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Concurrent chemoradiotherapy versus radiotherapy alone for patients with locally advanced esophageal squamous cell carcinoma in the era of intensity modulated radiotherapy: a propensity score-matched analysis

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Abstract

Background: To investigate the survival benefit of concurrent chemoradiotherapy (CCRT) for patients with locally advanced esophageal squamous cell carcinoma (ESCC) during the years of intensity-modulated radiotherapy (IMRT).

Methods: Medical records of 1089 patients with ESCC who received IMRT from January 2005 to December 2017 were retrospectively reviewed. A total of 617 patients received CCRT, 472 patients received radiotherapy (RT) alone. Propensity score matching (PSM) method was used to eliminate baseline differences between the two groups. Survival and toxicity profile were evaluated afterward.

Results: After a median follow-up time of 47.9 months (3.2–149.8 months), both overall survival (OS) and progression-free survival (PFS) of the CCRT group were better than those of the RT alone group, either before or after PSM. After PSM, the 1-, 3-, and 5-year OS of RT alone and CCRT groups were 59.0% versus 70.2%, 27.7% versus 40.5% and 20.3% versus 33.1%, respectively (p < 0.001). The 1-, 3-, and 5-year PFS were 39.4% versus 49.0%, 18.3% versus 30.4% and 10.5% versus 25.0%, respectively (p < 0.001). The rates of ≥ grade 3 leukopenia and radiation esophagitis in the CCRT group were higher than that of RT alone group (p < 0.05). There was no significant difference in the probability of radiation pneumonitis between the two groups (p = 0.167). Multivariate Cox analysis indicated that female, EQD2 ≥60 Gy and concurrent chemotherapy were favorable prognostic factors for both OS and PFS.

Conclusions: Concurrent chemotherapy can bring survival benefits to patients with locally advanced ESCC receiving IMRT. For patients who cannot tolerate concurrent chemotherapy, RT alone is an effective alternative with promising results.

KEYWORDS
concurrent chemoradiotherapy, esophageal cancer, intensity-modulated radiotherapy, propensity score

INTRODUCTION

Esophageal cancer (EC) is a common malignancy with poor prognosis, and China is the country with the largest number of new cases and deaths every year. According to a national epidemiological research conducted in 2015,[1] the numbers of new diagnosed cases and deaths of esophageal cancer in China have reached 478 000 and 375 000, ranking third and fourth, respectively, among all malignant tumors. Unlike most Western countries, the pathological type of esophageal cancer in China is still dominated by squamous cell carcinoma (SCC), and patients with esophageal squamous cell carcinoma (ESCC) account for more than 90% of all EC patients.[2,3]

Because of insufficient promotion of annual endoscopy screening, a certain portion of patients in China present with advanced disease at diagnosis and are not suitable for esophagectomy. For these patients, definitive concurrent chemoradiotherapy (CCRT) has become the standard of care as recommended by most guidelines since the Radiation Therapy Oncology Group (RTOG) 85-01 study.[4–6] However, in clinical practice, a considerable number of RTOG 85-01 patients could not tolerate concurrent chemoradiation for various reasons (i.e., advanced age, poor general condition, poor nutritional status, obvious weight loss, patient refusion, etc.). For this group of patients, the most commonly used treatment is radiotherapy (RT) alone.

In the RTOG85-01 study, the 5-year survival rate of patients in the RT alone group was just 0, which indicates that RT alone is very ineffective in treating locally advanced EC. According to the clinical experience and some contemporary large retrospective analysis results,[7–9] however, the survival outcome of patients receiving RT alone is much better than that of RTOG 85-01. Besides, as a research started in the 1980s, RTOG 85-01 used the conventional two-dimensional radiotherapy (2DRT), whereas radiation techniques have been evolving rapidly in last few decades. The emergence of three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT) has greatly improved the conformality of dose distribution, making it possible to increase the dose of the planning target volume without increasing the irradiation dose to adjacent normal tissues.[10] Many studies have shown that advanced radiation techniques have reduced the incidence of side effects and improved the local control of EC patients.[11] Unfortunately, there are very limited reports on the survival and prognosis of patients receiving RT alone using the aforementioned advanced radiation technique (i.e., IMRT), and there are even fewer studies comparing the survival results of patients receiving RT alone with that of patients receiving CCRT in the era of IMRT.

Therefore, we conducted this retrospective study to collect data of patients receiving IMRT alone and compare with the survival of patients receiving CCRT in the same period, in the hope of providing a baseline reference of treatment standard and prognosis for patients with advanced EC.

METHODS

Patient eligibility

A total of 2180 EC patients who received IMRT at the Cancer Hospital of the Chinese Academy of Medical Sciences (CAMS) from 2005–2017 were included. The study was approved by the Independent Ethics Committee of Cancer Institute and Hospital, CAMS. Patients were excluded if they had: (1) planned or salvage esophagectomy ($n = 207$); (2) missing clinical data ($n = 22$); (3) missing follow-up data ($n = 23$) or <3 months follow-up time ($n = 67$); (4) distant metastasis at initial diagnosis ($n = 109$); (5) prior active malignancies (other than curable non-melanoma skin cancer or in situ cervical cancer) within 5 years ($n = 115$); (6) received sequential chemotherapy (either before or after radiotherapy) ($n = 124$); (7) received concurrent molecular target drugs ($n = 131$); (8) received palliative treatment (radiation dose <40 Gy or palliative radiation field) ($n = 54$); (9) histological types other than SCC (e.g., adenocarcinoma, small cell carcinoma, and so on; $n = 55$); (10) stage I–II disease ($n = 184$). After exclusions, 1089 patients stayed in the final analysis cohort (CCRT = 617, RT alone = 472) (Figure 1). It is worth mentioning that the American Joint Committee on Cancer (AJCC) staging manual adopted in this study was the 6th edition, and the included stage IVB patients were only patients with supraclavicular or abdominal (paracardial, left stomach, abdominal trunk) lymph node metastasis, whereas patients with more distant lymph node metastasis or organ metastases were not included.

