Nutritional Treatment Combined with Concurrent Chemo-Radiotherapy in Locally Advanced Esophageal Cancer: A Retrospective Analysis

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Research

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Abstract

Background: The incidence of malnutrition is high in patients with locally advanced esophageal cancer during concurrent chemo-radiotherapy. This study aimed to explore the effects of nutritional treatment on the nutritional status and the incidence of toxic side effects of chemo-radiotherapy in patients with advanced esophageal cancer.

Methods: Clinical data of patients that underwent concurrent chemo-radiotherapy at our institution between February 2019 and December 2020 were retrospectively analyzed. A total of 150 patients were included; 85 patients who underwent nutritional management were included in the intervention group and 65 without nutritional support in the control group. NRS-2002 and PG-SGA scores, serum nutritional parameters, toxic side effects, and treatment completion rate were analyzed before and during chemo-radiotherapy at 0, 2, 4, and 6 weeks.

Results: There was no statistical difference between the two groups before concurrent chemo-radiotherapy (P>0.05). After treatment, the NRS-2002 and PG-SGA scores were significantly lower in the intervention group than in the control group (P=0.002 and 0.001, respectively). The body weight, BMI, Hgb, and lymphocyte count decreased in both groups, but the difference was not statistically significant in the intervention group (P>0.05). ALB and PALB were both increased in the intervention group, and the increase of PALB was statistically significant (P=0.001). ALB and PALB were decreased in the control group, and the decrease in ALB was statistically significant (P=0.000). Furthermore, a statistically significant decrease in grip strength was found in the control group compared to the intervention group (P=0.003). The incidence of complications were as follows: myelosuppression(35% vs. 46%, P=0.194), radiation esophagitis (33% vs. 53%, P=0.027), radiation pneumonitis (1.7% vs. 3.3%, P=0.298), hemorrhage or perforation (1.7% vs. 5%, P=0.309). In addition, only three patients in the intervention group did not complete their course of radiation treatment, while ten patients in the control group had interrupted or delayed radiotherapy (95% vs. 83.3%, P = 0.040).

Conclusions: Nutritional treatment was beneficial for maintaining the nutritional status, reducing treatment toxicities, and improving the completion rates of chemo-radiotherapy in patients with locally advanced esophageal cancer.

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%[1], while the incidence of malnutrition developing at the time of diagnosis in esophageal cancer is reported to be 80%[2]. Malnutrition can lead to positioning errors, decreased accuracy, sensitivity, and therapeutic effect 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 can decrease CRT-related side effects and improve the quality of life in patients with head and neck and colorectal cancer[5, 6]. Rainer Fietkau et al.[7]demonstrated that enteral nutrition with EPA and DHA would benefit patients with esophageal cancer by improving functional status during CRT. Nevertheless, to the best of our knowledge, the impact of nutritional status has not been investigated in patients treated with concurrent CRT for esophageal cancer, and the standard of nutritional intervention has not yet been established.

Material And Methods

Study population

A total of 150 patients with locally advanced esophageal squamous cell carcinoma and treated with concurrent CRT between February 2019 and December 2020 were included in our study. They were randomly divided into an intervention and a control group. The control group received conventional education conducted by a nurse at the radiotherapy center, a general talk on nutrition before the start of therapy and providing brochures on nutrition in cancer patients, etc. The intervention group received individualized and relatively more intensive nutritional support, as mentioned below. Clinical characteristics were collected, including age, gender, tumor location, tumor stage and events, and toxicity induced by CRT. Nutritional parameters were also collected, including body weight, Body Mass Index (BMI), and handgrip strength, as well as serum tests such as albumin (ALB), prealbumin (PALB), and hemoglobin (Hgb).

Chemo-radiotherapy

Radiotherapy

RT 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 GTV (Gross tumor volume) includes the primary tumor (GTVp) and metastatic lymph nodes (GTVnd). GTVp was delineated by combining CT, barium meal, and gastroscopy. The gross volume of metastatic lymph nodes (GTVnd) was assessed based on any cervical lymph node ≧10mm and tracheoesophageal groove lymph node≧5mm on CT or MR. The CTV (clinical target volume) included the GTVp with an additional radial margin of at least 5-6mm and longitudinal margin of at least 30mm. The CTV was adjusted according to the specific organ at risk. The Planning tumor volume (PTV) was defined as CTV with a 5mm margin in all directions. The prescribed dose was 41.4 to 50.4Gy given in 23 to 28 fractions according to NCCN guidelines.

