Prognostic biomarkers of survival in oropharyngeal squamous cell carcinoma: Systematic review and meta-analysis

James W. Rainsbury, MRCS,[1] Waseem Ahmed, MRCS,[1] Hazel K. Williams, PhD,[2] Sally Roberts, PhD,[3] Vinidh Paleri, FRCS (ORL-HNS),[4] Hisham Mehanna, FRCS (ORL-HNS)[1]

[1]Institute of Head and Neck Studies and Education (InHANSE), University Hospital, Coventry, United Kingdom, [2]Department of Cellular Pathology, Queen Elizabeth Hospital, Edgbaston, Birmingham, United Kingdom, [3]Institute of Cancer Research, University of Birmingham, Birmingham, United Kingdom, [4]Department of Otolaryngology, The Newcastle-upon-Tyne Hospitals NHS, Foundation Trust, Newcastle, United Kingdom.

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ABSTRACT: *Background.* Human papillomavirus (HPV) positivity improves prognosis in patients with oropharyngeal squamous cell carcinoma (OPSCC). Combining HPV status with other biomarkers may improve its prognostic power.

Methods. The approach was a literature search for longitudinal studies of biomarkers in OPSCC, with systematic review and meta-analysis.

Results. In all, 3130 articles were identified; 32 satisfied the inclusion and exclusion criteria. On meta-analysis, there was a significant overall survival (OS) benefit for patients with HPV positive and p16 positive tumors. There was some evidence of improved OS of OPSCC patients with raised bcl2; amplification of 11q3 and loss of 16q genes; and low c-met, ki67, IMD, PLK, FHIT, nuclear surviving, or nuclear cyclin D1. However, none of these was suitable for meta-analysis.

Conclusion. Survival from OPSCC is associated with several biomarkers, which constitute potential targets for research into improving the prognostic power of HPV in OPSCC. Larger trials are needed, with standardization of cut-points and adherence to consensus reporting guidelines. © 2012 Wiley Periodicals, Inc. *Head Neck* **35: 1048–1055, 2013**

KEY WORDS: biomarker, human papillomavirus, oropharyngeal cancer, prognostic, survival

INTRODUCTION

Human papillomavirus (HPV) status carries a favorable prognosis in patients with oropharyngeal squamous cell carcinoma (OPSCC) and is by far the most significant development in prognostication in head and neck cancer in the last 3 decades.[1] A recent meta-analysis of prognostic efficacy of HPV status showed a 28% reduced risk of dying and 49% reduced risk of locoregional recurrence.[2]

However, it has also been recently recognized that it is possible to further refine the prognostic ability of HPV status, by its combination with clinical characteristics, such as smoking status, tumor, and nodal stage. It is now acknowledged that a more reliable method of prognostic classification is required, and now constitutes one of the most important clinical and research questions in head and neck cancer.[1]

Unlike other head and neck squamous cell carcinomas (HNSCCs) that have shown slight decline, OPSCC has shown a significant increase in incidence, especially in the Western world. It is now the fastest rising head and neck cancer in the United Kingdom, its incidence doubling between 1990 and 2006.[3] In the United States, the incidence of OPSCC increased by 22% from 1.53 per 100,000 to 1.87 per 100,000 between 1999 and 2006, after showing no change between 1975 and 1999.[4] Similar trends have been demonstrated in other developed countries. This rise is thought to be a result of an increase in the prevalence of HPV-related OPSCC, prompting talk of an epidemic.[5]

Until recently, studies of HNSCC have not successfully identified clinically useful biomarkers of prognosis. This has been mainly due to the use of small sample sizes from single institutions, with tumors from heterogeneous head and neck subsites that have received a variety of treatments. By using improved study designs, several biomarkers, notably HPV status and p16, have lately shown promise in prognostication in HNSCC. Studies have demonstrated that other biomarkers, including epidermal growth factor receptor (EGFR), hypoxia inducible factor/carbonic anhydrase IX (HIF-2α/CAIX), HIF-1α, Bcl-2, Ki-67, and vascular endothelial growth factor (VEGF), may also show prognostic efficacy.[6–14]

To identify potential targets for further research on improving prognostication for OPSCC, we undertook a systematic review and meta-analysis to identify biomarkers that have demonstrated prognostic significance for survival, specifically for patients with primary OPSCC.

