Original Article

A propensity score-matched analysis to evaluate the benefit of adjuvant therapy on disease recurrence of esophageal squamous cell carcinoma after R0 esophagectomy

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Background: Esophageal squamous cell carcinoma (ESCC) is common in China and has a poor prognosis despite radical surgery. Guidelines around the use of adjuvant therapy (AT) in ESCC are indecisive. We assessed the benefit of AT on recurrence-free survival (RFS) in Chinese patients with ESCC using propensity score (PS) matching.

Methods: This retrospective cohort study used hospital electronic medical records (EMRs) of 523 adults diagnosed between 2013 to 2019 with pathologically confirmed ESCC after R0 esophagectomy without neoadjuvant therapy. PSs were calculated using a generalized linear regression model based on demographic, clinical, and pathologic features. Patients with and without AT were matched using nearest neighbor method and caliper value 0.05. Subgroup analyses were stratified by PS.

Results: Younger patients with more advanced/poorly differentiated disease were more likely to receive AT (P<0.05). There were 137 matched pairs in the AT/No AT groups. After matching, the AT group tended to have longer median RFS [95% confidence interval (CI): 2.21 years (1.54–3.20)] than the No AT group [1.75 years (1.37–2.21)] (P=0.18). The benefit was significant in patients with PS ≥0.40 [hazard ratio 0.55, 95% CI: 0.32–0.87, median RFS (95% CI): 2.22 years (1.30–3.52) versus 1.23 years (0.90–1.64), P=0.03]. In other PS subgroups, median RFS was similar in AT and No AT groups.

Conclusions: After adjusting for baseline characteristics, AT tended to improve RFS after R0 esophagectomy in Chinese patients, with significant benefit associated with a higher PS score. The utility of PS to guide patient selection for AT in clinical practice needs further investigation.

Keywords: Esophageal cancer; propensity score matching (PS matching); recurrence-free survival (RFS); squamous cell carcinoma; survival

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Introduction

Background

Esophageal cancer is a common, aggressive cancer associated with high mortality (1). Surgery plays a key role in locally advanced disease (2). Nevertheless, recurrence occurs in 38% of patients following radical surgery, with 75% of recurrences occurring within the first 2 years (3). There are marked geographic and ethnic differences in the epidemiology of esophageal cancer (4). Incidence rates are highest in southeast Asian countries and some parts of Africa, and esophageal squamous cell carcinoma (ESCC) predominates over esophageal adenocarcinoma in these regions (5,6).

Esophageal cancer is the fifth most common cause of cancer death in China, resulting in 876,000 deaths annually (7). China accounts for 53% of global cases of ESCC and 18% of esophageal adenocarcinoma (6). Overall 5-year survival [2012–2015] was 27.7% in men and 36.7% in women but is lower (13.3%, both sexes) in patients presenting with stage III–IV disease (8,9). In China, endoscopic screening is routinely conducted in some high-risk areas, defined as having an annual incidence >30 per 100,000 inhabitants (5).

Rationale and knowledge gap

Treatment of ESCC is evolving, with increasing use of neoadjuvant therapy which is now recommended for resectable, locally advanced ESCC (10). This is based on numerous studies showing significant survival benefits after R0 esophagectomy in patients who received neoadjuvant chemotherapy and/or radiation (11-13). The benefits of post-surgical chemotherapy or chemoradiotherapy for patients with ESCC remain unclear. The randomized, controlled, double-blind CheckMate-577 study found that adjuvant nivolumab therapy improved disease-free survival by 33% in patients with stage II or III esophageal or gastroesophageal junction cancer who had received neoadjuvant chemoradiotherapy followed by R0 esophagectomy but had residual pathological disease in the surgical specimen (14). Subsequently, the National Comprehensive Cancer Network in the United States recommends adjuvant chemoradiation for patients with R0 resection who are node positive or node negative with pT3, pT4a adenocarcinoma and who have not received preoperative chemoradiation or chemotherapy (15). No recommendations are provided regarding the use of adjuvant therapy (AT) in ESCC after R0 resection without neoadjuvant therapy in these guidelines. Recent Chinese guidelines note that it is still controversial whether patients with ESCC should accept routine post-operative adjuvant chemotherapy, and that adjuvant chemotherapy or chemoradiation may be considered for patients with stage T4a or N1–3 disease (10). Furthermore, the toxicity of post-operative adjuvant treatment may be substantial, potentially delaying recovery and/or leading to premature discontinuation of treatment (16). Identification of individuals most likely to benefit from AT could help to inform the benefit vs risk for individual patients and aid clinical decision-making.

Highlight box

Key findings

- After adjusting for baseline characteristics, adjuvant therapy improved recurrence-free survival in Chinese patients after R0 esophagectomy.
- Median recurrence-free survival was significantly longer after adjuvant therapy in patients with higher propensity scores.

What is known and what is new?

- Clinical guidelines for post-operative treatment of squamous esophageal cancer are lacking.
- Our study shows that patients with specific characteristics may benefit most from adjuvant therapy.

What is the implication, and what should change now?

- To date, the use of propensity scores as a predictive model is not widespread nor widely accepted. However, in view of the current absence of clinical guidelines for post-operative treatment of esophageal squamous cell carcinoma, the utility of propensity scores as a predictive tool warrants further investigation.

Objective

This study aimed to elucidate the benefits of AT on disease recurrence or death in Chinese patients with ESCC after R0 using a propensity score (PS) matched analyses. We conducted the study during the period when neoadjuvant therapy was not routinely administered for the treatment of patients with esophageal cancer in our department (up until 2019), allowing us to evaluate the impact of AT alone on survival. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-806/rc).