Chemotherapy

The TP regimen (T represents paclitaxel; P represents cis-platinum) was provided for chemotherapy. 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, the nutritional risk was assessed from three aspects: disease status, nutritional status, and age. Patients with a total score of ≥3 points were considered "at-risk" for malnutrition. PG-SGA is a nutritional assessment method specially designed for cancer patients to grade malnutrition severity based on weight, food intake, symptoms, activity, and physical function. According to 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 whole treatment.

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 20-25kcal/(kg·d) for bedridden patients and 25-30kcal/(kg·d) for active patients. The recommended protein requirement was 1.2-2g/(kg·d). Treatment principle: 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. "The whole nutritional management path of patients with esophageal cancer during concurrent CRT" is shown in Figure 1.

Body Weight and Body Mass Index

The patient's body weight was provided by the patient himself. Patients were asked to record their weight on a weekly basis during the treatment course. The body weight measurement was performed on the same scale. Patients were preferably weighed wearing light indoor clothes and without shoes. Height was measured during the hospital visit. 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.[8] The blood parameters were collected every two weeks.

Handgrip strength (HGS)

HGS 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. We marked the results to the nearest 1.0kg, and the average of the three HGS were compared with the standard values[9]

Treatment Toxicity and completion of treatment

The occurrence of acute radiotherapy toxicity was evaluated and graded weekly by clinicians. Every week, we 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.

Statistical Analysis

All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) Statistics, version 23 (2015, IBM Corporation, New York, USA). χ^2 test and t-test were used to test the data. Numerical data were expressed as N (%), and measurement data were represented by x±SD. $P<0.05$ indicated a statistically significant difference.

Results

Baseline characteristics of the patients

In this study, 150 patients with esophageal cancer were assessed. Baseline characteristics are shown in Table 1. There were 85and 65 patients in each group, respectively. All the baseline characteristics were verified by homogeneity analyses, and the data between the two groups were well balanced.

Table 1
Baseline characteristics

Variables	Intervention group (n=85)	Control group (n=65)	P
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	
IVa	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
Lymphocyte(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 the intervention group was not significant (NRS-2002:P=0.585; PG-SGA: P=0.844), while a statistically significant increase was observed in the control group (NRS-2002:P=0.015; PG-SGA: P=0.002). After treatment, the difference in NRS-2002 and PG-SGA scores between the two groups was statistically significant (NRS-2002:P=0.002; PG-SGA: P=0.001; Fig. 2)

Table 2

Comparison of nutritional status before and after treatment $\bar{x}\pm S$

Variables	**Before chemo-radiotherapy**	**After chemo-radiotherapy**	***P**
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

Comparison before and after treatment in the group,*$P<0.05$; Comparison between groups after radiotherapy,$^{\#}P<0.05$.

Variables	Before chemo-radiotherapy	After chemo-radiotherapy	*P
#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	
Comparison before and after treatment in the group,*P<0.05 ; Comparison between groups after radiotherapy,#P<0.05.			

70% of patients experienced weight loss during concurrent CRT. The data suggested that the weight of the intervention group was better maintained than in the control group (intervention group:*P=0.406, control group:*P=0.031). Moreover, a statistical difference in the 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 the intervention group; however, no statistical significance was found (*P=0.21), while a significant decrease in ALB levels was found in the 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 baseline, the PALB of the control group increased significantly (*P=0.001). Meanwhile, although PALB in the control group decreased, it was not statistically significant (*P=0.302). A statistically significant difference in PALB was found between the two groups after chemo-radiotherapy (#P=0.000; Table 2).

In the control group, both the Hgb and lymphocyte count were significantly decreased (*P=0.000, 0.000, and 0.022, respectively) while both parameters remained nearly constant in the intervention group (*P=0.067 and 0.078, respectively). Furthermore, a significant decrease in WBC was observed between both groups (*P=0.000,0.000). After chemo-radiotherapy, the WBC and lymphocyte counts were comparable (#P=0.075 and 0.409, respectively). In contrast, the difference in Hgb between the two groups was significant (#P= 0.045; Table 2).

Handgrip strength was almost unchanged in the intervention group (*P=0.499), while it decreased significantly in the control group (*P=0.048). At the same time, the difference in HGS between the two groups after chemo-radiotherapy was statistically significant.(#P= 0.003; Table 2).

