Original Article

Two versus three to four cycles of neoadjuvant immunochemotherapy for locally advanced esophageal squamous cell carcinoma in real-world practice

Jinxian He[1,2], Gaofeng Liang[2], Hongyan Yu[2], Weiyu Shen[2], Jose M. Pimiento[3], Christopher J. Anker[4], Kazuo Koyanagi[5], Jiacong Liu[1], Jian Hu[1,6]

[1]Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Department of Thoracic Surgery, Ningbo Medical Center Lihuili Hospital, Ningbo University, Ningbo, China; [3]Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL, USA; [4]Division of Radiation Oncology, University of Vermont Cancer Center, Burlington, VT, USA; [5]Department of Gastroenterological Surgery, Tokai University School of Medicine, Kanagawa, Japan; [6]Key Laboratory of Clinical Evaluation Technology for Medical Device of Zhejiang Province, Hangzhou, China

Contributions: (I) Conception and design: J He, G Liang, H Yu, W Shen, J Liu, J Hu; (II) Administrative support: J He, J Hu; (III) Provision of study materials or patients: J He, J Hu; (IV) Collection and assembly of data: J He; (V) Data analysis and interpretation: J He; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jian Hu, PhD. Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Hangzhou 310003, China; Key Laboratory of Clinical Evaluation Technology for Medical Device of Zhejiang Province, Hangzhou, China. Email: dr_hujian@zju.edu.cn.

Background: There is currently no consensus on whether intensive cycles of neoadjuvant immunochemotherapy provide greater benefit than do less intensive cycles (two cycles) in esophageal cancer (EC). Therefore, in this study, we assessed the efficacy and safety of three to four cycles of neoadjuvant immunochemotherapy compared to two cycles for treating patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: This is a retrospective study of patients enrolled on previous clinical studies involving locally/regionally advanced ESCC (St. II–IVA) who received preoperative immunochemotherapy at the Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine from 2019 to 2021. In this study, patients were planned to receive 2–4 cycles of chemoimmunotherapy. In this secondary analysis, patients who received three to four cycles of neoadjuvant immunochemotherapy were compared to those receiving two cycles in terms of safety and oncologic outcomes. The follow-up duration required for inclusion was at least one year following surgery, or until the patient died or independently elected to cease treatment if less than one year.

Results: Our study identified a total of 142 participants, who were categorized into two groups based on the number of neoadjuvant treatment cycles: the two cycles group (2 cycles) (n=65) and the three to four cycles group (3–4 cycles) (n=77). Regarding the rate of major pathologic response (MPR), the rates for the 3–4 cycles and 2 cycles groups were 22.1% and 20.0%, respectively, although this difference was not statistically significant (P=0.25). Similarly, the rate of pathologic complete remission (pCR) was higher in the 3–4 cycles group at 14.3% compared to 7.7% in the 2 cycles group, but the difference did not reach statistical significance (P=0.07). However, the incidence of adverse events (AEs) classified as grade 3 or 4 was significantly higher in the 3–4 cycles group than in the 2 cycles group (36.4% *vs.* 18.5%; P=0.02). The median disease-free survival (DFS) for the 3–4 cycles group was 30.8 months [95% confidence interval (CI): not reached to not reached] and was not reached in the 2 cycles group (hazard ratio 2.35, 95% CI: 1.134–4.86; P=0.02). The 2 cycles group did not reach the median overall survival (OS) (hazard ratio 2.47, 95% CI: 1.08–5.53; P=0.045), with that in the 3–4 cycles group 34.9 months (95% CI: 24.5 to not reached). Interestingly, the survival outcomes were more favorable in the 2 cycles group for certain subgroups of patients: those who

were male, those with a history of smoking, those with a history of drinking, and those who did not achieve MPR.

Conclusions: Two cycles of neoadjuvant immunochemotherapy can be considered in locally advanced ESCC at high risk of developing toxicity with 3–4 cycles with similar oncologic outcomes.

Keywords: Locally advanced; esophageal squamous cell carcinoma (ESCC); neoadjuvant immunochemotherapy; treatment cycles; real-world practice

Submitted Aug 22, 2024. Accepted for publication Sep 25, 2024. Published online Oct 28, 2024.
doi: 10.21037/jtd-24-1365
View this article at: https://dx.doi.org/10.21037/jtd-24-1365

Introduction

Esophageal cancer (EC) is the seventh most common cancer in terms of incidence globally and is the sixth leading cause of cancer-related mortality (1). It is predominantly categorized into two histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (2). EAC is more common in Europe and the United States, while ESCC predominantly occurs in Asia, representing around 90% of all EC diagnoses in China (2,3).

A majority of patients are diagnosed with a locally advanced EC [American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system ≥ cT2 and/or cN1–3, M0] (4). Although surgery has always been the dominant therapy for EC, surgery alone is usually associated with high rates of recurrence or metastasis and with poor survival among patients with locally advanced EC (5). Consequently, multidisciplinary therapy involving chemotherapy or chemoradiation in addition to surgery has emerged as potential alternatives. The Japan Clinical Oncology Group study (JCOG9907) found that neoadjuvant chemotherapy (NAC) plus surgery could improve survival compared to surgery alone (6). The findings from the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) and Neo-adjuvant Chemoradiotherapy Followed by Surgery Versus Surgery for Locally Advanced Squamous Cell Esophageal Carcinoma Study (NEOCRTEC5010) indicated that patients with locally advanced EC who underwent neoadjuvant chemoradiotherapy (NCRT) in conjunction with surgery experience better survival outcomes than did those treated with surgery alone (7,8). As a result, the combination of NAC or NCRT followed by surgical resection is now considered the standard therapeutic approach for managing locally advanced EC. However, the postoperative recurrence rate is still high, and there remains a high risk of recurrence and metastasis (4). Therefore, the efficacy of neoadjuvant therapy still needs to be further improved to reduce postoperative recurrence and improve prognosis.

Over the past few years, immunotherapy targeting the programmed cell death protein 1–programmed death-ligand 1 immune checkpoint pathways has emerged as a significant component in the therapeutic arsenal of EC treatment, offering new avenues for disease management. The Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer Study (CheckMate 577) demonstrated that disease-free survival (DFS) was markedly extended among those who received adjuvant immunotherapy (nivolumab) as compared to those who received adjuvant chemotherapy (9). The Nivolumab Versus Chemotherapy for AdvancedOesophageal Squamous Cell Carcinoma

Highlight box

Key findings

- Intensive neoadjuvant immunochemotherapy may not be superior to a less intensive cycle (2 cycles) for patients with locally advanced esophageal squamous cell carcinoma (ESCC).

What is known and what is new?

- There is currently no consensus on whether a longer duration of neoadjuvant immunochemotherapy (i.e., 3–4 cycles) provides better outcomes as compared to a less intensive regimen (2 cycles) in ESCC.
- We conducted this retrospective study to determine whether an intensive cycle (3–4 cycles) of neoadjuvant immunochemotherapy is superior to a less intensive cycle (2 cycles) for patients with locally advanced ESCC.

What is the implication, and what should change now?

- Larger-sample, randomized controlled trials are needed to confirm the superiority of intensive cycles of neoadjuvant immunochemotherapy over less intensive cycles in treating locally advanced ESCC.