***Corresponding author:** H. Mehanna, Institute of Head and Neck Studies and Education, University Hospital, Coventry, United Kingdom.
E-mail: Hisham.Mehanna@uhcw.nhs.uk

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MATERIALS AND METHODS

Search methods for identification of studies

We performed an electronic search of the Cochrane Oral Health and ENT Groups Trials Register, MEDLINE, Zetoc, National Cancer Trials Database, Proquest Dissertations, and Theses Database, and the Conference Proceedings Citation Index from the start of each database until the end of July 2010. Search terms were compiled from the medical subject headings (MeSH) of review articles found during the preliminary search strategy (see Table 1).[15,16] A search was undertaken using an extensive range of terms covering head and neck neoplasms, immunohistochemical (IHC), and genomic biomarkers. A detailed search strategy is available from the authors on request. Reference lists from relevant articles were hand searched for further studies.

Criteria and selection process of studies included in this review

Abstracts identified by the search were reviewed independently by 2 reviewers (J. R., W. A.), after appropriate training and piloting. Training in critical appraisal was carried out by the senior author (H. M.) to ensure that selected articles were reviewed to an appropriate standard. During the piloting phase, the process of article selection and data extraction/analysis was tested on a smaller number of articles to highlight and address any problems before using it in earnest. Articles were selected for full review in accord with the following a priori eligibility criteria: studies reporting on patients with OPSCC even if part of a larger group with HNSCC, longitudinal cohort studies; IHC or genomic biomarker in tumor tissue; reported outcomes of overall survival or disease-specific survival (OS or DSS); and in the English language.

TABLE 1. Search terms used.

Group	Search terms	
Anatomic site	oropharynx	oral
	oropharyngeal	head and neck
Pathologic process	neoplasm	course
	mortality	disease progression
	neoplasm recurrence	
Study design	follow-up studies	epidemiologic studies
	prognostic	incidence
	predictive	
Biomarkers	serum markers	genomics
	urine markers	molecular sequence data
	exfoliative cytology	genes, viral
	cytodiagnosis	viral proteins
	immunohistochemistry	viruses
	neoplasm proteins	DNA methylation
	tumor markers, biological	genes p53
	molecular biology	genes, tumor suppressor
	molecular oncology	tumor suppressor protein
	biological markers	p53
	proto-oncogenes	promoter regions, genetic
	oncogenes	mutation
	genetic markers	molecular markers

The full texts of selected articles were retrieved for detailed scrutiny. Studies were excluded based on the following criteria: OPSCC survival data not specifically reported, in vitro studies, cross-sectional studies, case-control studies, fewer than 10 patients with OPSCC, included patients with distant metastases or recurrent disease, inadequate survival data for calculation of relative risk (RR), or data duplicated elsewhere.

Data extraction and management

After receiving training, 2 reviewers (J. R., W. A.) independently extracted data into a standard piloted template on a Microsoft Office Access database (Microsoft, Redmond, WA). The primary outcomes were OS and DSS. Where there were insufficient published data, we attempted to contact the authors by email on 2 occasions using the correspondence address provided in the articles.

Each reviewer also scored the studies for methodological quality in accord with criteria formulated using the guidelines published by Hayden and the REMARK (REporting recommendations for tumor MARKer) guidelines for prognostic studies (Table S1).[17,18] The factors assessed included study participation and attrition; prognostic factor under study; outcome and confounding factor measurement; and the quality of the analysis. As a part of this process, the laboratory methods used for identification and quantification of IHC biomarkers were critically appraised by an experienced pathologist (HW). Techniques for detecting HPV were appraised for adequacy by a molecular scientist with expertise in HPV detection (S. R.). In accord with the methodology described by Hayden and colleagues,[17] each quality criterion has up to 6 characteristics that define it. Studies were allocated a score depending on whether they did not meet (0 points), partly met (1 point), or completely met (2 points) the characteristics of each criterion. The reader is directed to Hayden et al for further details of the descriptors for each quality criterion. Quality assessment generated a score out of 12, with low-scoring papers likely to contain greater possibility of bias. Differences of opinion were resolved by discussion, then adjudication to the senior author. The scoring system was not designed for weighting data in a meta-analysis, but is included to allow readers to assess the strength of the data underlying the results reported in this study.

