Oral Oncology 82 (2018) 131–137

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Smoking impact on HPV driven head and neck cancer's oncological outcomes?

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ARTICLE INFO

Keywords:
Human papillomavirus (HPV)
Smoking/tobacco
Cancer
Oral/oropharynx/oropharyngeal
Prognosis
Outcomes
Survival

ABSTRACT

Introduction: HPV-driven oropharyngeal cancer (OPC) patients have a better prognosis than their HPV-negative counterparts but several studies have suggested that among HPV-positive patients those with a smoking history had worse oncological outcomes. The aim of our study is to characterize the interplay between tobacco consumption, patient and disease characteristics, and disease control.

Materials and methods: All patients diagnosed with HPV-driven OPC and treated with curative intent between 2007 and 2009 and 2011–2016 at Gustave Roussy cancer center were included (n = 282). Demographic, clinical, morphological and tobacco consumption were correlated with oncologic outcomes.

Results: 157 (56%) patients had a positive smoking history, including 23.8% who were smoking at the time of diagnosis and 37.6% who had a tobacco consumption exceeding 20 pack-years. In multivariate analysis, the strongest prognostic factor for survival was smoking status at cancer diagnosis, with a hazard ratio (HR) for non-smokers compared to smokers of 0.25 ([0.12, 0.50], p = 0.0001). Smoking history, either more than 20 pack-years or smoking at diagnosis, was associated with local relapse and distant relapse. There was no difference in terms of comorbidity (p = 0.32) and radiotherapy duration (p = 0.93) according to tobacco consumption.

Discussion: Smoking is frequent among patients with HPV-driven OPC and increases the risk of death and oncologic failure.

Introduction

HPV-driven oropharyngeal cancer (OPC) patients are characterized by a better prognosis than their HPV-negative counterparts with a 5 year mortality rate cut in half [1,2]. However this significant survival advantage is not homogeneous and several studies have suggested that among HPV-positive patients those with a smoking history had worse oncological outcomes and a significantly increased risk of death [2–8]. For instance, Huang et al. reported that the 5-year median overall survival was 89% in patients with stage I-II disease (95% CI 85–93%) and a tobacco consumption ≤20 pack year (PY) versus 64% (95% CI 56–73%) in those who smoked more [8]. This issue is critical because a large proportion of HPV-positive patients are current or former smokers at the time of diagnosis [7,9,10]. The proper identification of prognostic groups is essential to allow safe de-escalation strategies to be implemented [11].

Although tobacco consumption induces multiple other disorders (e.g. cardiac, respiratory diseases or cancers) that can affect overall survival [12], the reason why smoking impacts negatively cancer specific prognosis is still elusive. Tobacco could induce additional genetic alterations leading to a more aggressive phenotype but might also compromise treatment tolerance and delivery due to tobacco related comorbidities.

To date few studies have comprehensively assessed the impact of smoking on the oncologic outcomes of patients with HPV-driven OPC [4,5,7] and conflicting data have been reported by some investigators [13,14]. Therefore, we conducted this study to further characterize the interplay between tobacco consumption, patient and disease characteristics, disease control and survival.

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https://doi.org/10.1016/j.oraloncology.2018.05.007
Received 3 January 2018; Accepted 12 May 2018

Material and methods

Patient population

The present patient population consists of all p16 positive oropharyngeal cancer patients treated at Gustave Roussy Cancer Center from 2011 to 2016 (n = 230) and from 2007 to 2009 (n = 63) out of 801 oropharyngeal cancer patients treated during these 9 years.

These 2 periods were selected because (1) HPV status determination has been introduced as a systematic measure in our institution since 2011, and (2) HPV status of oropharyngeal cancer patients treated between 2007 and 2009 was assessed in a prior study [15].

Of these 293 patients, 11 patients were excluded due to the presence of metastases at diagnosis (n = 8) or because they were treated with surgery only (n = 3), leaving 282 patients for analysis.

Data collected

The electronic medical records of all patients were reviewed retrospectively to determine pretreatment clinical and disease characteristics, management details and outcomes. P16 status and HPV DNA were determined prospectively since 2011 and retrospectively before. Smoking status was collected as quantity in pack-years (number of packs of cigarettes smoked per day multiplied by the number of years smoked) and whether patients were smoking at diagnosis. Patients were divided into 3 groups: (1) Never-smokers (those who never used chewing tobacco, cigars, or pipes in their lifetime and those who smoked less than the equivalent of one pack-year in their lifetime.), (2) Former smokers (those who stopped smoking before cancer diagnosis) and (3) Current smokers (active tobacco users at the time of diagnosis) The American Society of Anesthesiology physical status classification system [16] (ASA score) was used as a proxy for comorbidity assessment as it was recorded in all patients. Tumors were classified according to the 8th TNM staging edition [17].

p16 expression and identification of HPV DNA

p16 expression was determined by immunohistochemistry (CINtec p16 Histology Kit, Roche mtm laboratories AG, Heidelberg, Germany) and HPV DNA by situ hybridization (Ventana HPV III Family 16, Ventana medical system) according to the manufacturer instructions. The detailed protocols are described in the Supplementary data (supplementary data file n°1). p16 immunohistochemistry was scored as positive if there was strong and diffuse nuclear and cytoplasmic staining present in > 70% of the malignant cells. All other staining patterns were scored as negative. p16 was used as a surrogate marker of HPV-infection.

