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Original Article

Maintenance chemotherapy for esophageal squamous cell carcinoma after standard concurrent chemoradiotherapy: a national propensity score matching cohort study

Szu-Wen Tseng[1*], Wan-Ming Chen[2,3,4*], An-Tzu Jao[4], Mingchih Chen[2,3], Ben-Chang Shia[2,3#], Szu-Yuan Wu[2,3,4,5,6,7,8,9,10#]

[1]Division of Medical Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [2]Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, Taipei, Taiwan; [3]Artificial Intelligence Development Center, Fu Jen Catholic University, Taipei, Taiwan; [4]Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [5]Department of Food Nutrition and Health Biotechnology, College of Medical and Health Science, Asia University, Taichung, Taiwan; [6]Division of Radiation Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [7]Department of Healthcare Administration, College of Medical and Health Science, Asia University, Taichung, Taiwan; [8]Cancer Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan, Taiwan; [9]Centers for Regional Anesthesia and Pain Medicine, Taipei Municipal Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; [10]Department of Management, College of Management, Fo Guang University, Yilan, Taiwan. [*]Equal contributors and co-first authors. [#]Equal contributors.

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Abstract: Esophageal squamous cell carcinoma (ESCC) is a common and aggressive cancer, and its standard treatment is concurrent chemoradiotherapy (CCRT). Maintenance chemotherapy is often used to help prevent cancer recurrence, but its efficacy for patients with ESCC receiving CCRT remains unclear. We conducted a large head-to-head propensity score matching cohort study to estimate the effects of maintenance chemotherapy on overall survival and cancer-specific survival in patients with ESCC receiving standard CCRT. After propensity score matching (PSM), we recruited 2724 patients with ESCC (2177 in the maintenance chemotherapy group and 547 in the non-maintenance chemotherapy group). The adjusted hazard ratios (95% confidence intervals) of all-cause mortality and cancer-specific mortality for the maintenance chemotherapy group were 1.15 (1.06-1.26, P = 0.0014) and 1.08 (0.88-1.29, P = 0.1320), respectively, compared with the non-maintenance chemotherapy group. We also found that older age, relatively lower body mass index (BMI), higher American Joint Committee on Cancer clinical stage, and poor response to CCRT as measured using the Response Evaluation Criteria in Solid Tumors were poor independent predictors of all-cause mortality and cancer-specific mortality. Our findings indicated that maintenance chemotherapy may not improve the survival of patients with ESCC who have received CCRT. Additionally, we identified several key prognostic factors for patients with ESCC receiving CCRT, including relatively low BMI and poor response to CCRT. Further research is needed to understand the benefits and risks of maintenance chemotherapy in similar patient populations in order to identify new therapies that could improve treatment responses.

Keywords: Esophageal cancer, esophageal squamous cell carcinoma, concurrent chemoradiotherapy, maintenance chemotherapy, prognostic factor

Introduction

Esophageal cancer is a leading cause of cancer-related deaths in Taiwan, and more than 95% of patients with esophageal cancer also have esophageal squamous cell carcinoma (ESCC) [1-3]. The pathological types of ESCC in Taiwan and other Asian countries tend to differ from those in Western countries, where esophageal adenocarcinoma is more common [4, 5]. In Taiwan, the standard treatment for esophageal cancer is concurrent chemoradiotherapy (CCRT), administered according to National Comprehensive Cancer Network (NCCN) guide-

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lines and regimens recommended by the INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial [6, 7]. Nevertheless, the response rate for patients with ESCC remains relatively low-approximately 50% [8], indicating the presence of residual tumors, which increase the risk of recurrence and lead to reduced survival. Consequently, some clinicians may consider using additional treatment options, such as esophagostomy or maintenance chemotherapy, in an attempt to promote patient survival [1, 2, 9].

Maintenance chemotherapy is often used after the initial chemotherapy regimen to help prevent cancer recurrence [10]. Maintenance chemotherapy involves the use of chemotherapy drugs to target any remaining cancer cells that were not eliminated by the initial treatment [11-18]. It is typically administered in low oral or intravenous doses and over a long period compared with the initial treatment [12-21]. Maintenance chemotherapy may be beneficial for treating certain types of cancer [11, 14-16], and its benefits may vary depending on the type of cancer and the specific patient population. In some cases [17, 18], maintenance chemotherapy may not provide any additional benefits after the initial treatment and may cause adverse effects.

No large-scale clinical trials have examined the efficacy of maintenance chemotherapy after concurrent CCRT in patients with ESCC. Many studies on the use of maintenance chemotherapy in esophageal cancer patients have included both squamous cell carcinoma and adenocarcinoma, as well as a variety of locations in the esophagus: the cervical part, the thoracic part, and the gastroesophageal junction (GEJ) [19-24]. Furthermore, these studies have had small sample sizes and have been poorly designed, making it difficult to determine whether maintenance chemotherapy affects patient prognoses [19-24]. Some studies have suggested that maintenance chemotherapy may promote survival in patients with esophageal cancer, whereas others have observed no such benefits [19-24]. Thus, whether maintenance chemotherapy promotes the survival of patients with ESCC receiving standard CCRT remains unclear. To address this knowledge gap, we conducted a large head-to-head PSM cohort study by using a real-world database to estimate the effects of maintenance chemotherapy on overall survival and cancer-specific survival in patients with ESCC receiving standard CCRT.

