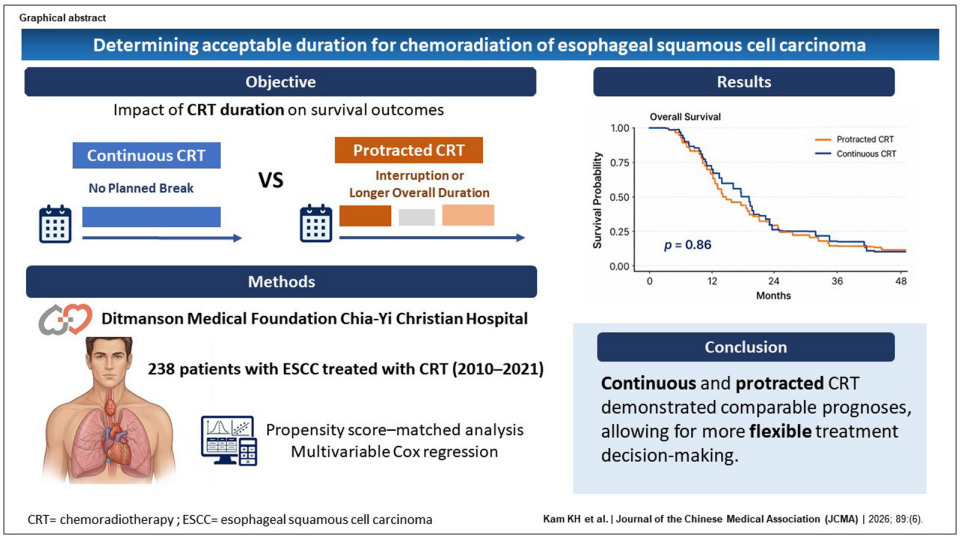
Determining acceptable duration for chemoradiation of esophageal squamous cell carcinoma

Kam-Hong Kam[a,b,c], Cheng-Yen Lee[d], Jia-Ming Chang[a], Hsin-Yi Yang[e], Chih-Chia Chang[d], Yuk-Wah Tsang[d], Yu-Wen Wang[d], Wei-Yu Wang[f], Chin-Ho Kuo[f], Ming-Yang Lee[f], Yin-Che Lu[f], Yu-Ting Lee[b,c,f,*], Michael W. Y. Chan[b,c,*]

[a]Thoracic Surgical Division, Department of Surgery, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan, ROC; [b]Department of Biomedical Sciences, National Chung Cheng University, Chiayi, Taiwan, ROC; [c]Epigenomics and Human Disease Research Center, National Chung Cheng University, Chiayi, Taiwan, ROC; [d]Department of Radiation Oncology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan, ROC; [e]Clinical Research Center, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan, ROC; [f]Division of Hematology and Oncology, Department of Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan, ROC



Abstract

Background: Chemoradiotherapy (CRT) remains the standard practice for patients with nonsurgical esophageal squamous cell carcinoma (ESCC). However, the impact of radiation duration is poorly understood. We aimed to determine the effect of CRT duration on the prognosis of patients with ESCC.

Methods: We retrospectively analyzed patients with ESCC treated with CRT at the Ditmanson Medical Foundation Chia-Yi Christian Hospital between January 1, 2010 and December 31, 2021. Patients were either treated with continuous CRT or protracted CRT, which was interrupted due to reassessment of disease status. Differences in survival according to the treatment strategy were examined using propensity score matching (PSM). The risk factors for survival and recurrence were analyzed using Cox regression models.

Results: A total of 238 patients who underwent CRT were included in our cohort. After 2:1 PSM, the continuous and protracted CRT groups comprised 41 and 82 patients, respectively. Median survival was 12.2 (interquartile range [IQR], 10.0-19.1) months for the protracted CRT group and 11.4 (IQR, 9.9-17.1) months for the continuous CRT group (p = 0.395). The multivariable analysis revealed that duration of radiation >90 days was an independent risk factor for survival (adjusted hazard ratio [HR], 2.14; 95% CI, 1.23-3.70, p = 0.006) and progression-free survival (adjusted HR, 1.74; 95% CI, 1.08-2.80, p = 0.022). In addition, a neutrophil-to-lymphocyte ratio >3 was associated with poor prognosis (adjusted HR, 1.83; 95% CI, 1.09-3.05, p = 0.02).