Treatment

All patients received computed tomography (CT) simulation and IMRT, and their image data were registered in the treatment planning system (Pinnacle; Philips Medical Systems). The gross tumor volume (GTV-T) was defined as the primary tumor. The GTV-T would be determined using all available resources (physical examination, upper gastrointestinal contrast, endoscopy, endoscopic ultrasonography, contrast CT-thorax/abdomen, contrast magnetic resonance imaging (MRI)-thorax/abdomen, positron emission tomography-CT [PET-CT], etc.) The gross lymph nodes volume (GTV-N) was defined as any lymph node diagnosed as or highly suspected as metastatic. The clinical target volume (CTV) comprised of a 0.5–0.8 cm lateral margin and a 3.0 cm longitudinal margin around GTV, a 0.5 cm uniform margin around GTV-N, and relevant lymphatic drainage areas. Planning target volume (PTV) was derived from CTV plus a uniform 0.5 cm margin. The boost volume (PGTV) was created by expanding GTV-T by 1.0 cm craniocaudally and 0.5 cm radially, and the GTV-N by a uniform 0.5 cm margin.

The median dose of CCRT and RT alone group was 59.92 Gy (range: 40.0–70.0 Gy) and 60.0 Gy (range: 40.0–70.0 Gy), respectively. The prescription to PTV varies from 1.8 Gy/fraction to 2.2 Gy/fraction whereas the prescription
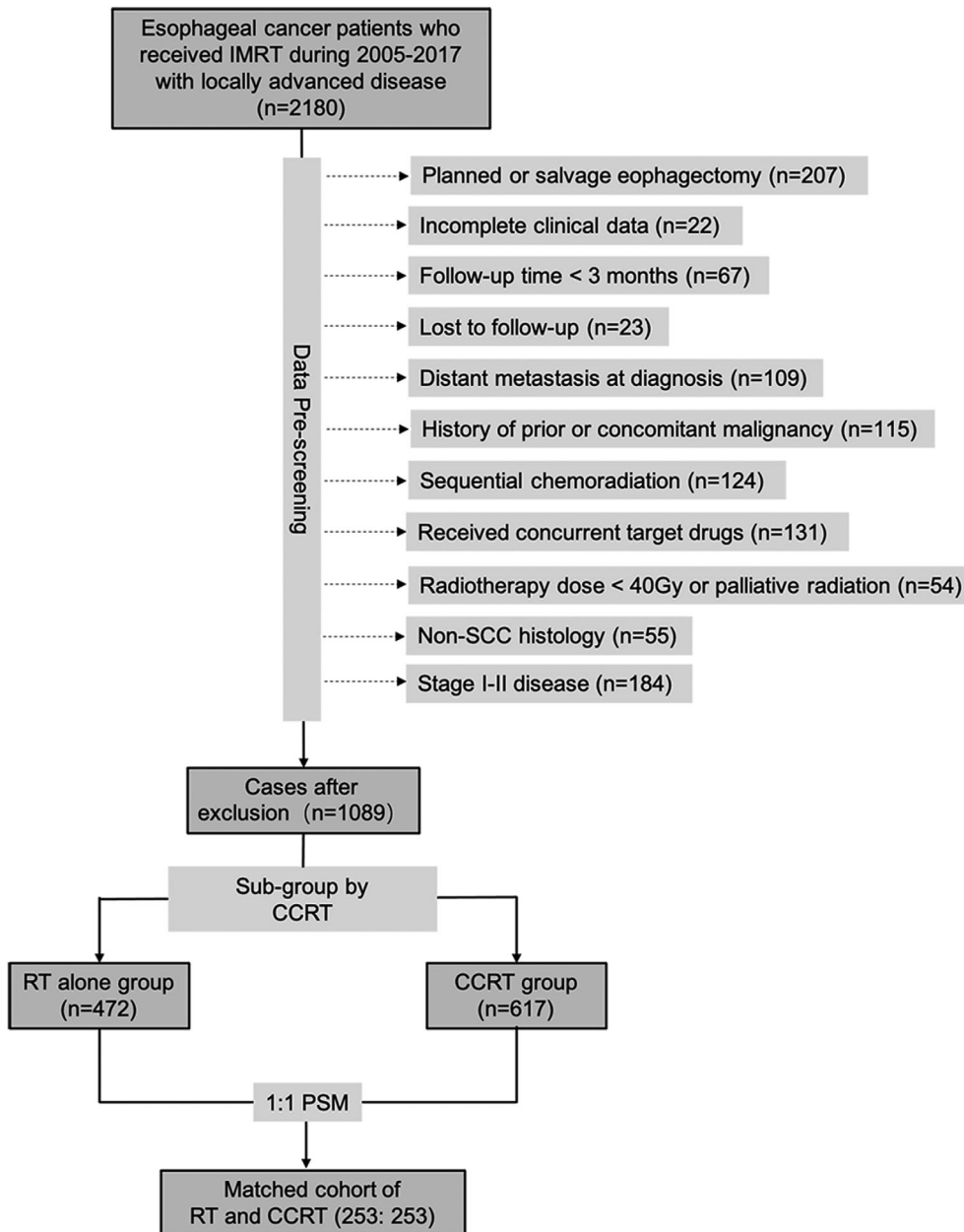
to PGTV varies from 2.0 Gy/fraction to 2.4 Gy/fraction (1 fraction per day, 5 fractions per week). Because the fractionation schemes have slight variations between patients, we converted the radiation dose of each patient into equivalent dose in 2.0 Gy/fration (EQD2) with an α/β of 10 in the final analysis.