Refractory or Intolerant to Previous Chemotherapy Study (ATTRACTION-3), Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer Study (KEYNOTE-181), and Camrelizumab Versus Chemotherapy for Advanced or Metastatic Oesophageal Squamous Cell Carcinoma Study (ESCORT) showed that immunochemotherapy as a second-line treatment of metastatic EC can provide a significant improvement in overall survival (OS) compared with chemotherapy (10-12). Moreover, the Pembrolizumab plus Chemotherapy Versus Chemotherapy Alone for Advanced Oesophageal Cancer Study (KEYNOTE-590) and Camrelizumab Versus Chemotherapy for Advanced or Metastatic Esophageal Squamous Cell Carcinoma Study (ESCORT-1st) reported that the integration of immunotherapy with chemotherapy as a first-line treatment for metastatic EC yielded a significant enhancement in OS when compared to chemotherapy administered in isolation (13,14). Given the rapid progress of immunotherapy in the field of postoperative adjuvant therapy, its application as first-line and second-line treatment in advanced EC are also highly anticipated, and studies [e.g., Camrelizumab combined with Chemotherapy as Neoadjuvant Therapy for Locally Advanced Esophageal Squamous Cell Carcinoma Study (ESPRIT), Preoperative Pembrolizumab plus Chemotherapy for Resectable Esophageal Squamous Cell Carcinoma Study (Keystone-001), Camrelizumab plus Chemotherapy Versus Concurrent Chemoradiotherapy as Neoadjuvant Therapy for Resectable Thoracic Oesophageal Squamous Cell Cancer Study (REVO)] examining different neoadjuvant immunotherapy combinations are in progress (15-17). The Tislelizumab Combined with Chemotherapy as Neoadjuvant Therapy for Surgically Resectable Esophageal Cancer Study (TD-NICE) and Camrelizumab and Chemotherapy as Neoadjuvant Treatment for Locally Advanced Esophageal Squamous Cell Carcinoma Study (NICE) found that immunotherapy plus chemotherapy as neoadjuvant therapy for surgically resectable EC was effective and tolerable (18,19). Meanwhile, the Preoperative pembrolizumab combined with Chemoradiotherapy for Oesophageal Squamous Cell Carcinoma Study (PALACE-1) found preoperative immunotherapy (pembrolizumab) combined with chemoradiotherapy was feasible and safe for patients with locally advanced and surgically resectable EC (20). What's more, Zhang *et al.* found that the 3-year OS rate after neoadjuvant chemoimmunotherapy (NCIT) was 73.3%, slightly higher than 39.7% after NCRT, with no statistically significant differences (P=0.883) (21). The results of the Neoadjuvant Chemotherapy with or without Camrelizumab in Resectable Esophageal Squamous Cell Carcinoma Study (ESCORT-NEO/NCCES01) confirmed that NCIT significantly improved the pathological complete remission (pCR) rate of locally advanced EC compared to NAC alone, and the overall safety was controllable (22).

To the best of our knowledge, there is currently no consensus regarding the number of cycles of neoadjuvant therapy, and there have been few studies performed comparing two cycles to a more intensive number of cycles in neoadjuvant therapy for patients with locally advanced ESCC. Several studies have reported that three cycles of preoperative chemotherapy for locally advanced EC did not result in better outcomes as compared to two cycles (23,24). In contrast, other research suggests that three cycles of neoadjuvant chemotherapy or immunochemotherapy for those with locally advanced ESCC increases tumor regression as compared to immunochemotherapy of two cycles (25-27). Consequently, we conducted this retrospective analysis to determine whether administering an intensive regimen of three to four cycles of neoadjuvant immunochemotherapy offers superior outcomes for patients with locally advanced ESCC as compared to two cycles of immunochemotherapy. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1365/rc).

Methods

Study design and patients

All patients in this article were selected from our previous clinical studies that involved neoadjuvant therapy for EC. The current study is a retrospective analysis of patients enrolled on these studies comparing safety and oncologic outcomes of those with locally advanced ESCC who received either 2 *vs.* 3–4 cycles of neoadjuvant chemoimmunotherapy at the Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, from 2019 to 2021. Included patients were divided into two groups according to neoadjuvant treatment cycles: a 2 cycles group and a 3–4 cycles group. This study was granted approval by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2021 IIT no. 742). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the principles of good clinical practice. All patients signed a written informed consent form.

The eligibility criteria for this study were as follows: (I) age between 18 and 80 years, (II) a histopathological diagnosis of ESCC as confirmed via gastroscopy, (III) pretreatment clinical staging of II-IVA as per the eighth edition of the AJCC TNM staging system (28), (IV) completion of 2–4 cycles of neoadjuvant immunotherapy in combination with chemotherapy, and (V) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Meanwhile, the exclusion criteria were as follows: a lack of comprehensive basic and therapeutic records [such as characteristics at baseline, adverse events (AEs) of neoadjuvant immunochemotherapy, surgical outcomes and pathological response, conditions of disease recurrence and metastasis, etc.]; previous cancer treatment including radiotherapy, interventional procedures, or pharmacological interventions; presence of autoimmune disorders or infectious diseases; ongoing systemic immunosuppressive therapy; a history of other types of malignancies; and presence of distant metastasis.

Treatment procedures

Before the initiation of neoadjuvant therapy, a comprehensive set of imaging assessments were conducted on the patients, encompassing esophageal computed tomography (CT) scans, endoscopic ultrasounds, positron emission tomography (PET)-CT scans, brain magnetic resonance imaging (MRI), and abdominal ultrasounds. Subsequently, all participants were administered 2–4 cycles of neoadjuvant immunochemotherapy, with each cycle lasting for 3 weeks. The immunotherapy protocol consisted of 200 mg of camrelizumab, 200 mg of sintilimab, 200 mg of tislelizumab, or 200 mg of pembrolizumab. Concurrently, the chemotherapy component included etoposide at a dosage of 100 mg per square meter of body surface area, and either cisplatin at 75 mg per square meter, or carboplatin with an area under the curve (AUC) of the drug plasma concentration set to equal 5. Throughout the neoadjuvant therapy phase, chest CT scans were performed every two cycles, continuing until the patient underwent surgery or decided to discontinue treatment. Routine blood tests and biochemical analyses were conducted on a weekly basis. Additionally, myocardial enzyme profiles, thyroid function tests, and coagulation function assessments were scheduled every three weeks. Evaluations of gastrointestinal and skin reactions were based on patients' self-reported symptoms and complaints. Evaluation of cTNM, ycTNM and ypTNM were carried out according to the 8th edition of AJCC TNM staging (28). After 2–4 cycles of neoadjuvant therapy, we would make an assessment on patients to see whether there was a surgical chance. If there was obvious tumor regression, surgery would be performed. The surgical techniques employed in this study included open radical surgery, video-assisted thoracoscopic surgery (VATS), and robot-assisted thoracoscopic surgery (RATS). The specific surgical approaches used were the McKeown and Ivor Lewis methods. In cases of lower-and middle-thoracic ESCC, the surgical treatment involved an Ivor Lewis esophagectomy accompanied by at least a two-field lymphadenectomy. Conversely, for upper-thoracic ESCC, the McKeown esophagectomy was the chosen method, which included a comprehensive three-field lymph node dissection of lymph nodes from the neck, thorax, and abdomen. Postoperatively, imaging evaluations were scheduled at intervals of 1 to 3 months. Following the surgical procedure, patients were administered chemotherapy in conjunction with immunotherapy, continuing up to the completion of six full cycles. Subsequently, the treatment protocol involved the continuation of immune checkpoint inhibitors (ICIs) monotherapy for a duration of 1–2 years or until there was documented evidence of disease progression. The follow-up duration required for inclusion was at least one year following surgery, or until the patient died or independently elected to cease treatment if less than one year. To collect follow-up data, we relied on patients' routine check-ups or ongoing treatments conducted at our hospital. In instances where direct access to patient records was not feasible, we resorted to contacting patients via telephone or through messaging platforms such as WeChat to ensure continuity.

End points and assessments

The primary outcomes of interest in this study were DFS and OS. DFS was measured from the date of surgery to the earliest occurrence of disease progression as per the Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1 (29)] or patient death. Meanwhile, OS was calculated from the date of surgery to the time of death from any cause.

The secondary outcomes of this study included the assessment of the objective response rate (ORR), the incidence and severity of AEs, and the extent of pathological response to treatment. The evaluation of tumor response to therapy was conducted using the RECIST 1.1, which classifies responses as follows: complete response (CR), the total absence of all target lesions; partial response (PR),

a reduction of at least 30% in the combined diameters of the target lesions; progressive disease (PD), an increase of at least 20% in the sum of the diameters of target lesions or the emergence of new lesions; and stable disease (SD), any response not satisfying the conditions for CR, PR, or PD. The ORR was determined by combining the rates of CR and PR. AEs were classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (30). The pathological response was quantified with the tumor regression grade (TRG) system, which is divided into four levels based on the guidelines from the College of American Pathologists and The National Comprehensive Cancer Network: TRG 0 indicates no viable cancer cells, including lymph nodes, TRG 1 indicates single cells or rare small groups of cancer cells, TRG 2 indicates residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells, and TRG 3 indicates extensive residual cancer with no evident tumor regression. The rates of pCR and major pathologic response (MPR) correspond to TRG 0 and TRG 0–1, respectively.

Statistical analysis

Categorical data are presented in terms of frequency distributions and their respective percentages, and group differences were assessed using the chi-square test or Fisher exact test, as appropriate. For continuous variables, the median and interquartile range (IQR) are reported, and group comparisons were conducted with the *t*-test or the Wilcoxon test depending on the data distribution. DFS and OS were analyzed using the Kaplan-Meier method, with group differences evaluated using the stratified log-rank test. The median follow-up duration was calculated with the reverse Kaplan-Meier method. Furthermore, Cox proportional-hazards models were used to examine the relationship between each variable under study and the survival outcomes. Statistical analyses were completed using R version 4.1.2 software (The R Foundation for Statistical Computing) and GraphPad Prism version 9.0 (GraphPad Software, La Jolla, CA, USA). A two-sided P value of less than 0.05 was considered to be significant.

