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Consolidation Chemotherapy Provided Survival Benefit for Esophageal Squamous Cell Carcinoma Patients Who Underwent Concurrent Chemoradiotherapy Lower Than 60 Gy

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ABSTRACT

Background: The efficacy of consolidation chemotherapy (CCT) following concurrent chemoradiotherapy (CCRT) has not been clearly defined in esophageal squamous cell carcinoma (ESCC). This study determined which patients with stage II-IVA ESCC benefitted from CCT.

Methods: 351 patients with ESCC were retrospectively reviewed. 185 patients received CCRT alone and 166 received CCRT plus CCT. Subset analyses were conducted on all patients' characteristics. Factors associated with survival were analyzed using the Kaplan–Meier method and a Cox proportional hazards model. The Propensity score matching (PSM) technique was used to compensate for differences in patients' characteristics.

Results: The median OS were 17.7 months and 38.4 months in the CCRT alone group and CCRT+CCT group ($p = 0.002$), respectively. Multivariable Cox regression analysis determined that CCT was associated with improved OS ($p = 0.002$, HR 0.592, 95% CI 0.423–0.829); After PSM, relative to the CCRT group, patients who received CCT experienced improved OS (17.7 months vs. 38.4 months, $p = 0.0139$). Subgroup analysis showed that CCT was more effective in radiation dose < 60 Gy ($p = 0.002$, HR 0.368, 95% CI 0.194–0.700). After matching between radiation dose, in the low dose cohort, the median OS was 13.2 months and 20.7 months in the CCRT alone group and CCRT+CCT group, respectively ($p = 0.0028$), the multivariate analysis results showed that CCT retained its statistical significance ($p = 0.002$, HR 0.353, 95% CI 0.183–0.681). In the high dose cohort, the median OS were 21.6 months and 23.6 months in the CCRT alone group and CCRT+CCT group, respectively ($p = 0.5512$).

Conclusions: We recommend that CCT treatment should be considered for ESCC patients who underwent CCRT using < 60 Gy. Further studies are needed to confirm these results.

Abbreviations: 2D-CRT, 2-dimensional conformal radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; CT, computerized tomography; CTV, clinical target volume; ESCC, esophageal squamous cell carcinoma; EUS, endoscopic ultrasonography; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; PSM, Propensity score matching; PTV, planning target volume.

1 | Introduction

In China, esophageal cancer has emerged as the third most common malignant tumor and the fourth leading cause of cancer deaths. The annual incidence rate of ESCC is 477.9 per 100000 people, while the standard mortality rate is 375.0 per 100000 people [1]. Esophageal squamous cell carcinoma (ESCC) is the major type of esophageal cancer in China and accounts for half of all global ESCC cases [2].

The results of the prospective, randomized Chemoradiotherapy for Esophageal Cancer (CROSS) trial suggest that neoadjuvant chemoradiotherapy plus surgery should be the standard of care for patients with resectable locally advanced esophageal cancer [3]. Concurrent chemoradiotherapy (CCRT) is an alternative to surgery in select circumstances: patients with cervical tumors, unresectable tumors that were diagnosed at a late stage which are, as well as not suitable for surgery due to poor general condition [4]. However, the outcomes of CCRT in patients with esophageal cancer were not satisfactory. These patients had an overall median survival time of 11.2–34.5 months as determined in previous perspective trials [5–12]. Even though intensity-modulated radiotherapy (IMRT) has demonstrated superiority in dosimetric conformity compared with 2-dimensional conformal radiotherapy (2D-CRT) and 3-dimensional conformal radiotherapy (3D-CRT) [13], many esophageal cancer patients treated with IMRT still experienced relapse (50%) and metastasis (48%) [14].

In landmark studies, consolidation chemotherapy (CCT) has been introduced to improve patients' survival after CCRT, which involved two cycles of CCT followed by two cycles concurrent chemotherapy using the same regimen [9, 15, 16]. In contrast, CCT was not adopted in others studies for reasons that has not yet been clarified [10, 17]. As far as we know, the efficacy of CCT after CCRT in ESCC has not been assessed in randomized controlled trial, while retrospective studies reported different outcomes due to inherent bias [18–21]. However the survival benefits of CCT in certain subgroups has not been previously reported. In this study, we retrospectively assessed the role of CCT for patients with ESCC who received CCRT to identify which patients would benefit from it.

2 | Patients and Methods

2.1 | Patients and Pretreatment Evaluation

For this retrospective study, we enrolled a consecutive series of ESCC patients who underwent definitive chemoradiotherapy at The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital and Tianjin Medical University Cancer Institute & Hospital between March 1, 2018 and September 31, 2022. Our study protocols were approved by the Zhengzhou University.

All patients had pretreatment evaluation that included a complete blood count, serum chemistry, endoscopic ultrasonography (EUS), barium swallow radiography, external ultrasonography of the neck, and a thoraco-abdominal computerized tomography (CT) scan and PET/CT when available. Before initiation of treatment, each patient was evaluated by a multidisciplinary team. Patients with curative intent but with unresectable tumors were treated with CCRT.