Methods

Study design and data source

This retrospective cohort study included patients who

underwent radical esophagectomy without neoadjuvant therapy between 2013 and 2019 at the Department of Thoracic Surgery, Ruijin Hospital, a top-tier tertiary hospital in China. The database has been maintained by the Department since January 2013 using retrospectively collected data from electronic medical records (EMRs). Each patient in the Department is assigned a unique code for de-identification of their data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional research ethics committee of Shanghai Ruijin Hospital (No. KY2022-29) and individual consent for this analysis was waived due to retrospective nature.

The EMR database contains detailed information about demographic characteristics, body mass index, smoking history (yes/no), history of alcohol use (yes/no), Eastern Cooperative Oncology Group performance status score, baseline comorbidities at surgery (cardiovascular disease, peripheral vascular disease, diabetes, respiratory disease, urinary system disease, chronic kidney disease, digestive disease, mental illness or other), surgery (type and approach, complications, post-operative hospitalization days), AT (yes/no), pathological characteristics (tumor location, size, histology, stage, and grade), and follow-up data including recurrence date and status (yes/no), living status (alive or dead), and date of death, if applicable. The pathologic stage grouping of patients is recorded according to the eighth edition of the American Joint Committee on Cancer Cancer Staging Manual (17). EMR data completeness and accuracy are double checked quarterly by senior surgeons as quality control to ensure the data match existing EMR records for each individual.

Elective esophagectomy was performed according to National Comprehensive Cancer Network guidelines (2). Ivor Lewis or McKeown were the most common approaches, and colon or gastric tubes were used to reconstruct the digestive tract after esophagectomy. The anastomotic mode was performed using stapling or traditional hand sewn techniques.

Patients treated at the department are routinely followed-up through outpatient clinics or phone interview at 6-month intervals for 3 years, and annually thereafter. Patients are followed up from the date of surgery until death from any cause or last follow-up, whichever comes first. Loss to follow-up is defined when patients cannot be contacted through either outpatient visit or phone calls. Reasons for loss to follow-up (such as follow-up refusal, wrong number, or non-existing number) are recorded. Three attempts to contact non-responders by phone are made.

Study population

The study population included all patients aged ≥18 years with pathologically confirmed squamous cell carcinoma (SCC) of the thoracic esophagus who had curative (R0) esophagectomy without neoadjuvant therapy between January 01, 2013 until December 31, 2019. R0 was defined as microscopically complete resection, with a negative margin as a direct contact (0 cm) clearance between the tumor and the surgical margin (18). Patients were excluded if they had adenocarcinoma or other histologic subtypes of esophageal cancer other than ESCC, recurrent or secondary esophageal cancer, multiple tumors, or metastatic disease.

Exposures and outcomes

AT was defined as at least one cycle of chemotherapy or radiotherapy given after esophagectomy, regardless of the regimen, dosage, or method of administration. Adjuvant treatment (yes/no) was identified from the EMRs.

Recurrence-free survival (RFS) was identified from the date of surgery until the first recurrence or death due to any cause, whichever came first. The date of recurrence was recorded from outpatient EMRs or phone interviews. Recurrence was defined as local regional recurrence, lymph node metastasis, or distant metastasis. Recurrence was evaluated by the multidisciplinary team based on thoraco-abdominal computerized tomography, endoscopy with or without biopsy, esophageal barium swallow, positron emission tomography, bone scintigraphy, or fine-needle aspiration cytology as required. Deaths occurring in hospital were identified from EMRs. Out-of-hospital deaths were recorded via phone interviews with relatives as part of routine follow-up. Patients who did not experience recurrence or death during the study period were censored at the time of last follow-up.

Statistical analysis

Demographic and clinicopathological categorical characteristics of patients exposed/not exposed to AT were described by frequencies and percentages. Categorical variables in each group were compared with the Chi-squared or Fisher's exact test, and continuous variables were compared with *t*-test or Mann Whitney *U* test. Missing data were described by reporting the proportion of missing data for that variable and the missing values were not imputed.

