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Original article

Prognostic value of nutritional and hematologic markers in head and neck squamous cell carcinoma treated by chemoradiotherapy

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ABSTRACT

Purpose: Malnutrition and systemic lymphopenia are common in many cancers and are associated with tumor progression. The purpose of this study was to investigate the prognostic values of nutritional and hematologic markers in patients with head and neck squamous cell carcinoma (HNSCC).

Methods: This prospective study included 153 patients with treatment-naïve HNSCC who underwent definitive chemoradiotherapy. Body weight, serologic and hematologic parameters were measured at baseline and after 2 months of treatment. Univariate and multivariate analyses using Cox proportional hazards model were used to identify predictors of progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS).

Results: Body weight, body mass index (BMI), serum albumin, total serum proteins, hemoglobin, and circulating neutrophil, lymphocyte, monocyte, and platelet counts significantly decreased, but neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) significantly increased after 2 months of treatment ($P < 0.05$ each). Multivariate analyses showed that pretreatment hypoalbuminemia and high NLR were independent predictors of PFS ($P < 0.01$ each). ECOG performance status, BMI < 18.5 kg/m^2 and NLR were independent predictors of CSS and OS ($P < 0.01$ each).

Conclusions: Our data support the evidence that several nutritional and hematologic markers are associated with the prognosis of HNSCC.

Patients with head and neck squamous cell carcinoma (HNSCC) have a high risk of being malnourished at the time of diagnosis or during treatment. Some studies reported that 30–60% of head and neck cancer patients have malnutrition, caused by complex factors, including tumor-and treatment-related symptoms, such as odynophagia, dysphagia, mechanical obstruction, anorexia, and fatigue [1]. Moreover, many patients have additional weight loss during and after therapy, because of a severe reduction in food intake, painful mucositis, and dysphagia [2,3] There are several studies reporting that poor nutritional status is correlated with poor clinical outcomes, and nutritional monitoring is important to evaluate the toleration of treatment [4–8].

Recently, some trials reported an association between systemic hematological markers and prognosis in human malignancies including HNSCC [9–11]. Complete blood counts, either alone or expressed as ratios, have been associated with cancer prognosis [8,11]. One study showed that pre-treatment lymphocytopenia and thrombocytosis are associated with a worse overall survival outcome in colorectal cancer [12]. Patients with HNSCC have been reported to have higher occurrence of neutrophilia and lymphopenia [11]. Moreover, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been studied in many malignancies, and higher pre-treatment ratios have been associated with a poorer prognosis [13–17]. Systemic hematologic markers may also help to predict an unfavorable prognosis in patients with HNSCC [11]. This correlation has been well documented in other types of human malignancies, but has rarely been studied in HNSCC patients. Therefore, we hypothesized that nutritional and systemic hematologic markers may be closely related to recurrence and survival outcomes in patients with HNSCC. The purpose of this study was to investigate the prognostic value of these markers.

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Methods

Study population

This study was conducted on treatment-naïve HNSCC patients of age >18-years, who were primarily treated with definitive chemoradiotherapy at our tertiary referral hospital between January 2010 and December 2012. The patients received regular examinations of body weight and circulating laboratory markers before, during, and after treatment. The exclusion criteria were: presence of distant metastasis ($n = 23$), induction chemotherapy or primary surgical treatment ($n = 96$), and second primary cancers prior to and at diagnosis ($n = 42$). The patients were screened prior to treatment. The patients ($n = 4$) with incomplete follow-up data of <1 year were also excluded from the final analysis. Overall, 153 patients were enrolled, including 129 men and 24 women, with a median age of 57 (range 16–78). None of these patients had prophylactic percutaneous endoscopic gastrostomy (PEG) tubes placed and the patients with malnutrition were evaluated for nutritional supports by the nutritionists. The tumors were staged according to the tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC 7th ed., 2010). This prospective observational study was reviewed by our Institutional Review Board and written informed consent was provided by each patient.

