Original Article

Prognostic nutritional index relevance in chemoradiotherapy for advanced oral cavity, oropharyngeal and hypopharyngeal cancer

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Background and Objectives: This study was designed to evaluate the impact of the prognostic nutritional index (PNI) on treatment-related toxicities and tolerance in patients with advanced head and neck cancers who were undergoing concurrent chemoradiotherapy (CCRT). **Methods and Study Design:** We retrospectively analyzed and compared the clinical characteristic, toxicities and survival of 143 patients with stage III, IVA, and IVB head and neck cancer who were treated with CCRT according to their PNI between 2007 and 2010. **Results:** Low PNI was correlated with T classification and advanced tumor stage. Patients with low PNI were less likely to tolerate CCRT, required tube feeding support more frequently and had higher percentages of grade 3/4 hematological toxicities, sepsis and toxic death. **Conclusions:** Pretreatment PNI predicts treatment-tolerance and toxicity in patients with advanced head and neck cancer undergoing CCRT.

Key Words: prognostic nutritional index, head and neck cancer, chemoradiotherapy, toxicities, malnutrition

INTRODUCTION

The majority of patients with head and neck cancer present with locally advanced disease at the time of diagnosis,[1] for which multimodal treatment including surgery, radiotherapy and chemotherapy are the main treatments.[2] Concurrent chemoradiotherapy (CCRT) for advanced head and neck cancer improves tumor control, survival rates, and chances of organ preservation.[3] Although the CCRT benefits, the appropriate management of CCRT related toxicity remains a clinical challenge during treatment period. Our previous report showed older patients were less likely to tolerate CCRT and tended to have more severe hematological toxicities and sepsis during treatment period.[4] Therefore, development of a useful tool to predict treatment tolerance and toxicities before CCRT is particularly important.

More than half of the patients with advanced head and neck cancer are malnourished at the time of diagnosis.[5] Malnutrition is a common complication of patients undergoing CCRT.[6] Malnutrition also impairs immune functions.[7] Prediction of treatment tolerance and toxicities by evaluating pretreatment immunonutritional status can be a useful means of identifying a strategy to prevent severe complications and possible improve outcome. Assessment of the systemic immunonutritional status has been introduced of the prognostic nutritional index (PNI), a continuous variable based on serum albumin concentration and total lymphocyte count in peripheral blood. The PNI was originated to assess the perioperative immunonutritional conditions and used to evaluate the risk of postoperative complications and mortality in patients undergoing gastrointestinal surgery.[8] Recently, the PNI has been demonstrated as a prognostic factor in various

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malignant tumors, including colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma, pancreatic cancer and small cell lung cancer.[9-17] Yang et al[18] also reported that low PNI predicts unfavorable distant metastasis-free survival in nasopharyngeal carcinoma. However, no studies have investigated the role of PNI as a potential predictive factor for CCRT related toxicities and tolerance in advanced head and neck cancer patients. We hypothesized that poor immunonutritional status assessed by PNI is associated with decreased treatment tolerance and increased side effects caused by CCRT. To test our hypothesis, we examined the correlation between pretreatment PNI and CCRT related toxicities and tolerance in advanced head and neck cancer patients undergoing CCRT.

