Survival and recurrence characteristics of patients with esophageal cancer with a pathological complete response after neoadjuvant immunochemotherapy followed by surgery: A multicenter propensity score matching study

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Abstract. The relationship between pathological complete response (pCR) and survival as well as recurrence characteristics in patients with locally advanced esophageal squamous cell carcinoma (ESCC) undergoing neoadjuvant immunochemotherapy has not been frequently investigated. The present study primarily examined the survival and recurrence patterns of pCR in these patients. Data were collected from 300 individuals diagnosed with stage II-III ESCC who underwent neoadjuvant immunochemotherapy followed by surgery across four medical centers between 2019 and 2024. The Cox proportional hazards model and the Kaplan-Meier method with propensity score matching (PSM) were utilized for survival analysis to examine the relationship between pCR and overall survival (OS) and recurrence-free survival (RFS). The recurrence patterns among patients were evaluated. Of the 300 patients included in the present study, 80 achieved a pCR. Univariate and multivariate analyses utilizing the Cox proportional hazards model demonstrated that pCR was a statistically significant prognostic factor for OS and RFS (P<0.05). Utilizing PSM based on the achievement of pCR, survival analysis conducted using the Kaplan-Meier method and log-rank test demonstrated that patients in the pCR group exhibited significantly improved RFS (P<0.05). However, no statistically significant difference was observed in OS (P>0.05). The recurrence rate in the pCR group was 11.2%, with a local recurrence rate of 7.5% and a distant recurrence rate of 3.7%. Both rates were significantly decreased compared with those in the non-pCR group (P<0.05). The mediastinal lymph node represented the most common site of recurrence in both groups. In patients with ESCC undergoing neoadjuvant immunochemotherapy, pCR indicated improved OS and RFS; however, the association between pCR and OS was not statistically significant. Concurrently, pCR was associated with reduced local and distant recurrence rates, and the recurrence pattern of patients in the pCR group differed from that of patients in the non-pCR group. Future research should involve larger sample sizes to elucidate the relationship between pCR and survival, as well as its influence on recurrence patterns.

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Abbreviations: ESCC, esophageal squamous cell carcinoma; pCR, pathological complete response; PSM, propensity score matching; OS, overall survival; RFS, recurrence-free survival; CT, computed tomography

Key words: esophageal cancer, neoadjuvant therapy, immunochemotherapy, pCR, OS, RFS, recurrence pattern

Introduction

Esophageal cancer is a prevalent upper digestive tract tumor, currently ranking seventh in terms of incidence and sixth in terms of mortality among all tumor types globally (1). In Asia, esophageal squamous cell carcinoma (ESCC) is the predominant pathological type of esophageal cancer, accounting for ~90% of all malignant tumors of the esophagus (2). Early esophageal cancer typically lacks specific symptoms, resulting

in most patients seeking medical treatment at mid-to-late stages. Currently, the main surgical methods for esophageal cancer include the Sweet procedure with a single incision on the left thoracotomy, the Ivor-Lewis procedure with two incisions on the right thoracotomy and abdomen, and the McKeown procedure with three incisions on the neck, right thoracotomy and abdomen. Those with surgically resectable esophageal cancer are primarily diagnosed with locally advanced disease (3). According to the findings of the NEOCRTEC5010 and CROSS trials, chemoradiotherapy is regarded as the standard treatment approach for these patients (4,5).

The emergence of immunotherapy has led to numerous clinical studies demonstrating its efficacy in the treatment of various tumors, including esophageal cancer (6-8). The KEYNOTE-590 study showed that immunotherapy combined with chemotherapy could improve the overall survival (OS) of patients with ESCC (9). The KEYNOTE-590 study demonstrated that the combination of immunotherapy and chemotherapy improved OS in patients with ESCC (10,11). Preoperative radiotherapy may increase perioperative complications and complicate surgical procedures. By contrast, neoadjuvant immunochemotherapy exhibits therapeutic efficacy comparable to that of neoadjuvant immunotherapy combined with chemoradiotherapy (12-14). Physicians have increasingly adopted neoadjuvant immunochemotherapy as a treatment for locally advanced ESCC, and the combination of platinum plus paclitaxel chemotherapy with immunotherapy drugs such as nivolumab, pembrolizumab, camrelizumab and sintilimab is currently widely used (15-17).

Pathological complete response (pCR) is characterized by the absence of histological evidence of tumor in the surgical resection specimen (18). Numerous studies have indicated that patients achieving pCR exhibit improved OS and recurrence-free survival (RFS) (19,20). Consequently, pCR has been utilized as a key indicator to assess the efficacy of neoadjuvant therapy in various clinical trials (19-21). Theoretically, patients achieving pCR may be cured; however, ~30% of these patients experience recurrence within 2 years post-surgery (19,21,22). Neoadjuvant immunochemotherapy has been gradually implemented as a treatment for ESCC over the past decade (10-14). Consequently, there is a lack of multicenter studies investigating the relationship between pCR and prognosis, as well as recurrence patterns in this patient population. The present study included data from 300 patients across four esophageal cancer treatment centers to investigate the impact of pCR on the prognosis and recurrence patterns in patients with ESCC undergoing neoadjuvant immunochemotherapy.

Materials and methods

Selection of patients. The present study included 300 patients diagnosed with locally advanced esophageal cancer, all of whom underwent surgical treatment across four medical centers between December 2019 and April 2024. The four medical centers were the Beijing Chest Hospital (Beijing, China), National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital (Shenzhen, China), Shaanxi Provincial People's Hospital (Xi'an, China) and Anyang Tumor Hospital (Anyang, China). The present study was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital (approval no. YW2024-3-1), Anyang Tumor Hospital (approval no. 2023YP18H01), Shaanxi Provincial People's Hospital (approval no. 2023K-S129) and Beijing Chest Hospital (approval no. 2023-ky-59). The patients provided written informed consent to participate.

