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Reduction in chemotherapy relative dose intensity decreases overall survival of neoadjuvant chemoradiotherapy in patients with locally advanced esophageal carcinoma

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Abstract

Background Many patients undergo dose reduction or early termination of chemotherapy to reduce chemoradiotherapy-related toxicity, which may increase their risk of survival. However, this strategy may result in underdosing patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC). This study aimed to analyze the relationship between the relative dose intensity (RDI) and survival outcomes in patients with LA-ESCC.

Methods This retrospective study assessed patients with LA-ESCC (cT2N + M0, cT3-4NanyM0) receiving neoadjuvant chemoradiotherapy (NCRT) with curative-intent esophagectomy. The patients received 2 courses of paclitaxel plus carboplatin (TC) combination radiotherapy prior to undergoing surgery. During NCRT, RDI was computed, defined as the received dose as a percentage of the standard dose, and the incidence of dose delays was estimated (≥ 7 days in any course cycle). The best RDI cutoff value (0.7) was obtained using ROC curve. The Kaplan–Meier survival curves were compared using the log-rank test, the treatment effect was measured using hazard ratios (HR) and 95% confidence intervals (CI).

Results We included 132 patients in this study, divided into RDI < 0.7 and RDI ≥ 0.7 groups using cut-off value of 0.7. RDI grade was an independent prognostic factor for OS. Baseline demographic and clinical characteristics were well balanced between the groups. There was no evidence that patients with RDI < 0.7 experienced less toxicity or those with RDI ≥ 0.7 resulted in more toxicity. However, patients with RDI < 0.7 who were given reduced doses had a worse overall survival [HR 0.49, 95% CI 0.27–0.88, $P = 0.015$]. The risk of a lower RDI increased with a longer dose delay time ($P < 0.001$).

Conclusion The RDI below 0.7 for avoiding chemoradiotherapy toxicity administration led to a reduction in the dose intensity of treatment and decreased overall survival.

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Keywords Esophageal cancer (ESCC), Locally advanced esophageal cancer (LA-ESCC), Neoadjuvant chemoradiotherapy (NCRT), Paclitaxel plus carboplatin regimen (TC), Relative dose intensity (RDI), Adverse events (AEs), Overall survival (OS)

Introduction

Esophageal cancer ranks as the eighth most common form of malignancy and the sixth leading cause of cancer-related deaths globally [1]. In Asian countries, notably China and Japan, esophageal squamous cell carcinoma (ESCC) is the predominant histological subtype, with locally advanced disease being the most prevalent stage among newly diagnosed patients [2]. Neoadjuvant chemoradiotherapy (NRCT) has become established as the standard treatment approach for non-metastatic but locally advanced esophageal squamous cell carcinoma (LA-ESCC) with curative intent [3–5].

Since the publication of the CROSS trial, the paclitaxel plus carboplatin (TC) chemotherapy regimen has been extensively utilized in neoadjuvant chemoradiotherapy for LA-ESCC [6]. The TC regimen has gained considerable popularity owing to its minimal toxicity. Our retrospective analysis demonstrated that the TC regimen is a safe and effective (equivalent) alternative to the paclitaxel plus cisplatin (TP) regimen for NCRT in patients with LA-ESCC [7]. Over the past decade, the focus of NCRT is the efficacy and safety of different chemotherapy regimens [7, 8]; however, little research has been conducted on chemotherapy dose in NCRT for patients with LA-ESCC.

Relative dose intensity (RDI) has recently emerged as an important measure that reflects the tolerability and degree of adherence to chemotherapy regimens [9]. RDI is defined as the ratio of the received dose intensity to the prescribed dose intensity, measured as the amount of drug delivered per unit time [10]. Clinical evidence suggests that improved outcomes can be achieved by using standard chemotherapy regimens in a dose-dependent manner. Patients who receive higher dose intensities tend to experience improved overall survival (OS), progression-free survival (PFS), and disease-free survival compared to those who receive lower dose intensities than planned [11]. RDI less than 85% is considered to be a clinically significant reduction from standard or planned therapy [12]. However, dose delays and reductions are common methods for mitigating chemotherapy-induced side effects. Despite the fact that maintaining RDI is important to achieve improved outcomes, a substantial proportion of patients are administered less than 85% of the recommended dose, and research indicates that less than half of patients receive the 85% suggested RDI dose [13].

Sufficient chemotherapy dose improves the clinical outcomes of various malignancies [14, 15]. However, few studies have explored the optimal strategy for the dose intensity of NCRT chemotherapy in patients with LA-ESCC. To explore the rationale for chemotherapy RDI in ESCC, we retrospectively analyzed the survival and toxicity of TC chemotherapy regimens with different dose intensities as neoadjuvant treatment for patients with resectable LA-ESCC.

Method

Patients

We conducted a retrospective review of patients with LA-ESCC who underwent NCRT followed by surgery at Sichuan Cancer Hospital and Institute between May 2017 and June 2021. Inclusion criteria were as follows: (1) A resectable LA-ESCC (cT1-2N + M0 or cT3–cT4NanyM0) as determined by the American Joint Committee on Cancer^{8th} edition [16]; (2) a score of 0 or 1 on the new Eastern Cooperative Oncology Group (ECOG) performance scale [17]; (3) following NCRT, resectional surgery was performed on patients; and (4) administration of TC chemotherapy regimen. Exclusion criteria were as follows: (1) prior treatment for primary tumors or nodes; (2) non-squamous cell carcinomas (including adenocarcinoma or small cell carcinoma); (3) patients who received chemotherapy alone, radiotherapy alone, or no treatment prior to surgery; and (4) patients did not complete standard chemotherapydue to personal reasons. The Institutional Review Board of Sichuan Cancer Hospital approved this retrospective study.