The inclusion criteria were defined as follows: an ESCC diagnosis with pathological evidence, an age $\geq$18 years, and American Joint Committee on Cancer (AJCC) 8th clinical stages II-IVA without metastasis, treated with CCRT of no less than 40 Gy. The exclusion criteria were: a history of cancer before ESCC diagnosis, distant metastasis, unclear staging, a non-ESCC histology, or the patients received other treatment before CCRT.

2.2 | Treatment

Radiation was delivered by using IMRT. The gross tumor volume (GTV) was defined as the primary tumor and positive lymph nodes on CT and EUS. The clinical target volume (CTV) was defined as the primary tumor plus 3 cm proximal and distal margins and a radial margin of 1.0 cm. The nodal CTV (CTVn) was defined as the nodal GTV (GTVn) plus a 1.0-cm expansion. CTVn also encompassed the region draining the lymphatics based on the discretion of radiation oncologists. The planning target volume (PTV) was determined by adding a 0.5 cm margin to the CTV. The PTV was covered by at least 95% isodose surface. The maximum dose within the PTV was not allowed to exceed 110% of the prescribed dose. The organs at risk for treatment planning included: lungs (the volume of lung receiving 20 Gy was $\leq$30%, and V30$\leq$20%), heart (the volume of heart receiving 40 Gy was $\leq$30%), and the spinal cord (the maximum dose was $\leq$45Gy). The median total dose and fraction size of radiotherapy in the low dose group and high dose group were 50.0 Gy (40–59.4 Gy, fraction size: 1.80–2.00 Gy) and 60.0 Gy (60.0–70.0 Gy, fraction size: 2.00 Gy), respectively.

Different concurrent chemotherapy regimens were administered during the study period. The majority of study patients received paclitaxel or docetaxel/cisplatin(65.8%), followed by fluorouracil/cisplatin (21.4%), and others (12.8%). CCT was conducted with the same regimen between 4 and 6 weeks after the completion of radiotherapy if patients did not present local progression or distant metastases. The median numbers of treatment cycles were 3 and 2 for concurrent chemotherapy and CCT.

2.3 | Evaluation and Follow-Up

After completion of CCRT, patients were subsequently evaluated every 3 months during the first year, then every 6 months until 5 years. During follow-up visits, clinical examinations included a complete blood count, serum chemistry blood tests, periodic EUS, barium swallow radiography, ultrasonography of the neck, thoraco-abdominal CT, and PET/CT when available. Recurrences and metastasis were established using histologic, cytologic, or explicit radiologic proof. After the period of clinical follow up, recurrence and survival data were obtained by telephone from the patient or the patients' family practitioner. The data was last updated in September, 2023. The median follow-up time was 28.1 months.

TABLE 1 | Clinical characteristics and survival-related factors of 351 patients with ESCC in univariate and multivariate analysis.

		Univariate analysis					Multivariate analysis	
Characteristic	**Patients, no. (%)**	**1-year (%)**	**2-year (%)**	**3-year (%)**	**Median (month)**	***p***		***p***
Sex								
Male	302 (86.0)	50	45	40	22.6	0.953		
Female	49 (14.0)	47	45	41	22.4			
Age at diagnosis (y)								
< 65	239 (68.1)	52	49	47	24.6	0.095		
≥ 65	112 (31.9)	46	38	23	19.0			
Tumor location								
Cervical	39 (11.1)	56	49	43	40.4	0.186		
Upper thoracic	129 (36.8)	53	48	43	31.7			
Middle thoracic	153 (43.6)	46	41	37	18.3			
Lower thoracic	30 (8.5)	47	37	30	22.5			
Karnofsky scale								
60–80	130 (37.0)	53	45	36	26.8	0.785		
≥ 90	221 (63.0)	48	45	39	21.6			
Weight loss								
No	253 (72.1)	52	46	38	24.8	0.020	1.523 (1.059–2.190)	0.023
Yes	98 (27.9)	38	32	27	16.4			
Tumor length								
< 4.5 cm	95 (27.1)	60	51	42	39.5	0.027		
≥ 4.5 cm	256 (72.9)	43	39	35	18.3			
T classification								
T2	26 (7.4)	75	53	32	40.5	0.057	1.363 (1.028–1.807)	0.031
T3	111 (31.6)	54	49	45	26.8			
T4	214 (61)	45	40	37	18.8			
N classification								
N0	82 (23.4)	62	56	50	38.4	0.009	1.342 (1.114–1.616)	0.002
N1	134 (38.2)	54	50	46	26.8			
N2	112 (31.9)	37	33	31	17.4			
N3	23 (6.6)	40	24	14	12.9			
Radiation dose								
< 60 Gy	116 (33.0)	40	37	33	17.4	0.024		
≥ 60 Gy	235 (67.0)	54	47	40	28.0			
Consolidation chemotherapy								
No	185 (52.7)	45	37	30	17.7	0.002	0.592 (0.423–0.829)	0.002
Yes	166 (47.3)	55	52	49	38.4			

