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Original article

Pre-therapeutic nutritional assessment for predicting severe adverse events in patients with head and neck cancer treated by radiotherapy

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SUMMARY

Background & aims: Malnutrition is common in patients with head and neck cancer (HNSCC). It may be related to severe adverse toxicity as a result of radiotherapy. The aim was to investigate nutritional screening factors for severe adverse events.

Methods: A retrospective chart review of 101 patients who underwent radiotherapy from 2009 to 2013 was performed. The relationships among severe adverse events and pretreatment nutritional parameters, including static variables (serum albumin, total protein, total lymphocyte counts, body mass index), dynamic variables (retinol-binding protein, transferrin, pre-albumin), and nutritional screening tools (Onodera's Prognostic Nutrition Index [O-PNI]; Nutrition Risk Index; Controlling Nutritional Status [CONUT] score; Nutritional Risk Screening 2002) were evaluated in addition to patient and treatment factors.

Results: According to the static parameters, approximately 30% of patients were malnourished before treatment. Twenty-four patients exhibited severe adverse events. On univariate analysis, combined chemotherapy, advanced staging, O-PNI <40, and CONUT score ≥5 were significant predictors of severe adverse events. Multivariate analysis revealed that O-PNI <40 and combined chemotherapy independently predict severe adverse events.

Conclusions: O-PNI is considered a useful nutritional factor for predicting severe adverse events in HNSCC patients undergoing chemoradiotherapy and facilitates the planning of aggressive nutritional interventions prior to treatment.

1. Introduction

Patients with head and neck squamous cell carcinoma (HNSCC) are often malnourished at the time of diagnosis, owing to dysphagia, anorexia, odynophagia, and mechanical obstruction [1]. Furthermore, they may also present with underlying chronic malnutrition at the time of presentation owing to tobacco and alcohol abuse, and unhealthy dietary habits [2]. In previous studies, malnutrition has been estimated in 30–50% of HNSCC patients [3,4]; variations in prevalence are attributed to various tumor localization and different definitions of malnutrition status. Malnutrition causes immunodepletion [5], reduced vitality, reduced resistance to the disease, and the potential for decreased wound healing [3]. Thus, malnutrition is closely associated with the incidence of severe adverse toxicity from radiotherapy (RT). Once severe adverse events occur, decreased oral food intake results in further malnutrition. This is clinically relevant, because severe adverse toxicity often leads to dose reductions, longer interruptions of treatment course [6], a prolonged hospitalization period, and impaired quality of life (QOL) [7]. Consequently, poor compliance with treatment and potential long-term severe toxicity adversely affects therapy efficacy [8]. Therefore, it has become essential to take nutritional status of the patients into account their management, as it helps determine the patient's tolerance of curative treatment. Investigation of nutritional factors predictive of severe adverse events may enable implementation of strategies for early and intensive nutritional interventions in high-risk patients prior to RT.

Although there are several parameters for evaluating nutritional status and many screening tools for nutritional risk have been assessed in the previous literature [9,10], no consensus has been

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reached concerning their use in HNSCC patients. The lack of well-defined prognostic and predictive factors hinders the possibility to provide tailored, individualized therapy to patients.

In the present study, we attempted to evaluate pre-therapeutic nutritional parameters, including biochemical data and several nutritional screening tools using convenient and objective variables to identify factors predictive of severe adverse events in HNSCC patients who underwent RT.

2. Material and methods

2.1. Patients

HNSCC patients who underwent RT in Saiseikai Utsunomiya Hospital between January 2009 and March 2013 were included in this retrospective study. Patients who underwent palliative RT or irradiation outside of the head and neck regions were eliminated. Patients previously treated with major surgery for resection and reconstruction of any head and neck organs were also excluded, while patients who underwent organ-preservation surgery, including laryngomicrosurgery, tonsillectomy, and partial glossectomy were included in this analysis. Tumors were staged according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC 7th ed., 2010) [11].

2.2. Treatment

In total, 101 patients were enrolled in this study. All patients were treated with intensity modulated RT (IMRT) in daily fractions of 2.0 Gy, 5 days per week. Of these, 71 patients underwent RT as primary definitive therapy with total doses of 60–66 Gy, and 30 patients underwent postoperative irradiation with total doses of 50–60 Gy. Induction chemotherapy (ICT) consisted in TPF schedule (docetaxel 70 mg/m^2 on day 1, cisplatin 70 mg/m^2 on day 1, and 5-fluorouracil 700 mg/m^2 from days 1–4), and was used in 30 cases with advanced cancer. Seventy-two patients received concurrent chemoradiotherapy (CCRT) according to the PF regimen (cisplatin 70 mg/m^2 on days 1 and 22, and 5-fluorouracil 700 mg/m^2 from days 1–4 and days 22–25) or CDDP only (cisplatin 70 mg/m^2, infused on days 1 and 22). Acute adverse effects of RT were assessed using the third version of the Common Terminology Criteria for Adverse Events (CTCAE), as described in the Appendix. Grades 3 and 4 were considered severe adverse effects.

