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Evaluation of the Effectiveness and Safety of Maintenance Therapy in Unresectable Locally Advanced Esophageal Squamous Cell Carcinoma

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Abstract

Background: Esophageal cancer is a formidable disease that ranks as the seventh highest cause of cancer-related mortality globally. The majority of patients receive a diagnosis at an advanced stage, rendering them ineligible for surgical surgery. Consensus on the clinical efficacy and safety of maintenance therapy after first-line treatment for patients with unresectable locally advanced esophageal squamous cell carcinoma (ESCC) is absent. This study sought to retrospectively evaluate the efficacy and safety of maintenance therapy in patients with unresectable locally advanced ESCC following standard first-line treatment utilising real-world data.

Methods: Patients with unresectable locally advanced ESCC who attained disease control following standard initial treatment were retrospectively enrolled and categorised into a maintenance group and an observation group. The primary endpoints were overall survival (OS) and progression-free survival (PFS). Multivariable Cox regression and propensity score-matched analysis were conducted to compare outcomes between the two groups. Exploratory analyses evaluated the influence of treatment duration and regimen type.

Results: Among 241 enrolled patients (92 receiving maintenance therapy and 149 under observation), maintenance therapy significantly enhanced median OS (53.8 months vs. 29.4 months; $P < 0.001$) and PFS (24.6 months vs. 12.9 months; $P = 0.002$). Multivariable analysis validated separate protective effects for OS (HR = 0.51) and PFS (HR = 0.62), consistent post-propensity score matching. Subgroup advantages were significant among patients < 65 years of age, with a history of smoking, or tumors > 1.4 cm. Patients undergoing more than 8 cycles exhibited improved OS and PFS (both $P < 0.001$). Adverse events were primarily classified as grade 1–2 (hypothyroidism 16.3%); grade ≥3 occurrences were observed in 9.8% (including two fatalities due to severe pneumonia).

Conclusion: Maintenance therapy after standard initial treatment markedly enhanced OS and PFS in patients with unresectable locally advanced ESCC, while maintaining a manageable safety profile.

Background

Esophageal cancer continues to be one of the most prevalent malignancies globally, with consistently elevated incidence and fatality rates, ranking 11th and 7th, respectively, among all cancers. GLOBOCAN 2022 estimates indicate roughly 510,000 new diagnoses and 445,000 annual deaths due to this disease[1]. In China, esophageal cancer was responsible for 187,500 of the 2,574,200 total cancer fatalities, placing fifth among cancer-related deaths[1, 2]. Esophageal squamous cell carcinoma (ESCC) is the primary pathogenic variant in China, accounting for nearly 90% of all occurrences[3]. Its growth is intricately linked to regional distribution, dietary practices (including scalding hot food, hot tea, and pickled foods), smoking, and alcohol consumption[4] .

Most patients are discovered at an advanced stage because to the lack of characteristic early-stage symptoms, causing the optimal opportunity for curative surgical resection to be missed, which leads to a poor prognosis[5, 6]. The RTOG 85 – 01 trial, a pivotal phase III research, established concurrent chemoradiotherapy as the standard treatment for patients with locally advanced esophageal cancer. This study revealed that the integration of chemotherapy and radiotherapy markedly enhanced 5-year survival rates from 5–10% to 26%, in contrast to conventional treatments such surgery or radiotherapy alone[7]. Based on this evidence, platinum-based definitive chemoradiotherapy (dCRT) has been recognised as the standard treatment for patients with unresectable locally advanced ESCC, and is consistently endorsed as a high-level evidence-based option by both international and national guidelines, including the NCCN and CSCO guidelines[8, 9]. Nonetheless, despite the effectiveness of dCRT, locoregional recurrence and distant metastases persist often, and long-term results are unsatisfactory[10, 11].

A significant difficulty in managing these patients is consolidating initial responses, delaying disease progression, and converting short-term tumor control into prolonged survival. In this situation, maintenance therapy has arisen as a potential approach. Maintenance therapy is typically characterised as the ongoing administration of one or more efficacious, low-toxicity agents after initial treatment in patients who have attained disease control, aiming to consolidate the benefits of the initial treatment, postpone disease progression, and ultimately extend overall survival[12]. This therapy has shown distinct survival benefits in several advanced malignancies [13–17]. In recent years, immune checkpoint inhibitors (ICIs) have demonstrated remarkable performance in patients with advanced esophageal cancer, generating interest in their application as maintenance therapy after dCRT for unresectable locally advanced ESCC[18–20]. Numerous prospective studies indicate that employing PD-1/PD-L1 inhibitors as consolidation or maintenance therapy after dCRT may produce favourable long-term survival outcomes in patients with unresectable locally advanced ESCC[21, 22]. In addition, the phase III SKYSCRAPER-07 trial[23] recently presented preliminary data at the 2025 ESMO congress, indicating that atezolizumab monotherapy as maintenance therapy significantly enhanced both overall survival (OS) and progression-free survival (PFS) in comparison to placebo.

Chemotherapy maintenance methods have concurrently demonstrated potential efficacy[24–26]. A phase III trial indicated that capecitabine monotherapy as maintenance therapy after dCRT resulted in a median overall survival of 44.2 months ($P = 0.04$) with a favourable tolerability profile[27]. A phase II research shown that in older patients with ESCC, single-agent S-1 maintenance therapy for four cycles resulted in a median overall survival of 22.6 months, accompanied by acceptable toxicity[28]. Similarly, the Chinese Society of Clinical Oncology (CSCO) guidelines advocate for consolidation chemotherapy in patients exhibiting good performance status, substantial lymph node involvement, advanced stage, or poorly differentiated tumors[9].

The role of maintenance therapy in unresectable locally advanced ESCC has yet to be definitively established. Critical unsolved enquiries encompass the optimal therapeutic technique, the ideal duration and timing of beginning, the patient subgroups most likely to derive benefit, and if this approach provides a measurable survival benefit with acceptable safety relative to observation alone.

This retrospective study aims to assess the long-term effectiveness and safety of maintenance therapy compared to observation alone in patients with unresectable locally advanced ESCC who had completed standard initial treatment. We analysed OS, PFS, and adverse events (AEs), using multivariate and subgroup analyses to determine independent prognostic factors and patient groupings most likely to derive benefit. Our findings offer empirical information to guide therapeutic decision-making concerning maintenance therapy in this context.

Methods

1. Study Population

This single-center, retrospective study enrolled patients with newly diagnosed, unresectable locally advanced ESCC at the Affiliated Hospital of North Sichuan Medical College from January 1, 2020, to December 31, 2024, based on established qualifying criteria. The criteria for inclusion were as follows: (1) Diagnosis of unresectable locally advanced ESCC according to the 2024 CSCO recommendations, characterised as clinical stage cT1b-4bN0M0 or cT1-4bN+M0, including physician-assessed unresectability, surgical contraindications, or patient refusal; (2) Histologically verified ESCC; (3) Following the completion of guideline-recommended primary treatment—definitive concurrent chemoradiotherapy (category 1A), systemic therapy plus radiotherapy (category 2A), or definitive radiotherapy (category 2A) per 2024 CSCO guidelines—patients must have achieved clinical disease control, defined as complete response (CR), partial response (PR), or stable disease (SD) according to RECIST 1.1 criteria[29]; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (5) Proper organ and bone marrow functionality. The exclusion criteria comprised: (1) A history of additional malignancies; (2) Progressive disease (PD) either during initial therapy or at post-treatment response evaluation; (3) An estimated survival of no more than 6 months due to concomitant diseases; (4) Incomplete or absent clinical data.

The Institutional Review Board of Affiliated Hospital of North Sichuan Medical College accepted the study (permission No. 2025ER623-1) and waived the necessity for individual informed consent owing to the retrospective character of the analysis.

2. Study Grouping

Patients were categorized into two groups according to their receipt of maintenance therapy after attaining disease control post-initial treatment: the maintenance group and the observation group. All patients were mandated to have a follow-up imaging evaluation to verify disease control (CR/PR/SD) subsequent to initial treatment.