Patients and methods

Study cohort

Data for this cohort study were obtained from the Taiwan Cancer Registry Database (TCRD). We included patients who had received a diagnosis of ESCC between January 1, 2008, and December 31, 2018. The index date was the date of completion of standard CCRT for ESCC, and the follow-up period ran from the index date to December 31, 2020. The TCRD of the Collaboration Center of Health Information Application contains detailed cancer-related information on patients, including clinical stage, treatment modalities, chemotherapy regimens, chemotherapy doses, pathology, radiation modalities and doses, and treatment protocols [2, 25, 26]. The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and exclusion criteria

The inclusion criteria were being ≥ 18 years old; having a diagnosis of ESCC; having clinical stage I-IVA disease without metastasis, according to the eighth edition of the American Joint Committee on Cancer (AJCC); and having an Eastern Cooperative Oncology Group performance status of 0 or 1. We excluded patients with a history of cancer prior to ESCC diagnosis, distant metastasis, missing sex data, age younger than 18 years, unclear staging, an unclear Response Evaluation Criteria in Solid Tumors (RECIST) response after CCRT, unknown cigarette smoking or alcohol use, or non-squamous cell carcinoma histology. In addition, patients who had undergone esophagostomy followed by CCRT were excluded to ensure that the results related to the survival effects of maintenance chemotherapy for ESCC after standard CCRT were not confounded.

Standard CCRT for ESCC was defined as the administration of platinum-based chemotherapy (e.g., cisplatin or carboplatin) combined with intensity-modulated radiation therapy (total dose: 5000-5040 cGy/28fx [7]). The incidence

of comorbidities was scored using the Charlson comorbidity index (CCI) [27-29]. Only comorbidities observed in the 6 months prior to the index date were included, and these comorbidities were coded and classified according to the corresponding *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes or *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes at the first inpatient visit or after more than two outpatient visits.

Maintenance chemotherapy

This paper defines maintenance chemotherapy as regimens containing fluorouracil alongside leucovorin, capecitabine, cisplatin, or oxaliplatin administered in combination with each other or with other chemotherapy agents, such as irinotecan or docetaxel, based on the recommendations of medical oncologists [19-21]. Maintenance chemotherapy for ESCC after CCRT was administered for at least six cycles over 6 months.

PSM

To control for potential confounders when comparing the survival outcomes of the maintenance and non-maintenance chemotherapy groups, all patients were matched using PSM based on the following variables: age, sex, body mass index (BMI), year of diagnosis, AJCC clinical stage, RECIST response after CCRT, cigarette smoking habits, alcohol consumption habits, and CCI scores (**Table 1**). The maintenance and non-maintenance chemotherapy groups were matched at a ratio of 1:4 by using the greedy matching method with a caliper of 0.2 [30]. Continuous variables are presented as means ± standard deviations where appropriate.

Outcome measures

The primary outcome was all-cause mortality among PSM patients with ESCC receiving maintenance or non-maintenance chemotherapy after standard CCRT. The secondary outcome was cancer-specific mortality.

Statistical analysis

We determined the association between maintenance chemotherapy and survival outcomes in patients with ESCC who received standard CCRT. We used the Kaplan-Meier method to estimate the cumulative incidences of all-cause mortality and cancer-specific mortality in the maintenance and non-maintenance chemotherapy groups, and the log-rank test was used to determine between-group differences. Because residual imbalance can remain after PSM has been applied to a large sample [31, 32], we used univariate and multivariate Cox regression analysis to estimate crude hazard ratios (HRs) and adjusted HRs (aHRs) with 95% confidence intervals (CIs) for all-cause mortality and cancer-specific mortality in both groups. In addition, sensitivity analyses were conducted to evaluate the risk of all-cause mortality and cancer-specific mortality in subgroups based on age, BMI, AJCC clinical stage, and RECIST response after CCRT. All analyses were performed using SAS (version 9.4), and two-tailed $P < 0.05$ was considered statistically significant.

Results

Clinicopathological characteristics

This study enrolled 4676 patients with ESCC receiving standard CCRT, namely 4129 in the non-maintenance chemotherapy group and 547 in the maintenance chemotherapy group. **Table 1** presents the characteristics of the two groups before PSM. Before PSM, the maintenance chemotherapy group had a younger average age, higher advanced AJCC clinical stages, and a poorer RECIST response after CCRT compared with the non-maintenance chemotherapy group. After PSM, 2724 patients with ESCC were included in the study (2177 in the maintenance chemotherapy group and 547 in the non-maintenance chemotherapy group), and all confounding factors were balanced between the two groups. The median follow-up duration after the index date was 2.44 years. The all-cause mortality rates were 83.14% and 91.04% for the matched non-maintenance and maintenance chemotherapy groups, respectively ($P < 0.0001$). The cancer-specific mortality rates were 85.99% and 89.21% for the matched non-maintenance and maintenance chemotherapy groups, respectively ($P = 0.6083$).