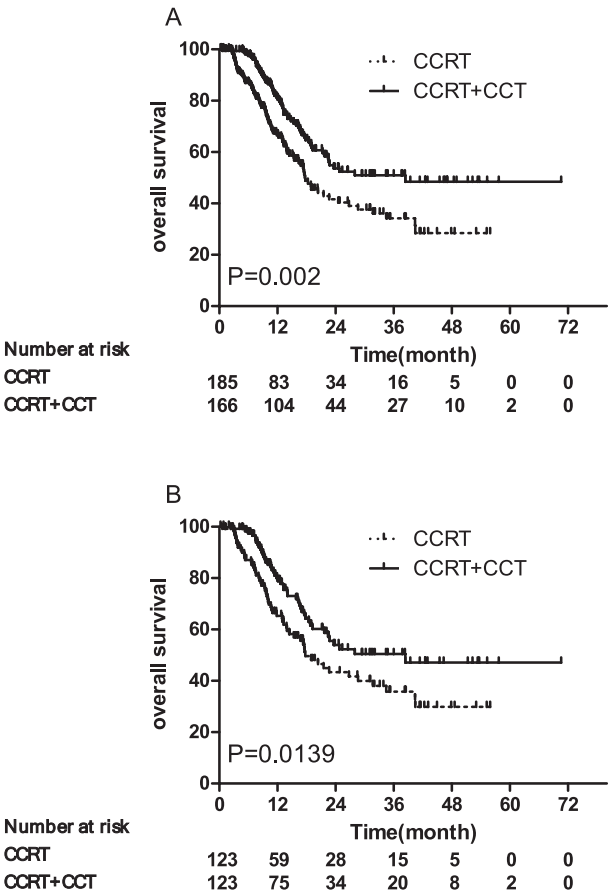


FIGURE 1 | Kaplan–Meier survival curves for the CCRT plus CCT group and the CCRT alone group. (A) Overall survival for entire group. (B) Overall survival after matching. CCRT: Concurrent chemoradiotherapy; CCT: Consolidation chemotherapy. *p* values were calculated by the unadjusted log-rank test.

2.4 | Statistical Analysis

We compared overall survival (OS) in this study, since OS is the gold standard to judge the curative effect of cancer patients [22]. The OS was calculated from the beginning of CCRT until death from any cause or the last follow-up. The survival curves were constructed using the Kaplan–Meier method. Differences between the curves were analyzed using the log-rank test. Univariate and multivariate analyses using a Cox-proportional hazards model were performed to evaluate potential prognostic factors for OS. Hazard ratios were calculated with the use of a Cox regression model including treatment alone (primary analysis) and after adjustment for baseline stratification factors. Either the Chi-square or the Fisher exact test was used for categorical data. PSM (including age, sex, tumor location, Karnofsky scale, weight loss, tumor length, T stage, N stage, radiation dose) was performed to minimize the effects of treatment selection bias and potential confounding factors. All patients in the CCRT group were matched at a ratio of 1:1 to those in the CCRT+CCT group according to the propensity scores by means of the global optimum method. All P values are two-sided. *p* values of less than 0.05 were considered to indicate statistical significance. Statistical calculations were performed using SPSS software (version 24.0).

3 | Results

3.1 | Patient Characteristics

We enrolled 351 patients with ESCC who did not have distant metastases and received CCRT (Table 1). The majority of patients were male (86.0%). The median age of the whole group was 62 years (range, 34–80 years). These patients had tumors located in the cervical, the upper, middle, or lower thoracic regions were 39(11.1%), 129(36.8%), 153(43.6%), and 30(8.5%), respectively. 98(27.9%) of patients had weight loss before treatment, and 256(72.9%) of patients had tumor length ≥ 4.5 cm. 244(63.8%) of patients had clinical T4 disease. 116(33.0%) received radiotherapy < 60 Gy (median: 50.0 Gy, mean: 49.9 Gy, 36–59.40 Gy) and 235(67.0%) received radiotherapy ≥ 60 Gy (median: 60.0 Gy, mean: 60.7 Gy, 60–70 Gy) with IMRT. Among these patients, 185(52.7%) received CCRT alone (CCRT group) and 166(47.3%) received CCRT plus CCT (CCRT+CCT group).

3.2 | Univariate and Multivariate Cox Proportional Hazard Analysis

The 1, 2, and 3-year OS rates were 50%, 44% and 40% for the entire study population. The median OS was 22.6 months. In the CCRT alone group, the 1, 2, and 3-year OS rates were 45%, 37%, 30%; in the CCRT+CCT group, the 1, 2, and 3-year OS rates were 55%, 52%, 49% (Table 1). The median OS were 17.7 months and 38.4 months in the CCRT alone group and CCRT+CCT group ($p = 0.002$), respectively (Figure 1A). Univariate analysis demonstrated that weight loss, tumor length, N classification, radiation dose, and CCT were significant predictive prognostic factors for OS. All variables were then put into a multivariate Cox proportional hazard analysis and the results showed that CCT was associated with an improved OS ($p = 0.002$, HR 0.592, 95% CI 0.423–0.829). In addition, weight loss, T classification, and N classification were associated with an increased risk of death.