In the maintenance group, patients who attained disease control following standard initial treatment underwent scheduled, periodic systemic anti-tumor medication. The precise regimen was established by the attending physician, taking into account the patient's clinical status, preferences, and drug availability, which included immunotherapy monotherapy (PD-1 inhibitor), chemotherapy monotherapy (administered intravenously or orally), targeted monotherapy, or chemoimmunotherapy (PD-1 inhibitor combined with chemotherapy).

In the observation group, patients who attained disease control following standard initial treatment received regular follow-up and monitoring without additional anti-tumor medication until disease progression or mortality occurred. Subsequent evaluations were conducted in accordance with guideline recommendations, using contrast-enhanced chest computed tomography and upper gastrointestinal radiography every 2 to 3 months. Should disease development transpire, second-line or subsequent therapy may be commenced at the physician's discretion, contingent upon the patient's performance status and tumor features.

3. Treatment Protocols

All enrolled patients had standard initial treatment as defined in the qualifying criteria. Radiotherapy was provided in accordance with guideline recommendations[30], with a total dose varying from 50.0 to 60.4 Gy (including local boost), delivered in daily fractions of 1.8–2.0 Gy, five days per week. Chemotherapy regimens consisted of platinum-based doublets. Patients had a minimum of one cycle of concurrent chemoradiotherapy or two sessions of sequential chemoradiotherapy.

Treatment in the maintenance group commenced 4–8 weeks post-initial treatment and persisted until disease progression, intolerable toxicity, patient withdrawal, or the conclusion of 2 years. Maintenance regimens comprised: immunotherapy monotherapy (toripalimab, sintilimab, camrelizumab, penpulimab, or tislelizumab, each 200 mg intravenously every 3 weeks); chemotherapy monotherapy (capecitabine 850–1000 mg/m² orally twice daily on days 1–14, repeated every 3 weeks; S1 administered orally twice daily on days 1–14, repeated every 3 weeks, with dosage based on body surface area: 40 mg for < 1.25 m², 50 mg for 1.25–1.5 m², or 60 mg for ≥ 1.5 m²; or paclitaxel 60–80 mg/m² intravenously on day 1, repeated every 3 weeks); targeted monotherapy (anlotinib 8 mg orally once daily on days 1–14, repeated every 3 weeks); and chemoimmunotherapy (a PD-1 inhibitor at the same dosage plus capecitabine, S1, or paclitaxel at the same dosage). The agent selection may either proceed with the initial regimen or be altered according to tolerance levels. For patients necessitating regimen modifications (transitioning PD-1 inhibitors due to adverse

effects or de-escalating from combination therapy to monotherapy), the principal analysis was conducted based on the originally designated maintenance regimen (intention-to-treat principle).

4. Tumor Response Evaluation

Per RECIST 1.1, tumor responses were assessed as follows: (1) CR: total eradication of all target and non-target lesions, with no emergence of new disease; (2) PR: a reduction of ≥ 30% in the aggregate diameters of target lesions compared to baseline (defined as the first imaging assessment following treatment); (3) PD: an increase of ≥ 20% in the aggregate of target lesions compared to the nadir (with an absolute increase exceeding 5 mm), the emergence of at least one new lesion, or unequivocal progression of non-target lesions; (4) SD: shrinkage inadequate to meet the criteria for PR or an increase insufficient to meet the criteria for PD.

5. Outcomes

The principal goals were OS and PFS, whereas the secondary endpoints comprised objective response rate (ORR) and disease control rate (DCR). OS was defined as the duration from the initial diagnosis to death from any cause or the last follow-up. The definition of PFS differed according to group allocation. In the maintenance group, PFS was determined from the initiation date of maintenance therapy to the date of first documented disease progression (according to RECIST 1.1) or death from any cause. For patients in the observation group, a simulated starting point was established based on the median duration from the conclusion of initial treatment to the commencement of maintenance therapy noted in the maintenance group. The PFS for patients in the observation group was computed from the simulated start point to the date of the first documented disease progression (according to RECIST 1.1) or death from any cause. ORR was defined as the percentage of efficacy-evaluable patients in the maintenance group who attained CR or PR; DCR was defined as the percentage achieving CR, PR, or SD. An efficacy-evaluable patient is defined as one who has completed at least one contrast-enhanced CT or PET-CT during maintenance therapy, with comprehensive imaging data for RECIST 1.1 evaluation.

Patients were followed through January 31, 2026, by a retrospective analysis of hospital medical data and direct patient follow-up via telephone communications.

6. Safety Assessment

To thoroughly assess therapy safety, AEs were recorded distinctly for several treatment periods. In the initial treatment phase, all grade ≥ 2 AEs occurring during standard initial treatment were documented for all patients, including those later assigned to the maintenance and observation groups. This established the baseline safety profile and facilitated the evaluation of comparability between the two groups for beginning treatment toxicity. In the maintenance phase (applicable solely to the maintenance group), newly emerged AEs or AEs that escalated by at least one grade relative to the initial treatment phase (and attained grade ≥ 2) were documented. The AEs were ascribed to maintenance therapy. All AEs were evaluated in accordance with the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). The incidence of immune-related adverse events (irAEs) was meticulously documented.

7. Statistical Analysis

Statistical analyses were conducted utilising R software (version 4.5.2). Continuous variables are expressed as mean ± standard deviation, while categorical variables are represented as number (%). Comparisons between groups were conducted using the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as applicable. Survival curves were constructed by the Kaplan-Meier method and analysed using the log-rank test. Univariable and multivariable Cox proportional hazards models were employed to compute hazard ratios (HR) with 95% confidence intervals (CI); Variables with $P < 0.10$ in univariable analysis, along with variables deemed clinically relevant, were incorporated into the multivariable model. A sensitivity study utilising propensity score matching (1:1 nearest-neighbor matching, calliper = 0.4) was conducted to assess the robustness of the findings. Subgroup analyses were illustrated through forest plots, and interaction tests were employed to determine subgroups that may derive advantages from maintenance therapy. Exploratory investigations assessed survival outcomes across several maintenance regimes (immunotherapy monotherapy, chemotherapy/targeted monotherapy, and chemoimmunotherapy). Restricted cubic splines (RCS) were employed to model the dose-response connection between maintenance cycle count and mortality risk, as well as to establish a threshold for categorising patients into short-cycle and long-cycle groups. All statistical tests were bilateral, and a P value of less than 0.05 was deemed statistically significant.

Results

1. Patient Characteristics

Of the 3,942 patients initially screened, 241 met the eligibility criteria and were included in the final analysis, comprising 92 in the maintenance group and 149 in the observation group (Fig. 1).

The baseline characteristics of both groups are presented in Table 1. The average age of the entire cohort was 70.3 ± 8.2 years, with patients in the maintenance group substantially younger than those in the observation group (67.4 ± 8.5 vs. 72.0 ± 7.5 years, $P < 0.001$). No notable variations were detected between the two groups for sex, smoking history, alcohol consumption history, tumor size, tumor length, tumor location, multi-segment involvement, or ECOG PS (all $P > 0.05$). The maintenance group exhibited a much greater percentage of patients with stage III (71% compared to 54%) and stage IVA (21% compared to 13%) disease (overall $P < 0.001$). Concerning initial treatment characteristics, the maintenance group exhibited markedly elevated rates of initial chemotherapy administration (83% vs. 46%), initial immunotherapy (74% vs. 28%), receipt of ≥ 4 cycles of chemotherapy (73% vs. 18%), and ≥ 4 cycles of immunotherapy (42% vs. 7.4%), alongside a diminished proportion of high-dose radiotherapy (defined by a median threshold of 59.4 Gy), with all $P < 0.001$. These baseline imbalances were accounted for in the subsequent Cox analysis and propensity score-matched (PSM) analyses.