It is required that at least 95% of the PTV received the prescribed dose. Dose volume histograms were adopted to assess the quality of the treatment plan and the exposure of organs at risk (OAR). The volume of lung tissue receiving 20 Gy or more should not exceed 28% of the total lung volume (V20 lung <28%). The mean dose of lung tissue should be lower than 16 Gy (D_{mean} lung <16 Gy). Other dose constraints to OARs include: V40 heart <30%, V30 heart <40%, V40 stomach <40%, D_{max} stomach <55–60 Gy, V40 small

intestine <40%, D_{max} small intestine <55 Gy, V30 liver <30%, V20 kidney <30%, and D_{max} spinal cord PRV < 45 Gy. Image-guided radiotherapy was applied to all patients either by electronic portal imaging device or cone beam computed tomography.

For patients receiving CCRT, the most commonly used concurrent chemotherapeutic regimen was the combination of taxane and platinum-based regimen ($n = 484$, 78.4%), followed by the combination of fluorouracil and platinum-based regimen ($n = 55$, 8.9%), and some patients also received single-agent fluorouracil ($n = 64$, 10.4%) or platinum ($n = 9$, 1.5%) for concurrent chemotherapy. For more detailed chemotherapy regimens before and after PSM, please refer to Table S1.

The most common reasons for not receiving concurrent chemotherapy include: (1) obvious weight loss before

treatment, weak general condition, and poor performance status; (2) elderly patients; (3) serious cardiopulmonary complications or insufficient hepatic or renal functions; and (4) patients' or relatives' refusal.

Follow-up and outcome measures

In brief, patients were assessed every 3 months for the first 2 years after RT, every 6 months for the next 3 years, and then once annually. Assessments included barium esophagram; CT of neck, chest and upper abdomen with contrast; ultrasonography of the neck and upper abdomen; and conventional blood and biochemistry studies. PET-CT and fine-needle aspiration cytology were performed if needed. Bone scan was performed in case of bone pain or abnormally elevated serum alkaline phosphatase, and cranial MRI was performed if clinically indicated.

Overall survival (OS) was measured as the interval between the beginning of RT to the date of death from any cause or final follow-up. Progression-free survival (PFS) was defined as the interval between the end of RT and the date of first recurrence or death from any cause. Patients who had not experienced progression or death by the last follow-up were administratively censored. Acute and late toxicities were scored according to the Common Toxicity Criteria for Adverse Events, version 4.0.[12]

Statistical analysis

Descriptive statistics, including frequencies and percentages for categorical variables, and mean and standard deviation for quantitative variables, were computed to summarize patient characteristics for the entire cohort and for each treatment group. Between-group comparisons to evaluate imbalances in covariates were conducted using t-tests and χ^2 test for quantitative and categorical variables, respectively.

To adjust unbalanced covariates, propensity score matching (PSM) method was used.[13] The propensity score for each patient was estimated with a logit model that included the following variables: age, sex, Karnofsky performance score (KPS), tumor-node-metastasis (TNM) stage, tumor location, radiation dose and the year of diagnosis. Setting caliper = 0.10, matching ratio = 1:1, two comparable groups of patients were created with 253 patients in each group.

OS time and PFS time were estimated using Kaplan–Meier (KM) plots and compared by log-rank test. Cox regression model was used to perform multivariate analyses of the effect of covariates on OS and PFS. The results of the Cox models were expressed as hazard ratios (HRs) along with the 95% confidence intervals (95% CIs). The incidence of toxicities was compared by χ^2 test and Fisher's exact test. The significance level was set as p-value <0.05. All computations were conducted in R 2.13.0.

RESULTS

Patient and treatment characteristics

A total of 1089 patients were involved in this study, including 617 patients in the CCRT group and 472 patients in the RT alone group. The majority of patients received static IMRT (82.2%), and 17.7% patients received volumetric-modulated arc therapy (VMAT). The patient, tumor, and treatment characteristics were summarized in Table 1.

Patients in CCRT group were more likely to be younger (59 years old [median age] for CCRT vs. 71 years old [median age] for RT alone, $p < 0.001$), male (86.5% for CCRT vs. 78.0% for RT alone, $p < 0.001$), to have better performance status (4.2% KPS ≤70 for CCRT vs. 16.3% for RT alone, $p < 0.001$), to have M+ stage (M+ 35.0% vs. 21.2%, $p < 0.001$) and advanced TNM stage (stage IV 35.0% vs. 21.2%, $p < 0.001$), to be diagnosed at more recent times (2011–2017 84.1% vs. 70.3%, $p < 0.001$).

The propensity score–matched cohort included 253 patients in the CCRT group and 253 patients in the RT alone group, and all the selected covariates were well-balanced between the two matched groups (see Table 1).