Chemoradiotherapy regimens

The chemotherapy regimen consisted of a paclitaxel dose of 135 mg/m^2 (day 1), while carboplatin administered at an area under the curve of AUC = 4 mg/mL/min (day 1) at weeks one and four, spanning two cycles. Chemotherapy dosages and any necessary adjustments were determined under the supervision of medical oncologists. The delineation of the gross tumor volume (GTV) was based on clinical imaging modalities such as esophagoscopy, computed tomography (CT), and positron emission tomography-CT. In these 132 patients, 7 patients underwent positron emission tomography-CT. The clinical target volume (CTV) encompassed the GTV plus a 2–3 cm margin in the cranial-caudal direction and a 0.5 cm margin in the transverse plane, ensuring that the

CTV boundary did not extend beyond anatomical constraints such as blood vessels. The median total radiotherapy dose was 40 Gy (2.0 Gy/fraction). Concurrently, intensity-modulated radiotherapy commenced with the initial chemotherapy cycle and continued for five days a week for 4–5 weeks of radiotherapy.

Calculation of relative dose intensity and dose delay

Dose intensity was defined as the amount of drug (paclitaxel at 135 mg/m^2 and carboplatin at AUC = 4 delivered to a patient within a week of treatment. The achieved dose intensity was determined as the total dose of the individual drug received in the first two cycles for each individual agent per body surface area divided by the number of days from the beginning (cycle 1, day 1) to the end (cycle 2, day 21) of treatment for every patient. The RDI of paclitaxel and carboplatin was calculated for each patient using the following equation: actual dose intensity/standard dose intensity. The actual dose intensity was calculated by dividing the total dose delivered by the total chemotherapy duration. Average dose-intensity values for each individual drug and 95% confidence intervals (CIs) will not be detailed in this article. Statistical distributions of the RDI and treatment duration are provided. Dose delay was defined as the delay in the next treatment cycle by ≥ 7 days.

Efficacy evaluation

Effectiveness was evaluated through key metrics, including the pathological complete response (pCR) rate, R0 resection rate, OS, and PFS. pCR was defined as the absence of any residual invasive tumor in the surgical resection specimen (GR0). R0 was defined as microscopically negative surgical margins. Defined the quality of resection (R) using the surgical and pathological report, resection status was characterized as R0, R1 (microscopic tumor at any margin), and R2 (macroscopically incomplete resection). OS was calculated from the date of neoadjuvant therapy initiation to the date of death from any cause, or censored until the date of last follow-up. PFS was calculated from the start date of therapy to the date of progression or death, whichever is earlier. For PFS, chest chest CT or MRI or esophagoscopy scan were repeated at least every 3 to 6 months for 2 years, then every 12 weeks until disease progression. Laboratory blood examination were tested at each visit, including routine blood test, liver and renal function, coagulation tests and tumor markers were completely tested.

Statistical analysis

Statistical analyses were performed using the R software (R version 4.0.3; http://www.R-project.org, The R Foundation). The best RDI cut-off value of 0.7 was obtained using the Cox proportional hazard model according to OS, R package involved: timeROC (for analysis), ggplot2 package (for visualization). Cut-off values to dichotomize the risk factors were calculated with receiver operating characteristics (ROC) curve analysis, with the best cutoff value selected from the point of the ROC curve with the shorter orthogonal distance to the optimum cutoff value. Meanwhile, LA-ESCC patients were classified into the RDI < 0.7 group and RDI ≥ 0.7 group based on the optimal cutoff from the ROC curve analysis. Univariate and multivariate Cox regression analyses were used to analyze the effects of risk factors and clinicopathological features on the prognosis of patients with LA-ESCC. Survival times were analyzed by Kaplan–Meier survival analysis using a log-rank test for curve comparisons. Continuous variables are presented as mean (SD) if normally distributed or median (interquartile range [IQR]) if not normally distributed. Categorical variables are expressed as counts (percentages). Comparisons were made using two-tailed unpaired Student's t-tests and p values < 0.05 were considered statistically significant. Survival benefits were measured using hazard ratios (HR) and its 95% CI.

Result

Population characteristics

Among 321 eligible patients, 132 met the inclusion criteria. The median RDI was 0.74 (range 0.45–1.05). The ROC curve revealed 0.7 as the optimal cutoff value for the RDI. RDI was < 0.7% in 38.6% of the patients. Patients were split into two groups, with RDI < 0.7 and RDI ≥ 0.7 levels, according to the best cut-off value.

A total of 132 patients were assigned between July 7, 2017, and June 21, 2021, to the RDI < 0.7 (n = 51) or RDI ≥ 0.7 (n = 81) groups. Baseline characteristics (Table 1) were well balanced between the two groups. The majority of patients were ≤ 65 years (RDI < 0.7 group, 70.6%; RDI ≥ 0.7 group, 72.4%). There were more males than females (84.8% versus 15.2%), with a mean age of 59.9 ± 6.9 years. According to the TNM stage, most patients (73.9%) were classified as stage III. Based on clinical records, we further contrast comorbidities before the treatment such as diabetes, chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease (CHD) and hepatitis B mellitus were also investigated. There were no statistical difference in comorbidities between the RDI < 0.7 and RDI ≥ 0.7 groups (sTable 5).

