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Original Research Article

Impact of nutritional intervention on concurrent chemo-radiotherapy outcomes in locally advanced esophageal cancer: A pharmacological perspective

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Abstract

Purpose: *To determine the pharmacological implications of nutritional intervention and the occurrence of toxic side effects in patients with locally advanced esophageal cancer undergoing concurrent chemo-radiotherapy.*

Methods: *An extensive retrospective analysis of clinical data was carried out on individuals who received concurrent chemo-radiotherapy. 150 patients were included in the study, with 85 patients receiving nutritional management (intervention group) and 65 patients without nutritional support (control group). Assessments were conducted for Nutritional Risk Screening-2002 (NRS-2002) and patient-generated subjective global assessment (PG-SGA) scores, serum nutritional parameters, toxic side effects and treatment completion rates at 2, 4, and 6 weeks before and during chemo-radiotherapy.*

Results: *After concurrent chemo-radiotherapy, intervention group exhibited significantly lower NRS-2002 and PG-SGA scores compared to control group (p = 0.002 and 0.001, respectively). Intervention group had a statistically significant increase in PALB (p = 0.001) and ALB, while control group experienced a significant decline in ALB (albumin) and PALB (pre-albumin) levels. Grip strength also significantly decreased in control group compared to intervention group (p = 0.003). Intervention group showed a significantly lower incidence of radiation esophagitis. Moreover, a smaller proportion of patients in intervention group experienced interruptions or delays in radiotherapy compared to control group (95 % vs. 83.3 %).*

Conclusion: *Nutritional intervention has a pharmacological impact on maintaining nutritional status, reducing treatment toxicities and improving the completion rates of chemo-radiotherapy in patients with locally advanced esophageal cancer. Further investigations and longer-term studies are warranted to shed more light on the potential impact of nutritional interventions on the overall survival rates of these patients*

Keywords: *Esophageal cancer, Chemo-radiotherapy, Nutritional intervention, Pharmacological, Toxicity*

INTRODUCTION

In more than 70 % of patients with esophageal cancer, surgery is not indicated at diagnosis, requiring concurrent chemo-radiotherapy (CRT). The 5-year survival rate of esophageal cancer is less than 30 % while the incidence of malnutrition developing at the time of diagnosis in esophageal cancer has been reported to be 80 % [1,2]. Malnutrition results in misalignment, reduced precision, sensitivity and therapeutic efficacy of radiotherapy. Moreover, it has been established that concurrent CRT worsens the nutritional status of this patient population, leading to a weight loss of 5 - 10 kg [3]. Malnutrition before chemo-radiotherapy is reportedly related to poor tumor response and clinical outcomes [4].

Nutritional interventions in cancer patients have received increasing attention domestically and abroad. It has been suggested that nutritional counseling reduce the side effects associated with chemoradiotherapy (CRT) and enhance the quality of life for patients with head and neck, and colorectal cancer [5,6].

Rainer Fietkau *et al* illustrated that enteral nutrition containing EPA and DHA could be beneficial for patients with esophageal cancer, enhancing their functional status during CRT [7]. Nevertheless, as far as is known, the impact of nutritional status has not been investigated in patients treated with concurrent CRT for esophageal cancer and the standards for nutritional intervention have not yet been established. This study therefore seeks to determine the pharmacological implications of nutritional intervention and the occurrence of toxic side effects in patients with locally advanced esophageal cancer undergoing concurrent chemo-radiotherapy.

METHODS

Study population

This study comprised 150 patients diagnosed with locally advanced esophageal squamous cell carcinoma, who underwent concurrent CRT from February 2019 to December 2020. They were divided into an intervention group (85 patients) and a control group (65 patients).

Inclusion criteria

Patients with confirmed diagnosis of locally advanced esophageal squamous cell carcinoma, age between 18 and 75 years and were eligible for concurrent chemoradiotherapy (CRT) were included.

Exclusion criteria

Patients were excluded if they had distant metastasis, previous esophageal surgery or radiation therapy, severe comorbidities that could affect nutritional status (e.g., chronic renal failure, liver cirrhosis), inability to comply with the study protocol, presence of other malignancies or participation in another clinical trial during the study period.