All-cause mortality

Maintenance chemotherapy was a significant and poor independent predictor of all-cause

Table 1. Characteristics of maintenance and non-maintenance chemotherapy for patients with ESCC after standard CCRT

	Before Propensity Score Matching					After Propensity Score Matching				
	Non-Maintenance Chemotherapy N = 4129		Maintenance Chemotherapy N = 547		*P* Value	Non-Maintenance Chemotherapy N = 2177		Maintenance Chemotherapy N = 547		*P* Value
	N	%	N	%		N	%	N	%	
Age, Years (mean ± SD)	58.74 ± 10.44		56.31 ± 8.71		< 0.0001	56.67 ± 9.13		56.31 ± 8.71		0.4117
Age, Years Median (IQR, Q1-Q3)	58.00 (51.00-65.00)		55.00 (50.00-62.00)		< 0.0001	56.00 (50.00-62.00)		55.00 (50.00-62.00)		0.4467
Age Group, Years					< 0.0001					0.8508
≤ 50	905	21.92%	140	25.59%		561	25.77%	140	25.59%	
51-60	1580	38.27%	235	42.96%		935	42.95%	235	42.96%	
61-70	1061	25.70%	134	24.50%		551	25.31%	134	24.50%	
≥ 70	583	14.12%	38	6.95%		130	5.97%	38	6.95%	
Sex					0.4825					0.3043
Women	3911	94.72%	522	95.43%		2098	96.37%	522	95.43%	
Men	218	5.28%	25	4.57%		79	3.63%	25	4.57%	
BMI					0.0758					0.7080
< 18.5	754	18.26%	115	21.02%		459	21.08%	115	21.02%	
18.5-23	2314	56.04%	315	57.59%		1253	57.56%	315	57.59%	
24-26	708	17.15%	85	15.54%		326	11.71%	85	15.54%	
≥ 27	353	8.55%	32	5.85%		139	6.38%	32	5.85%	
Years of Diagnosis					0.6577					0.7687
2008-2010	1128	27.32%	153	27.97%		630	28.94%	153	27.97%	
2011-2013	1600	38.75%	201	36.75%		814	37.39%	201	36.75%	
2014-2018	1401	33.93%	193	35.28%		733	33.67%	193	35.28%	
AJCC Clinical Stage					< 0.0001					0.9202
I	177	4.29%	16	2.93%		54	2.48%	16	2.93%	
IIA	698	16.90%	59	10.79%		255	11.71%	59	10.79%	
IIB	1025	24.82%	112	20.48%		460	21.13%	112	20.48%	
IIIA	535	12.96%	58	10.60%		246	11.30%	58	10.60%	
IIIB	711	17.22%	99	18.10%		406	18.65%	99	18.10%	
IVA	989	23.80%	203	37.11%		756	34.73%	203	37.11	
RECIST Response After CCRT					< 0.0001					0.9405
CR	650	15.74%	46	8.41%		180	8.23%	46	8.41%	
PR	1579	38.23%	216	39.49%		869	39.91%	216	39.49%	
SD	288	6.98%	50	9.14%		205	9.42%	50	9.14%	
PD	1612	39.04%	235	42.96%		923	42.40%	235	42.96%	

Cigarette Smoking					0.9222					0.4937
Never	476	11.53%	63	11.52%		224	10.29%	63	11.52%	
Current	2785	67.45%	373	68.19%		1469	67.48%	373	68.19%	
Quit	868	21.02%	111	20.29%		484	22.23%	111	20.29%	
Alcohol Consumption					0.3388					0.2837
Never	583	14.12%	66	12.07%		218	10.01%	66	12.07%	
Moderate	2678	64.86%	370	67.64%		1475	67.75%	370	67.64%	
Heavy	868	21.02%	111	20.29%		484	22.23%	111	20.29%	
CCI Score										
Mean (SD)	0.99 ± 1.27		0.93 ± 1.14		0.2567	1.02 ± 1.26		0.93 ± 1.14		0.1126
Median (IQR, Q1-Q3)	0.00 (0.00-2.00)		0.00 (0.00-2.00)		0.6552	0.00 (0.00-2.00)		0.00 (0.00-2.00)		0.2776
CCI Score					0.9016					0.4872
0	2185	52.92%	291	53.20%		1122	51.54%	291	53.20%	
1	1944	47.08%	256	46.80%		1055	48.46%	256	46.80%	
CCI										
Congestive Heart Failure	116	2.80%	9	1.70%	0.1127	50	2.30%	9	1.70%	0.1208
Dementia	0	0.00%	0	0.00%	0.9999	0	0.00%	0	0.00%	0.9999
Chronic Pulmonary Disease	749	18.10%	98	17.90%	0.8983	377	17.30%	98	17.90%	0.7534
Rheumatic Disease	27	0.70%	3	0.60%	0.7716	18	0.80%	3	0.60%	0.5047
Liver Disease	1-217	29.50%	169	30.90%	0.494	711	32.70%	169	30.90%	0.8427
Diabetes With Complications	145	3.50%	15	2.70%	0.3522	68	3.10%	15	2.70%	0.9737
Hemiplegia and Paraplegia	0	0.00%	0	0.00%	0.9999	0	0.00%	0	0.00%	0.9999
Renal Disease	150	3.6%	11	2.00%	0.0506	71	3.30%	11	2.00%	0.4206
Acquired Immunodeficiency Syndrome	0	0.00%	0	0.00%	0.9999	0	0.00%	0	0.00%	0.9999
Outcomes										
All-Cause Death					< 0.0001					< 0.0001
No	814	19.71%	49	8.96%		367	16.86%	49	8.96%	
Yes	3315	80.29%	498	91.04%		1810	83.14%	498	91.04%	
Cancer Death					< 0.0001					0.6083
No	1006	24.36%	59	10.79%		305	14.01%	59	10.79%	
Yes	3123	75.64%	488	89.21%		1872	85.99%	488	89.21%	

