Systematic Review

Prognostic biomarkers of human papilloma virus (HPV)-positive neoplasia of the upper aerodigestive tract: a systematic review

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Background: HPV-positivity in oropharyngeal cancer represents a distinct biological entity in terms of underlying genetics and clinical behaviour. Next-generation sequencing has enabled researchers to identify biomarkers associated with neoplasia that may aid in predicting tumour behaviour and offer potential treatment targets. This systematic review aims to evaluate the current known prognostic biomarkers of human papilloma virus (HPV)-positive upper aerodigestive tract (UADT) neoplasia.

Methods: Data sources include Embase (1947–2015), Medline (1946–2015), Cochrane Central Register of Controlled Trials, Cochrane ENT Disorders Group Trials Register and mRCT. The above sources were searched on 19th December 2015 using a comprehensive strategy for studies evaluating clinical outcomes of known prognostic biomarkers of HPV-positive UADT. Articles were limited to English language and human subjects. All studies that provided original data on the clinical implications of biomarkers in HPV-positive neoplasia were included. Outcomes relating to malignant conversion, recurrence, regional and metastatic spread as well as response to treatment were evaluated.

Results: The search returned 4,702 records with thirty-one case series included in the final qualitative synthesis. These encompassed studies evaluating overall survival (n=21), disease-specific survival (n=10), recurrence (n=23), response to treatment (n=2) and risk of metastasis (n=2) with some studies evaluating more than one outcome. Overexpression of p53 and EGFR were not found to be reliable indicators of prognosis with studies demonstrating mixed results.

Conclusions: It is well established that HPV-positivity correlates with improved prognosis in most UADT squamous cell carcinoma (SCC). However, there are no reliable biomarkers that can predict which tumours may fall into the more aggressive subset in this group.

Keywords: Squamous cell carcinoma (SCC); human papilloma virus (HPV); biomarker; oncogene; tumour suppressor gene

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Introduction

Head and neck malignancy is the sixth most common cancer globally with an incidence of half a million cases per year (1). More than 90% of these are squamous cell carcinoma (SCC), a genetically heterogenous neoplasm (2). Head and neck SCC is primarily associated with alcohol and tobacco consumption however human papilloma virus (HPV) infection is becoming increasingly common as a predisposing factor. HPV is thought to promote malignant transformation by surpassing cell cycle checkpoints and thus causing genomic instability. Inverted papilloma (IP) is a locally aggressive, benign sinonasal neoplasm, notable for its tendency for local recurrence and potential for malignant transformation. The incidence of malignant transformation varies in the literature but is largely regarded to be between 5% and 15% (3). Whilst HPV has been implicated in the pathogenesis of IP and its malignant transformation to SCC, studies have not consistently demonstrated a true connection between the virus and IP (4-6). The relationship between HPV and recurrence or malignant transformation of benign IP remains controversial.

In oropharyngeal SCC, HPV positivity represents a distinct biological entity, both in terms of its underlying genetics and clinical behaviour. Next generation sequencing has enabled researchers to begin identifying biomarkers associated with HPV-positive and negative SCC, which can aid in predicting tumour behaviour as well as offering potential targets for treatment in the future. HPV positive tumours have already been demonstrated to have lower mutation rates than their HPV-negative counterparts and mutated genes rarely overlap between these two groups (7,8).

P16, a cyclin dependent kinase inhibitor, is frequently underexpressed in HPV-negative oropharyngeal SCC and overexpressed in HPV positive tumours. Thus, P16 is utilized as a first-line test for determination of HPV status as well as serves as an independent prognostic tool (9,10).

Currently, the gold standard of care of HPV positive cancers involves either surgery with adjuvant radiotherapy +/– chemotherapy or definitive concurrent chemoradiotherapy (11,12). HPV positive oropharyngeal SCC is associated with an improved prognosis and better response to treatment. This finding has been replicated in sinonasal malignancy (13) but remains to be proven in other subsites. Despite this association, a small subset of HPV-positive patients have been demonstrated to have less favourable outcomes. Whilst tobacco smoking has been implicated as a risk factor for poorer outcomes (14,15), few other poor prognostic factors in HPV-positive SCC have been described in the literature. Approximately 10% of HPV positive patients are at high risk of developing distant metastasis and whilst this rate is similar to that of HPV-negative tumours, metastasis in HPV positive cancers tend to occur later and be more disseminated (16-18). This study aims to systematically review the literature and assess the evidence for known biomarkers in HPV positive neoplasia of the upper aerodigestive tract (UADT), that may aid in predicting which patients may go on to have poorer outcomes or respond poorly to treatment.

Methods

A systematic review was performed to evaluate the literature regarding prognostic biomarkers in HPV positive neoplasia of the UADT. The methods of this review were in keeping with PRISMA guidelines (19) and/or the Cochrane Handbook for Systematic Reviews of Interventions where applicable (20).

Eligibility criteria

Studies containing original data pertaining prognostic outcomes of any biomarkers in HPV positive neoplasia of the UADT were considered for inclusion in this study. HPV-positive status was defined by polymerase chain reaction (PCR), *in situ* hybridization (ISH) or P16 immunohistochemistry (IHC). No age or comorbidity restrictions were applied. Studies assessing biomarkers in both HPV-positive and negative neoplasia were included only if they reported extractable data pertaining specifically to HPV-positive tumours. Case series, case-control studies, crossover studies, cohort studies and randomized controlled trials (RCTs) were included. Only manuscripts published in English were eligible; reviews, guidelines, letters, and editorials with no original data were excluded, as were case reports, conference abstracts, *in vitro* and animal studies.

