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Original Article

Impact of Time to Treatment Initiation in Patients with Human Papillomavirus-positive and -negative Oropharyngeal Squamous Cell Carcinoma

C. Grønhøj [*], D. Jensen [*], C. Dehlendorff [†], C. Nørregaard [*], E. Andersen [‡], L. Specht [§], B. Charabi [*], C. von Buchwald [*]

[*] *Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Denmark*
[†] *Statistics and Pharmacoepidemiology, Danish Cancer Society Research Center, Denmark*
[‡] *Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark*
[§] *Department of Oncology, Rigshospitalet, University of Copenhagen, Denmark*

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Abstract

Aims: The distinct difference in disease phenotype of human papillomavirus-positive (HPV+) and -negative (HPV−) oropharyngeal squamous cell cancer (OPSCC) patients might also be apparent when assessing the effect of time to treatment initiation (TTI). We assessed the overall survival and progression-free survival (PFS) effect from increasing TTI for HPV+ and HPV− OPSCC patients.

Materials and methods: We examined patients who received curative-intended therapy for OPSCC in eastern Denmark between 2000 and 2014. TTI was the number of days from diagnosis to the initiation of curative treatment. Overall survival and PFS were measured from the start of treatment and estimated with the Kaplan–Meier estimator. Hazard ratios and 95% confidence intervals were estimated with Cox proportional hazard regression.

Results: At a median follow-up of 3.6 years (interquartile range 1.86–6.07 years), 1177 patients were included (59% HPV+). In the adjusted analysis for the HPV+ and HPV− patient population, TTI influenced overall survival and PFS, most evident in the HPV− group, where TTI >60 days statistically significantly influenced overall survival but not PFS (overall survival: hazard ratio 1.60; 95% confidence interval 1.04–2.45; PFS: hazard ratio 1.46; 95% confidence interval 0.96–2.22). For patients with a TTI >60 days in the HPV+ group, TTI affected overall survival and PFS similarly, with slightly lower hazard ratio estimates of 1.44 (95% confidence interval 0.83–2.51) and 1.15 (95% confidence interval 0.70–1.88), respectively.

Conclusion: For patients treated for a HPV+ or HPV− OPSCC, TTI affects outcome, with the strongest effect for overall survival among HPV− patients. Reducing TTI is an important tool to improve the prognosis.

Key words: Human papillomavirus; oropharyngeal cancer; treatment initiation

Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing in the Western world, mainly due to human papillomavirus (HPV)-associated tumours [1,2]. The distinct difference between HPV+ and HPV− OPSCCs is evident when assessing the mutational profile [3], histopathology [4] and clinical features [5]. For head and neck squamous cell carcinoma, a prolonged interval between diagnosis and treatment initiation (TTI) affects survival [6,7], although varying findings have been published [8,9]. Decreasing the TTI might be a costly and resourceful manoeuvre, hence the effect of TTI on prognosis is important to evaluate.

In Denmark, patients treated for an OPSCC are well suited for assessing the effect of TTI due to similar diagnostic procedures and treatment modalities for the HPV+ and HPV− patient population, but with a significantly different

Author for correspondence: C. von Buchwald, Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. Tel: +45-354-52370.

E-mail address: christian.von.buchwald@rh.regionh.dk (C. von Buchwald).

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prognosis [10]. To our knowledge, no study has addressed the impact of TTI for OPSSC stratified for HPV status. The effect of TTI may provide valuable information on tumour aggressiveness and offer insights into treatment optimisation. The purpose of this population-based study was to assess the impact of TTI in patients treated with curative intent for an HPV+ and HPV− OPSCC.

Materials and Methods

The Eastern Denmark region comprises 46% of the approximately 5.5 million inhabitants of Denmark. We included patients diagnosed with OPSCC in Eastern Denmark from 2000 to 2014 [1,11,12]. Patients were identified through the Danish Head and Neck Cancer (DAHANCA) group database [13] and validated through the national Danish Pathology Data Registry (DPDR) [14]. All tumours were re-evaluated by an expert head and neck pathologist, who also assessed p16 overexpression [15]. All tumours were also examined for HPV DNA by polymerase chain reaction. Tumours were categorised as HPV+ if both HPV+ and p16+, whereas remaining combinations (e.g. HPV−/p16+) were categorised as HPV− [16,17]. Data were obtained from medical files and DAHANCA. The date of diagnosis was registered as the date of diagnostic verification based on biopsy specimens as registered in the DPDR. We excluded patients with TTI greater than 365 days because of concerns regarding misregistration, together with non-squamous histology, therapy with palliative intent and incomplete data on days from diagnosis to treatment.