Independent prognostic factor for OS and PFS

To study the prognosis-related factors, univariate and multivariate independent prognostic Cox analyses was performed. Univariate and multivariate analyses demonstrated that RDI grade was an independent

Table 1 Patient characteristics

Variables	Total ($n=132$)	RDI < 0.7 ($n=51$)	RDI ≥ 0.7 ($n=81$)	P
Age, years, n(%)				0.779
< 65	95 (72.0)	36 (70.6)	59 (72.8)	
≥ 65	37 (28.0)	15 (29.4)	22 (27.2)	
Sex, n (%)				0.174
Male	112 (84.8)	46 (90.2)	66 (81.5)	
Female	20 (15.2)	5 (9.8)	15 (18.5)	
BMI Grade, n (%)				0.763
< 18.5	5 (3.8)	1 (2)	4 (4.9)	
18.5 ≤ BMI ≤ 24	82 (62.1)	33 (64.7)	49 (60.5)	
> 14	45 (34.1)	17 (33.3)	28 (34.6)	
ECOG, n (%)				1
0	120 (90.9)	46 (90.2)	74 (91.4)	
1	12 (9.1)	5 (9.8)	7 (8.6)	
Smoking, n (%)				0.098
Yes	87 (65.9)	38 (74.5)	49 (60.5)	
No	45 (34.1)	13 (25.5)	32 (39.5)	
Drinking, n (%)				0.157
Yes	86 (65.2)	37 (72.5)	49 (60.5)	
No	46 (34.8)	14 (27.5)	32 (39.5)	
Tumor location, n (%)				0.173
Uper	23 (17.4)	5 (9.8)	18 (22.2)	
Midle	45 (34.1)	18 (35.3)	27 (33.3)	
Lower	64 (48.5)	28 (54.9)	36 (44.4)	
Clinical T stage, n (%)				0.075
T2	6 (4.5)	0 (0)	6 (7.4)	
T3	109 (82.6)	44 (86.3)	65 (80.2)	
T4a	11 (8.3)	3 (5.9)	8 (9.9)	
T4b	6 (4.5)	4 (7.8)	2 (2.5)	
Clinical N stage, n (%)				0.202
N0	3 (2.3)	1 (2)	2 (2.5)	
N1	44 (33.3)	12 (23.5)	32 (39.5)	
N2	68 (51.5)	29 (56.9)	39 (48.1)	
N3	17 (12.9)	9 (17.6)	8 (9.9)	
Stage, n (%)				
II	5 (3.8)	1 (2)	4 (4.9)	0.566
III	96 (72.7)	36 (70.6)	60 (74.1)	
IVA	31 (23.5)	14 (27.5)	17 (21)	

BMI Body mass index, *ECOG* Eastern Cooperative Oncology Group performance

prognostic factor for OS (HR = 0.513, 95% CI = 0.284–0.926, $P=0.027$). None of the other factors such as age, sex, or ECOG score were independent predictors ($P>0.05$) (Table 2). Supplementary Table 1 shows the univariate analysis for PFS. The results demonstrated that neither RDI nor other clinical characteristics were associated with PFS.

Toxicity of concurrent chemoradiotherapy

As shown in Table 3, all patients completed chemotherapy; of these, 23 patients received a second cycle of chemotherapy by adjusting the dose, which was compared to the first cycle of chemotherapy. No significant differences in second-cycle dose reductions were observed between the two groups ($P=0.374$), mainly because the patients

Table 2 Univariate and multivariate Cox hazard regression analysis of OS

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age				
< 65	Reference			
≥ 65	0.86 (0.43,1.7)	0.658	0.71 (0.33, 1.54)	0.383
Sex				
Male	Reference			
Female	1.1 (0.49,2.47)	0.815	1.5 (0.4, 5.6)	0.545
BMI Grade				
< 18.5	Reference			
18.5 ≤ BMI ≤ 24	0.42 (0.13,1.4)	0.16	0.33 (0.08, 1.39)	0.131
> 14	0.44 (0.13,1.54)	0.201	0.38 (0.09, 1.54)	0.175
ECOG				
0	Reference			
1	1.9 (0.74,4.86)	0.18	1.51 (0.55, 4.14)	0.423
Smoking				
Yes	Reference			
No	1.1 (0.58,2.08)	0.763	1.05 (0.28, 3.87)	0.943
Drinking				
Yes	Reference			
No	1.18 (0.63,2.24)	0.602	1.43 (0.42, 4.96)	0.568
Tumor location				
Uper	Reference			
Midle	1.64 (0.69,3.89)	0.258	1.42 (0.53, 3.75)	0.485
Lower	0.87 (0.36,2.09)	0.752	0.58 (0.2, 1.67)	0.309
Clinical T stage				
T2	Reference			
T3	1.21 (0.29,5.05)	0.795	0.76 (0.16, 3.51)	0.722
T4a	1.81 (0.37,8.99)	0.466	1.3 (0.24, 6.97)	0.76
T4b	2.71 (0.45,16.36)	0.278	1.3 (0.17, 9.72)	0.796
Clinical N stage				
N0	Reference			
N1	1.08 (0.14,8.14)	0.941	0.54 (0.07, 4.52)	0.572
N2	0.71 (0.09,5.35)	0.742	0.28 (0.03, 2.39)	0.243
N3	2.48 (0.32,19.5)	0.388	1 (0.11, 8.95)	0.999
Dose delay				
No	Reference			
Yes	1.16 (0.63,2.13)	0.632		
RDI				
RDI < 0.7	Reference			
RDI ≥ 0.7	0.49 (0.27,0.88)	0.015	0.4 (0.201, 0.793)	0.007