3.3 | Survival After Matching Propensity Scores

Before matching, compared with the patients in CCRT group, a greater number of patients in the CCRT+CCT group were < 65 years (75.3% vs. 61.1%), had tumors located in cervical (11.4% vs. 10.8%) and upper thoracic areas (45.2% vs. 29.2%), with Karnofsky scale ≥ 90 (73.5% vs. 53.5%), and received radiotherapy ≥ 60 Gy (71.9% vs. 61.6%), (Table 2). After matching, patients characteristics were balanced between the high dose and low dose cohorts ($p > 0.05$), each group consisted of 123 patients. Relative to the CCRT group, patients who received CCT experienced improved OS (17.7 months vs. 38.4 months, $p = 0.0139$), (Figure 1B).

3.4 | Subgroup Analysis

The results of subgroup analyses of overall survival are shown in Table 3. CCT was more effective in males ($p = 0.001$, HR 0.535, 95% CI 0.371–0.772), age < 65 years ($p = 0.004$, HR 0.564 95% CI 0.374–0.860), Karnofsky scale ≥ 90 ($p = 0.001$, HR 0.499,

TABLE 2 | Clinical characteristics of 351 patients in the CCRT and CCRT+CCT groups after propensity score matching.

	Before matching			After matching		
Characteristic	**CCRT (*N*=185)**	**CCRT+CCT (*N*=166)**	***p***	**CCRT (*N*=123)**	**CCRT+CCT (*N*=123)**	***p***
Sex						
Male	159	143	0.957	109	103	0.268
Female	26	23		14	20	
Age at diagnosis (y)						
<65	114	125	0.006	87	86	0.889
≥65	71	41		36	37	
Tumor location						
Cervical	29	19	0.004	17	13	0.466
Upper thoracic	54	75		42	50	
Middle thoracic	89	64		52	53	
Lower thoracic	22	8		17	7	
Karnofsky scale						
60–80	86	44	<0.001	48	42	0.427
≥90	99	122		75	81	
Weight loss						
No	127	126	0.130	96	88	0.240
Yes	58	40		27	35	
Tumor length						
<4.5 cm	45	55	0.222	24	32	0.224
≥4.5 cm	140	116		99	91	
T classification						
T2	14	12	0.847	12	10	0.610
T3	56	55		35	42	
T4	115	99		76	71	
N classification						
N0	47	35	0.402	29	32	0.873
N1	66	68		44	47	
N2	57	55		41	37	
N3	15	8		9	7	
Radiation dose						
<60 Gy	71	45	0.025	34	42	0.270
≥60 Gy	114	121		99	81	

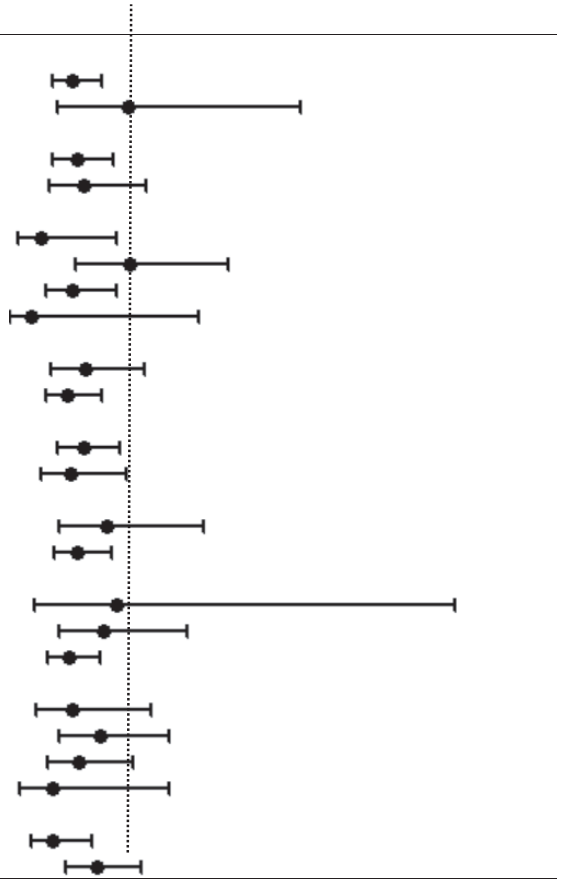
95% CI 0.323–0.772), Tumor length ≥4.5 cm ($p=0.005$, HR 0.570, 95% CI 0.383–0.848), T4 stage ($p=0.001$, HR 0.500, 95% CI 0.327–0.764), radiation dose <60 Gy ($p=0.002$, HR 0.368, 95% CI 0.194–0.700). The OS was 24.8 months/13.2 months (CCRT+CCT group/CCRT alone group) in patients with radiation dose <60 Gy (Figure 2A). The OS was not significantly different in the ≥60 Gy cohort (Figure 2B).

3.5 | PSM According to Radiation Dose

After matching, patients characteristics were balanced between the high dose and low dose cohort ($p>0.05$), (Table 4). Each group consisted of 110 patients. In the low dose cohort, 45 received CCT, the median OS for this cohort was 13.2 months and 20.7 months in the CCRT alone group and CCRT+CCT group,

TABLE 3 | Univariate hazard ratio plots for treatment effect on overall survival by baseline characteristics (HR < 1 favors consolidation chemotherapy).