Information sources

A systematic electronic search was performed until December 19th 2015 on the Embase (1974–2015), Medline (1946–2015) databases as well as Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, current issue), Cochrane Ear, Nose and Throat Disorders Group Trials Register and mRCT (metaRegister

Table 1 Search strategy

Papilloma
[1] exp Papilloma, inverted
[2] exp Papilloma
[3] (epithelial papilloma OR schneiderian papilloma OR papillary sinusitis OR soft papilloma OR transitional cell papilloma OR inverting papilloma OR inverted papilloma).mp
[4] [1] OR [2] OR [3]
SCC
[5] exp Carcinoma, squamous cell
[6] (dysplasia OR metaplasia OR atypia OR carcinoma in situ)
[7] (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC*).mp
[8] [5] OR [6] OR [7]
Nasal cavity
[9] exp Nose
[10] exp Nasal cavity
[11] exp nasal mucosa
[12] exp paranasal sinuses
[13] exp paranasal sinus diseases
[14] exp nasopharynx
[15] (nose OR nasal$ OR sinus$ OR rhinosinus$ OR paranasal$ OR rhiniti$ OR nasosinus$ OR pansinus$).mp
[16] [9] OR [10] OR [11] OR [12] OR [13] OR [14] OR [15]
Oral cavity and oropharynx
[17] exp Mouth
[18] exp Lip
[19] exp Tongue
[20] exp Mouth mucosa
[21] exp Salivary glands
[22] (oral$ or intra-oral$ or intraoral$ or "intra oral$" or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek$ or gum$ or palatal$ or palate$ or "head and neck").mp.
[23] [17] OR [18] OR [19] OR [20] OR [21] OR [22]
HPV
[24] exp tumor virus
[25] exp papillomavirus infections
[26] (hpv* or papillomavir* or (papilloma* and vir*) OR human papilloma virus).mp.
[27] [24] OR [25] OR [26]
[43] [4] OR [8]
[44] [16] OR [23]
[37] [43] AND [44] AND [27]

SCC, squamous cell carcinoma; HPV, human papilloma virus.

of Controlled Trials including www.ClinicalTrials.gov). Reference lists of identified publications were scanned for additional studies.

Search methods

A search strategy was designed for each database (*Table 1*) to identify all studies evaluating prognostic biomarkers of HPV-positive neoplasia of the UADT.

Study selection

One author (PL Sacks) reviewed and selected trials found in the searches and evaluated them against the inclusion criteria. In cases where PL Sacks was unsure as to whether the trial was relevant, a second review author (R Harvey) was consulted. Initial screening was upon title review, with brief abstract review if there was uncertainty. The remaining selection underwent stringent abstract review, with discussion between reviewers if uncertain about relevance of individual studies. The full texts of the subsequent selection were analyzed, with study exclusion if not relevant.

Data extraction

A structured data collection form was used for data extraction. The data extraction sheet was pilot-tested on ten randomly-selected included studies and refined accordingly. One review author (PL Sacks) extracted the following data from included studies and a second author (R Harvey) was consulted if any uncertainty arose:

- Study characteristics including study design, inclusion and exclusion criteria, total number of patients, total number of HPV-positive patients, HPV detection method, primary intervention, outcomes assessed, biomarkers assessed and length of follow-up;
- Population demographics including age, gender, smoking and alcohol status, diagnosis, stage at diagnosis;
- Outcomes including percentage of biomarker expressed in population, overall survival, disease-specific survival, recurrence, response to treatment and distant metastasis.

Summary measures

Proportions of individual biomarker expression were

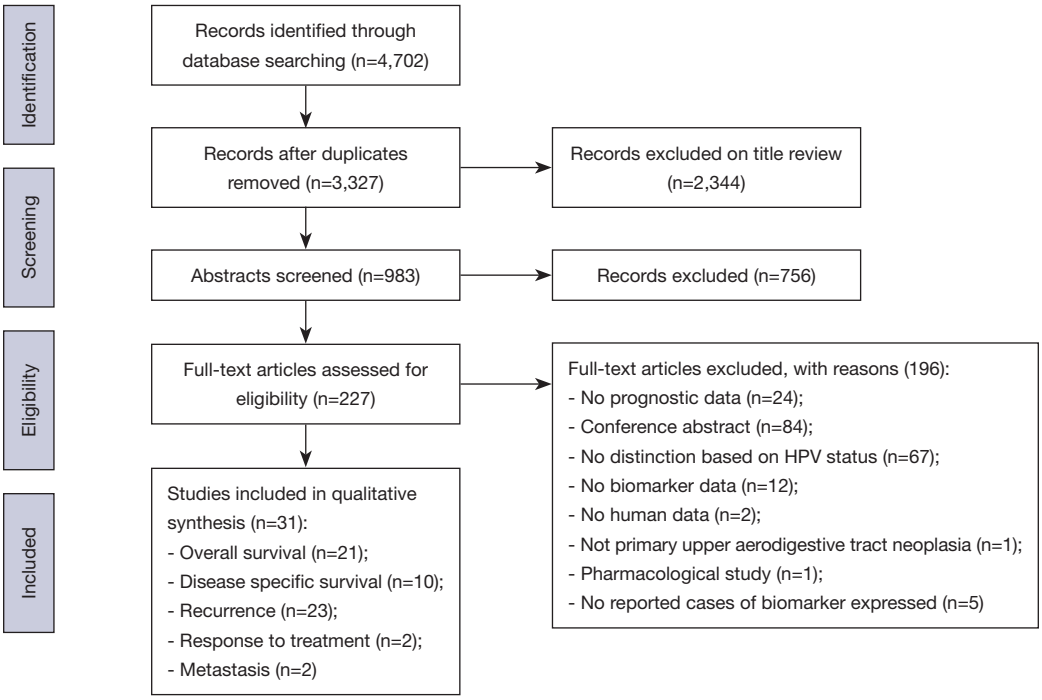

Figure 1 PRISMA flow diagram illustrating selection process.

calculated manually. Hazard ratios and 95% confidence intervals for each prognostic outcome were extracted from manuscripts when available.

