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Nutritional status and risk factors for malnutrition in CRC patients undergoing neoadjuvant therapy.

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Abstract

Colorectal cancer is one of the most common malignancies in China and worldwide. Neoadjuvant radiochemotherapy has inspiring therapeutic effect in treating colorectal cancer with high risk of recurrence. However, malnutrition is prevalent in patients with colorectal cancer and causes clinical deterioration. To investigate the impact of neoadjuvant radiochemotherapy on the nutritional status of colorectal cancer patients, we interviewed 310 colorectal cancer patients, collected information, and analysed the relationship between risk factors, Adverse Events (AEs), and nutritional status using the screening tool of NRS2002. The results showed that patients in nutritional risk increased from 83.9% to 92.2% after anti-cancer therapy. In addition, the one identified as undernourished increased from 15.2% to 19.6% during the same period. Importantly, the nutritional risk was estimated to exist in 86.9% of patients older than 65 years, which is significantly lower in younger patients (80.9%). Additionally, constipation, diarrhoea, and oedema/ascites were the leading symptoms jeopardizing colorectal patients' nutritional status. Patients identified as being at risk at the first-admission assessment had a higher incidence of anticancer therapy-related AEs compared with no-risk patients. In conclusion, considerable patients with colorectal cancer were in poor nutritional status before and after neoadjuvant therapy. Comprehensive nutritional assessment and appropriate nutritional intervention is necessary in the treatment of colorectal cancer.

Keywords: Colorectal cancer, Neoadjuvant therapy, Nutrition, Risk factors.

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Introduction

Colorectal Cancer (CRC) is one of the most deadly malignancies with approximately 376300 new cases diagnosed in 2015 and will account for 191000 deaths in China [1]. Due to the prevalence of obesity and unhealthy behaviors, there has been a marked increase in the incidence during the recent decades. Neoadjuvant therapy and standard surgical technique involves total mesorectal excision have dramatically decreased the rate of recurrence and increased long-term survival in colorectal patients [2]. However, clinical outcome in patients with CRC still unfavorable and was considered to be associated with sustained malnutrition [3]. Complications from malnutrition may deteriorate prognosis of malignancy and increase management costs.

Malnutrition is a structural and functional alteration of the body composition, which encompasses both nutrient loss and nutrient gain [4]. In the radiochemotherapuetic scenario where there occurs malnutrition, there is a lack of energy, protein, vitamin, and trace elements for hematogenesis, defense against infection, optimal organ function, and rehabilitation [5]. As for gastrointestinal cancer, which affects the intake and absorption of nutrients, patients have poorer nutritional status and higher complication frequency than those with other malignant tumors [6]. Reasonably, a higher incidence of malnutrition is seen in gastrointestinal cancer patients undergoing radiochemotherapy, and results in severe adverse events (AEs) on clinical outcomes [7,8]. Indeed, the selection of screening tools and the relation between specific AEs and malnutrition is still controversial.

Prompt and precise diagnosis is an important aspect of effective management of malnutrition. A variety of laboratory test and anthropometric measurements that associated with the morbidity and mortality in clinic are employed in assessing malnutrition, including weight change, arm muscle circumference, tricipital skin fold thickness, serum albumin and prealbumin, serum creatinine, nitrogen balance [9]. These methods allow nutrition assessment to be an integral part of routine clinical practice to optimize nutritional support for critically ill patients. However, the evaluation of nutritional status over a short period is still difficult and quite challenging,

since most of these indicators could merely reflect long-term variation of nutrient supply and may underestimate short-term nutrient demand [10]. Practically, some indicators have other obvious limitations, such as time consuming, poor specificity, expertise requests and low predictive value [10].

The Nutritional Risk Screening 2002 (NRS-2002) is a tool proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines mainly for detecting indications for nutritional support [11]. Our study is to evaluate the nutritional situation of CRC inpatients using NRS2002; to investigate the risk factors of malnutrition in CRC; and to evaluate the relation between nutritional risk and AEs in those patients during neoadjuvant therapy in order to improve clinical outcomes.