Abbreviations: ESCC, esophageal squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; BMI, body mass index; RECIST, Response Evaluation Criteria in Solid Tumors; AJCC, American Joint Committee on Cancer; PSM, propensity score matching; CCI, Charlson comorbidity index; N, number; SD, standard deviation; IQR, interquartile range; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 2. Cox proportional regression model of all-cause mortality for propensity score-matched patients with ESCC after standard CCRT

	Crude HR (95% CI)	*P* Value	Adjusted HR* (95% CI)	*P* Value
Chemotherapy (ref. Non-Maintenance Chemotherapy)				
Maintenance Chemotherapy	1.18 (1.08-1.29)	0.0002	1.15 (1.06-1.26)	0.0014
Age Group, Years (ref. 18-50)				
51-60	1.06 (1.02-1.34)	0.0009	1.07 (1.02-1.95)	0.0019
61-70	1.24 (1.16-1.93)	0.0008	1.13 (1.70-1.92)	0.0006
> 70	1.97 (1.33-2.22)	0.0066	1.90 (1.77-2.05)	0.0038
Sex (ref. Women)				
Men	0.84 (0.7-1.02)	0.0734	0.84 (0.69-1.03)	0.0924
BMI (ref. < 18.5)				
18.5-23	0.79 (0.71-0.88)	< 0.0001	0.80 (0.72-0.9)	< 0.0001
24-26	0.73 (0.64-0.84)	< 0.0001	0.76 (0.66-0.88)	0.0002
≥ 27	0.65 (0.54-0.79)	< 0.0001	0.71 (0.58-0.86)	0.0004
Years of Diagnosis (ref. 2008-2010)				
2011-2013	0.90 (0.83-0.99)	0.0255	0.96 (0.83-1.12)	0.6112
2014-2018	0.90 (0.82-0.99)	0.0237	0.96 (0.82-1.12)	0.5689
AJCC Clinical Stage (ref. stage I)				
IIA	1.53 (1.15-2.04)	0.0033	1.54 (1.16-2.06)	0.0030
IIB	1.69 (1.28-2.23)	0.0002	1.70 (1.29-2.24)	0.0002
IIIA	1.92 (1.45-2.56)	< 0.0001	2.06 (1.55-2.74)	< 0.0001
IIIB	2.07 (1.57-2.73)	< 0.0001	2.16 (1.63-2.85)	< 0.0001
IVA	2.72 (2.07-3.57)	< 0.0001	2.69 (2.05-3.53)	< 0.0001
RECIST Response After CCRT (ref. CR)				
PR	1.79 (1.5-2.15)	< 0.0001	1.64 (1.37-1.97)	< 0.0001
SD	1.69 (1.35-2.12)	< 0.0001	1.60 (1.27-2.00)	< 0.0001
PD	2.20 (1.84-2.63)	< 0.0001	2.11 (1.76-2.53)	< 0.0001
Cigarette Smoking (ref. never)				
Current	1.28 (0.77-2.12)	0.3430	1.01 (0.61-1.68)	0.9715
Quit	1.00 (0.92-1.07)	0.8886	1.02 (0.94-1.09)	0.6950
Alcohol Consumption (ref. never)				
Moderate	1.00 (0.81-1.23)	0.9663	0.97 (0.78-1.19)	0.7596
Heavy	1.19 (0.92-1.54)	0.1808	1.04 (0.80-1.35)	0.7685
CCI Score (ref. CCI = 0)				
≥ 1	1.06 (0.93-1.21)	0.3488	1.08 (0.95-1.24)	0.2568