METHODS

Study site and population

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No.: 201701087B0). Patients who were confirmed by biopsy to have stage III, IVA, or IVB head and neck squamous cell carcinomas (TNM stage reclassified according to the American Joint Committee on Cancer staging system published in 2002) of the oral cavity, oropharynx, and hypopharynx, and who were treated with primary CCRT were eligible for this study. Patients with clinical evidence of acute infection or who were diagnosed with recurrent tumors, distant metastases, other concomitant active cancers, or chronic active inflammation were excluded from the study. Between January 2007 and December 2010, we retrospectively reviewed the records of 154 patients with stage III, IVA, and IVB head and neck squamous cell carcinomas who had undergone CCRT at our institution. All patients received follow up until December 2012. Eleven patients were excluded from the study. Six patients withdrew from the study during the CCRT schedule, and were not present for follow-up diagnosis due to poor financial support (three patients) and relocation (three patients). Three patients underwent repeat CCRT for recurrent disease, and two were diagnosed with a concomitant active cancer. A total of 143 patients who received CCRT were included in the analysis. All patients received intensity-modulated or arc technique radiotherapy on 5 consecutive days each week at a conventional fractionated daily dose of 1.8 or 2 Gy. The total prescribed dose for radiotherapy was 70–74 Gy. The initial treatment volume included the tumor bed and regional lymphatics. After receiving 46–50 Gy, the treatment area was reduced to irradiate the tumor bed and regional lymph nodes. Breaks from radiotherapy were suggested if the following conditions occurred: (1) severe hematological (grade ≥3 neutropenia and pancytopenia), or non-hematological toxicity (grade ≥3 mucositis grade and emesis), (2) body weight loss greater than 10% of the pretreatment value, (3) dehydration due to the onset of absolute dysphagia, and (4) critical medical morbid status including sepsis, hyperglycemia and unexplained febrile episodes. Before radiotherapy breaks were taken, patients were informed of the benefits and disadvantages of delaying radiotherapy schedules. If a patient's performance status did not improve from toxicities or comorbidities, or declined after medical therapy, e.g., for example Eastern Cooperative Oncology Group (ECOG) performance status ≥3, radiotherapy was discontinued permanently according to the physician's judgment. The chemotherapy regimens were administered according to the treatment guidelines at our institution, including cisplatin 40 mg/m^2 every week or 100 mg/m^2 every 3 weeks.

Data collection

For each case, we recorded age, sex, primary site of disease, TNM tumor stage at diagnosis (American Joint Committee on Cancer), Eastern Cooperative Oncology Group performance status, exposure to smoking, body weight before and after treatment and biological parameters [serum albumin (Alb) and peripheral blood total lymphocyte count (TLC)]. Only those measurements take fewer than 7 days prior to treatment initiation were included. Treatment tolerance was evaluated by assessing the total dose of radiation delivered, the total dose of cisplatin received, completion rate of planned radiotherapy, overall treatment time of radiotherapy, the occurrence of sepsis (cultures from the bloodstream were used to detect the presence of pathogens that made the patients ill and febrile), the hematological toxicity grade ≥3 (including leukopenia, neutropenia, thrombocytopenia, and anemia), the mucositis/pharyngitis grade ≥3, and the nausea/vomiting grade ≥3, according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria.[19] Toxic death was defined as death related to treatment during CCRT.

Prognostic nutritional index

The pretreatment peripheral blood samples were collected to obtain the serum albumin and total lymphocyte count. The pretreatment prognostic nutritional index (PNI) was calculated as 10 × serum albumin value (g/dL) + 0.005 × peripheral lymphocyte count (per mm^3).[8]

Statistical analysis

Statistical analyses were performed using the SPSS statistical package, version 18.0 (SPSS, Inc., Chicago, IL, USA). Either independent Student t-tests (two tailed) (for age, body weight loss, total dose of radiotherapy and dose of cisplatin received, overall treatment time of radiotherapy), or the Pearson chi-square (X^2) test (for sex, tumor site, TNM stage, exposure to smoking, completion rate of planned radiation, feeding tube placement, occurrence of ≥ grade 3 toxicities, sepsis and toxic death) was used for statistical comparisons between the different PNI groups.

RESULTS

Before CCRT initiation, the patients' ages ranged from 26 to 54 years (median, 54 years), and the dominant sex was male (93.0%). The median value of PNI was 36.1 (range, 20.1-50.3). There was no consensus of optimal cut-off levels for PNI since an inherent enrollment difference exists in variations of disease, ethnicity, and measurement methodology among studies. We thus arbitrarily stratified patients according to the median level of PNI. The clinicopathologic characteristics of the 143 patients enrolled, including 72 in the low PNI group and 71 in the high PNI group, are summarized in Table 1. Patients with low PNI

Table 1. Demographic characteristics of patients before treatment according to the prognostic nutritional index (PNI)

