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REVIEW

Rate of locoregional recurrence among patients with oropharyngeal squamous cell carcinoma with known HPV status: a systematic review

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ABSTRACT

Background: We aimed to review systematically the literature on locoregional recurrence rates in patients with HPV-positive and -negative oropharyngeal squamous cell carcinoma (OPSCC).

Methods: PubMed and Embase databases were systematically searched using key words such as human papillomavirus, oropharyngeal squamous cell carcinoma with local, regional, and locoregional recurrence.

Results: Nine studies (2974 patients with known HPV-status, 59% HPV-positive) were included. Among the HPV-positive and -negative patients, 69% and 58% had lymph node metastasis at diagnosis. At a median time to recurrence ranging from 8.4 to 13.2 months among the included studies, we found that a weighted average of 9% and 26% for HPV-positive and -negative patients experienced locoregional recurrence. Overall, the median follow-up time ranged from 21 to 83 months among the included studies.

Conclusion: Recurrence rates for HPV-positive and -negative OPSCC patients were 9% and 26%, respectively, equating to an almost three times higher rate of locoregional recurrence among HPV-negative patients compared to HPV-positive patients.

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Introduction

In recent decades, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been increasing, especially the HPV-positive type compared to the HPV-negative [1–4]. The HPV-positive tumors have proved to be a subtype with distinct molecular and clinical features [5,6]. HPV-negative patients are more likely to have a significant history of smoking and high alcohol intake as opposed to HPV-positive patients [7]. Furthermore, HPV-positive patients tend to be younger, male, with higher income and higher education [8]. Patients with HPV-positive OPSCC have also shown better prognosis and survival rates compared to the HPV-negative patients, regardless of treatment regimen [9–11].

Further, patients who are positive for both HPV-DNA and p16 (HPV-DNA+/p16+) have shown a significantly better overall survival rate compared to HPV-DNA-/p16+, or HPV-DNA+/p16- patients, who may be considered HPV-positive in studies using either HPV-DNA or p16 status solely when defining HPV-status [12]. Referring to a recent systematic review, the risk of distant progression was lower in HPV-positive patients compared to HPV-negative patients [13]. The rate of locoregional recurrences in the two groups has not yet been fully explored. This study aimed to systematically review the literature on locoregional recurrence rates in patients with HPV-positive and -negative OPSCC.

Material and methods

PubMed and Embase databases were systematically searched by one author (J.A.) and last updated on 25 June 2019. We searched for studies evaluating the rate of local and regional recurrence among OPSCC patients with known HPV-status.

The main keywords used in the search strategy were human papillomavirus, oropharyngeal squamous cell carcinoma, local, regional, locoregional, and recurrence. Language restriction to English was imposed, and studies were limited to human studies. See Supplementary for the full search strategy.

Inclusion criteria were studies that included both HPV-positive and -negative OPSCC patients and the reported rate of locoregional recurrence after the primary cancer in relation to HPV status. Articles that determined HPV-status based on anything other than tumor tissue (e.g., oral rinses) and studies with a cohort of fewer than 100 patients with known HPV status were excluded.

We collected information on the total number of patients, number of HPV-positive and -negative patients, number of

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locoregional recurrences within each group, N-stage, T-stage, treatment modalities, median follow-up time, and time to recurrence.

Results

The literature search generated 1652 articles, of which nine [14–22] were included (Figure 1). In total, the cohort consisted of 3668 patients (range: 121–1244 patients per study) treated for primary OPSCC, of which HPV status was known for 2974 patients. HPV-positive patients numbered 1740 (58.5%), and 1234 patients (41.5%) were HPV-negative. At diagnosis, 1206 HPV-positive patients (82.6%) and 710 HPV-negative patients (70.6%) had lymph node metastases (≥N1). Of the HPV-positive patients, a weighted average of 55.9% and 43.9% had T-stages 1–2 and 3–4, respectively. For the HPV-negative patients, the weighted average was 35.8% and 60.7%. The 7th edition of the UICC tumor classification was used in all studies.

One-hundred fifty-nine HPV-positive patients and 318 HPV-negative patients experienced locoregional recurrence, corresponding to a weighted average of 9.1% and 25.8%, respectively. Median follow-up time was 49.3 months (range: 1.2–126 months) (Table 1).

Three studies [15,18,20] reported the median time to recurrence. One study found that the median time to recurrence was 1.1 years and 0.9 years for HPV-positive and -negative patients, respectively. The two other studies did not differentiate between HPV-positive and -negative patients and found the overall median time to recurrence was 8.4 months and 9 months.

