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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*

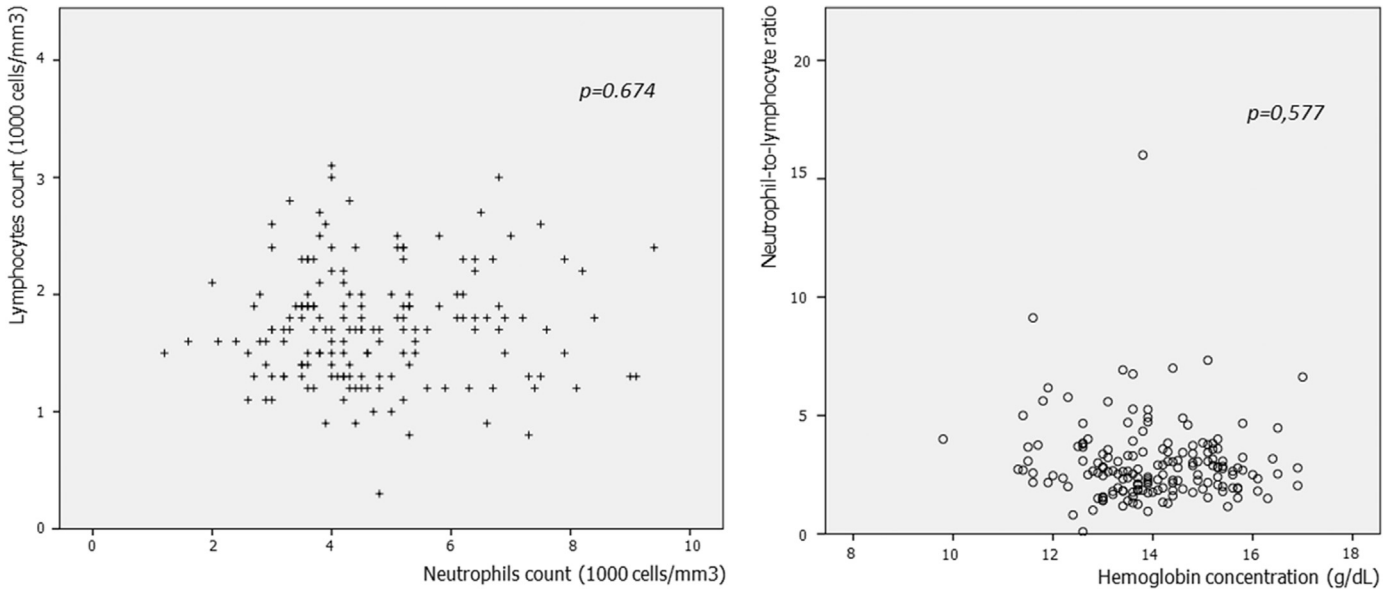

Fig. 1. Graph plot of patients according to relationship between their lymphocytes count and their neutrophils count, and to relationship between their hemoglobin concentration and their neutrophil-to-lymphocyte ratio.

platinum-based concurrent chemotherapy. The median neutrophil-to-lymphocyte ratio (NLR) in the cohort was 2.65 (range, 0.09–16). The characteristics were well balanced between the groups of patients according to the presence or not of either pre-treatment anemia, or an NLR above 5 (Table 1). Anemia and an NLR > 5 were not associated among patients (p = 0.167). Hemoglobin and the NLR were not correlated, as neutrophil counts and lymphocyte counts (Fig. 1). Only three patients in the cohort had both anemia and an NLR > 5, thereby no composite score with 0, 1 or 2 positive criteria could be rigorously assessed. An NLR > 5 was associated with the 8th edition of AJCC stage (p = 0.0289), and there was a significant linear trend towards a higher rate of an NLR > 5 among patients with more advanced stages (p = 0.0080). However, since NLR was related to stage, stage was included as a co-variant (stage I versus stage II-III) in multivariate analysis. Eventually, smoking history was not correlated with anemia or an NLR > 5 (Table 1).