The inclusion criteria were as follows: i) Histological confirmation of ESCC through endoscopic biopsy before treatment; ii) preoperative clinical stage of T1b-2N1-3M0 or T3-4aN0-3M0 (patients with T1b-2N0M0 do not receive neoadjuvant therapy due to the early stage of disease, while patients with TxNxM1 do not undergo surgical treatment due to distant metastasis); and iii) all patients underwent esophagectomy following neoadjuvant immunochemotherapy. The criteria for exclusion were: i) Patients who died within 30 days following surgery; ii) patients who did not achieve radical resection verified by postoperative pathology; iii) patients without differentiation information in the postoperative pathology report; and iv) history of radiotherapy before surgery. The case selection process is illustrated in Fig. 1. The biopsy and postoperative pathological findings for all patients were validated by two experienced pathologists. The TNM staging was based on the 8th edition of the American Joint Committee on Cancer staging manual for esophageal cancer (23).

Treatment and follow-up. Pre-treatment diagnosis and clinical staging were conducted, encompassing endoscopy, enhanced computed tomography (CT) scans and Doppler ultrasound of the neck. Positron emission tomography (PET) scans were performed when deemed necessary. All patients in the present study were evaluated by a multidisciplinary team (MDT) consisting of specialists in surgery, oncology, pathology, radiology and radiotherapy. Decisions concerning the neoadjuvant therapy regimen, surgical timing and method, and postoperative adjuvant therapy were determined after an MDT discussion. The surgical techniques included the Ivor-Lewis or McKeown procedures with thoracic and abdominal lymph node dissection. In instances of suspected lymph node metastasis in the neck, three-field lymphadenectomy was regarded as a viable option. The Sweet surgery was indicated exclusively for patients with esophagogastric junction cancer and those who were unsuitable for right-sided thoracotomy.

Patients receiving neoadjuvant therapy should undergo a re-evaluation of the neck, chest and abdomen using enhanced CT 3-4 weeks after the second cycle of treatment. In the first 2 years, patients were scheduled for follow-up visits at 3-month intervals, after which the frequency was reduced to once a year. Subsequent evaluations included enhanced CT scans of the head, neck and chest, in addition to hematological analyses. Endoscopy, bone scans, ultrasound examinations and PET-CT were performed as indicated when necessary.

Statistical analysis. The χ^2 test and Fisher's exact test were applied to compare characteristics among groups. The Kaplan-Meier method was utilized to estimate OS and RFS, and the log-rank test was used to compare survival outcomes between groups. The Cox proportional hazards model was selected for regression analysis, incorporating

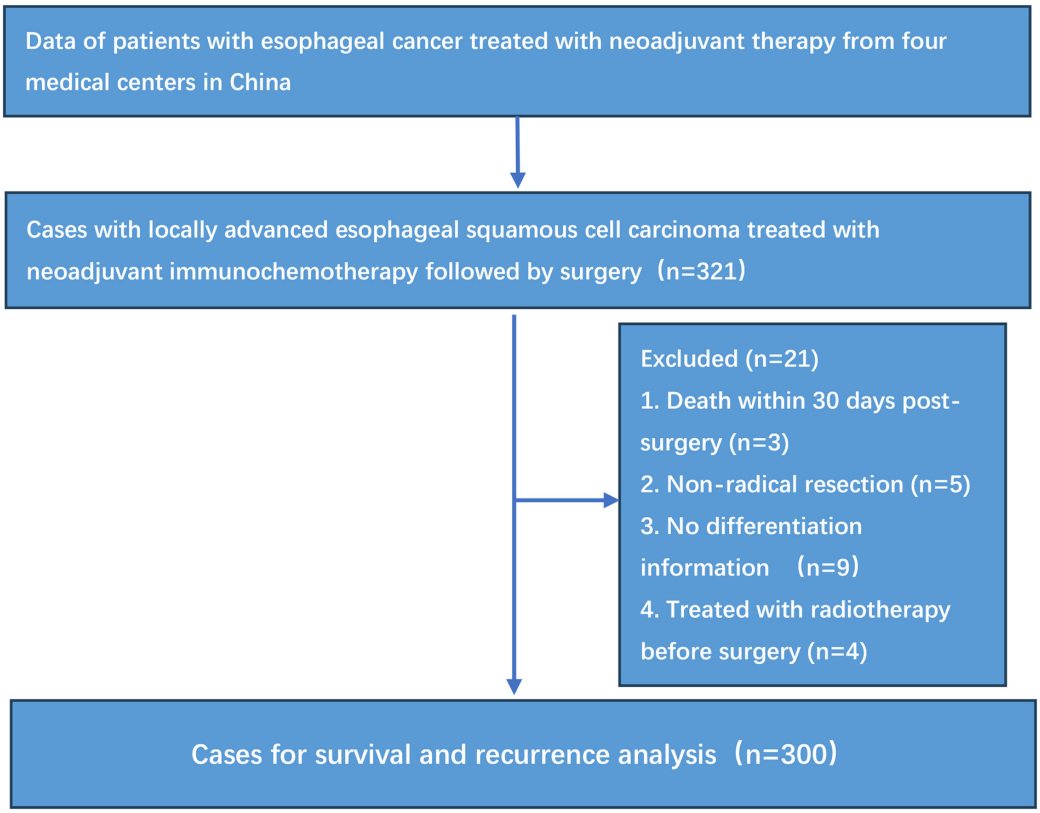

Figure 1. Flow diagram of case selection.

variables with a P-value <0.1 from the univariate analysis into the multivariate analysis. Propensity score matching (PSM) was employed to reduce data bias and confounding variables, with a caliper value set at 0.05 for the analysis. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using R software (version 4.4.3; Posit Software, PBC), utilizing the 'survminer' (version 0.5.0; https://rpkgs.datanovia.com/survminer/index.html) and 'survival' (version 3.8-3; https://github.com/therneau/survival) packages for survival analysis and the visualization of survival curves and forest plots. The 'matchit' (version 4.7.2; https://kosukeimai.github.io/MatchIt) package enabled PSM. Pie charts were generated utilizing the 'ggplot2' (version 3.5.2; https://ggplot2.tidyverse.org) package. The optimal cut-off value for age was established using the X-tile software (version 3.6.1; https://medicine.yale.edu/lab/rimm/research/software).

