Effect of Weight Loss on Survival in Esophageal Cancer Patients undergoing Neoadjuvant Chemoradiotherapy and Surgery

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Abstract: Objective This study aimed to determine the impact of weight loss during neoadjuvant chemoradiotherapy on the survival of patients with esophageal carcinoma. **Methods** We retrospectively examined 102 consecutive patients with esophageal carcinoma who underwent neoadjuvant chemoradiotherapy followed by radical resection at Sichuan Cancer Hospital & Institute between 2003 and 2017. The patients were divided into three groups based on the amount of body weight lost during neoadjuvant chemoradiotherapy: severe weight loss (>10%), high weight loss (5%~10%), and low weight loss (< 5%). The correlations of weight loss with toxicity, progression-free survival, and overall survival were investigated. **Results** The median overall survival was 49.7 months in the low weight loss group compared with 35.4 and 25.1 months in the high and severe weight loss groups ($P = 0.041$). The 1-year overall survival rates in the severe, high, and low weight loss groups were 62.5%, 85.0%, and 90.7%, respectively; the corresponding 3-year overall survival rates were 21.9%, 47.3%, and 68.8%, respectively, and the corresponding 5-year overall survival rates were 21.9%, 31.0%, and 44.4%, respectively. The multivariate analysis indicated that a pathological complete response and severe weight loss were independent prognostic factors for overall survival. Any leukopenia ($P = 0.024$), leukopenia of at least grade 3 ($P = 0.021$), and anemia ($P = 0.042$) occurred more frequently in the severe weight loss group. **Conclusions** Weight loss during neoadjuvant CRT is an independent and adverse prognostic factor in esophageal carcinoma patients, whereas a stable weight confers a better prognosis.

Key words: Esophageal cancer; Prognosis; Weight loss; Neoadjuvant chemoradiotherapy; Toxicity

Introduction

Neoadjuvant chemoradiotherapy (CRT) followed by surgery has been established as an effective treatment for patients with locally advanced esophageal cancer. Several well-designed randomized controlled trials have demonstrated that neoadjuvant CRT improved outcome measures compared with surgery alone, including the R0 resection, pathological complete response (pCR), locoregional control, and survival rates [1-3]. However, the overall survival (OS) varies in such patients, and some fail to benefit from neoadjuvant chemoradiotherapy, indicating a need to identify the factors associated with the prognosis and provide more information about the most appropriate clinical interventions to improve outcomes among high-risk patients. One such factor is weight loss, which is common and often occurs by the time of diagnosis or during treatment in patients with esophageal cancer [4-8]. Although weight loss before treatment has been shown to be a key prognostic indicator of the OS in such patients [9-

12], the impact of weight loss during neoadjuvant CRT on the long-term survival of patients with esophageal cancer remains unknown. Therefore, this retrospective study aimed to investigate the association of weight loss during neoadjuvant CRT with survival outcomes in patients with esophageal cancer.

Materials & Methods

Study design and participants

A total of 102 patients with esophageal squamous cell cancer undergoing neoadjuvant CRT followed by surgery at Sichuan Cancer Hospital & Institute from March 2003 to August 2017 were retrospectively identified. Enrolled patients met the following inclusion criteria: ① newly diagnosed, histologically-confirmed primary esophageal squamous cell cancer; ② clinically stage II or III before treatment according to the 2002 American Joint Committee on Cancer Staging System (version 6.0); ③ Karnofsky performance score ≥ 80 ; and ④ patients underwent neoadjuvant chemoradiotherapy followed by radical esophagectomy. The exclusion criteria were as follows: ① missing weight records pre- or post-CRT; ② metastatic disease before or during preoperative treatment; ③ non-squamous cell carcinoma; and ④ other active malignancy (except for basal cell carcinoma of the skin). The patient

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demographics, neoadjuvant treatment, toxicity, weight records and follow-up results were reviewed in detail from the medical records and the follow-up system. The current study was undertaken in accordance with the ethical standards of the World Medical Association Declaration of Helsinki. A waiver of informed consent was requested, and this study was approved by Sichuan Cancer Hospital & Institute.

