of adjuvant therapy for patients with EAC following neoadjuvant therapy and surgical resection. However, analysis results from the Affiliated Jinling Hospital, Medical School of Nanjing University in China, suggested that adjuvant therapy might confer a survival advantage for patients with EAC after undergoing neoadjuvant therapy and esophagectomy. Consequently, additional high-quality studies from diverse geographical regions are warranted to elucidate the optimal indications for adjuvant therapy.

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References

[1] BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424. https://doi.org/10.3322/caac.21492

[2] BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA et al.Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2020; 70: 313. https://doi.org/10.3322/caac.21609

[3] LI X, CHEN L, LUAN S, ZHOU J, XIAO X et al. The development and progress of nanomedicine for esophageal cancer diagnosis and treatment. Semin Cancer Biol 2022; 86: 873–885. https://doi.org/10.1016/j.semcancer.2022.01.007

[4] ANDO N, KATO H, IGAKI H, SHINODA M, OZAWA S et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012; 19: 68–74. https://doi.org/10.1245/s10434-011-2049-9

[5] VAN HAGEN P, HULSHOF MC, VAN LANSCHOT JJ, STEYERBERG EW, VAN BERGE HENEGOUWEN MI et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012; 366: 2074–2084. https://doi.org/10.1056/NEJMoa1112088

[6] SHAPIRO J, VAN LANSCHOT JJB, HULSHOF M, VAN HAGEN P, VAN BERGE HENEGOUWEN MI et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16: 1090–1098. https://doi.org/10.1016/S1470-2045(15)00040-6

[7] AJANI JA, D'AMICO TA, BENTREM DJ, CHAO J, CORVERA C et al. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019; 17: 855–883. https://doi.org/10.6004/jnccn.2019.0033

[8] KELLY RJ, AJANI JA, KUZDZAL J, ZANDER T, VAN CUTSEM E et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med 2021; 384: 1191–1203. https://doi.org/10.1056/NEJMoa2032125

[9] VON DOBELN GA, KLEVEBRO F, JACOBSEN AB, JOHANNESSEN HO, NIELSEN NH et al. Neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus or gastroesophageal junction: long-term results of a randomized clinical trial. Dis Esophagus 2019; 32. https://doi.org/10.1093/dote/doy078

[10] VISSER E, EDHOLM D, SMITHERS BM, THOMSON IG, BURMEISTER BH et al. Neoadjuvant chemotherapy or chemoradiotherapy for adenocarcinoma of the esophagus. J Surg Oncol 2018; 117: 1687–1696. https://doi.org/10.1002/jso.25089

[11] STAHL M, WALZ MK, RIERA-KNORRENSCHILD J, STUSCHKE M, SANDERMANN A et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer 2017; 81: 183–190. https://doi.org/10.1016/j.ejca.2017.04.027

[12] Zieren HU, Muller JM, Jacobi CA, Pichlmaier H, Muller RP et al. Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. World J Surg 1995; 19: 444–449. https://doi.org/10.1007/BF00299187

[13] FRITZ A, PERCY C, JACK A (Eds.) WHO Library Cataloguing in Publication Data International classification of diseases for oncology (ICD-O) – 3rd edition, 1st revision. 1. Neoplasms – classification. I. World Health Organization. II. ICD-O. ISBN 978 92 4 154849 6 (NLM classification: QZ 15) ISBN 978 92 4 069212 1 (PDF)

[14] TEPPER J, KRASNA MJ, NIEDZWIECKI D, HOLLIS D, REED CE et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol 2008; 26: 1086–1092. https://doi.org/10.1200/JCO.2007.12.9593

[15] SCHREIBER D, RINEER J, VONGTAMA D, WORTHAM A, HAN P et al. Impact of postoperative radiation after esophagectomy for esophageal cancer. J Thorac Oncol 2010; 5: 244–250. https://doi.org/10.1097/JTO.0b013e3181c5e34f

[16] MOKDAD AA, YOPP AC, POLANCO PM, MANSOUR JC, REZNIK SI et al. Adjuvant Chemotherapy vs Postoperative Observation Following Preoperative Chemoradiotherapy and Resection in Gastroesophageal Cancer: A Propensity Score-Matched Analysis. JAMA Oncol 2018; 4: 31–38. https://doi.org/10.1001/jamaoncol.2017.2805

[17] DRAKE J, TAUER K, PORTNOY D, WEKSLER B. Adjuvant chemotherapy is associated with improved survival in patients with nodal metastases after neoadjuvant therapy and esophagectomy. J Thorac Dis 2019; 11: 2546–2554. https://doi.org/10.21037/jtd.2019.05.66

[18] SEMENKOVICH TR, YAN Y, SUBRAMANIAN M, MEYERS BF, KOZOWER BD et al. A Clinical Nomogram for Predicting Node-positive Disease in Esophageal Cancer. Ann Surg 2021; 273: e214–e221. https://doi.org/10.1097/SLA.0000000000003450

[19] ZHENG SY, QI WX, ZHAO SG, CHEN JY. No survival benefit could be obtained from adjuvant radiotherapy in esophageal cancer treated with neoadjuvant chemotherapy followed by surgery: A SEER-based analysis. Front Oncol 2022; 12: 897476. https://doi.org/10.3389/fonc.2022.897476

[20] LEE Y, SAMARASINGHE Y, LEE MH, THIRU L, SHARGALL Y et al. Role of Adjuvant Therapy in Esophageal Cancer Patients After Neoadjuvant Therapy and Esophagectomy: A Systematic Review and Meta-analysis. Ann Surg 2022; 275: 91–98. https://doi.org/10.1097/SLA.0000000000005227

[21] ELLIOTT JA, DOCHERTY NG, ECKHARDT HG, DOYLE SL, GUINAN EM et al. Weight Loss, Satiety, and the Postprandial Gut Hormone Response After Esophagectomy: A Prospective Study. Ann Surg 2017; 266: 82–90. https://doi.org/10.1097/SLA.0000000000001918

[22] Kubo Y, Miyata H, Sugimura K, Shinno N, Asukai K et al. Prognostic Implication of Postoperative Weight Loss After Esophagectomy for Esophageal Squamous Cell Cancer. Ann Surg Oncol 2021; 28: 184–193. https://doi.org/10.1245/s10434-020-08762-6

[23] NOORDMAN BJ, VERDAM MGE, LAGARDE SM, SHAPIRO J, HULSHOF M et al. Impact of neoadjuvant chemoradiotherapy on health-related quality of life in long-term survivors of esophageal or junctional cancer: results from the randomized CROSS trial. Ann Oncol 2018; 29: 445–451. https://doi.org/10.1093/annonc/mdx726

[24] PARK SY, KIM DJ, SUH JW, BYUN GE. Risk Factors for Weight Loss 1 Year After Esophagectomy and Gastric Pull-up for Esophageal Cancer. J Gastrointest Surg 2018; 22: 1137–1143. https://doi.org/10.1007/s11605-018-3749-2