A qualitative synthesis was performed where a thematic organisation was created based on endpoint of each study. Outcomes assessed included treatment effects, severity effects and overall mortality.

Results

Search results

The search strategy found 4,702 records. This was reduced to 3,327 after the removal of duplicates. Title and abstract review excluded a further 3,100 articles, leaving 227 full text articles to be assessed for eligibility. There were 31 studies included in the final qualitative synthesis (*Figure 1*). All 31 articles were case series and all investigated malignant disease of the UADT. Twenty-four articles looked exclusively at oropharyngeal or oral SCC. Characteristics of included studies are described in *Table 2*.

Qualitative synthesis and thematic organisation

Study outcomes were organised into broad thematic groups. These included 21 studies evaluating overall survival, ten studies evaluating disease specific survival, 23 studies evaluating recurrence, two studies evaluating response to treatment and two studies evaluating risk of metastasis with some studies evaluating more than one outcome

Overall survival

There were 21 studies evaluating overall survival with a total number of 25 biomarkers investigated. There were five studies evaluating epidermal growth factor receptor (EGFR) with a total of 254 patients. Two studies (9,50) found that overexpression of EGFR was associated with worse overall survival whilst three studies (39,44,51) demonstrated no correlation amongst HPV-positive patients. There were four studies evaluating p53 with a total of 107 patients. Amongst HPV-positive patients, two studies (9,24) found that overexpression of p53 correlated with worse overall survival whilst two studies (27,46) found no correlation. Two studies (43,48) evaluated VEGF with a total of 78 patients and both found overexpression of VEGF to be associated with worse overall survival. Two studies (27,46) evaluated pRb with a total of 53 patients and both found no correlation with overall survival. Correlations of other

Table 2 Characteristics of included studies

Author	Year	Study design	Diagnosis	Primary intervention	Total no. patients (n)	No. HPV+ patients (n)	HPV diagnosis method	Age (mean/ median) (years)	Gender (% female)	% smokers	Biomarker(s) assessed
Qian *et al.* (21)	2015	Case series	OPSCC	NR	96	68	NR	57	17.7%	80.2%	Heregulin, HER3
Zhang *et al.* (22)	2015	Case series	OPSCC	NR	1,008	233	PCR or ISH	55.8	13.5%	75.5%	SNP in promoter region of FAS and FASLG
Balermpas *et al.* (23)	2014	Case series	All HNSCC	Radiotherapy	106	42	P16 IHC	60.6	20.7%	55%	CD68+, CD163+, CD11B+
Kim *et al.* (24)	2014	Case series	OPSCC	Chemotherapy	74	21	PCR	70	7%	NR	P53, beta-tubulin, BCL2, ERCC1
Ko *et al.* (25)	2014	Case series	Oral and OPSCC	Surgery	167	36	ISH	56	18.6%	65.5%	miR21
Liu *et al.* (26)	2014	Case series	OPSCC	Surgery and Radiotherapy	105	48	PCR/P16 IHC	58.5	20%	75.2%	Ki67
Ryu *et al.* (27)	2014	Case series	Tonsillar SCC	Surgery	42	30	PCR	58	9.5%	64.3%	Cyclin D1, pRB, p53
Tertipis *et al.* (28)	2014	Case series	Tongue SCC	Radiotherapy	278	207	Multiplex assay	60	24.6%	64.7%	LMP10
Vainshtein *et al.* (29)	2014	Case series	Stage III or IV OPSCC	Radiotherapy	198	184	PCR or ISH	55	10.9%	56.6%	EGFR
Zhang *et al.* (30)	2014	Case series	OPSCC	NR	846	158	PCR or ISH	55.6	13.1%	62.7%	TNF-alpha
Bauman *et al.* (31)	2013	Case series	Stage III–IV HNSCC	Chemo-radiotherapy	90	56	P16 IHC	NR	12%	77%	ERCC1
Chandarana *et al.* (32)	2013	Case series	OP and oral SCC	Radiotherapy	85	26	P16 IHC	57.2 (oral), 52.3 (OP)	74.1%	88.2%	EGFR
Chiosea *et al.* (33)	2013	Case series	HPV+ OPSCC	Chemo-radiotherapy	75	75	ISH	56	14.7%	53.3%	PIK3CA
Kaka *et al.* (34)	2013	Case series	HPV+ OPSCC	Chemo-radiotherapy	15	15	P16 IHC/CISH	59	14%	57%	P53, NOTCH
Scantlebury *et al.* (35)	2013	Case series	OPSCC	Surgery	202	150	RNA ISH/P16 IHC	56.8	11.9%	70.8%	Cyclin D1
Song *et al.* (36)	2013	Case series	OPSCC	NR	658	102	PCR	55.3	14.4%	63.4%	SNP in nucleotide excision repair pathway
Badoual *et al.* (37)	2012	Case series	All HN SCC	NR	64	32	INNO-LiPA genotyping extra assay	NR	34%	NR	PD-1-positive cells, CD8+, CD4+

