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Anemia and neutrophil-to-lymphocyte ratio are prognostic in p16-positive oropharyngeal carcinoma treated with concurrent chemoradiation

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ABSTRACT

Objectives: We investigated the prognostic value of pre-treatment hematological parameters in patients with p16-positive oropharyngeal squamous-cell carcinoma (OPSCC).

Material and methods: Neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), and hemoglobin concentration measurement (Hb), were collected on day one of treatment. Endpoints were overall survival (OS) and progression-free survival (PFS). All patients were planned to receive concurrent chemoradiation. Staging were reviewed according to the recent AJCC 8th edition.

Results: We included 167 patients in this study. In multivariate analyses, a smoking history > 30 packyears was associated with decreased OS ($p = 0.009$; HR, 3.4827) and PFS ($p = 0.042$; HR, 2.421); Hb < 12 g/dL was associated with impaired OS ($p = 0.007$; HR, 6.527) and PFS ($p = 0.014$; HR, 4.092); an NLR > 5 before treatment was associated with decreased OS ($p = 0.042$; HR, 2.945). Hemoglobin concentration and the NLR were not correlated ($p = 0.577$), nor anemia and an NLR > 5 ($p = 0.167$). Patients with an NLR > 5 had a significantly higher rate of disease recurrence (30.8% vs. 8.4%, $p = 0.0299$, RR = 3.922, 95% CI 1.351–11.386).

Discussion: We found hemoglobin level and the NLR to be independent prognostic factors in p16-positive OPSCC patients. This approach is to be considered for further clinical investigations, and its significance in treatment decision-making should be further explored.

1. Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is steadily rising in most of developed countries, related to oncogenic human papillomavirus (HPV) infection [1]. Fortunately, HPV-driven OPSCC carry a comparatively better prognosis as compared to HPV-negative tobacco-driven lesions [2]. Traditional variables of risk stratification in oropharynx (that is, TNM staging based on anatomical parameters only whatever the HPV status) provided limited value and did not properly describe HPV-positive disease with respect to prognosis or behavior. Consequently, the very recent 8th edition of the American Joint Committee on Cancer (AJCC) staging manual for head and neck cancer, will include now a specific staging system for HPV-related OPSCC [3]. Actually, the previous edition staging algorithms lost their relevance because of changing significance of respective local and lymph nodes involvements, and because of reduced differences in outcomes between stages due to increased response to treatment. In fact, the pathobiological process in HPV-positive OPSCC is distinct and many studies have demonstrated an increased radiosensitivity [4–6]. Arguments for intrinsic features show an altered DNA repair, differences in activated repopulation signaling-pathways, and downregulated cell cycle control mechanisms [4,5]. However, tumor oxygenation and antitumoral immunity are two main factors related to the tumor microenvironment that are nowadays increasingly explored to explain the higher sensitivity to radiation and the better outcomes, as well as in the prospect of developing new diagnosis and prognosis tools [4,6].

Hematological parameters are simple markers, related to tumor oxygenation as well as to systemic inflammation [7,8]. The prognosis values of some of them such as hemoglobin concentration, leukocytes count, lymphocytes count, or neutrophil-to-lymphocyte ratio, has been previously assessed and demonstrated in solid neoplasms including head and neck cancer [9–19]. Our objective was, therefore, to assess the prognostic significance of anemia and systemic inflammation, in a retrospective cohort of p16-positive OPSCC patients.

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2. Patients and methods

2.1. Study design

The study was performed after approval was received from the local Research Ethics Committee, in accordance with the World Medical Association – Declaration of Helsinki - ethical principles for medical research. We retrospectively reviewed patients who underwent concurrent chemoradiation between 2003 and 2016 at our Cancer Center for an oropharyngeal squamous cell carcinoma. We included patients with an available HPV-positive status, diagnosed according to the positivity of p16 expression staining assessed by immunohistochemistry (CINtec p16 Histology Kit, Roche mtm laboratories AG, Heidelberg, Germany) as recommended by the 8th edition of the AJCC staging for head and neck cancer [3]. We determined the presence of viral DNA using in-situ hybridization method (Ventana HPV III Family 16, Probe B, Ventana Medical Systems, Tucson, AZ, USA). We extracted data on pre-treatment biological counts in our medical records. Hematological parameters assessed were: neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio, hemoglobin concentration measurement. Initial hematologic parameters were collected on day one of treatment for concurrent platin-based chemotherapy, or on day one of initial loading dose for concurrent cetuximab.