Survival results

The median follow-up time of the whole cohort of surviving patients was 47.9 months (3.2–149.8 months), of which 47.9 months (3.2–149.8 months) in the CCRT group and 47.7 months (4.2–124.9 months) in the RT alone. Median OS time of the entire cohort was 18.8 months (95% CI, 17.2–20.4 months), and the median PFS time was 10.3 months (95% CI, 9.3–11.4 months). For patients receiving RT alone, the 1-, 3-, and 5-year OS rates before PSM were 60.5%, 27.7%, and 20.9%, respectively. The 1-, 3-, and 5-year PFS rates were 41.3%, 18.7%, and 12.2%, respectively.

The addition of concurrent chemotherapy has further improved both OS and PFS. Figure 2 presents the survival curves comparing RT alone with CCRT both before and after PSM. Compared with the RT alone group, the CCRT group had better OS and PFS rates whether before or after PSM (before-match OS: log-rank $p < 0.001$ [Figure 2(a)]; after-match OS: log-rank $p < 0.001$ [Figure 2(b)]; before-match PFS: log-rank <0.001 [Figure 2(c)]; after-match PFS: log-rank $p < 0.001$ [Figure 2(d)]).

Among the 253 matched pairs in the PSM sample, the adjusted median OS was longer in the CCRT group (21.8 months; 95% CI 16.5–27.2 months) compared with the RT alone group (15.0 months; 95% CI 12.5–17.5 months). The adjusted median PFS was also longer in the CCRT group (11.6 months; 95% CI 8.9–14.2 months) compared with the RT alone group (7.9 months; 95% CI 6.8–8.9 months). In the after-matched cohort, the 1-, 3-, and 5-year OS rates of RT alone and CCRT group were 59.0% versus 70.2%, 27.7% versus 40.5%, and 20.3% versus 33.1%, respectively. For PFS rates, the 1-, 3-, and 5-year PFS rates

TABLE 1 Patient, tumor, and treatment characteristics before and after PSM

Variables	Overall n = 1089	%	Before matching RT alone n = 472	%	CCRT n = 617	%	p	After matching RT alone n = 253	%	CCRT n = 253	%	p
Age	63 (29–89)		71 (41–89)		59 (29–81)		<0.001	61 (40–69)		61 (33–69)		1.000
<70 years	789	72.5	220	46.6	569	92.2		208	82.2	208	82.2	
≥70 years	300	27.5	252	53.4	48	7.8		45	17.8	45	17.8	
Sex							<0.001					1.000
Male	902	82.8	368	78.0	534	86.5		209	82.6	209	82.6	
Female	187	17.2	104	22.0	83	13.5		44	17.4	44	17.4	
KPS							<0.001					0.658
≤70	103	9.5	77	16.3	26	4.2		27	10.7	24	9.5	
>70	986	90.5	395	83.7	591	95.8		226	89.3	229	90.5	
Tumor location							0.411					0.569
Cervical	36	3.3	17	3.6	19	3.1		9	3.6	5	2.0	
Upper	322	29.6	129	27.3	193	31.3		78	30.8	85	33.6	
Middle	540	49.6	246	52.1	294	47.6		129	51.0	121	47.8	
Lower	191	17.5	80	16.9	111	18.0		37	14.6	42	16.6	
T stage							0.595					0.306
T1	10	0.9	3	0.6	7	1.1		2	0.8	0	0.2	
T2	32	2.9	12	2.5	20	3.2		9	3.6	5	2.0	
T3	503	46.2	221	46.8	282	45.7		106	41.9	117	46.2	
T4	542	49.8	236	50.0	306	49.6		136	53.8	130	51.4	
TX	2	0.2	0	0.0	2	0.3		0	0.0	1	0.2	
N stage							0.110					0.315
N0	74	6.8	40	8.5	34	5.5		19	7.5	16	6.3	
N1	1012	92.9	430	91.1	582	94.3		232	91.7	237	93.7	
NX	3	0.3	2	0.4	1	0.2		2	0.8	0	0.0	
M stage							<0.001					0.448
M0	773	71.0	372	78.8	401	65.0		189	74.7	188	74.3	
M1a	120	11.0	35	7.4	85	13.8		17	6.7	24	9.5	
M1b	196	18.0	65	13.8	131	21.2		47	18.6	41	16.2	
TNM stage (6th)							<0.001					0.418
III	772	70.9	372	78.8	401	65.0		189	74.7	188	74.3	
IVA	121	11.1	36	7.6	85	13.8		17	6.7	24	9.5	
IVB	196	18.0	64	13.6	131	21.2		47	18.6	41	16.2	
Year of diagnosis							<0.001					0.762
2005–2010	238	21.9	140	29.7	98	15.9		65	25.7	68	26.9	
2011–2017	851	78.1	332	70.3	519	84.1		188	74.3	185	73.1	
Radiation technique							0.271					0.660
Static IMRT	886	81.4	393	83.3	493	79.9		203	80.2	199	78.7	
VMAT	202	18.5	79	16.7	123	19.9		50	19.8	54	21.3	
Tomo	1	0.1	0	0.0	1	0.2		0	0.0	0	0.0	
EQD2							0.223					0.112
<60 Gy	295	27.1	119	25.2	176	28.5		62	24.5	78	30.8	
≥60 Gy	794	72.9	353	74.8	441	71.5		191	75.5	175	69.2	