Results

Baseline characteristics. Of the 300 patients included in the present study, 80 achieved pCR, whereas 220 did not (Table I). The median age was 67 and a significant proportion (67.3%) of the participants were aged ≥63 years. Furthermore, ~68.3% of the patients were male. Most patients (61.3%) had a BMI ranging between 18.5 and 23.9, which indicated that they were primarily classified as normal weight. Patients with a history of smoking, alcohol consumption and a family history of cancer constituted 42.0, 33.7 and 27.7% of the study population, respectively. The majority of patients were categorized as stage III, with 55.0% presenting with moderately differentiated tumors. Furthermore, ~84.7% of the cases exhibited tumors with a length of ≥4 cm. Additionally, ~86.0% of patients underwent 1-2 cycles of neoadjuvant immunochemotherapy, whereas only 14.0% received ≥3 cycles of neoadjuvant treatment. Furthermore, ~87.7% of patients underwent the McKeown procedure, 8.6% received the Ivor-Lewis procedure and 3.7% underwent the Sweet procedure, with ~71.0% of cases treated with minimally invasive surgery.

Prognostic factor analysis. Univariate analysis was performed on all 300 patients, employing the Cox proportional hazards regression model (Table II). The P-values for two variables, differentiation and pCR, were <0.1 for OS. The P-values for five variables (age, sex, differentiation, cycles of neoadjuvant therapy and pCR) were all <0.1 for RFS. The aforementioned variables were integrated into the multivariate analysis (OS, Fig. 2; RFS, Fig. 3). The results of the multivariate analysis for OS demonstrated that only pCR reached statistical significance (P<0.05). In the context of RFS, age, sex, cycles of neoadjuvant therapy and pCR were identified as statistically significant prognostic factors (P<0.05).

Survival analysis after PSM. To reduce bias, 1:1 PSM was conducted on all included cases. All variables included in the present study, except pCR, were used to calculate the propensity score. A total of 80 cases were included in the matched dataset, with no statistical differences observed in the distribution of all variables between the pCR and non-pCR group after PSM. Before PSM, the propensity scores of the unmatched treated group (pCR cases) were mostly concentrated in the >0.6 range, while the propensity scores of the unmatched control group (non-pCR

Table I. Baseline characteristics of original and matched datasets.

	Original dataset				Matched dataset			
Variable	Total (n=300)	Non-pCR (n=220)	pCR (n=80)	P-value	Total (n=80)	Non-pCR (n=40)	pCR (n=40)	P-value
Age, years				0.510				1.000
≤63	98 (32.7)	69 (31.4)	29 (36.2)		31 (38.8)	15 (37.5)	16 (40.0)	
>63	202 (67.3)	151 (68.6)	51 (63.7)		49 (61.3)	25 (62.5)	24 (60.0)	
Sex				0.147				0.811
Female	95 (31.7)	64 (29.1)	31 (38.8)		26 (32.5)	14 (35.0)	12 (30.0)	
Male	205 (68.3)	156 (70.9)	49 (61.3)		54 (67.5)	26 (65.0)	28 (70.0)	
BMI				0.880				0.451
<18.5	26 (8.67)	18 (8.18)	8 (10.0)		12 (15.0)	4 (10.0)	8 (20.0)	
18.5-23.9	184 (61.3)	136 (61.8)	48 (60.0)		44 (55.0)	23 (57.5)	21 (52.5)	
≥24	90 (30.0)	66 (30.0)	24 (30.0)		24 (30.0)	13 (32.5)	11 (27.5)	
Smoker				0.412				1.000
No	174 (58.0)	124 (56.4)	50 (62.5)		52 (65.0)	26 (65.0)	26 (65.0)	
Yes	126 (42.0)	96 (43.6)	30 (37.5)		28 (35.0)	14 (35.0)	14 (35.0)	
Alcohol consumption				0.692				0.621
No	199 (66.3)	144 (65.5)	55 (68.8)		57 (71.2)	30 (75.0)	27 (67.5)	
Yes	101 (33.7)	76 (34.5)	25 (31.2)		23 (28.7)	10 (25.0)	13 (32.5)	
Family history				1.000				0.274
No	217 (72.3)	159 (72.3)	58 (72.5)		63 (78.8)	34 (85.0)	29 (72.5)	
Yes	83 (27.7)	61 (27.7)	22 (27.5)		17 (21.2)	6 (15.0)	11 (27.5)	
Differentiation				<0.001				0.848
Well	91 (30.3)	30 (13.6)	61 (76.2)		47 (58.8)	23 (57.5)	24 (60.0)	
Moderate	165 (55.0)	156 (70.9)	9 (11.2)		16 (20.0)	9 (22.5)	7 (17.5)	
Poor	44 (14.7)	34 (15.5)	10 (12.5)		17 (21.2)	8 (20.0)	9 (22.5)	
Length, cm				0.655				1.000
<4	46 (15.3)	32 (14.5)	14 (17.5)		13 (16.2)	6 (15.0)	7 (17.5)	
≥4	254 (84.7)	188 (85.5)	66 (82.5)		67 (83.8)	34 (85.0)	33 (82.5)	
cTNM				0.244				0.348
II	36 (12.0)	23 (10.5)	13 (16.2)		12 (15.0)	8 (20.0)	4 (10.0)	
III	264 (88.0)	197 (89.5)	67 (83.8)		68 (85.0)	32 (80.0)	36 (90.0)	
No. of cycles of neoadjuvant therapy				0.625				1.000
1-2	258 (86.0)	191 (86.8)	67 (83.8)		65 (81.2)	33 (82.5)	32 (80.0)	
≥3	42 (14.0)	29 (13.2)	13 (16.2)		15 (18.8)	7 (17.5)	8 (20.0)	
Surgery				0.041				0.755
McKeown	263 (87.7)	193 (87.7)	70 (87.5)		68 (85.0)	33 (82.5)	35 (87.5)	
Ivor Lewis	26 (8.6)	16 (7.3)	10 (12.5)		12 (15.0)	7 (17.5)	5 (12.5)	
Sweet	11 (3.7)	11 (5.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Approach				0.287				0.439
Minimally invasive	213 (71.0)	152 (69.1)	61 (76.2)		60 (75.0)	32 (80.0)	28 (70.0)	
Open	87 (29.0)	68 (30.9)	19 (23.8)		20 (25.0)	8 (20.0)	12 (30.0)	