Toxicity and completion rates after treatment

Table 3
Comparison of toxicity after treatment n(%)

Variables	Intervention group	Control group	χ^2	P
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%)		

Moreover, the incidence of radiation esophagitis in the intervention group was lower than in the control group (P=0.027). No significant difference in pneumonitis, myelosuppression and hemorrhage or perforation was found between the two groups. Only three patients in the intervention group did not complete the radiation plan, while ten patients in the control group experienced dose reductions or delays (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 can negatively affect the outcomes [10]. Meanwhile, radiation and chemotherapy can also exacerbate the occurrence of malnutrition. A statistically significant difference in nutritional parameters was found in the present study in both groups during treatment. This finding suggests that the systematic and standard nutritional therapy used in the intervention group played an influential role in improving treatment efficacy and mitigating toxic side effects. The nutritional status in the intervention group was stable or improved, while it significantly worsened in the control group during the treatment.

Nutritional status

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, a significant increase in NRS-2002 and PG-SGA scores was observed in the control group until the 5th week, where they gradually stabilized. A similar trend has been documented for PG-SGA scores during the nutritional assessment of patients with nasopharyngeal carcinoma[11]. In our study, after nutrition intervention, no significant increase in NRS-2002 and PG-SGA scores was observed in the intervention group. In contrast, significantly lower scores were found in the intervention group than in the control group ($P<0.05$). We also found that the variation in BMI, ALB, PALB, and Hgb was consistent with NRS-2002 and PG-SGA scores, consistent with the literature[12].

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[13]. A substantial decline in body weight and BMI can reflect the deterioration in nutritional status. It has been reported that nutrition interventions effectively prevent weight loss and complications in patients undergoing CRT[14]. Patel JD et al. [15] suggested that maintaining body weight could improve overall patient survival. In our present study, nutritional treatment was recommended to maintain the nutritional status of patients during CRT. However, contrasting studies have suggested that dysphagia could be improved, and body weight could be maintained after CRT in patients with esophageal cancer without nutritional interventions[16, 17]. Moreover, it has been suggested that BMI exerted little effect on the outcomes of esophageal cancer patients [18, 19]; the underlying mechanisms remain unclear and could be related to lifestyle or the pathological type of esophageal tumor[20].

Tumor patients are prone to varying degrees of decreased serum protein levels (including PALB and ALB), caused by protein synthesis disorders and abnormal protein metabolism. It is widely acknowledged that PALB and ALB are sensitive nutritional parameters that can evaluate the nutritional status of cancer patients[21]. In our study, patients in both groups had normal ALB and PALB levels with normal liver function before CRT. However, these markers decreased significantly in the control group after treatment, caused by poor nutrition. ALB and PALB levels in the intervention group increased; however, only the increase in PALB was statistically significant. It has been established that PALB migrates faster during electrophoresis and presents with a prealbumin peak before albumin in electropherograms. PALB are more sensitive markers of malnutrition than ALB and could account for the difference between PALB and ALB levels observed in our study.

Malnutrition can be 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. If the weight does not increase in time, muscle strength may also decrease[22]. Handgrip strength (HGS) has been documented to predict deterioration in nutritional status[23]. 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. Engelen M et al. and Prado CM et al.[24, 25]suggested that nutritional support in cancer patients could improve HGS. 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[26].

Treatment toxicities

Most unplanned treatment interruptions result from severe treatment toxicities. Importantly, the alleviation of toxicity severity through nutritional treatment[27] can reduce the associated health care costs.

Myelosuppression is a common complication encountered during chemo-radiotherapy, presenting as decreased hematopoiesis[28]. In the present study, the WBC count was significantly reduced in both two groups. In contrast, Hgb and lymphocyte count were decreased only in the control group, which reflected the high incidence of myelosuppression. With the current results, we could not prove that a better nutritional status could decrease the occurrence of myelosuppression during CRT due to the significant decline in WBC count in the intervention group, which was not in accordance with the literature.[28]

The present findings indicated a meaningful association between nutritional treatment during CRT and a reduced incidence of CRT-related esophagitis and pneumonitis, consistent with the literature[29]. Radiation esophagitis is a common acute reaction during radiotherapy in patients with esophageal cancer, mainly presenting as pain and dysphagia. The latter is a widely acknowledged contributing factor to malnutrition[30]. In our study, the incidence of dysphagia in the intervention group was lower than in the control group. The risks of radiation pneumonitis were minimized due to the application of a 3D-CRT technique and strict control of lung V_{20}. The outcomes of patients with locally advanced esophageal carcinoma undergoing concurrent CRT are intricately linked to the nutritional status and the dose of RCT. Chemo-radiotherapy is often interrupted or delayed during clinical practice due to treatment toxicities that can influence the therapeutic effect. Consistently, delayed treatment is often associated with a poor prognosis[31]. The current study showed that nutritional treatment in the intervention group led to better treatment completion rates.