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	Study design	Diagnosis	Primary intervention	Total no. patients (n)	No. HPV+ patients (n)	HPV diagnosis method	Age (mean/ median) (years)	Gender (% female)	% smokers	Biomarker(s) assessed
Gubanova *et al.* (38)	2012	Case series	OPSCC	NR	40	20	PCR	58.2	20%	47.5%	SMG1, ATM, ATR
Husain *et al.* (39)	2012	Case series	All HNSCC	NR	101	29	P16 IHC	NR	18.4%	80.7%	EGFR
Lim *et al.* (40)	2012	Case series	All HNSCC	Radiotherapy	87	28	P16 IHC	56.6	13.7%	NR	ATM
Park *et al.* (41)	2012	Case series	OPSCC	Surgery	86	46	PCR	62.1	16.3%	69.8%	pRB, cyclin D1, CDK4, p21
Hao *et al.* (42)	2011	Case series	SCC neck node unknown primary	Chemo-radiotherapy	55	30	CISH and PCR	54.8	16.4%	76.4%	ERCC1
Moeller *et al.* (43)	2011	Case series	All HNSCC	Radiotherapy	89	36	PCR	60	18%	64%	Ku80
Al-Swiahb *et al.* (9)	2010	Case series	OPSCC	Surgery	220	33	PCR	51.3	42%	79%	P53, EGFR
Hong *et al.* (44)	2010	Case series	OPSCC	NR	270	99	PCR/P16 IHC	59.8	21%	NR	EGFR
Nichols *et al.* (45)	2010	Case series	OPSCC	Chemo-radiotherapy	68	53	ISH	NR	14.7%	51.5%	Bcl2
Chung *et al.* (46)	2009	Case series	Stage IV tonsillar SCC	Chemo-radiotherapy	46	23	PCR	53	13%	<50%	P53, pRB, p21
Fallai *et al.* (47)	2009	Case series	OPSCC	Chemo-radiotherapy	78	9	PCR	56.4	92%	NR	P53
Fei *et al.* (48)	2009	Case series	Tonsillar SCC	NR	85	42	PCR or P16 IHC	59	18.8%	NR	VEGF, EGFR
Klussmann *et al.* (49)	2009	Case series	OPSCC	Radiotherapy	60	28	PCR/P16 IHC	60	22%	80%	11q13 amplification, 16q loss, 9p loss
Kumar *et al.* (50)	2008	Case series	Stage III and IV OPSCC	Chemotherapy	42	25	PCR	62	24%	78%	EGFR, P53, BCL-xL

OPSCC, oropharyngeal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NR, not reported; HPV, human papilloma virus; PCR, polymerase chain reaction; ISH, in situ hybridization; IHC, immunohistochemistry; P16, protein 16 (inhibitor of cyclin dependent kinases); CISH, chromogenic in situ hybridization; RNA, ribonucleic acid; INNO-LiPA, innogenetics; HER3, human epidermal growth factor receptor 3; SNP, single nucleotide polymorphism; FAS, Fas cell surface death receptor; FASLG, FAS ligand; CD, cluster of differentiation; P53, protein 53; BCL2, B-cell lymphoma 2; ERCC1, excision repair cross-complementation group 1; miR21, microRNA-21; Ki67, marker of proliferation Ki-67; pRB, retinoblastoma protein; LMP10, low molecular weight protein 10; EGFR, epidermal growth factor receptor; TNF-alpha, tumour necrosis factor alpha; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD-1, programmed cell death protein 1; SMG1, suppressor with morphogenetic effect on genitalia; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3 related; p21, protein 21; CDK4, cyclin dependent kinase 4; VEGF, vascular endothelial growth factor; BCL-xL, B-cell lymphoma-extra large.

biomarkers evaluated in less than two studies can be found in *Table 3*.

Disease specific survival

There were ten studies evaluating disease specific survival with a total number of eight biomarkers investigated. EGFR was evaluated in three studies, including a total of 93 patients and correlated with worse disease specific survival in all three studies (32,48,50). Correlations of other biomarkers evaluated in less than two studies can be found in *Table 4*.

Locoregional recurrence

There were 23 studies evaluating rates of locoregional recurrence with 37 biomarkers investigated. There were four studies evaluating EGFR with a total of 354 patients. One study (48) found that overexpression of EGFR was associated with increased rates of recurrence whilst three studies (29,39,44) demonstrated no correlation amongst HPV-positive patients. There were four studies evaluating p53 with a total of 98 patients. Amongst HPV-positive patients, two studies (27,47) found that overexpression of p53 correlated with increased recurrence rates whilst two studies (43,46) found no correlation. Three studies evaluated ERCC1 with a total of 186 patients. Two studies (36,42) demonstrated no correlation between ERCC1 levels and recurrence. However, one study (31) demonstrated increased recurrence rates with higher expression of ERCC1. Two studies evaluated pRb with a total of 53 patients. One study (27) demonstrated increased recurrence rates with overexpression in pRb whereas one study (46) found no correlation. Two studies evaluated loss of ataxia telangiectasia mutated (ATM) with a total of 64 patients. One study (43) found that ATM loss correlated with increased recurrence rate whereas one study found no correlation (40). Correlations of other biomarkers evaluated in less than two studies can be found in *Table 5*.