Treatments and procedures

Control group received conventional education conducted by a nurse at the radiotherapy center, a general talk on nutrition conducted before the start of therapy and brochures on nutrition for cancer patients were also provided. The intervention group received individualized and relatively more intensive nutritional support, and as detailed below, clinical characteristics, including age, gender, tumor location, tumor stage and treatment-related toxicities were collected. Nutritional parameters, such as body weight, Body Mass Index (BMI) and handgrip strength, as well as serum markers including albumin (ALB), prealbumin (PALB) and hemoglobin (Hgb) were also collected. This study was approved by the Ethical Committee of Jiangsu Province Hospital of Chinese Medicine and Affiliated Hospital of Nanjing University of Chinese Medicine (approval no. 2021NL-151-02) and was conducted in accordance with the guidelines of Declaration of Helsinki [8].

Chemo-radiotherapy

Radiotherapy

This was performed in the supine position and a thermoplastic body-frame mask was used for immobilization. A photon of 6 MV energy (Varian Eclipse 8.6 treatment planning system) was used for Intensity-modulated radiotherapy (IMRT). The gross tumor volume (GTV) included primary tumor (GTVp) and metastatic lymph nodes (GTVnd). The GTVp was delineated by combining CT, barium meal and gastroscopy while GTVnd was assessed based on cervical lymph node ≥ 10 mm and tracheoesophageal groove lymph node ≥ 5 mm on CT or MR. The clinical target volume (CTV) included GTVp with an additional radial margin of at least 5 - 6 mm and longitudinal margin of at least 30 mm. The CTV was adjusted according to the specific organ at risk. The planning tumor volume (PTV) was defined as CTV with a 5 mm margin in all directions. The prescribed radiation dose ranged from 41.4 to 50.4 Gy, administered in 23 to 28 fractions following the NCCN guidelines.

Chemotherapy

All patients received paclitaxel liposome (135 mg/m^2, IV, D1) and carboplatin (area under the curve (AUC) 5 mg/mL per min, IV, D1) in each 3-week cycle for 2 cycles between radiotherapy. The treatment plan was determined by an experienced clinician. Adjuvant chemotherapy after concurrent CRT was performed in some patients based on their clinical status.

Nutritional management

The Nutritional Risk Screening-2002 (NRS-2002) and the patient-generated subjective global assessment (PG-SGA) were applied for nutritional screening and evaluation. According to the NRS-2002, nutritional risk evaluation considered three factors: the patient's medical condition, nutritional state and age. Patients who scored ≥ 3 points were classified as "at-risk" for malnutrition. However, PG-SGA, a specialized assessment tool for cancer patients, classifies the severity of malnutrition based on factors including weight, dietary intake, symptoms, activity level and physical function. Based on PG-SGA scores, patients were divided into: no malnutrition (0 - 1 points), suspected malnutrition (2 - 3 points), moderate malnutrition (4 - 8 points) and severe malnutrition groups (≥ 9 points). NRS-2002 and PG-SGA were used to assess the nutritional status every week during the treatment period.

Nutritional therapy regimens

The treatment goals were to meet the 90 % fluid target demand, ≥ 70 % (70 - 90 %) energy target demand, 100 % protein target demand and 100 % micro-nutrient target demand. The energy requirement was 20 - 25 kcal/kg per day for bedridden patients and 25 - 30 kcal/kg per day for active patients. The recommended protein requirement was 1.2 - 2 g/kg per day. Principle of therapy and Nutritional education was provided according to the "five-step treatment principle", and one of the following was selected: oral nutritional supplement (ONS), total enteral nutrition (TEN), partial parenteral nutrition (PPN) and total parenteral nutrition (TPN). When the basic regimen could meet 60 % of the target energy demand for 3 - 5 days, the previous step was selected as shown in Figure 1.

Body weight and body mass index

Patients were asked to record their weight on a weekly basis during the course of treatment using a uniform scale (kg). Patients were weighed, preferably while wearing light indoor clothes and without shoes, by healthcare professionals or staff. Height was measured during the hospital visit. The BMI was calculated using weight (kg)/height^2 (m^2).