Abbreviations: CCRT, concurrent chemoradiotherapy; EQD2, equivalent dose in 2 Gy/fraction; IMRT, intensity-modulated radiotherapy; KPS, Karnofsky performance score; PSM, propensity score matching; RT, radiotherapy; Tomo, tomotherapy; VMAT, volumetric-modulated arc therapy.
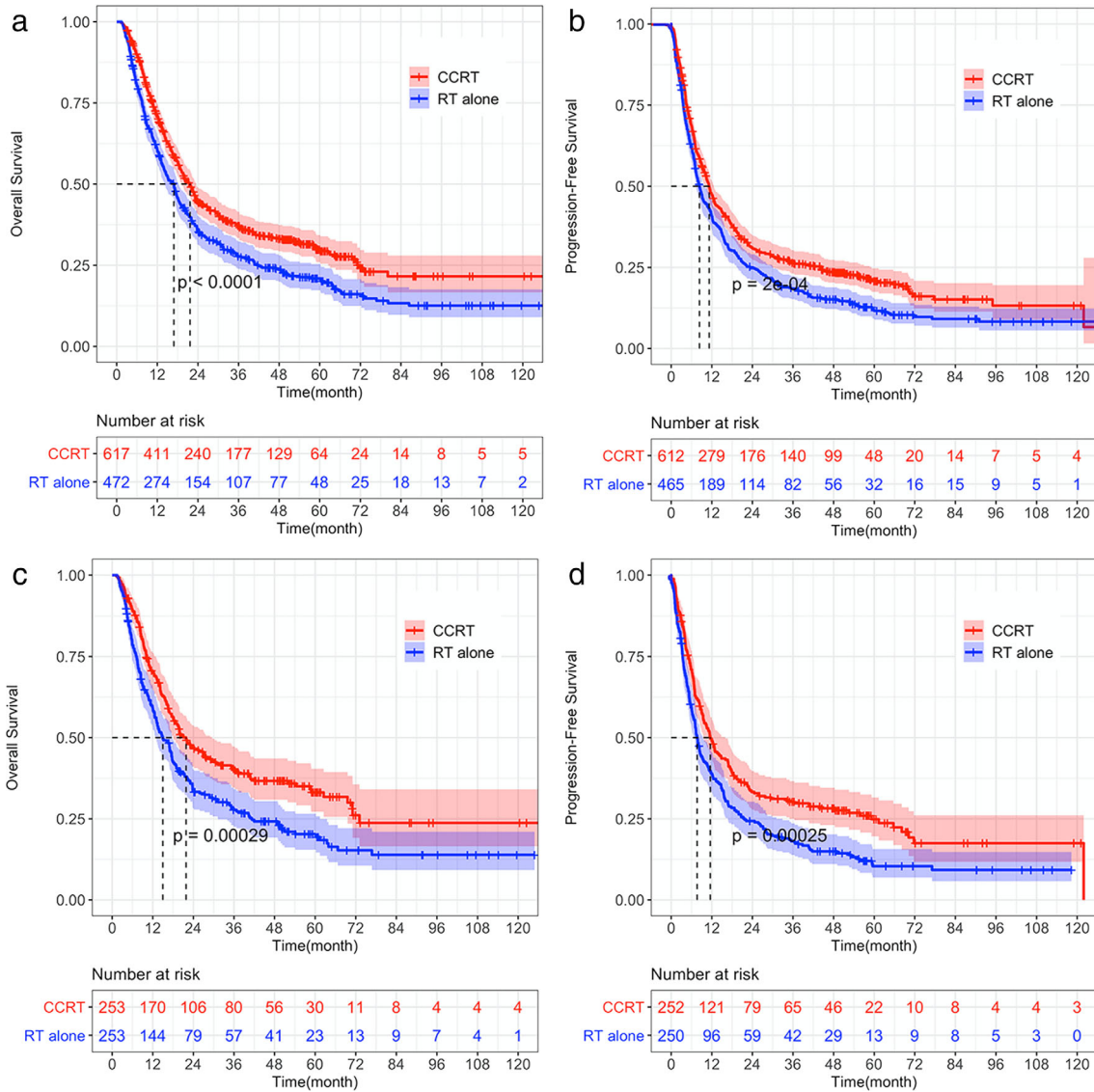
FIGURE 2 OS and PFS of patients receiving RT and CCRT both before and after PSM. Kaplan–Meier (KM) estimates of (a) OS before PSM, with 95% CIs. (b) OS after PSM, with 95% CIs. (c) PFS before PSM, with 95% CIs. (d) PFS after PSM, with 95% CIs. Blue curve represents survival in the RT alone group; red curve, survival in the CCRT group

of RT alone and CCRT group were 39.4% versus 49.0%, 18.3% versus 30.4%, and 10.5% versus 25.0%, respectively.

Subgroup analysis

To further explore the potential beneficiaries of concurrent chemotherapy, we conducted several subgroup analyses of OS in the PSM sample (Table 2). Results showed that male ($p = 0.001$), age <70 years ($p < 0.001$), stage III ($p < 0.001$) patients, patients with middle ($p = 0.023$) or lower ($p = 0.020$) thoracic disease, and patients diagnosed between 2011 and 2017 ($p < 0.001$) could benefit from CCRT. Besides, patients also benefit from CCRT no matter their KPS >70 ($p = 0.002$) or ≤70 ($p = 0.039$), EQD2 ≥60 Gy ($p = 0.003$) or <60 Gy ($p = 0.008$), received static IMRT

($p = 0.023$) or VMAT ($p < 0.001$). Marginal survival difference was observed between RT alone and CCRT group in female ($p = 0.059$) and stage IVB patients ($p = 0.074$). Figure 3 shows the subgroup analysis of age. Among the 506 paired patients, the vast majority were non-elderly patients ($n = 416$). Among 90 elderly patients (age over 70 years) in the matched sample, CCRT did not show survival benefit over RT alone ($p = 0.808$). In non-elderly patients, the OS rate of the CCRT group was better than that of the RT alone group ($p < 0.001$).