Response to treatment

There were two studies evaluating response to treatment with one biomarker investigated in each study. ERCC1 correlated with better response to treatment (31) and SMG-1 negative tumours correlated with higher radiation sensitivity (38) (*Table 6*).

Distant metastasis

There were two studies evaluating rates of distant metastasis with four biomarkers investigated in total. Only NOTCH was found to be lower in patients developing distant metastasis (34) with p53, CD163 and CD11b showing no correlation (23,34) (*Table 7*).

Discussion

It is well described that particularly in the oropharyngeal literature, HPV-positive neoplasia represents a distinct

Table 3 Biomarkers predicting overall survival (OS)

Biomarker	Studies (n)	Patients (n)	% of tumours expressing biomarker	Summary
EGFR	5	254	50%	2 studies—low expression EGFR associated with high OS: P=0.01, no HR reported (Al-Swiahb *et al.*, 2010); P=0.03, no HR reported (Kumar *et al.*, 2008)
				3 studies—no correlation with overall survival: P=0.4, no HR reported (Husain *et al.*, 2012); P=0.22, HR 1.86 (95% CI, 0.68–5.13) (Qian *et al.*, 2015); P=0.29, HR 1.42 (95% CI, 0.39–5.19) (Hong *et al.*, 2010)
p53	4	107	14%	2 studies—low expression p53 associated with high OS: P≤0.01, no HR reported (Al-Swiahb *et al.*, 2010); P=0.01, no HR reported (Kim *et al.*, 2014)
				2 studies—no correlation with overall survival: P=0.48, no HR reported (Chung *et al.*, 2009); P=0.43, HR 0.43 (95% CI 0.13-1.45) (Ryu *et al.*, 2014)

Table 3 (*continued*)

Table 3 (*continued*)

Biomarker	Studies (n)	Patients (n)	% of tumours expressing biomarker	Summary
VEGF	2	78	59.50%	2 studies—high VEGF correlated with worse OS: P=0.06, HR 2.94 (95% CI, 0.94–12.91) (Fei *et al.*, 2009); P=0.04, no HR reported (Moeller *et al.*, 2011)
pRB	2	53	11.30%	2 studies—no correlation with OS: P=0.21, no HR reported (Chung *et al.*, 2009); P=0.272, HR 0.47 (95% CI, 0.12–1.80)] (Ryu *et al.*, 2014)
p21	1	23	78%	1 study—no correlation with OS: P=0.66, no HR reported (Chung *et al.*, 2009)
Cyclin D1	1	150	3.70%	1 study—intensity of expression associated with better OS: P=0.038, no HR reported (Scantlebury *et al.*, 2013)
ERCC1	1	30	50%	1 study—no correlation with OS: P=0.58, HR 1.5 (95% CI, 0.3–6.8) (Hao *et al.*, 2012)
PD-1+ve cells	1	32	59%	1 study—high numbers of PD-1+ T cells correlated with better OS: P=0.025, HR 0.13 (95% CI, 0.02–0.067) (Badoual *et al.*, 2013)
CD8+	1	32	53%	1 study—no correlation with better OS: P=0.6, HR 0.7 (95% CI, 0.14–3.6) (Badoual *et al.*, 2013)
CD4+	1	32	68.70%	1 study—no correlation with OS: P=0.7, HR 1.36 (95% CI, 0.22–8.6) (Badoual *et al.*, 2013)
CD163+	1	42	42.90%	1 study—no correlation with OS: P=0.112, no HR reported (Balermpas *et al.*, 2014)
CD11B+	1	42	53.60%	1 study—no correlation with OS: P=0.394, no HR reported (Balermpas *et al.*, 2014)
SMG1	1	20	15%	High SMG1 expression correlated with poor OS: no P value nor HR (Gubanova *et al.*, 2012)
Beta tubulin	1	21	4.70%	Class III beta tubulin correlated with better OS: P=0.012, no HR reported (Kim *et al.*, 2014)
11q13 amp	1	28	7.10%	1 study—11q13 amp associated with worse OS: P=0.02, no HR reported (Klussman *et al.*, 2009)
16q loss	1	28	28.60%	1 study—16q loss associated with improved OS: P=0.01, no HR reported (Klussman *et al.*, 2009)
9p loss	1	28	10.70%	1 study—9p loss associated with worse OS: P<0.0015, no HR reported (Klussman *et al.*, 2009)
Ku80	1	36	NR	1 study—no correlation with OS (data not reported) (Moeller *et al.*, 2011)
CDK4	1	46	43.50%	1 study—high CDK4 associated with worse OS: P=0.011, HR 2.91 (95% CI, 2.25–3.38) (Park *et al.*, 2012)
Heregulin	1	57	47.40%	1 study—high heregulin correlated with worse OS: P=0.049, HR 3.30 (95% CI, 0.94–11.57) (Qian *et al.*, 2015)
HER3	1	67	49.30%	1 study—no correlation with OS: P=0.94, HR 0.82 (95% CI, 0.31–2.22) (Qian *et al.*, 2015)
HER2	1	68	50%	1 study—no correlation with OS: P=0.85, HR 1.10 (95% CI, 0.41–2.91) (Qian *et al.*, 2015)
LMP10	1	207	44.44% nuclear	1 study—nuclear [P=0.162, HR 1.673 (95% CI, 0.813–3.445)] nor cytoplasmic [P=0.164, HR 0.590 (95% CI, 0.281–1.240)] expression not correlated with OS (Tertipis *et al.*, 2014)
			47.83% cytoplasm	
Bcl2	1	53	39.60%	1 study—high Bcl2 correlated with worse OS: P=0.0064, HR 6.9 (95% CI, 1.7–27) (Nichols *et al.*, 2010)
Ki67	1	48	54.10%	1 study—no correlation with OS: P=0.144, HR 0.21 (95% CI, 0.08–0.56) (Liu *et al.*, 2014)