The patients were divided into three groups based on the extent of body weight lost during neoadjuvant chemoradiotherapy: severe weight loss (> 10%; SWL group), high weight loss (5%~10%; HWL group), and low weight loss (< 5%; LWL group).

Neoadjuvant chemoradiotherapy

All patients underwent neoadjuvant CRT and surgery. The external beam radiotherapy was performed with a 6~10 MV linear accelerator. Irradiation was scheduled to deliver a total dose of 36~40 Gy to the primary tumor and any positive regional lymph nodes in fractions of 2~3 Gy daily on five consecutive days per week for 2~4 weeks. One of two dual-agent chemotherapy regimens was used (either cisplatin plus 5-fluorouracil or cisplatin plus paclitaxel) and was administered every three weeks in two cycles, concurrent with the radiotherapy. All patients underwent radical esophagectomy 3~8 weeks after the completion of preoperative radiotherapy.

Surgery

Surgery was carried out after a median of 6 weeks (3~8 weeks) of rest after neoadjuvant CRT. The primary surgical procedure in each case was determined by an experienced medical group. Ivor Lewis esophagogastrectomy or McKeown esophagogastrectomy was selected according to tumor location and lesion length.

Measurements and follow-up

Patient's weights were measured at the initial visit and weekly thereafter. Weight loss during neoadjuvant treatment was defined as the difference between the baseline weight and the final weight recorded after completing all neoadjuvant treatment. The OS was measured from the first day of treatment to the day of mortality or last follow-up, if the patient was still alive. The progression-free survival (PFS) was defined as the time between the initiation of treatment and disease progression or mortality from any cause. A pCR was defined as follows: the absence of viable tumor cells with only fibrotic masses or cellular mucin pools present in the area of the primary tumor and lymph nodes. Acute toxicities occurring during CRT were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) and the Radiation Therapy Oncology Group criteria. After surgery, follow-up evaluations were conducted every 3~6 months for the first

2 years and every 6~12 months thereafter. Data regarding the medical history, physical examination, blood tests, endoscopy results, and computed tomography scans of the neck, chest, or abdomen were collected.

Statistical analysis

Analyses were performed using IBM SPSS Version 20 (SPSS Statistics V20, IBM Corporation, New York, USA). Continuous variables are presented as the means (standard deviation, SD) or as medians (95% confidence interval) and were compared using Student's *t*-tests. Categorical variables were compared between groups with *chi*-squared or Fisher's exact tests, as appropriate. Survival curves were generated using the Kaplan-Meier method, and differences between groups were assessed by the log-rank test. Multivariate Cox proportional hazards models were used to identify independent prognostic factors for OS, with only those variables that were statistically significant in univariate Cox models being included. All statistical tests were two-sided and the significance level was set at 0.05.

Results

Patient characteristics

The data for 102 patients with esophageal squamous cell cancer who had undergone neoadjuvant CRT followed by surgery during the study period were analyzed. The overall weight loss during neoadjuvant CRT ranged from -8.89% to 16.67% (median: 5.2%).

To investigate the effects of weight loss on the prognosis, patients were categorized into three subgroups based on their weight loss during neoadjuvant treatment. The SWL group comprised 16 patients (15.7%), the HWL group comprised 42 patients (41.2%), and the LWL group comprised 44 patients (43.1%). There were no significant differences in the gender, age, cTN stage, Karnofsky performance score, lesion length, primary lesion site, or chemotherapy regimen among the subgroups (Table 1). In addition, there were no significant differences between the three groups in terms of the pathological outcomes after neoadjuvant CRT, including the ypT stage, ypN stage, pCR, and pathologic downstaging rates.

Toxicity due to CRT

Regarding the toxicity associated with neoadjuvant CRT, we found that the complication rates tended to be comparable among the groups. However, any grade leukopenia ($P = 0.024$), leukopenia of at least grade 3 ($P = 0.021$), and anemia ($P = 0.042$) occurred more frequently in the SWL group (Table 2).

Survival outcomes

The median follow-up duration across the whole study population was 33 months. A Kaplan-Meier analysis of the OS showed a significant difference among the groups.