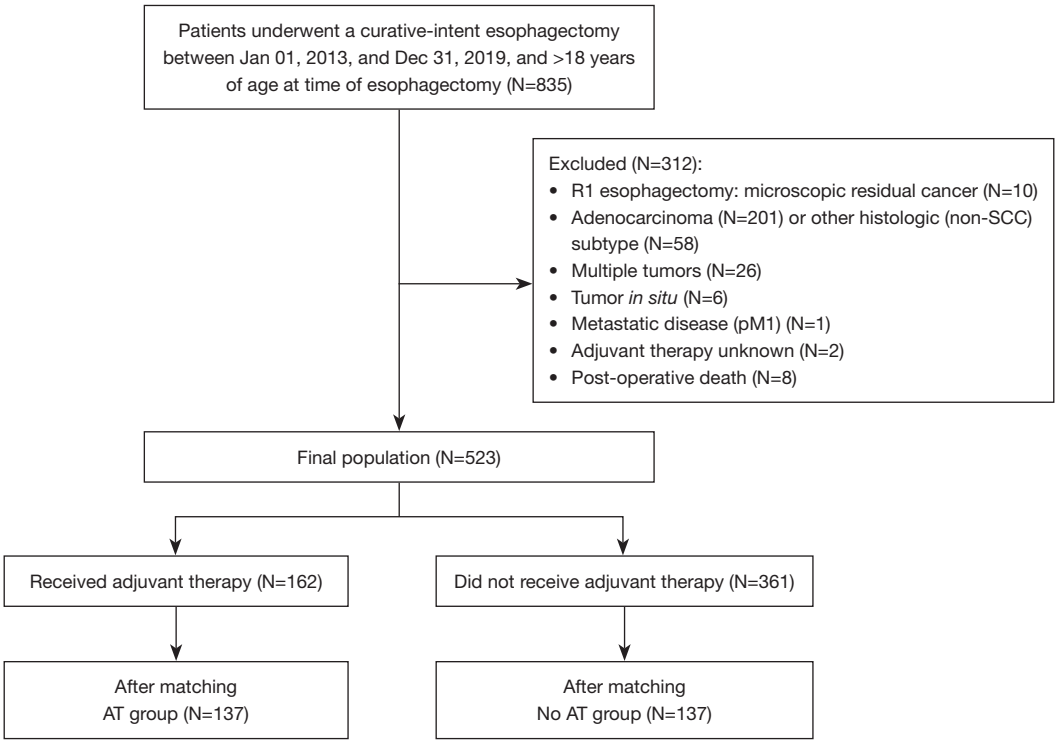


Figure 1 Patient selection. SCC, squamous cell carcinoma; AT, adjuvant therapy.

PSs were calculated using a generalized linear regression model that included 16 potential confounders: age, sex, body mass index, smoking history, alcohol consumption, Eastern Cooperative Oncology Group performance status score, baseline comorbidities, post-operative hospitalization days, tumor location, size, pathological stage T, N, and differentiation grade, surgery type, surgery approach and post-operative complications. Since tumor size is not included in the tumor-node-metastasis (TNM) staging system, we used the mean tumor size of the whole cohort as the cut-off for tumor size.

Patients exposed/not exposed to AT (AT group/No AT group) were matched 1:1 with no replacement using the nearest neighbor method and caliper value 0.05 to evaluate rates of RFS, a composite endpoint including recurrence and death. The caliper was determined as 0.25 standard deviations (SDs) based on the results of Cochran and Rubin (19). Characteristics before and after matching were described. Patients were stratified into four groups based on their PS (<0.20, ≥0.20 to <0.30, ≥0.30 to <0.40, and ≥0.40). Treated and untreated patients within each PS stratum have approximately similar PS values with a similar distribution of baseline variables. Calculating the treatment effect in each PS group allows identification of the subgroup of patient characteristic most likely to be associated with the maximum treatment effect (20).

Kaplan-Meier curves and log-rank tests were used to compare RFS in the AT and No AT groups before and after matching in the overall cohort and in PS subgroups.

Sensitivity analyses were conducted by PS matching of 13 variables (excluding surgical approach, type, and post-operative complications from the original 16 variables) using a caliper of 0.05, and by PS matching of 6 covariates that were significantly associated with AT with caliper 0.01 (age, hospitalization days, size, pathological stage T, N, and differentiation grade).

Results

There were 835 adult patients who underwent esophagectomy for ESCC at our institution (Ruijin Hospital, Shanghai Jiao Tong University School of Medicine) during the study period (*Figure 1*). Of these, 523 patients were enrolled in the study population, of whom 162 (30.9%) received AT and 361 did not. A total of 312 (60.0%) patients experienced recurrence or death over a median follow-up period of

4.15 years (interquartile range, 2.92–4.73 years). In the unmatched cohort, patients who were younger, underwent shorter hospitalization, had larger tumor size, advanced pathological T and N stages, or poorly differentiated tumor, were more likely to receive AT (all P<0.05) (*Table 1*).

After PS matching, 274 patients (137 in each group) were matched from the cohort. The matched AT and No AT groups were similar in terms of demography and clinicopathological characteristics (*Table 1*).

RFS

Before matching, patients in the AT group tended to have shorter RFS compared with patients in the No AT group. Median RFS was 1.84 years [95% confidence interval (CI): 1.51–2.57] in the AT group and 2.67 years (95% CI: 2.35–3.46) in the No AT group (P=0.058) (*Figure 2A*). This trend was reversed after PS matching, whereby median RFS tended to be longer in the AT group (2.21 years, 95% CI: 1.54–3.20) than the No AT group (RFS 1.75 years, 95% CI: 1.37–2.21) (P=0.18) (*Figure 2B*, *Table 2*).

Subgroup analyses

The distribution of PS before and after matching is provided in Figure S1 and shows a marked difference in

