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Neoadjuvant immunochemotherapy for locally advanced esophageal squamous cell carcinoma in real-world practice: an analysis of the clinical outcomes and long-term survival, and the feasibility of using major pathological response as a surrogate endpoint

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Abstract

Background Neoadjuvant immunochemotherapy is expected to become the standard treatment mode for locally advanced esophageal squamous cell carcinoma (ESCC). This study aims to analyze the clinical outcomes and long-term survival of neoadjuvant immunochemotherapy for locally advanced ESCC, and explore the feasibility of using major pathological response (MPR) as a surrogate endpoint.

Methods This real-world retrospective study consecutively included eligible patients with stage II–IVA locally advanced ESCC who received neoadjuvant immunochemotherapy and surgery between 2019 and 2022 at the Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine.

Results This study collected a total of 166 patients, and ultimately included 126 patients after screening. The objective response rate (ORR) was 69.8% (88/126). The incidence of grade 3–4 adverse events (AEs) was 13.5% (17/126). MPR was observed in 49 (38.9%) patients, and 24 (19.0%) patients achieved a complete pathological response (pCR). The median progression-free survival (PFS) was 31.7 months and the 3-year PFS rate was 56.3%. The median overall survival (OS) was not reached and the 3-year OS rate was 70.6%. The median PFS of the non-MPR group was 25.0 months, with the MPR group not achieved (hazard ratio [HR], 2.503; 95% CI 1.359–4.610; $P=0.0022$). The median OS in the non-MPR group was 31.7 months and not reached in the MPR group (HR, 3.607; 95% CI 1.576–8.254; $P=0.0012$). MPR is an independent prognostic factor affecting OS (HR, 2.522; 95% CI 1.018–6.401; $P=0.046$).

Conclusions Neoadjuvant immunochemotherapy is safe and effective for locally advanced ESCC, and can result in certain survival benefits. MPR can serve as a surrogate endpoint for predicting long-term OS.

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Keywords Esophageal squamous cell carcinoma (ESCC), Locally advanced, Neoadjuvant immunochemotherapy, Survival, Surrogate endpoint

Introduction

According to the global cancer statistics released in 2024, esophageal cancer (EC) ranks 11 th in the cancer incidence rate and 8 th in the case fatality rate [1]. EC is divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Unlike Europe and America, where EAC is mainly found, the most common pathological subtype of EC in East Asia is ESCC, and over 90% of EC patients in China are ESCC [2]. In the past, patients with EC were usually in the middle and late stages when they were diagnosed, and the traditional treatment method was simple surgical treatment. Therefore, the overall survival (OS) rate of EC at 5 years was usually not more than 25% [3, 4]. The results of two important multicenter prospective studies (CROSS and NEOCRTEC5010), based on neoadjuvant chemoradiation (nCRT), have increased this number to nearly 50%, establishing nCRT combined with surgery as the standard treatment for locally advanced resectable ESCC and receiving strong recommendations from the National Comprehensive Cancer Network (NCCN) guidelines [5–7]. However, the overall recurrence and metastasis rate under the current standard treatment mode still exceeds 50%, and long-term follow-up suggests that the damage caused by local radiation therapy may increase patient's resistance, short-term safety risk, and long-term non-tumor factor mortality rate [8]. It is urgent to explore a more effective and safer neoadjuvant treatment mode.

In recent years, immune checkpoint inhibitors (ICIs) have made progresses in the treatment of multiple solid tumors [9, 10]. The expression of programmed cell death ligand 1 (PD-L1) and the degree of tumor mutation burden (TMB) are considered to be positively correlated with the efficacy of programmed cell death protein 1 (PD-1) inhibitors [11, 12]. ESCC is considered to benefit from PD-1 inhibitors due to its high expression of PD-L1 and TMB [13–17]. Chemotherapy has immune activation properties, which can promote immunogenic cell death (ICD) of tumor cells and trigger anti-tumor immune responses, so immunochemotherapy can have better efficacy [18–21]. In addition, multiple studies (like: CheckMate 648 [nivolumab], ESCORT-1 st [camrelizumab], KEYNOTE-590 [pembrolizumab], ORIENT-15 [sintilimab]) have confirmed that first-line immunochemotherapy brings longer progression free survival (PFS) and long-term OS compared with chemotherapy alone in advanced EC [22–25].

In recent years, phase 1b and phase 2 clinical studies (such as TD-NICE [tislelizumab], NICE [camrelizumab], and ESONICT-1 [sintilimab]) on neoadjuvant immunochemotherapy for locally advanced resectable EC have mainly been conducted in China, and revealed the good short-term efficacy and safety [26–28]. The primary endpoints of these studies are mostly major pathological response (MPR) or pathological complete response (pCR). The pCR rate of neoadjuvant immunochemotherapy for EC ranges from 16.7% to 50.0%, and the MPR rate ranges from 41.7% to 72.2% [26–28]. Compared with the pCR rate of 43.2% to 49% after nCRT [5, 6], there is no significant advantage, and there is no disclosure of OS data for 3 years or more. At present, the relevant phase 3 clinical studies are still being designed or carried out, and it is necessary to wait for a longer time to further verify the long-term efficacy. The above studies are mainly small sample intervention clinical studies, and their efficacy in the real world is also rarely reported. Therefore, we believe that timely reviewing the effectiveness and safety of immunochemotherapy for ESCC in the real world is of great significance. Long-term OS is the gold standard for assessing overall efficacy. Although many clinical researchers have chosen pCR or MPR as alternative endpoints to accelerate the promotion of effective new treatment options, their alternative effects have not yet accumulated sufficient evidence [29]. In the real world, MPR is usually easier to achieve than pCR, and the diagnostic criteria is clearer.