Blood tests

Data for serum albumin level (ALB), prealbumin (PALB), hemoglobin (Hgb), Lymphocyte count and white blood cell (WBC) count were collected from the hospital information system. Bone marrow depression was observed and graded according to the National Cancer Institute-Common Toxicity Criteria version 3.0 [9]. The blood parameters were collected every two weeks.

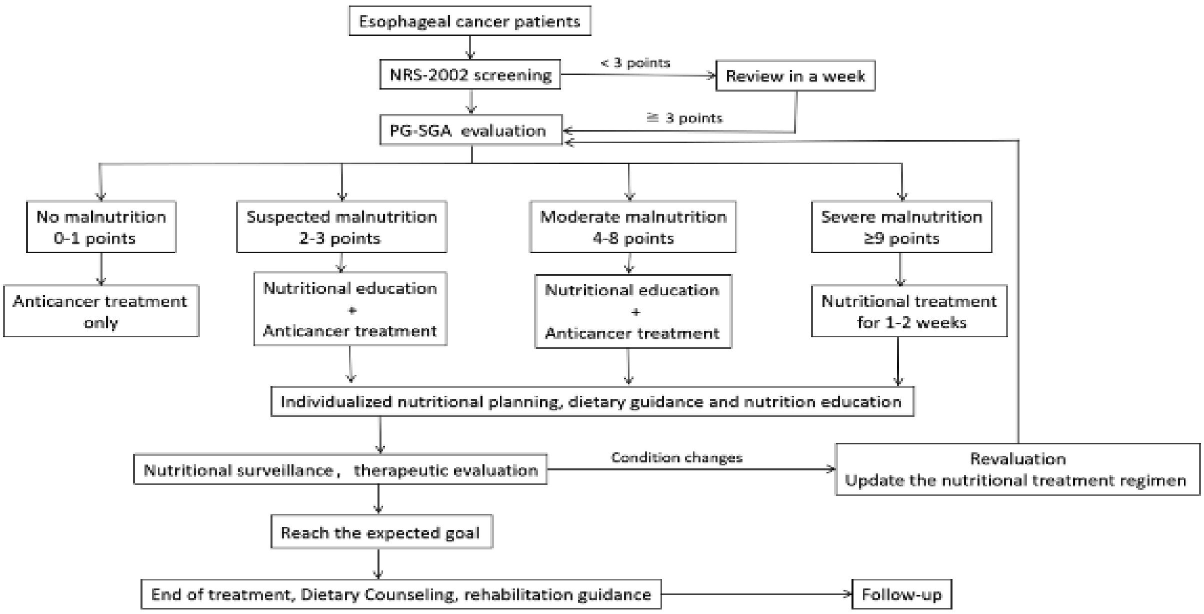

Figure 1: Flowchart showing the nutritional management path of patients with esophageal cancer during concurrent CRT

Handgrip strength (HGS)

Handgrip strength was measured with an electronic hand dynamometer every week. The patients underwent three consecutive HGS tests under the guidance of a clinician, preferably with their non-dominant hands. The results were rounded to the nearest 1.0 kg and the average value of the three-handgrip strength (HGS) measurements were compared with established standard values [10].

Treatment toxicity

The occurrence of acute radiotherapy toxicity was evaluated and graded weekly by clinicians. The medical team of researchers evaluated the occurrence of radiation pneumonia and radiation esophagitis during the treatment period according to the Radiation Therapy Oncology Group (RTOG) criteria for the classification of acute radiation injuries and calculated the probability of radiation injury of grade 2 and above. The incidence of myelosuppression was evaluated by an observed decline in white blood cells. At the same time, the rate of treatment completion was assessed.

Completion of treatment

Complete treatment delivery was defined as the administration of radiotherapy dose within 6 weeks and 2 courses of chemotherapy during irradiation. Complete treatment delivery is defined as the administration of the prescribed radiotherapy dose within 6 weeks, along with two courses of chemotherapy concurrently administered during the irradiation phase. Treatment compliance was evaluated by the rate of complete treatment delivery.