Treatment and follow-up

All patients were treated according to our standardized workflow. After an initial consultation with a staff head and neck surgeon, patients underwent additional workup, including an exam under anesthesia with a direct laryngoscopy and imaging of the head and neck and chest. Each patient was then seen in a multidisciplinary tumor board, consisting of at least a head and neck surgeon, a radiation oncologist, a medical oncologist, and a radiologist. Clinical exam was performed again at this stage and the therapeutic options discussed with the patient. Oropharyngeal cancer patients are in majority treated with radiotherapy at our institution, initially with 3D conformal radiotherapy and since 2008 with intensity modulate radiotherapy. The prescribed dose is 70 Gy in 33 fractions to the gross disease, with a prophylactic dose of 54–60 Gy to uninvolved areas at risk of relapse administered as a simultaneous integrated boost. Concomitant chemotherapy, either using bolus cisplatin or weekly cetuximab, was routinely administered to these locally advanced patients. Surgery was routinely performed in case of residual disease either clinical or on PET-CT at three months after the completion of radiotherapy. Patients are seen six weeks following treatment, and then every three months for two years, every six months for until 5 years and yearly afterwards.

Statistical analysis

Proportions were compared using the Fisher exact test. Follow-up was estimated using the reverse Kaplan–Meier method [12]. Overall survival (OS), progression-free survival (PFS), local, regional and distant control rates were estimated using the Kaplan–Meier method. Survival times were defined as the time between the multidisciplinary meeting and the first event. Events were death from any cause for overall survival (OS) and death or tumor progression for PFS. Survival curves were compared using the log-rank test for the univariate analysis and in a multivariate ascending stepwise Cox regression for the multivariate analysis (MVA). Variables associated with disease-free or overall survival with a p-value < 0.20 were included in the MVA. In the Cox model, continuous variables were dichotomized. All reported p values are two-sided, and p-values lower than 0.05 were considered significant. Analyses were conducted using SAS version 9.3.

Results

Patient characteristics

Patient and tumor characteristics, overall and according to smoking status, are presented in Table 1. Mean age was 60.3 years, 73% of the patients were male, and 56% (n = 157) had a positive smoking history, including 23.8% who were smoking at the time of diagnosis and 37.6% who had a tobacco consumption exceeding 20 pack-years. 108 patients (38.3%) were never smokers. Among all patients, who were all p16 positive, HPV DNA was analyzed in 92.9% (missing analysis for 20 patients, 7.1%), and the test was positive in 230 patients (87.8% of the analyzed patients). The false positive rate of p16 detection, i.e. the percent of p16 positive patients with negative HPV DNA, was 12.2%. The most represented T and N stages were T1-T2 (n = 148, 52.5%) and N1-N2b (n = 157, 55.7%). There was 117 ICON-S stage I patients (41.5%), 80 stage II patients (28.4%) and 85 stage III (30.1%). Tumors were mostly located in the tonsillar region (n = 177, 62.8%). All patients received radiotherapy, and 235 (83.3%) received concomitant systemic treatment, mostly using cisplatin (80.4%). Thirty patients (10.6%) had nodal or tumor surgery as part of their treatment.

When comparing patient and tumor characteristics between never and ever smokers, only age and gender showed a significant association with smoking status. Smokers tended to be younger (p = 0.002) and more frequently male (p = 0.0003) than non-smokers. However, there was no difference in terms of ASA score (p = 0.32), concomitant treatment (p = 0.42) or radiotherapy duration (median duration of 49 days in both groups, p = 0.93). Radiotherapy duration was similar in all three ASA groups (p = 0.89).

Overall survival

Median follow-up was 37 months, and 40 patients have died during the course of follow-up. Two and four-years survival rates are respectively 90.4% and 85.7% (Fig. 1). In univariate analysis (Table 2), older age, the negativity of HPV DNA, a positive smoking history, advanced T-stage or advanced ICON-S stage were significant prognostic factors for overall survival. In multivariate analysis, the strongest prognostic factor for survival was smoking status at cancer diagnosis, with a hazard ratio (HR) for non-smokers compared to smokers of 0.25 [0.12, 0.50], p = 0.0001. Age older than 60 years was the other significant factor (p = 0.05) while HPV DNA testing and advanced N stage were close to significance (p = 0.08 and 0.07 respectively).