



Review

Survival for HPV-positive oropharyngeal squamous cell carcinoma with surgical versus non-surgical treatment approach: A systematic review and meta-analysis



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ABSTRACT

The optimal management of human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) with primary surgical versus non-surgical treatment is unclear. The objective of this systematic review was to evaluate the literature and compare survival for primary surgical versus non-surgical treatment of HPV-positive OPSCC. We performed a comprehensive literature search of multiple electronic databases for relevant articles up to February, 2017. Studies reporting mortality or hazard ratio (HR) for overall survival (OS) in primary HPV-positive OPSCC patients were eligible. Seventy-three articles were eligible, of which 66 included single-modality (19 surgical, 47 non-surgical), and 7 included both surgical and non-surgical modalities. There were no randomized studies comparing outcomes between both modalities. In a meta-analysis of both-modality studies, OS with surgical treatment was not significantly different from non-surgical treatment (pooled HR 1.12; 95% CI: 0.35, 3.57). There was significant heterogeneity between studies ($I^2 = 82.4\%$). Among single-modality studies, the mortality rate was lower with surgical [pooled proportion 0.15 (95% CI: 0.09, 0.21)] versus non-surgical treatment [0.20 (95% CI: 0.15, 0.24)]. In a subgroup analysis, OS was higher for HPV-positive versus HPV-negative OPSCC, irrespective of the treatment modality. We conclude that there is an absence of high-quality studies that compare survival for HPV-positive OPSCC treated with primary surgical versus non-surgical approach. The available data suggest no statistical or clinically meaningful difference in survival between the two approaches. HPV-positivity was a key prognostic factor irrespective of treatment modality. Further high-quality studies with consistent data reporting are needed to inform the choice for optimal treatment modality for HPV-positive OPSCC.

Introduction

Head and neck cancer epidemiology has drastically changed over the last two decades due to emergence of a distinct subset of human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) [1,2]. The HPV prevalence in oropharyngeal malignancies rose from 16.3% during the 1980s to 72.7% during the 2000s [2]. With treatment, this disease has very favorable oncologic outcomes compared to the traditional tobacco and alcohol-driven, non-HPV OPSCC

[3–7]. High survival rates of 80–90% are mainly associated with the overexpression of p16, a tumor suppressor protein and a reliable surrogate marker for HPV [8–18]. With such high survival rates, it is important to select a treatment approach that preserves excellent oncologic control while minimizes morbidity and maximizes function and quality of life.

The National Comprehensive Cancer Network (NCCN) guidelines recommend both surgery, followed by adjuvant therapy and non-surgical, (chemo) radiation-based therapy as management options for

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OPSCC. HPV-positive OPSCC is demonstrated to be more sensitive to the non-surgical, (chemo)radiation-based treatment modalities than its non-HPV counterpart with favorable oncologic outcomes observed in several studies [19–21]. To reduce the toxicity burden from non-surgical treatment [22–24], and concurrent with the rise in the incidence of HPV-positive OPSCC, the use of function-preserving, minimally invasive transoral surgical approaches has also increased. These surgical approaches are shown to achieve high oncologic control with reduced overall morbidity and mortality [13–15,25–27].

There are several studies that report outcomes of HPV-positive OPSCC treated surgically or non-surgically in separate cohorts. However, studies comparing the outcomes of patients with HPV-positive OPSCC treated with primary surgical versus non-surgical treatment are scarce and mainly observational [28–30]. A Phase II randomized trial [31], designed to compare outcomes between primary transoral surgery and radiation for early-stage OPSCC is underway but there is currently no high-quality evidence that supports one treatment approach over another in HPV-positive OPSCC [32]. Such evidence is important to inform treatment recommendations and plan de-escalation trials [6,32,33]. Therefore, the objective of this study was to conduct a systematic review of all studies published *hitherto* that report the outcomes for HPV-positive OPSCC patients managed with primary surgical or non-surgical approach. The primary aim was to obtain adjusted estimates of survival for HPV-positive OPSCC treated with surgery versus non-surgery. A secondary aim was to assess the effect of a particular treatment type, primary surgery or non-surgery, on survival in HPV-positive versus non-HPV OPSCC.

Methods

The systematic review and meta-analysis were conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) of Observational Studies in Epidemiology guidelines. The study protocol was registered on PROSPERO (registration number: CRD42017059562).