Table 1 Clinical and pathological characteristics of patients.

Variables	LWL group	HWL group	SWL group	P
Clinical variables				
Age, years				0.756
≤60	29	28	9	
>60	15	14	7	
Sex				0.548
Male	37	32	14	
Female	7	10	2	
KPS score				0.687
90–100	27	22	10	
80	17	20	6	
Length of the lesion, cm				0.563
≤ 5	16	19	5	
> 5	28	23	11	
Primary lesion site				0.352
Upper	12	7	1	
Middle	24	26	13	
Lower	8	9	2	
cT stage				0.523
2	8	4	2	
3	21	26	11	
4	15	12	3	
cN stage				0.206
N0	22	13	6	
N+	22	29	10	
Chemotherapy regimen				0.165
PF	31	27	7	
TP	13	15	9	
Pathological variables				
ypT stage				0.379
0	20	13	5	
1~2	16	14	7	
3~4	8	15	4	
ypN stage				0.502
N0	29	24	8	
N+	15	18	8	
Achievement of pCR				0.126
Yes	19	10	4	
No	25	32	12	
Pathological downstaging				0.141
Yes	39	32	11	
No	5	10	5	

Abbreviations: KPS, Karnofsky Performance Score; pCR, pathological complete response; TP, cisplatin with paclitaxel; PF, cisplatin with 5-fluorouracil; LWL, low weight loss (< 5% of the body weight loss); HWL, high weight loss(loss of 5-10% of the body weight); SWL, sever weight loss (loss of > 10% of the body weight); cT stage, clinical tumor stage; cN stage, clinical node stage; ypT stage, pathological tumor stage after neoadjuvant chemoradiotherapy; ypN stage, pathological node stage after neoadjuvant chemoradiotherapy.

The median OS was 25.1 months (95% CI, 5.1~45.1) in the SWL group ($P = 0.041$), 35.4 months (95% CI, 19.7~51.1) in the HWL group, and 49.7 months (95% CI, 36.6~62.8) in the LWL group. The respective OS rates in the SWL, HWL,

and LWL groups were 62.5%, 85.0%, and 90.7% at 1 year; 21.9%, 47.3%, and 68.8% at 3 years; and 21.9%, 31.0%, and 44.4% at 5 years (Figure 1). The median progression-free survival rates were 25.0 months (95% CI, 11.6~38.4)

Figure 1 A comparison of the overall survival for patients in the LWL, HWL, and SWL groups. Abbreviations: LWL, low weight loss (< 5% body weight loss); HWL, high weight loss (loss of 5%~10% of body weight); SWL, severe weight loss (loss of > 10% of body weight)

Figure 2 A comparison of the progression-free survival for patients in the LWL, HWL, and SWL groups. Abbreviations: LWL, low weight loss (< 5% body weight loss); HWL, high weight loss (loss of 5%~10% of body weight); SWL, severe weight loss (loss of > 10% of body weight)

in the SWL group, 28.8 months (95% CI, 17.3–40.3) in the HWL group, and 35.6 months (95% CI, 25.2–46.0) in the LWL group ($P = 0.411$; Figure 2).

As shown in Table 3, the univariate analysis revealed that severe weight loss ($>10\%$) during neoadjuvant CRT and an advanced pathological T or N stage were associated with a poor OS, whereas achieving pCR and downstaging were associated with a better OS. The multivariate analysis subsequently indicated that achieving pCR and sustaining less weight loss during neoadjuvant CRT were independent predictors of a more favorable OS (Table 4).

Discussion

It is apparent that the survival of patients with esophageal cancer is determined by not only the tumor pathology, but also host-related factors, such as the nutritional status [13–17]. The patient's body weight, serum albumin and hemoglobin levels, and the Patient Generated Subjective Global Assessment score (PG-SGA) are the most commonly-used methods for evaluating the nutritional status. However, body weight measurement is perhaps the most crucial indicator, and is both inexpensive and easy to perform.