Results

Characteristics at baseline

Our study identified 142 consecutive patients who received one of the two neoadjuvant treatment cycle plans: the 2 cycles group (n=65) and the 3–4 cycles group (n=77). The baseline characteristics of the patients are detailed in *Table 1*. Upon comparison, no significant disparities were observed between the two groups with respect to age, gender, ECOG performance status, smoking habits, alcohol consumption, presence of comorbid conditions, tumor location, histological grading, administered immunotherapy protocols, or the clinical staging of the disease.

Response to neoadjuvant therapy

Figure 1A illustrates the percentage change in the maximum diameter of the target lesion relative to the baseline tumor size in patients. A significant reduction in the maximum diameter was noted at the conclusion of the second cycle (*Figure 1B*), third cycle (*Figure 1C*), and fourth cycle (*Figure 1D*) when compared to the initial measurements. Additionally, a significant shrinkage in tumor diameter was observed posttreatment during the third cycle (*Figure 1E*) and the fourth cycle (*Figure 1F*) in comparison to the measurements at the end of the second cycle. It is important to note that there were no instances of CR in either group. The rate of PR for the 2 cycles group was 66.2%, whereas that for the 3–4 cycles group was 75.3% (P=0.23; *Figure 2A*). The ORR in the two groups was 93.8% and 93.5%, respectively.

Toxicity

Our study did not encounter any previously unreported AEs, as detailed in *Table 2*. The 2 cycles group had an AE incidence rate of 93.8% (61/65), while the 3–4 cycles group had a slightly higher rate of 98.7% (76/77) (P=0.12). The incidence of anemia in the 3–4 cycles group was significantly higher than that in the 2 cycles group (84.4% *vs.* 69.2%; P=0.03), but no significant differences were observed in the types of other AEs between the two groups. The incidence of grade 3–4 AEs was 36.4% (28/77) in the 3–4 cycles group and 18.5% (12/65) in the 2 cycles group (P=0.02). The majority of grade 3–4 AEs were hematological disorders. The incidence of grade 3–4 anemia in the 3–4 cycles group was also significantly higher than that in the 2 cycles group (28.6% *vs.* 12.3%; P=0.02), but no significant differences were noted in the incidence of other grade 3–4 AEs between the two groups. These AEs were promptly addressed and resolved following appropriate symptomatic treatment.

Table 1 Characteristics of the full cohort (n=142) at baseline

Variable	Total, n=142	2 cycles, n=65	3–4 cycles, n=77	P
Age (years)	66.5 (59.0–71.0)	65.0 (57.5–70.0)	67.0 (60.0–71.5)	0.60
Gender				0.58
Male	129 (90.8)	60 (92.3)	69 (89.6)	
Female	13 (9.2)	5 (7.7)	8 (10.4)	
ECOG performance status				0.62
0	84 (59.2)	37 (56.9)	47 (61.0)	
1	58 (40.8)	28 (43.1)	30 (39.0)	
Smoking status				0.67
Never	65 (45.8)	31 (47.7)	34 (44.2)	
Ever	77 (54.2)	34 (52.3)	43 (55.8)	
Drinking status				0.61
Never	71 (50.0)	31 (47.7)	40 (52.0)	
Ever	71 (50.0)	34 (52.3)	37 (48.0)	
Comorbidities				
Diabetes mellitus	13 (9.2)	6 (9.2)	7 (9.1)	0.98
Hypertension	44 (31.0)	18 (27.7)	26 (33.8)	0.44
Pathological grade				0.77
G1	8 (5.6)	5 (7.7)	3 (4.0)	
G2	71 (50.0)	32 (49.2)	39 (50.6)	
G3	36 (25.4)	17 (26.2)	19 (24.7)	
Unknown	27 (19.0)	11 (16.9)	16 (20.8)	
Tumor location				0.97
Locus superior	21 (14.8)	10 (15.4)	11 (14.3)	
Locus medialis	78 (54.9)	35 (53.8)	43 (55.8)	
Locus inferior	43 (30.3)	20 (30.8)	23 (29.9)	
Immunotherapy regimen				0.09
Camrelizumab, 200 mg	99 (69.7)	52 (80.0)	47 (61.0)	
Sintilimab, 200 mg	19 (13.4)	6 (9.2)	13 (16.9)	
Tislelizumab, 200 mg	16 (11.3)	4 (6.2)	12 (15.6)	
Pembrolizumab, 200 mg	8 (5.6)	3 (4.6)	5 (6.5)	
cT stage				0.32
T2	19 (13.4)	11 (16.9)	8 (10.4)	
T3	81 (57.0)	32 (49.2)	49 (63.6)	
T4a	7 (4.9)	3 (4.6)	4 (5.2)	
T4b	35 (24.6)	19 (29.2)	16 (20.8)	
cN stage				0.20
N0	15 (10.6)	9 (13.8)	6 (7.8)	
N1	49 (34.5)	19 (29.2)	30 (39.0)	
N2	72 (50.7)	36 (55.4)	36 (46.8)	
N3	6 (4.2)	1 (1.5)	5 (6.5)	
c stage				0.63
II	19 (13.5)	10 (15.4)	9 (8.0)	
III	78 (63.5)	33 (50.8)	45 (48.0)	
IVA	45 (23.1)	22 (33.8)	23 (44.0)	

Data are presented as n (%) or median (IQR). ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