Abbreviations: ESCC, esophageal squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; BMI, body mass index; RECIST, Response Evaluation Criteria in Solid Tumors; AJCC, American Joint Committee on Cancer; PSM, propensity score matching; CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio; aHR, adjusted hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *All covariates presented in **Table 2** were adjusted.

mortality in patients with ESCC receiving standard CCRT. The aHR (95% CI) of all-cause mortality for the maintenance chemotherapy group was 1.15 (1.06-1.26, *P* = 0.0014) compared with the non-maintenance chemotherapy group. Additionally, we found that older age, lower BMI, higher AJCC clinical stage, and poor RECIST response after CCRT were poor independent predictors of all-cause mortality (**Table 2**). The aHRs (95% CI) of all-cause mortality for the age groups of 51-60, 61-70, and > 70 years; BMI groups of 18.5-23, 24-26, and ≥ 27; AJCC clinical stages of IIA, IIB, IIIA, IIIB, and IVA; and RECIST partial response (PR), stable disease (SD), and progressive disease (PD) were 1.07 (1.02-1.95), 1.13 (1.70-1.92), 1.90 (1.77-2.05),

0.80 (0.72-0.9), 0.76 (0.66-0.88), 0.71 (0.58-0.86), 1.54 (1.16-2.06), 1.70 (1.29-2.24), 2.06 (1.55-2.74), 2.16 (1.63-2.85), 2.69 (2.05-3.53), 1.64 (1.37-1.97), 1.60 (1.27-2.00), and 2.11 (1.76-2.53), respectively, compared with the reference group of age = 18-50 years, BMI < 18.5, AJCC clinical stage I, and RECIST complete response (CR).

Cancer-specific mortality

After PSM, maintenance chemotherapy was a nonsignificant and poor independent predictor of cancer-specific mortality. The aHR (95% CI) for cancer-specific mortality in the maintenance chemotherapy group was 1.08 (0.88-1.29, P = 0.1320) compared with the non-maintenance chemotherapy group. Nevertheless, we observed that older age, lower BMI, higher AJCC clinical stage, and poor RECIST response to CCRT were poor independent predictors of cancer-specific mortality. Specifically, compared with the reference group of aged = 18-50 years, BMI < 18.5, AJCC clinical stage I, and RECIST CR, the aHR (95% CI) for cancer-specific mortality was higher for patients in the following categories: age = 51-60, 61-70, and > 70 years (aHR 1.14-1.34); BMI = 18.5-23, 24-26, and ≥ 27 (aHR 0.80-0.69); AJCC clinical stages IIA, IIB, IIIA, IIIB, and IVA (aHR 1.71-3.08); and RECIST PR, SD, and PD (aHR 1.71-2.41) (**Table 3**).

Sensitivity analysis

The results of sensitivity analyses revealed that maintenance chemotherapy was associated with a significant increase in all-cause mortality in the subgroups of patients with AJCC clinical stage I-IIIA and RECIST CR or PR (**Table 4**). These findings suggested that maintenance chemotherapy might not have been beneficial for overall survival in these particular subgroups of patients with ESCC. Moreover, maintenance chemotherapy did not significantly increase cancer-specific mortality in patients with ESCC receiving CCRT (**Table 4**).

Kaplan-Meier survival curves

The 2-year overall survival rates for patients in the non-maintenance chemotherapy and maintenance chemotherapy groups were 34.66% and 28.89%, respectively (P < 0.0001; **Figure 1**). Additionally, the 2-year cancer-specific survival rates for patients in the non-maintenance chemotherapy and maintenance chemotherapy groups were 30.66% and 28.89%, respectively (P = 0.0916; **Figure 2**). These results suggested that maintenance chemotherapy might not have improved the survival of patients with ESCC receiving CCRT.

Discussion

Many studies on maintenance chemotherapy for esophageal cancer have included both adenocarcinoma and squamous cell carcinoma, as well as various locations in the esophagus, including the cervical part, thoracic part, and GEJ [19-21]. By contrast, our study focused solely on cervical and thoracic ESCC. Our study was the largest PSM study to date to examine the impact of maintenance chemotherapy on the survival of patients with ESCC receiving standard CCRT, and the findings indicated that maintenance chemotherapy might not have improved the survival of the analyzed patients (**Tables 2-4**). In addition, we found that older age, lower BMI, higher AJCC clinical stage, and poor response to CCRT based on the RECIST were poor independent predictors of both all-cause mortality and cancer-specific mortality.

