Original Article

First-line induction or consolidation chemotherapy combined with concurrent chemoradiotherapy for esophageal squamous cell carcinoma

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Background: The RTOG 85-01 trial established that definitive concurrent chemoradiotherapy (CCRT) is the standard treatment for inoperable, locally advanced esophageal carcinoma, as well as for patients who decline surgery. The present study aims to compare the impact of three treatment modalities, CCRT, induction chemotherapy (ICT) followed by CCRT (ICT + CCRT), and CCRT followed by consolidation chemotherapy (CCT) (CCRT + CCT), on the survival of patients with inoperable esophageal squamous cell carcinoma (ESCC).

Methods: This retrospective analysis was conducted with 391 patients with ESCC who underwent radical CCRT with induction or CCT or CCRT only from January 2016 to October 2020 at the Fourth Hospital of Hebei Medical University in Shijiazhuang, Hebei province, China. Propensity score matching (PSM) analyses were performed. The primary outcome measure was efficacy included overall survival (OS) and progression-free survival (PFS). The final follow-up date ended on 31 May 2024.

Results: It showed a significantly better survival curve for OS in the CCRT + CCT group than the CCRT group (P=0.02, χ^2=5.503). It showed a significantly better survival curve for PFS in the CCRT + CCT group than the CCRT group (P=0.002, χ^2=9.788). It showed a significantly better survival curve for OS in the CCRT + CCT group than the ICT + CCRT group (P=0.046, χ^2=3.986). It showed a significantly better survival curve for PFS in the CCRT + CCT group than the ICT + CCRT group (P=0.01, χ^2=6.610). No significant differences were showed in treatment-related adverse events. Lesion length, N-staging, and combination of radiotherapy and chemotherapy were the independent prognostic factors for OS and PFS.

Conclusions: For inoperable ESCC patients, CCRT + CCT showed the best OS and PFS rates than ICT + CCRT and CCRT. There were no significant differences in treatment-related adverse events. Lesion length, N-staging, and combination of radiotherapy and chemotherapy were the independent prognostic factors for OS and PFS.

Keywords: Chemoradiotherapy; consolidation chemotherapy (CCRT); esophageal neoplasms; esophageal squamous cell carcinoma (ESCC)

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Introduction

Esophageal cancer is responsible for over half a million cancer-related deaths globally each year (1), with squamous-cell carcinoma constituting approximately 85% of cases (2). Esophageal squamous cell carcinoma (ESCC) was more prevalent among Asian countries than Western ones and should have mentioned the its uniquely more response rate compared with esophageal adenocarcinoma (EA). Surgical intervention is recommended for the treatment of early-stage esophageal cancer; however, the majority of patients present with advanced disease, rendering them ineligible for surgery (3). Radiation therapy plays a crucial role in the multidisciplinary management of esophageal carcinoma. The RTOG 85-01 trial established that definitive concurrent chemoradiotherapy (CCRT) is the standard treatment for inoperable, locally advanced esophageal carcinoma, as well as for patients who decline surgery (4,5). According to the pivotal RTOG 8501, only 36 out of the 61 patients enrolled in combined modality completed the per protocol treatment. It would be explained partly that after finishing CCRT, some of them declined the consolidation therapy due to delayed recovery from treatment-related toxicities. Nevertheless, the impact of incorporating induction chemotherapy (ICT) or consolidation chemotherapy (CCT) into CCRT on patient survival and treatment-related toxicity remains undetermined.

A prospective, multicenter phase 2 study by Satake *et al.* (6) demonstrated that ICT followed by CCRT (ICT + CCRT) performed a better complete response (CR) rate than traditional treatment. However, the previous study primarily assessed the immediate efficacy of the two treatment groups, without evaluating long-term survival outcomes. The study's scope was limited, including only 33 patients, and utilized three-dimensional conformal radiation therapy (3D-CRT), which differs from the currently favored intensity-modulated radiation therapy (IMRT). Additionally, some studies have reported that ICT combined with CCRT is more effective than CCRT alone (7-9), while others have found no significant difference between the two treatment modalities (10,11). Similarly, research comparing CCRT followed by CCT (CCRT + CCT) with CCRT alone has yielded mixed results, with some studies indicating superior efficacy of CCRT + CCT (12), while others report no significant advantage (13). Notably, previous studies often compared only two of the three treatment strategies, omitting a comprehensive evaluation of all three approaches. A prospective randomized trial by Yoon *et al.* (14) concluded that, for neoadjuvant radiotherapy followed by surgery, the addition of ICT did not improve the outcome. However, for patients with inoperable ESCC, there remains no conclusive evidence regarding the potential survival benefits of integrating ICT or CCT with the standard CCRT regimen.