Table 1
Baseline characteristics of patients

Characteristic	Overall *N* = 241[1]	Observation group *N* = 149[1]	Maintenance group *N* = 92[1]	*P* value[2]
Age (years)	70.3 (8.2)	72.0 (7.5)	67.4 (8.5)	< 0.001
Sex				0.6
Male	149 (62%)	94 (63%)	55 (60%)	
Female	92 (38%)	55 (37%)	37 (40%)	
Smoking history				0.3
No	154 (64%)	99 (66%)	55 (60%)	
Yes	87 (36%)	50 (34%)	37 (40%)	
Alcohol consumption history				0.3
No	172 (71%)	110 (74%)	62 (67%)	
Yes	69 (29%)	39 (26%)	30 (33%)	
Stage				< 0.001
II	56 (23%)	48 (32%)	8 (8.7%)	
III	146 (61%)	81 (54%)	65 (71%)	
IVA	39 (16%)	20 (13%)	19 (21%)	
Tumor size (cm)	1.4 (0.6)	1.4 (0.6)	1.5 (0.5)	0.2
Tumor length (cm)	4.7 (2.0)	4.7 (1.8)	4.8 (2.4)	0.9
Tumor location				0.2
Cervical	20 (8.3%)	13 (8.7%)	7 (7.6%)	
Upper	84 (35%)	59 (40%)	25 (27%)	
Middle	108 (45%)	59 (40%)	49 (53%)	
Lower	29 (12%)	18 (12%)	11 (12%)	
Multi-segment involvement				0.8
No	198 (82%)	123 (83%)	75 (82%)	
Yes	43 (18%)	26 (17%)	17 (18%)	
ECOG PS				0.6
0	15 (6.2%)	8 (5.4%)	7 (7.6%)	
1	221 (92%)	137 (92%)	84 (91%)	
2	5 (2.1%)	4 (2.7%)	1 (1.1%)	
Initial chemotherapy cycles				< 0.001
< 4 cycles	147 (61%)	122 (82%)	25 (27%)	
≥ 4 cycles	94 (39%)	27 (18%)	67 (73%)	
Initial immunotherapy cycles				< 0.001
< 4 cycles	191 (79%)	138 (93%)	53 (58%)	
≥ 4 cycles	50 (21%)	11 (7.4%)	39 (42%)	
Radiation dose				< 0.001
Low dose (≤ 59.4 Gy)	115 (48%)	54 (36%)	61 (66%)	
High dose (> 59.4 Gy)	126 (53%)	95 (64%)	31 (34%)	

[2]Wilcoxon rank-sum test; χ^2 test or Fisher's exact test

Characteristic	Overall *N* = 241[1]	Observation group *N* = 149[1]	Maintenance group *N* = 92[1]	*P* value[2]
Initial treatment type				< 0.001
Definitive Radiotherapy	117 (49%)	90 (60%)	27 (29%)	
Definitive Concurrent Chemoradiotherapy	37 (15%)	15 (10%)	22 (24%)	
Systemic Therapy with Radiotherapy	87 (36%)	44 (30%)	43 (47%)	
Receipt of initial chemotherapy				< 0.001
No	96 (40%)	80 (54%)	16 (17%)	
Yes	145 (60%)	69 (46%)	76 (83%)	
Receipt of initial immunotherapy				< 0.001
No	132 (55%)	108 (72%)	24 (26%)	
Yes	109 (45%)	41 (28%)	68 (74%)	
[1]Mean (SD); n (%)				
[2]Wilcoxon rank-sum test; χ^2 test or Fisher's exact test				

2. Survival Analysis

The median OS in the entire group was 35.6 months (95% CI: 32.3–42.6), whereas the median PFS was 15.2 months (95% CI: 12.9–20.3). Maintenance therapy was linked to a substantial prolongation of OS and PFS. The median OS was 53.8 months (95% CI: 42.3–not attained) in the maintenance group, in contrast to 29.4 months (95% CI: 26.1–34.7) in the observation group ($P < 0.001$). The median PFS was 24.6 months (95% CI: 15.2–48.1) compared to 12.9 months (95% CI: 11.9–17.0) ($P = 0.002$). The 1, 2, 3, and 5 OS rates were 94.6%, 81.9%, 66.5%, and 37.5% in the maintenance group, in contrast to 81.2%, 60.1%, 40.5%, and 17.7% in the observation group. The respective PFS rates were 69.2%, 51.2%, 41.4%, and 26.3% in the maintenance group, compared to 57.0%, 34.1%, 22.2%, and 14.6% in the observation group (Fig. 2A, B). Of the 92 patients in the maintenance group, 85 (92.4%) had comprehensive imaging follow-up data accessible for response assessment. Based on RECIST 1.1 criteria, the optimal overall responses during therapy were: CR in 1 patient (1.2%), PR in 20 patients (23.5%), SD in 57 patients (67.1%), and PD in 7 patients (8.2%). The ORR was 24.7% (21/85), and the DCR was 91.8% (78/85).

To identify independent prognostic factors for overall survival (OS), univariable and multivariable Cox regression analyses were performed. Variables exhibiting $P < 0.10$ in univariable analysis (maintenance therapy, age, tumor length, initial chemotherapy cycles, receipt of initial chemotherapy, and receipt of initial immunotherapy), along with clinically significant variables (sex, stage, ECOG PS, and tumor size), were incorporated into the multivariable model. Multivariable analysis indicated that maintenance treatment was an independent protective factor for OS (HR = 0.51; 95% CI: 0.31–0.83; $P = 0.006$); no other variables achieved statistical significance (all $P > 0.05$). For PFS, both univariable and multivariable Cox models were employed, incorporating variables with $P < 0.10$ in univariable analysis (maintenance therapy, tumor length, ECOG PS, tumor size, initial chemotherapy cycles, and receipt of initial chemotherapy) alongside clinically significant variables (age, sex, and stage) in the multivariable model. Maintenance therapy continued to be an independent protective factor for PFS (HR = 0.62; 95% CI: 0.41–0.93; $P = 0.020$), while the other variables were not statistically significant (all $P > 0.05$). Comprehensive results are provided in Table 2 (OS) and **Supplementary Table 1** (PFS).

Table 2
Univariate and multivariate Cox regression analyses of OS

Variable	Univariable analysis		Multivariable analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Maintenance therapy (maintenance vs observation)	0.43 (0.29–0.64)	< 0.001	0.51 (0.31–0.83)	0.006
Age (years)	1.04 (1.01–1.06)	0.002	1.02 (0.99–1.05)	0.178
Sex (female vs male)	0.93 (0.65–1.33)	0.696		
Smoking history (yes vs no)	0.88 (0.61–1.26)	0.483		
Alcohol consumption history (yes vs no)	0.96 (0.65–1.41)	0.832		
Stage (III/II)	0.74 (0.50–1.09)	0.127	0.77 (0.49–1.21)	0.262
(IVA/II)	0.72 (0.42–1.22)	0.223	0.73 (0.36–1.47)	0.372
ECOG PS	1.34 (0.68–2.63)	0.395	1.13 (0.56–2.26)	0.730
Tumor size (cm)	1.15 (0.88–1.51)	0.309	1.30 (0.93–1.83)	0.130
Tumor length (cm)	1.07 (0.99–1.16)	0.077	1.08 (0.99–1.19)	0.080
Tumor location (Upper vs middle)	0.76 (0.51–1.13)	0.174		
(Lower vs middle)	1.15 (0.67–1.97)	0.608		
(Cervical vs middle)	1.14 (0.63–2.08)	0.663		
Multi-segment involvement (yes vs no)	1.11 (0.71–1.75)	0.643		
Initial chemotherapy cycles (≥ 4 vs < 4)	0.56 (0.39–0.81)	0.002	1.06 (0.62–1.83)	0.824
Initial immunotherapy cycles (≥ 4 vs < 4)	0.86 (0.54–1.36)	0.519		
Radiation dose(high vs low)	1.01 (0.71–1.42)	0.977		
Receipt of initial chemotherapy (yes vs no)	0.59 (0.42–0.83)	0.003	0.91 (0.49–1.71)	0.777
Receipt of initial immunotherapy (yes vs no)	0.59 (0.41–0.84)	0.003	0.91 (0.51–1.59)	0.730

3. Sensitivity Analysis

To assess the robustness of our basic multivariable analysis, we conducted a PSM sensitivity analysis using 1:1 nearest-neighbor matching with a calliper of 0.4. This resulted in 48 appropriately matched patient pairs (n = 96). The matching technique effectively equilibrated baseline covariates, with the absolute standardised mean differences (SMD) for the majority of variables remaining below 0.2, signifying a favourable balance between the two groups (Fig. 3C).