Table 1 Characteristics of patients before and after matching

Variables	Before matching							After matching						
	Total (N=523)		No AT (N=361)		AT (N=162)		P	Total (N=274)		No AT (N=137)		AT (N=137)		P
	N	%	N	%	N	%		N	%	N	%	N	%	
Sex														
Male	432	82.6	292	80.89	140	86.42	0.14	237	86.5	121	88.32	116	84.67	0.48
Female	91	17.4	69	19.11	22	13.58		37	13.5	16	11.68	21	15.33	
Age (years)	62.8 (7.9)		64.1 (7.9)		60.2 (7.3)		<0.01	61.5 (7.5)		62.1 (7.9)		60.8 (7.2)		0.14
<65	285	54.49	178	49.31	107	66.05	<0.01	173	63.14	87	63.5	86	62.77	>0.99
≥65	238	45.51	183	50.69	55	33.95		101	36.86	50	36.5	51	37.23	
BMI (kg/m^2)	22.6 (3.0)		22.5 (3.0)		22.8 (3.1)		0.27	22.7 (3.0)		22.4 (2.8)		22.9 (3.1)		0.14
<18.5	40	7.65	28	7.76	12	7.41	0.74	19	6.93	10	7.3	9	6.57	0.62
18.5–24.9	365	69.79	255	70.64	110	67.9		192	70.07	99	72.26	93	67.88	
≥25	118	22.56	78	21.61	40	24.69		63	22.99	28	20.44	35	25.55	
Smoking														
No	274	52.39	192	53.19	82	50.62	0.64	129	47.08	60	43.8	69	50.36	0.33
Yes	249	47.61	169	46.81	80	49.38		145	52.92	77	56.2	68	49.64	
Drinking														
No	323	61.76	233	64.54	90	55.56	0.05	154	56.2	77	56.2	77	56.2	>0.99
Yes	200	38.24	128	35.46	72	44.44		120	43.8	60	43.8	60	43.8	
ECOG score														
0	410	78.39	287	79.5	123	75.93	0.36	208	75.91	103	75.18	105	76.64	0.89
1	113	21.61	74	20.5	39	24.07		66	24.09	34	24.82	32	23.36	
Comorbidity														
No	227	43.4	155	42.94	92	56.79	0.78	118	43.07	59	43.07	59	43.07	>0.99
Yes	296	56.6	206	57.06	90	55.56		156	56.93	78	56.93	78	56.93	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Before matching							After matching						
	Total (N=523)		No AT (N=361)		AT (N=162)		P	Total (N=274)		No AT (N=137)		AT (N=137)		P
	N	%	N	%	N	%		N	%	N	%	N	%	
Hospital days	21.8 (16.9)		24.7 (18.4)		20.7 (13.0)		0.05	21.2 (15.8)		20.6 (13.9)		21.7 (13.7)		0.52
≤18	263	50.29	165	45.71	98	60.49	0.01	147	53.65	72	52.55	75	54.74	0.81
>18	260	49.71	196	54.29	64	39.51		127	46.35	65	47.45	62	45.26	
Approach														
Open	347	66.35	243	67.31	104	64.2	0.49	177	64.6	87	63.5	90	65.69	0.80
Laparoscopic/robot	176	33.65	118	32.69	58	35.8		97	35.4	50	36.5	47	34.31	
Surgery type														
Ivor Lewis	462	88.34	318	88.09	144	88.89	>0.99	241	87.96	121	88.32	120	87.59	>0.99
McKeown	61	11.66	43	11.91	18	11.11		33	12.04	16	11.68	17	12.41	
Post-operative complications														
No	275	52.58	187	51.8	88	54.32	0.64	139	50.73	70	51.09	69	50.36	>0.99
Yes	248	47.42	174	48.2	74	45.68		135	49.27	67	48.91	68	49.64	
Location														
Upper	23	4.4	16	4.43	7	4.32	0.14	12	4.38	6	4.38	6	4.38	0.98
Middle	250	47.8	184	50.97	66	40.74		122	44.53	60	43.8	62	45.26	
Lower	133	25.43	83	22.99	50	30.86		75	27.37	37	27.01	38	27.74	
GEJ	117	22.37	78	21.61	39	24.07		65	23.72	34	24.82	31	22.63	
Tumor size (cm)	3.5 (1.7)		3.3 (1.5)		4.0 (2.1)		<0.01	3.7 (1.8)		3.5 (1.4)		3.8 (2.1)		0.19
≤3.5 cm	313	59.85	232	64.27	81	50	<0.01	152	55.47	77	56.2	75	54.74	0.90
>3.5 cm	210	40.15	129	35.73	81	50		122	44.53	60	43.8	62	45.26	
Stage T														
T1	112	21.41	92	25.48	20	12.35	<0.01	34	12.41	16	11.68	18	13.14	0.99
T2	106	20.27	79	21.88	27	16.67		53	19.34	27	19.71	26	18.98	
T3	298	56.98	186	51.52	112	69.14		181	66.06	91	66.42	90	65.69	
T4	7	1.34	4	1.11	3	1.85		6	2.19	3	2.19	3	2.19	
Stage N														
N0	280	53.54	219	60.66	61	37.65	<0.01	116	42.34	57	41.61	59	43.07	0.97
N1	138	26.39	83	22.99	55	33.95		90	32.85	47	34.31	43	31.39	
N2	71	13.58	42	11.63	29	17.9		42	15.33	20	14.6	22	16.06	
N3	34	6.5	17	4.71	17	10.49		26	9.49	13	9.49	13	9.49	
Differentiation grade														
G1	19	3.63	15	4.16	4	2.47	0.03	6	2.19	3	2.19	3	2.19	0.50
G2	291	55.64	204	56.51	87	53.7		155	56.57	82	59.85	73	53.28	
G3	213	40.73	142	39.34	71	43.83		113	41.24	52	37.96	61	44.53	

Data are presented as mean (standard deviation) or number with percentage. AT, adjuvant therapy; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance score; GEJ, gastroesophageal junction; N/%, number and percentage of patients in the designated category.