Therefore, this study was launched to analyze the clinical outcomes and long-term survival of neoadjuvant immunochemotherapy for locally advanced ESCC in the real world, and explore the feasibility of using MPR as a surrogate endpoint.

Methods

Participants

This real-world retrospective study collected clinical data of all stage II–IVA locally advanced resectable EC patients who received neoadjuvant immunochemotherapy and surgery at the Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine from the hospital's electronic medical record system between November 2019 and June 2022, and screened patients according to the following criteria: (I) age ≥ 18 and ≤ 80 years; (II) histopathologically diagnosed as ESCC by endoscopic; (III) eastern cooperative oncology group (ECOG) performance status (PS) of 0 or

1; (IV) receipt of 2–4 cycles neoadjuvant immunochemotherapy; (V) no receipt of concurrent radiation therapy; and (VI) complete general clinical data and neoadjuvant therapeutic information.

Neoadjuvant immunochemotherapy and surgery

Prior to neoadjuvant therapy and surgery, all patients underwent systematic imaging evaluations, including computed tomography (CT) of the chest and abdomen, endoscopic ultrasound, positron emission tomography (PET)–CT, and brain magnetic resonance imaging (MRI).

All patients received 2–4 cycles of ICI combined with chemotherapy. The selected ICIs are all approved by the US Food and Drug Administration (FDA) for immunotherapy of EC: pembrolizumab, camrelizumab, sintilimab, and tislelizumab, and the dose of ICIs is 200 mg, q3w. The chemotherapy regimen is platinum containing dual drug therapy, which involves cisplatin/carboplatin combined with paclitaxel or fluorouracil plus cisplatin/carboplatin. The specific chemotherapy treatment plan is determined by the attending physician based on the patient's specific condition and body surface area.

All surgeries were performed by the same surgical team, including McKeown and Ivor Lewis EC radical resection. Prior to conducting this study, the surgical team had completed a large number of radical resection surgeries, including open radical surgery, video-assisted thoracoscopic surgery (VATS), and da Vinci robot-assisted thoracoscopic surgery (RATS). Whether to undergo minimally invasive surgery is determined by the surgeon based on the patient's wishes and a comprehensive evaluation of the patient's tumor condition. For upper EC, the distance from the tumor edge to the resection edge should be greater than 2 cm in principle, and for middle and lower EC, the distance from the resection edge should be greater than 5 cm. All cases underwent intraoperative frozen pathological analysis of the tumor margins. All patients underwent dual field lymph node dissection (chest and abdominal lymph nodes), and whether to perform neck lymph node dissection depends on the patient's condition.

Data

Data used for statistical analysis included: 1) baseline characteristics: gender, age, body mass index (BMI), ECOG–PS, smoking status, drinking status, hypertension, diabetes, cardiac disease, tumor location, clinical tumor-node-metastasis (cTNM) stage, type of ICI and cycles of neoadjuvant therapy; 2) response to neoadjuvant therapy (objective response rate [ORR]) and immunotherapy-related adverse events (irAEs); 3) surgery and pathological response: surgical time, number of lymph node dissection, surgical path, surgical method, post-neoadjuvant pathologic tumor-node-metastasis (ypTNM) stage, degree of tumor differentiation, R0 resection status, MPR and pCR); 4) postoperative complications: anastomotic stenosis, anastomotic leakage, chylothorax, empyema, incision infection, postoperative bleeding, pleural effusion, recurrent laryngeal nerve (RLN) injury; and 5) survival and recurrence follow-up data (progression-free survival [PFS] and OS).

We used the eighth edition of the American joint commission on cancer (AJCC) TNM staging [30] to obtain cTNM and ypTNM. The ORR was evaluated on the basis of the response evaluation criteria in solid tumor version 1.1 (RECIST 1.1) [31], which meant that the target lesion was reduced by more than 30%. AEs were graded according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0. MPR was defined as the percentage of residual active tumor cells in the tumor bed $\leq 10\%$, regardless of whether there were residual active tumor cells in the lymph nodes. The definition of pCR was the absence of active tumor cells in the primary tumor area and all excised lymph nodes. PFS was defined as the time from the receipt of neoadjuvant therapy to tumor recurrence, death, or the last follow-up. OS was defined as the time from receiving neoadjuvant therapy to death for any reason or the last follow-up.

Statistical analysis

The results of continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as numbers (percentages). Student's *t* test or Wilcoxon test was used to analyze continuous variables, and Pearson chi-square test or Fisher's exact test was applied to analyze categorical variables. Kaplan–Meier method was adopted to obtain PFS and OS, and stratified log-rank test was used to compare differences between groups. Cox proportional hazards regression model was adopted to explore and identify independent influencing factors on survival outcomes. First, we performed univariate Cox regression on each variable, and then included statistically significant variables in multivariate Cox regression. $P < 0.05$ was considered statistically significant. Statistical analysis was conducted using SPSS software version 26.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA).