3.2. Survival outcomes

The median follow-up was 32 months (range in surviving patients, 6–138 months). Seventeen patients (10.2%) had a recurrence: three local recurrences only, three regional recurrences only, two metastatic recurrences only, six locoregional recurrences, two local and metastatic recurrences, and one regional and metastatic recurrence. We reported the Kaplan-Meier curves for OS and PFS according to the 8th edition of AJCC staging for HPV-driven oropharyngeal squamous cell carcinoma in Fig. 2.

In multivariate analyses, both pretreatment anemia and NLR > 5 were associated with decreased OS and PFS (Fig. 3). We reported the univariate and multivariate analyses in Table 2. Patients with an NLR > 5 had a significantly higher rate of recurrence (30.8% vs. 8.4%, p = 0.0299, RR = 3.922, 95% CI 1.351–11.386), all of them at least local recurrent disease. One recurrence was only local, two were locoregional, and one was both local and metastatic. Patients with initial anemia had a higher rate of recurrence but the increase was not statistically significant (23.1% vs. 9.1%, p = 0.1347). As expected, smoking history was associated with survival, and the significant threshold in this series was thirty packyears (Table 2).

We analyzed outcomes in the patients with both p16-positive and DNA-positive cancer. As in the entire p16-positive cohort, significant factors associated with OS and PFS in univariate analyses were smoking history superior to 30 packyears, anemia, and NLR > 5. In multivariate analyses, smoking history superior to 30 packyears and anemia were associated with decreased OS and PFS.

4. Discussion

Both hemoglobin concentration and the neutrophil-to-lymphocyte ratio (NLR) before treatment were independent prognostic criteria associated with survival in HPV-driven oropharyngeal squamous-cell carcinoma (OPSCC) treated with concurrent chemoradiation in our series.

The NLR is a simple analysis that can be used in daily practice. Therefore it is a mechanism marker increasingly used to explore the association between cancer progression and the systemic inflammatory response [18]. In fact, neutrophils and lymphocytes have different influences regarding cancer progression [7,21]. Neutrophil infiltration is thought to enhance tumor growth and progression by remodeling the extracellular matrix and activating inflammatory markers. Lymphocyte infiltration, meanwhile, is thought to be the main component of controlling cancer progression, especially T4 helper and T8 suppressor lymphocytes that decline markedly in the cell-mediated immune system [7]. Thus an elevated NLR might be associated with a poorer prognosis in patients with cancer. Actually, the NLR has been shown to be significantly associated with survival in overall head and neck squamous-cell carcinoma in several previous studies including oropharyngeal localization [10,11,13–15,17,18,22]. Charles et al. [14] found that an NLR > 5 was associated with decreased overall survival and recurrence-free survival in their series of 66 patients with OPSCC treated with radiotherapy, of whom 84% of available p16 status were positive. In a larger series of 251 patients with OPSCC treated with chemoradiation Young et al. [17] reported that an NLR > 5 was associated with a lower locoregional control, but unfortunately they did not have HPV status available so they could not introduce it in multivariate analyses. The prognostic impact of neutrophils, monocytes, and leukocytes on HPV-related OPSCC has been previously reported by Huang et al. [23]. They found an inversed relationship between pre-treatment myeloid cells (pro-tumoral: neutrophils and monocytes) versus lymphocytes (anti-tumoral) on recurrence-free survival and overall survival in HPV-positive OPSCC. It is conceivable that NLR would be a stronger predictor for survival. In our series, we found that NLR is a prognostic factor associated with survival independently of the disease stage.