Multivariate analyses in after-PSM cohort

The multivariate Cox regression analysis for OS and PFS after PSM is summarized in Table 3. Factors that related to

TABLE 2 Subgroup comparisons of OS between CCRT and RT alone group in the after-match cohort
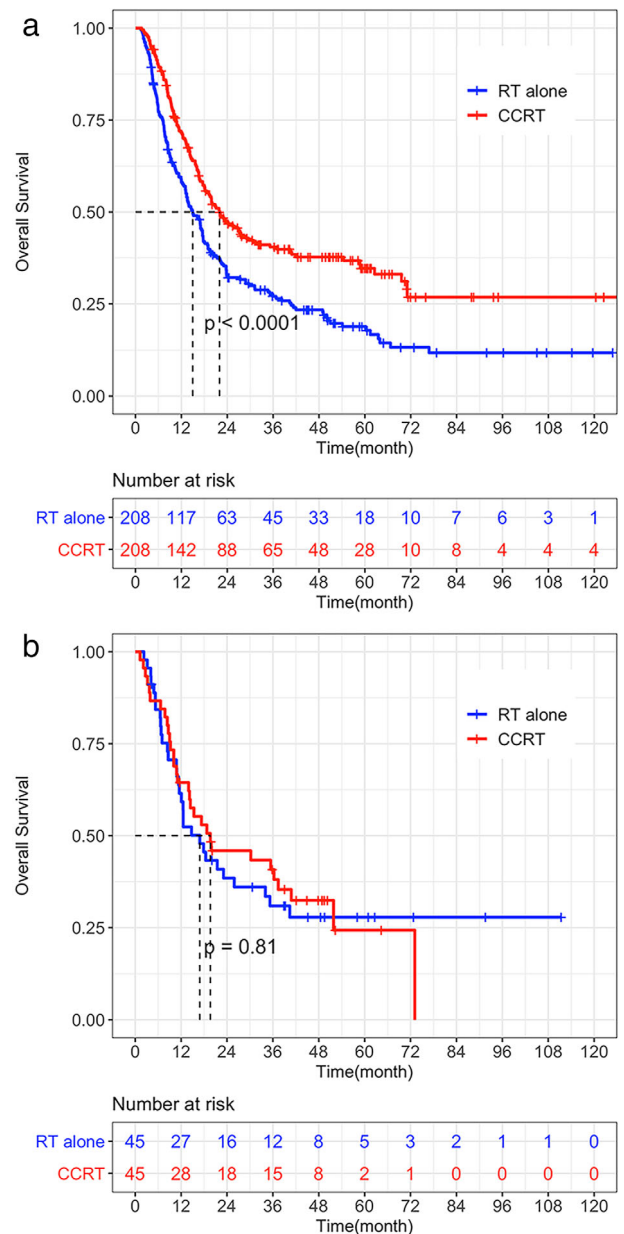
Variables	RT alone n (%)	CCRT n (%)	p
Age			
<70 years	208 (82.2)	208 (82.2)	0.000
≥70 years	45 (17.8)	45 (17.8)	0.808
Sex			
Male	209 (82.6)	209 (82.6)	0.001
Female	44 (17.4)	44 (17.4)	0.059
KPS			
≤70	27 (10.7)	24 (9.5)	0.039
>70	226 (89.3)	229 (90.5)	0.002
Tumor location			
Cervical	9 (3.6)	5 (2.0)	0.422
Upper	78 (30.8)	85 (33.6)	0.023
Middle	129 (51.0)	121 (47.8)	0.020
Lower	37 (14.6)	42 (16.6)	0.155
TNM stage (6th)			
III	189 (74.7)	188 (74.3)	0.000
IVA	17 (6.7)	24 (9.5)	0.482
IVB	47 (18.6)	41 (16.2)	0.074
Radiation technique			
Static IMRT	203 (80.2)	199 (78.7)	0.023
VMAT	50 (19.8)	54 (21.3)	0.000
Y of diagnosis			
2005–2010	65 (25.7)	65 (25.7)	0.572
2011–2017	188 (74.3)	188 (74.3)	0.000
EQD2			
<60 Gy	62 (24.5)	78 (30.8)	0.008
≥60 Gy	191 (75.5)	175 (69.2)	0.003

Abbreviations: CCRT, concurrent chemoradiotherapy; EQD2, equivalent dose in 2 Gy per fractions; IMRT, intensity-modulated radiotherapy; KPS, Karnofsky performance score; OS, overall survival; RT, radiotherapy; VMAT, volumetric-modulated arc therapy.