BMI Body mass index, *ECOG* Eastern Cooperative Oncology Group performance, *RDI* Relative dose intensity

could not tolerate chemoradiotherapy-related adverse events (AEs).

Acute AEs (occurring within 3 months of NCRT) during chemoradiotherapy were graded according to the Common Terminology Criteria for Adverse Events version 4.0. The severity of RT-induced esophagitis and pneumonitis was graded according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring criteria [18]. Hematologic and non-hematologic AEs of grade ≥ 3 were observed in 39 (29.5%) and 21 (15.9%) patients, respectively, in the intention-to-treat population (Table 4). Patients treated with RDI ≥ 0.7 (33.3%)

Table 3 Grade 3 and higher chemoradiotherapy relative adverse events

Variables	Total ($n=132$), n (%)	RDI < 0.7 ($n=51$), n (%)	RDI ≥ 0.7 ($n=81$), n (%)	p
Dose adjustment	23 (17.4)	7 (13.7)	16 (19.8)	0.374
Hematologic	38 (28.8)	11 (21.6)	27 (33.3)	0.118
Leukopenia	34 (25.8)	12 (23.5)	22 (27.2)	0.642
Anemia	0(0)	0(0)	0 (0)	1
Thrombocytopenia	1 (0.8)	1 (2)	0 (0)	0.386
Neutropenia	29 (22.0)	9 (17.6)	20 (24.7)	0.341
Non-hematologic	21(15.9)	8 (15.7)	13 (16)	0.956
Nauseau	8 (6.1)	2 (3.9)	6 (7.4)	0.484
Vomiting	4 (3.0)	1 (2)	3 (3.7)	1
Esophagitis	3 (2.3)	1 (2)	2 (2.5)	1
Febrile neutropenia	1 (0.8)	1 (2)	0 (0)	0.386
Radiation pneumonitis	1 (0.8)	1 (2)	0 (0)	0.386

Table 4 Pathological findings and surgical outcomes

Variables	Total ($n=132$)	RDI < 0.7 ($n=51$)	RDI ≥ 0.7 ($n=81$)	p
Perineural invasion, n (%)				0.526
Negative	20 (15.2%)	9 (17.6%)	11 (13.6%)	
Positive	112 (84.8%)	42 (82.4%)	70 (86.4%)	
Lymphovascular invasion, n (%)				0.732
Negative	14 (10.6%)	6 (11.8%)	8 (9.9%)	
Positive	118 (89.4%)	45 (88.2%)	73 (90.1%)	
Resection margins, n (%)				0.287
R0	126 (95.5%)	48 (94.1%)	78 (96.3%)	
R1	4 (3.0%)	1 (2%)	3 (3.%7)	
R2	2 (1.5%)	2 (3.9%)	0 (0%)	
pCR, n (%)				0.951
Yes	41 (31.1%)	16 (31.4%)	25 (30.9%)	
No	91 (68.9%)	35 (68.6%)	56 (69.1%)	
TRG, n(%)				0.307
TRG 1a	52 (39.4%)	20 (39.2%)	32 (39.5%)	
TRG 1b	30 (22.7%)	8 (15.7%)	22 (27.2%)	
TRG 2	41 (31.1%)	20 (39.2%)	21 (25.9%)	
TRG 3	9 (6.8%)	3 (5.9%)	6 (7.4%)	
Postop.T, n (%)				0.82
T0	82 (40.8)	21 (42)	61 (40.4)	
T1-2	64 (31.8)	17 (34)	47 (31.1)	
T3-4	55 (27.4)	12 (24)	43 (28.5)	
Postop.N, n (%)				0.097
N0	140 (69.7)	40 (80)	100 (66.2)	
N +	61 (30.3)	10 (20)	51 (33.8)	

pCR Pathologic complete remission, *TRG* Tumor regression grade

had a higher incidence tendency to hematologic grade ≥ 3 AEs than those in the RDI < 0.7 (23.5%) group, but the difference was not statistically significant ($P = 0.229$). There was no evidence that patients with RDI ≥ 0.7 experienced more toxicity or that patients with RDI < 0.7 resulted in less toxicity (all $P > 0.05$). All the AE grades are presented in Supplementary Table 2.

Surgical and pathological outcomes

Among the 51 patients in the RDI < 0.7 group, 48 (96%), 1 (2%), and 2 (3.9%) achieved R0, R1, and R2 resections, respectively. Eighty-seven patients (96.6%) in the RDI ≥ 0.7 group achieved R0 resection, and 3 patient (3.4%) achieved R1 resection. Overall, 66 of 201 patients achieved pCR (33.3%). The pCR rate did not differ significantly between the lower- and higher-RDI groups (31.4% vs. 34.5%, $P = 0.708$). No statistically significant intergroup differences were noted in perineural invasion, lymphovascular invasion, resection margins, or pCR rates (all $P > 0.05$) (Table 4). The postoperative complications were not significantly different between the two groups (Supplementary Table 3).