Conclusion: This study demonstrated that continuous CRT and protracted CRT resulted in similar prognoses; however, a radiotherapy duration exceeding 90 days was associated with inferior survival. These findings have implications for treatment planning in patients with ESCC.

Keywords: Chemoradiotherapy; Esophageal squamous cell carcinoma; Radiotherapy duration; Radiotherapy interruption

Lay Summary: For patients with esophageal cancer who cannot undergo surgery, the standard treatment is a combination of chemotherapy and radiation (CRT). This study investigated whether the total duration of this treatment impacts patient survival. We compared continuous CRT to protracted CRT, which involves pausing treatment to reassess the disease. The study found that both treatment strategies resulted in similar survival times (approximately 11 to 12 months). However, a critical finding was that if the total radiation duration exceeded 90 days, patients had a significantly worse outcome. In conclusion, while treatment interruptions for reassessment are acceptable, completing radiotherapy within 90 days remains critical for optimal outcomes. These findings support a more flexible treatment strategy, allowing planned interruptions to reassess disease status.

1. INTRODUCTION

Esophageal squamous cell carcinoma (ESCC) is a leading cause of cancer-related deaths in Taiwan.[1] Esophagectomy is the standard for patients with locally advanced ESCC; nevertheless, the adoption of a trimodal strategy with preoperative chemoradiotherapy (CRT) has improved the long-term survival in patients with resectable disease.[2–4] Nonetheless, CRT alone remains the standard approach for patients with inoperable disease or who are not fit for esophagectomy.[5,6]

Notably, not all patients with ESCC undergo surgery after neoadjuvant CRT (nCRT). Although consolidation CRT may be delivered to achieve a higher cumulative dose of radiation, interruptions during CRT occur for a variety of reasons, including CRT adverse effects and poor nutritional status; these interruptions can lead to negative outcomes in many types of cancer.[7,8] For esophageal cancer in particular, a response evaluation after nCRT is mandatory for surgical planning. The radiation dosing schedule for uninterrupted CRT is well characterized[5,9]; however, CRT without surgery is typically not planned. Furthermore, assessment of tumor response and replanning often lead to prolonged treatment times, which may be detrimental to treatment outcomes; the impact of such delays is unknown. Therefore, the object of our investigation was to explore the impact of protracted CRT on survival in patients with ESCC.

2. METHODS

2.1. Study population

We retrospectively reviewed patients with new diagnoses of ESCC who were treated at Ditmanson Medical Foundation Chia-Yi Christian Hospital between January 1, 2010, and December 31, 2021. Patients with early-stage disease who were treated with endoscopic submucosal dissection (ESD), endoscopic mucosal resection (EMR), or esophagectomy, and patients with prior or concurrent cancer diagnoses were excluded. Furthermore, patients who were followed up for <6 months were excluded to minimize confounding and immortal time biases.

2.2. Outcome measures

The following clinical information was collected for all participants: age, sex, body mass index, comorbidities (including hypertension, cardiovascular disease, chronic kidney disease, cerebral vascular disease, chronic hepatitis C, chronic hepatitis B, liver cirrhosis, type 2 diabetes mellitus, tuberculosis, and cancer), laboratory data (including complete blood, white blood cell, differential cell, neutrophil-to-lymphocyte ratio [NLR] and platelet counts), cumulative dose of radiation, and chemotherapy.

Here, we defined progression-free survival (PFS) as the period from the last fraction of radiotherapy to the date of disease recurrence or disease progression. Overall survival (OS) was computed between the date of diagnosis and the date of death or last follow-up visit.

2.3. Continuous and protracted CRT

Patients who were unsuitable for esophagectomy, refused esophagectomy, or had inoperable disease were treated with definitive continuous CRT, which involved conventional fractionated radiotherapy (1.8-2.0 Gy per fraction, 5 days per week) with concurrent platinum-based chemotherapy. The accumulative radiation dose was between 40 and 80 Gy and delivered via volumetric modulated arc radiotherapy with inverse treatment planning. This group was defined as the continuous CRT group.