2.3. Parameters

Pre-therapeutic nutritional parameters were selected based on inexpensive, readily available, and convenient variables. Data collection was completed before the initiation of RT. Total protein (TP), serum albumin (Alb), total lymphocyte count (TLC), and body mass index (BMI, kg/m^2) were assessed as static nutritional parameters. The values of TP, Alb, TLC, and BMI were considered "low" when below 6.5 g/dl, 3.5 g/dl, 1600/μl, and 18.5 kg/m^2, respectively. Rapid turnover protein (RTP) including retinol-binding protein (RBP), transferrin (TF), and pre-albumin (Pre-Alb) were measured as dynamic nutritional parameters. These parameters indicated malnutrition when RBP <2.4 mg/dl, TF <200 mg/dl, and Pre-Alb <22 mg/dl. Furthermore, nutritional screening tools such as Onodera's Prognostic Nutrition Index (O-PNI), Nutrition Risk Index (NRI), Controlling Nutritional Status (CONUT) score, and Nutritional Risk Screening 2002 (NRS 2002) were assessed. O-PNI is a widely used method prospectively to predict surgical outcomes in oncology for esophageal and gastrointestinal cancer. O-PNI was calculated according to the formula: $10 \times \text{Alb} + 0.005 \times \text{TLC}$. Consistent with previous reports in which patients with O-PNI <40 were considered high risk for surgery, we designated 40 as the cut-off value of O-PNI [12]. NRI, which is utilized for prospective prediction of the surgical risk for gastric cancer was calculated according to the formula: $10.7 \times \text{Alb} + 0.0039 \times \text{TLC} + 0.11 \times \text{Zn} - 0.044 \times \text{Age}$ (Zn; μg/dl, Age; years). Likewise, based on the criteria used by gastrointestinal surgeons, severe malnutrition was defined as NRI <55 [13]. CONUT score was calculated using the concentration of Alb, TLC, and total cholesterol [14], and NRS 2002 combines data from nutritional status, severity of disease, and age [15], as described in the Appendix. Total scores of CONUT ≥5 and NRS 2002 ≥3 were considered to represent low nutritional status.

A comparative assessment among these nutritional variables and severe adverse events was performed to identify predicting risk factors.

Furthermore, as other personal and clinical factors, including age, sex, comorbidity (existence of diabetes), smoking and alcohol status, Eastern Cooperative Oncology Group (ECOG) status and tumor stage (T classification, overall staging) were assessed. In addition, treatment factors, including history of surgery prior to RT, ICT, or CCRT, and irradiation subsites (pharynx, larynx, and oral cavity) were comparatively evaluated to detect predicting factor of severe adverse toxicity.

2.4. Statistical analysis

Categorical variables were expressed as counts and percentages. For univariate analysis, these were compared using Chi-square test or Fisher's exact test. Continuous variables were expressed as means ± SD (ranges) and were analyzed using the paired *t*-test. To identify the major significant predictors, the variables that showed significant association in the univariate analysis were selected, and multivariate logistic regression models were calculated to provide estimates for the odds ratios (OR) of severe adverse events associated with each parameter, and their 95% confidence intervals (CI). Two-sided p values of <0.05 were considered statistically significant. All statistical analysis were performed using SPSS software for Windows (IBM, Armonk, NY, USA).

This study was conducted in compliance with the postulates of the Declaration of Helsinki on medical protocol and was approved by the Institutional Research and Ethics Committee.

3. Results

This retrospective study included 86 men and 15 women with mean age of 67.6 ± 11.4 years (range, 36–97 years). The most common subsite of tumors was larynx (n = 47, 46.5%), followed by hypopharynx (n = 25, 24.8%), oropharynx (n = 16, 15.8%), epipharynx (n = 4, 4.0%), and oral cavity (n = 9, 8.9%). Approximately half the patients (n = 48) had locally advanced disease (T3–4), and 66 patients (65.3%) had an advanced overall stage (III–IV). All patients' ECOG status was 0 (fully active) or 1 (restricted).

Of the 101 patients, 24 (23.7%) had severe adverse toxicity; of these, 13 had multiple events. The main adverse events were mucositis (n = 16), followed by dermatitis (n = 8), pain (n = 8), dysphagia (n = 7), hoarseness (n = 3), fatigue (n = 2), and laryngeal edema (n = 1). These events had been advanced in severity at days 40–50 during treatment. Four patients had Grade 4 toxicity and could not complete their planned treatment course. In addition, ten patients were obliged to reduce or cease the second cycle of chemotherapy because of severe toxicity. Table 1 presents clinical and treatment characteristics according to the incidence, or absence, of severe adverse events. In the univariate analysis, overall staging (p = 0.048) was found to be a significant risk factor for severe adverse toxicity. Although the rate of severe adverse events was higher in female patients, this was not statistically significant;

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