Data are presented as n (%). pCR, pathological complete response.

cases) were mostly concentrated in the <0.2 range. However, after PSM, the propensity scores of the matched treated group (pCR cases) and the matched control group (non-pCR cases) were distributed within the same intervals; the propensity scores of

Table II. Univariate analysis of OS and RFS before propensity score matching.

		OS		RFS	
Variable	Total (n=300)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years			0.125		0.061
≤63	98 (32.7)	Reference		Reference	
>63	202 (67.3)	1.50 (0.89-2.54)		1.55 (0.98-2.47)	
Sex			0.208		0.011
Female	95 (31.7)	Reference		Reference	
Male	205 (68.3)	1.40 (0.83-2.36)		1.88 (1.14-3.08)	
BMI			0.812		0.141
<18.5	26 (8.67)	Reference		Reference	
18.5-23.9	184 (61.3)	1.00 (0.43-2.34)		1.27 (0.54-2.95)	
≥24	90 (30.0)	0.84 (0.34-2.10)		1.85 (0.78-4.40)	
Smoker			0.469		0.246
No	174 (58.0)	Reference		Reference	
Yes	126 (42.0)	1.19 (0.75-1.89)		1.27 (0.85-1.91)	
Alcohol consumption			0.126		0.144
No	199 (66.3)	Reference		Reference	
Yes	101 (33.7)	1.44 (0.90-2.30)		1.36 (0.90-2.06)	
Family history			0.468		0.381
No	217 (72.3)	Reference		Reference	
Yes	83 (27.7)	1.20 (0.73-1.99)		1.22 (0.78-1.89)	
Differentiation			0.004		0.009
Well	91 (30.3)	Reference		Reference	
Moderate	165 (55.0)	2.71 (1.40-5.24)		1.75 (1.04-2.96)	
Poor	44 (14.7)	3.09 (1.42-6.72)		2.59 (1.39-4.82)	
Length, cm			0.249		0.952
<4	46 (15.3)	Reference		Reference	
≥4	254 (84.7)	1.54 (0.74-3.20)		1.02 (0.58-1.80)	
cTNM			0.623		0.368
II	36 (12.0)	Reference		Reference	
III	264 (88.0)	1.20 (0.57-2.52)		1.37 (0.69-2.73)	
No. of cycles of neoadjuvant therapy			0.127		0.030
1-2	258 (86.0)	Reference		Reference	
≥3	42 (14.0)	1.57 (0.88-2.81)		1.74 (1.05-2.88)	
Surgery			0.571		0.138
McKeown	263 (87.7)	Reference		Reference	
Ivor Lewis	26 (8.67)	1.36 (0.65-2.86)		0.69 (0.30-1.59)	
Sweet	11 (3.67)	1.45 (0.53-4.01)		2.04 (0.89-4.67)	
Approach			0.179		0.217
Minimally invasive	213 (71.0)	Reference		Reference	
Open	87 (29.0)	1.39 (0.86-2.24)		1.31 (0.85-2.02)	
pCR			<0.001		<0.001
No	220 (73.3)	Reference		Reference	
Yes	80 (26.7)	0.24 (0.11-0.53)		0.24 (0.12-0.47)	

Data are presented as n (%). pCR, pathological complete response; OS, overall survival; RFS, recurrence free survival.

most cases were in the ranges of 0.0-0.2 and 0.6-0.8 (Fig. 4). The distribution of the propensity score was more consistent between pCR and non-PCR groups after matching, which indicated that a successful match was attained after PSM. Survival curves were produced before and after PSM, and log-rank tests were performed. Before PSM, OS and RFS in the pCR group were superior compared with those in the non-pCR group (P<0.05; Fig. 5). After PSM, the survival curve indicated that the pCR