In contrast, patients with resectable or borderline-resectable disease were treated with nCRT, which comprised platinum-based chemotherapy and a radiotherapy dose of 36 Gy, with interruptions for reassessment of disease status. Patients underwent esophagectomy or resumed CRT based on resectability and patient choice. Patients who did not have esophagectomy after nCRT were defined as the protracted CRT group.

2.4. Statistical analysis

Propensity score matching (PSM) with a 2:1 ratio was used to compare the patients in the continuous and protracted CRT groups. The propensity scores were calculated using a logistic regression model with relevant clinical factors, including age, sex, clinical stage, location of tumor site, cumulative dose of radiation (categorized as ≥50.4 and <50.4 Gy), and comorbidities.

Baseline characteristics are described as the total number (n) and proportion (%). Association between categorical variables was compared using either Pearson's chi-square test or Fisher's exact test. Hazard ratios (HRs) and 95% CIs were estimated under the Cox proportional hazards model. Risk factors with p value of <0.1 in the univariate model were then selected for inclusion in the multivariate analysis.

Survival curves were illustrated with the Kaplan-Meier method. Statistical analyses, data management, and survival curves were performed with R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1. Clinical characteristics

Between 2011 and 2021, 546 patients with newly diagnosed ESCC were treated at the Ditmanson Medical Foundation

*Address correspondence. Dr. Yu-Ting Lee, Division of Hematology and Oncology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, 539, Zhongxiao Road, Chiayi 600, Taiwan, ROC. E-mail address: ytl10228@gmail.com (Y.-T. Lee); Dr. Michael W. Y. Chan, Department of Biomedical Sciences, National Chung Cheng University, 168, Section 1, University Road, Chiayi 621, Taiwan, ROC. E-mail address: biowyc@ccu.edu.tw (M.W.Y. Chan).

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Chia-Yi Christian Hospital. We excluded 139 patients with prior or concurrent cancer diagnoses and 73 non-SCC-type cases. The analysis did not include 20 patients with stage I disease who underwent ESD or EMR, as well as two patients with an unknown stage. Seventy-four patients were followed up for <6 months, including 48 with disease progression or disease-related complications, 15 with uncontrolled sepsis, 1 with ischemic bowel disease, 1 with a complication of esophagectomy, 1 with pancreatic adenocarcinoma, and 7 for unknown reasons. Of 238 patients who received CRT, 72 who underwent esophagectomy were excluded from the analysis. Ultimately, 166 patients were enrolled in the final cohort, and the majority were male (97.6%) (Fig. 1). The median age was 56 (interquartile range [IQR], 51-63) years, and patients were followed up for a median of 11.7 (IQR, 9.6-17.1) months. In general, the cumulative radiation dose was slightly higher in the protracted CRT group than in the continuous CRT group (66 vs 63 Gy, respectively, p = 0.049). Clinical characteristics are summarized in Table 1.

3.2. Survival and recurrence

Clinical stage was the most notable prognostic factor in our cohort. Median survival was >24 months among patients with stage I or II disease. In contrast, for stage III and IV disease, median OS was 14.2 and 10.8 months, respectively (Fig. 2).

After PSM, we found no significant differences in OS or PFS between the two treatment groups (Figs. 3 and 4). Median survival was 12.2 (IQR, 10.0-19.1) months for the protracted CRT group and 11.4 (IQR, 9.9-17.1) months for the matched continuous CRT group (Fig. 2), with an HR of 0.93 (95% CI, 0.60-1.42, p = 0.740). Regarding recurrence or progression, median time to progression was 8.3 (IQR, 5.9-14.4) and 8.5 (IQR, 6.8-11.9) months in the protracted and continuous CRT groups, respectively, and the HR was 0.88 (95% CI, 0.58-1.35, p = 0.582).

3.3. Risk factors for OS and PFS

Although the clinical stage was the most important risk factor for survival outcomes, our data showed that a duration of radiation ≥90 days was an independent risk factor for OS (adjusted HR, 2.14; 95% CI, 1.23-3.70, p = 0.006) and for PFS (adjusted HR, 1.74; 95% CI, 1.08-2.80, p = 0.022). Furthermore, NLR >3 was a predictor for OS (adjusted HR, 1.83; 95% CI, 1.09-3.05, p = 0.02) but not for PFS. Treatment outcomes were not affected by protracted CRT (Tables 2 and 3).