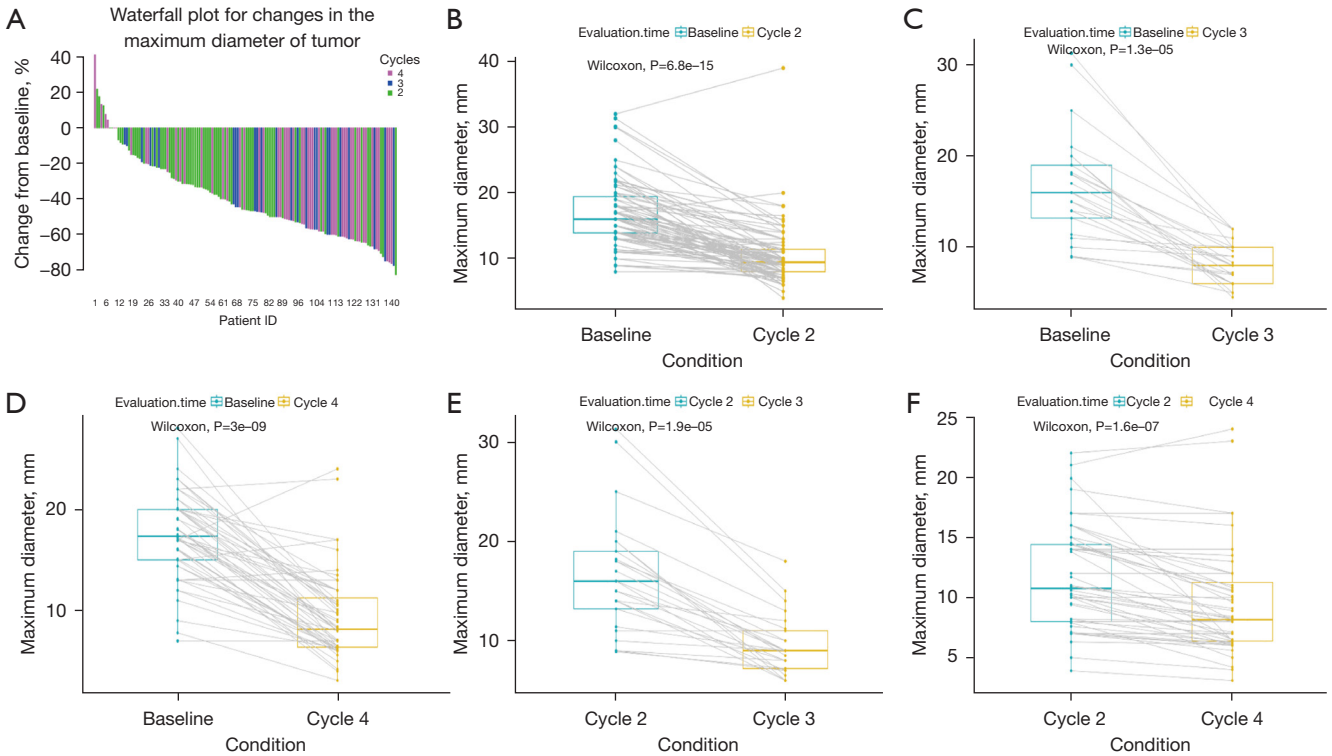

Figure 1 Changes in the maximum diameter of the target lesion during neoadjuvant therapy. (A) The percentage change in the maximum diameter of target lesion from the baseline to the end of the last neoadjuvant immunochemotherapy cycle in the full cohort (n=142). (B) The change of the maximum diameter of the target lesion from the baseline to the end of the second cycle of neoadjuvant immunochemotherapy in patients who received two cycles of neoadjuvant immunochemotherapy (n=65). (C) The change of the maximum diameter of the target lesion from the baseline to the end of the third cycle of neoadjuvant immunochemotherapy in patients who received three cycles of neoadjuvant immunochemotherapy (n=25). (D) The change of the maximum diameter of the target lesion from the baseline to the end of the fourth cycle of neoadjuvant immunochemotherapy in patients who received four cycles of neoadjuvant immunochemotherapy (n=52). (E) The change of the maximum diameter of the target lesion from the end of the second cycle to the end of the third cycle of neoadjuvant immunochemotherapy in patients who received three cycles of neoadjuvant immunochemotherapy (n=25). (F) The change of the maximum diameter of the target lesion from the end of the second cycle to the end of the fourth cycle of neoadjuvant immunochemotherapy in patients who received four cycles of neoadjuvant immunochemotherapy (n=52).

Surgery and pathological response

Among those that received neoadjuvant chemoimmunotherapy, 109 patients (postoperative population) underwent surgery. In the 2 cycles group, 4 patients did not undergo surgery due to the occurrence of metastatic disease and 4 patients declined surgery. In the 3–4 cycles group, 5 patients did not undergo surgery due to the occurrence of metastatic disease and 20 patients declined surgery. The surgical outcomes and the pathological responses are summarized in *Table 3*. There was a greater proportion of patients who underwent VATS and RATS in the 3–4 cycles group than in the 2 cycles group. Moreover, 100.0% of patients in the 2 cycles group and 98.1% of those in the 3–4 cycles group successfully underwent R0 resection. There were no significant differences in the surgical outcomes or postoperative complications, and there were no recorded perioperative mortalities. Examination of the ypTNM stage distribution revealed a higher number of patients classified in stage 0 in the 3–4 cycles group. Meanwhile, the MPR rate in the 3–4 cycles and 2 cycles groups were 22.1% and 20.0%, respectively, although this difference was not statistically significant (P=0.25; *Figure 2B*). Similarly, the rate of pCR was higher in the 3–4 cycles group at 21.2% as compared to 7.7% in the 2 cycles group (P=0.07; *Figure 2C*).

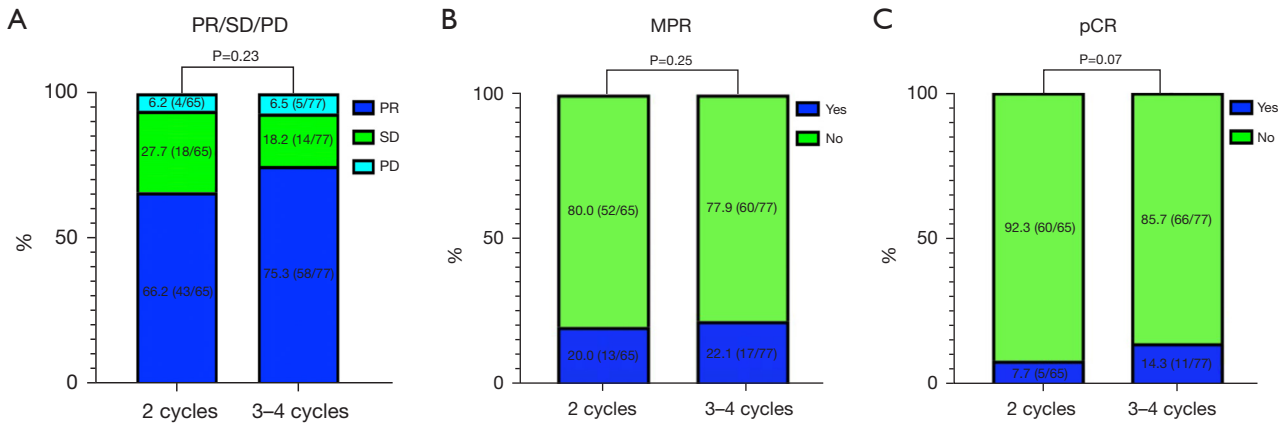

Figure 2 The distribution conditions of clinical response in the full cohort (n=142), and pathological response in the PP population (n=109) between the two cycles group and three to four cycles group: (A) PR/SD/PD, (B) MPR, and (C) pCR. Clinical response included partial PR, SD, and PD. Pathologic response included MPR and pCR. PR, partial remission; SD, stable disease; PD, progressive disease; MPR, major pathologic response; pCR, pathological complete remission; PP, postoperative.

Table 2 AEs of neoadjuvant immunochemotherapy in the full cohort (n=142)

Event	Any grade				Grade 3 or 4			
	Total, n=142	2 cycles, n=65	3–4 cycles, n=77	P	Total, n=142	2 cycles, n=65	3–4 cycles, n=77	P
Any AEs	137 (96.5)	61 (93.8)	76 (98.7)	0.12	40 (28.2)	12 (18.5)	28 (36.4)	0.02
Hematologic								
Leukopenia	26 (18.3)	11 (16.9)	15 (19.5)	0.70	5 (3.5)	3 (4.6)	2 (2.6)	0.66
Agranulocytosis	26 (18.3)	11 (16.9)	15 (19.5)	0.70	5 (3.5)	3 (4.6)	2 (2.6)	0.66
Anemia	110 (77.5)	45 (69.2)	65 (84.4)	0.03	30 (21.1)	8 (12.3)	22 (28.6)	0.02
Thrombocytopenia	30 (21.1)	9 (13.8)	21 (27.3)	0.051	2 (1.4)	1 (1.5)	1 (1.3)	>0.99
Gastrointestinal								
Nausea	34 (23.9)	15 (23.1)	19 (24.7)	0.82	0 (0.0)	0 (0.0)	0 (0.0)	NA
Emesis	27 (19.0)	12 (18.5)	15 (19.5)	0.88	0 (0.0)	0 (0.0)	0 (0.0)	NA
Diarrhea	20 (14.1)	8 (12.3)	12 (15.6)	0.58	0 (0.0)	0 (0.0)	0 (0.0)	NA
Constipation	27 (19.0)	9 (13.8)	18 (23.4)	0.15	0 (0.0)	0 (0.0)	0 (0.0)	NA
Hepatic injury	34 (23.9)	12 (18.5)	22 (28.6)	0.16	6 (4.2)	2 (3.1)	4 (5.2)	0.69
Renal injury	31 (21.8)	12 (18.5)	19 (24.7)	0.37	0 (0.0)	0 (0.0)	0 (0.0)	NA
Skin reaction	72 (50.7)	34 (52.3)	38 (49.4)	0.73	5 (3.5)	1 (1.5)	4 (5.2)	0.38
Hypothyroidism	1 (0.7)	1 (1.5)	0 (0.0)	0.46	0 (0.0)	0 (0.0)	0 (0.0)	NA
Coagulation disorders	1 (0.7)	1 (1.5)	0 (0.0)	0.46	0 (0.0)	0 (0.0)	0 (0.0)	NA
Esophageal fistula	1 (0.7)	1 (1.5)	0 (0.0)	0.46	0 (0.0)	0 (0.0)	0 (0.0)	NA

Data are presented as n (%). AEs, adverse events; NA, not achieved.