Statistical analysis

All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software (v23; 2015, IBM Corporation, New York, USA). Statistical analyses were conducted using the χ^2 test for categorical data and the t-test for numerical data. Categorical data was presented as N (%), while measurement data was expressed as mean ± standard deviation (SD). A significance level of $p < 0.05$ was used to determine statistical significance.

RESULTS

Baseline characteristics of the patients

In this study, 150 patients with esophageal cancer were assessed. Baseline characteristics are shown in Table 1. All baseline characteristics were verified by homogeneity analyses and the data between the two groups were well balanced.

Table 1: Baseline characteristics of study participants

Variable	Intervention group (n=85)	Control group (n=65)	*P*-value
Age {mean (range)}	54.6 (32-77)	55.5 (32-81)	0.896
Gender (n)			1.0
Male	65	54	
Female	20	11	
Location (n)			0.752
Cervical	3	1	
Upper thoracic	13	16	
Middle thoracic	41	28	
Lower thoracic	28	20	
Stage (n)			0.835
I	8	5	
II	30	21	
III	32	27	
IV	15	12	
Nutritional assessment			
Weight (kg)	62.38±7.72	61.10±6.67	0.503
BMI (kg/m^2)	22.24±2.46	21.90±3.00	0.638
NRS-2002	2.47±0.80	2.43±1.20	0.902
PG-SGA	6.53±1.43	6.67±1.07	0.690
WBC (g/L)	6.73±1.18	6.98±1.41	0.460
Hgb (g/L)	124.03±16.25	125.53±17.91	0.740
Lymphocytes (10^9/L)	1.97±0.96	1.94±1.01	0.907
PALB (mg/L)	198.37±52.49	202.43±56.84	0.778
ALB (g/L)	38.94±4.12	39.01±4.13	0.950
Handgrip strength (kg)	32.19±4.21	32.54±3.78	0.745

Nutritional status

During concurrent CRT, the NRS-2002 and PG-SGA scores of both groups increased to a certain extent. The increase in scores in intervention group was not significant (NRS-2002: *p* = 0.585; PG-SGA: *p* = 0.844), while a statistically significant increase was observed in control group (NRS-2002: *p* = 0.015; PG-SGA: *p* = 0.002). After treatment, the differences in NRS-2002 and PG-SGA scores between the two groups were statistically significant (NRS-2002: *p* = 0.002; PG-SGA: *p* = 0.001; Figure 2)

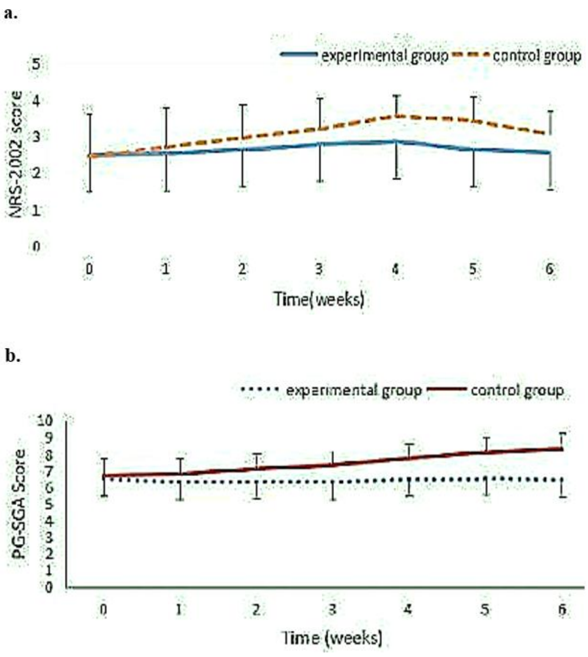

Figure 2: NRS-2002 (a) and PG-SGA (b) scores of the two groups during concurrent CRT. Explanation of the horizontal axis values: 0 = Before radiotherapy or on admission; 1-6 = 1 - 6 weeks after the start of treatment

