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Pattern of and survival following loco-regional and distant recurrence in patients with HPV+ and HPV− oropharyngeal squamous cell carcinoma: A population-based study

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ABSTRACT

Objectives: The incidence of human papillomavirus (HPV) positive oropharyngeal squamous cell carcinoma (OPSCC) is increasing. Currently, data is sparse on the pattern and timing of recurrence. This long-term study concerning both HPV- and p16-status aimed to report predictive factors, pattern, timing of loco-regional recurrence (LRR) and distant recurrence (DR), and survival following recurrence in patients diagnosed with OPSCC.

Material and methods: We included patients diagnosed with OPSCC from 2000 to 2014 in Eastern Denmark, who were treated with curative intent. Tumors were defined as HPV-positive when they were both HPV-DNA and p16-positive. Time-to-failure and -death were estimated by the Kaplan-Meier method. Cox proportional hazards models were used to evaluate predictors of failure.

Results: The cohort consisted of 1244 consecutive patients with OPSCC of which 288 patients (23%) experienced recurrence. Of these patients, the majority (n = 197/1244; 16%) experienced LRR and the remaining (n = 91/1244; 7%) DR. Significantly more HPV-negative patients experienced recurrence (n = 170/486; 35%) compared to HPV-positive patient (n = 112/726; 15%). DR occurred for both groups predominantly to the lung (n = 63/91; 69.2%) followed by the liver and bone. Factors influencing risk of LRR included gender, T-classification, and HPV-status. The same variables influenced risk of DR in addition to the UICC-8 classification, N-classification, pack years of smoking, and performance status. HPV-status was the strongest risk factor for LRR and DR.

Conclusion: LRR and DR occur significantly less often in HPV-positive patients compared with HPV-negative patients. HPV-status is an independent and strong predictor of recurrence. DR most commonly occurs to the lungs, irrespective of HPV-status.

Introduction

The incidence of patients diagnosed with human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) is increasing. Nevertheless, this OPSCC group has a markedly better prognosis compared with the tobacco-related (HPV−) OPSCCs [1–3]. Regardless, up to 25% of patients with HPV+ OPSCC encounter disease recurrence within three years of completed treatment [4–6]. The risk of short-term loco-regional failure is reported low for patients with HPV+ or p16+ (a surrogate marker for HPV) tumors compared to patients with HPV or p16 negative tumors. This has however only been examined in smaller, selected i.e. non-population-based cohorts and a combined evaluation of both HPV and p16 status has not been performed [7–9]. As recently demonstrated, combined HPV/p16-status is a significantly better prognostic marker than HPV-DNA and p16 alone [10]. Hence, it remains unknown how combined HPV/p16-status relates to pattern-of and time-to loco-regional recurrence (LRR) or distant recurrence (DR).

From non-population-based cohorts or case-series, unusual patterns of recurrence for patients with HPV+ OPSCC are reported, including unexpected late failures, atypical locations of failures, and highly aggressive disease [11–14]. Furthermore, it has been proposed that late, distant metastases, especially to the lung, might be a leading cause of death specifically for the HPV+ patients [5,15,16], although this is not

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a unanimous finding [6,11].

The management of OPSCC in Denmark has focused on radiotherapy as the primary modality, as this ensures the best possibility of organ conservation [17]. Curative radiotherapy regimens consisted of 66–68 GY, divided into 33–34 fractions given 6 days a week. From 2007, stage III-IV (UICC 7th) patients were offered concurrent chemotherapy (primarily weekly cisplatin 40 mg/sqm), if tolerated, whilst a minority were treated with cetuximab. In Denmark, the treatment for head and neck cancer will be initiated within one month of diagnosis for the vast majority [18,19].

The specific sites of LRR and DR for HPV + and HPV − patients have only scarcely been examined. Thus, it is currently difficult to counsel patients following recurrence, and data is also sparse when designing clinical trials. We therefore examined the pattern and timing of LRR and DR in a population-based, consecutive cohort of OPSCC patients with known covariates, and combined tumor HPV- and p16-status.

Methods

We included patients diagnosed with OPSCC in Eastern Denmark from 2000 to 2014 treated with curative intent. Using the unique resident-code from the Danish Civil Registration System, we linked two national registries; the prospectively maintained Danish Head and Neck Cancer Group (DAHANCA) [20] database and the Danish Pathology Data Bank (DPDB) [21] to identify patients. The DAHANCA database contains information on all head and neck cancers from the time of diagnosis and during follow-up. The DPDB is a mandatory, real-time system, where pathology departments report data on all patho-anatomical samples examined in Denmark. Patient-data was retrieved from these databases as well as medical records. All tumor specimens were re-evaluated by an expert head and neck pathologist. Evaluation of p16 overexpression and HPV DNA PCR is described in detail elsewhere [3,22,23]. Tumors were classified as HPV-positive (HPV +) if they were both HPV + and p16 + . Remaining combinations of HPV and p16 (e.g. HPV + /p16 −) were classified as HPV-negative (HPV −).