Results

Baseline characteristics

This study collected a total of 166 patients, and ultimately included 126 patients after screening. Included patients were divided into two groups according to whether they achieved MPR: MPR group ($n = 49$) and non-MPR group ($n = 77$). The flowchart of this study is depicted in Fig. 1.

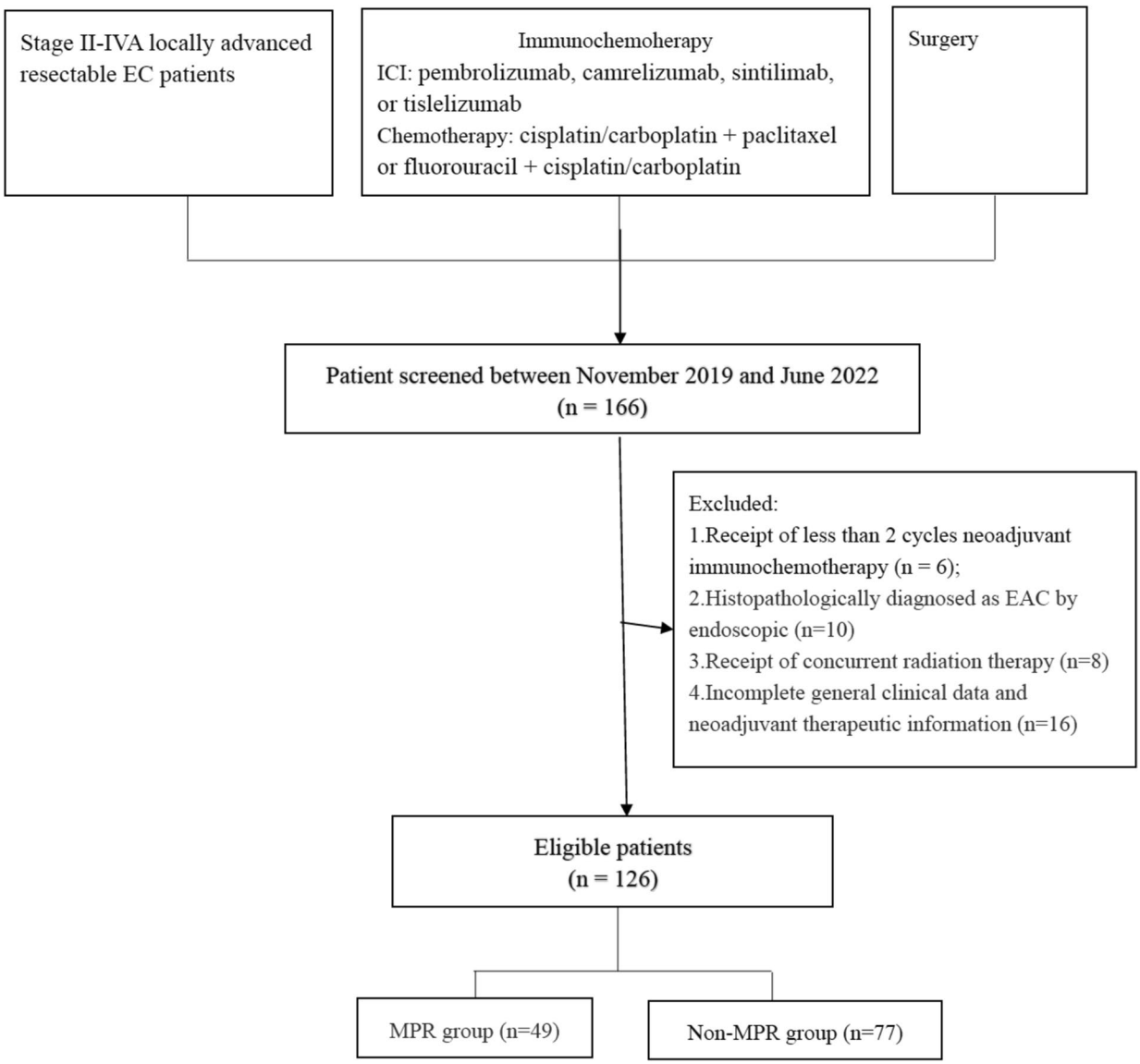

Fig. 1 Flowchart of this study. EC: esophageal cancer; EAC: esophageal adenocarcinoma; ICI: immune checkpoint inhibitor; MPR: major pathologic response

Baseline characteristics of these patients are shown in Table 1. There were no significant differences between the two groups in gender, age, BMI, ECOG PS, smoking history, drinking history, comorbidities, tumor location, clinical stage, type of ICI and cycles of neoadjuvant therapy.

Response to neoadjuvant therapy and adverse events

A total of 88 patients (69.8%) achieved ORR, and the reduction in tumor diameter on imaging is shown in Fig. 2. The ORR in the MPR group was 71.4% (35/49) and 68.8% (53/77) in the non-MPR group (P= 0.843). In this study, irAEs were composed of skin reaction (23.0%, 29/126), hepatic injury (16.7%, 26/126), hematologic toxicity (75.4%, 95/126), gastrointestinal toxicity (35.8%, 45/126), and fatigue (18.3%, 23/126), with grade 3–4 irAEs rates of 1.6%, 3.2%, 3.2%, 4.8%, and 1.6%, respectively. There was no statistically significant difference (P> 0.05) in irAEs between the MPR group and the non-MPR group, as shown in Table 2.