The main outcome was overall survival, i.e. death from any cause; the secondary outcome was progression-free survival (PFS), i.e. progression or death. Survival time was defined as the time from curatively intended treatment initiation until death or the end of follow-up. PFS was defined as the time from curatively intended treatment initiation until first biopsy or imaging-verified progression, death or the end of follow-up.

Permission for the retrieval of data from medical files was granted by the Danish Patient Safety Authority (3-3013-1390/1).

Statistical Analysis

We categorised TTI into three prespecified groups: 0–30 days, 31–60 days and >60 days based on data from similar studies [6]. Overall survival and PFS were estimated with the Kaplan–Meier estimator. Hazard ratios and 95% confidence intervals were computed with Cox proportional hazard regression. Covariates available for adjustment included age, gender, HPV status, T-stage, UICC-7 stage, treatment modality, year of diagnosis, smoking status, including number of pack years, and performance score. Age was included as a continuous linear variable in the models and the hazard ratios reported per 10 years increase in age at diagnosis. For smoking, both pack years and smoking status were considered. Pack years was included as a linear term in the model and reported per 10 pack year increase. Pack years for non-smokers was set to the average pack years among smokers, which implies that the estimate for smoking (yes/no) corresponds to comparing a smoker with an average number of pack years with a non-smoker. HPV+ and HPV− patients were analysed in separate models. We analysed TTI as a continuous variable included in the model through a restricted cubic spline. The main analyses were carried out on complete cases, but as a sensitivity analysis missing values were imputed using the substantive model compatible fully conditional specification [18]. We tested the proportional hazards assumption by testing for trends in the Schoenfeld residuals. All analyses were carried out in R version 3.3.3 using a 5% significance level and two-sided tests where appropriate [19].

Results

At a median age of 59.8 years, 1177 patients (59% HPV+) met inclusion criteria (Table 1, Supplementary Table S1). The median follow-up time was 3.6 years (interquartile range 1.86–6.07 years). Age, gender, treatment modality, stage, T-stage and smoking showed a significant difference when stratified for HPV status (Table 2). Also, TTI varied significantly based on HPV status, with a median TTI of 35 and 41 days for HPV+ and HPV− patients, respectively, $P < 0.001$ (Table 1).

The TTI distribution revealed that 19% ($n = 221$) of the total cohort had a TTI >60 days, and stratified on HPV status, 17% and 21% had a TTI >60 days for the HPV+ and HPV− groups, respectively. During the recruitment period of 2000–2014, the median TTI was 36 days and decreased by 4.21 days per year ($P < 0.001$) (Figure 1). Notably we found a significant difference in the median TTI based on HPV status; 35 days for HPV+ and 41 days for HPV− ($P < 0.001$). In the period 2011–2014, the median TTI was 31 days (30 days for HPV+; 33 days for HPV−; $P < 0.001$). When stratifying patients based on tumour and patient characteristics, we found significant differences in TTI, e.g. treatment modality (median TTI, 48 days and 32 days, for radiotherapy (RT) and radiotherapy/chemotherapy (RTC/RTC) and surgery, respectively; $P < 0.001$), T classification (median TTI, 33.5 days, 37 days, 37 days and 42 days, for T1, T2, T3 and T4 respectively; $P < 0.001$) and performance score (median TTI of 36 days versus 43 days for PS0 versus PS1+; $P < 0.001$). Stage and gender showed no association with TTI. The median TTI for patients primarily treated with surgery ($n = 23$; 2%) was 13 days.

Impact of Time to Treatment Initiation on Overall Survival and Progression-free Survival

In the adjusted analysis, increased TTI was associated with shorter overall survival and PFS for both the HPV+ and HPV− group. For the HPV− group, a TTI >60 days (hazard ratio 1.60; 95% confidence interval 1.04–2.45) significantly predicted a higher risk of death compared with a TTI of 0–30 days, whereas a TTI of 31–60 days did not indicate an effect on outcomes (Table 2, Figure 2; Supplementary Table

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