The definition of HPV status varied between the studies. Three studies based it on a combination of p16 and HPV-DNA, two studies solely on p16, one study solely on HPV16-DNA, one study solely on E6/E7 viral protein, and one study based it on a combination of HPV-DNA and E6/E7 mRNA. One study did not specify their definition of HPV-positivity (Table 1).

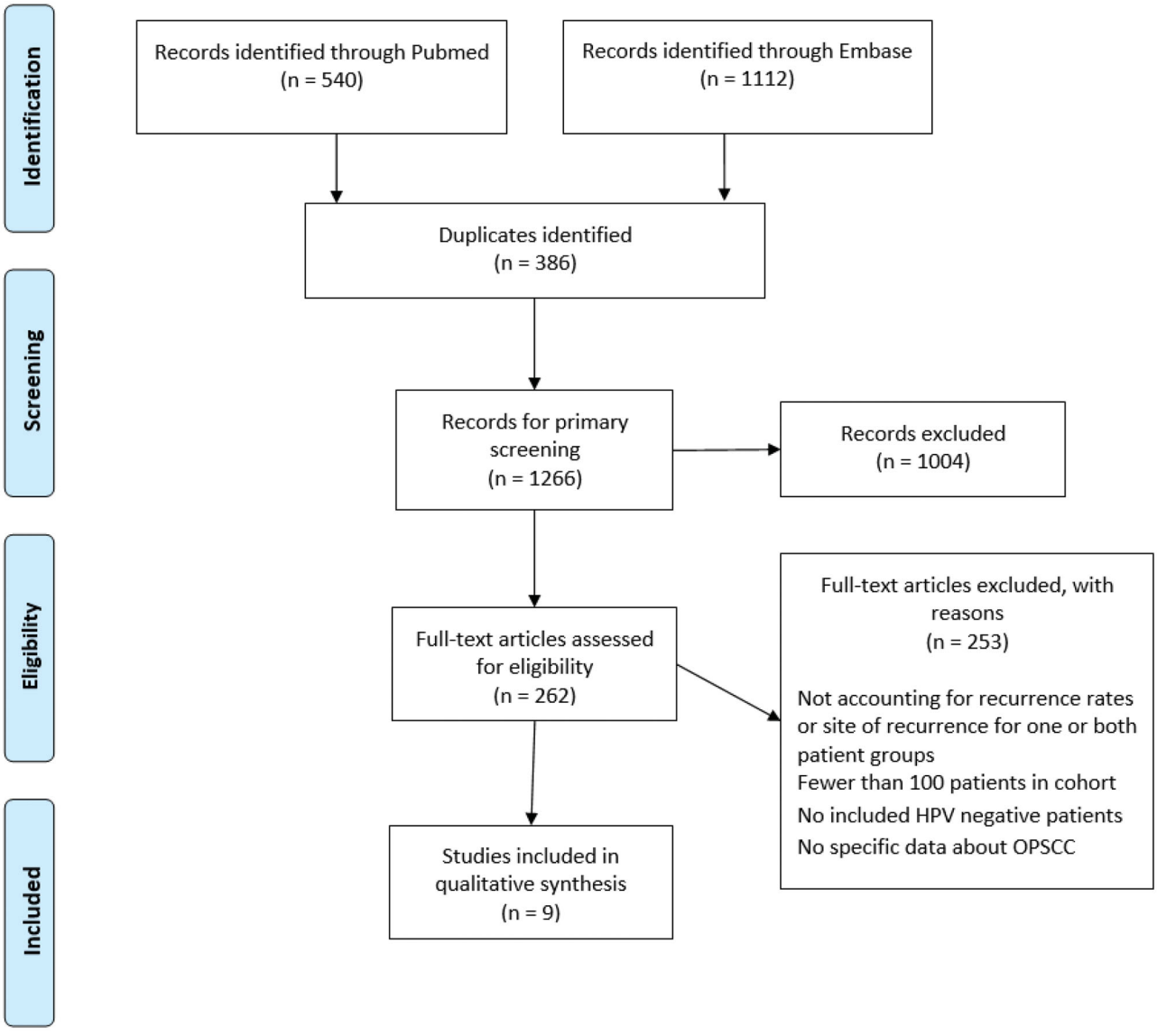

Figure 1. PRISMA flow chart. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Table 1. Study characteristics for the included studies.