	Low PNI	High PNI	*p* value
No. of patients	72	71	
Age (mean±SD), years	55.8±11.1	54.1±11.6	0.390
Gender, n (%)			0.497
Male	68 (94.4)	65 (91.5)	
Female	4 (5.6)	6 (8.5)	
TNM stage, n (%)			0.092
III	11 (15.3)	19 (26.8)	
IVA, IVB	61 (84.7)	52 (73.2)	
T classification, n (%)			0.014
T1	5 (6.9)	6 (8.5)	
T2	10 (13.9)	22 (31.0)	
T3	13 (18.1)	18 (25.4)	
T4	44 (61.11)	25 (35.2)	
N classification, n (%)			0.762
N0	17 (23.6)	20 (28.2)	
N1	8 (11.1)	9 (12.7)	
N2	40 (55.6)	38 (53.5)	
N3	7 (9.7)	4 (5.6)	
Tumor site, n (%)			0.885
Oral cavity	22 (30.6)	24 (33.8)	
Oropharynx	29 (40.3)	26 (36.6)	
Hypopharynx	21 (29.2)	21 (29.6)	
ECOG performance status, n (%)			0.365
0, 1	61 (84.7)	56 (78.9)	
2	11 (15.3)	15 (21.1)	
Exposure to smoking, n (%)			
Yes	61 (84.7)	61 (85.9)	0.840
No	11 (15.3)	10 (14.1)	
BMI (mean±SD), kg/m^2	22.5±4.97	23.7±3.77	0.190

PNI: Prognostic nutritional index; SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; BMI: Body mass index; TNM: tumor, node, metastasis.

were more likely to have an advanced T classifications (p=0.014) and tumor stage (p=0.092) (Table 1). As shown in Table 2, we compared treatment tolerance and toxicities between the two groups and found that patients with lower PNI were less likely to tolerate CCRT. This was true even when patients with low PNI received a significantly lower dose of cisplatin (p=0.018), had a lower completion rate of planned radiotherapy (p=0.052), or had a longer overall radiotherapy treatment time of radiotherapy (p=0.045). The total dose of radiation received was not different. Weight loss (p=0.124) is greater in low PNI group and the necessity for a feeding tube (p=0.021) was more common concerns in the low PNI group. There were no differences between the groups regarding the frequencies of grade 3/4 mucositis/pharyngitis and grade 3/4 nausea/vomiting during the CCRT period. Patients with low PNI have higher likelihoods of grade 3/4 hematological toxicities (p=0.044), sepsis (p=0.029), and toxic death (p=0.055). In the high PNI group, one patient died of neutropenic sepsis. In the low PNI group, four patients died of neutropenic sepsis, one died of empyema, and one died of tumor bleeding.

DISCUSSION

A low PNI implies a decrease in albumin and/or lymphocytes. Serum albumin is an important indicator of the host

Table 2. A comparison between treatment tolerance and treatment toxicities

	Low PNI	High PNI	*p* value
Total dose of RT completed, Gy	63.9±14.5	67.0±12.1	0.160
Completion rate of planned RT, %	88.9	97.2	0.052
Overall treatment time of RT, days†‡	54.1±4.9	52.4±3.8	0.045
Total dose of cisplatin completed, mg/m^2†	171±72.1	198±60.6	0.018
Weight loss, %†	-5.6±7.1	-3.7±6.6	0.124
Feeding tube placement, %	50.0	31.0	0.021
Grade 3/4 mucositis/pharyngitis, %	30.6	28.2	0.754
Grade 3/4 nausea/vomiting, %	30.6	23.9	0.375
Grade 3/4 any hematological toxicities, %	34.7	19.7	0.044
Sepsis during CCRT, %	19.7	7.0	0.029
Toxic death (grade 5 toxicity), %	8.3	1.4	0.055

PNI: Prognostic nutritional index; CCRT: Concurrent chemoradiotherapy; RT: radiotherapy.
†Data are expressed as mean±standard deviation.
‡Overall treatment time of RT limited to patients that complete the planned treatment.

inflammatory response and nutritional status.[20] The absolute lymphocyte count has been also assumed as an important participant in preventing cancer by initiating cytotoxic immune response.[21] Taken together, this existing evidence indicates that malnutrition and lymphocytopenia may serve as indicators of chronically impaired immune system. The median value of PNI reported in previous studies ranged between 40 and 60.[12-18,22] However, the median value of PNI was 36.1 in our study, which is relative lower than previous study. The possible explanation could be that only patients with locally advanced head and neck cancer were included in our study and patients with advanced tumor usually presented with malnutrition and impaired immune status.[23] Our study showed that low pretreatment PNI correlated with higher T classification and advanced tumor stage. It is unsurprising that higher T classification usually indicate larger tumor and may cause obstruction or swallowing impairment related symptoms and signs, which results in malnutrition. In addition, more advanced tumor may cause more systemic inflammation response reaction and abnormal metabolism, which may result in immunodeficiency. More importantly, patients with a low PNI were less likely to tolerate CCRT in this study. Overall, these patients had a relatively lower completion rate of planned radiotherapy, longer overall radiotherapy treatment time, and limited doses of cisplatin. Patients with a low PNI also require feeding tube support more frequently. Moreover, patients with a low PNI were more likely to manifest severe (grade 3/4) hematological toxicities, sepsis during the CCRT period, and even toxic death.