Therefore, we undertook this study to compare the effects of the three treatment modalities—CCRT, ICT + CCRT, and CCRT + CCT—on the survival of patients with inoperable ESCC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-599/rc).

Highlight box

Key findings

- Concurrent chemoradiotherapy followed by consolidation chemotherapy (CCRT) is the most beneficial for survival.

What is known and what is new?

- Definitive concurrent chemoradiotherapy is the standard treatment for inoperable, locally advanced esophageal carcinoma.
- The impact of incorporating induction chemotherapy or consolidation chemotherapy into CCRT on patient survival and treatment-related toxicity remains undetermined.

What is the implication, and what should change now?

- In clinical practice, consolidation chemotherapy should be added after definitive concurrent chemoradiotherapy treatment for inoperable, locally advanced esophageal squamous cell carcinoma.

Methods

Study population

This retrospective analysis included 391 patients with ESCC who underwent radical CCRT with induction or CCT, or CCRT alone, between January 2016 and October 2020 at the Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China. The inclusion criteria for the study were as follows: (I) age 18–80 years; (II) histologically or pathologically confirmed ESCC; (III) Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1; (IV) no prior treatment; (V) comprehensive staging performed using barium esophagogram X-ray, chest-enhanced computed tomography (CT), electronic gastroscopy, endoscopic ultrasound, or positron emission tomography (PET)-CT, according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system; (VI) treatment with either CCRT, ICT + CCRT, or

CCRT + CCT; (VII) radiotherapy delivered using IMRT at a dose of ≥50 Gy, with a conventional chemotherapy regimen administered at radical doses; (VIII) patients were inoperable or refused to receive surgery for any reasons. Exclusion criteria included: (I) distant organ metastases; (II) active infection or autoimmune diseases; (III) multifocal esophageal carcinoma; (IV) concurrent other malignancies; (V) receipt of palliative therapy; (VI) total number of chemotherapy cycles >6; (VII) receipt of other treatment modalities; (VIII) incomplete clinical or follow-up data.

We collected baseline clinical data from enrolled patients, including gender, age, ECOG PS, pathology type, tumor location, lesion length on X-ray, T stage, N stage, clinical stage, radiation dose, chemotherapy regimen and cycles, and data on treatment-related adverse events. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University (No. 20240214) and individual consent for this retrospective analysis was waived.

Treatment

The chemotherapy regimens of ICT, CCRT, and CCT were as follows: fluorouracil (750–1,000 mg/m^2, i.v., d1–4, q3w) plus cisplatin (75–100 mg/m^2, i.v., d1, q3w); paclitaxel (135–175 mg/m^2, i.v., d1, q3w) plus cisplatin (75 mg/m^2 i.v., d1, q3w). The chemotherapy regimens of ICT and CCT were the same as it is corresponding CCRT. The cycles of ICT and CCT were two cycles. The interval between ICT and CCRT, and the interval between CCRT and CCT were 3–4 weeks.

Patients were immobilized in the head, neck, shoulder, or chest position using a thermoplastic mask, and were scanned and positioned under a CT simulator with a slice thickness of 3–5 mm. The target areas were delineated using a treatment planning system (TPS) with a 6-MV X-ray. Beam numbers and radiation angles were manually adjusted to optimize the treatment plan. The criteria for target delineation were as follows: (I) gross tumor volume (GTV) included the primary tumor and metastatic lymph nodes identified via imaging; (II) clinical target volume (CTV) was defined as extending 3–5 cm cranially and caudally, and 0.5–1.0 cm laterally from the GTV; (III) planned target volume (PTV) encompassed an additional 0.5-cm margin beyond the CTV. All patients received prophylactic irradiation of the lymphatic drainage areas, defined as CTV1, with PTV1 including a uniform 0.3-cm margin beyond CTV1. The prescribed dose volume required that 95% of PTV1 receive 50.4–54 Gy in 28–30 fractions, at 180–200 cGy per fraction, administered 5 times per week; similarly, 95% of PTV was to receive 60–64 Gy in 28–30 fractions, at 200–215 cGy per fraction, also administered 5 times per week. Dose constraints for organs at risk (OARs) were set according to established guidelines, with a mean dose to both lungs of <13 Gy, V20 ≤30%, V30 ≤20%; mean heart dose ≤30 Gy, V30 ≤40%, V40 ≤30%; and maximum spinal cord dose <45 Gy. The maximum transverse diameter and volume of the GTV were calculated using the TPS. Dose-volume histograms (DVHs) were employed to calculate the mean doses for GTV, PTV, and PTV1, and to ensure that 95% of these volumes received the prescribed doses.