Methods

Patients

From January 2014 to December 2015, a total of 310 patients (range from 41 to 71 years old) diagnosed with colon adenocarcinoma liver metastasis or rectal cancer, were considered as high-risk groups for late recurrence (defined as those with a Clinical Risk Score (CRS) of ≥ 3) [12] at our institution. They were recommended to receive neoadjvant chemotherapy or radiochemotherapy before surgery, and recruited in our study. There were 187 male and 123 female patients. Patients with other primary tumor in the previous 5 years and comorbidities unfit for the radiochemotherapy were excluded from this study. Baseline patient evaluation consisted of clinical examination, laboratory tests, colonoscopy with biopsy, and abdominal Computer Tomography-scan (CT-scan) and Magnetic Resonance Imaging (MRI).

Therapy

Patients with liver metastases in this study received 3 weekly cycles of preoperative chemotherapy: CapeOX-oxaliplatin (130 mg/m^2, i.v. gtt, 2 h infusion, day 1) and capecitabine (1000 mg/m^2, p.o, Bid, 1-14 d). Patients with rectal cancer received a total dose of 45 Gy (1.8 Gy per fraction, 5 fractions per week for 5 weeks) in conjunction with 3 cycles of CapeOX-oxaliplatin before surgery.

Nutritional assessment

NRS2002 can reflect the nutritional risk and the severity of disease, and consists of 5components. It includes: (I) the impact of primary disease severity on nutritional status; (II) body weight changes during the last 1 to 3 months; (III) changes in dietary intake in preceding week; (IV) Body Mass Index (BMI); and (V) the nutritional risk score plus 1 for patients over 70 years old. Patients were classified according to the total scores: at no risk, 0; at low risk, 1-2; at medium risk, 3-5; and at high risk, >5 of malnutrition. Undernourishment is defined as BMI<18.5 kg/m^2 or serum Albumin (ALB) level<35 g/L.

All patients were interviewed by trained medical staffs within 24 h of first admission to collect the baseline information, including demographic information, medical data, and information about nutritional status according to the items in the NRS2002. Patients were interviewed again before operation to conduct reassessment. Patients unable to communicate with the study's personnel were excluded. Participants were informed about the aim of the study and signed consent forms. This study was approved by the Ethics Committee of Zhuji People's Hospital.

Statistical analysis

All data were presented as $\bar{x} \pm S$ or percentages, and processed by using SPSS22.0 statistical software. Differences in data were either measured by chi-square test, or compared with Mann-Whitney test. A P value<0.05 was considered statistically significant.

Results

Demographic data

The demographic data of 310 patients (male: female=1.52:1) upon admission were listed in Table 1. The median age of these patients was 56.3 ± 17.2 years old and 68.1% of the population was older than 65 years. The primary tumor site was rectum (34.2%), colon (63.95) and colorectum (1.9%). In our patient population, 173 (55.8%) patients had stage II disease, and 137 (45.2%) cases were graded stage III. Cardiovascular disease (31.3%), diabetes (25.2%), chronic lung diseases (13.5%), liver diseases (4.8%), and kidney diseases (24.2%) were the most common comorbidities observed in our population. The BMI was 23.8 ± 6.2 kg/m^2 in average. Notably, undernourishment was observed in 15.2% of patients (47/310) at first admission, who had either a substandard BMI value or a low serum ALB level. Before surgery the number has risen to 19.6% (61/310), suggesting a deterioration of nutritional status among patients after radiochemotherapy.

Table 1. *Demographic information of patients.*

Feature	Values (N (%))
Gender	
Male	187 (60.3)
Female	123 (39.7)
Age	
≥ 65	153 (68.1)
<65	157 (31.9)
Tumor site	
Colon	198 (63.9)
Colorectum	6 (1.9)
Rectum	106 (34.2)

Stage	
II	173 (55.8)
III	137 (45.2)
Fundamental diseases	
Cardiovascular disease	97 (31.3)
Diabetes	78 (25.2)
Lung diseases	42 (13.5)
Liver diseases	15 (4.8)
Kidney diseases	75 (24.2)

BMI[#] (kg/m^2)	23.8 ± 6.2
Under weight	47 (15.2)
Normal weight	154 (49.7)
Over weight and obese	112 (36.1)
ALB level	
<35 g/L	41 (13.2)
≥ 35 g/L	269 (86.8)
[#]Values expressed as median ± SD.	