During concurrent CRT, 70 % of patients experienced weight loss. The data suggests that intervention group better maintained their weight compared to control group (intervention group: *p* = 0.406, control group: *p* = 0.031). Moreover, a statistical difference in body weight was observed between the two groups after chemo-radiotherapy (*p* = 0.003). The BMI results were consistent with the changes in body weight (Table 2). After chemo-radiotherapy, an increase in ALB was observed in intervention group. However, the increase was not statistically significant (*p* = 0.21), while a significant decrease in ALB levels was seen in control group (*p* = 0.000). Moreover, a statistically significant difference in ALB was found between the two groups after chemo-radiotherapy (*p* = 0.003; Table 2). Compared with the baseline, PALB in control group showed a significant increase (*p* = 0.001). In contrast, although PALB decreased in intervention group, this change was not statistically significant (*p* = 0.302). Notably, a significant difference in PALB was observed between the two groups after chemo-radiotherapy (*p* = 0.000; Table 2).

In control group, both Hgb and lymphocyte count were significantly decreased (*p* = 0.000, 0.000, and 0.022, respectively). Conversely, these parameters remained relatively stable in intervention group (*p* = 0.067 and 0.078, respectively). Additionally, a significant decrease in WBC was noted in both groups (*p* = 0.000, 0.000). After chemo-radiotherapy, the WBC and lymphocyte counts became comparable (*p* = 0.075 and 0.409, respectively). However, there remained a significant difference in Hgb between the two groups (*p* = 0.045; Table 2). Handgrip strength remained nearly unchanged in intervention group (*p* = 0.499) but exhibited a significant decrease in control group (*p* = 0.048). Consequently, a statistically significant difference in HGS between the two groups after chemo-radiotherapy was observed (*p* = 0.003; Table 2).

Toxicity and completion rates after treatment

While the incidence of radiation esophagitis in intervention group was found to be lower than in control group (*p* = 0.027), there were no notable distinctions in the incidence of pneumonitis, myelosuppression, hemorrhage, or perforation between the two groups. Three patients in intervention group did not complete the radiation plan (two due to severe myelosuppression and one for financial difficulties), while ten patients in control group experienced dose reductions or delays (six were due to severe myelosuppression, one for acute cerebral infarction, two for radiation pneumonitis and one for financial difficulties) (*p* = 0.040; Table 3).

DISCUSSION

It has been established that malnutrition frequently occurs in patients with esophageal cancer. Malnutrition-related complications during concurrent CRT has an adverse impact on the outcomes [11]. Additionally, radiation and chemotherapy further contribute to the development of malnutrition. This study revealed statistically significant variations in nutritional parameters within both groups during the treatment phase. This finding suggests that the systematic and standard nutritional therapy used in intervention group played an influential role in improving treatment efficacy and mitigating toxic side effects.

Table 2: Comparison of nutritional status before and after treatment

Variable	Before chemo-radiotherapy	After chemo-radiotherapy	**P*-value
Weight (kg)			
Intervention group	62.38±7.72	60.74±7.14	0.406
Control group	61.10±6.67	57.09±7.15	0.031
$^{\#}p$	0.503	0.003	
BMI			
Intervention group	22.24±2.46	21.67±2.31	0.363
Control group	21.90±3.00	20.10±2.98	0.026
$^{\#}p$	0.638	0.030	
ALB (g/L)			
Intervention group	38.94±4.12	40.41±4.42	0.21
Control group	39.01±4.13	32.19±4.52	0.000
$^{\#}p$	0.950	0.000	
PALB (mg/L)			
Intervention group	198.37±52.49	248.5±60.02	0.001
Control group	202.43±56.84	186.87±56.97	0.302
$^{\#}p$	0.778	0.000	
Hgb (g/L)			
Intervention group	124.03±16.25	107.13±12.72	0.067
Control group	125.53±17.91	103.03±11.37	0.000
$^{\#}p$	0.740	0.045	
WBC (g/L)			
Intervention group	6.73±1.18	3.98±0.71	0.000
Control group	6.98±1.41	3.27±0.68	0.000
$^{\#}p$	0.460	0.075	
Lymphocyte (10^9/L)			
Intervention group	1.97±0.96	1.53±0.93	0.078
Control group	1.94±1.01	1.32±1.01	0.022
$^{\#}p$	0.907	0.409	
Handgrip strength (kg)			
Intervention group	32.19±4.21	32.89±3.54	0.499
Control group	32.54±3.78	30.07±3.48	0.048
$^{\#}p$	0.745	0.003	

***Note*:** Comparison within the group before and after treatment: $^{*}P < 0.05$, Comparison between the two groups after radiotherapy: $^{\#}P < 0.05$.