Outcomes and follow-up

The primary outcome measures were overall survival (OS) and progression-free survival (PFS). The secondary outcome measure focused on treatment-related adverse events. Since all three groups received radiotherapy via IMRT at equivalent doses, we specifically assessed the extent of myelosuppression induced by different chemotherapy regimens to gauge treatment-related adverse events. Efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). OS was defined as the time from the initiation of antitumor treatment to death from any cause, irrespective of disease status or date of last follow-up. PFS was defined as the duration from the start of anticancer treatment to the first instance of disease progression, death, or last follow-up. Acute toxicities, including leukocytopenia, neutropenia, anemia, thrombocytopenia, transaminitis, hyperbilirubinemia, and nausea/vomiting, were assessed using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0). Patients were systematically monitored and followed up, through hospital visits and telephone interviews. Follow-up assessments included ultrasound, barium esophagogram, CT, magnetic resonance imaging, cytology, other imaging, and pathological evaluations, along with hematological tests. Patients were reviewed every 1 to 3 months during the first 2 years post-treatment, and every 6 to 12 months thereafter.

Statistical analysis

All recorded data were analyzed using SPSS (version 27.0, IBM Corporation, Armonk, NY, USA). Pearson Chi-

squared test was used to assess the correlation between different categorical variables. The OS and PFS rates were calculated using the Kaplan-Meier method, and a log-rank test was used to assess survival differences between groups. The median and 95% confidence interval (CI) were calculated. We performed Cox regression analyses of possible prognostic factors, including factors with P<0.1 in the univariate analyses in the multivariate Cox regression analyses, and factors with P<0.05 were considered as independent prognostic factors and their hazard ratio (HR) and 95% CI were calculated. Then, in order to reduce the heterogeneity and increase the stability of the results, we performed PSM analyses. All other statistical analyses were performed with P<0.05 on two sides as statistically significant.

Results

Patients characteristics

A total of 391 patients were included in this study, of which the patients are from January 2016 and October 2020. Among these, 222 patients received CCRT, 107 received ICT followed by CCRT (ICT + CCRT), and 62 received CCRT followed by CCT (CCRT + CCT). The study comprised 296 male patients (75.7%), with a median age of 62 years (interquartile range, 55.0–68.0 years). The mean lesion length observed on X-ray was 5.6 cm. The distribution of tumor location was as follows: 47 patients (12.0%) had cervical esophageal tumors, 134 (34.3%) had upper thoracic, 184 (47.1%) had mid thoracic, and 26 (6.6%) had lower thoracic tumors. The majority of patients were staged as T4 (66.0%) and N1 (41.7%). The median radiotherapy dose administered was 61.5 Gy (range, 60.0–63.0 Gy). *Table 1* shows the detailed characteristics before PSM.

Survival before PSM

The final follow-up date ended on 31 May 2024. The median follow-up duration for the whole patients was 53.2 months (range, 1.4–90.1 months). The median and 95% CI of OS in CCRT, ICT + CCRT, and CCRT + CCT were 25.4 (20.5–30.5), 27.1 (21.3–32.9), and 37.2 (28.7–45.7) months, respectively. *Figure 1* shows the Kaplan-Meier curves of OS in the three groups. It showed a significantly better survival curve for OS in the CCRT + CCT group than the other two groups (P=0.02), while there was no significant difference between CCRT and ICT + CCRT groups. The 1-, 3-, and 5-year OS rates of CCRT + CT were 90.3% (86.5–94.1%), 51.6% (45.3–57.9%), and 29.7% (23.6–35.8%), respectively. The median and 95% CI of PFS in CCRT, ICT + CCRT, and CCRT + CCT were 25.3 (19.1–31.5), 25.7 (22.6–28.9), and 33.1 (25.1–41.1) months, respectively. *Figure 2* shows the Kaplan-Meier curves of PFS in the three groups. It showed a significantly better survival curve for PFS in the CCRT + CCT group than the other two groups (P=0.045), while there was no significant difference between CCRT and ICT + CCRT groups. The 1-, 3-, and 5-year PFS rates of CCRT + CT were 85.5% (range, 81.0–90.0%), 40.2% (range, 33.6–46.8%), and 19.3% (range, 13.0–25.6%), respectively.