Statistical analysis

Dichotomous survival outcomes were expressed as relative risk (RR) with 95% confidence intervals (CIs). Only data for OPSCC were used. Wherever feasible, data were taken directly from the included studies. Where survival outcomes were not explicitly reported, it was often possible to calculate these from data provided within the paper. Survival data for individual biomarkers from more than 1 study were grouped and meta-analysis was performed where possible. RevMan 5 software was used to calculate pooled estimates of effect using the Mantel–Haenszel method, Z-statistic for effect size, p value, and

I^2 heterogeneity statistics (Review Manager [RevMan], Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Where little or no heterogeneity was present ($I^2 \leq 50\%$), a fixed-effects model for meta-analysis was used; where there was significant heterogeneity ($I^2 > 50\%$), a random-effects model was used.[19] Sensitivity analyses were performed by removing each trial in turn from a meta-analysis to establish the extent to which they contributed to heterogeneity and to the overall result.

RESULTS

Results of the search

In all, 3130 potentially relevant titles were identified during the initial search, of which 296 studies were subjected to full review, and 32 were included in the final selection. Reasons for exclusion are detailed in Figure 1.[1,6–11,20–44] The included studies examined 26 different biomarkers using a variety of cut-points to demarcate patients with low levels of a given biomarker from those with high levels. A number of methods were used to define these cut-points, including: previously published cut-points, the median value, absolute presence or absence of the marker, and the use of an arbitrary figure. Median follow-up periods, where stated, ranged from 17 to 66 months. Survival outcomes for HPV, p53 expression, p53 mutation status, intratumoral microvessel density (as measured by CD31 expression), EGFR, p16, and ki67 were reported in more than 1 study, but data suitable for meta-analysis were available only for HPV, p16, HIF1α, and p53 expression (Table 2). Only 1 paper that met the inclusion criteria reported data on DSS, so we present the OS data only.

Quality assessment, risk of bias, and heterogeneity in included studies

The quality assessments of the studies included in this review are shown in Table S1 (supporting information, online only). Scores ranged from 5 to 11, out of a maximum possible score of 12. Common areas of weakness included: failure to adjust for confounding factors such as smoking, alcohol intake, performance score, and treatment; and the use of an arbitrary or data-dependent cut-point.

There was a high degree of heterogeneity ($I^2 > 50\%$) among studies included in the pooled OS analysis for p53 ($I^2 = 65\%$).

Human papillomavirus studies

Eighteen studies included evaluable OS data about HPV in OPSCC (Table S2; supporting information, online only).[1,10,21,22,25–29,32,33,35,42–45] The minimum proportion of HPV 16 patients in these studies was 79%[32] and the maximum was 100%.[45] Twelve studies used polymerase chain reaction (PCR) to detect HPV DNA,