4. DISCUSSION

For squamous cell carcinoma, the treatment duration has been reported to be directly correlated with local control. Withers et al[10] demonstrated that every day of delayed constant dose treatment decreased local control by 1%. In contrast, for a constant treatment duration, every 1 Gy increase improved local control by 2%.[10] Our analysis had comparable results. We found that radiation duration >90 days was a risk factor for survival and recurrence. In an attempt to improve locoregional control, RTOG INT 0123, a randomized clinical trial, compared chemoradiation using a higher dose (64.8 Gy/1.8 Gy) or a standard dose (50.4 Gy/1.8 Gy) combined with cisplatin-based chemotherapy; the treatment duration was prolonged in the high-dose group. No significant differences either in locoregional failure (52% vs 56%) or in 2-year OS (31% vs 40%) were found between the high- and standard-dose arms.[3]

This study also suggested that patients who did not undergo esophagectomy after nCRT had a similar prognosis to those who received continuous CRT. Interestingly, our previous

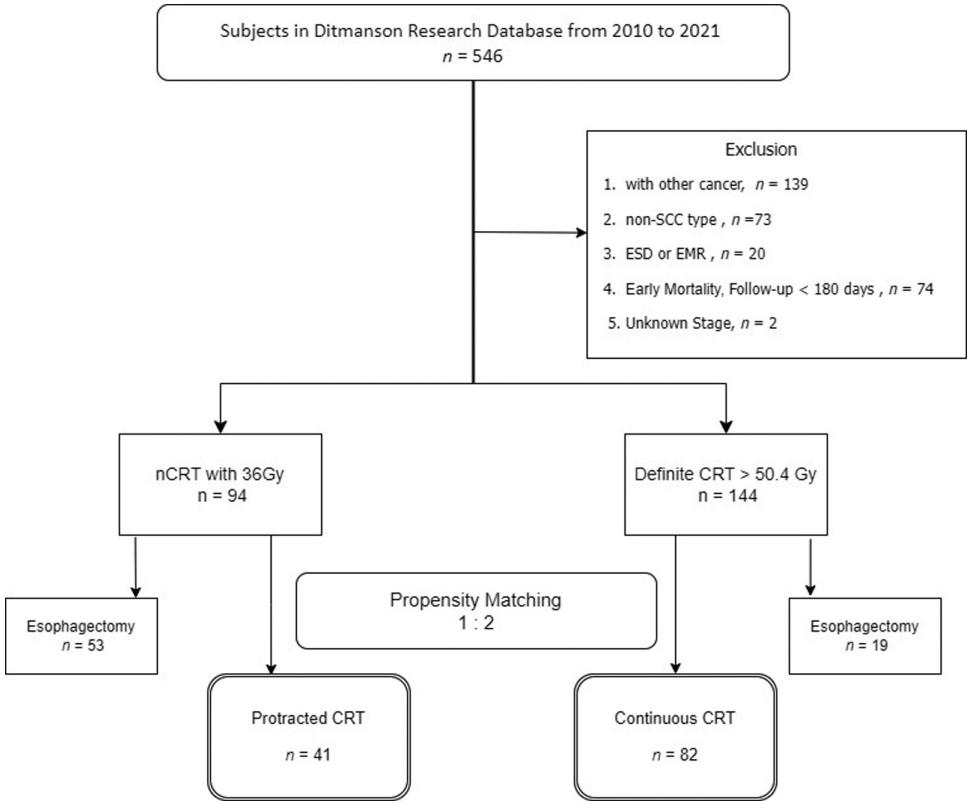

Fig. 1 Flowchart of patient enrollment.