In the matched cohort, maintenance therapy correlated with a significantly prolonged median OS (47.9 vs. 26.5 months; HR = 0.42; 95% CI: 0.24–0.73; *P* = 0.002) and median PFS (18.8 vs. 12.2 months; HR = 0.60; 95% CI: 0.37–0.98; *P* = 0.039) in comparison to observation (Fig. 3A, B). The effect estimates from the PSM analysis (OS: HR = 0.42, *P* = 0.002; PFS: HR = 0.60, *P* = 0.039) were consistent with those from the primary multivariable Cox regression (OS: HR = 0.51, *P* = 0.006; PFS: HR = 0.62, *P* = 0.020), with no change in statistical significance. The results confirm the robustness of the survival benefit associated with maintenance therapy after adjusting for potential confounders.

4. Subgroup Analysis

Predefined subgroup analyses were conducted for the following variables: age, sex, smoking history, alcohol consumption history, stage, tumor size, tumor length, initial chemotherapy cycles, initial immunotherapy cycles, radiation dose, receipt of initial chemotherapy, receipt of initial immunotherapy, tumor location, and multi-segment involvement. The ECOG PS was excluded from the subgroup analysis due to just 5 patients (2.1%) having a PS score of ≥ 2, which constitutes an insufficient sample size for significant subgroup stratification.

Subgroup analyses for OS are illustrated as a forest plot in Fig. 4. Interaction tests indicated significant effect modification by age (P = 0.027), smoking history (P = 0.011), and tumor size (P = 0.046). A more pronounced OS benefit from maintenance therapy was observed in patients aged < 65 years (HR = 0.16; 95% CI: 0.05–0.47), those with a smoking history (HR = 0.22; 95% CI: 0.10–0.45), and those with tumor size > 1.4 cm (HR = 0.26; 95% CI: 0.14–0.48). In all other subgroups, the HR point estimates were consistently less than 1, and none of the interaction tests achieved statistical significance (all interaction P > 0.05), showing a relatively uniform OS benefit across subgroups. Nonetheless, the confidence intervals were broad in subgroups with comparatively small sample sizes, including stage II (merely 8 patients in the maintenance group), stage IVA (39 total), age ≥ 75 years (16 in the maintenance group), lower tumor location (29 total), multi-segment involvement (43 total), and individuals who did not receive initial chemotherapy or immunotherapy, necessitating prudent interpretation. The forest plot for PFS is presented in **Supplementary Fig. 1**. All interaction tests yielded no statistical significance (all P > 0.05), and the HR point estimates were consistently below 1 across all categories, indicating that the PFS benefit of maintenance therapy was uniformly consistent without notable heterogeneity. Similar caution is required for subgroups with restricted sample numbers, as previously indicated, where confidence intervals were extensive.

5. Exploratory Analyses within the Maintenance Therapy Cohort

5.1. Comparison of efficacy among different maintenance therapy regimens

A total of 92 patients in the maintenance therapy group received three different regimens: chemotherapy/targeted monotherapy (n = 25), immunotherapy monotherapy (n = 46), and chemoimmunotherapy (n = 21).

Survival analysis **(**Fig. 5A, B**)** indicated that the median OS for the three regimens was 42.3 months for chemotherapy/targeted monotherapy, 57.3 months for immunotherapy monotherapy, and not achieved for chemoimmunotherapy (P = 0.34). The median PFS was 18.8, 24.6, and 33.8 months, respectively (P = 0.89). In comparison to chemotherapy/targeted monotherapy, the HR for immunotherapy monotherapy and chemoimmunotherapy were 0.62 (95% CI: 0.28–1.36) and 0.52 (95% CI: 0.19–1.41) for OS, and 0.90 (95% CI: 0.46–1.75) and 0.83 (95% CI: 0.37–1.83) for PFS, respectively. The ORR were 12.0%, 28.3%, and 23.8% (P = 0.297), whereas the DCR were 80.0%, 84.8%, and 90.5% (P = 0.641). Consequently, within the constrained sample size of this trial, no significant differences were detected among the three maintenance regimens in OS, PFS, or short-term efficacy, while numerically superior trends were identified for regimens involving immunotherapy.

5.2. Treatment Cycles and Survival Outcomes

RCS models were employed to analyse the correlation between the number of maintenance cycles and survival outcomes. The number of cycles exhibited a significant correlation with OS (P overall < 0.001; P for nonlinear = 0.096) and PFS (P overall < 0.001; P for nonlinear = 0.57) (**Supplementary Fig. 2**). Despite the nonlinearity tests failing to achieve statistical significance, the RCS curves visually indicated a persistent decline in the risk of mortality and disease progression with an increasing number of maintenance cycles.

To further quantify the association between cycle count and prognosis and to identify a potential clinical benefit threshold, exploratory analyses were performed using different cutoff values. The largest significant survival disparity was noted when patients were stratified at 8 cycles (the median): long-cycle group (> 8 cycles, n = 48) against short-cycle group (≤ 8 cycles, n = 44), yielding a HR of 0.21 (95% CI: 0.09–0.49; P < 0.001). With this ideal cutoff, the long-cycle group exhibited a median OS of 63.3 months (95% CI: 57.3–not reached) and a median PFS of 46.1 months (95% CI: 33.8–not reached). In the short-cycle cohort, the median OS was 35.6 months (95% CI: 31.4–not attained), and the median PFS was 12.5 months (95% CI: 10.5–16.6). Both differences were statistically significant (P < 0.001 for each; Fig. 6). Multivariable Cox regression established that an extended maintenance period (> 8 cycles) is an independent protective factor for both OS (HR = 0.19; 95% CI: 0.08–0.47; P < 0.001) and PFS (HR = 0.19; 95% CI: 0.10–0.38; P < 0.001).

6. Safety analysis

AEs in the two groups throughout the initial treatment phase are summarized in Table 3. The maintenance group had markedly elevated occurrences of leukopenia (62.0% vs. 26.8%), anemia (44.6% vs. 20.1%), neutropenia (38.0% vs. 13.4%), and thrombocytopenia (18.5% vs. 9.4%) compared to the observation group (all P < 0.05). The maintenance group also exhibited significantly elevated incidence of grade ≥ 3 AEs, including leukopenia (22.8% vs. 4.7%), neutropenia (19.6% vs. 8.1%), and anemia (8.7% vs. 2.0%). No substantial difference was noted in the occurrence of irAEs between the two groups (P > 0.05). In the maintenance group of 92 patients, AEs were primarily classified as grade 1–2, with the most prevalent being hypothyroidism (16.3%), thrombocytopenia (9.8%), and neutropenia (6.5%) as outlined in **Supplementary Table 2**. Nine patients (9.8%) experienced grade ≥ 3 AEs, including two fatalities (2.2%) resulting from severe pneumonia (both grade 5). The residual grade ≥ 3 events were ALT elevation (2 instances, 2.2%), and one instance each of AST elevation, leukopenia, rash, thrombocytopenia, and anemia (1.1% each). Nine patients (9.8%)

discontinued treatment due to AEs, which included increased liver enzymes, hypothyroidism, rash, cytopenia, and cardiovascular incidents. IrAEs primarily consisted of hypothyroidism, with a single occurrence (1.1%) of immune-related pneumonitis.

Generally, the majority of patients tolerated maintenance therapy effectively; nonetheless, critical incidents like severe pneumonia require consideration. During follow-up, prevalent symptoms in the observation group comprised exacerbated dysphagia, pain, weight loss, and cough; this data was excluded from the safety analysis for maintenance therapy.