Table 1 Baseline characteristics

Characteristics	Total, $n = 126$	MPR group, $n = 47$	Non-MPR group, $n = 79$	*P* value
Sex, *n* (%)				1.000
Male	113 (89.7)	44 (89.8)	69 (89.6)	
Female	13 (10.3)	5 (10.2)	8 (10.4)	
Age (years), mean ± SD	64.3 ± 8.1	65.2 ± 7.7	63.7 ± 8.3	0.312
BMI (kg/m^2), mean ± SD	21.8 ± 2.9	21.8 ± 3.4	21.8 ± 2.6	0.996
ECOG PS, *n* (%)				0.143
0	63 (50.0)	29 (59.2)	34 (44.2)	
1	63 (50.0)	20 (40.8)	43 (55.8)	
Smoking status, *n* (%)				0.718
Ever	59 (46.8)	24 (49.0)	35 (45.5)	
Never	67 (53.2)	25 (51.0)	42 (54.5)	
Drinking status, *n* (%)				0.356
Ever	54 (42.9)	24 (49.0)	30 (39.0)	
Never	72 (57.1)	25 (51.0)	47 (61.0)	
Comorbidities, *n* (%)				
Hypertension	32 (25.4)	11 (22.4)	21 (27.3)	0.675
Cardiac disease	22 (17.5)	9 (18.4)	13 (16.9)	1.000
Diabetes mellitus	10 (7.9)	2 (4.1)	8 (10.4)	0.314
Tumor location, *n* (%)				0.648
Locus superior	17 (13.5)	5 (10.2)	12 (15.6)	
Locus medialis	43 (34.1)	18 (36.7)	25 (32.5)	
Locus inferior	66 (52.4)	26 (53.1)	40 (51.9)	
Clinical stage, *n* (%)				0.963
II	14 (11.1)	6 (12.2)	8 (10.4)	
III	77 (61.1)	30 (61.2)	47 (61.0)	
IVA	35 (27.8)	13 (26.5)	22 (28.6)	
Treatment cycles, *n* (%)				0.750
2	57 (45.2)	20 (40.8)	37 (48.1)	
3	41 (32.5)	17 (34.7)	24 (31.2)	
4	28 (22.0)	12 (24.5)	16 (20.8)	
Type of ICI, *n* (%)				0.455
Camrelizumab	69 (54.8)	30 (61.2))	39 (50.6)	
Sintilima	38 (30.2)	14 (28.6)	24 (31.2)	
Pembrolizumab	12 (9.5)	4 (8.2)	8 (10.4)	
Tislelizumab	7 (5.6)	1 (2.0)	6 (7.8)	

MPR: major pathological response; SD: standard deviation; BMI: body mass index; ECOG PS: eastern cooperative oncology group performance status; ICI: immune checkpoint inhibitor

Surgery, pathological response and postoperative complications

Major pathological response (MPR) was observed in 49 (38.9%) patients, and 24 (19.0%) patients achieved a pCR. There were significant differences in the ypT stage, ypN stage and pathological grade between the MPR group and the non-MPR group ($P < 0.05$), as shown in Table 3. The highest incidence of postoperative complication among all patients is pleural effusion, accounting for 23% (29/126). The differences in the incidence of postoperative complications between the MPR group and the non-MPR group were not statistically significant (Table 4).

Survival

The median follow-up time was 27.3 months (95% confidence interval [CI], 24.7 to 30.0) in this study. Overall, the median PFS is 31.7 months (95% CI 24.0–NA) (Fig. 3A), while the median OS has not been achieved (Fig. 3B). The 3-year PFS rate was 56.3% and the 3-year OS was 70.6%. The median PFS in the non-pCR group was 25.0 months (95% CI 19.4–30.6) and not reached in

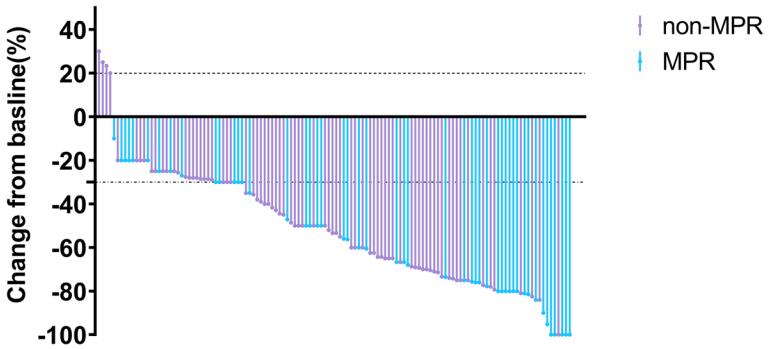

Fig. 2 Percentage change in the maximum diameter of target lesion compared with the baseline tumor size. MPR: major pathologic response