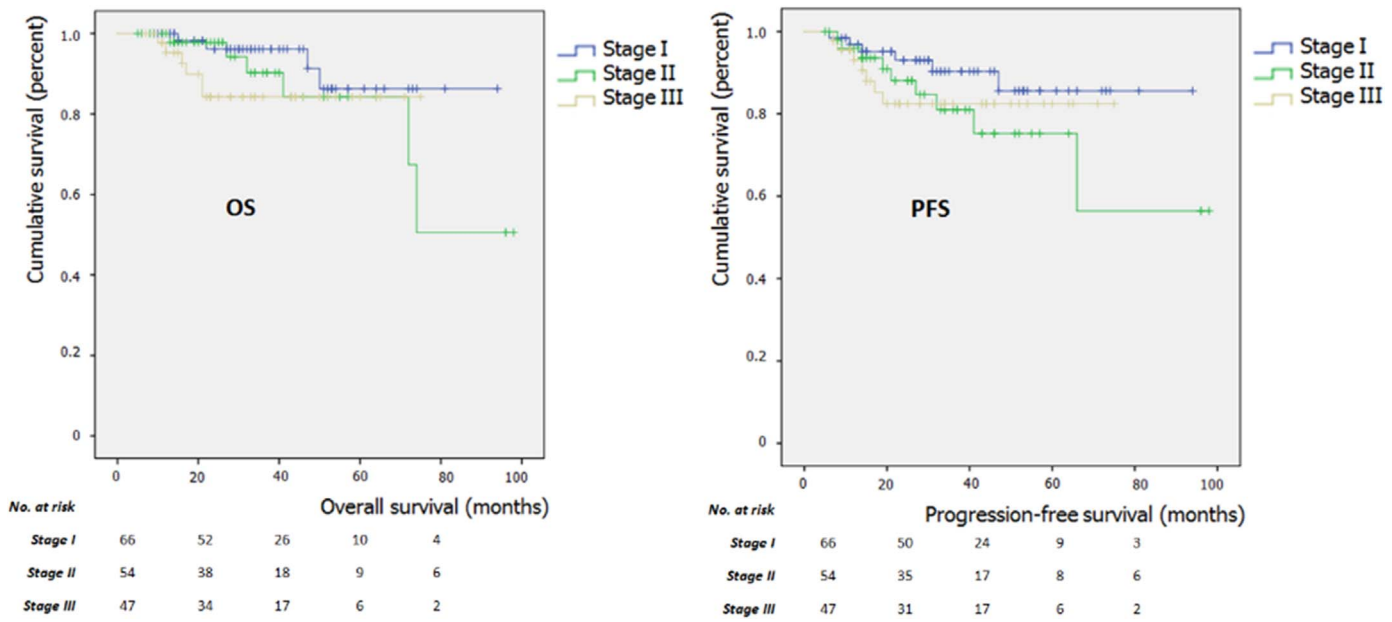

Fig. 2. Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS) of 167 patients treated with concurrent chemoradiation for a p16-positive oropharyngeal squamous-cell carcinoma, according to the AJCC 8th edition staging.

The worse prognosis of patients with anemia before treatment has been previously well established in solid neoplasms including head and neck cancer treated with radiation [24–30]. The physiopathology remains discussed. Low hemoglobin concentration might exacerbate the preexisting hypoxia that is often present in tumors by decreasing oxygen-carrying capacity so hampering the response of tumor cells to cytotoxic therapy [8,31]. In a retrospective analysis of the DAHANCA 5 trial, Lassen et al. [32] found an absence of benefit of adding nimorazole, a hypoxic cell radiosensitizer, to radiotherapy in patients with p16-positive OPSCC as compared to a significant benefit in locoregional control in patients with p16-negative OPSCC. They hypothesized that it was because p16-positive tumors might be less hypoxic. However, other studies including further publications by the same team showed no significant difference in hypoxia between HPV-positive and HPV-negative tumors [33–35]. Hypoxia then might be associated with treatment outcomes because of decreasing radiation efficacy, as well as being a marker of disease aggressiveness. More recently, Shoultz-Henley et al. [12] confirmed in a large retrospective series of 433 patients with OPSCC treated with concurrent chemoradiation that anemia before treatment was a significant prognostic factor associated with impaired survival (HR 2.4, 95% CI 1.7–3.4). Unfortunately, the HPV status was positive in only 109 patients amid 140 patients with known status (32% of the series) and they did not report an analysis specifically in this subgroup of patients with HPV-driven OPSCC. Furthermore, among numerous hematological parameters, they found a platelet concentration above 350,000 cells per millimeters square to be the best promising predictor of prognosis. But in our series, only two patients had this high platelet level before treatment, and we preferred not to give any statistical conclusion about so few patients. Whatever, our results agree with previous publications and showed that pretreatment low hemoglobin level was associated with a higher rate of loco-regional recurrences in our series. Papillomavirus-related tumors have been shown to be more radiosensitive and to have a better prognosis than p16-negative tobacco-driven cancer [2,4]. However, further studies should help answer whether hemoglobin concentration can be a hematological marker predictive of response to treatment among patients with p16-positive OPSCC. For example, combining hemoglobin concentration with in-vivo imaging methods for detection of tumor hypoxia, such as PET imaging [36], could help distinguish patients with high-risk tumors in this HPV-related tumors population. These patients with high-risk tumors which are perhaps less radiosensitive than expected could benefit from treatment intensification such as radiation dose-escalation or anti-hypoxic drugs, and should be explored in clinical trials [37].