Table 3
Safety comparison of initial treatment

Adverse events	Observation group (n = 149)	Maintenance group (n = 92)	*P* value
Leukopenia	40 (26.8%)	57 (62.0%)	< 0.001
Radiation esophagitis	50 (33.6%)	29 (31.5%)	0.779
Anemia	30 (20.1%)	41 (44.6%)	< 0.001
Neutropenia	20 (13.4%)	35 (38.0%)	< 0.001
Thrombocytopenia	14 (9.4%)	17 (18.5%)	0.048
Hypokalemia	6 (4.0%)	5 (5.4%)	0.753
Hypothyroidism	3 (2.0%)	6 (6.5%)	0.088
AST elevation	2 (1.3%)	3 (3.3%)	0.373
ALT elevation	3 (2.0%)	1 (1.1%)	1.000
Radiation pneumonitis	1 (0.7%)	1 (1.1%)	1.000
Radiation dermatitis	0 (0.0%)	2 (2.2%)	0.145
Immune myocarditis	1 (0.7%)	0 (0.0%)	1.000
Vomiting	0 (0.0%)	1 (1.1%)	0.382
Nausea	0 (0.0%)	1 (1.1%)	0.382
Allergic dermatitis	0 (0.0%)	1 (1.1%)	0.382
Decreased appetite	0 (0.0%)	1 (1.1%)	0.382
Data are presented as n (%). P values were calculated using Fisher's exact test.			

Discussion

Definitive chemoradiotherapy is the standard of care for unresectable locally advanced ESCC, yet recurrence rates remain high and long-term survival is unsatisfactory. Consequently, consolidating the initial response and delaying disease progression presents a significant therapeutic challenge. Although maintenance therapy has established roles in multiple solid tumors, robust evidence in ESCC is lacking. This real-world retrospective study sought to evaluate the efficacy and safety of maintenance therapy compared to observation alone in patients with unresectable locally advanced ESCC following standard initial treatment, with the objective of guiding clinical practice.

This study demonstrated that maintenance therapy prolonged median OS by 24.4 months (53.8 vs. 29.4 months), resulting in a 49% decrease in mortality risk (HR = 0.51). Likewise, median PFS was prolonged by 11.7 months (24.6 vs. 12.9 months), reflecting a 38% decrease in the probability of progression (HR = 0.62). Multivariable analysis and PSM sensitivity analysis repeatedly indicated a survival benefit of maintenance therapy, affirming the reliability of these results. This outcome corresponds with recent progress in ICIs for esophageal cancer treatment. Numerous clinical studies have investigated the efficacy of PD-1 inhibitors given concurrently with chemoradiotherapy and continued as maintenance therapy in locally advanced ESCC, reporting median PFS ranging from 7 to 16 months, and median OS exceeding 30 months in most studies or not reached[18, 22, 31, 32]. Given that some studies included patients with advanced or metastatic ESCC, the absolute survival benefits reported were smaller than those observed in our study. Nevertheless, the overall trend of survival improvement with maintenance therapy remained broadly consistent. Moreover, the SKYSCRAPER-07 trial[23], which focused on maintenance therapy in patients with unresectable locally advanced ESCC, reported preliminary results showing a median PFS of 29.1 months (95% CI: 19.0–36.3) and a median OS not reached in the atezolizumab monotherapy maintenance group. The results align with our findings, and the substantial data from this extensive phase III trial further corroborate the dependability of the survival benefit noted with maintenance therapy. Notably, although our study demonstrated significant benefits in both OS and PFS, the median PFS in the maintenance group was 24.6 months, indicating that half of the patients still experienced disease progression within approximately two years. This discovery underscores the necessity for additional exploration of resistance mechanisms to maintenance therapy and ensuing treatment methods.

Subgroup analyses revealed that the OS benefit of maintenance therapy was more pronounced in patients aged < 65 years, those with a history of smoking, and those with a maximum tumor diameter > 1.4 cm. Younger patients generally have better performance status and organ function reserve, which may translate into greater tolerance to long-term maintenance therapy and thus greater treatment exposure. A study conducted by the Sun Yat-sen University Cancer Center examined the effect of smoking on OS in patients with metastatic ESCC undergoing first-line immunotherapy. The findings indicated that smoking was an independent adverse prognostic factor (HR = 2.72, $P < 0.001$), with non-smokers having significantly longer survival (1,294 vs. 920 days) [33]. This finding seems to contradict our study, which indicated that patients with a smoking history experienced better survival benefits from maintenance therapy. Several factors may explain this discrepancy. First, our study only included patients who achieved disease control after standard initial treatment, thereby excluding those with advanced or metastatic disease. It is possible that the adverse prognostic impact of smoking is most pronounced in the advanced-stage patients, and the exclusion of these patients may explain why smokers in our study appeared to derive greater benefit from maintenance therapy. Second, a lung cancer study reported that SBS4 exposure and tumor mutational burden (TMB) were highly correlated, and that elevated TMB and increased neoantigen burden are associated with improved response to ICIs[34]. Additionally, a basic study in lung squamous cell carcinoma demonstrated that smoking is closely linked to carcinogenesis and that smokers have significantly higher TMB than non-smokers[35]. Together, these findings suggest that smoking may enhance immune responsiveness via elevated TMB, potentially leading to greater neoantigen activation and better immunotherapy benefit. However, elevated TMB may also indicate greater tumor heterogeneity, which could partly explain why half of the patients in the maintenance group still experienced disease progression within two years. Third, despite efforts to adjust for confounding factors, the retrospective design of this study leaves the possibility that unmeasured variables may have influenced the results. Similarly, patients with larger tumors may derive more pronounced benefit from maintenance therapy simply because they have more room for tumor shrinkage. Furthermore, across all other subgroups, the point estimates of HR for maintenance therapy were below 1, and none of the interaction tests reached statistical significance, suggesting that the benefit of maintenance therapy is broadly applicable. Even in small subgroups, such as patients with stage II, stage IVA, or age ≥ 75 years, the HR consistently favored maintenance therapy, further supporting its broad applicability.

Exploratory analyses within the maintenance group comparing different regimens showed no statistically significant differences in OS or PFS across immunotherapy monotherapy, chemotherapy/targeted monotherapy, and chemoimmunotherapy regimens. This result may be due to the limited sample size and insufficient statistical power. The ORR and DCR in the chemoimmunotherapy group were similar to those in the immunotherapy monotherapy group (23.8% vs. 28.3%, and 90.5% vs. 84.8%, respectively), suggesting no clear additive benefit of combination therapy. This may be due to the reduced dose intensity of chemotherapy used in the maintenance phase, as well as the small sample size, which might have precluded the detection of a potential synergistic effect. Analysis of the relationship between maintenance cycle count and prognosis revealed a significant association. Although RCS models showed no clear nonlinear pattern, the overall association with mortality risk was highly significant (P overall < 0.001), with a continuous decline in the risk of death as the number of cycles increased. We performed exploratory analyses using various cutoff values for the number of maintenance cycles and found that the median (8 cycles) yielded the most pronounced survival difference. Patients in the long-cycle group (> 8 cycles) exhibited a significantly prolonged median OS and PFS compared to those in the short-cycle group (≤ 8 cycles). Following multivariable correction, an extended maintenance period continued to serve as an independent protective factor for both OS and PFS (HR = 0.19). This finding supports a dose-response relationship for maintenance therapy, indicating that adequate treatment exposure is a prerequisite for survival benefit. In clinical practice, the 8-cycle cutoff may serve as a benchmark for treatment adherence and early efficacy. Therefore, patients who tolerate therapy well and show no disease progression should be encouraged to complete at least 8 cycles to derive optimal benefit. Nevertheless, the cutoff value for cycle number in this study was derived from exploratory analyses and requires confirmation in prospective studies. Notably, the observed dose-response relationship suggests that longer maintenance therapy duration is associated with greater survival benefit. However, evidence from other solid tumors, such as a systematic review in non-small cell lung cancer, suggested that discontinuing ICI therapy after two years did not significantly compromise survival compared with continued treatment, whereas irAEs accumulated over time[36]. Accordingly, a two-year treatment duration was established as the cessation point in our study. Even so, the direct applicability of this cutoff to patients with unresectable locally advanced ESCC necessitates prospective validation.