Table 3 Surgical outcomes and pathological response in the PP population (n=109)

Variable	Total, n=109	2 cycles, n=57	3–4 cycles, n=52	P value
Surgical approach				0.10
Open	39 (35.8)	25 (43.9)	14 (26.9)	
VATS	57 (52.3)	26 (45.6)	31 (59.6)	
RATS	11 (10.1)	4 (7.0)	7 (13.5)	
VATS-open	2 (1.8)	2 (3.5)	0 (0.0)	
Operation time (min)	280.0 (244.0–324.0)	275.5 (241.8–330.0)	281.0 (249.0–318.0)	0.65
Estimated blood loss (mL)	100.0 (50.0–100.0)	100.0 (50.0–100.0)	100.0 (50.0–100.0)	0.68
Resection margin				0.48
R0	108 (99.1)	57 (100.0)	51 (98.1)	
R1	1 (0.9)	0 (0.0)	1 (1.9)	
Number of lymph node dissections during surgery	18.5 (11.0–29.0)	21.5 (11.0–32.0)	17.0 (11.3–27.0)	0.96
Length of hospital stay (days)	18.0 (14.0–23.0)	20.0 (14.3–24.0)	18.0 (14.0–21.0)	0.93
Postoperative complications				
Overall	23 (82.4)	14 (75.0)	9 (82.4)	0.48
Aspiration pneumonia	6 (5.5)	3 (5.3)	3 (5.8)	>0.99
Anastomotic leak	6 (5.5)	3 (5.4)	3 (5.9)	>0.99
Tracheoesophageal fistula	1 (0.9)	1 (1.8)	0 (0.0)	>0.99
Chyle leak	1 (0.9)	1 (1.8)	0 (0.0)	>0.99
Anastomotic stenosis	2 (1.8)	1 (1.8)	1 (0.0)	>0.99
Gastroparesis	1 (0.9)	1 (1.8)	0 (0.0)	>0.99
Intestinal obstruction	2 (1.8)	1 (1.8)	1 (0.0)	>0.99
Diaphragmatic paralysis	1 (0.9)	1 (1.8)	0 (0.0)	>0.99
Delayed incision healing	1 (0.9)	1 (1.8)	0 (0.0)	>0.99
Postoperative bleeding	1 (0.9)	1 (1.8)	0 (0.0)	>0.99
Abdominal infection	1 (0.9)	0 (0.0)	1 (0.0)	0.48
Pathological response				0.08
TRG 0	16 (14.7)	5 (8.8)	11 (21.2)	
TRG 1	14 (12.8)	8 (14.0)	6 (11.5)	
TRG 2	56 (51.4)	35 (61.4)	21 (40.4)	
TRG 3	23 (21.1)	9 (15.8)	14 (26.9)	
ypTNM stage				0.45
0	16 (14.7)	5 (8.8)	11 (21.2)	
I	11 (10.1)	6 (10.5)	5 (9.6)	
II	32 (29.4)	19 (33.3)	13 (25.0)	
IIIA	9 (8.3)	4 (7.0)	5 (9.6)	
IIIB	40 (36.7)	22 (38.6)	18 (34.6)	
IVA	1 (0.9)	1 (1.8)	0 (0.0)	

Data are presented as n (%) or median (IQR). PP, postoperative; VATS, video-assisted thoracoscopic surgery; RATS, robot-assisted thoracoscopic surgery; TRG, tumor regression grade; TNM, tumor-node-metastasis; IQR, interquartile range.

Table 4 Conditions of disease recurrence and metastasis in the PP population (n=109)

Recurrence and metastasis	2 cycles, n=57	3–4 cycles, n=52	P value
Overall	13 (22.8)	18 (34.6)	0.17
Anastomotic recurrence	4 (7.0)	2 (3.8)	0.76
Any distant recurrence	9 (15.8)	13 (25.0)	0.23
Site of distant metastasis			
Brain	1 (1.8)	2 (3.8)	0.94
Liver	0 (0.0)	2 (3.8)	0.23
Bone	4 (7.0)	3 (5.8)	>0.99
Lung	1 (1.8)	3 (5.8)	0.55
Lymph node	2 (3.5)	1 (1.9)	>0.99
Renicapsule	1 (1.8)	2 (3.8)	>0.99

Data are presented as n (%). PP, postoperative.

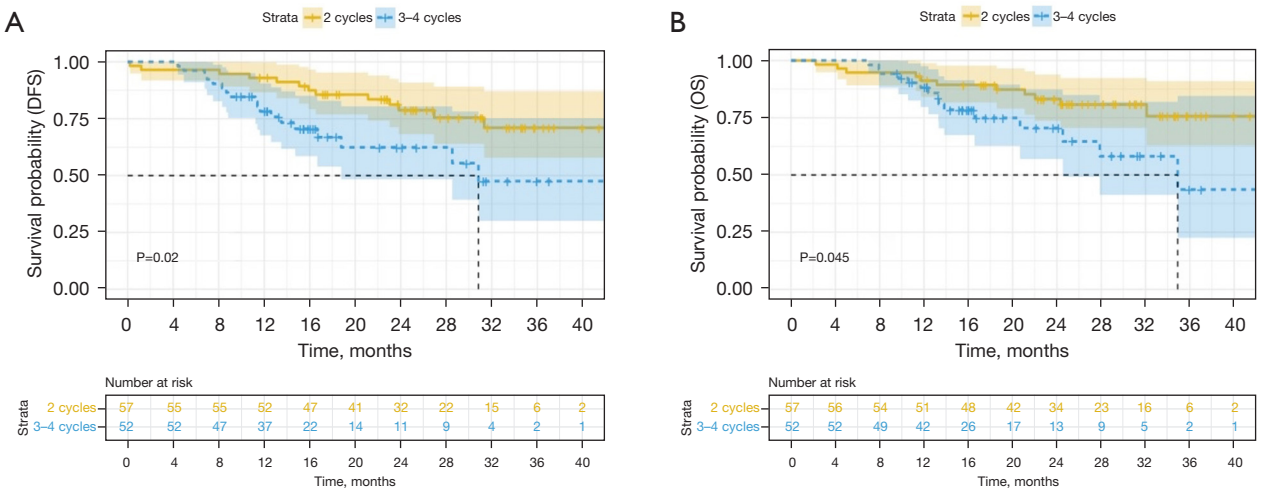

Figure 3 Kaplan-Meier curves of (A) DFS and (B) OS in the PP population (n=109) between the two cycles group and three to four cycles group. DFS, disease-free survival; OS, overall survival; PP, postoperative.

Survival

As of the data cutoff date in April 2023, we successfully collected follow-up data from the postoperative population, which included 57 cases from the 2 cycles group and 52 cases from the 3–4 cycles group. The median duration of follow-up for the 2 cycles group was 27.5 months [95% confidence interval (CI): 25.1 to 33.3 months]. In contrast, the median follow-up for the 3–4 cycles group was 17.6 months [95% CI: 16.0 to 25.4 months]. Among the postoperative population, 22.8% (13/57) patients experienced recurrence and metastasis in the 2 cycles group, and 34.6% (18/52) patients experienced recurrence and metastasis in the 3–4 cycles group (*Table 4*). The conditions of disease recurrence and metastasis in the two group were similar, with no significant differences (P>0.05).

The median DFS in the 3–4 cycles group was 30.8 months (95% CI: 18.8 to not reached) and was not reached in the 2 cycles group [hazard ratio (HR) 2.35, 95% CI: 1.14–4.86; P=0.02] (*Figure 3A*). In the 2 cycles group, the DFS rates at one, two, and three years were 93.0%, 80.7%, and 77.2%, respectively, while those in the 3–4 cycles group were 84.6%, 69.2%, and 65.4%, respectively. The 2 cycles group did not reach median OS (HR 2.47; 95% CI: 1.08–5.53;

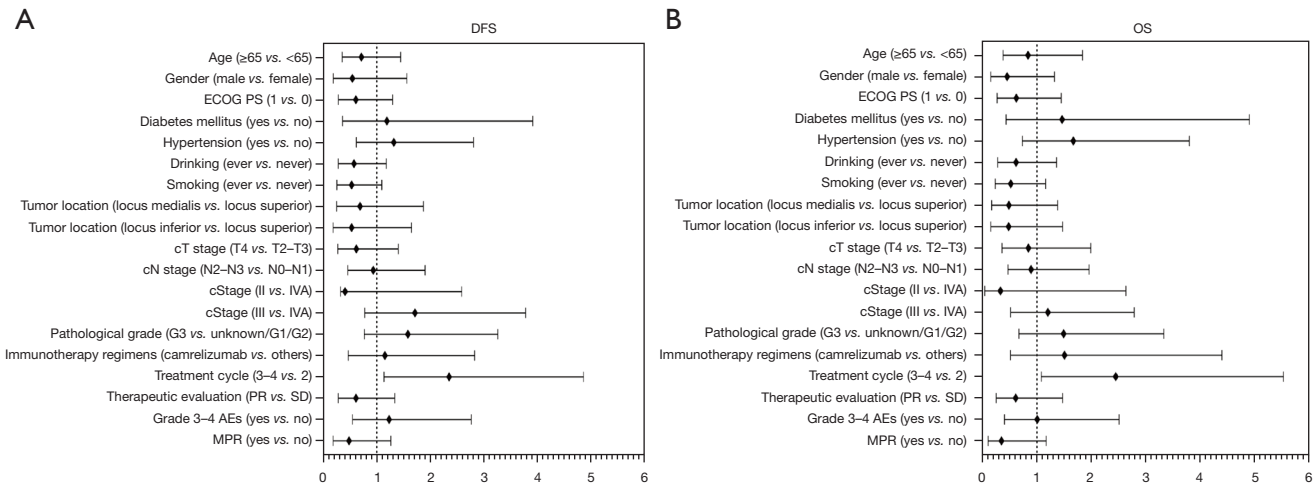

Figure 4 Forest plot of hazard ratio for (A) DFS and (B) OS in the PP population (n=109). The description of the x-axis is hazard ratio (HR). PP, postoperative; DFS, disease-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial remission; SD, stable disease; AE, adverse event; MPR, major pathologic response.