Table 3: Comparison of toxicity after treatment

Variable	Intervention group	Control group	χ^2	*P*-value
Myelosuppression			1.690	0.194
Yes	30 (35%)	30 (46%)		
No	55 (65%)	34 (54%)		
Radiation esophagitis			4.887	0.027
Yes	28 (33%)	34 (53%)		
No	57 (67%)	31 (47%)		
Radiation pneumonitis			1.034	0.298
Yes	1 (1.7%)	8 (11.7%)		
No	84 (98.3%)	57 (88.3%)		
Hemorrhage or perforation			1.034	0.309
Yes	1 (1.7%)	3 (5%)		
No	84 (98.3%)	62 (95%)		
Completion rates			4.227	0.040
Yes	81 (95%)	54 (83.3%)		
No	4 (5%)	11 (16.7%)		

The nutritional status in intervention group was stable or improved, while it significantly worsened in control group during the treatment.

Both NRS-2002 and PG-SGA are suitable for screening and evaluating the nutritional status of patients undergoing chemo-radiotherapy for esophageal cancer. In this study, control group displayed a noteworthy rise in NRS-2002 and PG-SGA scores up to the 5th week, after which they exhibited a gradual stabilization. A similar trend has been documented for PG-SGA scores during the nutritional assessment of patients with nasopharyngeal carcinoma [12]. However, no significant increase in NRS-2002 and PG-SGA scores was observed in intervention group after nutrition intervention. In contrast, significantly lower scores were found in intervention group than in control group. It was also discovered that the variations in BMI, ALB, PALB and Hgb were consistent with NRS-2002 and PG-SGA scores and with the literature [13].

Body weight and BMI are convenient indicators that reflect the nutritional status of cancer patients during clinical practice. In this regard, a study revealed that a low BMI was associated with poor survival and prognosis in esophageal cancer patients [14]. A significant drop in body weight and BMI indicates a decline in nutritional status. It has been reported that nutritional interventions effectively prevent weight loss and complications in patients undergoing CRT [15]. Furthermore, Patel and co-workers posit that preserving body weight might enhance overall patient survival [16]. In the current research, nutritional treatment was recommended to sustain patients' nutritional status during CRT. However, several studies have also indicated that dysphagia could be improved and body weight could be maintained in esophageal cancer patients after CRT without nutritional interventions [17,18]. Furthermore, it has also been suggested that BMI has a limited impact on the outcomes of esophageal cancer patients [19]. The underlying mechanisms remain unclear and could be associated with lifestyle factors or the histological type of esophageal tumor [15]. Tumor patients are prone to varying degrees of decreased serum protein levels (including PALB and ALB), resulting from disruptions in protein synthesis and irregular protein metabolism. It is widely acknowledged that PALB and ALB are sensitive nutritional indicators for assessing the nutritional status of cancer patients [16].

In this study, patients in both groups had normal ALB and PALB levels with normal liver function before CRT. Nonetheless, these markers experienced significant declines post-treatment in control group due to inadequate nutrition. Conversely, the ALB and PALB levels increased in intervention group, with a statistically significant increase observed in PALB. It is well established that PALB migrates faster during electrophoresis and exhibits a pre-albumin peak preceding albumin in electropherograms. Prealbumin is considered a more sensitive marker of malnutrition than ALB, which could explain the distinct PALB and ALB level changes observed in this study. Malnutrition is assessed by body weight, BMI and a series of blood tests. It is well acknowledged that an essential characteristic of cancer malnutrition or cachexia is muscle loss [21]. If the weight does not increase in time, muscle strength may also decrease [13]. Handgrip strength (HGS) has been documented to predict deterioration in nutritional status [3]. In this study, HGS levels decreased in patients who did not receive nutritional treatment (p = 0.048). Reversing the loss of muscle mass is difficult in cancer patients. Prado *et al* suggested that nutritional support in cancer patients could improve HGS [6]. It remains unclear why muscle strength is decreased in this patient population. One hypothesis is that HGS increases due to high-intensity exercise, while HGS decreases with less exercise during radiotherapy and chemotherapy for tumor patients [16].