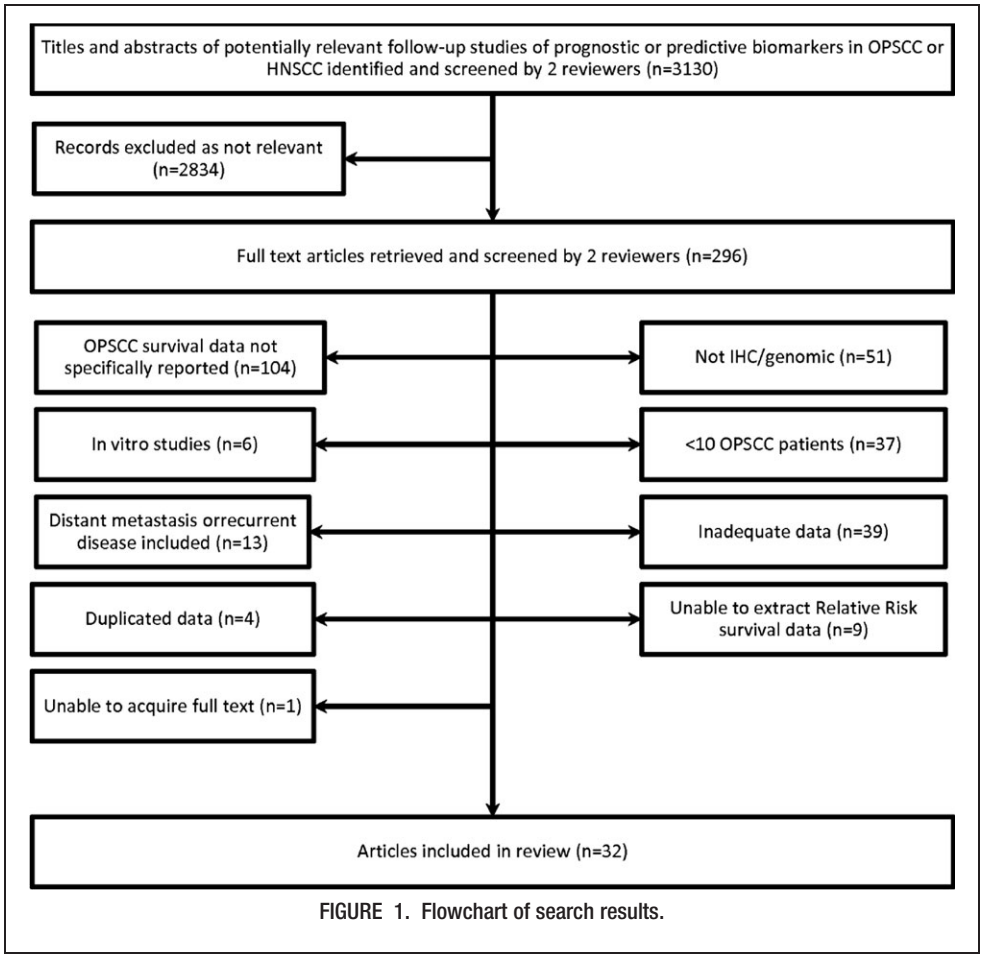


FIGURE 1. Flowchart of search results.

TABLE 2. Overall survival benefits for OPSCC for meta-analyzed biomarkers.

References	Biomarker studied	Pooled RR (95% CI)
10,1,20,21,22,25,26,27,28,29 32,33,35,42,43,44,45,46	HPV	**0.43 (0.37–0.50)***
1,20,22,28,35,42	p16	**0.43 (0.35–0.53)***
10,11,23,32,34,40,41,42	p53 protein	0.82 (0.59–1.12)
8,48	HIF1α	1.27 (0.91–1.77)

Abbreviations: OPSCC, oropharyngeal squamous cell carcinoma; RR, relative risk; CI, confidence interval; HPV, human papillomavirus; HIF1α, hypoxia inducible factor 1 alpha.
* Highlights significant result ($p < .00001$).

whereas 6 studies used variations of DNA in situ hybridization (ISH). Survival analysis ranged from 36 months[1,33] to >10 years,[25] and was not stated in 4 studies.[29,32] Median follow-up ranged from 17 to 58 months.

OS data for HPV were available from 16 studies, which included 673 HPV-positive and 732 HPV-negative patients.[1,10,20,22,26,27,32,33,35,42–46] Where HPV status was measured by PCR (11 studies; 313 HPV-positive, 510 HPV-negative), pooled results favored HPV-positive tumors (RR = 0.43, 95% CI = 0.36–0.52, $I^2 = 45\%$, $Z = 8.91$, $p < .00001$) (Table 3). Where ISH was used (5 studies; 360 HPV-positive, 222 HPV-negative), the results were similar (RR = 0.43, 95% CI = 0.32–0.56, $I^2 = 0\%$, $Z = 6.01$, $p < .00001$) (Table 4).

p16 studies

Six studies examined the effect of p16 overexpression on OS in OPSCC (Table S3; supporting information, online only).[1,20,22,28,35,42] All used staining proportion as their cut-point variable, one of which used automated quantitative IHC analysis (AQUA),[22] and the other 5 used staining proportions estimated by pathologists. The cut-off for analysis, where stated, ranged between 25% and 70% of cells stained for p16 positive. There was little heterogeneity between studies.

Significantly better OS was seen in p16-positive tumors (RR = 0.39, 95% CI = 0.31–0.49, $I^2 = 0\%$, $Z = 7.86$, $p < .00001$) (Table S4; supporting information, online only). Sensitivity analysis was performed on the 4 studies where p16 cut-off was stated, all of which had a cut-off $\geq$ 25% p16 positivity.[1,20,28,35] The beneficial effect of p16 positivity retained significance when these studies alone were included (RR = 0.41, 95% CI = 0.32–0.53, $I^2 = 23\%$, $Z = 6.93$, $p < .00001$), and also when only the 2 studies with cut-off $\geq$ 50% were included (RR = 0.35, 95% CI = 0.26–0.48, $I^2 = 0\%$, $Z = 6.50$, $p < .00001$).[1,35]