P=0.045), while the median OS in the 3–4 cycles group was 34.9 months (95% CI: 24.5 to not reached) (*Figure 3B*). For the 2 cycles group, the OS rates at one, two, and three years were 91.2%, 84.2%, and 80.7%, respectively, while those for the 3–4 cycles group were 88.5%, 76.9%, and 71.2%, respectively. Furthermore, expect for treatment cycle length, univariate Cox regression analysis revealed no statistically significant associations between the patients' baseline characteristics and DFS (*Figure 4A*) or OS (*Figure 4B*).

We subsequently performed subgroup analyses to identity the possible factors that might affect DFS and OS of the postoperative population in 2 cycles and 3–4 cycles groups (*Table 5*). We found the DFS between the 2 cycles group and 3–4 cycles group was significantly different in patients ≥65 years old (HR 3.30, 95% CI: 1.07–10.15; P=0.04), male patients (HR 2.74, 95% CI: 1.25–6.00; P=0.01), ever-smokers (HR 5.27, 95% CI: 1.56–17.81; P=0.008), ever-drinkers (HR 5.13, 95% CI: 1.51–17.43; P=0.009), patients with SD (HR 5.72; 95% CI: 1.28–25.59; P=0.02), and patients without MPR (HR 2.58, 95% CI: 1.17–5.67; P=0.02). The 2 cycles group demonstrated superior DFS compared to the 3–4 cycles group in patients ≥65 years old, male patients, ever-smokers, ever-drinkers, patients with SD, and patients without MPR. Among individuals aged 65 years and above, the median duration of DFS in the group treated with 3–4 cycles was 30.8 months (95% CI: 25.6–36.1 months). In the group treated with 2 cycles, the median DFS was not achieved, and this difference was statistically significant (P=0.03) (*Figure 5A*). In the male patient cohort, the median duration of DFS for those in the 3–4 cycles group was 30.8 months (95% CI: 15.0–46.6 months), whereas the 2 cycles group had a median DFS that was not reached, representing a statistically significant difference (P=0.009; *Figure 5B*). Among patients with a history of smoking, the median DFS for the 3–4 cycles group was 30.8 months (95% CI: 8.8–52.8 months), while the 2 cycles group's median DFS was not reached, representing a statistically significant difference (P=0.004; *Figure 5C*). For patients with a history of alcohol consumption, the median DFS in the 3–4 cycles group was 30.8 months (95% CI: 17.1–44.5 months), and again, the 2 cycles group's median DFS was not reached, representing a statistically significant difference (P=0.004; *Figure 5D*). In patients with SD, the 3–4 cycles group had a median DFS of 11.4 months (95% CI: 11.0–11.8 months), which contrasted with the 2 cycles group's median DFS of 31.3 months (95% CI: 17.0–45.7 months), and this difference was statistically significant (P=0.01; *Figure 5E*). Finally, among patients without MPR, the 3–4 cycles group's median DFS was 28.5 months (95% CI: 15.4–41.6 months), and the 2 cycles group's median DFS was not reached, representing a statistically significant difference (P=0.02; *Figure 5F*).

We also found the OS between 2 cycles group and 3–4 cycles group was significantly different in male patients (HR 2.54, 95% CI: 1.07–6.03; P=0.04), ever-smokers (HR

Table 5 Possible factors that might affect DFS and OS for 3–4 cycles and 2 cycles of treatment in the PP population (n=109)

Variables	Groups	3–4 *vs.* 2 cycles					
		DFS			OS		
		HR	95% CI	P value	HR	95% CI	P value
Age (years)	≥65	3.295	1.069–10.151	0.04	2.54	0.825–7.813	0.10
	<65	1.988	0.741–5.332	0.17	1.887	0.603–5.909	0.28
Gender	Male	2.735	1.247–5.998	0.01	2.535	1.067–6.027	0.04
	Female	0.855	0.117–6.241	0.88	0.775	0.108–5.544	0.80
ECOG PS	1	2.993	0.821–10.907	0.10	1.987	0.528–7.469	0.31
	0	1.982	0.821–4.782	0.13	2.124	0.793–5.688	0.13
Smoking status	Ever	5.265	1.557–17.807	0.008	9.011	1.909–42.530	0.005
	Never	1.408	0.557–3.563	0.47	0.962	0.337–2.742	0.94
Drinking status	Ever	5.128	1.508–17.433	0.009	6.299	1.251–31.727	0.03
	Never	1.389	0.559–3.453	0.48	1.287	0.500–3.315	0.60
c stage	IVA	4.014	0.996–16.188	0.051	3.865	0.959–15.575	0.057
	II–III	1.795	0.759–4.245	0.18	1.598	0.604–4.227	0.35
Clinical response	SD	5.72	1.279–25.588	0.02	4.045	0.959–17.056	0.057
	PR	2.096	0.883–4.974	0.09	1.841	0.712–4.760	0.21
Grade 3–4 AEs	Yes	6.058	0.718–51.119	0.10	3.803	0.435–33.250	0.23
	No	1.905	0.832–4.358	0.18	2.031	0.834–4.944	0.12
Pathologic response	Non-MPR	2.578	1.171–5.671	0.02	2.63	1.128–6.135	0.03
	MPR	1.713	0.273–10.739	0.57	0.575	0.049–6.747	0.66

DFS, disease-free survival; OS, overall survival; PP, postoperative; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; SD, stable disease; PR, partial response; AE, adverse event; MPR, major pathologic response.

9.01, 95% CI: 1.91–42.53; P=0.005), ever-drinkers (HR 6.30, 95% CI: 1.25–31.73; P=0.03), and patients without MPR (HR 2.63, 95% CI: 1.13–6.14; P=0.02). OS was more favorable in the 2 cycles group for certain subgroups of patients: those who were male, ever-smokers, ever-drinkers, and those who did not achieve MPR. Among male patients, the median OS for the 3–4 cycles group was 34.9 months (95% CI: 22.3–47.5 months). In contrast, the 2 cycles group's median OS was not reached, and this difference was statistically significant (P=0.03; *Figure 6A*). For patients with a history of smoking, the median OS in the 3–4 cycles group was 27.9 months (95% CI: 19.4–36.3 months), whereas the 2 cycles group's median OS was not reached, indicating a highly significant difference (P<0.001; *Figure 6B*). In patients with a history of alcohol consumption, the median OS for the 3–4 cycles group was 34.9 months (95% CI: 24.6–45.2 months), while the 2 cycles group's median OS was not reached, and this difference was statistically significant (P=0.01; *Figure 6C*). For patients without MPR, the median OS in the 3–4 cycles group was 27.8 months (95% CI: 17.6–38.1 months), and the 2 cycles group's median OS was not reached, representing a statistically significant difference (P=0.02; *Figure 6D*).