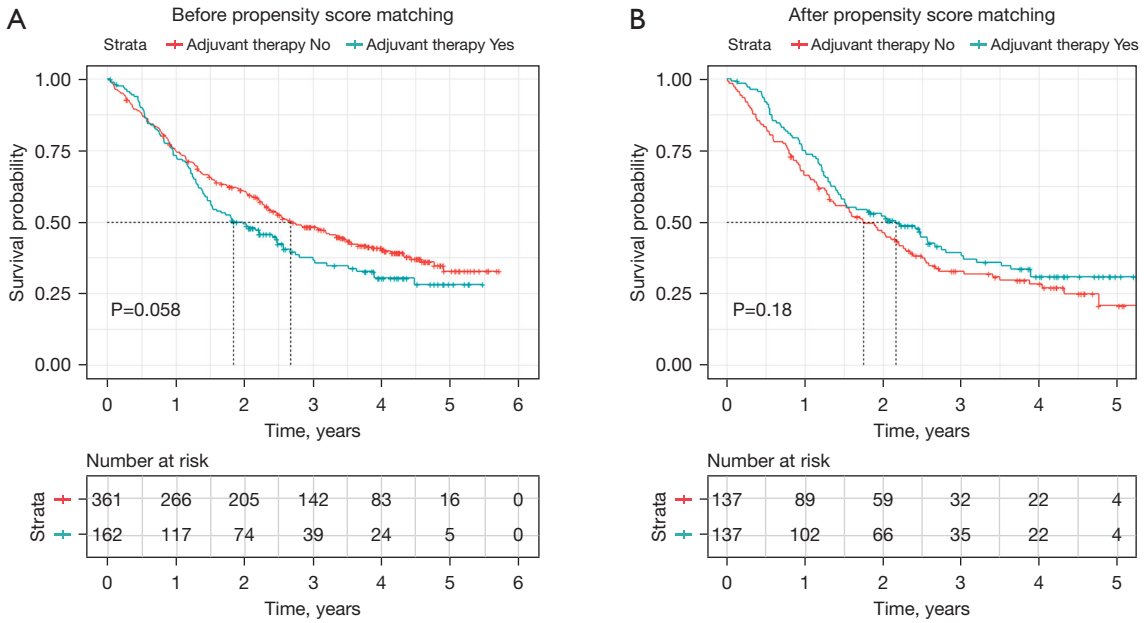


Figure 2 Kaplan-Meier curves (log-rank tests) for recurrence-free survival in patients who did/did not receive adjuvant therapy. (A) Before matching. (B) After matching.

Table 2 Median recurrence-free survival of patients after propensity score matching with 16 variables and caliper 0.1

Variables	Median RFS (95% CI)		HR (95% CI)	P
	AT group	No AT group		
All	2.21 (1.54–3.20)	1.75 (1.37–2.21)	0.79 (0.52–1.17)	0.18
PS subgroups				
PS <0.20	1.52 (1.32–2.09)	1.52 (1.07–1.98)	1.00 (0.68–1.45)	0.38
0.20≤ PS <0.30	2.20 (1.85–2.62)	2.00 (1.43–2.47)	0.91 (0.57–1.32)	0.54
0.30≤ PS <0.40	1.85 (1.45–2.46)	2.11 (1.46–2.56)	1.14 (0.66–1.58)	0.83
PS ≥0.40	2.22 (1.30–3.52)	1.23 (0.90–1.64)	0.55 (0.32–0.87)	0.03

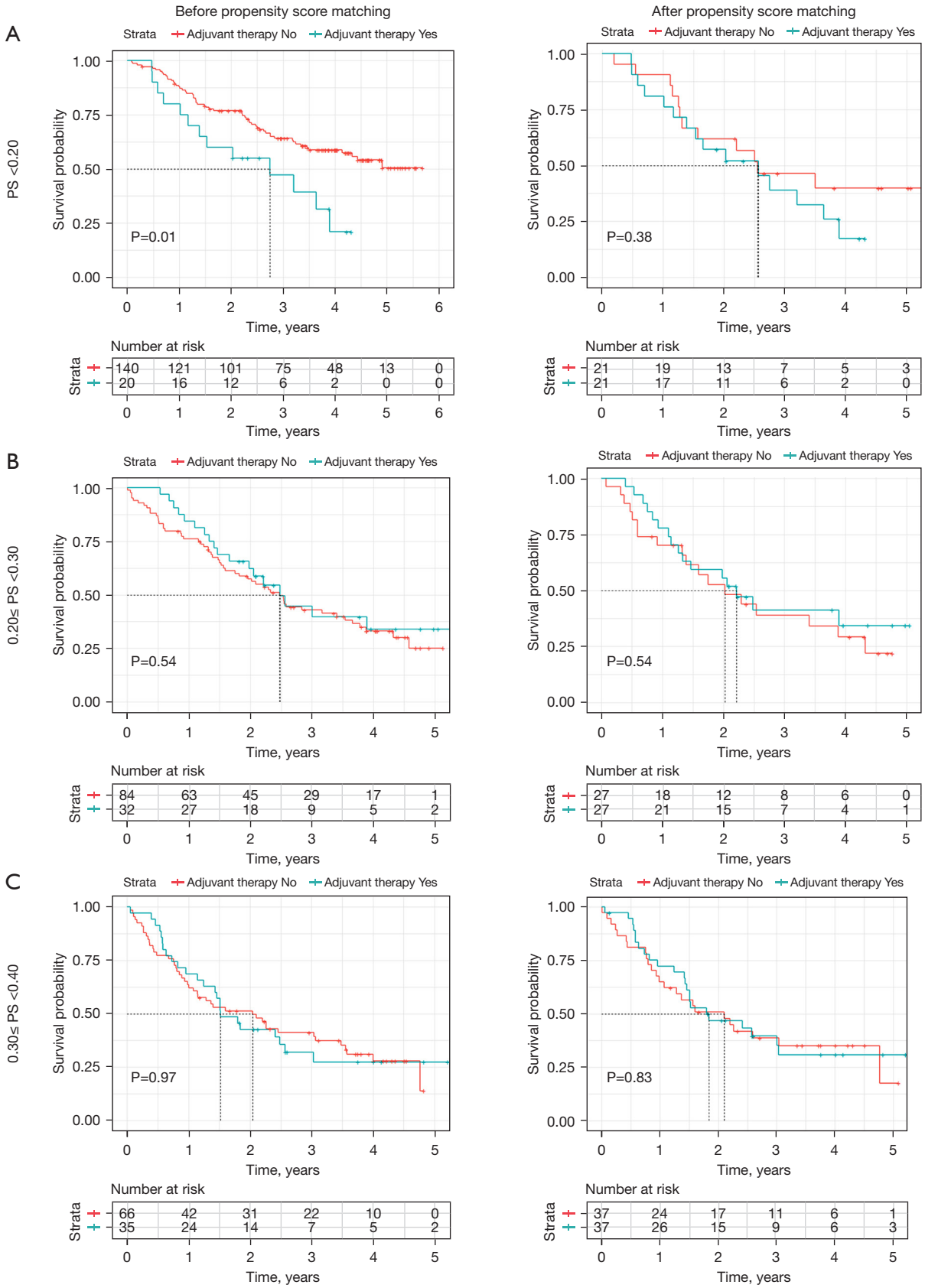
RFS, recurrence-free survival; CI, confidence interval; AT, adjuvant therapy; HR, hazard ratio; PS, propensity score.