During the initial treatment phase, the maintenance group had higher rates of hematologic toxicities than the observation group, likely due to more intensive initial treatment (greater exposure to chemotherapy and immunotherapy). Nonetheless, grade ≥ 3 adverse events were acceptable in both groups and did not preclude maintenance therapy. During the maintenance phase, AEs were predominantly grade 1–2, with hypothyroidism being the most common (16.3%), consistent with the safety profiles of PD-1 inhibitors[37]. Grade ≥ 3 serious adverse events occurred in 9 patients (9.8%), including two deaths (2.2%) from severe pneumonia, indicating that although maintenance therapy was generally well tolerated, fatal events warrant caution. IrAEs were manageable, and most patients successfully completed treatment with early recognition and standardized management.

Several limitations of this study should be acknowledged. First, as a single-center retrospective study, selection and information biases are inherent; although multivariable correction and PSM were applied, unmeasured confounding cannot be excluded. Second, maintenance regimens were heterogeneous, reflecting real-world practice. This heterogeneity limited direct comparisons between different strategies and resulted in small subgroup sample sizes with wide confidence intervals, precluding definitive conclusions about comparative efficacy. Third, the small sample size in certain subgroups warrants cautious interpretation of subgroup findings. Finally, incomplete data on biomarkers such as PD-L1 expression and TMB precluded molecular-level stratification analyses.

Conclusions

Maintenance therapy after standard initial treatment markedly extends OS and PFS in patients with unresectable locally advanced ESCC, decreasing the mortality risk by 49% and the progression risk by 38%, while maintaining a manageable safety profile. The quantity of maintenance cycles is intricately linked to prognosis, and the completion of a minimum of 8 cycles may be requisite for maximal survival benefit.

Abbreviations

AEs	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
Cox	Cox proportional hazards model
CR	Complete response
CSCO	Chinese Society of Clinical Oncology
CTCAE 5.0	Common terminology criteria for adverse events version 5.0
DCR	Disease Control Rate
dCRT	Definitive Chemoradiotherapy
ECOG PS	Eastern cooperative oncology group performance status
ESCC	Esophageal squamous cell carcinoma
HR	Hazard ratio
ICIs	Immune checkpoint inhibitors
irAEs	Immune-related adverse events
NCCN	National comprehensive cancer network
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PR	Partial response
PSM	Propensity score matching
RCS	Restricted cubic spline
RECIST 1.1	Response evaluation criteria in solid tumors version 1.1
SD	Stable disease
SMD	Standardized mean difference
TMB	Tumor mutational burden

Declarations

Ethical approval and consent to participate: The study was approved by the Institutional Review Board of Affiliated Hospital of North Sichuan Medical College, which waived the requirement for individual informed consent due to the retrospective nature of the analysis.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Author Contributions: Chuanyu You: conceptualization, methodology, investigation, data curation, formal analysis, writing - original draft. **Tian Xu:** methodology, investigation, data curation, formal analysis, writing - original draft. **Qilin Wang:** investigation, data curation, writing - original draft. **Juncai Ye:** formal analysis, data curation. **Xueping Yang:** investigation, data curation. **Xingyu Chen:** investigation, validation. **Jiahao Chen:** investigation, validation. **Guangzeng Zhou:** investigation, validation. **Yan Gui:** conceptualization, resources, supervision, project administration, writing - review and editing.