The pathological response was assessed using the tumor regression grade (TRG) of the Becker criteria. As shown in the Supplementary Table 3, 52 (39.4%), 30 (22.7%), 41 (31.1%), and 9 (6.8%) patients had no residual tumor (TRG 1a), < 10% residual tumor per tumor area (TRG 1b), 10%–50% residual tumor per tumor area (TRG 2), and > 50% residual tumor per tumor area (TRG 3), respectively. The differences in the TRG scores between the two groups were not statistically significant ($P = 0.31$).

Survival

The median follow-up was 37.29 months in the censored patients. OS and PFS for recurrence in patients grouped according to various average RDI are shown in Figs. 1 and 2. OS was significantly higher in the high group than in the low group when the RDI cut-off points of 0.7 was used. In the RDI ≥ 0.7 group, the 3- and 5-year OS was 77.9% and 63%, and the 5-year PFS was 51.1%. In the RDI < 0.7 group, the 3- and 5-year OS was 57.7% and 51.9%, and the 5-year PFS was 46.7%. Patients with RDI < 0.7 who were given reduced doses had a worse OS (HR 0.49, 95% CI 0.27–0.88, $P = 0.015$) and a slightly worse PFS (HR 0.68, 95% CI 0.41–1.13, $P = 0.138$).

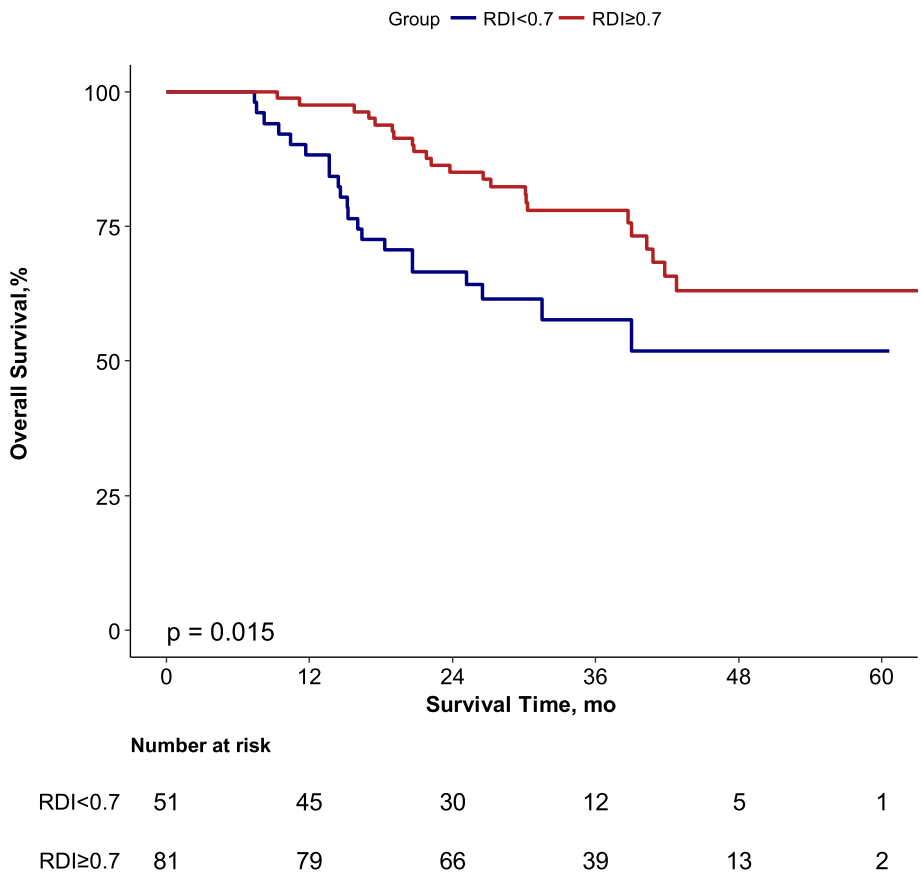

Fig. 1 OS curve of two RDI groups

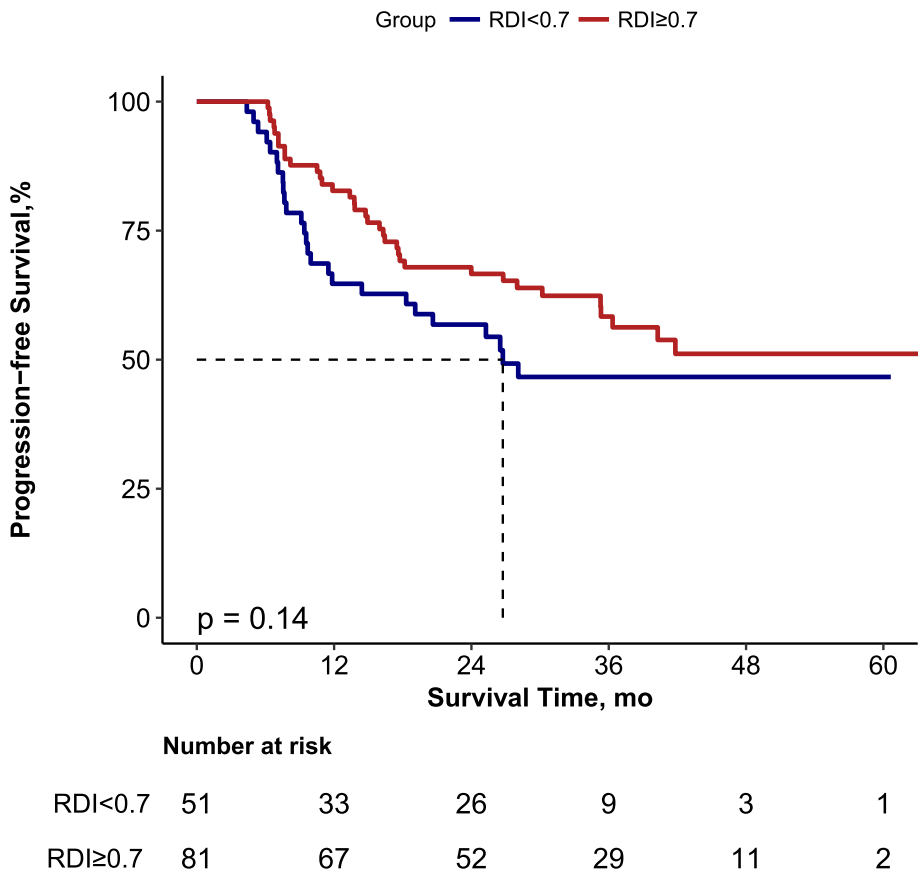

Fig. 2 PFS curve of two RDI groups

Correlation analyses of RDI and patient characteristics

We further explored the association between RDI and patients' clinical characteristics. As shown in Supplementary Table 4, dose delay was the only factor associated with an RDI < 0.7. The mean delay time was 3.8 ± 0.8. The RDI < 0.7 group average dose-delay time was 4.3 ± 0.9. The RDI ≥ 0.7 group average dose-delay time was 3.5 ± 0.6 (Supplementary Table 3). 60.8% patients in the RDI < 0.7 group and 12.3% in the RDI ≥ 0.7 group experienced dose-delay ($P < 0.001$).

Patient clinical characteristics such as age, sex, body mass index (BMI), tumor location, and tumor stage were not significantly associated (Table 1). In addition, no correlation was found between the RDI and chemoradiation-related AEs such as leukopenia, anemia, neutropenia, nausea, and vomiting (all $P > 0.05$) (Table 3). There was no statistical correlation between the RDI and other surgical and pathological outcomes, such as R0 resection rate, TRG grade, pCR rate, perineural invasion, and lymphovascular invasion (Table 4).

Discussion