Indeed, unintentional weight loss is a major concern both before and during the treatment of cancer. Several studies have demonstrated that weight loss before esophageal cancer resection might be related to the postoperative survival [6–12]. To our knowledge, no

research has focused on weight loss during neoadjuvant CRT or on the relationship between this weight loss and the survival outcomes in patients with esophageal cancer. In our study, the range of weight loss during neoadjuvant CRT was -8.89% to 16.67% (median: 5.2%), with 45.1% , 39.2% , and 17% of patients experiencing LWL, HWL, and SWL, respectively. The Kaplan–Meier analysis revealed that the OS was significantly lower in the SWL group compared with the HWL and LWL groups ($P < 0.05$), whereas the multivariate analysis revealed that severe weight loss was a risk factor for a poor OS. Overall, the median OS was much higher in the LWL group (49.7 months) than in the HWL group (34.1 months); however, the difference was not significant ($P = 0.105$). This may due to the limited sample sizes, indicating the need for a larger sample in future research.

Although it remains unclear why weight loss affects the survival outcomes in patients with esophageal cancer, some hypotheses have been suggested. One potential reason is that weight loss during neoadjuvant CRT is accompanied by insufficient energy and nutrient intake that is required for body growth, tissue repair, disease recovery, normal physiological function, and immune function (especially cell-mediated immunity). A deficit in energy and nutrient intake may impair the nutritional and performance status, increase the risk of treatment-related toxicity, and impair the efficacy of therapy for esophageal cancer, especially when the weight loss is severe [18–20]. In addition, highly

Table 2 Toxicities during neo-adjuvant chemoradiotherapy.

Toxicities	LWL group n = 44 (%)	HWL group n = 42 (%)	SWL group n = 16 (%)	P
Leukopenia				
Any grade	32 (72.7)	37 (88.1)	16 (100.0)	0.024
≥Grade 3	12 (27.3)	21 (50.0)	10 (62.5)	0.021
Anemia				
Any grade	20 (45.5)	24 (57.1)	13 (81.3)	0.042
≥Grade 3	3 (6.8)	2 (4.8)	2 (12.5)	0.511
Thrombocytopenia				
Any grade	7 (15.9)	11 (26.2)	3 (18.8)	0.541
≥Grade 3	0 (0.0)	3 (7.1)	1 (6.3)	0.164
Anorexia/ Vomiting				
Any grade	17 (38.6)	18 (42.9)	8 (50.0)	0.741
≥Grade 3	1 (2.3)	3 (7.1)	2 (12.5)	0.209
Radiation esophagitis				
Any grade	16 (36.4)	12 (28.6)	7 (43.8)	0.521
≥Grade 3	1 (2.3)	3 (7.1)	1 (6.3)	0.469
Radiation pneumonitis				
Any grade	7 (15.9)	7 (16.7)	3 (18.8)	1.000
≥Grade 3	1 (2.3)	0 (0.0)	1 (6.3)	0.290

Abbreviations: LWL, low weight loss; HWL, high weight loss; SWL, severe weight loss

Table 3 Results of the univariate analysis demonstrating factors associated with overall survival.

Subgroup	HR (95% CI)	P
Weight loss during neoadjuvant CRT		
Low weight loss	1.00	
High weight loss	1.641 (0.902~2.982)	0.105
Severe weight loss	2.519 (1.175~5.402)	0.018
Age, years		
≤ 60	1.00	
> 60	1.199 (0.668~2.153)	0.544
Sex		
Male	1.00	
Female	1.255 (0.660~2.386)	0.488
KPS score		
90~100	1.00	
80	1.358 (0.780~2.365)	0.279
Length of the lesion, cm		
≤ 5	1.00	
> 5	1.021 (0.595~1.752)	0.940
Tumor location		
Upper	1.00	
Middle	0.619 (0.326~1.177)	0.144
Lower	0.846 (0.383~1.869)	0.679
cT stage		
2	1.00	
3	1.148 (0.445~2.961)	0.775
4	2.059 (0.763~5.556)	0.154
cN stage		
N0	1.00	
N+	1.423 (0.818~2.476)	0.212
Chemotherapy regimens		
PF	1.00	
TP	0.986 (0.548~1.776)	0.963
ypT stage		
0	1.00	
1~2	1.624 (0.844~3.126)	0.147
3~4	2.307 (1.179~4.513)	0.015
ypN stage		
N0	1.00	
N+	2.119 (1.233~3.642)	0.007
Achievement of pCR		
Yes	1.00	
No	2.367 (1.284~4.362)	0.006
Downstaging		
Yes	1.00	
No	2.461 (1.284~4.717)	0.007