FIGURE 3 Subgroup analysis of patients receiving RT and CCRT in the after-PSM sample. Kaplan–Meier (KM) estimates of OS of (a) elderly patients (≥70 years old). (b) Non-elderly patients (<70 years old). Blue curve represents survival in the RT alone group; red curve, survival in the CCRT group

promising survival included female (OS: HR = 0.59, 95% CI 0.43–0.80, $p = 0.001$; PFS: HR = 0.65, 95% CI 0.49–0.86, $p = 0.003$), concurrent chemotherapy (OS: HR = 0.63, 95% CI 0.51–0.78, $p < 0.001$; PFS: HR = 0.66, 95% CI 0.54–0.81, $p < 0.001$) and EQD2 ≥ 60 Gy (OS: HR = 0.67, 95% CI 0.53–0.78, $p = 0.001$; PFS: HR = 0.71, 95% CI 0.57–0.88, $p = 0.002$). Factors that related to inferior survival was stage IVA or IVB disease. Survival did not differ by age (<70 vs. ≥70 years), KPS, tumor location, radiation technique, or year of diagnosis.

Toxicities

We further compared the profile of treatment-related toxicities between RT alone and CCRT group in the matched cohort. As shown in Table 4, the incidences of greater than or equal to grade 2 thrombocytopenia, greater than or equal to grade 2/3 leukopenia, and radiation esophagitis in the CCRT group were significantly higher than those in the RT alone group (all of which $p < 0.05$). The most common grade 3–4 toxicities were leucopenia (12.4%) and radiation esophagitis (10.9%) in the CCRT group, whereas the most common grade 3–4 toxicity in the RT alone group was radiation esophagitis (5.9%). There were five and three cases of treatment-related deaths in the CCRT and RT alone group respectively, all of which were attributed to grade 5 radiation

TABLE 3 Results of multivariate Cox analysis for PFS and OS in the after-PSM cohort

Variables	PFS HR (95% CI)	p	OS HR (95% CI)	p
Age				
<70 years	1 (Ref)	–	1 (Ref)	–
≥70 years	0.89 (0.69–1.17)	0.409	0.90 (0.67–1.20)	0.456
Sex				
Male	1 (Ref)	–	1 (Ref)	–
Female	0.65 (0.49–0.86)	0.003	0.59 (0.43–0.80)	0.001
KPS				
≤70	1 (Ref)	–	1 (Ref)	–
>70	0.75 (0.55–1.03)	0.073	0.73 (0.53–1.02)	0.061
Tumor location		0.867		0.723
Cervical	1 (Ref)	–	1 (Ref)	–
Upper	0.94 (0.47–1.87)	0.851	0.94 (0.47–1.88)	0.858
Middle	0.89 (0.45–1.77)	0.747	0.87 (0.44–1.72)	0.681
Lower	0.94 (0.46–1.93)	0.864	1.03 (0.50–2.11)	0.944
TNM stage (6th)		0.001		0.001
III	1 (Ref)	–	1 (Ref)	–
IVA	1.72 (1.20–2.45)	0.003	1.76 (1.22–2.55)	0.003
IVB	1.38 (1.06–1.80)	0.017	1.44 (1.09–1.90)	0.010
Y of diagnosis				
2005–2010	1 (Ref)	–	1 (Ref)	–
2011–2017	1.27 (0.99–1.62)	0.058	1.11 (0.86–1.44)	0.406
Radiation technique				
Static IMRT	1 (Ref)	–	1 (Ref)	–
VMAT	1.07 (0.82–1.40)	0.600	1.08 (0.81–1.45)	0.601
EQD2				
<60 Gy	1 (Ref)	–	1 (Ref)	–
≥60 Gy	0.71 (0.57–0.88)	0.002	0.67 (0.53–0.85)	0.001
Concurrent chemotherapy	0.66 (0.54–0.81)	<0.001	0.63 (0.51–0.78)	<0.001

Abbreviations: 95% CI, 95% confidence interval; EQD2, equivalent dose in 2 Gy per fractions; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; OS, overall survival; PFS, progression-free survival; PSM, propensity score matching; VMAT, volumetric-modulated arc therapy; Tomo, tomotherapy.

pneumonitis. No significant difference was seen in the incidences of radiation pneumonitis between the two groups ($p = 0.167$).

DISCUSSION

Our research confirms the efficacy of concurrent chemotherapy in treating patients with locally advanced ESCC by combining with IMRT. According to the matched results, the 5-year OS of the CCRT group was as high as 33.1%, and the concurrent chemotherapy increased the 1-, 3-, and 5-year OS rates of RT alone group by 11.2%, 12.8%, and 12.8%, and the 1-, 3-, and 5-year PFS rates by 9.6%, 12.1%, and 14.5%, respectively. Although the incidence of toxicities also increased accordingly, the general incidence of grade 3–4 toxicities in the CCRT group was still within the acceptable range (the most common grade 3–4 side effects is

leukopenia, with a 12.4% incidence). Besides, CCRT did not increase the incidence of radiation-related pneumonitis or treatment-related mortality, indicating that for patients with locally advanced ESCC, definitive IMRT concurrent with chemotherapy are safe and tolerable.