p53 studies

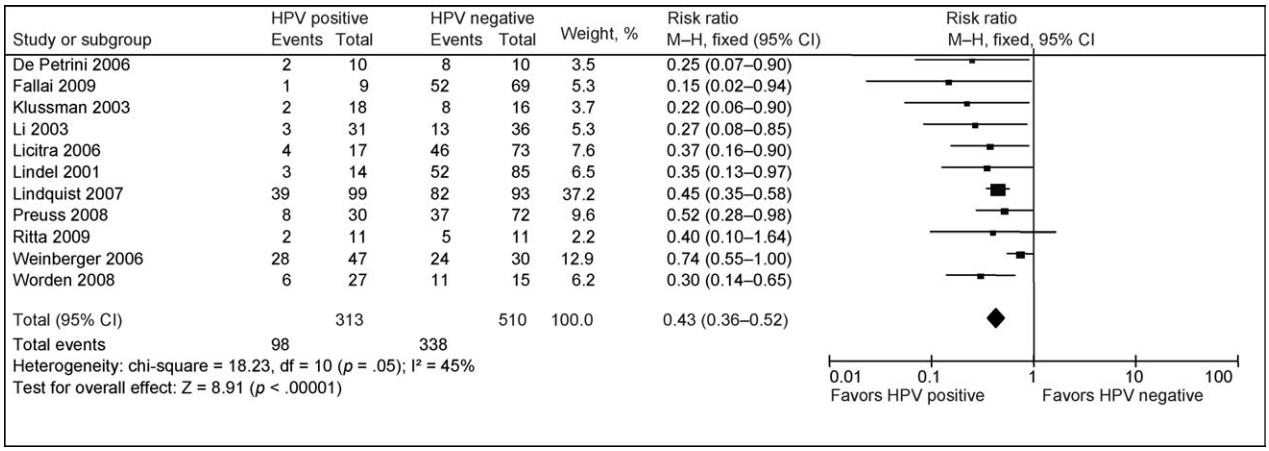
Nine studies investigated the effect of p53 on survival in OPSCC (Table S5; supporting information, online only),[10,11,23,27,32,34,40–42] Two of these studies used gene mutation status as the biomarker, rather than the level of p53 immunostaining, and did not undergo meta-analysis since there were only 2 studies and it was also unclear whether they were investigating the same gene mutations.[27,47] Six studies used proportion of p53-positive cells as their biomarker,[10,23,32,40–42] and 1 used a combination of staining intensity and proportion.[34]

Overall, 315 p53-high and 261 p53-low tumors were studied. The cut-point for defining "p53-positive'' tumors was 10% positive staining for p53 in 3 studies,[40–42] but varied in each of the other studies, ranging from any p53 staining to 67% staining. One was semiquantitative, including both a subjective assessment of staining intensity and an objective quantification of the proportion of p53-positive cells.[34] The minimum period for survival analysis was 24 months, and the maximum was >60 months. Median follow-up ranged from 28 to 41 months.

Pooled results demonstrated a marginal beneficial effect of high p53 on OS that was not statistically significant (RR = 0.82, 95% CI = 0.69–1.12, $I^2 = 65\%$, $Z = 1.24$, $p = 0.21$) (Table 5).[10,11,23,32,34,40–42]

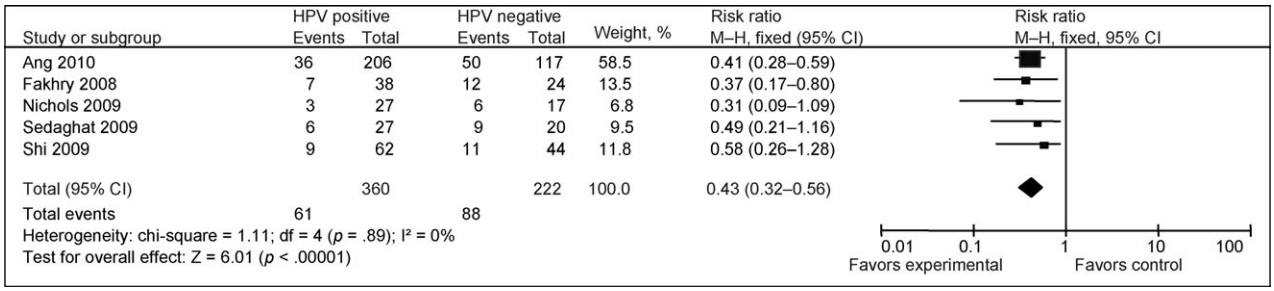
A sensitivity analysis showed that the study by Caminero et al[41] was the source of most of the heterogeneity,

TABLE 3. Overall survival of patients with oropharyngeal SCC by HPV status (PCR studies).