Previously, our research group assessed whether the TC regimen was superior to the TP regimen, and demonstrated that the TC regimen was a safe and equivalent alternative to the TP regimen for NCRT in patients with LA-ESCC [7]. To further explore the effects of the chemotherapy dose, we analyzed 132 patients with complete TC regimen chemotherapy doses and grouped them using a cutoff RDI of 0.7. Our study indicated that patients who received higher doses did not experience more toxicity and those who received lower doses experienced less toxicity. Patients who were administered reduced doses had a worse significantly OS (HR 1.947, 95% CI 1.079–3.542, $P = 0.015$) and a worse tendency PFS (HR 1.471, 95% CI 0.883–2.45, $P = 0.14$). The two groups showed no significant differences in perineural invasion, lymphovascular invasion, or resection margins. The relationship between the RDI and short-term efficacy was further analyzed. Dose-delay was the only factor associated with low RDI. To the best of our knowledge, this

is the first study to compare the chemotherapy RDI in patients with LA-ESCC undergoing NCRT.

The importance of RDI in advanced unresectable solid tumors has been well recognized in recent years [11, 19]. A recent meta-analysis evaluated the impact of the RDI on survival in adult patients with solid tumor cancer receiving non-adjuvant-based chemotherapy regimens. Significantly shorter OS at RDI < 80% vs. ≥ 80% and < 85% vs. ≥ 85% was observed upon meta-analysis of four carboplatin-based studies for breast, non-small cell lung, or ovarian cancer, and three FOLFOX-/FOLFIRI-/FOLFIRINOX-based studies for colorectal or pancreatic cancer [11]. The results suggested longer OS with RDI ≥ 80% or ≥ 85% for both regimens, indicating longer OS with higher-RDI in advanced solid tumors. In our study, the best cut-off value of RDI calculated using the ROC curve was 70%, which was used as the criterion for subgrouping. The RDI ≥ 0.7 group had significantly higher OS than the RDI < 0.7 group. Cox regression analysis further confirmed that the RDI was an independent prognostic factor affecting survival. Therefore, it can be preliminarily deduced that an RDI of 70% can satisfy the balance of survival benefits. Patients with lower-RDI who were administered reduced doses had worse OS ($P = 0.015$). Thus, the results of the current study, as well as earlier studies, suggest that maintaining the RDI has a positive impact on survival.