EGFR, epidermal growth factor receptor; p53, protein 53; VEGF, vascular endothelial growth factor; pRB, retinoblastoma protein; p21, protein 21; ERCC1, excision repair cross-complementation group 1; PD-1, programmed cell death protein 1; CD, cluster of differentiation; SMG1, suppressor with morphogenetic effect on genitalia; CDK4, cyclin dependent kinase 4; HER3, human epidermal growth factor receptor 3; LMP10, low molecular weight protein 10; BCL2, B-cell lymphoma 2; Ki67, marker of proliferation Ki-67; HR, hazard ratio; CI, confidence interval.

Table 4 Biomarkers predicting disease specific survival (DSS)

Biomarker	Studies (n)	Patients (n)	% expressed	Summary
EGFR	3	93	50.5%	3 studies—EGFR correlated with worse DSS: P=0.04, no HR reported (Kumar *et al.*, 2008); P=0.04, no HR reported (Fei *et al.*, 2009); P=0.01, no HR reported (Chandarana *et al.*, 2013)
p53	1	35	5%	1 study—no correlation with DSS: P=0.272, no HR reported (Kim *et al.*, 2014)
ERCC1	1	30	50%	1 study—no correlation with DSS: P=0.85, HR 1.2 (95% CI, 0.2–8.5) (Hao *et al.*, 2011)
MiR21	1	36	28%	1 study—no correlation with DSS: P=0.486, no HR reported (Ko *et al.*,2014)
PIK3CA mutation	1	75	31%	1 study—no correlation with DSS: P=0.8, no HR reported (Chiosea *et al.*, 2013)
CDK4	1	46	43%	1 study—high CDK4 associated with worse DSM: P=0.007, HR 2.91 (95% CI, 2.25–3.38) (Park *et al.*, 2012)
Cyclin D1	1	150	58.8%	1 study—intensity of expression associated with worse DSS: P=0.015, no HR reported (Scantlebury *et al.*, 2013)
Ki67	1	48	56%	1 study—no correlation with OS: P=0.137, HR 0.23 (95% CI, 0.08–0.68) (Liu *et al.*, 2014)

EGFR, epidermal growth factor receptor; p53, protein 53; ERCC1, excision repair cross-complementation group 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; CDK4, cyclin dependent kinase 4; Ki67, marker of proliferation Ki-67; HR, hazard ratio; CI, confidence interval.

Table 5 Biomarkers predicting risk of recurrence

Biomarker	Studies (n)	Patients (n)	% expressed	Summary
p53	4	98	16.1%	2 studies—high p53 expression correlated with increased risk of recurrence: P=0.046, HR 0.31 (95% CI, 0.10–0.98) (Ryu *et al.*, 2014); P<0.01, no HR reported (Fallai *et al.*, 2009)
				2 studies—no correlation with recurrence: P=0.54, no HR reported (Chung *et al.*, 2009); data not reported (Moeller *et al.*, 2011)
EGFR	4	354	46.7%	1 study—high EGFR expression correlated with increased risk of recurrence: P=0.02, no HR reported (Fei *et al.*, 2009)
				3 studies—no correlation with recurrence: P=0.97, no HR reported (Husain *et al.*, 2012); P=0.73, HR 3.84 (95% CI, 0.48–30.84) (Hong *et al.*, 2010); P=0.205, HR 1.71 (95% CI, 0.75–3.87) (Vainshtein *et al.*, 2014)
ERCC1	3	186	38.7%	2 studies—no correlation with recurrence: P=0.75, HR 0.7 (95% CI, 0.1–4.5) (Hao *et al.*, 2010); P=0.138, HR 0.4 (95% CI, 0.1–1.3) (Song *et al.*, 2013) 1 study—ERCC1 correlated with increased recurrence rates: ERCC1 (FL297): P=0.04, HR 10.1 (no 95% CI); ERCC1 (4F9): P=0.04, HR 13.7 (no 95% CI) (Bauman *et al.*, 2013)
pRB	2	53	11.3%	1 study—low pRB associated with decreased risk of recurrence: P=0.01, HR 0.08 (95% CI, 0.02–0.35) (Ryu *et al.*, 2014)
				1 study—no correlation with recurrence: P=0.54, no HR reported (Chung *et al.*, 2009)
ATM	2	64	10.7%	1 study—no correlation with recurrence (data not reported) (Lim *et al.*, 2012) 1 study—ATM loss correlated with increased recurrence rate: P=0.03, no HR reported (Moeller *et al.*, 2011)
ATR	1	36	NR	1 study–ATR loss correlated with increased risk of recurrence: P=0.03, no HR reported (Moeller *et al.*, 2011)

Table 5 (*continued*)

Table 5 (*continued*)