Treatment and follow-up

All patients underwent primary definitive chemoradiotherapy. The radiotherapy, consisting of intensity-modulated radiation, was administered in daily fractions of 1.8 or 2.0 Gy 5 days per week for 7–8 weeks. The median radiation dose for all patients was 70.0 Gy (range: 60.0–74.8 Gy). The chemoradiotherapy consisted of the previously described radiation plus high-dose cisplatin (80–100 mg/m^2), infused on days 1, 22, and 43. The initial tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 2 months after the completion of chemoradiotherapy [18]. All patients received physical and endoscopic examinations at every clinic visit after completion of the initial treatments: every 1–3 months in the first year, every 2–4 months in the second and third years, every 6 months in the fourth and fifth years, and annually thereafter. Post-treatment imaging was first performed 1–4 months, and every 6 months in the first and second years, and 1–2 years thereafter. Any clinical or radiological suspicion of index tumor recurrence or of the presence of second primary cancers was confirmed by biopsy and specific diagnostic tests. Patients with confirmed recurrence or second primary cancers were scheduled for salvage or palliative treatment.

Variables

Characteristics such as age, sex, clinical TNM staging, tumor location, Eastern Cooperative Oncology Group (ECOG) status, underlying comorbidities, smoking status, alcohol consumption, chemotherapy cycles, recurrence during or after treatment, and death were recorded. One drink was defined as 15.6 mL of pure ethanol (100%) [19]. Co-existing morbidity was categorized according to the Charlson Comorbidity Index (CCI) [20]. Body weight, body mass index (BMI, kg/m^2), serum albumin, total serum proteins, hemoglobin, complete blood counts with circulating lymphocyte count (CLC), circulating monocyte count (CMC), circulating neutrophil count (CNC), circulating platelet count (CPC), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR) were obtained within 2 weeks before the beginning of radiotherapy and at 2 months after the end of treatment. Hypoalbuminemia was defined as a serum albumin level below 3.3 g/dL and anemia as a serum hemoglobin level below 13 g/dL in men and 12 g/dL in women. The CBC counts were dichotomized by the median value for examining their association with recurrence and survival.

Statistical analysis

Continuous variables were expressed as medians (ranges) or means (standard deviations), and categorical variables were expressed as numbers and percentages. A paired t-test with Bonferroni correction was used to compare body weight, BMI, serum albumin, total serum proteins, hemoglobin, and CBC count at the time of initial staging with the measurements obtained 2 months after starting the treatment. The Kaplan–Meier method was used for progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) curve estimation. The log-rank test and Cox proportional hazards models were used to examine the significance of differences in recurrence or survival outcomes associated with the tested clinicopathological variables. Multivariate Cox proportional hazards regression analyses were performed with backward elimination including variables with P values <0.05 on univariate analyses. The estimated hazard ratio (HR) and 95% confidence interval (CI) were calculated. All tests were two-sided, and P values <0.05 were considered significant. All statistical analyses were performed using IBM SPSS software version 21.0 (IBM, Armonk, NY).

Results

Patient characteristics

Table 1 summarizes the clinical characteristics of the 153 eligible patients. The most common site of primary tumors was the oropharynx (33.3%), followed by the nasopharynx (31.4%), the larynx (18.3%), and the hypopharynx (17.0%). Among the 153 study patients, 70 (45.8%) had locally advanced disease (T3–4), 120 (78.4%) were N+, and 131 (85.6%) had an advanced overall stage (III–IV). Of three planned cycles of concurrent chemotherapy using high-dose cisplatin, only one and two cycles were performed in 2 (1.3%) and 32 (20.9%) patients, respectively, because of their poor compliance and toxicity. However, all study patients completed the planned course of radiotherapy with the total dose of 70.0 Gy (range: 60.0–74.8 Gy). The total duration of treatment was median 8 weeks (range 7–15 weeks). A complete response was achieved in 135 patients (88.2%) and a partial response in 17 (11.1%), while progressive disease occurred in one patient (0.7%). Of 18 patients without complete response, 15 (83.3%) underwent salvage surgery. After a median follow-up of 39.5 months (range 20.1–62.6 months), 27 (17.6%) patients died of the index cancer, 3 (2.0%) patients died of other causes, and 39 (25.3%) patients had local, regional, or distant site recurrence. At the last follow-up, 116 (75.8%) patients were alive without disease and 7 (4.6%) were alive with disease. Three-year PFS, CSS, and OS were 73.8%, 84.6%, and 82.4%, respectively.

Post-treatment changes in nutritional and systemic hematologic markers

Supplementary Table S1 lists the baseline, pre-treatment characteristics and their changes after 2 months of treatment. Body weight, BMI, serum albumin, total serum proteins, hemoglobin, CNC, CLC, CMC, and CPC were significantly decreased after treatment ($P < 0.05$ each). Most hematologic markers significantly decreased, while NLR and PLR significantly increased ($P < 0.05$ each). When the values were separately analyzed in men and

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