Eligibility criteria

Studies were eligible if they involved patients with HPV-positive primary OPSCC, and reported the hazard ratio (HR) for overall survival with 95% confidence intervals (CIs) or the number of deaths. Studies were excluded if they involved, (i) patients with non-OPSCC or unknown primaries of the head and neck, (ii) patients with unresectable or recurrent OPSCC, (iii) lacked HPV data, and (iv) lacked original patient data and outcomes of interest.

Search protocol and study selection

The published literature was searched using strategies created by a medical librarian for HPV-positive OPSCC treated with primary surgical or non-surgical therapy. The treatment approach was considered as “primary surgical” if patients received surgery alone or surgery with adjuvant therapy, and as “primary non-surgical if patients received radiation or chemoradiation alone or with planned neck dissection. The search strategies were established using a combination of standardized terms and key words, and were implemented in Ovid Medline, Embase, Scopus, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, Clinicaltrials.gov, and WHO International Clinical Trials Registry Platform. Searches were completed for all articles published up to February, 2017. Full search strategies are provided in the [Supplemental Appendix](#). The articles were screened by two authors independently in two phases. The first phase involved screening for relevance based on the title and abstract. After exclusion of the non-relevant articles, the remaining articles were reviewed in full-text by the two investigators to determine their final eligibility in the second

phase.

Data collection process

The data extraction was performed by two authors (PS, OAK) using a standardized excel spreadsheet. All disagreements were resolved through consensus and expert opinion was sought as necessary. Data was collected for the key variables related to the study, patient, tumor, treatment, follow-up, and outcomes. The study-related variables included year of publication, author, institution, country, study design, and study enrolment period. The patient-related variables included age, gender, race, performance status, comorbidities, and smoking status. The tumor-related variables of tumor stage, nodal stage, HPV status, and HPV method of detection [p16 immunohistochemistry (IHC) or Deoxyribonucleic acid (DNA) Polymerase Chain Reaction (PCR) or *in-situ* hybridization (ISH)] were recorded. Treatment details included type of resection approach [open, transoral, transoral laser microsurgery, transoral robotic surgery], adjuvant therapy, type of non-surgical approach [radiation alone or concurrent chemoradiation (CCRT) or induction chemotherapy followed by CCRT], radiation technique, and chemotherapy regimen. Information about the follow-up, outcomes of recurrence, death, Kaplan-Meier survival and HR estimates, surgical complications, and treatment-related toxicity were collected.

Data analysis

The principal summary measures were the: (i) HR with 95% CIs for overall survival (OS), and (ii) proportion of mortality after treatment with surgical or non-surgical modalities. In the absence of adjusted HR (aHR), the unadjusted HR (uaHR) was recorded when available. If neither adjusted nor unadjusted HR was reported, the number of deaths was collected to calculate the proportion of mortality within each treatment group. When data was only available as Kaplan Meier curves but the numbers at risk at different time points were available, numerical data was extracted using a web-based tool (<http://arohatgi.info/WebPlotDigitizer/>), and then HR was estimated using method described by Tierney et al. [34]. For incomplete data, we contacted the study authors to obtain further information.

A description of the included studies, structured around the type of intervention, study population and tumor characteristics, and the type of outcome, was conducted. Quantitative meta-analysis for the summary measures of proportion of mortality and HR for OS were performed with STATA 15.0 statistical software. The random effects model was used for pooled data in order to account of clinical heterogeneity even if statistical heterogeneity was not evident. For each of the two treatment groups, we computed and compared the pooled estimates for HR and proportion of mortality. Stratified analyses were performed to assess the impact of study quality and study sample size on the results.

Assessment of heterogeneity and publication bias

Heterogeneity of effects between studies was assessed by using the I^2 statistic. $I^2 > 50\%$ was considered evidence of significant heterogeneity. Funnel plots and Egger test were used to assess publication bias.