Abbreviations: SCC, squamous cell carcinoma; HPV, human papillomavirus; PCR, polymerase chain reaction; M–H, Mantel–Haenszel; CI, confidence interval; df, degrees of freedom; I^2, degree of heterogeneity; Z, effect size.

TABLE 4. Overall survival of patients with oropharyngeal SCC by human papillomavirus status (in situ hybridization studies).



Abbreviations: SCC, squamous cell carcinoma; HPV, human papillomavirus; ISH, in situ hybridization; M–H, Mantel–Haenszel; CI, confidence interval; df, degrees of freedom; I^2, degree of heterogeneity; Z, effect size.

and removal of this study changed an insignificant effect size to a significant one (RR = 0.70, 95% CI = 0.56–0.88, $I^2 = 0\%$, $Z = 3.01$, $p = .003$). A further sensitivity analysis (still excluding this study) was performed using the 5 studies that quantified p53 staining proportion (rather than using a qualitative measure of staining intensity or a combination of the 2).[10,23,32,40,42] The effect of any p53 positivity in this analysis did not reach significance (RR = 0.75, 95% CI = 0.56–1.01, $I^2 = 0\%$, $Z = 1.90$, $p = .06$). Further analysis was performed of the 4 studies where cut-off was $\leq$25% p53 staining proportion. Again, the effect was not significant (RR = 0.77, 95% CI = 0.54–1.09, $I^2 = 0\%$, $Z = 1.45$, $p = .15$).[10,23,40,42]

Neither study examining p53 mutation status yielded significant associations. RR (95% CI) for each study was 1.14 (0.49–2.65)[27] and 1.34 (0.93–1.92).[47]

Hypoxia inducible factor 1α studies

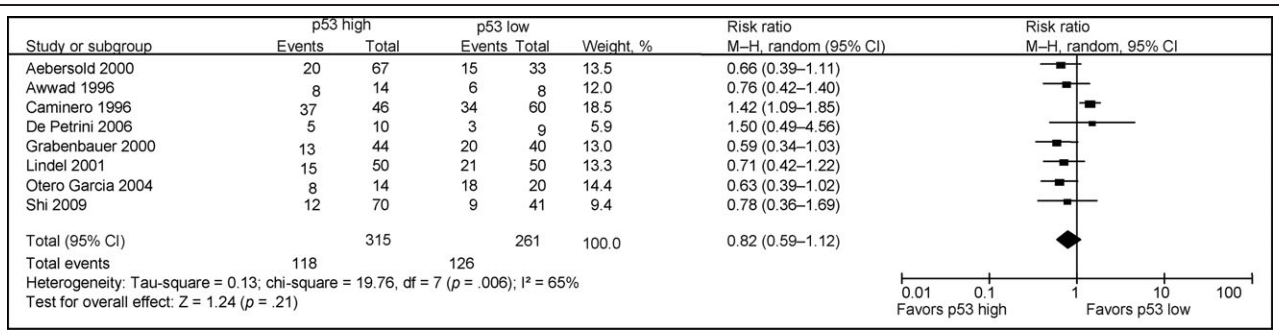
Two studies looked at the effect of HIF1α level on OS (Table S6; supporting information, online only).[8,48] Both used staining proportion as the cut-point variable with a cutoff point of 10%. Pooled HIF1α level did not have a significant effect on OS (RR = 1.27, 95% CI = 0.91–1.77, $I^2 = 19\%$, $Z = 1.42$, $p = .16$).

Other biomarkers

Three studies provided data on OS with respect to EGFR expression (Table S7; supporting information, online only).[6,7,42] No studies reported EGFR gene copy number separately for OPSCC. None of the studies using EGFR showed significant associations with survival. Two studies investigated the effect of ki67 expression on OS[10,11] (Table S8; supporting information, online only). One of the papers showed a significant survival association and the other did not. Two studies looked at intratumoral microvessel density,[32,40] using IHC analysis of CD31-positive microvessels per high-powered microscopic field (Table S9; supporting information, online only). Both papers showed significant associations with survival. For each of the markers cited earlier, there were few studies examining that particular marker and they used widely varying cut-points that were not comparable, so they were not subjected to meta-analysis. The results of those papers are detailed in Table S10; supporting information, online only.