Author	Institution	Year of publication	No. of patients in cohort	No. of patients with known HPV status	No. of HPV+ patients (%)	No. of HPV+ patients with N-stage 1 or above at diagnosis (%)	No. of HPV+ patients with locoregional recurrences (%)	No. of HPV- patients (%)	No. of HPV- patients with N-stage 1 or above at diagnosis (%)	No. of HPV- patients with locoregional recurrences (%)
Posner et al. [14]	The Tisch Cancer Institute, Mount Sinai Medical Center, New York, NY, USA	2011	264	111	56 (50.5)	43 (76.8)	7 (12.5)	55 (49.5)	43 (78.2)	23 (41.8)
Sher et al. [15]	Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, TX, USA	2012	163	120	89 (74.2)	N/D	6 (6.7)	31 (25.8)	N/D	8 (25.8)
Jouhi et al. [16]	Department of Otorhinolaryngology – Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland	2017	201	176	107 (60.8)	107 (100)	6 (5.6)	69 (39.2)	69 (100)	1 (1.5)
Lacau St. Guily et al. [17]	Assistance Publique-Hopitaux de Paris (AP-HP), Department of Otolaryngology-Head and Neck Surgery, Tenon Hospital, Paris, France	2017	354	340	92 (27.1)	81 (88)	10 (10.5)	248 (72.9)	185 (74.6)	64 (26)
de Veij Mestdagh et al. [18]	Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands	2019	284	251	122 (48.6)	N/D	8 (6.6)	129 (51.4)	N/D	21 (16.3)
O'Sullivan et al. [19]	Room 5-624, Princess Margaret Hospital, 610 University Ave, Toronto, Ontario, Canada M5G 2M9	2013	899	505	382 (75.6)	262 (68.6)	43 (11.3)	123 (24.4)	57 (46.3)	48 (39)
Gronhoj et al. [20]	Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark	2018	1244	1212	726 (59.9)	618 (85.1)	68 (9.4)	486 (40.1)	335 (68.9)	129 (26.5)
Bledsoe et al. [21]	Case Western Reserve University, School of Medicine, Cleveland, OH, USA	2013	121	121	97 (80.2)	95 (97.9)	3 (3.3)	24 (19.8)	21 (87.5)	6 (26.3)
Evans et al. [22]	Velindre Cancer Center, Whitchurch, Cardiff CF14 2TL, UK	2013	138	138[a]	69 (50)[a]	N/D	8 (11.6)[a]	69 (50)[a]	N/D	18 (26.1) [a]
		Total no. of patients Weighted average	3668	2974	1740 58.5%[b]	1206 82.6%[c]	159 9.1%[c]	1234 41.5%[b]	710 70.6%[d]	318 25.8%[d]

Continued.

Table 1. Continued.

Author	No. of HPV + patients with T1–T2 at time of diagnosis (%)	T-stage			Median follow up time (range)	Definition of HPV-status	Treatment
		No. of HPV + patients with T3–T4 at time of diagnosis (%)	No. of HPV − patients with T1–T2 at time of diagnosis (%)	No. of HPV − patients with T3–T4 at time of diagnosis (%)			
Posner et al.	28 (49)	28 (51)	11 (20)	44 (80)	83 months (77–93)[e] 82 months (68–86)[f]	E6 and E7 viral protein	ST
Sher et al.	N/D	N/D	N/D	N/D	36 months	HPV16 DNA (PCR)	ST or RT or CRT or surgery + CRT
Jouhi et al.	N/D	N/D	N/D	N/D	3–5 years	p16 IHC	Surgery ± RT ± CT or RT ± CT
Lacau St. Guily et al.	45 (49)	47 (51)	101 (41)	147 (59)	26.7 months	HPV DNA PCR and E6/E7 mRNA	Surgery or RT or ICT
de Veij Mestdagh et al.	N/D	N/D	N/D	N/D	43 months (1.4–126)	N/D	RT ± CT
O'Sullivan et al.	N/D	167 (44)	N/D	63 (51)	3.9 years	p16 IHC	RT ± CT
Gronhoj et al.	N/D	N/D	N/D	N/D	3.9 years	HPV DNA PCR and p16 IHC	RT ± CT
Bledsoe et al.	64 (66)	33 (34)	5 (21)	19 (79)	20.8 months (5.8–63)	HPV DNA (ISH) and p16 IHC	CRT
Evans et al.	N/D	N/D	N/D	N/D	4.9 years (0.1–10.1)	HPV DNA (PCR) and p16 IHC	surgery ± RT or RT ± CT
Total (%)	137 (56)	275 (44)	117 (48)	273 (43)			
Weighted average	55.92%	43.86%	35.78%	60.67%			

N/D: no data.
ST: sequential therapy (i.e., induction chemotherapy followed by chemoradiotherapy); RT: radiotherapy; CT: chemotherapy; CRT: chemoradiotherapy; ICT: induction chemotherapy; N/D: no data.
[a]Patients classified with equivocal HPV-status (i.e., HPV DNA+/p16- or HPV DNA-/p16+) are included as HPV-negative in these figures
[b]Has been calculated with weight based on the total number of patients with known HPV-status.[c]Has been calculated with weight based on the total number of HPV-positive patients.
[d]Has been calculated with weight based on the total number of HPV-negative patients.
[e]HPV-positive patients.
[f]HPV-negative patients.