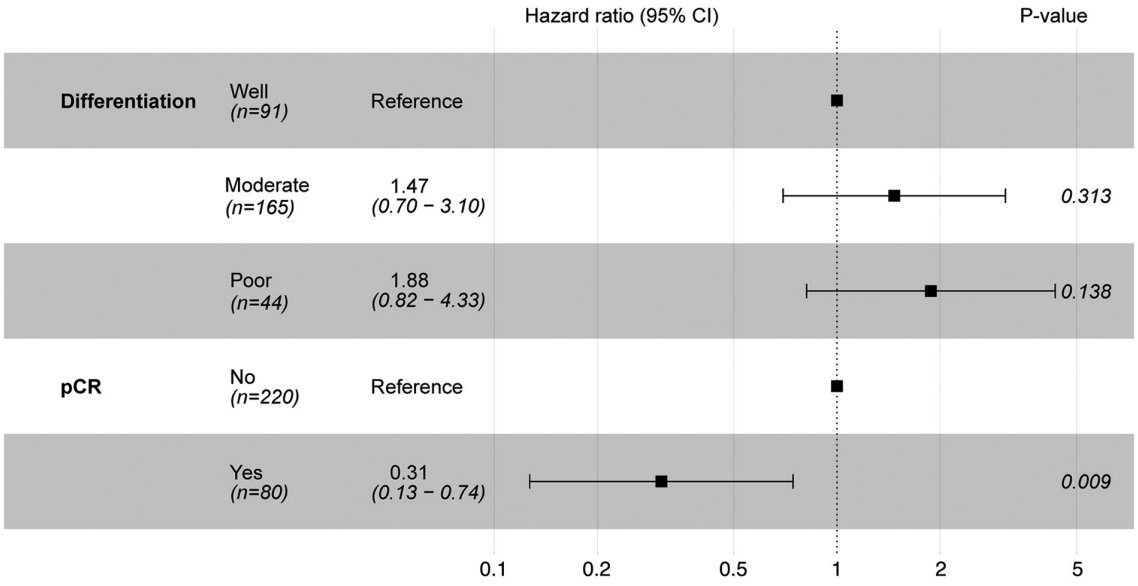

Figure 2. Forest plot of multivariate analysis of OS by Cox proportional hazards model. OS, overall survival; CI, confidence interval; pCR, pathological complete response.

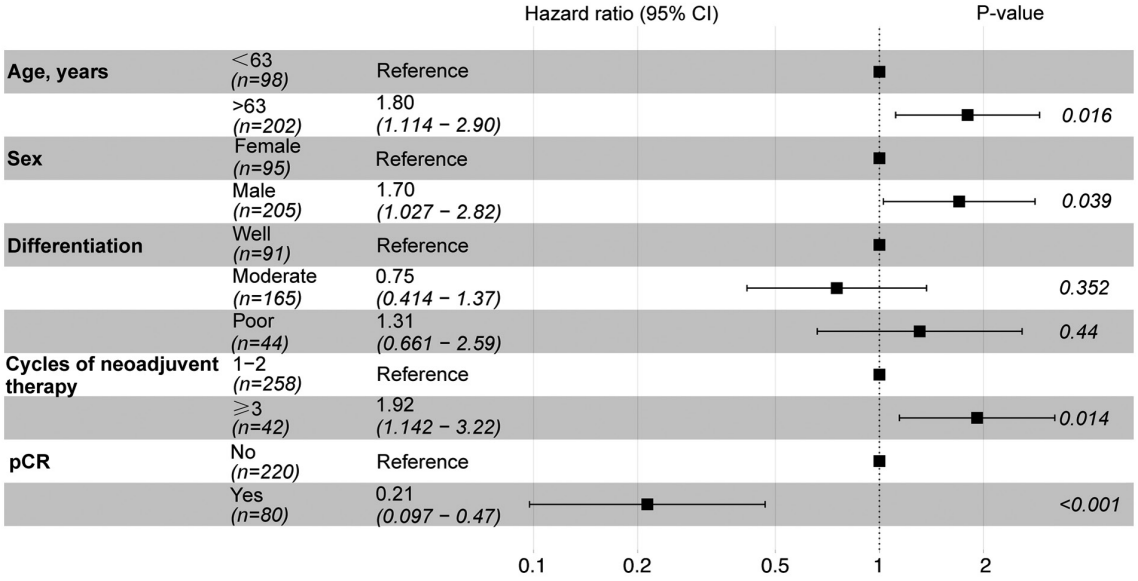

Figure 3. Forest plot of multivariate analysis of RFS by Cox proportional hazards model. RFS, recurrence free survival; CI, confidence interval; pCR, pathological complete response.

group exhibited superior survival compared with the non-pCR group. However, this was only statistically significant for RFS (P<0.05), while the P-value for OS was 0.16.

Patterns of recurrence. Among the 300 cases analyzed in the present study, 93 cases exhibited recurrence (Table III). The recurrence rate in the pCR group was 11.2%, whereas the rate in the non-pCR group was 38.2%. A statistically significant difference was observed between these two groups (P<0.05). Additionally, categorization of recurrence sites into local-regional and distant recurrence demonstrated that the local-regional recurrence rate (23.2%) and distant recurrence rate (15.0%) in the non-pCR group were higher compared with those in the pCR group (7.5 and 3.7%, respectively), with the differences being statistically significant (P<0.05). The distribution of recurrence sites in the pCR group (Fig. 6A) compared with the non-pCR group (Fig. 6B) was assessed. The mediastinal lymph node emerged as the predominant site of recurrence in both groups. In both groups, local-regional recurrence sites encompassed mediastinal lymph nodes, supraclavicular lymph nodes and multiple sites. Furthermore, ~3.6% of patients in the non-pCR group experienced anastomotic recurrence, while no patients in the pCR group exhibited such recurrence. Both groups exhibited metastases to the lung and peritoneum as distant metastatic sites. In the pCR group, 22.2% of cases exhibited peritoneal metastasis, while 11.1% exhibited lung metastasis. No bone, liver, retroperitoneal lymph node or multiple organ metastases were recorded. In the non-pCR group, multiple organ and bone metastases were the most prevalent, comprising ~10.7% of patients, whereas