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Figures

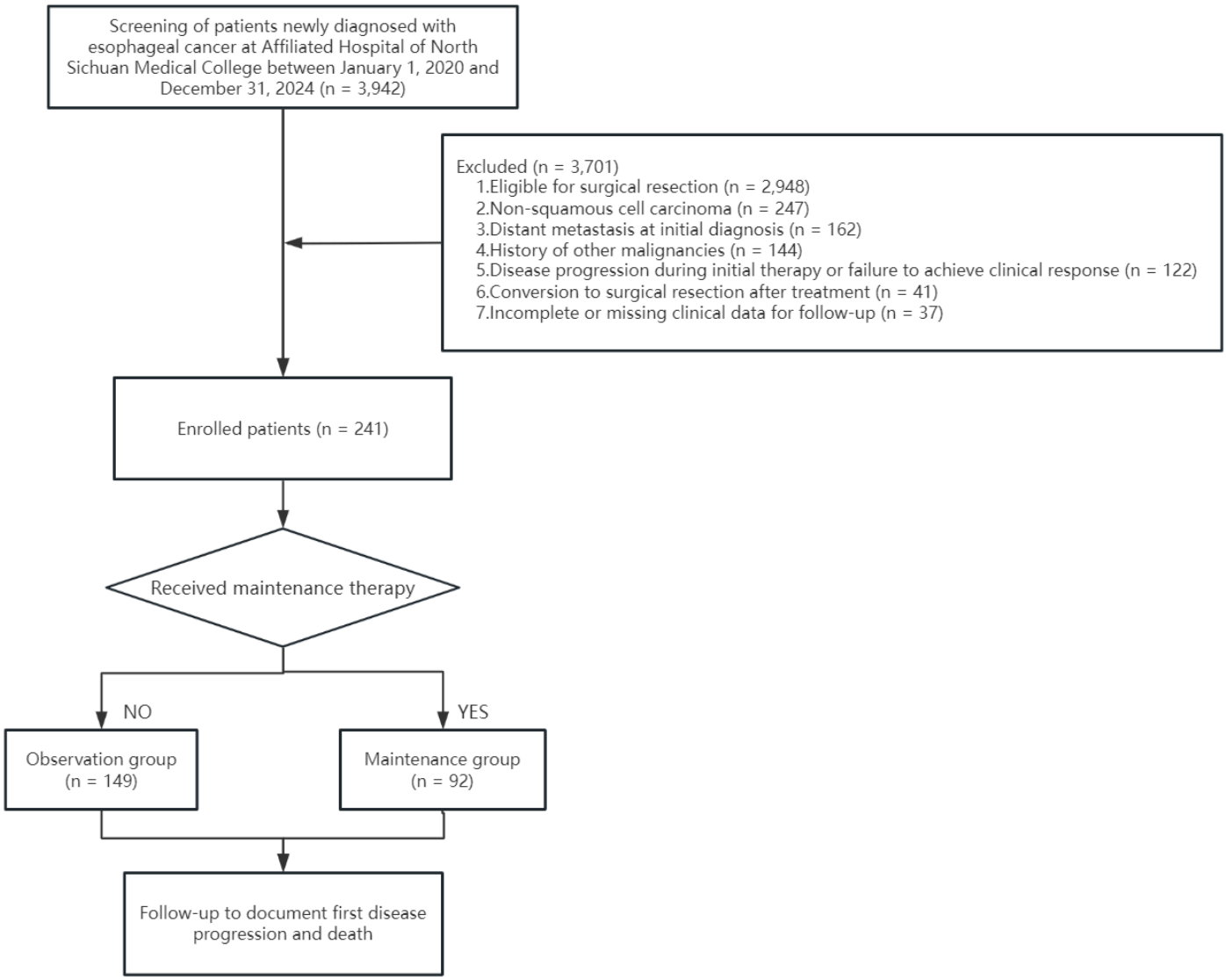


Figure 1

Flowchart of patient selection

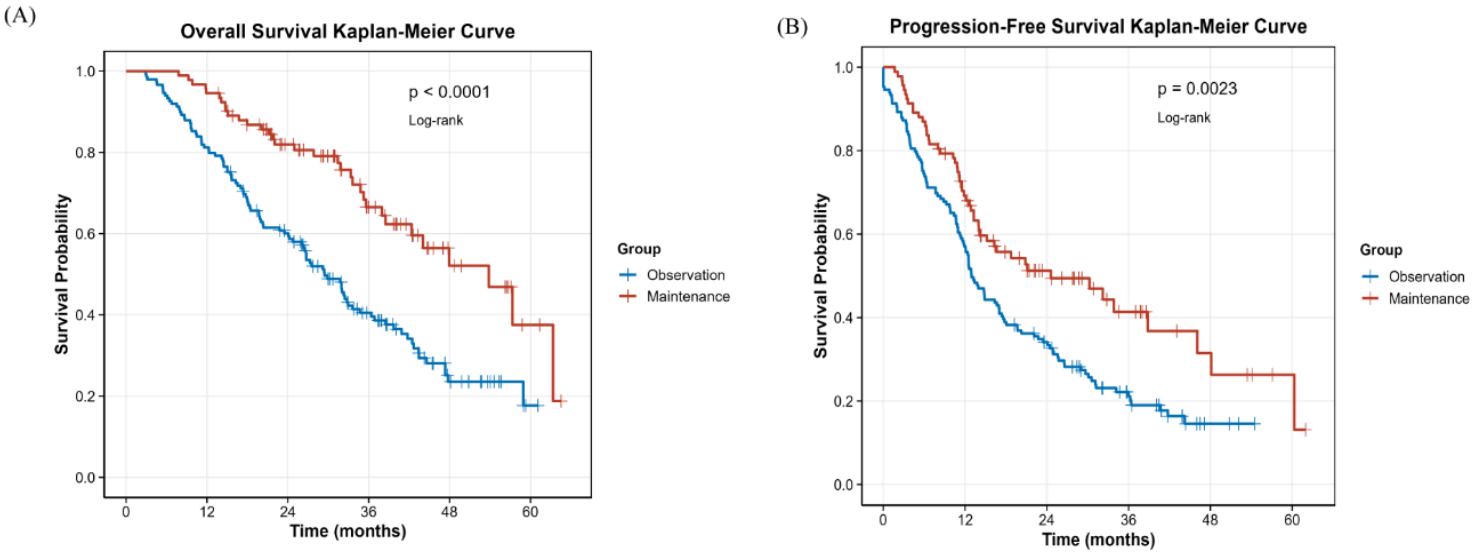


Figure 2

Kaplan-Meier curves for OS (A) and PFS (B) in the overall study cohort.

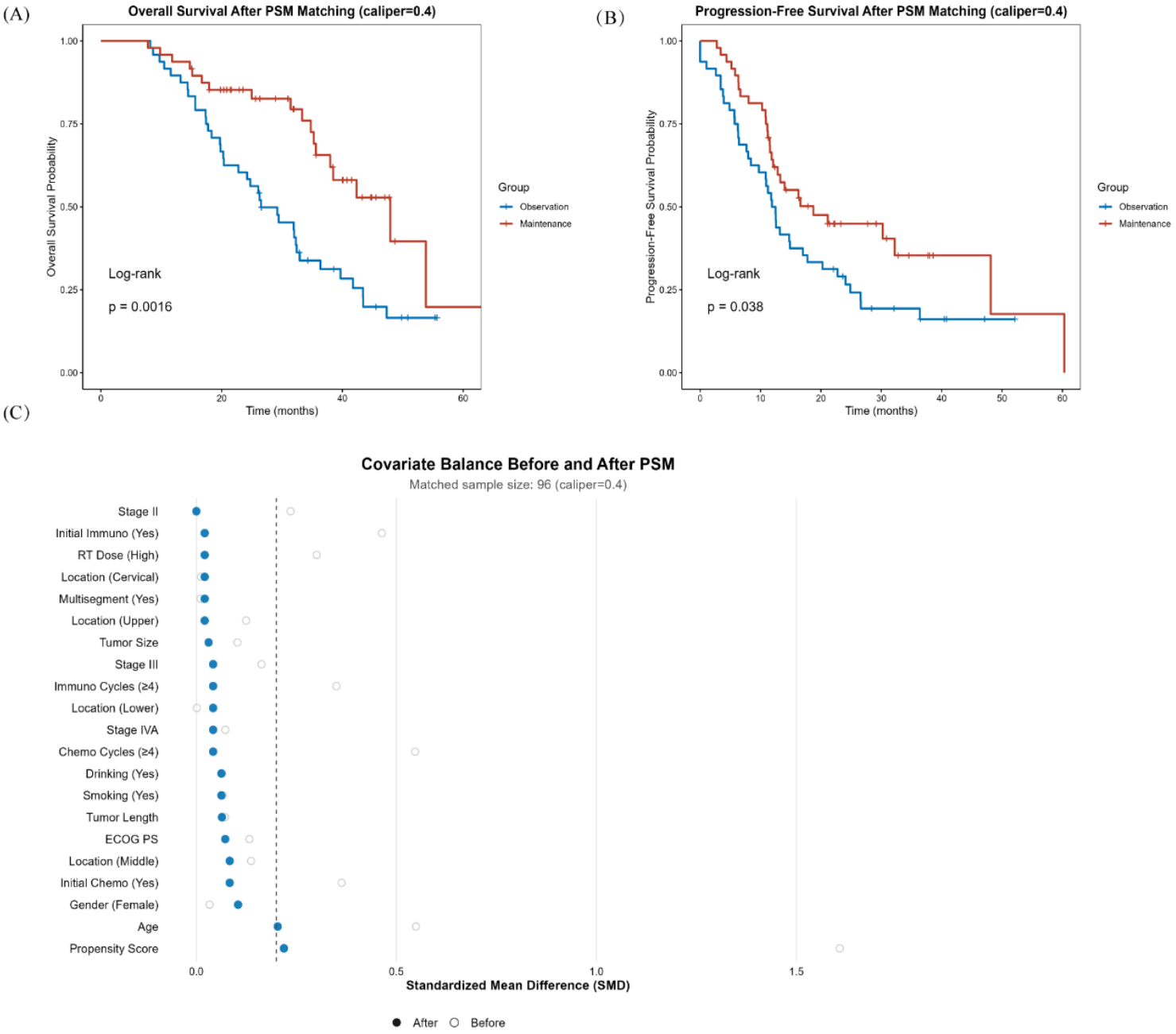


Figure 3

Analysis of the Propensity Score-Matched Cohort

(A) Comparison of OS between the two groups after matching
(B) Comparison of PFS between the two groups after matching

(C) Balance assessment plot (Love plot) displaying SMD for all baseline covariates before and after matching, confirming the effectiveness of the matching procedure.