Prognostic factors before PSM

Table 2 shows the results of Univariate and multivariate Cox regression of prognostic factors for OS and PFS before PSM.

The univariate Cox regression analyses demonstrated that location, length on X-ray, T-staging, N-staging, and CCRT + CCT regimen were the prognostic factors that significantly affected OS; and length on X-ray, T-staging, N-staging, and CCRT + CCT regimen were the prognostic factors that significantly affected PFS.

We included factors that were significant in the univariate analyses in the multivariate Cox regression analyses and the results showed that T-staging [HR (95% CI): 1.910 (1.088–3.354); P=0.02], N-staging [HR (95% CI): 1.593 (1.244–2.039); P<0.001], and CCRT + CCT regimen [HR (95% CI): 0.639 (0.455–0.898); P=0.01] were the independent prognostic factors for OS; T-staging [HR (95% CI): 1.981 (1.124–3.493); P=0.02], N-staging [HR (95% CI): 1.543 (1.205–1.973); P<0.001), and CCRT + CCT regimen [HR (95% CI): 0.667 (0.475–0.936); P=0.02] were the independent prognostic factors for PFS.

Survival after PSM

Table 3 shows the detailed characteristics after PSM, showing that there are no significant differences in baseline characteristics among three groups. *Figure 3A* shows the Kaplan-Meier curves of OS between CCRT + CCT and CCRT. It showed a significantly better survival curve for OS in the CCRT + CCT group than the CCRT group (P=0.02, χ^2=5.503). *Figure 3B* shows the Kaplan-Meier curves of PFS between CCRT + CCT and CCRT. It showed a

Table 1 Characteristics of patients before PSM

Characteristics	Patients, n (%)			χ^2	P value
	CCRT (n=222)	ICT + CCRT (n=107)	CCRT + CCT (n=62)		
Gender				1.653	0.44
Male	163 (73.4)	83 (77.6)	50 (80.6)		
Female	59 (26.6)	24 (22.4)	12 (19.4)		
Age (years)				7.401	0.03
≥60	139 (62.6)	60 (56.1)	27 (43.5)		
<60	83 (37.4)	47 (43.9)	35 (56.5)		
Location				10.241	0.16
C	26 (11.7)	9 (8.4)	12 (19.4)		
UT	74 (33.3)	35 (32.7)	25 (40.3)		
MT	109 (49.1)	56 (52.3)	19 (30.6)		
LT	13 (5.9)	7 (6.5)	6 (9.7)		
Length on X-ray (cm)				2.703	0.26
≥5	135 (60.8)	73 (68.2)	35 (56.5)		
<5	87 (39.2)	34 (31.8)	27 (43.5)		
T-staging				9.503	0.15
1	1 (0.5)	0	0		
2	10 (4.5)	6 (5.6)	5 (8.1)		
3	65 (29.3)	22 (20.6)	24 (38.7)		
4	146 (65.8)	79 (73.8)	33 (53.2)		
N-staging				14.149	0.03
0	62 (27.9)	18 (16.8)	10 (16.1)		
1	87 (39.2)	47 (43.9)	29 (46.8)		
2	67 (30.2)	38 (35.5)	16 (25.8)		
3	6 (2.7)	4 (3.7)	7 (11.3)		
Clinical staging				10.077	0.04
II	32 (14.4)	11 (10.3)	9 (14.5)		
III	43 (19.4)	26 (24.3)	23 (37.1)		
IVA	147 (66.2)	70 (65.4)	30 (48.4)		
Radiation dose (Gy)				4.429	0.11
≥62	71 (32.0)	39 (36.4)	13 (21.0)		
<62	151 (68.0)	68 (63.6)	49 (79.0)		

PSM, propensity score matching; ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT; C, cervical; UT, upper thoracic; MT, middle thoracic; LT, lower thoracic.