Conclusions

In conclusion, our study suggests that nutritional treatment is beneficial to maintain nutritional status, improve the treatment completion rate, and reduce treatment-related toxicities and healthcare costs of patients with advanced esophageal cancer. However, data on overall survival was not collected due to the relatively short duration of our study, warranting further investigations.

Abbreviations

NRS Nutrition Risk Screening

PG-SGA Patient-Generated Subjective Global Assessment

BMI Body mass index

ALB Albumin

PALB Prealbumin

CRT Concurrent chemo-radiotherapy

Hgb Hemoglobin

WBC White blood cell

IMRT Intensity-modulated radiotherapy

GTV Gross tumor volume

CT Computerized tomography

CTV Clinical target volume

PTV Planning tumor volume

NCCN National Comprehensive Cancer Network

ONS Oral nutritional supplement

TEN Total enteral nutrition

PPN Partial parenteral nutrition

TPN Total parenteral nutrition

HGS Handgrip strength

RTOG Radiation Therapy Oncology Group

Declarations

Ethical review committee statement: This study was approved by the institutional

review board of Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine (2021NL-151-02).

Consent for publication：Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

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Competing interests: The authors declare that they have no competing interests.

Authors' contributions：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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Figures

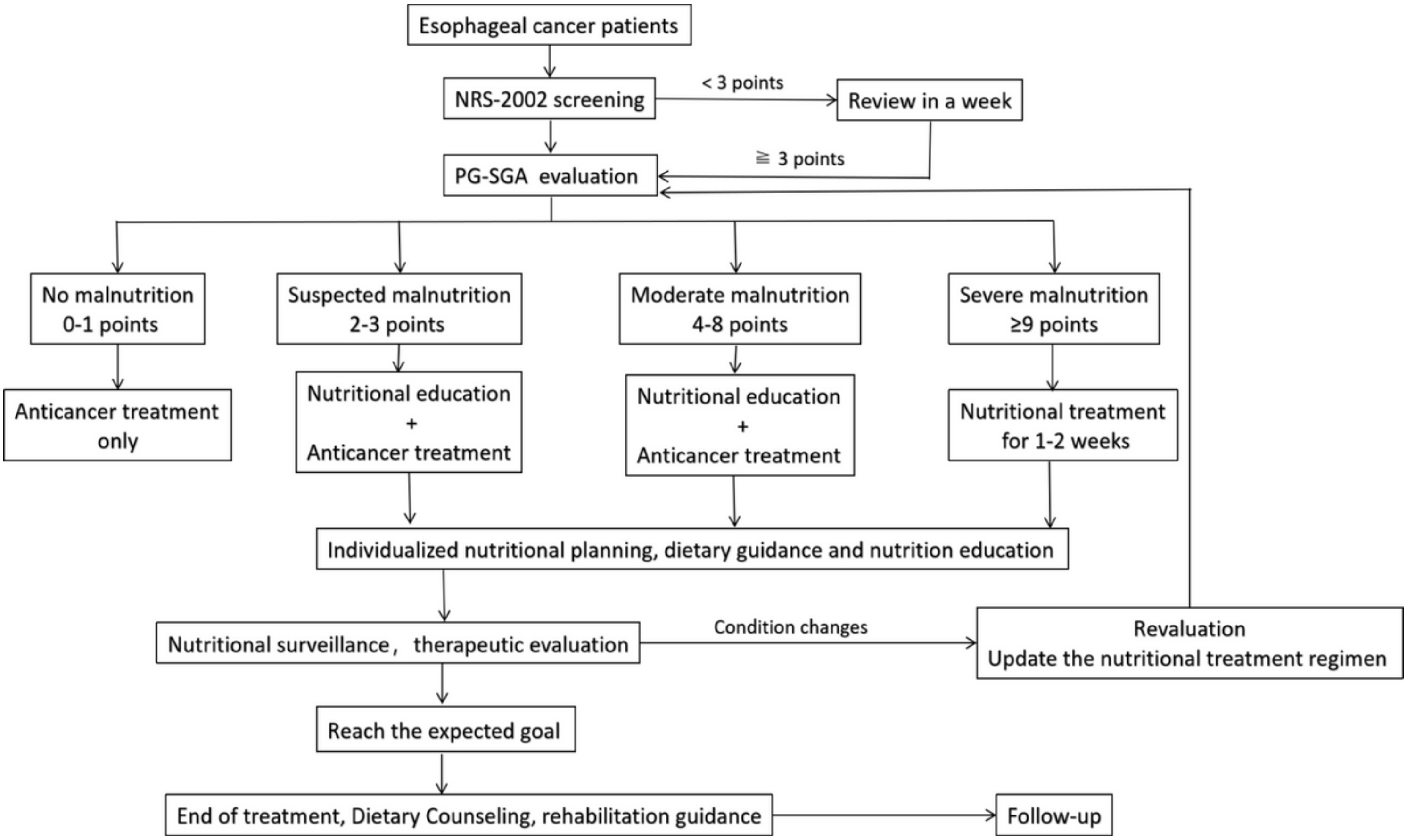

Figure 1

The whole nutritional management path of patients with esophageal cancer during concurrent CRT