Biomarker	Studies (n)	Patients (n)	% expressed	Summary
P21	1	23	78%	1 study—no correlation with recurrence: P=0.43, no HR reported (Chung *et al.*, 2009)
PD-1+ve cells	1	32	59%	1 study—no correlation with recurrence (data not reported) (Badoual *et al.*, 2013)
CD163+	1	42	42.9%	1 study—no correlation with recurrence: P=0.146, no HR reported (Balermpas *et al.*, 2014)
CD11B+	1	42	53.6%	1 study—no correlation with recurrence: P=0.418, no HR reported (Balermpas *et al.*, 2014)
Ki67	1	48	56%	1 study—Ki67 positivity inversely associated with recurrence: P=0.015, HR 0.21 (95% CI, 0.08–0.56) (Liu *et al.*, 2014)
Cyclin D1	1	150	58.8%	1 study—intensity of expression correlated with recurrence: P=0.014, no HR reported (Scantlebury *et al.*, 2013)
VEGF	1	42	59%	1 study—no correlation with recurrence: P=0.4, HR 1.43 (95% CI, 0.63–3.53) (Fei *et al.*, 2009)
SMG1	1	20	28%	1 study—low SMG-1 correlated with decreased incidence of recurrence (no P value nor HR) (Gubanova *et al.*, 2012)
16q loss	1	28	29%	1 study—16q loss correlated with decreased rate of recurrence: P=0.008, no HR reported) (Klussmann *et al.*, 2009)
9p loss	1	28	11%	1 study—9p loss correlated with decreased rate of recurrence: P=0.04, no HR reported (Klussmann *et al.*, 2009)
miR21	1	36	28%	1 study—no correlation: P=0.564, no HR reported (Ko *et al.*, 2014)
Ku80	1	36	NR	1 study—no correlation (data not reported) (Moeller *et al.*, 2011)
E-cadherin	1	36	NR	1 study—E-cadherin expression correlated with increased risk of recurrence: P=0.04, no HR reported (Moeller *et al.*, 2011)
Bcl2	1	53	39.6%	1 study—high Bcl2 correlated with higher risk of recurrence: P=0.004, HR 7.6 (95% CI, 1.9–30) (Nichols *et al.*, 2010)
CDK4	1	46	43.5%	1 study—high CDK4 associated with increased recurrence: P=0.009, HR 2.87 (95% CI, 2.51–3.46) (Park *et al.*, 2012)
Heregulin	1	68	47.4%	1 study—no correlation with recurrence: P=0.309, no HR reported (Qian *et al.*, 2015)
XPC rs2228000	1	102	47.1%	1 study—SNP correlated with increased rate of recurrence: P=0.051, HR 1.6 (95% CI, 1.0–4.1) (Song *et al.*, 2013)
XPC rs2228001	1	102	29.4%	1 study—no correlation with recurrence: P=0.523, HR 0.7 (95% CI, 0.3–2.0) (Song *et al.*, 2013)
XPA rs1800975	1	102	51.9%	1 study—no correlation with recurrence: P=0.933, HR 1.0 (95% CI, 0.4–2.4) (Song *et al.*, 2013)
XPD rs1799793	1	102	56.9%	1 study—SNP correlated with increased rate of recurrence: P=0.002, HR 0.2 (95% CI, 0.1–0.5) (Song *et al.*, 2013)
XPD rs13181	1	102	55.9%	1 study—no correlation with recurrence: P=0.100, HR 0.4 (95% CI, 0.2–1.1) (Song *et al.*, 2013)
XPG rs17655	1	102	31.4%	1 study—SNP correlated with increased rate of recurrence: P=0.036, HR 0.1 (95% CI, 0.0–0.9) (Song *et al.*, 2013)

Table 5 (*continued*)

Table 5 (*continued*)

Biomarker	Studies (n)	Patients (n)	% expressed	Summary
LMP10	1	207	44.4% nucleus; 47.8% cytoplasm	1 study—fraction of nuclear expression correlated with lower incidence of recurrence: P=0.009, HR 2.25 (95% CI, 1.35–7.85); cytoplasm expression did not correlated: P=0.093, HR 2.07 (95% CI, 0.89–4.84) (Tertipis *et al.*, 2014)
TNF alpha-308 (rs1800629) GG	1	158	63%	1 study—GG genotype correlated with increased recurrence: P=0.005, HR 5.1 (95% CI, 1.4–18.4) (Zhang *et al.*, 2014)
TNF alpha-857 (rs1799724) CC	1	158	87%	1 study—no correlation with recurrence: P=0.594, HR 1.4 (95% CI, 0.3–5.9) (Zhang *et al.*, 2014)
TNF alpha-863 (rs1800630) CC	1	158	46.8%	1 study—CC genotype correlated with increased recurrence: P=0.007, HR 3.7 (95% CI, 1.5–9.1) (Zhang *et al.*, 2014)
TNF alpha-1031 (rs1799964) TT	1	158	69.6%	1 study—no correlation with recurrence: P=0.100, HR 0.6 (95% CI, 0.2–1.3) (Zhang *et al.*, 2014)
FAS1377 G>A GA+AA	1	233	8.5%	1 study—no correlation with recurrence: P=0.662, HR 0.8 (95% CI, 0.2–3.3) (Zhang *et al.*, 2015)
FAS670 A>G AA+GG	1	233	46.4%	1 study—AG+GG mutation associated with increased risk of recurrence: P<0.0001, HR 12.9 (95% CI, 3.8–43.6) (Zhang *et al.*, 2015)
FASLG844 C>T CC+TT	1	233	35.2%	1 study—AG+GG mutation associated with increased risk of recurrence: P<0.0001, HR 8.1 (95% CI, 3.6–18.6) (Zhang *et al.*, 2015)
FASLG124 A>G AG+GG	1	233	20.6%	1 study—no correlation with recurrence: P=0.100, HR 1.6 (95% CI, 0.8–3.3) (Zhang *et al.*, 2015)