Table 2. *Nutritional risks screening before neoadjuvant therapy (N (%)).*

Nutritional risk	Gender		Age		Undernourishment		Tumor site		Stage	
	Male	Female	≥ 65	<65	Yes	No	Colon	Rectum	II	III
No risk	28 (15.0)	22 (17.9)	20 (13.1)	30 (19.1)	2 (4.3)	48 (18.3)	17 (8.6)	31 (29.2)	37 (21.4)	13 (9.5)
Low risk	83 (44.4)	62 (50.4)	68 (44.4)	77 (49.0)	8 (17.0)	137 (52.1)	77 (38.9)	65 (61.3)	85 (49.1)	60 (43.8)
Middle risk	63 (33.7)	22 (17.9)	46 (30.1)	39 (24.8)	16 (34.0)	69 (26.2)	77 (38.9)	7 (6.6)	39 (22.5)	46 (33.6)
High risk	13 (6.9)	17 (13.8)	19 (12.4)	11 (7.0)	21 (44.7)	9 (3.4)	27 (13.6)	3 (2.8)	12 (6.9)	18 (13.1)
Z	0.943		2.233		7.076		7.539		3.655	
P value	0.346		0.026		0		0		0	

Nutrition risk in colorectal patients

Nutritional risk was evaluated with the NRS2002 test. At the baseline assessment, 260 cases (83.9%) exhibited nutritional risk at various levels. As shown in Table 2, the differences in incidence of nutritional risks were analysed as patients were categorized by gender, age and nourishment. No significant difference could be detected after adjusting for gender (Z=0.943, P=0.346). Nevertheless, the nutritional risk was estimated to exist in 86.9% of patients older than 65 years, which is significantly lower in younger patients (80.9%) (Z=2.233, P=0.026). Meanwhile, patients identified as undernourished before neoadjuvant therapy had relatively high risk of malnutrition (Z=7.076, P=0.000). We also investigated the relationship between disease features and nutritional status. The risk of malnutrition in colon cancer is significantly higher than that in the rectal cancer (Z=7.539, P=0.000), and patients with III stage disease were more likely to exhibit nutritional risk than patients with lower stage disease were (Z=3.655, P=0.000). The most common symptoms of CRC included constipation (72.9%), diarrhoea (62.9%), appetite loss (28.7%), abdominal distension (23.9%) and oedema/ascites (19.0%). Importantly, the results of NRS2002 assessment demonstrated that the gastrointestinal symptoms, including constipation (χ^2=6.702, P=0.010), diarrhoea (χ^2=5.674, P=0.017), and oedema/ascites (χ^2=8.741, P=0.003) aggravated nutritional risks. While neither abdominal distension, nor appetite loss was related to nutritional risks (Table 3).

Table 3. *Relationship between symptoms and the nutritional risk (N (%)).*

Risk factors	Nutritional risk		χ^2	P value
	No risk (n=50)	Have risk (n=260)		
Abdominal distension	11 (22.0)	63 (24.2)	0.114	0.734
Diarrhoea	24 (48.0)	171 (65.8)	5.674	0.017
Constipation	29 (58.0)	197 (75.8)	6.702	0.01
Edema/ascites	2 (4.0)	57 (21.9)	8.741	0.003
Appetite loss	15 (30.0)	74 (55.4)	0.048	0.825

Impact of chemotherapy on the nutritional status

After treated with 3 cycles of XELOX, patients facing CRC surgery were interviewed to evaluate the impact of radiochemotherapy. As shown in Table 4, these was a decrease in patients with no or lower risk, from 16.1 to 7.7% and 46.8% to 31.9%, respectively. Importantly, patients with risk were significantly increased from 83.8% to 92.3% (Z=6.049, P=0.000). Similar to the alteration of nutritional risk, the percentage of undernourished patients was also significantly raised from 15.2% at the baseline estimation to 28.1% before surgery (χ^2=15.232, P=0.000) (Table 5). These results strongly suggested that neoadjuvant therapy results in the possibility of

decreasing or jeopardizing nutrient intake in CRC patients whose normal food intake is already inadequate due to compromised digestive function. Furthermore, we investigated the role of nutritional status in the development of radiochemotherapy-related AEs. Compared with patients without risk, patients with nutritional risk before treatment had a higher incidence rate of anticancer therapy-related AEsin diarrhoea (Z=6.206, P=0.013), fatigue (Z=5.248, P=0.022), and vomiting (Z=6.060, P=0.014). However, nausea, anorexia, neutropenia and pain-abdomen were no statistically associated with nutritional risk as shown in Table 6.