Characteristic	MST (months)		*p*	HR (95% CI)
	CCRT + CCT	CCRT		
Sex				
Male	38.4	17.6	0.001	0.535 (0.371–0.772)
Female	22.5	24.6	0.981	0.989 (0.411–2.382)
Age at diagnosis (years)				
< 65	26.6	17.4	0.004	0.567 (0.374–0.860)
≥ 65	22.5	18.3	0.119	0.627 (0.346–1.134)
Tumor location				
Cervical	41.4	16.8	0.021	0.282 (0.098–0.888)
Upper thoracic	22.6	34.5	0.998	0.999 (0.556–1.794)
Middle thoracic	24.8	16.4	0.016	0.532 (0.315–0.899)
Lower thoracic	22.5	13.8	0.088	0.199 (0.025–1.563)
Karnofsky scale				
60–80	38.4	22.7	0.118	0.641 (0.366–1.124)
≥ 90	23.5	16.8	0.001	0.499 (0.323–0.772)
Weight loss				
No	38.4	19.0	0.018	0.620 (0.415–0.926)
Yes	17.8	13.9	0.038	0.522 (0.280–0.976)
Tumor length				
< 4.5 cm	39.5	40.4	0.557	0.820 (0.422–1.594)
≥ 4.5 cm	28.0	16.8	0.005	0.570 (0.383–0.848)
T classification				
T2	28.0	40.5	0.889	0.900 (0.223–3.640)
T3	38.4	24.8	0.453	0.789 (0.424–1.467)
T4	21.3	15.4	0.001	0.500 (0.327–0.764)
N classification				
N0	40.1	28.6	0.112	0.536 (0.245–1.170)
N1	26.8	26.8	0.325	0.755 (0.431–1.324)
N2	19.0	15.4	0.058	0.581 (0.328–1.027)
N3	24.8	7.1	0.111	0.367 (0.102–1.326)
Radiation dose				
< 60 Gy	24.8	13.2	0.002	0.368 (0.194–0.700)
≥ 60 Gy	38.4	24.6	0.130	0.730 (0.485–1.099)



respectively ($p = 0.0028$), the multivariate analysis results showed that CCT retained its statistical significance ($p = 0.002$, HR 0.353, 95% CI 0.183–0.681) (Table 5, Figure 2C). In the high dose cohort, 42 patients received CCT. In this cohort the median OS was 21.6 months and 23.6 months in the CCRT alone group and CCRT+CCT group, respectively ($p = 0.5512$), (Figure 2D).

3.6 | Comparing Chemotherapy Regimens

Here we compare the survival outcomes of CCT Regimens with either paclitaxel or docetaxel/cisplatin(DC), or fluorouracil/cisplatin(CF). In DC group, 132/231 received CCT, the 1, 2, and 3-year OS rates were 57%, 55%, 51%; in CF group, 38/75 received CCT, the 1, 2, and 3-year OS rates were 49%, 46%, 44% (Table 1). The median OS were 39.5 months and 32.6 months in DC group and CF group ($p = 0.150$), respectively (Table 6), The OS was higher in the DC group, although the difference between the two group was not significant($p = 0.150$).

3.7 | Impact of Radiation Dose and CCT on N Classifications

In the 8th TNM classification, N classification was no significant difference in prognosis when comparing the low and high dose groups or when comparing the CCRT alone group and CCRT+CCT group. High radiation dose only show a survival benefit for N3 stage($p = 0.045$). In the 6th TNM classification, positive lymph nodes in the cervical or abdominal cavity are considered distant metastases, so we attempted to classify patients by lymph regions. Notably, in subgroup analysis, patients with positive Cervical/abdominal lymph node, OS was 12.9 months in low dose group and 22.5 months in high dose group($p = 0.000$, HR 0.333, 95% CI 0.155–0.598). Similar OS improvement also observed in CCRT+CCT group compared with CCRT alone group, OS was 25.6 months and 14.4 months, respectively. ($p = 0.000$, HR 0.339, 95% CI 0.195–0.747) The association between treatment effect and node metastasis region in this study was similar to that both radiation dose and CCT involvement. In conclusion, lymph node metastasis based on region is a useful predictor in patient undergoing both radiation therapy and CCT (Table 7).

3.8 | Acute Adverse Events

As acute adverse effects, Grade 3–4 anemia were observed in 72 patients, including 24/116 in low dose group and 48/235 in high dose group. Grade 3–4 leukopenia was relatively high in both groups, 65/116 in low dose group and 113/235 in high dose group. Grade 3–4 thrombocytopenia and ALT/AST increasing were rare in both group. No Grade 3–4 creatinin increasing