baseline characteristics between the AT and No AT groups prior to matching. The mean PS was 0.39 (SD 0.16) for the AT group and 0.27 (SD 0.15) for the No AT group. Patients were grouped into strata according to their PS with the objective of balancing the observed variables between treated and untreated patients within each stratum (21).

In the lower stratum (PS <0.20), RFS was significantly shorter in the AT group than that in the No AT group (P=0.01), but this finding was not present after matching, with similar median RFS in the AT and no AT groups (P=0.38) (*Figure 3A*, *Table 2*). For the middle two strata, median RFS was similar in the AT and No AT groups before and after matching. (*Figure 3B*,*3C*, *Table 2*). The benefit of AT on RFS was significant in the highest PS stratum ≥0.40. In this stratum, the median RFS in the AT group was 2.22 years (95% CI: 1.30–3.52) versus 1.23 years (95% CI: 0.90–1.64) in the No AT group (hazard ratio 0.55, 95% CI: 0.32–0.87; P=0.03) (*Figure 3D*, *Table 2*). Demographic and disease features of patients in the PS ≥0.40 subgroups are given in Table S1.

Sensitivity analyses

Decreasing the number of matched variables to 13 and the



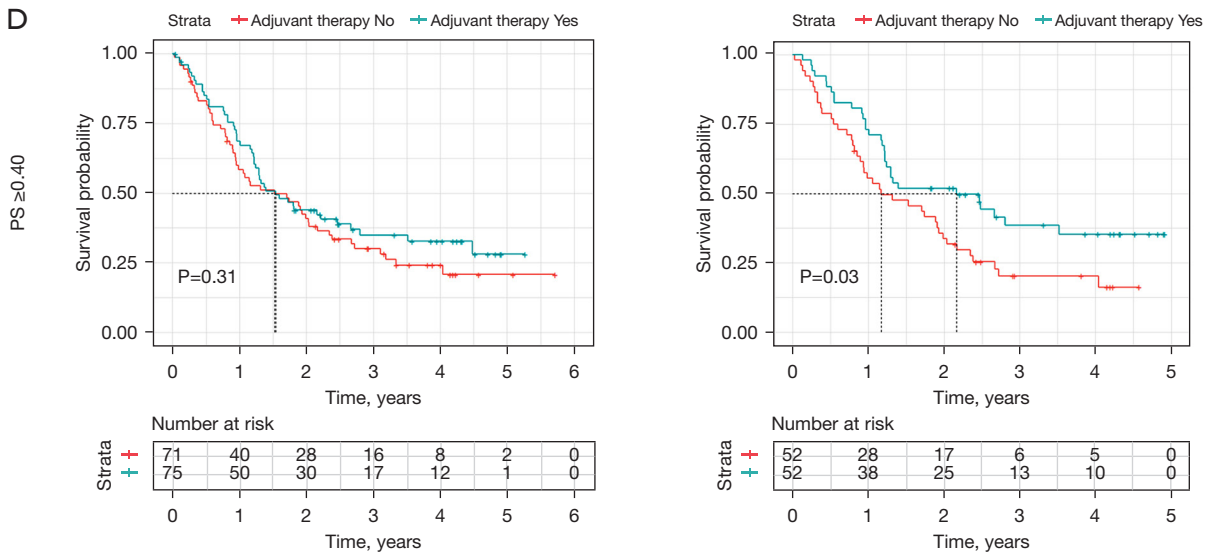


Figure 3 Kaplan-Meier curves (log-rank tests) for recurrence-free survival in patients who did/did not receive adjuvant therapy by PS stratum. (A) PS <0.20. (B) 0.20≤ PS <0.30. (C) 0.30≤ PS <0.40. (D) PS ≥0.40. PS, propensity score.

caliper to 0.05 decreased the number of matched subjects to 126 (Table S2). The results from the sensitivity analysis were similar to the main analysis (Figures S2,S3). Median RFS was significantly longer in the AT group compared to the No AT group (P=0.02) (Figure S4), especially in the subgroup of patients with a PS ≥0.40 (P=0.01) (Figure S3).

Limiting the matched variables to 6 factors found to be significantly associated with the use of AT (caliper =0.01) reduced the number of matched subjects to 123 (Table S3, Figure S5). Median RFS tended to be longer in the AT group compared to the No AT group (P=0.09) (Figure S6). In the subgroup analysis, RFS was significantly lower in the AT group than the No AT group in patients with a PS <0.20 (P=0.003) (Figure S7A). However, median RFS was longer in the AT group in other subgroups (Figure S7B-S7D) and showed statistical significance in the subgroup of patients with a PS ≥0.40 (P=0.02) (Figure S7D).

Discussion

Key findings

Younger patients with more advanced/poorly differentiated disease were more likely to receive AT (P<0.05). After adjusting for baseline characteristics, AT improved RFS in Chinese patients after R0 esophagectomy. The benefit was significant in patients with PS with the highest PSs. In other PS subgroups, median RFS was similar in AT and No AT groups.