Most unplanned treatment interruptions result from severe treatment toxicities. Importantly, alleviation of toxicity through nutritional treatment reduces the associated healthcare costs [5]. Myelosuppression is a common complication encountered during chemo-radiotherapy, presenting as decreased hematopoiesis [17]. In the present study, the WBC count was significantly reduced in both patient groups. In contrast, Hgb and lymphocyte counts decreased only in control group, which reflected the high incidence of myelosuppression. However, the results do not indicate if a better nutritional status could decrease the occurrence of myelosuppression during CRT due to the significant decline in WBC count in intervention group which is at variance with previous report [9]. The present findings do however indicate a meaningful association between nutritional treatment during CRT and a reduced incidence of CRT-related esophagitis and pneumonitis, consistent with the literature [11]. Radiation esophagitis is a common acute reaction during radiotherapy in patients with esophageal cancer, mainly presenting as pain and dysphagia, the latter widely recognized as a significant contributing factor to malnutrition [18]. This study revealed that intervention group had a lower incidence of dysphagia compared to control group. The risks of radiation pneumonitis were minimized due to the application of a 3D-CRT technique and strict control of lung V20. The outcomes of patients with locally advanced esophageal carcinoma undergoing concurrent CRT are intricately linked to the nutritional status and the dose of CRT. Chemo-radiotherapy is often interrupted or delayed during clinical practice due to the treatment of toxicities that influence the therapeutic effect. Consistently, delayed treatment is often associated with a poor prognosis [19]. The current study showed that nutritional treatment in intervention group led to better treatment completion rates.

Limitations of this study

This study comes with several limitations that need to be considered when interpreting the results. First, the sample size in this study was relatively small and the study was conducted at a single Medical Center. Consequently, the generalizability of the findings to larger and more diverse patient populations may be limited. Future research, with larger sample sizes and multi-center collaborations, could provide a more comprehensive understanding of the observations in this study. Another critical limitation arises from the retrospective design employed in this research. Retrospective studies are prone to various biases, including selection bias and issues related to data completeness and accuracy. Prospective studies with more rigorous data collection methods could offer more robust evidence. Moreover, the specific details of the nutritional interventions applied to patients were not extensively documented. Factors such as the type, duration and adherence to these interventions were also not thoroughly analyzed. A more in-depth investigation into these nutritional treatments could help elucidate their specific impacts on patient outcomes. In addition, the relatively short follow-up duration in this study might not capture the long-term effects of nutritional interventions. Extended follow-up periods would be beneficial to assess the sustainability of the observed nutritional improvements and their influence on treatment outcomes over time. Furthermore, this study included patients with various cancer stages. Since cancer stage significantly affect treatment outcomes, conducting subgroup analyses or matching patients based on their cancer stage could provide more precise insights.

CONCLUSION

Nutritional treatment plays a crucial role in maintaining the nutritional status, enhancing treatment completion rates and mitigating treatment-related toxicities and healthcare costs among patients grappling with advanced esophageal cancer. However, it's important to note that, due to the relatively short duration of this study, it was not feasible to collect comprehensive data on overall survival. Therefore, further investigations and longer-term studies are warranted to shed more light on the potential impact of nutritional interventions on the overall survival rates of these patients.

DECLARATIONS

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None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Jie Liu, Hong Lu and Pei Wang contributed equally to this work. YZ and DY directed the individual study. PW and YZ analyzed and interpreted the patient data regarding the nutritional index toxicity. JL and HL were a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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