Table 2 AEs of neoadjuvant immunochemotherapy

AEs	Total, *n* = 126	MPR group, *n* = 47	Non-MPR group, *n* = 79	*P* value
Skin reaction, *n* (%)				0.480
No	97 (77.0)	37 (75.5)	60 (77.9)	
Grade 1–2	27 (21.4)	12 (24.5)	15 (19.5)	
Grade 3–4	2 (1.6)	0 (0.0)	2 (2.6)	
Hepatic injury, *n* (%)				0.300
No	100 (79.4)	41 (83.7)	59 (76.6)	
Grade 1–2	22 (13.5)	8 (16.3)	14 (18.2)	
Grade 3–4	4 (3.2)	0 (0.0)	4 (5.2)	
Hematologic toxicity, *n* (%)				0.227
No	31 (24.6)	8 (16.3)	23 (29.9)	
Grade 1–2	91 (72.2)	39 (79.6)	52 (67.5)	
Grade 3–4	4 (3.2)	2 (4.1)	2 (2.6)	
Gastrointestinal toxicity, *n* (%)				0.624
No	81 (64.3)	29 (59.2)	52 (67.5)	
Grade 1–2	39 (31.0)	17 (34.7)	22 (28.6)	
Grade 3–4	6 (4.8)	3 (6.1)	3 (3.9)	
Fatigue, *n* (%)				0.427
No	103 (81.7)	39 (79.6)	64 (83.1)	
Grade 1–2	21 (16.7)	10 (20.4)	11 (14.3)	
Grade 3–4	2 (1.6)	0 (0.0)	2 (2.6)	

MPR: major pathological response; AEs: adverse events

the pCR group (hazard ratio [HR], 4.203; 95% CI 1.514–11.669; P= 0.0026) (Fig. 4A). The 1-year PFS rate and 3-year PFS rate in the non-pCR group were 84.5% and 50.5%, with that in the pCR group 100.0% and 82.6%. The median OS of the non-pCR group and pCR group was both not achieved (HR, 5.615; 95% CI 1.345–23.434; P= 0.0074) (Fig. 4B). The 1-year OS rate and 3-year OS rate in the non-pCR group were 95.1% and 66.0%, with that in the pCR group 100.0% and 91.3%. The median PFS in the non-MPR group was 25.0 months (95% CI 18.8–31.2) and not reached in the MPR group (HR, 2.503; 95% CI 1.359–4.610; P= 0.0022) (Fig. 4C). The 1-year PFS rate and 3-year PFS rate in the non-MPR group were 81.8% and 46.8%, with that in the MPR group 93.9% and 71.4%. The median OS of the MPR group was not achieved (HR, 3.607; 95% CI 1.576–8.254; P= 0.0012), with the non-MPR group 31.7 months (95% CI 28.9–34.5) (Fig. 4D). The 1-year OS rate and 3-year OS rate in the non-MPR group were 93.5% and 61.0%, with that in the MPR group 98.0% and 85.7%.

We conducted further analysis on the prognostic factors affecting OS after neoadjuvant therapy (Table 5). After cox regression analyses, we found that achieving MPR (HR, 3.607; 95% CI 1.576–8.254; P= 0.002) and

Table 3 Surgical outcomes

Characteristics	Total, $n=126$	MPR group, $n=47$	Non-MPR group, $n=79$	*P* value
Operation time (min), mean ± SD	305.48 ± 7.12	307.73 ± 80.41	304.05 ± 80.15	0.802
Number of lymph node dissection (*n*), mean ± SD	30.18 ± 1.17	28.37 ± 11.27	31.34 ± 14.16	0.218
Surgical path, *n* (%)				0.576
Open	53 (42.1)	9 (18.4)	17 (22.1)	
VATS	47 (37.3)	21 (42.9)	26 (33.8)	
RATS	26 (20.6)	19 (38.8)	34 (44.2)	
Surgical method, *n* (%)				0.707
McKeown	79 (62.7)	32 (65.3)	47 (61.0)	
Ivor–Lewis	47 (37.3)	17 (34.7)	30 (39.0)	
ypT stage, *n* (%)				**< 0.001**
T0–T1	39 (31.0)	29(59.2)	10 (13.0)	
T2–T4	87 (69.0)	20 (40.08)	67 (87.0)	
ypN stage, *n* (%)				**0.032**
N0–N1	104 (82.5)	45 (91.8)	59 (76.6)	
N2–N3	22 (17.5)	4 (8.2)	18 (23.4)	
Pathological grade, *n* (%)				**< 0.001**
Unknown	12 (9.5)	11 (22.4)	1 (1.3)	
G1	23 (18.3)	16 (32.7)	7 (9.1)	
G2	60 (47.6)	18 (36.7)	42 (54.5)	
G3	31 (24.6)	4 (8.2)	27 (35.1)	
R0 resection, *n* (%)				0.521
Yes	124 (98.4)	0 (0.0)	2 (2.6)	
No	2 (1.6)	49 (100.0)	75 (97.4)	

MPR: major pathological response; SD: standard deviation; VATS: video-assisted thoracoscopic surgery; RATS: robot-assisted thoracoscopic surgery

ypT stage 0–1 (HR, 3.015; 95% CI 1.249–7.278; $P=0.014$) were prognostic factors affecting OS. Then we included factors with P value < 0.2 in univariate analyses into multivariate cox regression analyses, and finally determined that achieving MPR (HR, 2.522; 95% CI 1.018–6.401; $P=0.046$) was an independent prognostic factor affecting OS after neoadjuvant therapy.