Considering patient tolerance, continuation of chemotherapy, and the reduction of chemotherapy-related side effects, dose reduction is commonly used in clinical practice for patients with LA-ESCC receiving NCRT. At present, studies on RDI chemotherapy in NCRT for LA-ESCC are scarce. The impact of the average RDI in neoadjuvant chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-NAC) for resectable LA-ESCC has shown that an average RDI of ≥ 80% improved prognosis in patients receiving DCF-NAC for ESCC [20]. To explore whether the same results were obtained when neoadjuvant radiation was added, we retrospectively analyzed 132 patients with LA-ESCC who underwent radical esophagectomy and lymphadenectomy after NCRT. Our findings indicated that when combined with neoadjuvant chemotherapy and radiotherapy, in patients who had reduced RDI > 30%, chemotherapy not only led to significantly worse OS, but also could not decrease the risk of hematologic and non-hematologic AEs.

Several factors are associated with chemotherapy RDI. Schraa et al. found that RDI < 85% was predicted by patients' age, febrile neutropenia, and hypersensitivity reactions to taxanes in patients with breast cancer receiving adjuvant chemotherapy treatment [21]. A multicenter analysis in the United States demonstrated that malnutrition was an independent predictor of chemotherapy dose reduction due to toxicity [22]. Ilana et al. retrospectively analyzed 237 patients with breast cancer and found that the RDI was not associated with BMI ($P = 0.71$) or pCR ($P = 0.31$); however, fewer dose delays were associated with pCR ($P = 0.02$) [23]. In our study, we performed a univariate logistic regression model correlation analysis to explore the association between the RDI and patients' clinical characteristics. Our results showed that 47 (35.6%) patients experienced dose delays due to personal reasons, whether initiated by the patient or the physician. Dose delay was the only factor associated with RDI < 0.7; BMI, pCR rate, TRG grade, and chemoradiation-related AEs were not significantly associated with RDI reduction (all $P > 0.05$). Thus, avoiding dose delays can effectively avoid dose intensity reduction.

RDI is a crucial metric for assessing the intensity of chemotherapy. Management of chemotherapy time and avoidance of dose delay across treatment modalities could contribute to the maintenance of a higher RDI and benefit survival in patients with LA-ESCC for NCRT. The chemotherapy dose can be appropriately reduced to ensure the safety profile of NCRT. However, we do not support the policy of reducing chemotherapy doses > 30% in patients with LA-ESCC. Dose reductions or delays in the administration of chemotherapy owing to toxicity, or with the intention of avoiding toxicity, lead to a reduction in the dose intensity of treatment and may decrease its therapeutic effect. Avoiding toxicity can cost them months (if not years) of survival.

This study has some limitations. First, this was a retrospective cohort study with potential selection bias compared to prospective randomized controlled studies. We considered propensity score matching for comparison but did not perform it due to the small number of subjects after matching. In addition, the follow-up duration was relatively short and the median OS was not reached. Moreover, in our cohort, episodes of AEs were underreported, given that this information was not prospectively gathered and that these mild events would not have warranted intervention or a change in treatment. Further large prospective studies with a systematic evaluation of the chemotherapy RDI in patients with LA-ESCC undergoing NCRT are needed. Our results can provide the fundamental for prospective explore optimal strategies for dose adjustment and toxicity management in LA-ESCC patients undergoing NCRT.

Conclusion

RDI below 0.7 for avoiding chemoradiotherapy toxicity administration led to a reduction in the dose intensity of treatment and decreased overall survival.

Abbreviations

AEs	Adverse events
CI	Instrumental activities of daily living
CT	Computed tomography
CTV	Clinical target volume
DCF-NAC	Neoadjuvant chemotherapy with docetaxel, cisplatin, and 5-fluorouracil
ESCC	Esophageal squamous cell carcinoma
GTV	Gross tumor volume
HR	Hazard ratio
ROC	Receiver operating characteristic
LA-ESCC	Locally advanced esophageal squamous cell carcinoma
NRCT	Neoadjuvant chemoradiotherapy
OS	Overall survival
pCR	Pathological complete response
PFS	Progression-free survival
RDI	Relative dose intensity
TC	Paclitaxel plus carboplatin
TP	Paclitaxel plus cisplatin
TRG	Tmor regression grade

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Li Jiang: Data collection, statistics, original draft. Jie Zhu: Conceptualization, review and editing the manuscript. Yi Wang: conducted the data analysis and developed the tracking and data collection programs. Xue Chen, Lei Wu and Gang Wan: data collection. Yongtao Han, Xuefeng Leng, Lin Peng: Executed esophagectomy. Qifeng Wang, Lin Peng and Jun Zhang: Monitor the clinical trial.

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Availability of data and materials
All data generated and analyzed in this study are included in this published article.

Declarations

Ethics approval and consent to participate
According to the ethical guide-lines of the Helsinki Declaration and was approved by the institutional review board of Sichuan Cancer Hospital & Institute. Written informed consents were obtained from all patients prior to treatment.

Consent for publication
All patients in the study provided written informed consent.

Competing interests
The authors declare no conflict of interest.