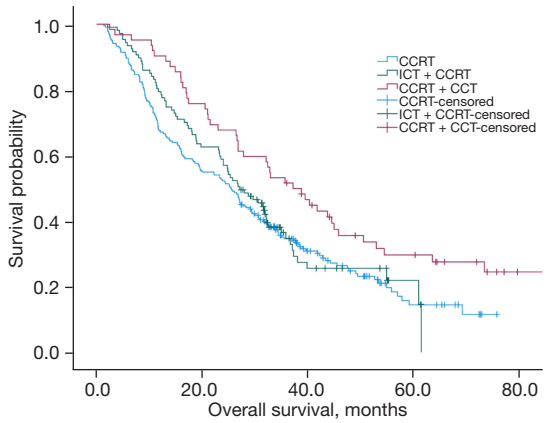

Figure 1 Kaplan-Meier curves of overall survival. ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT.

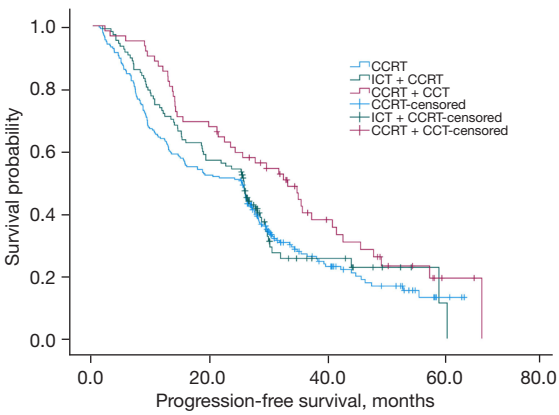

Figure 2 Kaplan-Meier curves of progression-free survival. ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT.

significantly better survival curve for PFS in the CCRT + CCT group than the CCRT group (P=0.002, χ^2=9.788).

Figure 3C shows the Kaplan-Meier curves of OS between CCRT + CCT and ICT + CCRT. It showed a significantly better survival curve for OS in the CCRT + CCT group than in the ICT + CCRT group (P=0.046, χ^2=3.986). *Figure 3D* shows the Kaplan-Meier curves of PFS between CCRT + CCT and ICT + CCRT. It showed a significantly better survival curve for PFS in the CCRT + CCT group than in the ICT + CCRT group (P=0.01, χ^2=6.610).

Prognostic factors after PSM

Table 4 shows the results of Univariate and multivariate Cox regression of prognostic factors for OS and PFS after PSM.

The univariate Cox regression analyses demonstrated that length on X-ray, N-staging, and combination of radiotherapy and chemotherapy were the prognostic factors that significantly affected OS; and length on X-ray, N-staging, and combination of radiotherapy and chemotherapy were the prognostic factors that significantly affected PFS.

We included factors that were significant in the univariate analyses in the multivariate Cox regression analyses and the results showed that length on X-ray [HR (95% CI): 0.911 (0.835–0.994); P=0.04], N-staging [HR (95% CI): 1.473 (1.176–1.844); P<0.001], and combination of radiotherapy and chemotherapy [HR (95% CI): CCRT *vs.* CCRT + CCT, 1.662 (1.071–2.579), P=0.02; ICT + CCRT *vs.* CCRT + CCT, 1.763 (1.129–2.755), P=0.01] were the independent prognostic factors for OS; length on X-ray [HR (95% CI): 0.910 (0.832–0.993); P=0.04], N-staging [HR (95% CI): 1.429 (1.142–1.789); P=0.002], and combination of radiotherapy and chemotherapy [HR (95% CI): CCRT *vs.* CCRT + CCT, 2.051 (1.309–3.215), P=0.002; ICT + CCRT *vs.* CCRT + CCT, 1.622 (1.041–2.530), P=0.03] were the independent prognostic factors for PFS.

Treatment-related adverse events

In terms of treatment-related adverse events, no significant differences were observed between three groups in grade ≥3 in grade acute radiological esophagitis, grade ≥3 acute radiological pneumonia, grade ≥2, and grade ≥3 myelosuppression (Table S1, Figure S1).

Discussion

Radiation therapy holds a necessary position in the comprehensive therapy of esophageal carcinoma. The RTOG 85-01 trial has verified that CCRT is most beneficial to radiation alone, with a favorable long-term survival for nonoperative esophageal cancer patients (4,5). The National Comprehensive Cancer Network also recommends radical chemoradiotherapy as the standard regimen (15). However, there have been no detailed and accurate recommendations on the combination of radiotherapy and chemotherapy.