Discussion

To our knowledge, this is the first real-world retrospective study to explore the relationship between MPR and long-term OS in locally advanced ESCC. All 126 locally advanced ESCC patients underwent surgical treatment after neoadjuvant immunochemotherapy, with an overall ORR rate of 69.8%, MPR rate of 38.9%, pCR rate of 19.0%, and incidence of grade 3–4 AEs of 13.5%. These indicators were similar to those disclosed Phase 2 clinical studies [26–28]. This preliminarily confirmed from a real-world perspective that neoadjuvant immunochemotherapy for locally advanced ESCC could have good short-term efficacy and safety. In this study, the median OS was not achieved, and the 3-year OS rate was 60.2%. OS is the gold standard for judging the long-term prognosis of tumor. The 3-year OS rate in this study was slightly lower than that (65.8%) in the NEOCRTEC5010, a classic clinical study of nCRT based on Chinese cases [32]. In addition, it was better than that (55.9%) in a real-world study that included 1267 nCRT patients [33]. This preliminarily confirmed that in the real world, neoadjuvant immunochemotherapy for locally advanced ESCC could have a long-term therapeutic effect no less than that of nCRT.

In the real world, patients often have lower tolerance to radiation therapy compared to chemotherapy alone. Previous studies have also suggested that the damage caused by local radiation therapy increases the risk of delayed surgery and long-term risk of non-tumor-related mortality [34–36]. Meanwhile, there are also reports indicating that irAEs may also lead to the failure of neoadjuvant therapy, resulting in patients losing the opportunity for surgery [37, 38]. In addition, the fibrosis of tumor tissue caused by immunotherapy is also considered to increase the difficulty of surgery. In this study, all patients successfully completed surgical resection, with an R0 resection rate of 98.4% and an average surgical time of 305.48 ± 7.12 min. Pleural effusion was the most

Table 4 Postoperative complications

Characteristics	Total, $n = 126$	MPR group, $n = 47$	Non-MPR group, $n = 79$	*P* value
Anastomotic stenosis, *n* (%)				0.281
No	123 (97.6)	49 (100.0)	74 (96.1)	
Yes	3 (2.4)	0 (0.0)	3 (3.9)	
Anastomotic leakage, *n* (%)				1.000
No	121 (96.0)	47 (95.9)	74 (96.1)	
Yes	5 (4.0)	2 (4.1)	3 (3.9)	
Chylothorax, *n* (%)				1.000
No	123 (97.6)	48 (98.0)	75 (97.4)	
Yes	3 (2.4)	1 (2.0)	2 (2.6)	
Empyema, *n* (%)				1.000
No	125 (99.2)	49 (100.0)	76 (98.7)	
Yes	1 (0.8)	0 (0.0)	1 (1.3)	
Incision infection, *n* (%)				0.521
No	124 (98.4)	49 (100.0)	75 (97.4)	
Yes	2 (1.6)	0 (0.0)	2 (2.6)	
Postoperative bleeding, *n* (%)				0.521
No	124 (98.4)	49 (100.0)	75 (97.4)	
Yes	2 (1.6)	0 (0.0)	2 (2.6)	
Pleural effusion, *n* (%)				1.000
No	97 (77.0)	38 (77.6)	59 (76.6)	
Yes	29 (23.0)	11 (22.4)	18 (23.4)	
RLN injury, *n* (%)				0.705
No	119 (94.4)	47 (95.9)	72 (93.5)	
Yes	7 (5.6)	2 (4.1)	5 (6.5)	

MPR: major pathological response; RLN: recurrent laryngeal nerve

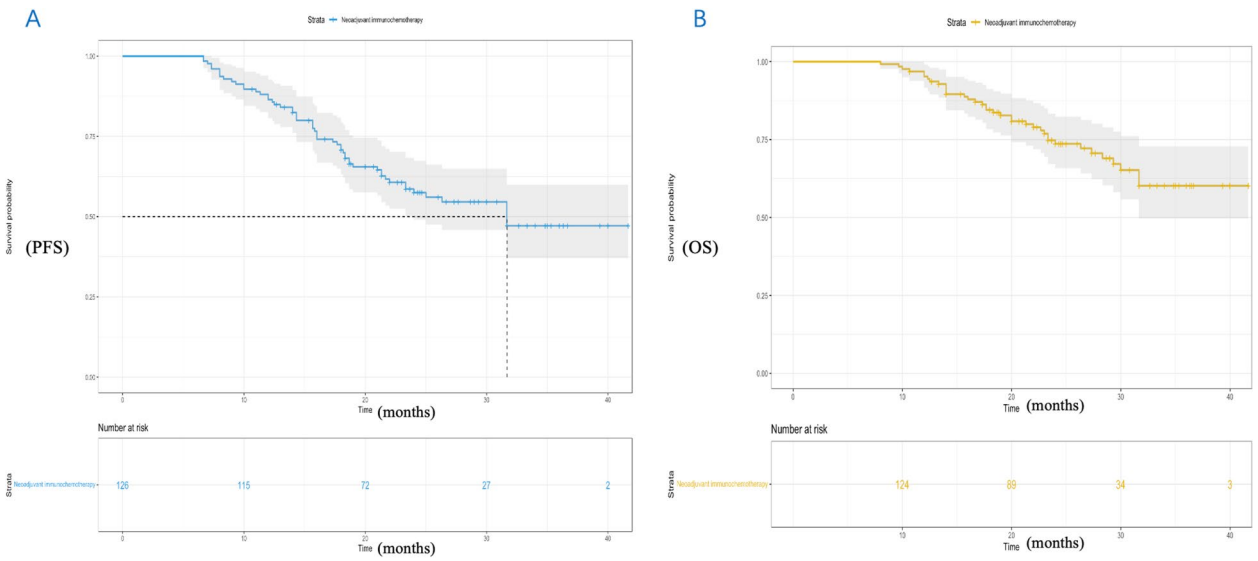

Fig. 3 Kaplan–Meier curves of PFS (**A**) and OS (**B**) for all patients. DFS: disease-free survival; OS: overall survival