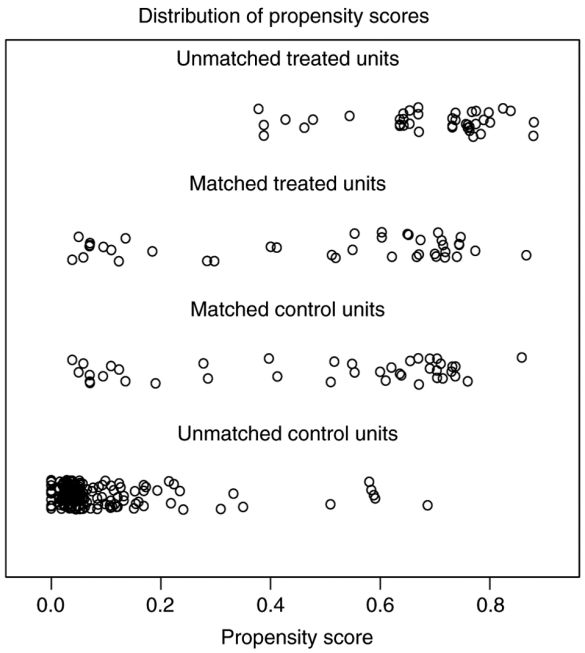

Figure 4. Chart of propensity scores distribution. Each unit represents a case; control units represent cases in the non-pCR group and treated units represent cases in the pCR group. pCR, pathological complete response.

liver metastases and peritoneal metastases were observed in 5.9 and 7.1% of patients, respectively. Additionally, ~1.2% of patients exhibited retroperitoneal lymph node metastases, representing the lowest incidence among all metastatic sites in the non-pCR group.

Discussion

Before 2021, the combination of chemotherapy and radiotherapy was regarded as the standard adjuvant treatment for locally advanced ESCC (24,25). The results of the NEOCRTEC5010 and CROSS trials indicated that neoadjuvant chemoradiotherapy was a superior treatment approach for resectable locally advanced esophageal cancer (4,26). In 2021, the KEYNOTE-590 study became the first clinical trial globally to demonstrate that immunotherapy enhanced survival rates in advanced esophageal cancer while maintaining a favorable safety profile, thereby transforming the treatment paradigm for this type of cancer (9). The research findings indicate that neoadjuvant immunochemotherapy represents an auspicious treatment approach for ESCC. As radiotherapy can potentially increase the difficulty and complications of esophagectomy, especially in Asia, for patients with locally advanced ESCC, an increasing number of physicians are selecting neoadjuvant immunochemotherapy as the preferred treatment approach (27). There are few clinical trials involving neoadjuvant immunochemotherapy over the past decade (11,12,14), a therapeutic approach that has only been widely employed in ESCC in recent years; therefore, the present study primarily focused on this patient population.

A number of previous studies on neoadjuvant therapy for various tumor types have identified an association between pCR and the prognosis of patients (28-30). Due to this association, pCR is frequently utilized as a significant endpoint in drug clinical trials, serving as a surrogate for OS, which necessitates extended follow-up for observation. The Food and Drug Administration of the United States has approved pCR as a surrogate endpoint for OS in breast cancer clinical trials (30). However, for esophageal cancer, the relationship between pCR and survival remains controversial. A systematic review of 40 clinical trials involving 55,344 patients undergoing neoadjuvant therapy for esophageal cancer found that pCR was not a valid surrogate endpoint for survival in clinical trials (31). However, other clinical trials on neoadjuvant therapy for esophageal cancer have demonstrated that treatment patterns enhancing the pCR rate could improve the OS and RFS of patients (20,32). Neoadjuvant immunochemotherapy for esophageal cancer has recently emerged, resulting in limited research on the prognostic value of pCR for the survival of patients with ESCC. The present study found that 80 out of 300 patients achieved pCR, with a pCR rate of 26.7%. This rate aligns with the previously reported pCR rates of 16.7-50% for neoadjuvant immunochemotherapy in ESCC (33). The present study utilized the Cox proportional hazards model to investigate prognostic factors, and demonstrated that pCR was a statistically significant prognostic factor for OS and RFS ($P<0.05$). To validate this conclusion, the patients were categorized into pCR and non-pCR groups, PSM was utilized to reduce the potential bias, and survival analysis was conducted on the matched dataset. The OS and RFS of the pCR group before PSM and the RFS of the pCR group after PSM were significantly superior to those of the non-pCR group ($P<0.05$). After PSM, the OS of the pCR group remained superior to that of the non-pCR group as indicated by the survival curve; however, this difference was not statistically significant ($P>0.05$). This may be attributed to the limited number of included cases, resulting in only 80 matched cases after PSM. By contrast, a previous study confirmed that pCR is weakly associated with OS in patients with ESCC with neoadjuvant therapy (31). As for the reason for this finding, a study has suggested that the measurement of pathological response is primarily based on the primary tumor site rather than on micrometastatic sites, but the reaction of micrometastases beyond the primary site is likely the principal factor influencing clinical outcomes (34). Another study has indicated that the potential survival benefit derived from the favorable treatment effect on local lesions may be counterbalanced by the adverse effects associated with the toxicity of neoadjuvant drugs, thus diminishing the association between pCR and survival (35). In summary, in conjunction with prior studies on neoadjuvant therapy for ESCC, the present study indicated that patients achieving pCR experienced improved survival benefits; however, this association was not consistently significant across all studies. Future clinical trials with improved designs and larger sample sizes are necessary to validate this conclusion.