Thirteen studies contained survival data about 19 other biomarkers.which are hepatocyte growth factor/scatter factor (HGF/SF), Bcl-Xl, c-met, Bcl2, platelet derived growth factor (PDGF) A and B, transforming growth factor (TGF) α, cyclo-oxygenase (COX) 2, 16q gene loss, 11q13 gene amplification, Polo-like kinase (PLK), $p16^{INK4a}$ gene deletion, fragile histine triad (FHIT), nuclear surviving, nuclear EGFR, CD3, major vault protein (MVP), nuclear cyclin D1, and pAKT. The results of these studies could not undergo meta-analysis, because the markers in question were reported in only 1 paper. The results of these studies are summarized in Table 6 and Table S11 (supporting information, online only).

TABLE 5. Overall survival of patients with oropharyngeal SCC by p53 protein level.



Abbreviations: SCC, squamous cell carcinoma; M–H, Mantel–Haenszel; CI, confidence interval; df, degrees of freedom; I^2, degree of heterogeneity; Z, effect size.

TABLE 6. Overall survival benefits for OPSCC of other included biomarkers.

Reference	Biomarker studied	Relative risk (95% CI)
Aebersold 2001b[9]	HGF/SF	1.02 (0.68–1.55)
	Bcl-Xl	1.30 (0.89–1.49)
	c-met	**3.72 (1.77–7.86)***
	Bcl2	**0.40 (0.22–0.71)***
Aebersold 2002[6]	PDGF-A	1.22 (0.95–1.57)
	PDGF-B	1.21 (0.92–1.59)
	TGFα	0.89 (0.54–1.47)
Chang 2004[24]	COX2	**1.36 (1.00–1.83)***
Klussman 2009[30]	16q gene loss	**0.47 (0.26–0.86)***
	11q13 gene amplification	**0.32 (0.21–0.49)***
Knecht 2000[31]	PLK	**4.30 (2.13–8.70)***
Licitra 2006[47]	$p16^{INK4a}$	1.16 (0.77–1.75)
Otero Garcia 2004[34]	FHIT	**1.62 (1.13–2.34)***
Preuss 2008[35]	Nuclear survivin	**5.66 (1.57–20.33)***
Psyrri 2005[7]	Nuclear EGFR	1.46 (0.68–3.10)
Rajjoub 2007[36]	CD3	0.65 (0.45–1.01)
Silva 2007[37]	MVP (DSS)	**1.88 (1.13–3.14)***
Yu 2005[39]	Nuclear cyclin D1	**3.61 (1.79–7.73)***
Yu 2007[38]	pAKT	1.56 (0.83–2.93)

Abbreviations: OPSCC, oropharyngeal squamous cell carcinoma; RR, relative risk; CI, confidence interval; COX2, cyclo-oxygenase 2; DSS, disease-specific survival; EGFR, epidermal growth factor receptor; FHIT, fragile histine triad; HGF/SF, hepatocyte growth factor/scatter factor; MVP, major vault protein; OS, overall survival; pAKT, serine/threonine protein kinase; PDGF, platelet-derived growth factor; PLK, Polo-like kinase; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.
* Highlights significant result.

DISCUSSION

Summary of main results

Combined estimates of effect demonstrated significant improvements in overall survival of patients with OPSCC who were HPV-positive or had high p16 expression. On meta-analysis, HIF1α and p53 showed no statistically significant association with OS.

Based on data from single studies, there was some evidence of improved OS of patients with OPSCC with amplification of 11q3 and loss of 16q genes; raised bcl2; and low c-met, ki67, IMD, Polo-like kinase (PLK), fragile histine triad (FHIT), nuclear surviving, and nuclear cyclin D1. However, none of these markers could undergo meta-analysis. Many of these studies had small sample sizes, so these results should be interpreted with caution.

Limitations of the study

By using an extensive search strategy and seeking unpublished data from research dissertations and conference proceedings, we attempted to ensure the completeness of the included results. However, non–English-language studies were not included, so there may be some relevant studies missed from this review. We were unable to find the full text of 1 research thesis,[49] and 5 studies presented data in such a way that we were unable to extract or calculate a relative risk and 95% CI.[12,47,50–52] Despite trying, we were unsuccessful in establishing contact with the authors of these papers, so they were excluded. To ensure that the studies included were as homogeneous as possible, the clinical question posed at the outset was intentionally a highly focused one. Our inclusion and exclusion criteria were therefore strict and, as a result, some important studies may be have been excluded from our review, usually because they reported combined results of heterogeneous patient groups.