Discussion

In contemporary practice, the protocol for treating patients with locally advanced ESCC typically involves neoadjuvant therapy prior to surgical resection. This preliminary therapeutic approach serves to diminish the tumor's size and downstage the disease, and subsequently, the surgical intervention aims to excise the tumor more comprehensively, thereby enhancing the prospects for improved patient outcomes. However, there still has

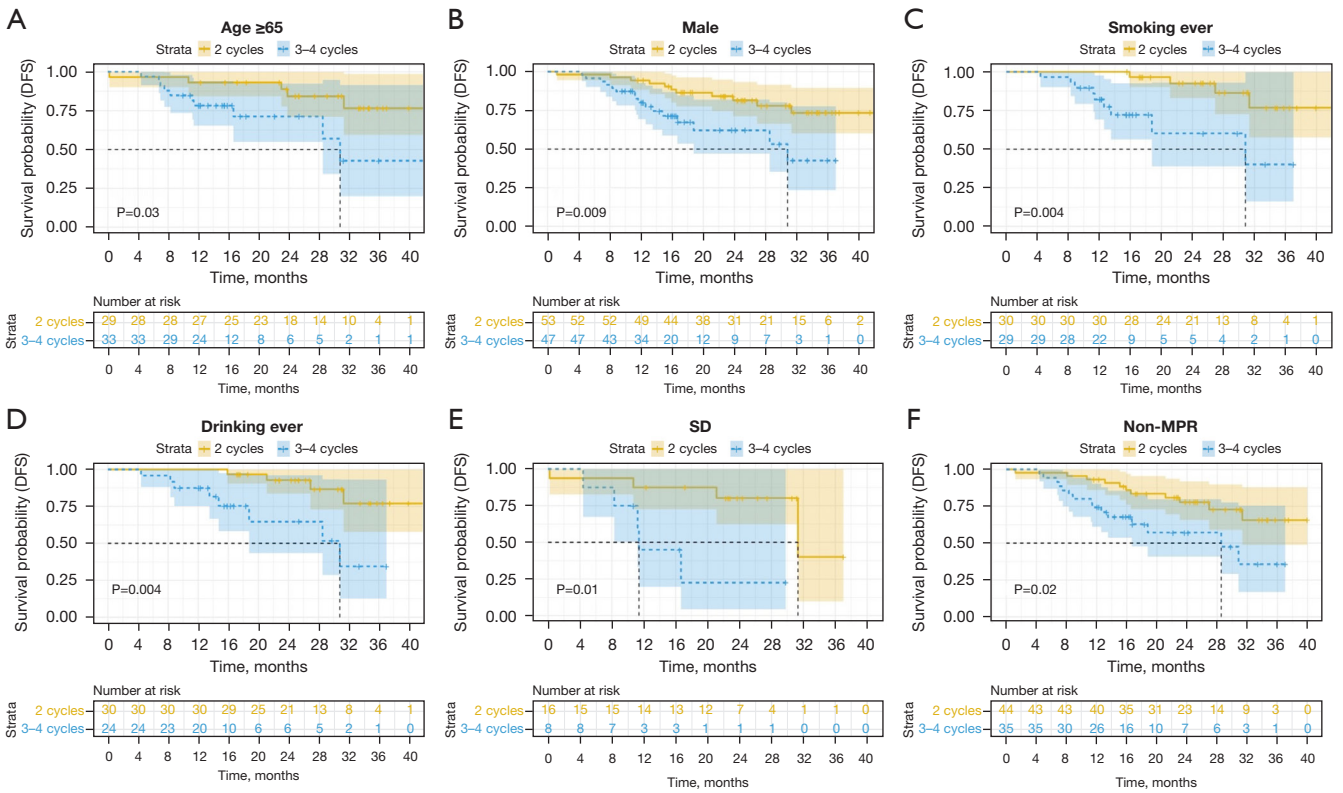

Figure 5 Kaplan-Meier curves of DFS between the two cycles group and three to four cycles group in (A) patients ≥65 years old (n=62), (B) male patients (n=100), (C) ever-smokers (n=59), (D) ever-drinkers (n=54), (E) patients with SD (n=24), and (F) patients without MPR (n=79). DFS, disease-free survival; SD, stable disease; MPR, major pathologic response.

been no consensus regarding the cycles of neoadjuvant immunochemotherapy for patients with locally advanced ESCC. Kubo *et al.* found that the survival of patients who do not exhibit a response to the initial two cycles of neoadjuvant chemotherapy in locally advanced EC might be worsened by a third cycle of neoadjuvant chemotherapy (23). Makino *et al.* reported that two cycles and three cycles of NAC could result in comparable tumor regression and survival benefits for patients with locally advanced ESCC (24). Shiraishi *et al.* found that three cycles of NAC could lead to a better tumor response compared to the two cycles (25). In Huang *et al.*'s study, three cycles of immunochemotherapy offered superior outcomes compared to two cycles of treatment regardless of downstaging or ORR (26). Yang *et al.* found that three cycles of neoadjuvant immunochemotherapy could increase tumor regression and improve survival outcomes (27). In our study, we assessed the efficacy and safety of intensive (three to four cycles) of neoadjuvant immunochemotherapy in locally advanced ESCC.

In our study, we found that three to four cycles of neoadjuvant immunochemotherapy increased tumor regression. Tumor sizes underwent a substantial reduction following the third and fourth treatment cycles, showing a marked decrease in comparison to the conclusion of the second cycle. Furthermore, the rates of MPR and pCR were also found to be superior in the 3–4 cycles group as compared to those in the 2 cycles group, which is in line with other studies. For instance, Huang *et al.* reported that the rate of T downstaging in a three-cycle group was significantly higher than that in a two-cycle group (81.4% *vs.* 65.1%) (26). Yang *et al.* showed that three cycles of treatment resulted in a notable enhancement in the T downstaging compared to two cycles (27). Finally, Shiraishi *et al.* found that the three-cycle group exhibited a significantly enhanced clinical response and also had a comparatively elevated rate of achieving pCR (25).

Despite the aforementioned pathologic response, in this study, we found that three to four cycles of neoadjuvant immunochemotherapy was associated with worse oncologic

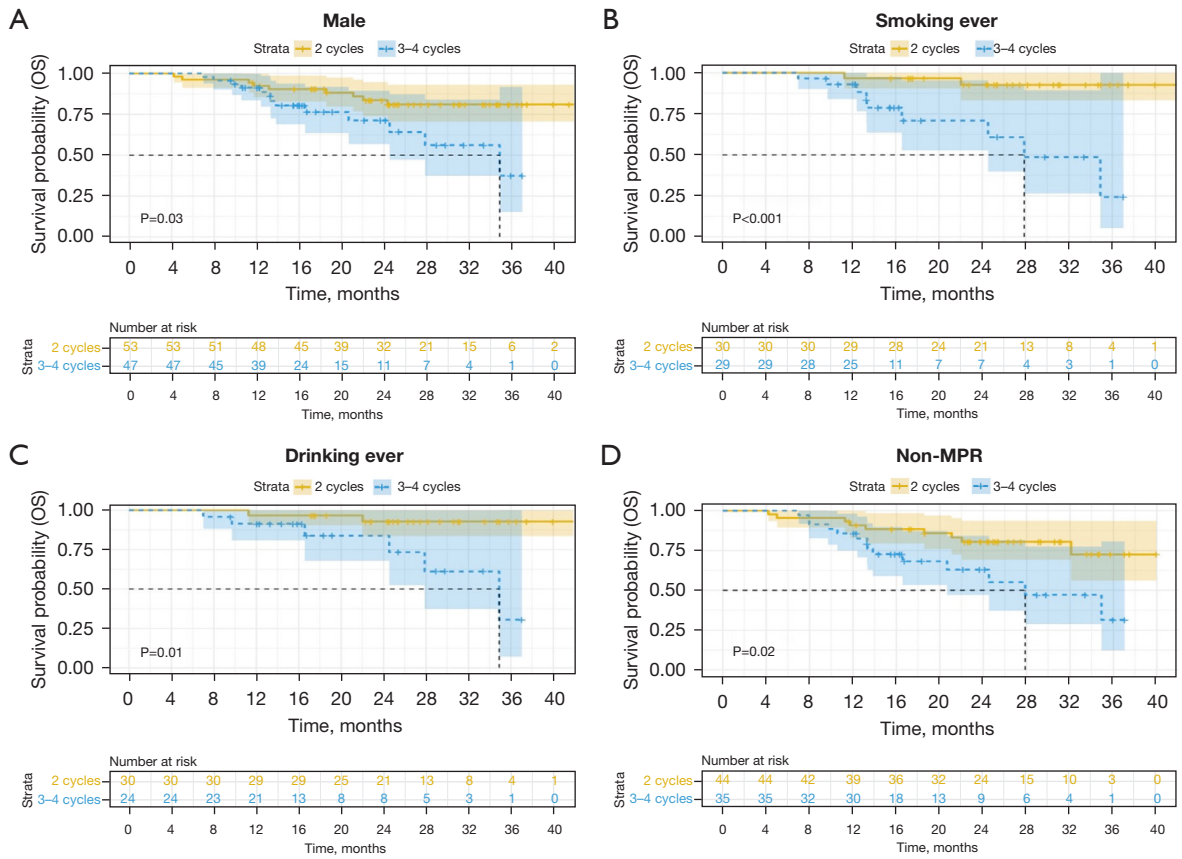

Figure 6 Kaplan-Meier curves of OS between the two cycles group and three to four cycles group in (A) male patients (n=100), (B) ever-smokers (n=59), (C) ever-drinkers (n=54), and (D) patients without MPR (n=79). OS, overall survival; MPR, major pathologic response.