Table 4. *Alteration of nutritional risk screening after neoadjuvant therapy (N (%)).*

Nutritional risk	First admission	After therapy
No risk	50 (16.1)	24 (7.7)
Lower risk	145 (46.8)	99 (31.9)
Middle risk	85 (27.4)	123 (39.7)
High risk	30 (9.7)	64 (20.6)
Z	6.049	
P value	0	

Table 5. *Relation between nutritional status and neoadjuvant therapy (N (%)).*

Nutritional status	First admission	After chemotherapy
Undernourishment		
Yes	47 (15.2)	87 (28.1)
No	263 (84.8)	223 (71.9)
χ^2	15.232	
P value	0	

Table 6. *Relationship between nutritional risk and treatment-related side effects (N (%)).*

Toxicity	Nutritional risk		χ^2	P value
	No risk (n=24)	Have risk (n=286)		
Diarrhoea	9 (37.5)	181 (63.3)	6.206	0.013
Fatigue	7 (29.2)	153 (53.5)	5.248	0.022
Nausea	8 (33.3)	109 (38.1)	0.215	0.642
Vomiting	5 (20.8)	134 (46.9)	6.06	0.014
Appetite loss	8 (33.3)	138 (48.3)	1.978	0.16
Neutropenia	13 (54.2)	137 (47.9)	0.35	0.555
Pain-abdomen	9 (37.5)	87 (30.4)	0.519	0.471

Discussion

CRC is one of the most common human malignant tumors and major public health issues in the world. Seventy percent of all malignant colorectal tumors arise in the colon, and it can disperse either locally or systemically in the liver and other long distant organs [13]. In patients with metastatic CRC, median cancer-specific survival time is 8.4 month and the 5-year cancer-specific survival rate is no more than 2% [14]. Therefore, multimodality treatment method, including surgery, preoperative and postoperative adjuvant therapy, has been employed to achieve better outcome in clinic. The therapeutic mechanism for radiochemotherapy is that radiation inhibits tumor cell proliferation and induces cell apoptosis thereby inhibits tumor growth, meanwhile chemotherapy could enhance radiotherapy effect [15]. Compared with postoperative radiochemotherapy alone, neoadjuvant therapy has the potential to reduce the incidence of distant failure in high-risk colorectal patients, increase sphincter preservation rates, and improve pathological complete response [16]. However, it is well known that the combined modality treatment of chemotherapy, radiotherapy and surgery can cause various acute and chronic symptoms that limit food intake and, thereby, deteriorate nutritional status [17].

Malnutrition occurs in 40%to 80% of cancer patients, prevailed in 50% to 80% of patients depending on tumor type, tumor location, tumor spread, anti-cancer agents received and the type of nutritional assessment tool used [18]. Researches in patients with head and neck cancer, breast cancer and gastrointestinal cancer have confirmed the increasing mortality resulting from malnutrition [8,19-21]. In fact, malnutrition rather than cancer and aggressive treatment contribute to about 80% of cancer-specific mortality [22]. Classic assessment methods including medical information collection and body index measurement can be easily performed as a non-invasive approach to evaluate patients' nutritional status. However, these medical information and physical index, which can only reflect long-term change of nutritional status, are sometimes overlooked or inadequate in recognize underlying malnutrition [23]. For a critically ill patient, muscle loss is very early and rapidly, 17% of muscle mass could be lose in 10 days in the intensive care unit [24].

Predictive parameters possessing both sensitivity and specificity for determining who is at high risk of nutrition are optimal for the clinician to design nutrition care plan in cancer treatment. Protein requirement can be determined by nitrogen balance, which is an objective and reliable indicator to reflect the equilibrium between protein synthesis and metabolism [25]. However, it's tedious and difficult to fulfil the requirement of collecting urine for exact 24 h. Serum protein level including total protein, albumin, prealbumin, and transferrin is another index to reflect protein nutritional status. Theoretically, serum protein should be more sensitive to reflect the change of nutritional status due to a short half-life. While their application is quite limited, it can be easily affected by fundamental diseases such as dehydration, infection, chronic renal dysfunction, and liver disease [26]. As previous study claimed that serum album is an index of inflammation or disease severity rather than a marker of malnutrition [27]. For these reasons, we did not include serum album into the assessment of nutritional status in this study. Additionally,

there are 115 patients (37.1%) at first admission were assessed as having above-middle risk and needed nutritional support, but only 47 patients (15.2%) were considered undernourished as estimated by BMI and ALB level. If only BMI or serum ALB is measured, an overweight patient or patient with normal serum albumin level may not be judged as having nutritional risk. To precisely predict nutritional risk and diagnose malnutrition, several composite assessment tools had been introduced into the clinical routine, such as NRS2002. Following assessment, the clinicians can specifies an individualized plan about nutritional intervention for patients with potential risk of nutritional deficiencies. Consequently, targeted nutritional therapy can be initiated within 24 to 48 h of admission.