This study observed that the response rate after standard CCRT for ESCC was poor, with high rates (approximately 45%) of SD and PD (**Table 1**). Maintenance chemotherapy is often considered for patients with ESCC in Taiwan; however, we found that this form of treatment did not improve overall survival and instead increased all-cause mortality but not cancer-specific mortality. After PSM to control for confounders-such as performance status, underlying diseases, clinical stages, and response to CCRT-the survival outcomes were still not improved by maintenance chemotherapy. In the sensitivity analysis, we observed that maintenance chemotherapy was associated with a significant increase in all-cause mortality in the subgroups of patients with ESCC who had AJCC clinical stage I-IIIA and a complete or partial response to CCRT based on the RECIST criteria (**Table 4**). These findings suggest that maintenance chemotherapy may not be beneficial for overall survival in these particular subgroups of patients with ESCC, especially in the early clinical stage (stages I-IIIA) and among those with better RECIST after CCRT (complete or partial

Table 3. Cox proportional regression model of cancer-specific mortality for propensity score-matched patients with ESCC after standard CCRT

	Crude HR (95% CI)	*P* Value	Adjusted HR* (95% CI)	*P* Value
Chemotherapy (ref. Non-Maintenance Chemotherapy)				
Maintenance Chemotherapy	1.11 (0.91-1.32)	0.1851	1.08 (0.88-1.29)	0.1320
Age Group, Years (ref. 18-50)				
51-60	1.15 (1.07-1.93)	0.0004	1.14 (1.28-1.84)	0.0008
61-70	1.23 (1.14-1.91)	0.0003	1.22 (1.12-1.81)	0.0002
> 70	1.33 (1.18-1.99)	0.3634	1.34 (1.24-1.91)	0.0712
Sex (ref. Women)				
Men	0.84 (0.69-1.01)	0.0686	0.83 (0.68-1.03)	0.0848
BMI (ref. < 18.5)				
18.5-23	0.78 (0.7-0.87)	< 0.0001	0.80 (0.71-0.89)	< 0.0001
24-26	0.72 (0.63-0.83)	< 0.0001	0.75 (0.65-0.87)	0.0001
≥ 27	0.63 (0.52-0.77)	< 0.0001	0.69 (0.56-0.84)	0.0002
Years of Diagnosis (ref. 2008-2010)				
2011-2013	0.91 (0.83-1)	0.0389	0.97 (0.83-1.13)	0.6950
2014-2018	0.90 (0.81-0.99)	0.0261	0.96 (0.81-1.12)	0.5839
AJCC Clinical Stage (ref. stage I)				
IIA	1.70 (1.25-2.32)	0.0008	1.71 (1.25-2.33)	0.0007
IIB	1.93 (1.43-2.6)	< 0.0001	1.93 (1.43-2.61)	< 0.0001
IIIA	2.18 (1.6-2.97)	< 0.0001	2.33 (1.71-3.17)	< 0.0001
IIIB	2.33 (1.72-3.15)	< 0.0001	2.41 (1.78-3.27)	< 0.0001
IVA	3.13 (2.32-4.2)	< 0.0001	3.08 (2.29-4.15)	< 0.0001
RECIST Response After CCRT (ref. CR)				
PR	1.87 (1.55-2.26)	< 0.0001	1.71 (1.41-2.06)	< 0.0001
SD	1.89 (1.33-2.13)	< 0.0001	1.80 (1.26-2.02)	0.0001
PD	2.28 (1.89-2.74)	< 0.0001	2.17 (1.80-2.62)	< 0.0001
Cigarette Smoking (ref. never)				
Current	1.09 (0.99-1.21)	0.0870	1.11 (0.98-1.25)	0.0972
Quit	0.99 (0.91-1.06)	0.6832	1.01 (0.93-1.09)	0.8520
Alcohol Consumption (ref. never)				
Moderate	1.20 (1.04-1.38)	0.0103	1.00 (0.81-1.22)	0.9747
Heavy	0.98 (0.92-1.04)	0.5598	1.01 (0.95-1.08)	0.7263
CCI Score (ref. CCI = 0)				
≥ 1	1.08 (0.95-1.24)	0.2568	1.07 (0.95-1.30)	0.1848

Abbreviations: ESCC, esophageal squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; BMI, body mass index; RECIST, Response Evaluation Criteria in Solid Tumors; AJCC, American Joint Committee on Cancer; PSM, propensity score matching; CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio; aHR, adjusted hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *All covariates presented in **Table 3** were adjusted.

response). According to the sensitivity analysis, maintenance chemotherapy did not significantly increase or decrease cancer-specific mortality in patients with ESCC receiving CCRT (**Table 4**). Therefore, the increase in all-cause mortality in the maintenance chemotherapy group may have been due to the toxicity of the treatment given that cancer-specific mortality is not influenced by maintenance chemotherapy.

Several factors were independent predictors of both all-cause mortality and cancer-specific mortality in patients with ESCC who received standard CCRT; these factors were older age,

Table 4. Sensitivity analysis of the association between maintenance and non-maintenance chemotherapy and cancer-specific or all-cause mortality in patients with ESCC after standard CCRT