Abbreviations: low weight loss (<5% of the body weight loss); high weight loss (loss of 5%~10% of the body weight); severe weight loss (loss of >10% of the body weight); KPS, Karnofsky Performance Score; pCR, pathological complete response; TP, cisplatin with paclitaxel, PF, cisplatin with 5-fluorouracil; cT stage, clinical tumor stage; cN stage, clinical node stage; ypT stage, pathological tumor stage after neoadjuvant chemoradiotherapy; ypN stage, pathological node stage after neoadjuvant chemoradiotherapy.

malignant tumors usually grow rapidly and have active metabolism, potentially leading to progressive body mass consumption and weight loss [21]. In this way, weight loss can be seen as a marker of a higher resting energy expenditure and more aggressive and rapid cancer proliferation, and as such, confers a worse prognosis.

A second potential reason for the association between weight loss and the OS is that greater weight loss during radiotherapy may cause positioning errors that reduce the accuracy and efficacy of radiotherapy. This has been demonstrated by Wu ZG et al. [22], who reported that positioning errors during radiotherapy increased with weight loss in patients with thoracic and abdominal cancers.

Another finding of our study is that less extensive weight loss may be protective against myelosuppression. Patients who had severe weight loss also had a substantially increased incidence of leukopenia and anemia compared with patients who had less weight loss, possibly because patients with less weight loss had a better nutritional status, which may have improved the recovery time from CRT-induced myelosuppression. A decreased hemoglobin concentration can also reduce tissue oxygenation and the radiosensitivity of cancer cells, further influencing the response of patients to CRT [23-27].

Severe weight loss may cause tumor-associated cachexia in certain patients. This syndrome of skeletal muscle mass depletion occurs due to systemic inflammation, anorexia, and mechanical and neuroendocrine changes [28]. Cancer

cachexia reflects a state of systemic inflammation in which elevations in various circulating inflammatory markers, such as serum C-reactive protein and interleukin-6, are associated with an increased risk of disease progression, tumor invasion, lymph node metastasis, and a poorer response to CRT [29-31]. When muscle loss causes greater physical burdens and disability, it is categorized as frailty and is associated with increased risks of all-cause mortality, postoperative mortality, and treatment-related complications [32].

Therefore, attention must be paid to the nutritional status of patients during anticancer therapy. Some prospective studies have demonstrated that nutritional support combined with anticancer therapy could prolong the survival in patients with head and neck cancer [33], gastric cancer [34], colorectal cancer [35], and esophageal cancer [36]. A pilot randomized controlled trial was performed in patients with locally advanced esophageal cancer undergoing neoadjuvant CRT, among whom 30 patients received a “walk-and-eat intervention” (nurse-supervised walking plus weekly nutritional advice after medical nutrition therapy) and 29 patients underwent care as usual. During neoadjuvant CRT, the patients who received the walk-and-eat intervention lost less body weight (-0.8 kg vs -3.5 kg, $P < 0.001$) compared to usual care group [37]. Nutritional interventions should be introduced early and tailored to each patient undergoing preoperative CRT for esophageal cancer. This should include a personalized weight and food intake evaluation,

Table 4 Results of the multivariate analysis demonstrating factors associated with overall survival.