A number of previous studies have explored CCRT and whether to combine it with ICT or CCT. A meta-

Table 2 Univariate and multivariate Cox regression of prognostic factors for OS and PFS before PSM

Variables	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	P value	HR (95% CI)	P value
OS				
Gender (female *vs.* male)	1.180 (0.892–1.562)	0.25	–	–
Age (<60 *vs.* ≥60 years)	1.126 (0.891–1.423)	0.31	–	–
Location (MT/LT *vs.* C/UT)	1.248 (0.986–1.579)	0.07	1.139 (0.898–1.445)	0.28
Length on X-ray (<5 *vs.* ≥5 cm)	0.795 (0.624–1.014)	0.07	0.928 (0.722–1.194)	0.56
T-staging (T3–4 *vs.* T1–2)	1.940 (1.110–3.391)	0.02	1.910 (1.088–3.354)	0.02
N-staging (N2–3 *vs.* N0–1)	1.611 (1.268–2.046)	<0.001	1.593 (1.244–2.039)	<0.001
Treatment options		0.02		0.04
ICT + CCRT *vs.* CCRT	0.920 (0.699–1.210)	0.55	0.897 (0.680–1.184)	0.44
CCRT + CCT *vs.* CCRT	0.619 (0.441–0.867)	0.005	0.639 (0.455–0.898)	0.01
PFS				
Gender (female *vs.* male)	0.854 (0.645–1.130)	0.27	–	–
Age (<60 *vs.* ≥60)	1.094 (0.865–1.384)	0.45	–	–
Location (MT/LT *vs.* C/UT)	1.223 (0.967–1.548)	0.09	1.135 (0.895–1.440)	0.30
Length on X-ray (<5 *vs.* ≥5 cm)	0.792 (0.621–1.009)	0.06	0.912 (0.709–1.174)	0.47
T-staging (T3–4 *vs.* T1–2)	1.998 (1.140–3.501)	0.02	1.981 (1.124–3.493)	0.02
N-staging (N2–3 *vs.* N0–1)	1.556 (1.226–1.976)	<0.001	1.543 (1.205–1.973)	<0.001
Treatment options		0.047		0.06
ICT + CCRT *vs.* CCRT	0.923 (0.701–1.214)	0.57	0.904 (0.685–1.193)	0.48
CCRT + CCT *vs.* CCRT	0.654 (0.467–0.916)	0.01	0.667 (0.475–0.936)	0.02

OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT; MT, middle thoracic; LT, lower thoracic; C, cervical; UT, upper thoracic.

analysis conducted by Wang *et al.* (16) found that ICT + CCRT and CCRT + CCT had a better 1-year OS rate than CCRT, while their 2-year OS rates were the same. They found that CCRT + CCT had a better 3-year OS rate than CCRT, while the 5-year rates were the same. Possible reasons for this conclusion from their research were that they were almost retrospective studies, and the doses of radiotherapy and chemotherapy regimens varied among studies. In addition to this, a meta-analysis conducted by Xia *et al.* (17) found that there were significant differences in OS and PFS for CCRT + CCT than CCRT alone, and there were no differences in treatment-related adverse effects between them, which were the same as our results. A retrospective study which included 599 ESCC patients found that there were no differences in OS and PFS rates between ICT + CCRT and CCRT (P=0.078 and P=0.532, respectively) (11), similar to our findings. However, another retrospective study which included 450 ESCC patients found that ICT + CCRT had better OS and PFS than CCRT, which is different from our findings. The reasons of these differences may be that their radiation therapy modalities included 3D-CRT, while patients in our study only received IMRT, which may contribute to the failure to reflect the difference in treatment on survival. Apart from this, a randomized phase 2 trial by Liu *et al.* (10) found that there were no differences in 3-year OS rate between ICT + CCRT and CCRT (41.8% *vs.* 38.1%, P=0.58), and there were no differences in treatment-related adverse effects