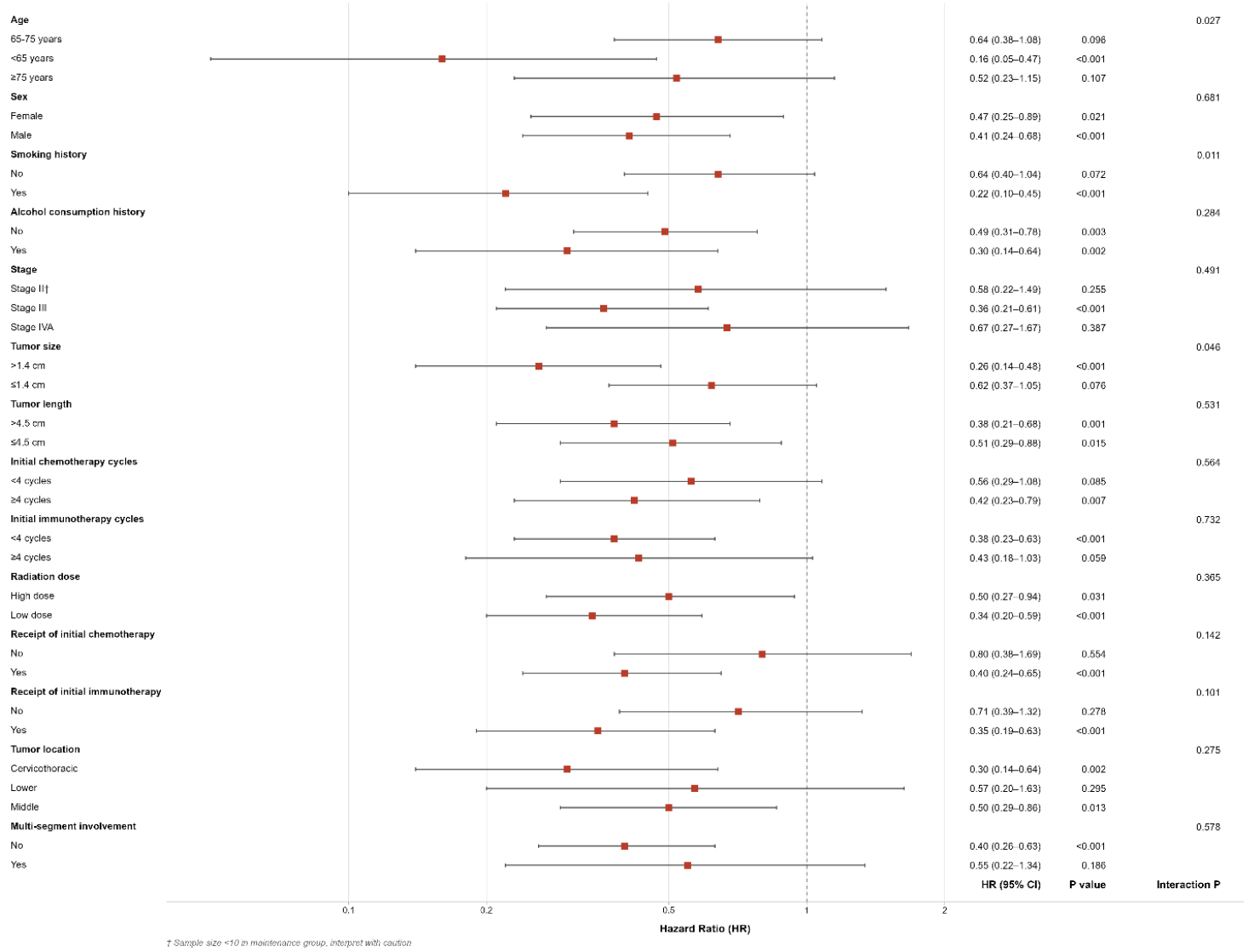


Figure 4

Subgroup analysis forest plot for OS

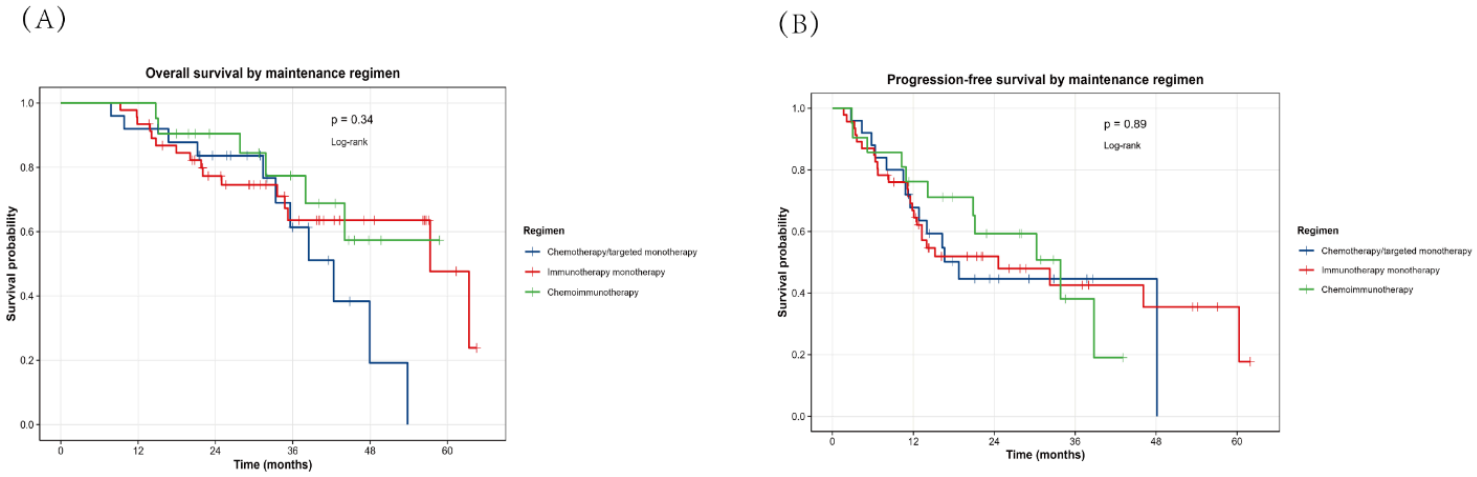


Figure 5

Comparison of OS (A) and PFS (B) among different maintenance therapy regimens

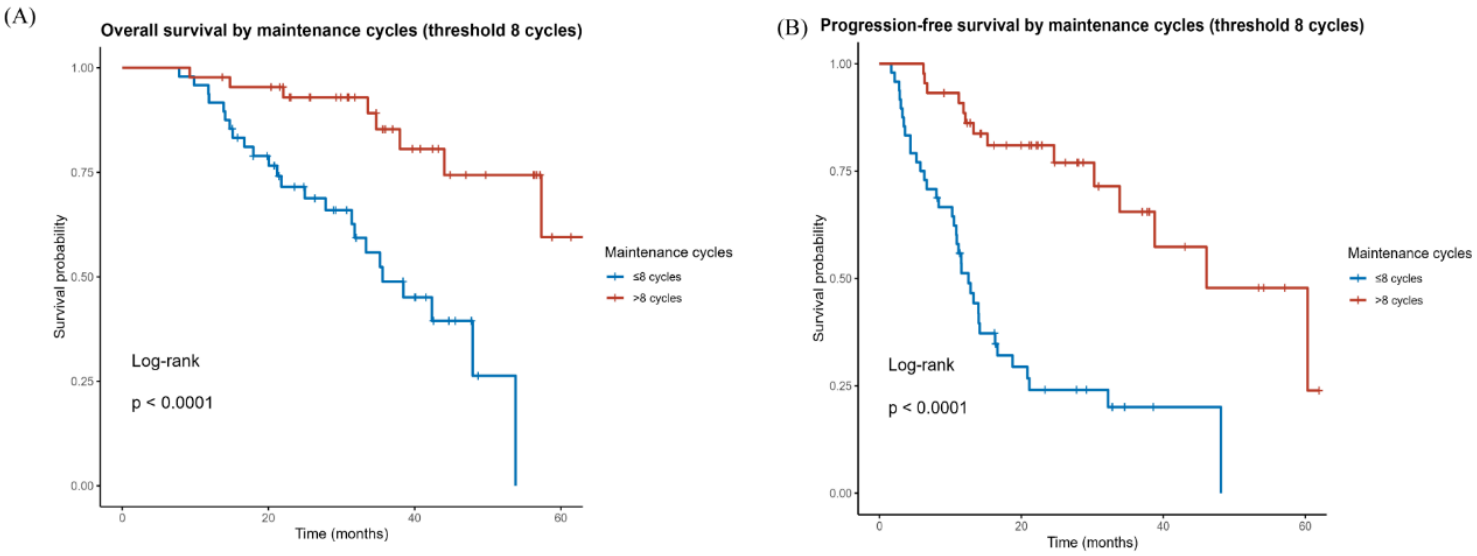


Figure 6

Kaplan-Meier curves of OS (A) and PFS (B) stratified by different maintenance therapy cycles (≤8 cycles vs. >8 cycles)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx
- SupplementaryFigure1.SubgroupanalysisforestplotforPFS.tiff
- SupplementaryFigure2.RestrictedcubicsplinefittingofthenumberofmaintenancetherapycycleswithoverallsurvivalAandprogressionfreesurvivalB.tif