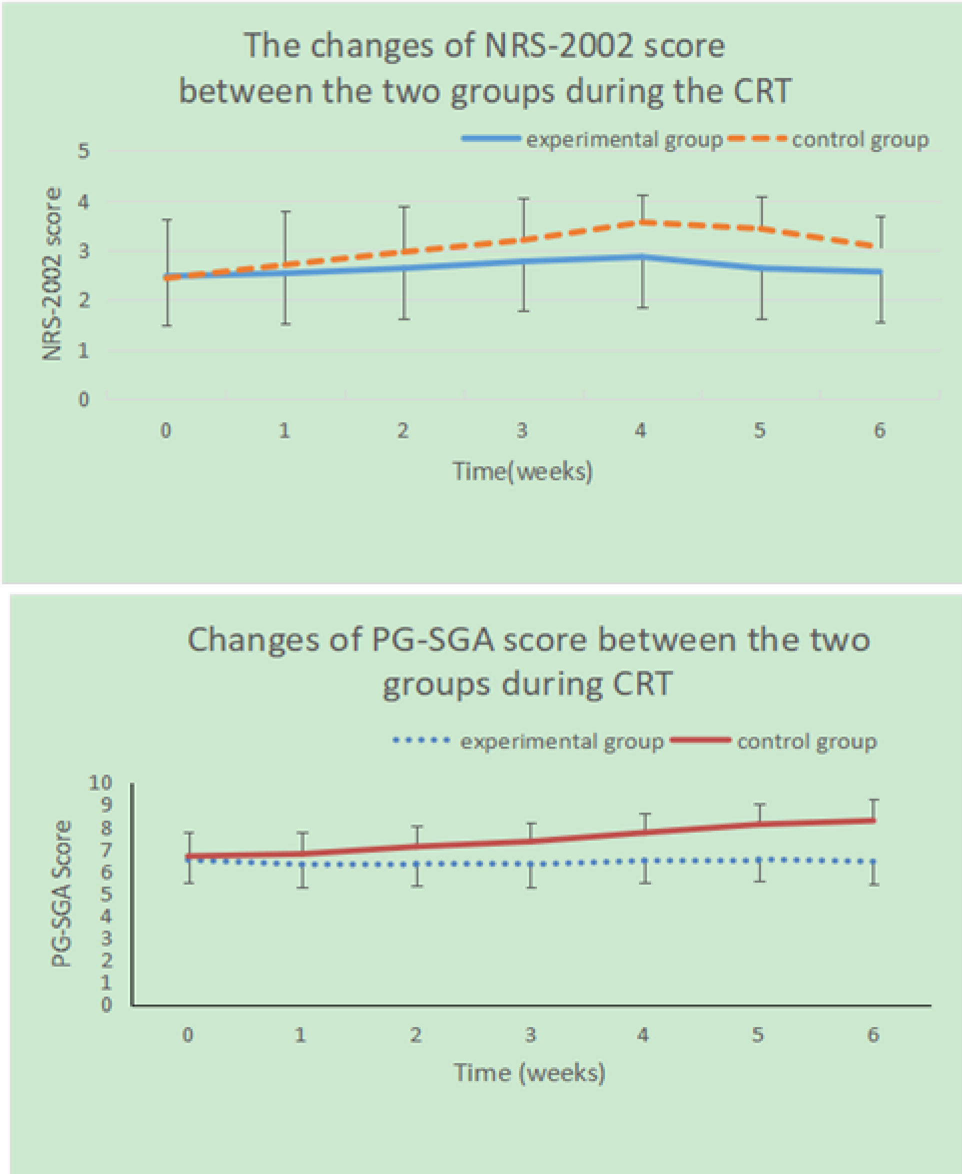

Figure 2

The changes in NRS-2002 and PG-SGA scores between the two groups during concurrent CRT

Description of abscissa numbers 0 Before radiotherapy or on admission 1-6 1-6 weeks after the start of treatment