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References

1. Uhlenhopp DJ, Then EO, Sunkara T, Gaduputi V. Epidemiology of esophageal cancer: update in global trends, etiology and risk factors. Clin J Gastroenterol. 2020;13:1010–21. https://doi.org/10.1007/s12328-020-01237-x.
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24:2137–50. https://doi.org/10.1200/JCO.2005.05.2308.
3. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v50–7. https://doi.org/10.1093/annonc/mdw329.
4. Kuwano H, Nishimura Y, Oyama T, Kato H, Kitagawa Y, Kusano M, et al. Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus April 2012 edited by the Japan Esophageal Society. Esophagus. 2015;12:1–30. https://doi.org/10.1007/s10388-014-0465-1.
5. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, et al. Esophageal and esophagogastric junction cancers, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17:855–83. https://https://doi.org/10.6004/jnccn.2019.0033.
6. Eyck BM, Van Lanschot JJB, Hulshof MCCM, van der Wilk BJ, Shapiro J, van Hagen P, et al. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: the randomized controlled CROSS trial. J Clin Oncol. 2021;39:1995–2004. https://doi.org/10.1200/JCO.20.03614.
7. Jiang L, Zhu J, Chen X, Wang Y, Wu L, Wan G, et al. Safety and efficacy of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in neoadjuvant chemoradiotherapy for patients with locally advanced esophageal carcinoma: a retrospective study. Radiat Oncol. 2022;17:218. https://doi.org/10.1186/s13014-022-02190-4.
8. Honing J, Smit JK, Muijs CT, Burgerhof JGM, de Groot JW, Paardekooper G, et al. A comparison of carboplatin and paclitaxel with cisplatinum and 5-fluorouracil in definitive chemoradiation in esophageal cancer patients. Ann Oncol. 2014;25:638–43. https://doi.org/10.1093/annonc/mdt589.
9. Weycker D, Barron R, Edelsberg J, Kartashov A, Lyman GH. Incidence of reduced chemotherapy relative dose intensity among women with early-stage breast cancer in US clinical practice. Breast Cancer Res Treat. 2012;133:301–10. https://doi.org/10.1007/s10549-011-1949-5.
10. Longo DL, Duffey PL, DeVita VT Jr, Wesley MN, Hubbard SM, Young RC. The calculation of actual or received dose intensity: a comparison of published methods. J Clin Oncol. 1991;9:2042–51. https://doi.org/10.1200/JCO.1991.9.11.2042.
11. Nielson CM, Bylsma LC, Fryzek JP, Saad HA, Crawford J. Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: a systematic review and meta-analysis. Oncologist. 2021;26:e1609–18-e18. https://doi.org/10.1002/onco.13822
12. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. J Clin Oncol. 2003;21:4524–31. https://doi.org/10.1200/JCO.2003.05.002.
13. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. N Engl J Med. 1995;332:901–6. https://doi.org/10.1056/NEJM199504063321401.
14. Liu J, Yang Y, Liu Z, Fu X, Cai X, Li H, et al. Multicenter, single-arm, phase II trial of camrelizumab and chemotherapy as neoadjuvant treatment for locally advanced esophageal squamous cell carcinoma. J Immunother Cancer. 2022;10: e004291. https://doi.org/10.1136/jitc-2021-004291.

15. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12:681–92. https://doi.org/10.1016/S1470-2045(11)70142-5.
16. Marano L, D'Ignazio A, Cammillini F, Angotti R, Messina M, Marrelli D, et al. Comparison between 7th and 8th edition of AJCC TNM staging system for gastric cancer: old problems and new perspectives. Transl Gastroenterol Hepatol. 2019;4:22. https://doi.org/10.21037/tgh.2019.03.09
17. Sok M, Zavrl M, Greif B, Srpčič M. Objective assessment of WHO/ECOG performance status. Support Care Cancer. 2019;27:3793–8. https://doi.org/10.1007/s00520-018-4597-z.
18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European-organization-for-research-and-treatment-of-cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341–6. https://doi.org/10.1016/0360-3016(95)00060-C.
19. Denduluri N, Lyman GH, Wang Y, Morrow PK, Barron R, Patt D, et al. Chemotherapy dose intensity and overall survival among patients with advanced breast or ovarian cancer. Clin Breast Cancer. 2018;18:380–6. https://doi.org/10.1016/j.clbc.2018.02.003.
20. Shiraishi O, Kato H, Momose K, Hiraki Y, Yasuda A, Shinkai M, et al. Impact of relative dose intensity of docetaxel, cisplatin, and 5-fluorouracil neoadjuvant chemotherapy on survival of esophageal squamous cell cancer patients. Oncology. 2023;101:203–12. https://doi.org/10.1159/000528937.
21. Schraa SJ, Frerichs KA, Agterof MJ, Hunting JCB, Los M, de Jong PC, Relative dose intensity as a proxy measure of quality and prognosis in adjuvant chemotherapy for breast cancer in daily clinical practice. Eur J Cancer. Oxford. England. 2017;79:152–7. https://doi.org/10.1016/j.ejca.2017.04.001.
22. Klute KA, Brouwer J, Jhawer M, Sachs H, Gangadin A, Ocean A, et al. Chemotherapy dose intensity predicted by baseline nutrition assessment in gastrointestinal malignancies: a multicentre analysis. Eur J Cancer. 2016;63:189–200. https://doi.org/10.1016/j.ejca.2016.05.011.
23. Usiskin I, Li F, Irwin ML, Cartmel B, Sanft T. Association of relative dose intensity with BMI and pathologic complete response in patients treated with neoadjuvant chemotherapy for breast cancer. Breast Cancer Res Treat. 2021;186:191–7. https://doi.org/10.1007/s10549-020-05994-8.

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