Table 1

Baseline characteristics

Characteristics	Total n = 166 n (%)	Protracted CRT n = 41 n (%)	Matched continuous CRT n = 82 n (%)	*p*
Gender				
Male	162 (97.6)	38 (92.7)	82 (100.0)	0.063
Female	4 (2.4)	3 (7.3)	0 (0)	
Median age, y (IQR)	56 (51-63)	56 (50-63)	55 (50-62)	0.768
NLR >3	81 (58.3)	18 (52.9)	45 (65)	0.324
BMI (kg/m$^{2)}$	22.3 (19.7-24.6)	21.5 (18.8-24.5)	23.2 (21.2-25.0)	0.149
Disease status				
Clinical stage				
I	4 (2.4)	1 (2.4)	3 (3.7)	0.747
II	15 (9.0)	6 (14.6)	8 (9.8)	
III	78 (47.0)	23 (56.1)	43 (52.4)	
IV	69 (41.6)	11 (26.8)	28 (34.1)	
Primary site				
Upper	46 (27.7)	9 (22.0)	27 (32.9)	0.441
Middle	88 (53.0)	25 (61.0)	44 (53.7)	
Lower	28 (16.9)	7 (17.1)	11 (13.4)	
EGJ	1 (0.6)			
Unclassified	3 (1.8)			
Staging with PET	13 (10.5)	2 (4.9)	11 (13.4)	0.254
Staging with EUS	30 (24.3)	12 (29.2)	18 (21.9)	0.436
Treatment modality				
Gastrostomy	74 (44.6)	34 (41.5)	14 (34.1)	0.566
Radiotherapy				
Cumulative dose (Gy)				
Median (range)	63 (36-81)	66 (36-68)	63 (40-81)	0.049
Mean (SD)	61.5 (7.6)	61.4 (8.9)	61.5 (6.8)	0.952
Dose of radiation >5040 cGy	133 (80.1)	37 (90.2)	73 (89.0)	1.000
Dose of radiation >6160 cGy	85 (51.2)	28 (68.3)	45 (54.9)	0.218
Duration of radiation	52 (44-74)	85 (70-101)	50 (44-56)	<0.001
Duration of radiation ≥90 days	30 (18.3)	19 (46.3)	5 (6.2)	<0.001
Chemoregimen				
Weekly cisplatin	6 (4.8)	0	6 (7.4)	0.327
Carboplatin/5-FU	10 (8.2)	4 (10)	6 (7.4)	
Cisplatin/5-FU	105 (85.4)	36 (90)	69 (85.2)	
Other	2 (1.6)	1	1	
Outcome				
Clinical RESPONSE (%)				
CR	22 (13.3)	5 (12.2)	14 (17.1)	0.058
PR	33 (19.9)	7 (17.1)	17 (20.7)	
SD	22 (13.3)	2 (4.9)	17 (20.7)	
PD	26 (15.7)	9 (22.0)	8 (9.8)	
NA/NE	63 (38.0)	18 (43.9)	26 (31.7)	
Duration of follow-up, months (IQR)	11.7 (9.6-17.1)	12.2 (10.0-19.1)	11.4 (9.9-17.1)	0.564
Progress-free survival (IQR)	8.5 (6.1-11.6)	8.3 (5.9-14.4)	8.5 (6.8-11.9)	0.591
Disease free	29 (23.5)	11 (26.8)	18 (21.9)	0.652
Comorbidities				
HTN	47 (28.3)	8 (19.5)	20 (24.4)	0.704
CVD	8 (4.8)	2 (4.9)	1 (1.2)	0.535
CKD	8 (4.8)	4 (9.8)	3 (3.7)	0.335
DM	38 (22.9)	8 (19.5)	17 (20.7)	1.000
CVA	6 (3.6)	1 (2.4)	3 (3.7)	1.000
HCV	7 (4.2)	1 (2.4)	0 (0.0)	0.723
HBV	21 (12.7)	6 (14.6)	10 (12.2)	0.925
Cirrhosis	41 (24.7)	11 (26.8)	19 (23.2)	0.824
TB	6 (3.6)	1 (2.4)	1 (1.2)	1.000

BMI = body mass index; CKD = chronic kidney disease; CR = complete response; CVA = Cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; EGJ = esophagogastric junction; Gy = Gray; HBV = hepatitis B; HCV = hepatitis C; HTN = hypertension; IQR = interquartile range; NA/NE = no available/not evaluated; NLR = neutrophil-to-lymphocyte ratio; PD = progression disease; PET = positron emission tomography; PR = partial response; SD = stable disease; TB = tuberculosis.

study reported a 2-year survival rate of 60.6% in the patients who underwent surgery after nCRT, compared with 36.6% in those who did not, which is consistent with other published reports.[9,11–13]