Subpopulation or Exposure	All-Cause Mortality		Cancer-Specific Mortality	
	aHR* (95% CI)	*P* Value	aHR* (95% CI)	*P* Value
Age Group, Years				
≤ 50 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.11 (0.96-1.28)	0.1651	1.13 (0.98-1.30)	0.1034
51-60 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.02 (0.86-1.20)	0.8637	1.03 (0.87-1.22)	0.7410
61-70 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	0.98 (0.74-1.32)	0.9186	1.03 (0.77-1.38)	0.8516
≥ 70 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	2.18 (0.85-5.57)	0.1049	1.78 (0.66-4.82)	0.2540
BMI				
< 18.5 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.08 (0.84-1.39)	0.5451	1.1 (0.85-1.41)	0.4818
18.5-23 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.02 (0.87-1.18)	0.8308	1.05 (0.90-1.23)	0.5275
24-26 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.15 (0.85-1.57)	0.362	1.19 (0.87-1.62)	0.2838
≥ 27 (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.76 (0.96-3.23)	0.0671	1.89 (0.92-3.49)	0.0517
AJCC Clinical Stage				
I (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.70 (1.15-3.86)	0.0019	1.59 (0.68-3.72)	0.2850
IIA (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.39 (1.02-1.90)	0.0374	1.06 (0.88-1.88)	0.4223
IIB (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.28 (1.02-1.60)	0.0312	1.13 (0.84-1.63)	0.3241
IIIA (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.35 (1.08-1.86)	0.0223	1.09 (0.81-1.92)	0.3459
IIIB (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.03 (0.81-1.32)	0.8051	1.10 (0.86-1.40)	0.4595
IVA (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.83 (0.71-1.98)	0.5325	1.85 (0.72-2.00)	0.1571
RECIST Response After CCRT				
CR (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.86 (1.11-2.45)	0.0025	1.89 (0.92-2.20)	0.2252
PR (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.18 (1.07-1.42)	0.0218	1.21 (0.91-1.46)	0.3430
SD (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.05 (0.88-1.26)	0.5629	1.08 (0.90-1.29)	0.4055
PD (ref. Non-Maintenance Chemotherapy)	1		1	
Maintenance Chemotherapy	1.02 (0.87-1.21)	0.7789	1.06 (0.87-1.25)	0.5156

Abbreviations: ESCC, esophageal squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; BMI, body mass index; RECIST, Response Evaluation Criteria in Solid Tumors; AJCC, American Joint Committee on Cancer; PSM, propensity score matching; CI, confidence interval; aHR, adjusted hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *All covariates presented in **Table 4** were adjusted.

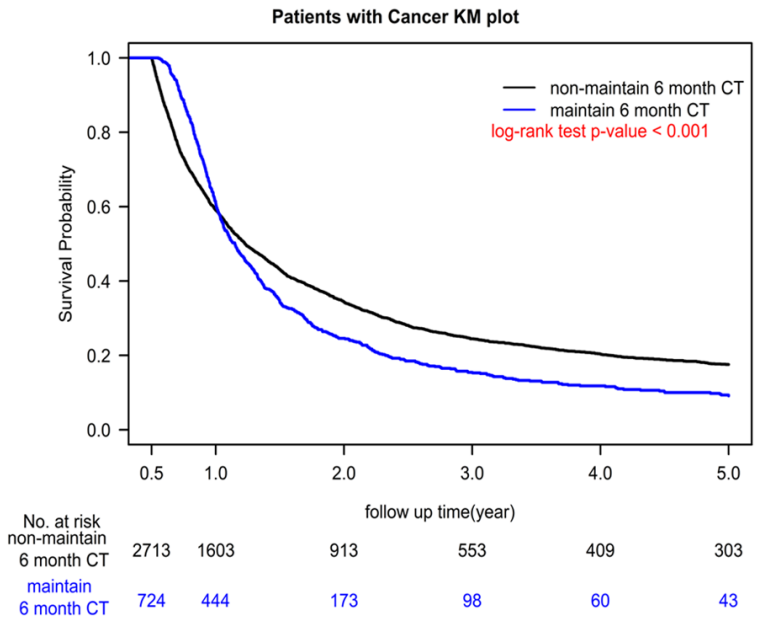

Figure 1. Kaplan-Meier overall survival curves for maintenance and non-maintenance chemotherapy for patients with ESCC after standard CCRT.

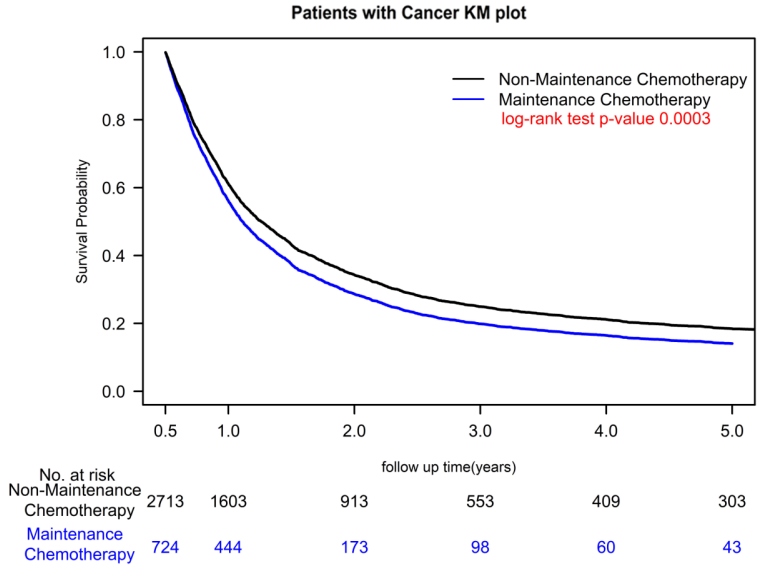

Figure 2. Kaplan-Meier cancer-specific survival curves for maintenance and non-maintenance chemotherapy for patients with ESCC After standard CCRT.