As expected, smoking history was a significant prognostic factor associated with survival in our study. Actually, Huang et al. [38] found smoking to be an independent survival predictor in their landmark study with a hazard ratio of 1.2 for every ten packyears smoking increment, and the threshold introduced in their recursive partitioning analysis was twenty packyears. We tested among our patients the Huang's threshold of twenty packyears, as well as an arbitrary threshold of ten packyears, as prognostic factors potentially associated with survival in our statistical models, but they were negative. The use of a ten-packyear cutoff may be preferred in order to increase generalizability as this is a cutoff used by previous authors, but neither ten nor twenty packyears were associated with survival. Naturally, the use of packyears for stratification can be discussed as it does not distinguish the carcinogenic effect of smoking intensity from the influence of duration of the habit. To divide smoking into never versus current/former smokers would have made sense in a tumorbiological way. However, among the advantages of the packyear method are its reproducibility between studies and the distinction between light- or never-smoking patients and heavy-smoking patients. It may be of importance in countries such as ours, where the prevalence of tobacco consumption remains unfortunately very high [39]. Thus, the high rate of smoking history in our country is probably an explanation of the relatively high significant threshold found in our series as compared to North-American studies [38].

Naturally, our study has several limitations. Firstly, although we tried to rigorously describe the unavoidable biases such as treatments, the retrospective nature of our study increases the risk of hidden biases that we could not take into account. Secondly, the number of relapse events was limited during the follow-up. It is, of course, due to the better prognosis of the HPV-related OPSCC. However, the number of events was large enough for hemoglobin level and neutrophil-to-lymphocyte ratio to be stastically significant