Common for all studies was that treatment was performed independently of HPV status. The most common treatment modality used by the included studies was primary radiotherapy with or without concomitant chemotherapy (Table 1). Four studies reported recurrence rates for local and regional recurrence specifically (Table S1).

Discussion

In this systematic review, we found that HPV-positive patients have a considerably lower rate of locoregional recurrence compared to HPV-negative patients.

This correlates well with the findings of O'Rorke et al. [23] on survival and recurrence in their review and meta-analysis comparing HPV-positive and -negative HNSCCs. They found that HPV-positive OPSCC patients were 63% less likely to experience a cancer recurrence than HPV-negative patients.

The HPV-positive group had a higher rate of N-site metastases at diagnosis (82.6%) compared to the HPV-negative (70.6%). Despite this, HPV-negative patients had a higher rate of locoregional recurrences. This correlates with the notion that HPV-positive tumors more frequently present with advanced overall tumor stage due to increased nodal involvement than HPV-negative tumors, yet they prove to have a better outcome [24,25].

There could be several reasons why HPV-negative patients have a higher rate of recurrence than HPV-positive patients. HPV-positive OPSCC patients are more likely to be younger at diagnosis and less likely to be smokers or have excessive alcohol intake leading to less comorbidity [9]. These factors could, by themselves, have a positive influence on prognosis, since older age, smoking, and alcohol negatively impact outcome [26,27]. Smoking has a negative impact on progression and survival for OPSCC patients regardless of HPV-status. A prior study found that there was a tendency for smoking with a low number of pack-years to have a larger negative impact on HPV-negative patients compared to HPV-positive, in relation to high numbers of pack-years, where there was no difference [7].

Nevertheless, it seems that HPV-positive cancers are biologically distinct from their HPV-negative counterparts, which could explain the difference in prognostic outcomes despite the same treatment [28]. The Cancer Genome Atlas Network has made a comprehensive genome characterization of HNSCCs, which shows that HPV-positive tumors present with widely different DNA-alterations than HPV-negative tumors [29,30].

The precise mechanisms underlying the differences in treatment response remain unknown. The favorable outcome associated with HPV-positive OPSCC could be tied to an increased sensitivity of virus-related cancers to radiation- or chemotherapy, attributed to the likely preserved expression of functional p53 [31–34]. It should be considered that treatment types differed between studies in this review. However, despite the theoretically (assumed) higher radio sensitivity, it is shown that prognosis for HPV-positive and -negative cases is independent of treatment modality. Sinha et al. found that overall survival was higher for HPV-positive

compared to HPV-negative patients, irrespective of the treatment type (surgical/non-surgical) [35]. Therefore, the better prognosis and treatment outcomes could be attributed to other factors.

Factors like immune surveillance of virus-specific tumor antigens, like high CD8+ T-cell infiltration, and lack of field cancerization may contribute to the better treatment outcome of HPV-positive OPSCC's overall survival and prognosis [36–39]. Further, one study found that HPV-positive tumors were not correlated with perineural invasion (PNI) or perivascular invasion (PVI), which have been reported as independent predictors of poor survival [40]. It was also found that HPV-driven tumors display a cohesive invasion pattern at the leading edge of the tumor [41]. This might offer an explanation for their improved clinical outcomes, despite the association with lymph node involvement [25].

Classification of HPV status varied between the articles included in this review. It should be considered that with such different classifications of HPV-positivity, some false-positives could have been included in the results. Correct classification of HPV-status is important, since HPV-DNA-/p16+ and HPV-DNA+/p16- tumors have a worse survival rate compared to HPV DNA+/p16+ [12,42,43].

To rule out false positives, algorithms that combine complementary assays can be used for HPV-detection. One algorithm, a three-step technique, could be used to overcome conflicting results between two tests [44]. First, p16 IHC is used to rule out all HPV negative cases, followed by HPV-ISH on the p16+ cases, to rule out false negatives. For the p16+/HPV ISH- cases, PCR-analysis could be performed to determine the presence or absence of HPV-DNA [45–47]. Nevertheless, RNA-ISH for E6/E7 mRNA, the gold standard for HPV-testing, is the most accurate method for HPV-detection since it confirms HPV-transcriptional activity, although it is technically demanding and not routinely available. However, there remains no consensus for HPV-testing in OPSCC, and practices are highly variable [46–48].

In conclusion, we found that HPV-negative OPSCC patients have an almost three times higher rate of locoregional recurrence compared to HPV-positive, despite less nodal involvement at the time of diagnosis.

Disclosure statement

The authors report no conflicts of interest.

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