Our study might face scrutiny because of the lower neoadjuvant radiation dose. Although the preoperative dose was relatively low, our cohort still achieved consistent surgical outcomes comparable to those with the standard radiation dose.[2,11,14] The effect of a lower preoperative radiation dose on treatment outcomes remains controversial, but it might benefit from reduced surgical complications. In a single-institution study comparing preoperative doses of 36 and 50.4 Gy, Lo et al[15] demonstrated that the 3-year OS and disease-free survival rates were superior in the higher dose group. However, there were increased rates of surgical complications, including acute respiratory distress syndrome (3% vs 13%) and anastomosis leak (5% vs 23%), in the group receiving the higher dose.[15] In contrast, in a nationwide study conducted by Keven et al,[16] a lower preoperative dose was associated with lower perioperative mortality rates and improved survival.[16]

NLR has been found to be a prognostic factor for several cancers.[17] Increased NLR might reflect increased activation of neutrophils by inflammatory mediators such as interleukin-6.[18] Furthermore, neutrophils also release pro-inflammatory cytokines, leading to cancer progression and resistance.[19] We demonstrated that a high NLR predicted shorter survival, which was consistent with previous studies.[20–24] The NLR cutoff value may range from 1.7 to 5, and our cutoff point was 3.[20] Another Taiwanese cohort study conducted by Ho et al[23] enrolled patients with ESCC who completed definitive CRT and determined that a baseline NLR >3.56 and follow-up NLR >7.4 correlated with worse OS.

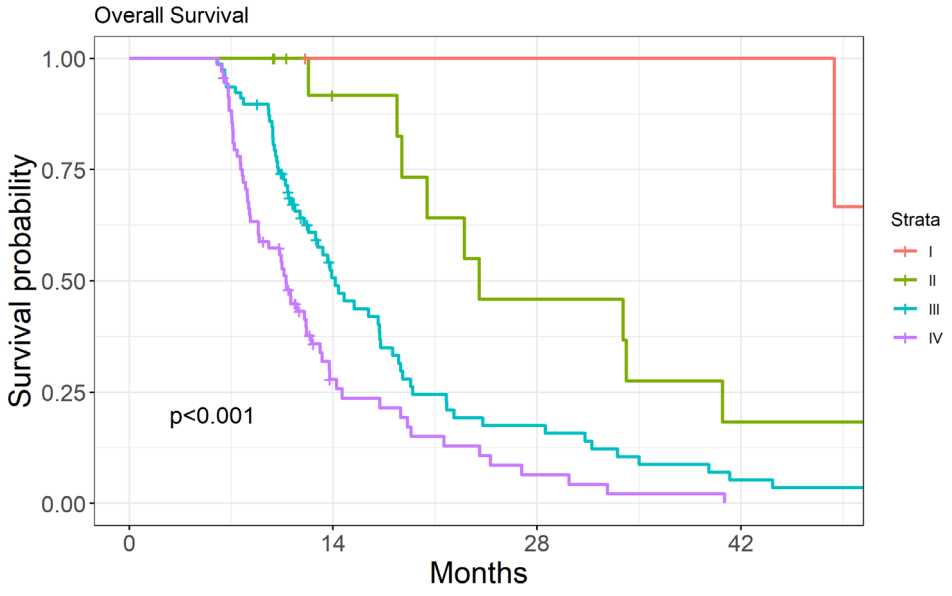

Fig. 2 Overall survival stratified by clinical stage.