lower BMI, higher clinical stage according to the AJCC, and poor response to CCRT. These findings were consistent with those of studies identifying older age and higher AJCC stages as poor prognostic factors for ESCC survival [2, 25, 26]. The prognostic factors of ESCC patients receiving standard CCRT are of particular interest. Few studies have investigated the association of BMI and RECIST after CCRT with all-cause mortality or cancer-specific mortality in ESCC patients after standard CCRT. Our study was the first to demonstrate that a lower BMI is associated with higher mortality, be it cancer-specific or all-cause mortality. Additionally, RECIST after CCRT was a significant prognostic factor for both all-cause mortality and cancer-specific mortality. This finding is in line with the use of the response rate after neoadjuvant chemotherapy as an effective predictive tool for overall survival in patients with breast cancer receiving neoadjuvant chemotherapy [33, 34]. Given that better RECIST after CCRT was significantly associated with overall survival and cancer-specific survival, identifying new agents to enhance the response rate of ESCC patients receiving CCRT is crucial.

The strengths of our study are described as follows. First, the study focused specifically on cervical and thoracic ESCC, whereas previous studies have covered a variety of locations and types of esophageal cancer [19-21]. Our approach allowed for more precise and relevant results for patients with cervical and thoracic ESCC. Second, our study was the largest PSM study to examine the impact of maintenance chemotherapy on the survival of patients with ESCC receiving standard CCRT. Its relatively large sample size increased the power of the study and yielded more reliable results. Finally, our use of the RECIST as a measure of response to CCRT allowed for more accurate and objective evaluation of treatment effectiveness.

This study had some limitations. First, it was not possible to determine the toxicity of the different treatments, and this aspect may have

influenced treatment-related mortality or other underlying factors that could have biased the estimates. However, we attempted to control for potential confounding factors by matching comorbidities and clinical stages according to the AJCC and selecting patients with similar physical activity levels as measured using their Eastern Cooperative Oncology Group performance statuses. Second, the study population consisted solely of Asian patients with ESCC, and thus the results may not be generalizable to other ethnic groups. Third, the small sample size in the sensitivity analysis may have limited the generalizability of the conclusions, particularly for the subgroups with relatively few patients. Fourth, diagnoses of comorbid conditions were based on ICD-9-CM and ICD-10-CM codes, which may not be entirely accurate. However, the Taiwan Cancer Registry Administration takes steps to verify the accuracy of diagnoses through chart reviews and patient interviews, and hospitals that are found to have discrepancies or have engaged in malpractice may face penalties. Fifth, unknown selection bias may have existed in the use of maintenance chemotherapy or non-maintenance chemotherapy. Therefore, a large-scale randomized trial is warranted to compare carefully selected patients undergoing suitable treatments in order to provide more definitive conclusions about the effectiveness of maintenance chemotherapy in treating patients with ESCC receiving standard chemotherapy.

Conclusion

Our results revealed that maintenance chemotherapy may not improve the survival rate of patients with ESCC who have received CCRT. However, further research is necessary to fully understand the potential benefits and risks of this treatment option in similar patient populations. Additionally, we identified several important prognostic factors for patients with ESCC receiving CCRT, including relatively low BMI and poor response to CCRT, as measured using the RECIST. These findings suggested a need for new therapies that could improve the response rate of patients with ESCC receiving CCRT given that better RECIST response after CCRT is significantly associated with improved overall survival and cancer-specific survival. Further research is required to explore potential treatment options and evaluate their effectiveness in enhancing the response rate and improving the survival of patients with ESCC.

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Disclosure of conflict of interest

None.

Abbreviations

ESCC, Esophageal squamous cell carcinoma; CCRT, Concurrent chemoradiotherapy; BMI, Body mass index; RECIST, Response Evaluation Criteria in Solid Tumors; AJCC, American Joint Committee on Cancer; PSM, Propensity score matching; CI, Confidence interval; aHR, Adjusted hazard ratio; NCCN, National Comprehensive Cancer Network; TCRD, Taiwan Cancer Registry Database; CCI, Charlson comorbidity index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; HR, hazard ratio; GEJ, gastroesophageal junction; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Address correspondence to: Dr. Szu-Yuan Wu, Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, No. 83, Nanchang Street, Luodong Township, Yilan 265, Taiwan. E-mail: szuyuanwu5399@gmail.com; Dr. Ben-Chang Shia, Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, Taipei, Taiwan. E-mail: 025674@mail.fju.edu.tw

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