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Research Article

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Prognostic Value of Nutritional Risk Screening-2002 in Esophageal Squamous Cell Carcinoma Treated by Curative Esophagectomy

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Abstract Objective: To investigate the prognostic values of Nutritional Risk Screening 2002 (NRS-2002) in patients with esophageal squamous cell carcinoma (ESCC) by curative esophagectomy.

Methods: A total of 227 patients with ESCC receiving standard curative esophagectomy from 2010 to 2012 were retrospectively analyzed. These patients were grouped for further analysis according to the median values of NRS-2002. Kaplan–Meier method was adopted to calculate and compare the progression-free survival (PFS) rates. The Cox proportional hazards model was used to carry out univariate and multivariate analyses.

Results: In univariate analysis, the following factors were significantly associated with PFS: T stage, N stage, TNM stage, differential grade, and NRS-2002 (all $P<0.05$). The multivariate Cox regression analysis showed that NRS-2002 (HR = 1.740; 95% CI 1.242-2.437; P = 0.001), differential grade (HR = 1.015; 95% CI 1.004-1.238P = 0.048)) and TNM stage (HR =1.350; 95% CI 1.121-1.696; P = 0.035) were independent prognostic factors for PFS in patients with ESCC after surgery.

Conclusion: This study demonstrated that NRS-2002 was a promising as predictive markers for predicting PFS in patients with ESCC receiving surgery.

Keywords Esophageal cancer, Surgery, Nutritional risk screening, Prognosis

Introduction

Esophageal cancer (EC) is the eighth common malignancy and the fifth common cause of cancer death all over the world [1]. Although the progress in the multi-disciplinary therapy, surgical resection remains the best curative method for non-metastatic patients. Nevertheless, most of the patients developed local relapse or distant metastasis after esophagectomy, so the 5-year overall survival (OS) rate is still low, and only ranges from 26.2% to 49.4% [2]. Therefore, it is critical to search biomarkers for distinguishing patients who are likely to develop recurrence following surgery from other ones.

It is generally recognized that the survival of cancer patient is determined not only by tumor pathology, especially for the tumor-node-metastasis (TNM) staging system, but also by host-related factors, such as the preoperative nutritional status. EC patients have a high risk of being malnourished at initial diagnosis, and the causes of malnutrition include a variety of mechanisms, both the systemic inflammatory response and the disorder of protein metabolism playing important roles. Tumor itself and the systemic inflammatory response can inhibit albumin synthesis, finally leading to a decrease in serum albumin concentration [3]. There were several researches demonstrating that poor nutritional condition was associated with poor clinical prognosis in

patients who undergone esophagectomy [4-6], therefore, nutritional monitoring is important to evaluate the toleration of treatment for ESCC. Currently, there are many assessment methods applied to nutritional evaluation, including the Subjective Global Assessment (SGA) [7], the Mini-Nutritional Assessment (MNA) [8] and Nutritional Risk Screening 2002 (NRS-2002) [9]. Among these, NRS-2002 is a new evaluation system, published by the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2002 and is based on 128 randomized controlled trials (RCT). It was the first system in the world that was developed via evidence-based medicine with a great advantage of predicting malnutrition risk [9]. The ESPEN recommends NRS-2002 for hospital use and screening purposes within 48 h of admission, with a final score of 3 or higher indicating nutritional risk [10]. Chen et al. [11] found that the standard of the NRS-2002 is feasible in China. Therefore, we hypothesized that nutritional markers may be closely related to recurrence and survival outcomes in patients with EC. The purpose of this study was to investigate the prognostic value of NRS-2002 score.

Materials and Methods

Patients

Between January 2010 and December 2012, a total of 227 esophageal carcinoma patients who underwent esophagectomy and lymph node dissections at the Department of Thoracic Surgery, Affiliated Taixing People's Hospital of Yangzhou University, were enrolled in this retrospective study. All patients were staged according to the American Joint Committee on Cancer staging manual (seventh edition, 2010) [12]. This research was approved by the Ethics Committee of The First Affliated Hospital of Soochow University. Informed consent was obtained from all individual participants included in this study.

Nutritional Assessment

Nutritional risk was assessed by NRS-2002 within 1 week prior to surgery [9]. NRS- 2002 takes into account impaired nutritional status (low, moderate or severe) and severity of disease (low, moderate or severe), with an adjustment for age of ≥70 years. Nutritional status was evaluated by three variables: body mass index (BMI), recent weight loss, and food intake during one week before treatment. For severity of disease, as an indicator of stress metabolism and increased nutritional requirements, a score between 1 and 3 was given according to the recommendations. A data collection sheet was used to obtain information about changes in the body weight, food intake and severity of disease according to the ESPEN guidelines [10].