outcomes compared with two cycles. In the group that received two cycles of treatment, the DFS rates at 1, 2, and 3 years were 93.0%, 80.7%, and 77.2%, respectively; meanwhile, those in the 3–4 cycles group were 84.6%, 69.2%, and 65.4%, respectively. Similarly, the OS rates for the 2 cycles group at 1, 2, and 3 years were 91.2%, 84.2%, and 80.7%, while those in the 3–4 cycles group were 88.5%, 76.9%, and 71.2%, respectively. Makino *et al.* reported comparable survival benefits between patients treated with two cycles or three cycles of NAC and found that those younger than 65 years tended to have improved survival outcomes with the administration of a three-cycle treatment regimen (24). In order to clarify the possible reasons for these distinct survival outcomes, we performed subgroup analyses. We found that the 2 cycles group demonstrated superior DFS compared to the 3–4 cycles group in patients ≥65 years old, male patients, ever-smokers, ever-drinkers, patients with SD, and patients without MPR. Furthermore, the 2 cycles group demonstrated superior OS compared to the 3–4 cycles group among male patients, ever-smokers, ever-drinkers, and patients without MPR. It is possible that these factors affect DFS and OS, and perhaps three to four cycles are not suitable for patients aged ≥65 years, male patients, ever-smokers, ever-drinkers, patients with SD, or patients without MPR. However, these results were based on a subset analysis that used a small sample size, and thus further investigation with a larger sample size and a randomized controlled design is required to validate these findings.

Our study did not encounter any new or unforeseen AEs. All treatment-related AEs were found to be manageable and within the tolerable range for patients. In terms of the overall incidence of AEs, there was no significant difference between the 3–4 cycles group and the 2 cycles group. However, it is worth noting that the rate of grade 3–4 AEs, predominantly observed in the form of hematological abnormalities such as anemia, was markedly higher in the 3–4 cycles group than in the 2 cycles group,

with percentages of 36.4% and 18.5%, respectively. The groups in Shiraishi *et al.*'s study both exhibited comparable overall toxicity rates, but the three-cycle group displayed a significantly increased incidence of grade 3–4 leukopenia and anemia compared to the two-cycle group, which was similar to our study (25). In contrast to our study, Huang *et al.* found that the toxicity associated with the third cycle of immunochemotherapy was mild, easily tolerated, and not accompanied by heightened treatment-related AEs as compared with that for the second cycle of treatment (26).

Several limitations of our study should be acknowledged. To begin, the study's retrospective nature and the modest size of the sample might have limited the statistical robustness of our findings. Consequently, validation through randomized controlled trials with larger cohorts is warranted. Additionally, the heterogeneity among patients and the variability in treatment protocols could have influenced the study outcomes. Finally, the relatively brief postoperative follow-up period in our study suggests that extended follow-up is essential for a comprehensive assessment of long-term outcomes.

Conclusions

Two cycles of neoadjuvant immunochemotherapy can be considered in locally advanced ESCC at high risk of developing toxicity with 3–4 cycles with similar oncologic outcomes. An intensive cycle of neoadjuvant immunochemotherapy consisting of three or four cycles may not better than two cycles for treating patients with locally advanced ESCC. Although three to four cycles of neoadjuvant immunochemotherapy increased tumor regression, it also increased toxicity and was associated with worse early survival outcomes.

Acknowledgments

Funding: This study was supported by the Ningbo Medical & Health Leading Academic Discipline Project (No. 2022-F02), the Ningbo Natural Science Foundation (No. 2023J224), the National Key Research and Development Program of China (No. 2022YFC2407303), the Major Science and Technology Projects of Zhejiang Province (No. 2020C03058), the Zhejiang Provincial Natural Science Foundation (No. Q23H020022), and the Research Center for Lung Tumor Diagnosis and Treatment of Zhejiang Province (No. JBZX-202007).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1365/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1365/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1365/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1365/coif). J.M.P. received honoraria from ASTELLAS and J&J Worldwide, and payment for participation in Advisory Board from Ferranova, and serves as the Chair of the Florida Chapter of the American College of Surgeons (FCACS) Surgical Education Committee. The other authors have no conflicts of interest to declare.

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. This study was granted approval by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2021 IIT no. 742). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the principles of good clinical practice. All patients signed a written informed consent form.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.

2. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015;64:381-7.
3. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19:5598-606.
4. Yang W, Niu Y, Sun Y. Current neoadjuvant therapy for operable locally advanced esophageal cancer. Med Oncol 2023;40:252.
5. Herskovic A, Russell W, Liptay M, et al. Esophageal carcinoma advances in treatment results for locally advanced disease: review. Ann Oncol 2012;23:1095-103.
6. 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.
7. 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.
8. Yang H, Liu H, Chen Y, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol 2018;36:2796-803.
9. 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.
10. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:1506-17.
11. Kojima T, Shah MA, Muro K, et al. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer. J Clin Oncol 2020;38:4138-48.
12. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol 2020;21:832-42.
13. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-71.
14. Luo H, Lu J, Bai Y, et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial. JAMA 2021;326:916-25.
15. Ma J, Zhang J, Yang Y, et al. 65P Camrelizumab combined with paclitaxel and nedaplatin as neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma (ESPRIT): A phase II, single-arm, exploratory research. Ann Oncol 2021;32:S1400.
16. Jiang H, Shang X, Xie Y, et al. Preoperative pembrolizumab plus chemotherapy for resectable esophageal squamous cell carcinoma (ESCC): The phase II Keystone-001 trial. Ann Oncol 2023;34:S872-3.
17. Yuan WP, Chen Y, Liu J, et al. Camrelizumab plus chemotherapy versus concurrent chemoradiotherapy as neoadjuvant therapy for resectable thoracic oesophageal squamous cell cancer (REVO): A multicenter, randomized, open-label, phase II trial. Ann Oncol 2023;34:S857.
18. Yan X, Duan H, Ni Y, et al. Tislelizumab combined with chemotherapy as neoadjuvant therapy for surgically resectable esophageal cancer: A prospective, single-arm, phase II study (TD-NICE). Int J Surg 2022;103:106680.
19. Liu J, Yang Y, Liu Z, et al. Multicenter, single-arm, phase II trial of camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma. J Immunother Cancer 2022;10:e004291.
20. Li C, Zhao S, Zheng Y, et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). Eur J Cancer 2021;144:232-41.
21. Zhang B, Zhao H, Wu X, et al. Perioperative outcomes of neoadjuvant chemotherapy plus camrelizumab compared with chemotherapy alone and chemoradiotherapy for locally advanced esophageal squamous cell cancer. Front Immunol 2023;14:1066527.
22. Qin J, Xue L, Hao A, et al. Neoadjuvant chemotherapy with or without camrelizumab in resectable esophageal squamous cell carcinoma: the randomized phase 3 ESCORT-NEO/NCCES01 trial. Nat Med 2024;30:2549-57.
23. Kubo Y, Makino T, Yamasaki M, et al. Three-Course Neoadjuvant Chemotherapy Associated with Unfavorable Survival of Non-responders to the First Two Courses for Locally Advanced Esophageal Cancer. Ann Surg Oncol 2023;30:5899-907.

24. Makino T, Yamasaki M, Tanaka K, et al. Multicenter randomised trial of two versus three courses of preoperative cisplatin and fluorouracil plus docetaxel for locally advanced oesophageal squamous cell carcinoma. Br J Cancer 2022;126:1555-62.
25. Shiraishi O, Makino T, Yamasaki M, et al. Two versus three courses of preoperative cisplatin and fluorouracil plus docetaxel for treating locally advanced esophageal cancer: short-term outcomes of a multicenter randomized phase II trial. Esophagus 2021;18:825-34.
26. Huang Y, Su X, Guo Q, et al. Are more courses of immunochemotherapy beneficial for the short-term outcome of locally advanced esophageal squamous cell carcinoma? Thorac Cancer 2023;14:1153-61.
27. Yang G, Su X, Huang Y, et al. Intensive cycles of neoadjuvant camrelizumab combined with chemotherapy in locally advanced esophageal squamous cell carcinoma: a single-arm, phase II trial. J Transl Med 2023;21:411.
28. Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. J Thorac Oncol 2017;12:36-42.
29. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
30. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Cite this article as: He J, Liang G, Yu H, Shen W, Pimiento JM, Anker CJ, Koyanagi K, Liu J, Hu J. Two versus three to four cycles of neoadjuvant immunochemotherapy for locally advanced esophageal squamous cell carcinoma in real-world practice. J Thorac Dis 2024;16(10):6999-7015. doi: 10.21037/jtd-24-1365