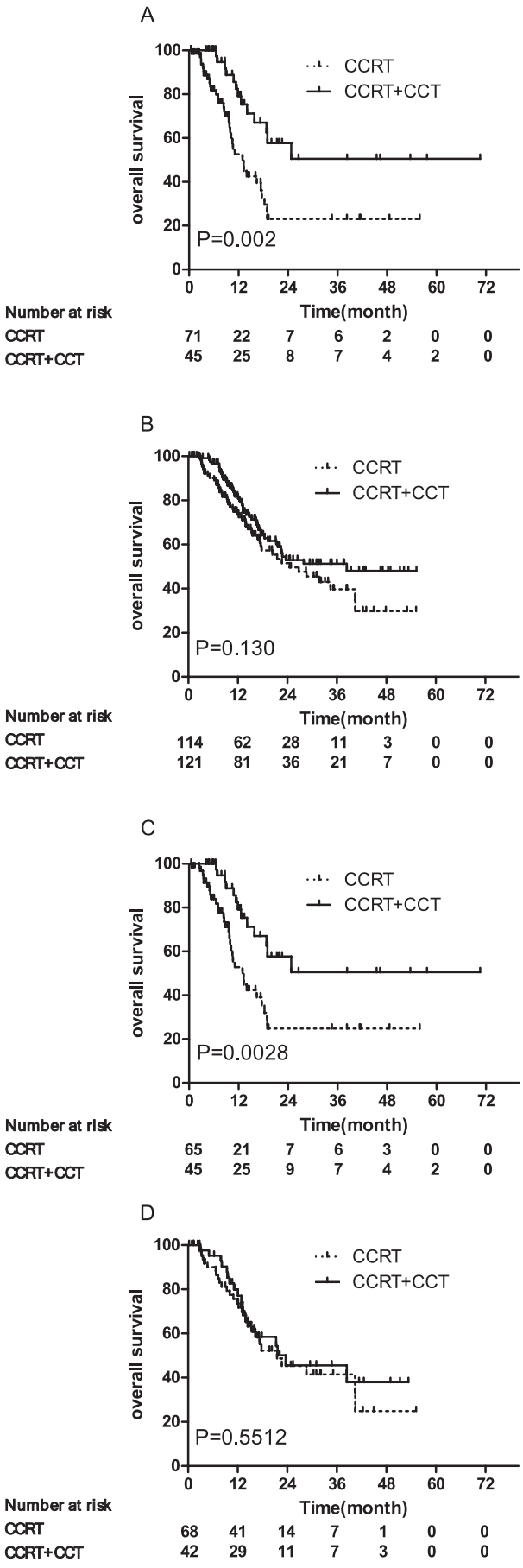


FIGURE 2 | Legend on next page.

FIGURE 2 | Kaplan–Meier survival curves for the CCRT plus CCT group and the CCRT alone group subgroup by radiation dose. (A) Overall survival for low dose cohort. (B) Overall survival for high dose cohort. (C) Overall survival for low dose cohort after matching. (D) Overall survival for high dose cohort after matching. CCRT: Concurrent chemoradiotherapy; CCT: Consolidation chemotherapy. *p* values were calculated by the unadjusted log-rank test.

occurred. All of above hematologic toxicity were not significant between low dose group and high dose group ($p > 0.05$). Grade 3–4 radiation esophagitis was observed in 9/116 patients in low dose group and 22/235 in low dose group. The grade 3–4 radiation esophagitis was higher in high dose group but difference was not significant may be related to the small sample size ($p = 0.063$). All of those patients recovered soon after completion of radiotherapy. There were no patients who had Grade 5 adverse effects. As a retrospective study, we missed some important data in the late phase, such as pulmonary fibrous change, pericardial effusion when were observed in some cases during clinical work (Table 8).

4 | Discussion

In this study, a poor survival outcome was observed in the T4 stage, N3 stage, with weight loss or treatment with a radiation dose < 60 Gy and CCRT alone stage. Our study addressed the survival outcome of CCRT alone and CCRT plus CCT in stage II-IVA ESCC patients. We demonstrated that CCT was associated with an improved OS (38.4 vs. 17.7 months, $p = 0.002$) compared with CCRT alone. Multivariate analysis revealed that CCT was an independent prognostic factor ($p = 0.002$, HR 0.592, 95% CI 0.423–0.829). CCT remained a significant predictive prognostic factor for OS after PSM ($p = 0.0182$).

To the best of our knowledge, no randomized trial to date has investigated the effectiveness of CCT after CCRT. CCT followed by CCRT has been administered in previous large prospective studies such as the RTOG 85–01 trial. In this trial two cycles of consolidation cisplatin/5-FU were performed in the CCRT group, resulting in a 5-year OS rate of 26% [23]. In addition, FFCD 9102 was a randomized trial that compared the OS of CCRT with CCRT followed by surgery. The same consolidation regimens were given in the CCRT arm. Patients who response to CCRT had a similar overall survival in both arms(17.7 months in the surgery arm compared with 19.3 months in the nonsurgery arm) [9]. The PRODIGE5/ACCORD17 trial added another 3 and 2 cycles CCT in the FOLFOX and cisplatin/5-FU arms, which resulted in median PFS scores of 9.7 and 9.4 months, respectively [5].

To date few studies have examined the effect of CCT in ESCC patients after CCRT. Retrospective studies performed in China evaluated CCT followed by CCRT. Wu et al. enrolled 67 ESCC patients who attained clinical complete response after CCRT. CCT improved the median OS (53.4 vs. 27.0 months, $p = 0.04$, HR 0.67, 95% CI 0.44–0.99) compared with CCRT alone, but failed to show an additional survival benefit after PSM [20]. This result

TABLE 4 | Clinical characteristics of 351 patients in the low dose and high dose groups after propensity score matching.