Follow up

After the completion of treatment, all patients were asked to return to the hospital for examination every 3 months for the first years, every 6 months for the next 2 years, and then annually. The duration of follow-up was calculated from the day of treatment to the day of death or May 2017.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Science (SPSS for Windows, version 17.0, SPSS Inc., Chicago, IL) program. The relationships between clinical characteristics and high/low NRS-2002 groups were examined by Chi-square test or Fisher's exact test. The Kaplan–Meier method and log-rank tests were used for 5-year PFS analyses. Univariate and multivariate analyses of Cox regression proportional hazard model were used to evaluate the influence of each variable on PFS with the enter method. Hazard ratio (HR) with 95% confidence interval (CI) was used to quantify the strength of the association between predictors and survival. A 2-tailed p-value ≤0.05 was considered statistically significant.

Results

Clinicopathological characteristics of patients

The basic characteristics of the studied patients are shown in Table 1. Among the 227 patients, 54 (24%) were female and 173 (76%) were male. The median age prior to surgery was 62 years (range 40–82 years). The location of the tumors mostly occurred in the middle third (149/227, 65%) and the lower third (69/227, 30%) of the esophagus. In stage III or lymph node-positive stage II–III ESCC patients receiving postoperative

chemoradiation; According to this criteria, in our cohort, 61 (27%) underwent esophagectomy alone, 166 (73%) received postoperative chemotherapy or radiotherapy. None of these patients received neoadjuvant therapy before surgery. The median follow-up period was 37 months (range 6–72 months). During the follow-up time, 159 (70%) occurred in tumor recurrences, (30 cases with surgical anastomosis recurrences, 79 cases with locally regional lymph node metastasis, and 50 cases with distant metastasis).

Table 1: Clinicopathological characteristics of 227 ESCC patients receiving surgery

Characteristic		**Patients, n (%)**
Sex	male	173 (76)
	female	54 (24)
Age	Mean±SD	62.44±0.48
	Median (range)	62.00 (40-82)
Tumor location	Upper 1/3	9 (5)
	Middle 1/3	149 (65)
	Lower 1/3	69 (30)
Differential grade	well	15 (7)
	moderately	152 (67)
	poor	60 (26)
T classification	T1+T2	93 (41)
	T3+T4	134 (59)
N classification	N0	119 (52)
	N1+N2	108 (48)
TNM stage	I	13 (6)
	II	107 (47)
	III	107 (47)
Adjuvant therapy	NO	61 (27)
	YES	166 (73)
Recurrence	NO	68 (30)
	YES	159 (70)
NRS-2002	Mean±SD	2.09±0.76
	Median (range)	2.00 (1.00-5.00)

PFS according to NRS-2002 status

For all patients, the median PFS time was 15 months (CI: 11.924-18.076); The PFS rates at the 1-, 3- and 5-year period were 60.8%, 33.9% and 19.8%, respectively; As is shown in Figure 1, in the NRS-2002 < 2.0 group, the 1-, 3-, and 5-year PFS rates were 65.7%, 41.2% and 37.3% separately, while in the NRS-2002 ≥ 2.0 group, the PFS rates were 56.8%, 7.2% and 5.6% respectively (χ^2=27.986, *P*=0.000).

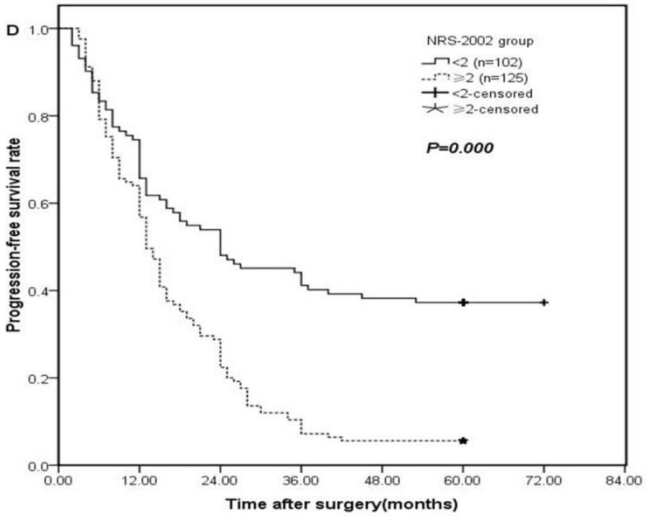

Figure 1: Kaplan–Meier survival curves for 1-, 3-, and 5-year PFS divided by NRS-2002 < 2 and NRS-2002 ≥ 2with ESCC patients receiving surgery

Univariate and multivariate survival analyses

The results of univariate and multivariate Cox analysis of the factors related to PFS were shown in Table 2. In univariate analysis, the following factors were significantly associated with PFS: T stage, N stage, TNM stage, differential grade and NRS-2002 (all $P<0.05$). The multivariate Cox regression analysis showed that NRS-2002 (HR = 1.740; 95% CI 1.242-2.437; $P = 0.001$), differential grade (HR = 1.015; 95% CI 1.004-1.238$P = 0.048$)) and TNM stage (HR =1.350; 95% CI 1.121-1.696; $P = 0.035$) were independent prognostic factors for PFS in patients with ESCC after surgery.