Table 3 Characteristics of patients after PSM

Characteristics	Patients, n (%)			χ^2	P value
	CCRT (n=62)	ICT + CCRT (n=62)	CCRT + CCT (n=62)		
Gender				4.531	0.10
Male	49 (79.0)	57 (91.9)	50 (80.6)		
Female	13 (21.0)	5 (8.1)	12 (19.4)		
Age (years)				0.566	0.75
≥60	26 (41.9)	30 (48.4)	27 (43.5)		
<60	36 (58.1)	32 (51.6)	35 (56.5)		
Location				10.008	0.12
C	9 (14.5)	4 (6.5)	12 (19.4)		
UT	25 (40.3)	19 (30.6)	25 (40.3)		
MT	25 (40.3)	33 (53.2)	19 (30.6)		
LT	3 (4.8)	6 (9.7)	6 (9.7)		
Length on X-ray (cm)				0.820	0.66
≥5	30 (48.4)	33 (53.2)	35 (56.5)		
<5	32 (51.6)	29 (46.8)	27 (43.5)		
T-staging				5.435	0.49
1	1 (1.6)	0	0		
2	5 (8.1)	3 (4.8)	5 (8.1)		
3	22 (35.5)	17 (27.4)	24 (38.7)		
4	34 (54.8)	42 (67.7)	33 (53.2)		
N-staging				3.314	0.77
0	12 (19.4)	12 (19.4)	10 (16.1)		
1	33 (53.2)	27 (43.5)	29 (46.8)		
2	12 (19.4)	19 (30.6)	16 (25.8)		
3	5 (8.1)	4 (6.5)	7 (11.3)		
Clinical staging				1.170	0.88
II	8 (12.9)	10 (16.1)	9 (14.5)		
III	21 (33.9)	25 (40.3)	23 (37.1)		
IVA	33 (53.2)	27 (43.5)	30 (48.4)		
Radiation dose (Gy)				0.417	0.81
≥62	16 (25.8)	15 (24.2)	13 (21.0)		
<62	46 (74.2)	47 (75.8)	49 (79.0)		

PSM, propensity score matching; ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT; C, cervical; UT, upper thoracic; MT, middle thoracic; LT, lower thoracic.

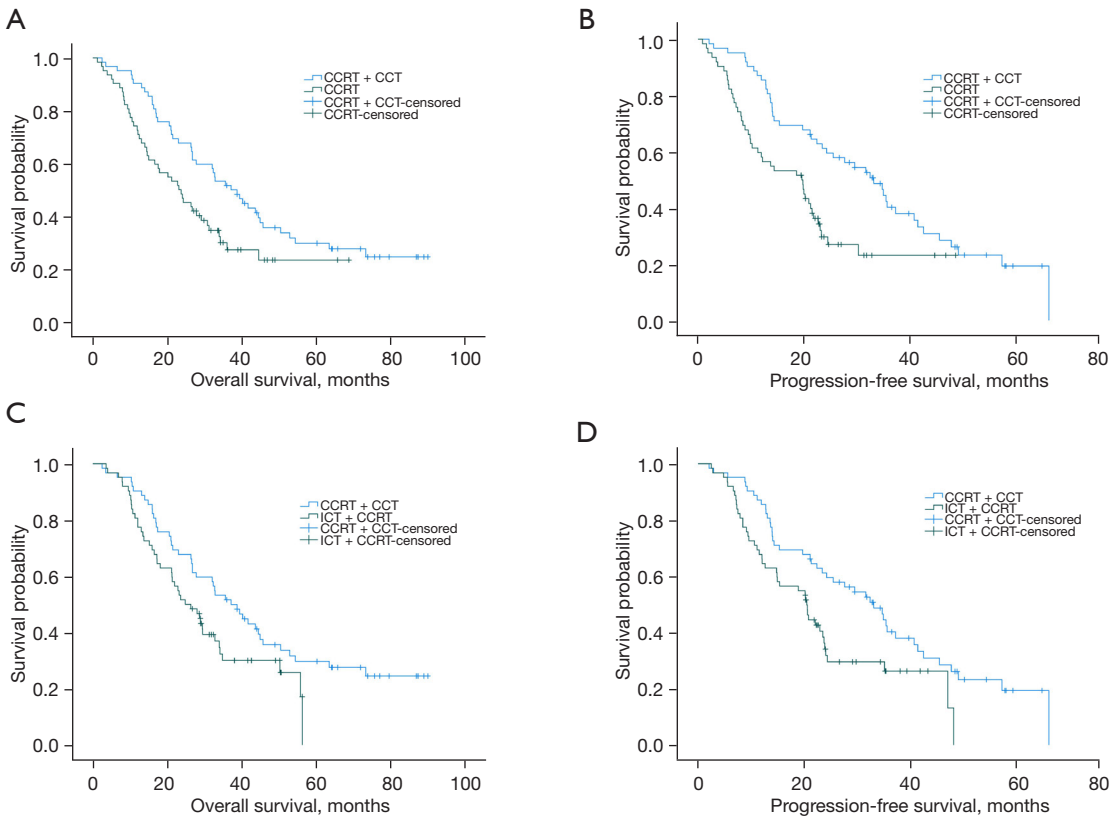

Figure 3 Kaplan-Meier curves of OS and PFS after PSM. (A) OS of CCRT + CCT *vs.* CCRT; (B) PFS of CCRT + CCT *vs.* CCRT; (C) OS of CCRT + CCT *vs.* ICT + CCRT; (D) PFS of CCRT + CCT *vs.* ICT + CCRT. ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT; OS, overall survival; PFS, progression-free survival.

between them, which are the same as our findings.