5. Conclusion

We studied the prognostic value of hemoglobin level and systemic

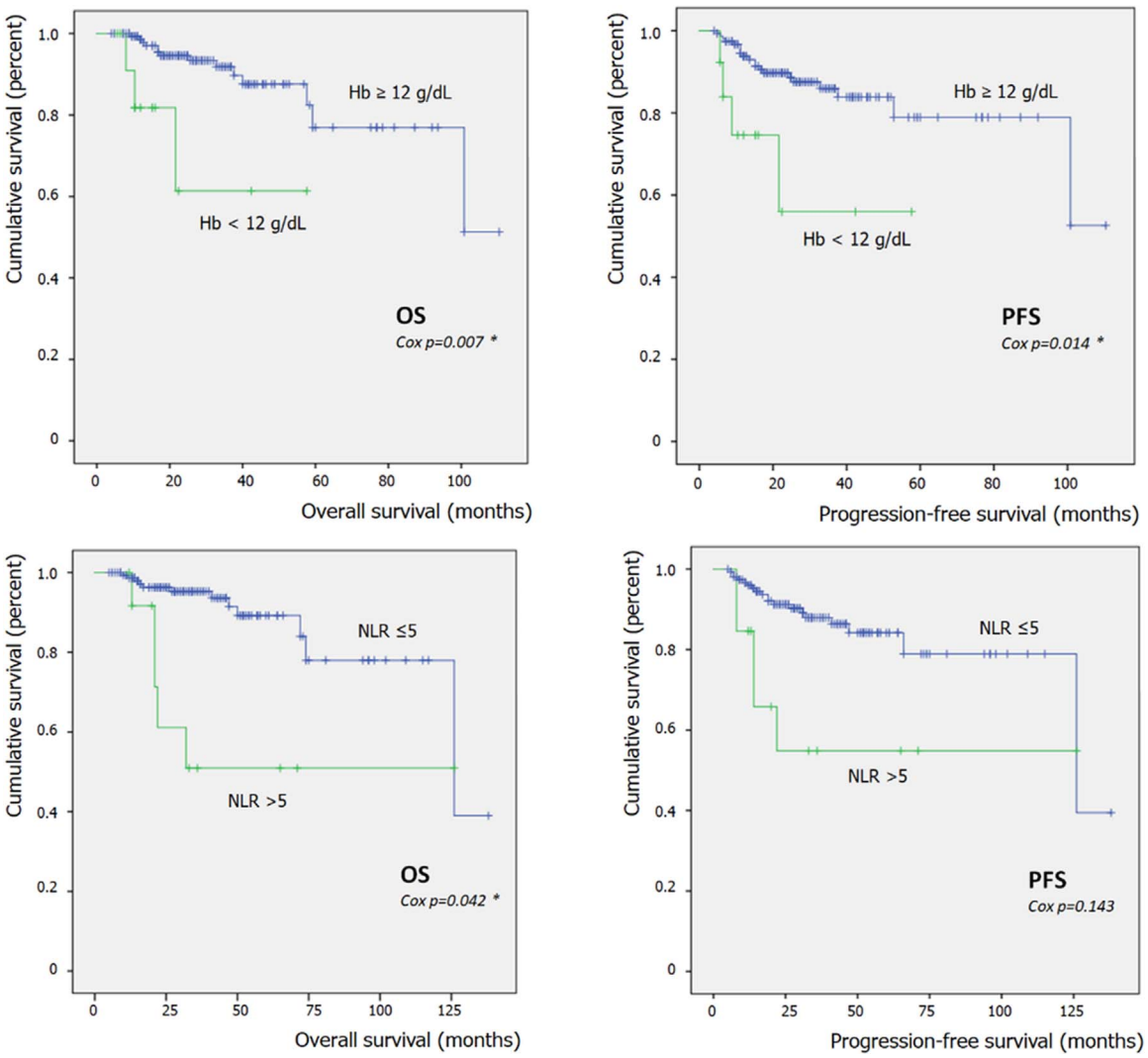

Fig. 3. Kaplan-Meier curves for overall survival (OS) and progression-free survival (PFS) of 167 patients treated with concurrent chemoradiation for a p16-positive oropharyngeal squamous-cell carcinoma, according to the hemoglobin (Hb) concentration and to the neutrophil-to-lymphocyte ratio (NLR).

inflammation markers before treatment in patients with p16-positive OPSCC treated with concurrent chemoradiation. We showed that hemoglobin concentration and the neutrophil-to-lymphocyte ratio are independent prognostic factors of survival. Their significance in treatment decision-making should be explored in further studies for treatment intensification.

Declaration of interest

The author Dr Philippe Gorphe is prepared to take responsibility for the integrity of the content of the manuscript. The material is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration. There was no affiliations or financial involvment in any organization or entity with a direct financial interest in the subject matter or materials of the

Table 2
Results of univariate and multivariate analyses of survival in 167 patients with p16-positive oropharyngeal squamous-cell carcinoma treated with concurrent chemoradiation.

Variable	Overall survival			Progression-free survival		
	Univariate	Multivariate		Univariate	Multivariate	
	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value
Smoking > 30 PA	***0.002*** *	*3.465 (1.267 – 9.482)*	*0.016* *	***0.028*** *	*2.286 (0.983 – 5.319)*	*0.055*
Age > 70 y	*0.647*			*0.849*		
HPV DNA	*0.262*			*0.141*		
Staging AJCC 8th edition	*0.279*			*0.570*		
Platin-based chemotherapy vs. cetuximab	*0.979*			*0.532*		
Neutrophilia	*0.151*			*0.429*		
Anemia	***0.004*** *	*4.846 (1.329 – 17.672)*	***0.017*** *	***0.008*** *	*3.638 (1.222 – 10.834)*	***0.020*** *
NLR > 5	***0.001*** *	*3.910 (1.313 – 11.643)*	***0.014*** *	***0.015*** *	*2.609 (0.945 – 7.204)*	*0.064*
NLR > 2.65	*0.227*			*0.190*		

research discussed in the manuscript. We certify that we have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript (e.g., employment, consultancies, stock ownership, honoraria). Co-authors have read and approved the paper.

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