Strengths and limitations

Strengths of the study are that we used a prospectively maintained database that captured patient information from routine clinical practice in a real-world setting. Patients are routinely followed up at regular intervals by the department, capturing long term outcomes that occurred out of hospital. Data in the database are structured and standardized with prespecified rules with a high level of completeness and few missing values.

Potential study limitations were the retrospective design that could be associated with information or selection bias. Although PS matching minimized selection bias, residual selection bias from unmeasured/unknown confounders could not be excluded. Our study was conducted at a single center and the results may not be generalizable to high-risk regions in China or to other countries where the epidemiology and treatment of esophageal cancer may be different. We had limited capacity for PS prediction and our findings need to be validated in other hospital settings and databases considering selection processes of patients for AT might be different. Finally, information of the type of AT administered (including immunotherapy) was not available in the database, and we were unable to assess the independent contributions of adjuvant chemotherapy versus radiotherapy due to limited sample size.

Comparison with similar researches

Our results point to a benefit of AT for some patients with ESCC after R0 esophagectomy and could contribute to clinical decision making for these patients. Nevertheless, the benefit of AT in patients with ESCC remains controversial and data from previous randomized trials and observational studies are not conclusive. A meta-analysis of 19 randomized controlled trials of patients with ESCC found that adjuvant chemoradiotherapy did not significantly improve overall survival compared to surgery alone (22). Another meta-analysis of 32 studies involving 7,985 patients found that neoadjuvant therapy provided a significant overall survival advantage compared to surgery alone and compared to surgery with AT, whereas there was no benefit of AT compared to surgery alone (23). Specifically for ESCC, AT after surgery versus surgery alone provided minimal survival advantage (hazard ratio 0.85, 95% CI: 0.70–1.3, P=0.10) (23). On the other hand, a later, randomized trial in China reported a significant benefit of AT in patients with stage IIB–III ESCC. Median disease-free survival was 48.3 months in subjects who received adjuvant radiotherapy or chemoradiotherapy, versus 17.5 months in the surgery alone group (24).

An observational study of 4,129 patients with ESCC conducted in a high-risk region of China concluded that patients with N1+ disease benefited from AT and surgery versus surgery alone, whereas there was no improvement for patients with stage N0 (25). Observational studies conducted in Chinese hospitals that employed PS matching have reported that AT decreased disease-free survival in patients with ESCC who had received neoadjuvant chemoradiotherapy (26), whereas another study showed that adjuvant chemotherapy significantly improved disease-free survival in patients with ESCC with N1 stage and with tumor <4.5 cm (27). Comparison of the results is hampered by confounding factors that appear to contribute to outcome, such as the use of neoadjuvant therapy, the type of AT employed, and the disease stage. Additionally, the contribution of regional differences in genetic polymorphisms on treatment response in ESCC is not currently known (28).

Explanations of findings

Patients with R0 esophagectomy for ESCC were more likely to receive AT if they had tumor size >3.5 cm, advanced pathological T and N stages, poorly differentiated tumors, and if they were younger and had spent fewer days in hospital, possibly reflecting generally improved fitness compared to older, potentially frailer patients. Prior to matching, the AT group tended to have shorter RFS compared with the No AT group. Given the potential confounding factors that strongly predict the likelihood of receiving adjuvant treatment, PS matching allowed us to estimate the treatment effect in patients with similar baseline characteristics. After matching, median RFS tended to be longer in the AT group and was significantly longer in the AT group with a higher PS score ≥0.40.

Our results suggest that AT could potentially provide a disease recurrence benefit to patients with ESCC, particularly the subgroup of patients with a higher PS score, which indicated an increased likelihood of treatment. This suggests that selection of patients with AT at our institution is based on surgeons' knowledge of the characteristics of patients who could potentially benefit from AT. However, there is no quantitative guidance for surgeons on how to select patients for AT. Our study provides a measurement based on PS score that could be used to guide selection of patients who may be expected to benefit from AT.

Despite the absence of significant clinical benefit of AT for the general population of patients with ESCC, we observed a highly statistically and clinically significant improvement in median RFS in the subgroup of patients with a PS ≥0.40. Patients in the AT group with a PS ≥0.40 appeared to be in overall better health than the No AT group, suggested by fewer comorbidities and fewer days in hospital. More patients in the AT group underwent an Ivor Lewis procedure in our cohort, which has been associated with improved patient outcomes compared to the McKeown procedure in Chinese patients (29). Of note, there were 34 patients in the AT group with a PS ≥0.40 who could not be matched. This was mainly due to patients in the AT group with very high PS scores were more likely to be indicated for AT and therefore could not be matched with No AT patients with similar characteristics.

Only two patients in the matched AT and No AT groups had a PS >0.6. Our results are thus applicable to patients with PS ≤0.6. A larger sample size is needed to assess the benefits of AT in patients with PS >0.6.

Our study suggests that a constellation of clinical and disease features could be used as a clinical tool to guide clinicians and patients in the decision whether to use AT in ESCC. Younger age, shorter hospitalization, larger tumor size, advanced tumor stages and poor grade were associated with AT use in the real-world setting, and these characteristics were even more pronounced in the cohort of patients with a PS ≥0.40. These results suggest that PS matching could

function as a tool to aid clinicians to select the best candidates for AT after R0 esophagectomy. As yet, the use of PS as a predictive model is not widespread nor widely accepted (30,31); however given the current absence of clinical guidelines for post-operative treatment of ESCC, the utility of PS as a predictive tool warrants further investigation.