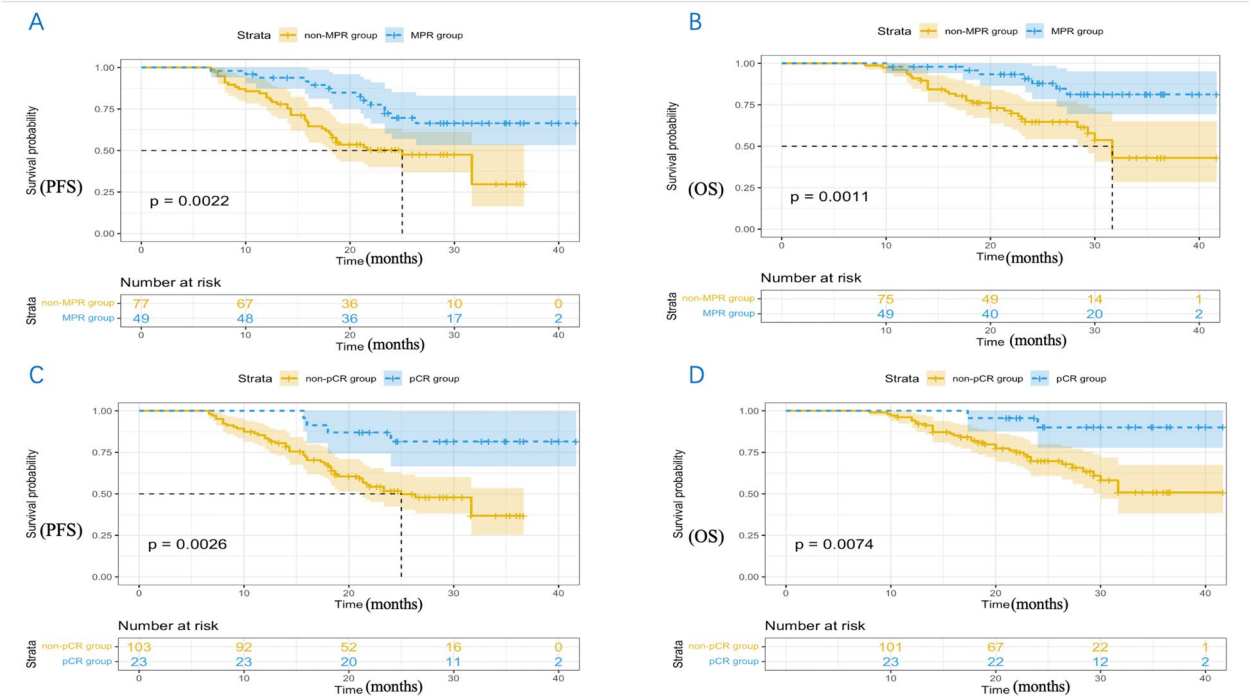

Fig. 4 Kaplan–Meier curves of PFS (**A**) and OS (**B**) between the MPR group and the non-MPR group, and PFS (**C**) and OS (**D**) between the pCR group and the non-pCR group. PFS: progression-free survival; OS: overall survival; MPR: major pathologic response; pCR: pathologic complete response

common postoperative complication, with an incidence rate of 23.0%. The incidence of grade 3/4 irAEs did not exceed 6.8%. It is worth noting that although 6 patients in this study were excluded from the final statistics due to only receipt of one cycle of immunochemotherapy, subsequent follow-up found that they ultimately received surgical treatment. These results suggest that in the real world, irAEs of neoadjuvant immunochemotherapy may be more acceptable to patients compared to nCRT, without increasing the risk of delayed surgery and the incidence of perioperative complications.

For a long time, researchers have tended to use pCR or MPR as the primary endpoint when conducting researches on neoadjuvant therapy. However, the long-term efficacy replacement effect of pCR or MPR has not yet received sufficient evidence-based support. In this study, the evaluation index for pCR was: complete evaluation of tumor resection and lymph node sampling, with no surviving tumor cells found; The evaluation index of MPR was: residual tumor cells in pathological detection of the primary tumor lesion ≤10%. Compared with pCR, the definition of MPR is broader and easier to diagnose in the real world. Exploring whether MPR can replace long-term OS may have more clinical significance. Multiple meta-analyses of neoadjuvant therapy for non-small cell lung cancer have confirmed that MPR can serve as an alternative indicator for long-term survival [29, 39, 40]. There is currently no research confirming the alternative role of MPR in neoadjuvant therapy for ESCC. In this study, 49 people (38.9%) achieved MPR. The median OS of the MPR group was not achieved (HR, 3.607; 95% CI 1.576–8.254; $P = 0.0012$), with the non-MPR group 31.7 months. The 3-year OS rate in the non-MPR group were 61.0%, with that in the MPR group 85.7%. Later, by incorporating factors that might affect long-term OS into multivariate cox analyses, the results showed that MPR was an independent predictor of long-term OS (HR, 2.522; 95% CI 1.018–6.401; $P = 0.046$). These results preliminarily confirmed that in the real world, ESCC who achieved MPR would have better prognosis after neoadjuvant immunochemotherapy, and MPR might have the potential to replace long-term OS. However, this conclusion still needs to be supported by larger real-world studies and prospective clinical researches.