Subgroup	HR (95% CI)	P
Weight loss during neoadjuvant CRT		
Low weight loss	1.00	
High weight loss	1.476 (0.790~2.759)	0.222
Severe weight loss	2.911 (1.320~6.419)	0.008
ypT stage		
0	1.00	
1~2	1.030 (0.396~2.680)	0.286
3~4	1.925 (0.579~6.403)	0.951
ypN stage		
N0	1.00	
N+	1.390 (0.698~2.770)	0.349
Achievement of pCR		
Yes	1.00	
No	3.173 (1.142~8.819)	0.027
Downstaging		
Yes	1.00	
No	1.686 (0.593~4.796)	0.327

Abbreviation: low weight loss (< 5% of the body weight loss); high weight loss (loss of 5%~10% of the body weight); severe weight loss (loss of >10% of the body weight); pCR, pathological complete response; ypT stage, pathological tumor stage after neoadjuvant chemoradiotherapy; ypN stage, pathological node stage after neoadjuvant chemoradiotherapy.

dietary counseling, and supplemental nutrition support (if necessary).

Several potential limitations of the present study should be acknowledged. First, this study was retrospective, which might have introduced heterogeneity and bias. In addition, previous studies have reported that skeletal muscle and visceral adipose tissue loss might be the underlying factors contributing to poor survival [38-40]; however, we did not evaluate the impact of changes in body composition during preoperative CRT. Despite these limitations, our study has clarified the importance of changes in body weight and highlights the need for nutritional support during neoadjuvant treatment in patients with esophageal squamous cell cancer. This can form the basis for prospective clinical trials with larger sample sizes. These trials should probe further into the relationship between weight loss and the OS in patients with esophageal cancer who undergo neoadjuvant CRT before surgery.

In conclusion, weight loss during neoadjuvant CRT compromises the survival of patients with esophageal cancer. Routine and accurate monitoring of weight changes, together with patient education, nutritional counseling, and proper nutritional support during neoadjuvant treatment, should be considered integral to the multidisciplinary care of patients with locally advanced esophageal cancer.

Future Perspective

The relationship between body weight loss and the survival of esophageal cancer patients is becoming clearer. However, there are still many areas of controversy and many areas where information is lacking. The relationships among nutritional therapy, body composition alterations and survival, and the value and impact of specific nutrients such as 3-PUFAs on the body weight and anti-cancer treatment outcomes, requires more in-depth research. Fortunately, there has been an increasing number of research studies focusing on these topics. The results of these studies will certainly provide more updated and powerful evidence for the importance of the nutritional status and nutritional treatment with regard to the outcomes of EC patients.

Executive Summary

1) Although weight loss before treatment has been shown to be a key prognostic indicator of the OS in EC patients, the impact of weight loss during neoadjuvant CRT on the long-term survival of patients with esophageal cancer remains unknown.

2) A total of 102 patients who underwent neoadjuvant chemoradiotherapy followed by surgery were divided into three groups based on the extent of body weight lost during neoadjuvant chemoradiotherapy: severe weight loss (> 10%), high weight loss (5%~10%), and low weight loss (< 5%).

3) This study revealed that the OS was significantly

lower in the severe weight loss group compared with the other groups.

4) A multivariate analysis indicated that a pCR and severe weight loss were independent prognostic factors for overall survival.

5) It remains unclear why weight loss affects the survival outcomes in patients with esophageal cancer. However, there are some hypotheses: ① weight loss during neoadjuvant CRT is accompanied by insufficient energy and nutrient intake; ② greater weight loss during radiotherapy may cause positioning errors which reduce the accuracy and efficacy of radiotherapy; ③ patients who had severe weight loss also had a substantially increased incidence of anemia, which reduced tissue oxygenation and therefore reduced the radiosensitivity of the tumor; ④ severe weight loss may cause tumor-associated cachexia and frailty, which are associated with increased risks of all-cause mortality.

6) Nutritional interventions should be introduced early and should be specifically targeted to each patient undergoing preoperative CRT for esophageal cancer.

Author Contributions

Jia Hua Lyu and Tao Li conceived the study, manuscript, and statistical analysis; Qi Feng Wang, Yong Tao Han, Long Liang, Lei Wu, and Lin Peng provided assistance with collecting clinical data; all authors read and approved the final manuscript.

Conflict of Interest

None of the authors has any conflict of interest to disclose.

Ethical disclosure

The present study was approved by the Institutional Review Board of Sichuan Cancer Hospital & Institute and was conducted in accordance with the guidelines of the International Conference on Harmonization/Good Clinical Practice and the principles of the Declaration of Helsinki.

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