Table 2: Univariate and multivariate Cox analysis of survival for 277 ESCC patients receiving surgery

Factors	Univariate Cox analysis			Multivariate Cox analysis		
	HR	***95%CI***	***P-value***	***HR***	***95%CI***	***P-value***
Age(<62/≥62)	0.854	0.636-1.146	0.293	-	-	-
Sex(male/female)	1.291	0.909-1.835	0.154	-	-	-
Location(upper+middle /lower)	1.143	0.834-1.566	0.405	-	-	-
Differential grade (Well +middle/poor)	1.216	1.091-1.425	0.012	1.015	1.004-1.238	0.048
T stage(T1+T2/T3+T4)	1.179	1.006-1.587	0.028	-	-	-
N stage(N0/N1+N2)	1.418	1.016-1.763	0.032	-	-	-
TNM stage(I+II/ III+IV**)**	1.468	1.101-1.845	0.021	1.350	1.121-1.696	0.035
NRS-2002(<2.0/≥2.0)	2.226	1.628-3.043	0.000	1.740	1.242-2.437	0.001

Discussion

Malnutrition is common in many cancers and is associated with tumor progression. In this clinical study, we investigated the significance for the survival prognosis of pre-treatment NRS-2002 score in patients with ESCC treated with surgery. This study indicated that NRS-2002 was independent risk factors for PFS; To the best of our knowledge, this is the first report to demonstrate the clinical significance of NRS-2002 in patients with ESCC by surgery.

Malnutrition has been recognized as an important prognostic factor in cancer patients. In 1980, Dewys et al [13] reported a shorter survival in malnourished compared with well-nourished patients, since then, the association between nutritional risk and clinical outcome has also been demonstrated in a large cohort of patients including different types of malignancies [14]. At present, there are many assessment methods applied to nutritional evaluation, among these, the nutritional risk screening 2002 (NRS-2002) is a valid method for identifying risk patients and those who will benefit from nutritional treatment [9]. A previous study has shown that 28% of patients were at nutritional risk based on NRS-2002, and 34 % were malnourished according to PG-SGA in head and neck cancer; NRS-2002 cut-off score of ≥2 compared with the nutritional status according to PG-SGA showed 77 % specificity and 98 % sensitivity. These results suggest that NRS-2002 seems to be a reliable indicator of malnutrition, while NRS-2002 with the cut-off score of ≥2 seems to be more reliable for nutrition screening in head and neck cancer patients prior to oncological treatment [15]. Because of PG-SGA requiring specialized nurses to implement and needing heavy workload and long-time evaluation in everyday clinical practice, in contrast, the methods of NRS-2002 is simple and fast, so our present study cohort adopts NRS-2002 as nutritional risk assessment tool to stratify patients in different groups. The results of this study showed that PFS of ESCC patients in the NRS-2002 < 2.0 group were obviously improved compared with patients in the NRS-2002 ≥ 2.0 groups. These result indicated that NRS-2002 might be an excellent instrument in predicting the association between nutritional risk and clinical outcome, therefore, preoperative nutritional support was necessary in ESCC patients with a preoperative nutritional score (NRS-2002) ≥2. NRS-2002 was the first one developed via evidence-based medicine in the world, with a great advantage of the prediction of malnutrition risk, and it was applicable for a preoperative assessment for patients with ESCC receiving surgery, with the characteristics of non-invasiveness, objective evaluation, convenience and generalization.

The limitations of this study are as follows: First, it was a single-institution, retrospective study. Second, relying on recalled weight, height and food intake from the medical record might have caused bias in assessing BMI and weight change, and ultimately had some effect on NRS-2002 rating; Third, 227 patients with ESCC were

enrolled in this study and the sample size is relatively small and may be insufficient to strengthen our results. Given these limitations, future larger randomized trials are needed to clarify these results.

In conclusion, this study demonstrated that NRS-2002 were promising as a predictive marker for predicting clinical outcomes in patients with ESCC receiving surgery. However, considering the retrospective nature of this study, large-scaled prospective trials are still warranted to verify our results.

Conflicts of Interest

The authors declare no competing financial interests.

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