2.2. Treatment and follow-up

All patients were planned to receive definitive radiotherapy (RT) with concomitant chemotherapy, with either cisplatin (100 mg/m^2 every 3 weeks on days 1, 22, and 43), carboplatin (70 mg/m^2 every 3 weeks on days 1, 22, and 43) plus fluorouracil (600 mg/m^2/day for four days on days 1, 22 and 43), or cetuximab (initial loading dose of 400 mg/m^2 one week prior to RT, followed by weekly injection at 250 mg/m^2 during RT). The decision of treatment was done according to the radiation oncologist preferences and to the status of the patient, and for most of patients receiving cetuximab the inclusion in a clinical trial (GORTEC 2007-01). The patients considered in the bioradiotherapy group with concurrent cetuximab alone received only cetuximab, either in the cetuximab-alone arm of the GORTEC 2007-01 trial or because of medical contraindication to platinum-based chemotherapy. Patients received either three-dimensional conformal radiotherapy or intensity-modulated radiotherapy. External beam definitive RT was delivered with a total dose of 70 Gy to the gross tumor volume in 35 fractions (range 30–35 fractions) at 5 fractions per week, with a median overall treatment time of 49 days (range 39–70 days). A dose of 60 Gy and 50–54 Gy were delivered to the intermediate- and low-risk clinical target volume (CTV). The CTVs were each expanded using 3–5 mm margins to generate their respective planning target volumes. Patient assessments in follow-up were done according to the national recommendations of the Société Française d'ORL [20].

2.3. Statistical analyses

Correlation analyses were done using linear regression tests. Our study endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the date of cancer diagnosis to the date of death or the date of the last follow-up for patients alive at last contact. PFS was defined as the time from the date of cancer diagnosis to the date of disease progression or death, or the date of the last follow-up for patients alive at last contact. Survival distributions were estimated by the Kaplan-Meier method. To evaluate the relationship between survival and all biological and/or clinical factors known to be relevant in oropharyngeal cancer, potential prognostic factors were included in the analyses: age, cancer staging, smoking history, performance status. Lymphopenia, neutrophilia, and anemia, were studied as dichotomous variables according to the reference values of the hospital laboratory (lymphocytes < 1000 cells/mm3 vs. ≥ 1000 cells/mm3, neutrophil < 7500 cells/mm3 vs. ≥ 7500 cells/mm3, and hemoglobin < 12 g/dL vs. ≥ 12 g/dL). The NLR was analyzed as a dichotomous variable, firstly according to the median value in the cohort, and secondly according to a cutoff of 5 which was used to categorize patients with high (NLR > 5) or low (NLR ≤ 5) systemic inflammation. This cutoff was chosen based on the systemic review of the NLR literature in cancer which showed an NLR > 5 as a predictive marker of cancer outcomes in over 30 studies of 15,500 cancer patients [18]. Survival curves were compared using the log-rank test. Variables identified with a p value < 0.1 in univariate analyses were included in the multivariate analysis using a Cox regression analysis model, to respectively identify independent prognostic variables of overall survival and progression-free survival. Statistics were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). The reported p values were two-sided when available, and p values below 0.05 were considered significant.

3. Results

3.1. Patients

We found 167 matching patients who fulfilled the inclusion criteria and were included in this study. The mean age was 59.2 years (range, 38–77). Patients and disease characteristics, biological parameters, and treatments, have been summarized in Table 1. Twenty-three patients received concurrent cetuximab alone, and 144 patients received

Table 1
Characteristics of patients with p16-positive oropharyngeal squamous-cell carcinoma treated with concurrent chemoradiation and included in our study.

		Overall	Hemoglobin			Neutrophil-to-lymphocyte ratio		
			< 12	**≥ 12**		**≤ 5**	**> 5**	
Total		167	13	154		154	13	
Age, *y, mean (range)*		59.2 y *(38–77)*	63 y	57.5 y	*p = 0.2942*	58 y	65 y	*p = 0.2942*
Sex	*Male, no. (%)*	126 *(75.4%)*	7	119	*p = 0.0881*	116	10	*p = 0.0881*
	Female, no. (%)	41 *(24.6%)*	6	35		38	3	
Smoking history	*≤ 30PY*	131 *(78.4%)*	11	120	*p = 0.7365*	8	123	*p = 0.1564*
	> 30PY	36 *(21.6%)*	2	34		5	31	
HPV DNA	*Positive*	134 *(80.2%)*	9	125	*p = 0.2898*	122	1	*p = 0.4677*
	Negative	33 *(19.8%)*	4	29		32	12	
AJCC 8th edition Staging	*Stage I*	66 *(39.5%)*	5	61		65	1	*p = 0.0289* *
	Stage II	54 *(32.3%)*	4	50		49	5	
	Stage III	47 *(28.2%)*	4	43		40	7	
Pre-treatment hematological parameters, *median*								
	Neutrophils (1000 cells/mm3)	4.4	5.00	4.30		4.25	7.3	*p < 0.0001**
	Lymphocytes (1000 cells/mm3)	1.7	1.30	1.70		1.7	1.2	*p < 0.0001**
	Neutrophil-to-lymphocyte ratio	2.65	3.67	2.63		–	–	
	Hemoglobin (g/dL)	13.9	11.60	14.05		13.9	13.6	*p = 0.1322*