One of the main weaknesses of the studies included was the lack of consensus about the definition of the cut-off for positivity of a particular biomarker. Many of the markers were continuous variables, so choosing a cut-point was difficult. Several studies used a data-dependent cut-point, for example the median of the range of biomarker values from the study sample. Although this may be an acceptable method for choosing a cut-point in large, population-based studies, the sample sizes in the included studies was relatively small, meaning that the cut-point and the survival outcomes based on it have limited wider applicability. Other studies used an arbitrary figure, such as 10% staining proportion; or a qualitative value, such as 1 based on the assessment of staining intensity by one or more pathologists (0, +, ++, +++). We took a pragmatic approach to the meta-analysis by adopting positivity and negativity as stated by the studies, and then by performing sensitivity analyses using different cut-point levels.

Although it would probably have been relevant to examine DSS in addition to OS, this was not feasible due to a lack of data on DSS in most of the articles reviewed. There were 7 studies that provided DSS data for HPV status, but the results did not differ greatly from the OS data presented in this review (RR = 0.39, 95% CI = 0.27–0.58, I^2 = 62%, Z = 4.64, $p <$ .00001).[21,25,27–29,46,47]

The confounding effect of the unadjusted data collected by most of the studies should be considered when interpreting the results, particularly with regard to the effect that HPV status may have had on it. The example of p53 illustrates this: although p53 mutations are found in approximately 40% of HNSCCs,[53] mutations of the p53 gene are very uncommon in the presence of HPV infection. It is now widely accepted that HPV-positive tumors carry a favorable prognosis,[20] so it may be that the reduced overall survival seen with p53 mutations reported by some authors for HNSCC simply reflects the better survival of wild-type p53 (wt-p53)/HPV-positive tumors. Indeed, one series of 90 patients with OPSCC found no survival benefit from p53 or p16 in HPV-negative patients.[47]

Implications for practice and research

Survival from OPSCC is associated with HPV and p16 status, which is in line with current thinking. It is clear that due to its significant prognostic effect, HPV status of tumors should now be taken into account when considering patients' prognosis. There are several other biomarkers that may influence survival in this group of patients, but they have not been studied in sufficient detail to draw a firm association. Further research into the less studied biomarkers is needed to improve the prognostic ability of HPV status in OPSCC and may also develop the understanding of the behavior of OPSCC in individual patients.[1]

EGFR positivity has been associated with poor survival in HNSCC in a number of studies,[54–56] so it was surprising that none of the studies included in this analysis demonstrated this relationship, especially given that EGFR-inhibiting drugs that have been shown to have a beneficial effect on outcome of patients with advanced HNSCC, and their use, is becoming increasingly widespread.[57] This may be due to the stringent inclusion criteria, which excluded studies in which multiple subsites of HNSCC were analyzed together. None of the 3 EGFR studies included found any influence on survival,[6,7,42] but there was a relatively high proportion of HPV-positive tumors in the samples. EGFR positivity is less common in HPV-positive tumors,[58] and the samples in these studies were not stratified by HPV positivity, which may have biased the results in a manner similar to that described earlier for p53.

Ultimately, the introduction of a panel of other tumor markers, in addition to HPV status by p16 or HPV DNA, into the staging of OPSCC may further improve the accuracy and reliability of prognostic information available to clinicians and patients, allowing them to make better-informed treatment choices. However, given the paucity of data on many promising tumor biomarkers, there is considerably more work required before this is possible. Reaching consensus on accepted cut-points of commonly investigated markers would significantly improve the utility of future studies. In addition, multi-institutional studies with pooling of cases, preferably within a randomized trial setting, are essential. Finally, reporting biomarker studies in accord with the REMARK guidelines should be mandatory for publication.

Our review examines the prognostic significance of various biomarkers; that is, the survival risk attributed to patients with a particular marker, without accounting for the type of treatment given. This is in contrast to predictive biomarkers, for which the outcome of interest relates to a specific treatment (eg, cisplatin chemoradiotherapy with particular dose of cisplatin and radiation). Unfortunately, only a very small minority of papers from our search detailed outcomes of interest for specific treatments: the majority contained patient samples with mixed treatment protocols. Thus, there remains a relative absence of useful data to guide treatment of individual patients in accord with the molecular profile of their tumor, which is probably of even greater interest than the prognostic data currently available. Authors of future biomarker studies should endeavor to present their results in a way that allows comparison of survival, recurrence, and response rates for specific treatments.

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