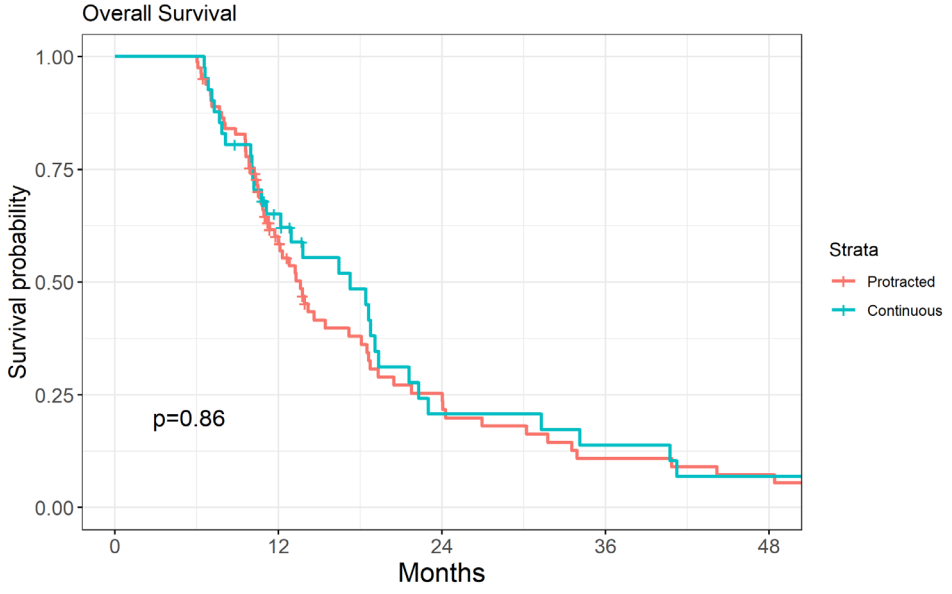

Fig. 3 Overall survival in the protracted and matched continuous definitive chemoradiotherapy groups.

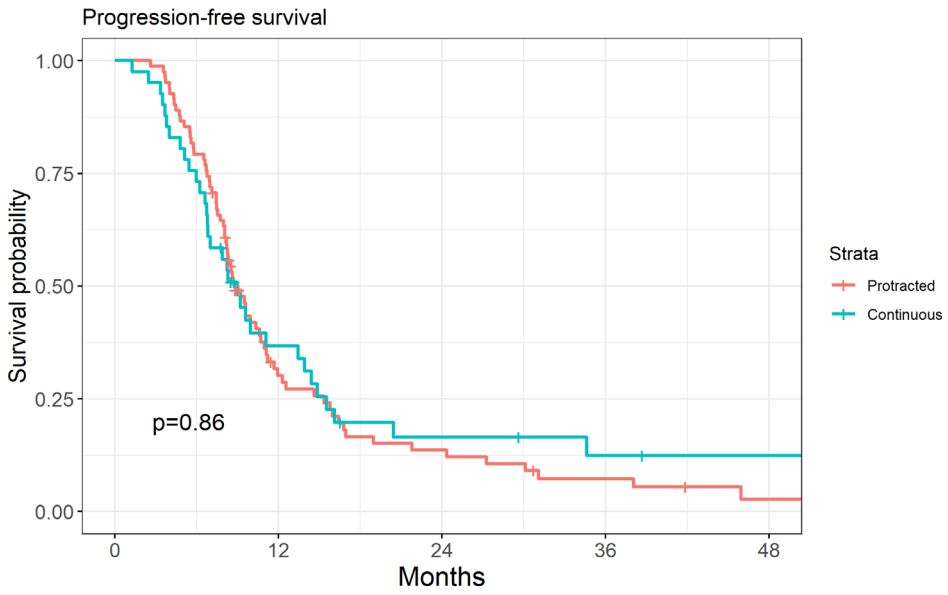

Fig. 4 Progression-free survival in the protracted and matched continuous definitive chemoradiotherapy groups.

Table 2

Risk factors for mortality

	Univariate		Multivariate	
Predictive variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	1.00 (0.98-1.02)	0.929		
Male gender	1.20 (0.29-4.91)	0.797		
BMI	0.96 (0.96-1.01)	0.161		
Site				
Upper	Reference			
Middle	1.16 (0.71-1.91)	0.541		
Low	1.15 (0.58-2.27)	0.672		
Clinical stage				
I + II	Reference			
III	5.26 (2.43-11.3)	<0.001	6.11 (2.50-14.9)	<0.001
IV	5.71 (2.55-12.7)	<0.001	5.68 (2.21-14.5)	<0.001
Neo-CRT	0.93 (0.60-1.42)	0.740		
Duration of radiation ≥90 days	2.00 (1.22-3.29)	0.005	2.14 (1.23-3.70)	0.006
Dose of radiation >61.6 Gy	0.91 (0.60-1.38)	0.190		
Chemoregimen				
Cisplatin-based	Reference	0.156		
Carboplatin-based	1.70 (0.81-3.54)			
NLR >3	1.56 (0.98-2.5)	0.058	1.83 (1.09-3.05)	0.020
HTN	1.47 (0.86-2.52)	0.155		
Cardiovascular disease	0.76 (0.18-3.11)	0.703		
CKD	0.43 (0.15-1.21)	0.112		
DM	1.06 (0.63-1.76)	0.818		
CVA	1.63 (0.51-5.19)	0.407		
HCV	3.91 (0.53-28.8)	0.180		
HBV	0.54 (0.28-1.06)	0.073	0.93 (0.41-2.06)	0.859
Cirrhosis	0.64 (0.40-1.02)	0.062	0.87 (0.50-1.52)	0.633
TB	0.21 (0.02-1.58)	0.129		