To the best of our knowledge, no research exists regarding the relationship between pCR and recurrence patterns in patients with ESCC treated with neoadjuvant immunochemotherapy; the present study represents the initial investigation concerning this population. Presently, research has predominantly focused on patients treated with neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (4,5,18,19,21,22). A study on esophageal cancer following neoadjuvant chemotherapy has demonstrated that the RFS of patients in the pCR group was superior to that of

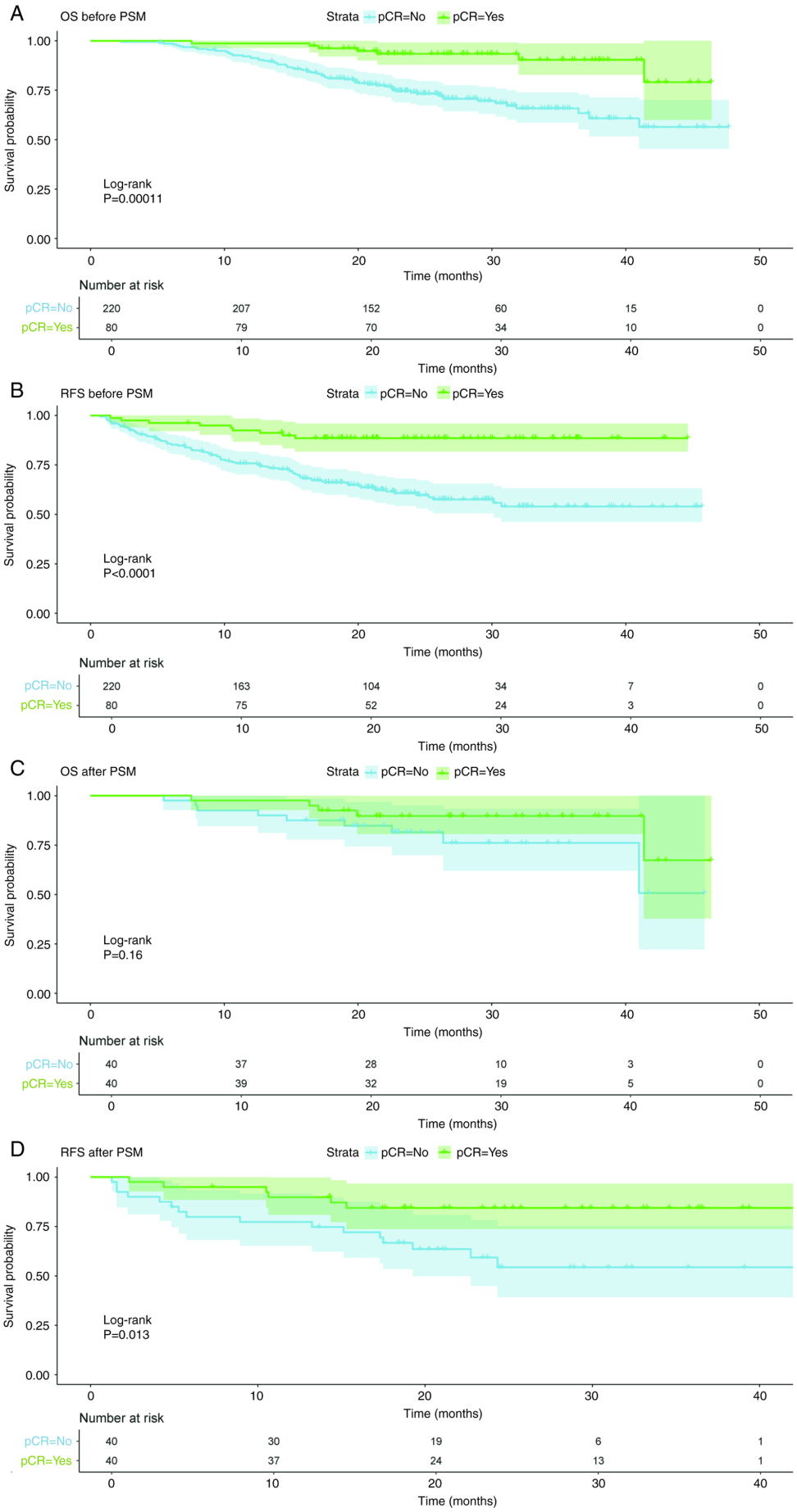

Figure 5. Kaplan-Meier curves of survival analysis. (A) OS before PSM; (B) RFS before PSM; (C) OS after PSM; (D) RFS after RFS. OS, overall survival; RFS, recurrence-free survival; PSM, propensity score matching; pCR, pathological complete response.

Table III. Comparison of recurrence patterns between the pCR group and the non-pCR group.

Recurrence pattern	Total (n=300)	Non-pCR (n=220)	pCR (n=80)	P-value
Recurrence				<0.001
No	207 (69.0)	136 (61.8)	71 (88.8)	
Yes	93 (31.0)	84 (38.2)	9 (11.2)	
Recurrence site				<0.001
No	207 (69.0)	136 (61.8)	71 (88.8)	
Loco-regional	57 (19.0)	51 (23.2)	6 (7.5)	
Distant	36 (12.0)	33 (15.0)	3 (3.7)	<0.001

Data are presented as n (%). pCR, pathological complete response.