In the subgroup analysis, for elderly patients (age 70 years or older), CCRT did not show a significant survival advantage over RT alone. This result is consistent with some recently published retrospective analyses of elderly patients.[14] This can be related to the poor tolerance of elderly patients for CCRT. In our study, of 45 patients over 70 years old that received CCRT, only 28.9% received dual-drug chemotherapy of taxane and platinum-based compounds, whereas 68.9% of patients received single-agent fluorouracil, which is significantly different from the chemotherapeutic regimens received by patients under 70 years old (89.9% patients received dual-drug chemotherapy). One should note that there is still lack of consensus on the

TABLE 4 Treatment-related toxicities of RT alone and CCRT groups in the after-PSM cohort

Toxicities	RT alone (%)	CCRT (%)	p
Anemia			0.142
Grade 1–2	16.2	22.4	–
Grade 3–4	0.4	0.8	–
Grade 5	0.0	0.0	–
≥Grade 2	3.2	6.8	0.069
≥Grade 3	0.4	0.8	0.216
Leukopenia			0.000
Grade 1–2	44.9	65.6	–
Grade 3–4	0.8	12.4	–
Grade 5	0.0	0.0	–
≥Grade 2	13.4	51.6	0.000
≥Grade 3	0.8	12.4	0.000
Thrombocytopenia			0.000
Grade 1–2	9.7	22.4	–
Grade 3–4	0.0	1.6	–
Grade 5	0.0	0.0	–
≥Grade 2	2.0	8.4	0.001
≥Grade 3	0.0	1.6	0.124
Esophagitis			0.002
Grade 1–2	69.5	75.8	–
Grade 3–4	5.9	10.9	–
Grade 5	0.0	0.0	–
≥Grade 2	40.2	50.4	0.023
≥Grade 3	5.9	10.9	0.046
Skin reaction			0.002
Grade 1–2	54.0	66.5	–
Grade 3–4	2.5	4.9	–
Grade 5	0.0	0.0	–
≥Grade 2	16.0	19.2	0.364
≥Grade 3	2.5	4.9	0.171
Pneumonitis			0.167
Grade 1–2	2.1	3.3	—
Grade 3–4	0.0	1.6	—
Grade 5	1.3	2.1	—
≥Grade 2	1.3	4.5	0.054
≥Grade 3	1.3	3.7	0.141

Abbreviations: CCRT, concurrent chemoradiotherapy; PSM, propensity score matching; RT, radiotherapy.

optimal treatment option for elderly patients with EC, and corresponding prospective randomized studies are needed to further explore the role of concurrent chemotherapy in elderly patients, as well as the best concurrent chemotherapy regimen and other issues.

Since the publication of RTOG 94-05[15] study, however, 50.4 Gy became the recommended radiation dose for EC patients receiving non-surgical treatment, physicians of our center are still more accustomed to applying higher dose prescriptions. In our multivariate Cox analysis after PSM, a higher radiation dose (EQD2 ≥60 Gy) was found to be an independent protective prognostic factor for both OS and PFS. RTOG 94-05 is a research conducted in the era of 2DRT. In recent years, the emergence of more advanced radiation techniques (3DCRT, IMRT, etc.) have made it possible to increase the dose of target volumes while reducing the exposure of adjacent normal tissues.[10,11] Numerous recently published retrospective analysis studies[16,17] and meta-analysis[18] also showed that patients with ESCC may benefit from high-dose radiotherapy. Chang et al.[17] analyzed 2061 patients with ESCC received IMRT-based CCRT registered in the Taiwan Cancer Registry database, 927 of whom received ≥60 Gy whereas 1134 patients received <60 Gy. Results showed that ≥60 Gy IMRT was a significant independent prognostic factor for OS (adjusted HR = 0.75; 95% CI, 0.63–0.83; $p < 0.0001$). Chen et al.[16] used PSM method to compare the survival of 253 ESCC patients receiving high-dose radiotherapy (≥60 Gy) and 241 patients receiving low-dose radiotherapy (50–50.4 Gy). The HR of death when high dose was compared to low dose was 0.75 (95% CI, 0.64–0.88). At present, a series of prospective clinical trials[19–22] applying simultaneous integrated boost-IMRT are in progress. Their results confirmed the safety and feasibility of high-dose IMRT concurrent with chemotherapy in patients with EC, and satisfactory local control and OS has been achieved.

It is true that the proportion of patients receiving concurrent chemotherapy in this study is relatively low when compared with most contemporaneous large-scale real-world reports in developed countries.[23] We have done a multivariable logistic regression analysis to assess factors that may affect the receipt of concurrent chemotherapy, and the results showed that age, KPS, TNM stage, and year of diagnosis were factors related to the receipt of CCRT (Table S2). In addition, we suppose that this phenomenon may also related to the advanced TNM stage, large tumor burden, poor general condition, and poor economic status of patients treated in our center. However, our research also confirmed that relatively satisfactory survival rates could be achieved even with IMRT alone for patients with locally advanced ESCC. In the pre-matched original sample, a total of 472 patients received IMRT alone as the radical treatment, the 1-, 3-, and 5-year OS rates of whom were 60.5%, 27.7%, and 20.9%, indicating the efficacy of RT alone in treating patients with advanced ESCC. Our results are consistent with other recently published researches,[24,25] and show a much better survival than that with patients treated by 2DRT.[7] All these results suggest that for patients with locally advanced ESCC who cannot receive CCRT, RT alone can be an effective and safe alternative with promising survival results.

There were several limitations associated with this study. First, this is a retrospective analysis. However, we mimicked randomization through propensity score matching, which eliminated potential bias by creating two comparable groups. Second, this was a single-institution study. However, the large sample size enhanced the reliability of the results.

In conclusion, this study confirmed the safety and efficacy of concurrent chemotherapy in patients with locally advanced ESCC receiving non-surgical treatment in the era of IMRT. For some patients who cannot receive or tolerate concurrent chemotherapy for various reasons, IMRT alone could bring promising survival results as an alternative option.

CONFLICT OF INTEREST

No authors report any conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.