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CVA = Cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; Gy = Gray; HBV = hepatitis B; HCV = hepatitis C; HR = hazard ratio; HTN = hypertension; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; Neo-CRT = neoadjuvant chemoradiotherapy; TB = tuberculosis.

Table 3

Risk factors for progression

	Univariate		Multivariate	
Predictive variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age	1.00 (0.98-1.02)	0.971		
Male gender	1.34 (0.42-4.27)	0.611		
BMI	0.97 (0.92-1.02)	0.343		
Site				
Upper	Reference			
Middle	1.00 (0.62-1.56)	0.974		
Low	1.06 (0.49-1.78)	0.850		
Clinical stage				
I + II	Reference			
III	3.73 (1.83-7.61)	<0.001	3.70 (1.68-8.12)	0.001
IV	3.97 (1.89-8.32)	<0.001	4.46 (1.90-10.2)	<0.001
Neo-CRT	0.88 (0.58-1.35)	0.582		
Duration of radiation ≥ 90 Days	1.75 (1.09-2.82)	0.020	1.64 (1.00-2.70)	0.047
Dose of radiation > 61.6 Gy	0.93 (0.63-1.38)	0.740		
Chemoregimen				
Cisplatin-based	Reference	0.232		
Carboplatin-based	1.56 (0.75-3.23)			
NLR >3	1.25 (0.81-1.93)	0.313		
HTN	1.70 (1.07-2.72)	0.024	1.49 (0.89-2.48)	0.124
Cardiovascular disease	0.53 (0.13-2.19)	0.386		
CKD	0.55 (0.22-1.39)	0.210		
DM	1.03 (0.64-1.66)	0.887		
CVA	1.61 (0.59-4.42)	0.347		
HCV	3.76 (0.51-27.7)	0.192		
HBV	0.52 (0.27-1.01)	0.054	0.93 (0.46-1.87)	0.847
Cirrhosis	0.67 (0.43-1.05)	0.083	0.96 (0.58-1.59)	0.895
TB	0.24 (0.03-1.85)	0.172		

BMI = body mass index; CKD = chronic kidney disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; DM = diabetes mellitus; Gy = Gray; HBV = hepatitis B; HCV = hepatitis C; HR = hazard ratio; HTN = hypertension; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; Neo-CRT = neoadjuvant chemoradiotherapy; TB = tuberculosis.

This study has several limitations. First, this was a retrospective study, and potential confounding factors could not be completely eliminated. For example, patients receiving continuous CRT might be medically inoperable. Second, the reasons for patients refusing surgery or their physical condition at diagnosis could not be investigated. Thus, we were unable to identify and adjust for possible competing factors. In this study, we excluded patients with early mortality, and all patients completed treatment. Based on the available data, it appears that our patients' health statuses were similar. Lastly, the role of immune checkpoint inhibitors (ICI) in adjuvant treatment of metastatic ESCC has previously been established.[24–26] Definitive CRT integrated with ICI is currently being investigated.[27] However, most of our patients did not receive ICI in subsequent salvage treatment, and we could not explore the impact of ICI in our research. Further prospective studies are required to validate these findings.

In conclusion, patients who underwent continuous or protracted CRT did not have significantly different survival outcomes. Moreover, we demonstrated no adverse effects with an overall treatment duration of <90 days, allowing for more flexible surgical planning. However, a radiotherapy duration >90 days resulted in worse survival outcomes, which has significant implications for clinical decision-making and treatment planning.

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