p53, protein 53; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; pRB, retinoblastoma protein; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3 related; p21, protein 21; PD-1, programmed cell death protein 1; CD, cluster of differentiation; VEGF, vascular endothelial growth factor; Ki67, marker of proliferation Ki-67; SMG1, suppressor with morphogenetic effect on genitalia; BCL2, B-cell Lymphoma 2; CDK4, cyclin dependent kinase 4; SNP, single nucleotide polymorphism; LMP10, low molecular weight protein 10; TNF-alpha, tumour necrosis factor alpha; FAS, Fas cell surface death receptor; FASLG, FAS ligand; HR, hazard ratio; CI, confidence interval.

Table 6 Biomarkers predicting response to treatment

Biomarker	Studies (n)	Patients (n)	% expressed	Summary
ERCC1	1	56	35.7%	1 study—ERCC1 (fl297): P=0.041; ERCC1 (4f9): P=0.016, correlated with better complete response (no HR reported) (Bauman *et al.*, 2013)
SMG1	1	20	28%	1 study—SMG1 negative tumours correlated with higher radiation sensitivity (no data values reported) (Gubanova *et al.*, 2012)

ERCC1, excision repair cross-complementation group 1; SMG1, suppressor with morphogenetic effect on genitalia; HR, hazard ratio; CI, confidence interval.

clinical and biological entity from that of HPV-negative neoplasia. When functioning properly, p53 responds to cellular injury resulting in cell cycle arrest, attempted DNA repair, and, if DNA repair is ineffective, apoptosis. Mutations in p53 have been well established in HPV-negative SCC with prevalence in the literature to be between 47–100% (7,8,52). In this study, mutated p53 was prevalent in only 14% of HPV-positive cases. Overexpression of p53 was not found to be a reliable indicator of prognosis in this review with studies demonstrating mixed results. This contrasts with that of HPV-negative neoplasia in the literature in which p53

Table 7 Biomarkers predicting risk of distant metastasis

Biomarker	Studies (n)	Patients (n)	% expressed	Summary
p53	1	15	NR	1 study—no correlation with metastasis: P=0.5, no HR reported (Kaka *et al.*, 2013)
NOTCH	1	15	NR	1 study—NOTCH lower in patients developing metastasis: P=0.04, no HR reported (Kaka *et al.*, 2013)
CD163	1	42	42.9%	1 study—no correlation with development of DM: P=0.140, no HR reported (Balermpas *et al.*, 2014)
CD11b	1	42	53.6%	1 study—no correlation with development of DM: P=0.417, no HR reported (Balermpas *et al.*, 2014)

p53, protein 53; CD, cluster of differentiation; HR, hazard ratio; CI, confidence interval; NR, not reported.

mutation has been demonstrated to be a poor prognostic indicator (53,54). EGFR activation induces cellular proliferation and prevents apoptosis. In the current review, EGFR overexpression showed 50% prevalence amongst HPV-positive patients, compared to more than 90% of HPV-negative or undifferentiated patients in the literature (55,56). Studies evaluating the prognostic value of EGFR showed mixed results in HPV-positive neoplasia, again contrasting the undifferentiated literature (55,56). Whilst there are a vast array of studies appraising prognostic biomarkers in UADT neoplasia, few studies differentiated between HPV-positive and negative tumours despite these essentially representing distinct pathologies. In this review, there were no biomarkers that reliably demonstrated prognostic value in HPV-positive tumours specifically in multiple studies.

All thirty-one included studies evaluated SCC of the UADT. There were no studies that met the inclusion criteria that evaluated prognostic biomarkers in HPV-positive benign neoplasia such as IP. Laryngeal papillomatosis is a relapsing remitting growth of the upper respiratory tract and is a benign manifestation of HPV. Recent studies have documented a high prevalence (20–50%) of laryngeal dysplasia in patients who have had a diagnosis of laryngeal papillomatosis (57-59). Whilst HPV has been implicated in the pathogenesis of IP and its malignant transformation to SCC, studies have not consistently demonstrated a true connection between the virus and IP nor whether or not HPV-positive IP behaves like HPV-positive malignant neoplasia, representing less aggressive disease (4-6).

Limitations in this analysis of the literature included the heterogeneity of the included studies such as differing primary modes of treatment, different population severity and variable follow-up periods. This restricts comparison of the studies and increases risk of confounding. Whilst there were many different biomarkers assessed in the various studies, few of these had more than one study to compare results. Meta-analysis was not considered appropriate due to the heterogeneity of populations, treatments and disease. Exclusion of studies that did not specifically examine HPV-positive neoplasia as distinct from HPV-negative neoplasia may have limited results, as the majority of studies identified in the search did not differentiate between these groups in their analysis.

Conclusions

It is well established that HPV-positivity correlates with improved prognosis in oropharyngeal SCC. However, there are no reliable biomarkers that can predict which tumours may fall into the more aggressive subset in this group. Further research is required to establish reliable prognostic biomarkers of HPV-positive SCC of the UADT. Furthermore, the influence of HPV on the behavioral or oncogenic influence in benign papilloma has yet to be fully defined.

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Footnote

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