Implications and actions needed

Further studies on PS prediction models are needed to assess their appropriateness as an index to guide patient selection for AT in clinical practice.

Conclusions

In conclusion, in real-world practice AT is targeted towards patients with aggressive/advanced disease, who are younger and who have spent fewer days in hospital, possibly reflecting increased fitness ability to tolerate adjuvant treatment. After adjusting for baseline characteristics, AT improved RFS in Chinese patients after R0 esophagectomy.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-806/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional research ethics committee of Shanghai Ruijin Hospital (No. KY2022-29) and individual consent for this analysis was waived due to retrospective nature.

References

1. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19:5598-606.
2. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. Lancet 2013;381:400-12.
3. Lou F, Sima CS, Adusumilli PS, et al. Esophageal cancer recurrence patterns and implications for surveillance. J Thorac Oncol 2013;8:1558-62.
4. Hongo M, Nagasaki Y, Shoji T. Epidemiology of esophageal cancer: Orient to Occident. Effects of chronology, geography and ethnicity. J Gastroenterol Hepatol 2009;24:729-35.
5. Domper Arnal MJ, Ferrández Arenas Á, Lanas Arbeloa Á. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol 2015;21:7933-43.
6. Grille VJ, Campbell S, Gibbs JF, et al. Esophageal cancer: the rise of adenocarcinoma over squamous cell carcinoma in the Asian belt. J Gastrointest Oncol 2021;12:S339-49.
7. International Agency for Research on Cancer. Globocan 2020. Cancer Today. Available online: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=935_900_160&key=asr&sex=1&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=0&include_nmsc_other=1#collapse-group-0-3. Accessed February 27, 2023.
8. Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health 2018;6:e555-67.
9. He Y, Quaresma M, Dos-Santos-Silva I. Stage-Specific Survival From Esophageal Cancer in China and Implications for Control Strategies: A Systematic Review and Meta-Analyses. Gastro Hep Adv 2023;2:426-37.
10. Health Commission Of The People's Republic Of China N. National guidelines for diagnosis and treatment of esophageal carcinoma 2022 in China (English version). Chin J Cancer Res 2022;34:309-34.
11. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
12. Yang H, Liu H, Chen Y, et al. Long-term Efficacy of Neoadjuvant Chemoradiotherapy Plus Surgery for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: The NEOCRTEC5010 Randomized Clinical Trial. JAMA Surg 2021;156:721-9.
13. Ando N, Kato H, Igaki H, 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.
14. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med 2021;384:1191-203.
15. NCCN Guidelines for esophageal and esophagogastric cancer; V4.2024, July 30, 2024. Available online: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
16. Matsuda S, Kawakubo H, Mayanagi S, et al. Surgery and adjuvant therapy after esophagectomy. Ann Esophagus 2021;4:17.
17. AJCC Cancer Staging Manual eighth edition. Amin MB, editor. American College of Surgeons, Chicago, IL; 2018.
18. Ajani JA, Barthel JS, Bentrem DJ, et al. Esophageal and esophagogastric junction cancers. J Natl Compr Canc Netw 2011;9:830-87.
19. Cochran WG, Rubin DB. Controlling bias in observational studies: A review. Sankhya: The Indian Journal of Statistics, Series A 1973;35:417-46.
20. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res 2011;46:399-424.
21. Benedetto U, Head SJ, Angelini GD, et al. Statistical primer: propensity score matching and its alternatives. Eur J Cardiothorac Surg 2018;53:1112-7.
22. Ma Z, Yuan M, Bao Y, et al. Survival of Neoadjuvant and Adjuvant Therapy Compared With Surgery Alone for Resectable Esophageal Squamous Cell Carcinoma: A Systemic Review and Network Meta-Analysis. Front Oncol 2021;11:728185.
23. Xiao X, Hong HG, Zeng X, et al. The Efficacy of Neoadjuvant Versus Adjuvant Therapy for Resectable Esophageal Cancer Patients: A Systematic Review and Meta-Analysis. World J Surg 2020;44:4161-74.
24. Ni W, Yu S, Xiao Z, et al. Postoperative Adjuvant Therapy Versus Surgery Alone for Stage IIB-III Esophageal Squamous Cell Carcinoma: A Phase III Randomized Controlled Trial. Oncologist 2021;26:e2151-60.

25. Yang W, Liu F, Xu R, et al. Is Adjuvant Therapy a Better Option for Esophageal Squamous Cell Carcinoma Patients Treated With Esophagectomy? A Prognosis Prediction Model Based on Multicenter Real-World Data. Ann Surg 2023;277:e61-9.
26. Li X, Luan S, Yang Y, et al. Trimodal Therapy in Esophageal Squamous Cell Carcinoma: Role of Adjuvant Therapy Following Neoadjuvant Chemoradiation and Surgery. Cancers (Basel) 2022;14:3721.
27. Qin RQ, Wen YS, Wang WP, et al. The role of postoperative adjuvant chemotherapy for lymph node-positive esophageal squamous cell carcinoma: a propensity score matching analysis. Med Oncol 2016;33:31.
28. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. Chin J Cancer 2012;31:281-6.
29. Wang J, Hu J, Zhu D, et al. McKeown or Ivor Lewis minimally invasive esophagectomy: a systematic review and meta-analysis. Transl Cancer Res 2020;9:1518-27.
30. Wyss R, Ellis AR, Brookhart MA, et al. The role of prediction modeling in propensity score estimation: an evaluation of logistic regression, bCART, and the covariate-balancing propensity score. Am J Epidemiol 2014;180:645-55.
31. Nowacki AS, Wells BJ, Yu C, et al. Adding propensity scores to pure prediction models fails to improve predictive performance. PeerJ 2013;1:e123.

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