Patients were categorized as having a disease-recurrence if curative-intended treatment was completed, deemed progression-free at follow-up, and presented imaging or biopsy-verified disease-recurrence in either a T-, N-, or M-site at subsequent check-ups. HPV + and HPV − patients followed the same follow-up schedule. T- and N-sites were categorized as a LRR and M-site as a DR. Time-to-recurrence was defined as time from diagnosis to the date of the first locoregional or distant recurrence. Patients who died before a recurrence were censored at time of death. Patients included were treated with curative intend radiotherapy consisted of 66–68 GY divided into 33–34 fractions given 6 days a week. From 2007 stage III-IV (UICC 7th) patients were offered concurrent chemotherapy (primarily weekly cisplatin 40 mg/sqm), if tolerated, whilst a minority were treated with cetuximab. Multivariate analyses were performed using the Cox proportional hazards model stratified for treatment with cisplatin. The assumption of proportional hazards was tested by log – log plots and model reduction was performed stepwise by a backwards elimination technique. Year of diagnosis and age was coded as a continues variables in the cox proportional hazard. Smoking, UICC8-stage, and T- and N-classification were coded as numeric values and gender, and HPV-status were coded dichotomic with references being women, and HPV − , respectively. Performance status was also coded dichotomic with reference being a performance status of zero compared to a performance status of one or above one. Survival curves were plotted using the Kaplan–Meier product limit estimator and compared using the log-rank test. Six patients were excluded from the survival analysis due to missing information on HPV-status. Five of these patients experienced LRR and one patient experienced DR. A p value < 0.05 was considered significant. All statistical analyses were performed in SPSS version 23 (SPSS Inc., Chicago, IL, USA) and the R-software version 3.2.4 [24].

Results

Cohort characteristics

The Eastern Region of Denmark comprises 46% of the approximately 5.5 million inhabitants in Denmark. From this region, a total of 1541 patients were diagnosed with OPSCC between 2000 and 2014 [3,22,23]. In total 1244 patients were treated with curative intent (Supp. Table 1). The median follow-up was for all patients 3.9 years and for surviving patients 5.0 years. Of these patients, a total of 492 deaths were registered with 164 deaths in the HPV + group.

The median time to recurrence in the HPV + group was 1.1 years versus 0.8 years in the HPV − group ($p = 0.4$). A total of 288 (23%) patients experienced recurrence with 112 patients in the HPV + group (15% of HPV patients) vs. 170 (35% of HPV − patients) in the group of HPV − despite that the HPV + group comprised 60% of the cohort ($p < 0.01$). The five-year risk for LRR or DR was 17.3% (95% CI 14.3–20.4%) for the HPV + and 42.1% (95% CI 36.8–47.3%) for the HPV − patients (Fig. 1).

Time to and survival following LRR

At a median time to LRR of 0.9 years (95% CI 0.7–1.0 years), 197 patients encountered LRR (35% HPV + patients). Of the HPV + patients 9.4% experienced LRR compared to 26.5% of HPV − patients. The HPV + group had a median time to LRR of 0.8 years (95% CI 0.5–1.5 years, range 0.2–8.1) and the HPV − group a median time to LRR of 0.9 years (95% CI 0.7–1.0, range 0.3–6.3). The median overall survival (OS) for the total cohort of patients with LRR was 1.1 years (95% CI 0.9–1.4) after the date of LRR. The 5-year OS for patients after loco-regional failure was 26.1% (95% CI 17.4–39.1) and 5.9% (95% CI 3.0–11.8) for the HPV + and HPV − groups, respectively (Fig. 2).

Time to and survival following DR

For the total cohort, 91 patients (47% HPV +) experienced a DR with a median time to DR of 1.0 years (95% CI 0.9–1.4). Of the HPV + patients 6.1% experienced DR compared to 9.7% of HPV − patients. Median time to DR was 1.5 years (95% CI 1.05–1.8, range 0.1–5.6) in the HPV + group and 0.9 years (95% CI 0.7–1.04, range 0.04–5.1)) in the HPV − group ($p = 0.1$). Median survival for patients with DR for

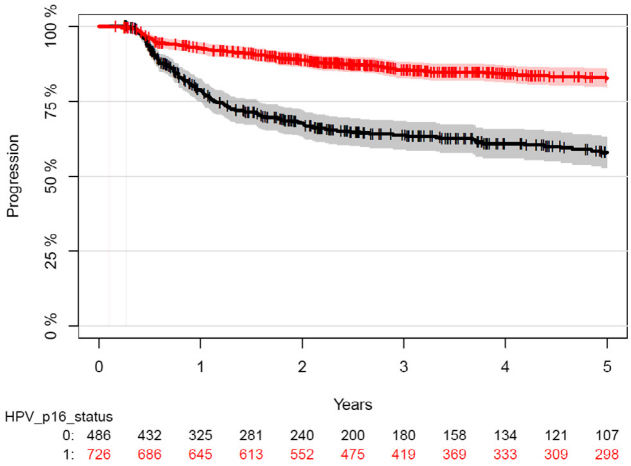

Fig. 1. Kaplan-Meier plot depicting risk of recurrence for patients with oropharyngeal cancer. Red line shows the HPV-positive patients and the black line shows the HPV-negative patient. 1 = HPV + , 0 = HPV − , Significant at $p < 1e^{-04}$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)