Characteristic	Before matching			After matching		
	Low dose ($N=116$)	High dose ($N=235$)	p	Low dose ($N=110$)	High dose ($N=110$)	p
Sex						
Male	102	200	0.473	96	94	0.694
Female	14	35		14	16	
Age at diagnosis (y)						
<65	76	163	0.467	72	72	1.000
≥ 65	40	42		38	38	
Tumor location						
Cervical	7	32	0.012	7	12	0.115
Upper thoracic	36	93		36	31	
Middle thoracic	64	89		60	51	
Lower thoracic	9	21		7	16	
Karnofsky scale						
60–80	41	89	0.645	41	42	0.889
≥ 90	75	146		69	68	
Weight loss						
No	77	176	0.094	77	74	0.663
Yes	39	59		33	36	
Tumor length						
<4.5 cm	25	70	0.102	25	25	1.000
≥ 4.5 cm	91	165		85	85	
T classification						
T2	7	19	0.787	7	8	0.493
T3	37	74		36	28	
T4	72	142		67	74	
N classification						
N0	20	62	0.083	20	26	0.677
N1	42	92		42	38	
N2	43	69		38	39	
N3	11	12		10	7	
Consolidation chemotherapy						
No	71	114	0.025	65	68	0.679
Yes	45	121		45	42	

was significantly better than our study but this was due in part because that study selected patients who had attained a complete clinical response after CCRT, which was associated with significantly improved survival than those responding poorly to CCRT [24, 25]. Chen et al. investigated 812 ESCC patients treated with CCRT, after PSM the median OS was 34.6 months in the observation group and 35.0 months in the consolidation group, with no statistical difference observed between groups (HR 0.96, 95% CI, 0.80–1.23, $p=0.92$) [26]. The OS was also superior compared with ours, However that may be primarily due to the fact that our study included more T4 (61.0% vs. 30.9%) and N3 (6.6% vs. 1.1%) stage patients, which have a decreased survival

rate. Wang et al. system reviewed six retrospective studies identified that CCT improved short term survival benefit(HR 0.542, $p < 0.001$, in 1 year) but not in long term(HR 0.923, $p = 0.555$, in 5 year) [18]. Lin et al. initiated population-based study found that CCT significantly prolonged OS for locally advanced ESCC patients after PSM(HR 0.67, 95% CI 0.52–0.86, $p = 0.002$) [27].

The role of CCT after CCRT for ESCC was controversial before the initiation of this study. Our findings are not consistent with the results of previous studies. However, our analysis initially demonstrated that the effect of CCT after CCRT in prolonging OS may be associated with patients' disease status and

TABLE 5 | Cox Proportional Hazard Regression Multivariate Model of Factors Predicting Survival in low dose cohort.

Characteristic	HR (95% CI)	*p*
Sex		0.893
Age		0.645
Tumor location		0.876
Karnofsky scale		0.947
Weight loss		0.892
Tumor length		0.604
T classification		0.222
N classification	1.518 (1.087–2.119)	0.014
Consolidation chemotherapy	0.353 (0.183–0.681)	0.002

TABLE 8 | Acute adverse events (CTCAE5.0).

	Grade		
	Grade 0–2	Grade 3–4	*p*
Anemia			
Low dose	92	24	0.567
High dose	187	48	
Leukopenia			
Low dose	51	65	0.170
High dose	122	113	
Thrombocytopenia			
Low dose	102	14	0.373
High dose	213	22	
ALT/AST increasing			
Low dose	111	5	0.343
High dose	228	7	
Creatinin increasing			
Low dose	116	0	1
High dose	235	0	
Radiation esophagitis			
Low dose	107	9	0.062
High dose	213	22	

TABLE 6 | Survival outcome of 170 patients received CCT with ESCC in univariate analysis.

Characteristic	Patient no. CCT/CCRT	Univariate analysis				*p*
		1-year (%)	2-year (%)	3-year (%)	Median (month)	
Chemotherapy regimens						0.150
Paclitaxel or docetaxel/cisplatin	132/231	57	55	51	39.5	
Fluorouracil/cisplatin	38/75	49	46	44	32.6	

TABLE 7 | Radiation and CCT treatment effect on overall survival by N classification.

	Radiation dose				CCT			
Characteristic	Low	High	*p*	HR	No	Yes	*p*	HR
N classification (8th)								
N0	NA	NA	0.237		40.1	28.6	0.112	
N1	17.6	NA	0.313		26.8	26.8	0.325	
N2	15.8	17.5	0.336		19.0	15.4	0.058	
N3	12.6	34.5	0.045	0.227	24.8	7.1	0.111	
Cervical/abdominal lymph node								
Negative	25.6	23.6	0.721		24.6	28.0	0.218	
Positive	12.9	22.5	0.000	0.333	14.4	25.6	0.001	0.339

treatment. A benefit in terms of increased OS after CCT was not consistently observed across all prespecified subgroups. CCT was more effective in males, age < 65 years and with KPS > 90, mainly because those patients had better general conditions. The benefit of CCT towards OS was almost equivalent among different tumor locations. Whether weight loss or not did not affect the efficacy of CCT. CCT had limitations for patients with tumor length < 4.5 cm and T2-3 stages, CCRT alone might be appropriate for such patients. A significant benefit was observed in patients in the T4 stage (HR 0.500, 95% CI 0.327–0.764) and tumor length ≥ 4.5 cm (HR 0.570, 95% CI 0.383–0.848). There was no difference in the hazard ratio associated with the N stage.