Patients with head and neck cancer are risk for nutritional deficiency.[24] CCRT are also considered to have negative impact on nutritional status.[25] Malnutrition damages immune functions and increases patient vulnerability to infection.[7] Our study proved that patients with low PNI were more likely to develop grade 3/4 hematological toxicities and increased risk of sepsis. This warrants great attention from physicians because sepsis can increase the risk of death during CCRT. Furthermore, the reported incidence rate of toxic death during CCRT is often less than 5%.[26-31] However, the toxic death rate in the low PNI group was 8.3% in current study, a much higher rate than the rate observed in the high PNI groups. The majority of toxic death patients died of infection. It is reasonable that patients with low PNI were usually malnourish and immunocompromised. Intensive treatment, such as CCRT, introduced in patients with low PNI increased risk of severe infection and ultimately increased risk of death. This finding is worth noting, as patient death during the course of treatment is a major concern for physicians when initiating therapy. Previous studies reported that pretreatment performance status, low body mass index, and a low total lymphocyte count are independent risk factors for early death during CCRT.[6] Our results indicate that the low PNI is also a risk factor for toxic death, suggesting that nutritional optimization is an important factor for patients with advanced head and neck cancer who plan to receive CCRT, and that pretreatment immunonutritional status assessed by PNI should be involved in clinical practice.

CCRT has been one of the main treatment strategies for locally advanced head and neck cancer.[2] During treatment, patients may suffer from many complications such as mucositis, dysphagia, nausea, and vomiting, which could lead to undernutrition and impaired immune functions. Patients with low PNI shown in this study were less likely to tolerate CCRT and more likely to develop grade 3/4 toxicities, infection and toxic death. Therefore, aggressive nutritional intervention and therapy for patients with low PNI are required throughout the CCRT period. Recently, nutrient support, via eicosapentaenoic acid (EPA) food components, has therefore attracted attention as a potential anti-tumor immunonutrition therapy.[32,33] We have previously conducted a randomized study and reported that the addition of several micronutrients and probiotics to an omega-3 fatty acid containing oral immune-enhanced nutritional supplement improved the maintenance of body weight, as well as serum albumin, and prealbumin levels in patients with head and neck cancer and cachexia who were undergoing CCRT.[34] Chitapanarux et al[35] also performed a randomized trial for an immune-enhanced formula containing arginine, glutamine, and Omega-3 fatty acids prescribed in head and neck cancer patients receiving CCRT and the result shows higher CCRT completion rate and decreased grade 3/4 hematologic toxicities in immune-enhanced formula group. Thus, improving the PNI via multimodal therapy, such as nutritional intervention and immune-enhanced formula may therefore help to improve a patient's condition, treatment tolerance, treatment-related toxicities in patients with advanced head and neck cancer undergoing CCRT. However, further large-scale prospective studies are required to fully determine whether improving the PNI will improve patient outcomes.

The limitations of this study include its retrospective, single-center design, and a potential bias in the selection of patients. Nevertheless, to our knowledge, this is the first study to assess the value of PNI in patients with advanced head and neck cancer treated with CCRT. This study used a simple and objective tool, the PNI, to examine patients' immunonutritional status and found that there is a strong association between the PNI and treatment-related toxicities. We also found that the PNI affects therapeutic tolerance. These results are particularly important, as they allow us to identify patients would be at a high risk of developing severe side effects, including toxic death, during the CCRT period. Therefore, patients with low PNI require more careful multidisciplinary assessment of their supportive care needs to ensure the successful completion of their treatment and to avoid subsequent treatment-related toxicities.

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AUTHOR DISCLOSURES

The authors declare that they have no competing interests and have no financial relationships with other organizations that may be grounds for a conflict of interest. All authors have nothing to disclose.

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