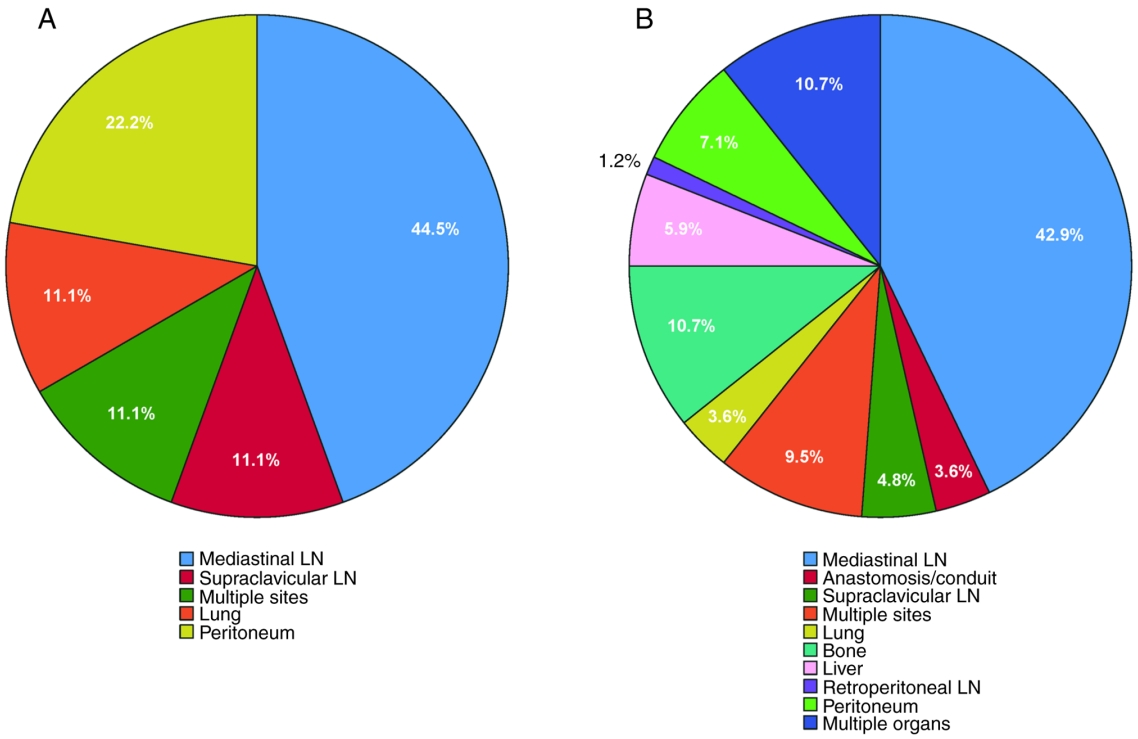

Figure 6. Pie charts of recurrence sites. Recurrence sites in (A) pCR group and (B) non-pCR group. pCR, pathological complete response; LN, lymph node.

the patients in the non-pCR group (36). In the present study, the RFS of the pCR group was also superior to that of the non-pCR group both before and after PSM, which indicated that patients with a pCR may have improved RFS among patients with ESCC treated with neoadjuvant immunochemotherapy. According to previous research, patients who achieved a pCR following neoadjuvant chemoradiotherapy had a recurrence incidence of 23.3-38.0% (37-39). The recurrence rate for the pCR group in the present study was 11.2%, which was significantly lower compared with that of the non-pCR group (P<0.05) and lower compared with the rates reported in prior literature (36,37). Some studies on neoadjuvant chemotherapy or chemoradiotherapy have shown that patients achieving pCR may experience both local and distant recurrences. However, the proportions of these recurrences differ across various studies (36-39). In the present study, the loco-regional and distant recurrence rates in the pCR group were significantly lower compared with those in the non-pCR group; however, a substantial proportion in each group exhibited local recurrence. The mediastinal lymph node was the most prevalent recurrence site in both groups, with mediastinal lymph node metastasis being observed in <50% of cases. In the pCR group, there were no instances of anastomotic recurrence, bone, liver, retroperitoneal lymph node or multiple organ metastasis. By contrast, metastasis was present at these sites in the non-pCR group. The limited number of cases achieving pCR may have led to some metastatic sites not being observed in this group. Future studies with larger sample sizes are anticipated to investigate the relationship between pCR and recurrence sites.

The present study had specific limitations. Firstly, the present study had a limited sample size, especially after PSM, leading to fewer matched cases, which may affect the research conclusions. Secondly, the present study was retrospective. Although the Cox proportional hazards model

and PSM were employed to reduce bias, some bias remains inevitable. Finally, the practices of different centers influence the immunochemotherapy regimen and the surgical approach. The variability in treatment plans may affect the conclusions. In summary, the growing acceptance of neoadjuvant immunochemotherapy for locally advanced ESCC requires additional prospective randomized controlled studies with larger sample sizes to clarify the association between pCR and prognosis, along with recurrence patterns. This research would establish a stronger basis for the treatment of patients with esophageal cancer. Additionally, there are numerous other factors, such as minimal residual disease or circulating tumor DNA, that may influence the prognosis of patients after neoadjuvant immunochemotherapy followed by surgery. In future studies, more potential prognostic indicators such as minimal residual disease or circulating tumor DNA could be added to construct a multivariate prediction model to improve the predictive ability.

In conclusion, in patients with ESCC undergoing neoadjuvant immunochemotherapy, pCR indicated improved OS and RFS; however, the association between pCR and OS was not statistically significant. Concurrently, pCR was associated with reduced local and distant recurrence rates, and the recurrence pattern of patients in the pCR group differed from that of patients in the non-pCR group. Future research should involve larger sample sizes to elucidate the relationship between pCR and survival, as well as its influence on recurrence patterns.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FW and XY drafted the manuscript. JZ and YH participated in the design of the study plan. YH and RY participated in the revision and language editing of the manuscript. FW, XY, JZ and RY participated in the collection of data. LY and DY participated in the statistical analysis. FW and XY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital (approval no. YW2024-3-1), Anyang Tumor Hospital (approval no. 2023YP18H01), Shaanxi Provincial People's Hospital (approval no. 2023K-S129) and Beijing Chest Hospital (approval no. 2023-ky-59). The patients/participants provided written informed consent to participate in the present study. The study was conducted in strict compliance with the Declaration of Helsinki (2013) and the Good Clinical Practice guidelines.

Patient consent for publication

The patients/participants provided written informed consent for the publication of any data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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