Remarkably, CCT interaction with radiation was significant. Among patients treated with radiation doses lower than 60 Gy, the median OS was 11.6 months longer among patients who received CCT than among those who received CCRT alone (24.8 months vs. 13.2 months, $p = 0.002$). Risk reduction by CCT was more evident among patients who received radiation doses lower than 60Gy compared with those receiving higher than 60 Gy (HR 0.368 95% CI 0.194–0.700 vs. HR 0.730, 95% CI 0.485–1.099). When we used PSM and split the data into a low dose cohort and a high dose cohort, CCT remained a significant predictive prognostic factor for OS in the low dose cohort ($p = 0.002$). Similar results were not observed in the high dose cohort. Current NCCN guidelines recommend a standard dose of 50.40 Gy for the treatment of esophageal cancer, according to the INT 0123 (Radiation Therapy Oncology Group 94–05) phase III trial [15]. This study reported a higher treatment-related mortality rate in the patients assigned to the 64.8Gy group but without survival benefit compared with 50.4 Gy (13.0 months vs. 18.1 months). However, the INT 0123 trial had its limitations. This study had a minority of patients with T4 stage (7.8%) and N+ stage (21.6%). In addition, treatment with conventional radiotherapy can lead to more potential damage to the lungs and heart compared with IMRT. Suh YG et al. reported that esophageal cancer patients treated with 2D-CRT and 3D-CRT of 60Gy or higher had better locoregional control and progression-free survival without a significant increase of in treatment-related toxicity [28]. Chang CL et al. analyzed 2061 patients with thoracic ESCC without distant metastasis who received CCRT with IMRT. Administration of a radiation dose > 60 Gy was a significant independent prognostic factor for overall survival ($p < 0.0001$, HR 0.75, 95% CI 0.68–0.83) [29]. However, recent multicenter phase 3 trial showed high dose radiation (60 Gy30 f/2 Gy, 59.4 Gy/33f/1.8 Gy) has no survival benifit but led to higher severe toxicities compared with low dose radiation (50 Gy25 f/2 Gy, 50.4 Gy/28f/1.8 Gy) [30, 31]. It should be noted that their scheme includes 2 cycles of consolidation chemotherapy after 6 cycles of concurrent chemotherapy. In our study, there was a tendency to increase the overall survival in the high dose group (28.0 months vs. 17.4 months, $p = 0.024$). The overall survival was significantly worse in the low dose group without CCT (13.2 months).

Several limitations were present in this study. First of all, the biases inherent to the nature of single-center and retrospective investigations were not completely avoided. However, we did utilize propensity score matching analysis to adjust the selection bias. Secondly, the lack of PET-CT in some patients may affect the accuracy of the staging. In addition, some important characteristics were not recorded such as tumor differentiation due to this being a non-operation type of therapy. The last limitation was that the median follow-up time was 28.1 months. Our study still needs further follow-up.

Consolidation chemotherapy was initially proposed as postoperative chemotherapy. Potential metastasis that cannot be detected clinically may occur before surgery. Chemotherapy is used to kill these residual cancer cells in order to prevent cancer recurrence and metastasis. Consolidation chemotherapy can eliminate small residual lesions in the blood or lymphatic system, reduce tumor recurrence rates, and improve cure rates. Postoperative adjuvant chemotherapy can improve the overall survival rate and disease-free survival of patients with esophageal squamous cell carcinoma after radical resection, but may only be effective for certain subgroups of patients depending on pathological stage or lymph node metastasis status. Radiation therapy uses high-energy radiation to directly attack cancer cells, disrupting their DNA structure and preventing them from further dividing. The residual cancer cells caused by insufficient radiotherapy dose can be equivalent to surgical failure to achieve R0 resection, especially T4 and positive lymph nodes in the cervical or abdominal cavity as mentioned earlier. For these high-risk patients, consolidation chemotherapy after radiotherapy further kills residual tumor cells and prolongs survival.

5 | Conclusion

In conclusion, our data indicate that CCT improves overall survival in patients received radiation dose < 60 Gy. We recommend that CCT should be considered for ESCC patients who underwent CCRT < 60 Gy, but not for those ≥ 60 Gy radiation. Further prospective studies are needed to confirm these results.

Author Contributions

H.Z., Q.W., B.T., and P.W. performed data acquisition, the statistical analysis and drafted the manuscript. H.Z. performed data acquisition and the statistical analysis. B.T. critically reviewed the manuscript,conceived of the study, and participated in its design. All authors read and approved the final manuscript.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The respective study was approval by Human Investigation Committee of The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China. The Human Investigation Committee allowed the use of patient data for research, provided that any person's related data are kept anonymous.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no Conflicts of Interest.

Data Availability Statement

There are ethical restrictions on sharing of de-identified data for this study. The ethics committee has not agreed to the public sharing of data as we do not have the participants' permission to share their anonymous data. It is likely given the nature of the dataset that patients may still be identifiable despite efforts to anonymise the data. Qualified and interested researchers may request access to the data by contacting Human Investigation Committee of The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital.

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