In a series of Phase 2 clinical studies previously reported and our real-world study, the overall MPR rate and pCR rate did not exceed the standard nCRT. However, our research findings suggested that the long-term efficacy of neoadjuvant immunochemotherapy might not be inferior to nCRT. A recent retrospective study involving 202 patients showed that although the pCR rate was still lower than that of the nCRT group,

Table 5 Univariate and multivariate cox regression analyses for OS

Characteristics	Number	Univariate analyses		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex			0.588		
Male	113	1.386 (0.425–4.516)			
Female	13	Reference			
Age			0.330		
≤ 65 Y	62	1.382 (0.721–2.651)			
> 65 Y	64	Reference			
ECOG PS			0.139		0.208
0	63	1.651 (0.850–3.210)		1.540 (0.787–3.013)	
1	63	Reference		Reference	
Smoking status			0.673		
Never	67	0.869 (0.452–1.668)			
Ever	59	Reference			
Drinking status			0.675		
Never	72	0.869 (0.450–1.676)			
Ever	54	Reference			
Tumor location			0.367		
Locus superior	17	1.152 (0.387–3.428)			
Locus medialis	43	1.636 (0.824–3.249)			
Locus inferior	66	Reference			
ORR			0.826		
Yes	88	1.083 (0.534–2.196)			
No	38	Reference			
Treatment cycles			0.332		
2	57	1.201 (0.529–2.727)			
3	41	0.647 (0.243–1.727)			
4	28	Reference			
MPR			**0.002**		**0.046**
Yes	49	3.607 (1.576–8.254)		2.522 (1.018–6.401)	
No	77	Reference		Reference	
cTNM stage			0.160		0.259
II	14	0.450 (0.129–1.568)		1.102 (0.320–3.793)	
III	77	0.538 (0.271–1.068)		1.913 (0.535–6.838)	
VIA	35	Reference		Reference	
Pathological grade			0.726		
Unknown	12	1.106 (0.332–3.684)			
G1	23	0.664 (0.217–2.033)			
G2	60	1.171 (0.515–2.663)			
G3	31	Reference			
ypT stage			**0.014**		0.175
T0–T1	39	3.015 (1.249–7.278)		1.983 (0.737–5.333)	
T2–T4	87	Reference		Reference	
ypN stage			0.206		
N0–N1	104	1.25 (0.766–3.446)			
N2–N3	22	Reference			
Grade 3–4 AEs			0.089		0.065
No	109	5.620 (0.770–41.009)		6.545 (0.889–48.169)	
Yes	17	Reference		Reference	

OS: overall survival; HR: hazard ratio; CI: confidence interval; ECOG PS: eastern cooperative oncology group performance status; ORR: objective response rate; MPR: major pathological response; AEs: adverse events

patients receiving immunochemotherapy had a better 3-year OS rate than those receiving NCRT (89.6% vs. 80.1%, $P = 0.035$) [41]. Multivariate Cox survival analysis showed an independent correlation between immunochemotherapy and better OS, which might be related to the long tail effect of immunochemotherapy. Previous studies have suggested that chemotherapy drugs such as oxaliplatin, cisplatin, and paclitaxel can upregulate the expression of PD-L1 in EC [42–45]. At the same time, chemotherapy drugs can induce ICD in tumors, turning"cold tumors"into"hot tumors"and better activating immune responses. This study did not include cases of combined nCRT, and more clinical studies based on nCRT combined immunotherapy are needed in the future to further explore better combination therapy methods.

This study provided a real-world perspective on neoadjuvant immunochemotherapy for locally advanced ESCC. However, as a retrospective study, our sample size is still limited and lacks inclusion of factors such as PD-L1 expression and TMB load that may affect MPR and OS. Although univariate analysis suggests that better tumor differentiation and earlier ypT stage might be associated with MPR, their causal relationship still needs to be validated by incorporating more clinical indicators and biological targets in the future.

Neoadjuvant immunochemotherapy for locally advanced ESCC can have good safety and long-term efficacy in the real world., enriching the evidence of this treatment model. Whether MPR is achieved is an independent prognostic factor for neoadjuvant immunochemotherapy for locally advanced ESCC. Patients who achieve MPR have longer DFS and OS, and can be used as an alternative endpoint for predicting long-term OS. Further researches are needed to identify these findings.

Author contributions

Jiacong Liu (Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing—original draft). Ziheng Wu (Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing—review and editing,). Shihong Zhou (Conceptualization, investigation, visualization, methodology, writing—original draft). Wang Lv (Conceptualization, investigation, visualization, methodology). Yiqing Wang (Conceptualization, investigation, visualization, methodology), Pinghui Xia (Conceptualization, investigation, visualization, methodology). Linhai Zhu (Conceptualization, investigation, resources, supervision, validation). Jian Hu (Conceptualization, funding acquisition, investigation, resources, supervision, validation). All authors contributed to the article and approved the submitted version.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This trial was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2024 IIT No. 0012), and done in accordance with the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice Guidelines. Written informed consent was obtained from patients so that we could acquire and use required information from their medical record in our hospital.

Competing interests

The authors declare no competing interests.

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