However, as far as we know, to date, there has not been a large multicenter randomized controlled trial to study this element. The advantages of this study over previous studies are that patients with all three treatment modalities were studied and compared at the same time, and that the doses of radiotherapy and chemotherapy were consistent across the groups in this study, leading to conclusions with some biases being avoided. There are also several limitations to this study. Firstly, this was a retrospective and single institution trial and might cause some bias. Secondly, our study compared the outcomes of CCRT, ICT + CCRT, and CCRT + CCT, but did not include an investigation of the combined regimen of ICT, CCRT, and CCT (ICT + CCRT + CCT). Thirdly, it is more interesting that how to determine cCR precisely after chemoradiation in order to omit surgery, which was the limitation in this study by the lack of information on cCR efficacy assessment. Fourthly, the choice of the three treatments was based on the choice of the doctor in charge at the time, and specific reasons are not available.

Conclusions

For inoperable ESCC patients, CCRT + CCT showed the best OS and PFS rates than ICT + CCRT and CCRT. There were no significant differences in treatment-related adverse events. lesion length, N-staging, and combination of radiotherapy and chemotherapy were the independent prognostic factors for OS and PFS.

Table 4 Univariate and multivariate Cox regression of prognostic factors for OS and PFS after PSM

Variables	Univariate Cox regression		Multivariate Cox regression	
	HR (95% CI)	P value	HR (95% CI)	P value
OS				
Gender (female *vs.* male)	1.171 (0.681–2.016)	0.57	–	–
Age (<60 *vs.* ≥60 years)	1.147 (0.750–1.754)	0.53	–	–
Location (MT/LT *vs.* C/UT)	1.197 (0.936–1.530)	0.15	–	–
Length on X-ray (<5 *vs.* ≥5 cm)	0.821 (0.756–0.904)	<0.001	0.911 (0.835–0.994)	0.04
T-staging (T3–4 *vs.* T1–2)	1.077 (0.776–1.496)	0.66	–	–
N-staging (N2–3 *vs.* N0–1)	1.597 (1.241–2.056)	<0.001	1.473 (1.176–1.844)	<0.001
Treatment options				
CCRT *vs.* CCRT + CCT	1.663 (1.082–2.557)	0.02	1.662 (1.071–2.579)	0.02
ICT + CCRT *vs.* CCRT + CCT	1.832 (1.184–2.835)	0.007	1.763 (1.129–2.755)	0.01
PFS				
Gender (female *vs.* male)	1.153 (0.669–1.988)	0.61	–	–
Age (<60 *vs.* ≥60 years)	1.098 (0.717–1.681)	0.67	–	–
Location (MT/LT *vs.* C/UT)	1.158 (0.904–1.484)	0.25	–	–
Length on X-ray (<5 *vs.* ≥5 cm)	0.820 (0.743–0.904)	<0.001	0.910 (0.832–0.993)	0.04
T-staging (T3–4 *vs.* T1–2)	1.125 (0.805–1.573)	0.49	–	–
N-staging (N2–3 *vs.* N0–1)	1.519 (1.185–1.946)	<0.001	1.429 (1.142–1.789)	0.002
Treatment options				
CCRT *vs.* CCRT + CCT	2.017 (1.300–3.128)	0.002	2.051 (1.309–3.215)	0.002
ICT + CCRT *vs.* CCRT + CCT	1.696 (1.098–2.620)	0.02	1.622 (1.041–2.530)	0.03

OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; MT, middle thoracic; LT, lower thoracic; C, cervical; UT, upper thoracic; ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; CCT, consolidation chemotherapy; ICT + CCRT, ICT followed by CCRT; CCRT + CCT, CCRT followed by CCT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-599/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-599/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics

Committee of the Fourth Hospital of Hebei Medical University (No. 20240214) and individual consent for this retrospective analysis was waived.

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