Indeed, 70% of total cases of CRC developed in patients over 65 years old, and the survival rate of them is much lower than average [28]. There are several factors associated with poor outcome of elderly patients. Firstly, it can be attributed to low socio-economic status, lack of access to healthcare services, and comorbid conditions [29]. Secondly, delayed diagnosis due to lower awareness of CRC might be one of the major factors that lead to the lower survival rate in Chinese elderly CRC population [30]. Finally, elderly cancer patients are prone to affect by malnutrition, especially those with gastrointestinal cancer [31]. NRS2002 was further recommended as a reliable and convenient tool to accurately identify elderly inpatients who have clinically significant malnutrition by the Nutrition Support Group for Geriatric Patients of the Chinese Society for Parenteral and Enteral Nutrition (CSPEN) to facilitate malnutrition diagnosis and help standardize malnutrition care [32]. Patients, whose NRS2002 scores higher than 3, were considered to have high nutritional risk, and the rest were thought to have low nutritional risk or be well-nourished. Previous studies using NRS2002 demonstrated that malnutrition is associated with high incidence of complications and morbidity, prolonged postoperative hospitalization, and delayed chemoradiation therapy in elderly patients with hematologic and solid tumors [33,34]. In our study, 83.8% of CRC patients facing neoadjuvant therapy had malnutrition risk, which was increased to 92.3% during treatment. Whereas, patients with no or low risk were decreased. We suppose that this dramatic alteration was associated with the gastrointestinal damage resulting from systematic chemotherapy and pelvic radiotherapy [35]. Additionally, nutritional risk was more common in patients 65 years of age or older in the present study, which was consistent with previous report [27]. On the other hand, data of gender differences in the prevalence of high risk of malnutrition in gastrointestinal cancer patients were quite controversial [7,8,36]. As demonstrated in the present study, no gender difference in the prevalence of high nutritional risk was observed in colorectal patients. Importantly, compared with rectal cancer, the nutritional status of patients with colon cancer was more likely to be affected, which was in coincidence with previous study [37]. Since rectal cancer occurs in the lower gastrointestinal tract, tumor in this region has less influence on the intake and absorption of nutrients [8].

Malnutrition was related with AEs of radio- or chemotherapy in previous studies [38]. However, the boundary between the symptoms of gastroenterology diseases and the side effects of anti-cancer therapy such as diarrhoea and appetite loss in previous studies is ambiguous [39-41]. In our study, diarrhoea, constipation, and oedema/ascites contributed to the increase of nutritional risk in patients with CRC before neoadjuvant therapy, while abdominal distension and appetite loss did not alter the nutritional status of our patient population. During radiochemotherapy, diarrhoea and vomiting are main causes of malnutrition in patients with CRC. While nausea, appetite loss, and pain-abdomen do not influence the nutritional status, even these symptoms might lead to a decrease in nutrient intake as well.

This study had several major limitations. First, the small population size might decrease the accuracy of the statistical analysis leading to an underestimated consequence of malnutrition. Second, due to short observation time and the limited availability of the precious sample, there were no analysis of the postoperative data, such as long-term survival outcome and the tumor regression grading [42]. Third, the impact of comorbid conditions and nutritional treatment on mortality, quality of life or tolerance to anti-cancer treatment was not analysed. Future studies should focus on obtaining such information.

Conclusion

To improve the outcome of CRC patients in old age, preoperative (neoadjuvant) chemoradiation therapy was introduced into the treatment strategy. As a result, it increased the feasibility of preserving surgery with desirable tolerability to chemotoxicity and sustained response rate. However, the prevalence of malnutrition and increase of nutritional risk during neoadjuvant radiochemotherapy are common among CRC patients as demonstrated in the present study, suggesting accurate nutritional assessment and appropriate nutritional intervention is necessary.

Conflict of Interest

No declaration.

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