Quality assessment

The study quality was assessed by two study investigators in a blinded manner, and disagreements were resolved through consensus. The National Heart, Lung, and Blood Institute “Quality Assessment Tool for Case Series Studies” [35] was modified to develop a study-specific quality assessment scoring in order to accurately assess the dimensions of study design, patient selection, patient exclusion from lack of HPV testing, adequacy of follow-up, analytic methods, and outcome reporting. These dimensions were graded with the following 9 questions

and scoring was performed on how the criteria were met relevant to our study:

1. Was this study primarily designed to assess OPSCC outcomes after treatment or the impact of p16/HPV on outcomes after treatment? (0 = No, if the focus of the study was to assess a non-HPV/p16 molecular or imaging marker on outcomes with a particular treatment or develop new staging; 1 = Yes)?
2. Was the study population (inclusion/exclusion criteria) clearly defined and the numbers excluded specified and explained (0 = No, 1 = Yes)?
3. Did lack of HPV testing result in patient exclusion from analysis (0 = > 25% exclusion or no information about the number of cases that could not be assessed for HPV; 1 = < 25%)
4. Were baseline patient and tumor characteristics reported by HPV status (0 = No, 1 = Yes) within each treatment modality?
5. Was the median follow-up sufficient to see an association between treatment approach and outcome? (0 = < 24 months or when not reported, 1 = \geq 24 months)
6. Was loss to follow-up/censoring 20% or less at the last follow-up (0 = loss of > 20% or not reported, 1 = loss of < 20% at 24 months; if not stated within text, the number at risk in the Kaplan Meier plots were referred for estimation)?
7. Was treatment-related complications or toxicity reported by HPV status within each treatment modality (0 = No, 1 = Yes)?
8. Was survival reported by tumor stage (T-category or AJCC stage) (0 = No, 1 = Yes)?
9. Was death or survival reported by HPV status within each treatment modality (0 = No, 1 = Yes)?

Results

Study selection

Our systematic search identified 4370 articles, which after removal of 2002 duplicate records, revealed a total of 2368 unique citations. The full text screening identified 920 articles that met the eligibility criteria of which 847 articles were excluded, leaving 73 articles for qualitative and quantitative analysis (Fig. 1). The main reasons for exclusion were lack of outcomes of interest (n = 523), and duplication in abstracts (n = 137). The number of studies for further subgroup analysis depending on the reported outcome is presented in Fig. 1.

Study and patient characteristics of the selected studies

Of the 73 articles in our qualitative analysis, 66 were single-treatment modality studies [surgical (19), non-surgical (47)], and 7 included outcomes for both-treatment modalities. Of the 7 both-treatment modality studies, one study reported outcomes for surgery and non-surgery in HPV-positive cases individually, and therefore, outcomes for the surgical group were analyzed under the single-modality surgical studies and those for the non-surgical group under the single-modality non-surgical studies (Fig. 1). Of the 66 single-treatment modality studies (65 manuscripts, 1 abstract [36]), a majority reported outcomes on a retrospectively-identified cohort (38) followed by prospectively-assembled cohort (27); one had a combination of both designs (1). In the surgical studies, HPV testing was retrospective in 12, prospective in 3, and both in 4, whereas in the non-surgical, it was retrospective in 35, prospective in 6 and both in 6. Of the 7 both-treatment modality studies, study cohort and HPV testing was retrospective in 6, and prospective in 1. All studies were published from 2001 to 2017. The enrolment period varied from 1990 to 2013, 1986 to 2014, and 1980 to 2013 in surgical, non-surgical and both-treatment modality studies, respectively. Three surgical (16%) [13,37,38] and 14 non-surgical (30%) [19,39–51] studies comprised patients from multiple institutions. Of the 19 surgical studies, aHR for OS (p16/HPV-positive vs.

p16/HPV-negative) was obtained from 5 (26%) studies [52–56], number of deaths from 11 (58%) [15,37,38,57–64], and both (aHR and death) from 3 (16%) [13,65,66]. Of the 47 non-surgical studies, HR for OS was obtained from 15 (32%) studies (12 aHR [41,45,50,67–74], 3 uaHR [39,75,76]), the number of deaths from 18 (38%) [36,44,46,51,77–90], and both from 14 (30%) studies (aHR in 7 [19,23,43,91–93], uaHR in 7 [40,47,49,94–97]). Of the 7 both-treatment modality studies, aHR was obtained from 4 (30%) [28,29,98,99], the number of death from 2 (20%) [11,100], and both from 1 [101]. HR was calculated for 2 non-surgical studies [47,96] and 1 both-treatment modality study [101].

Pertinent study, patient, tumor, treatment characteristics and outcomes of the individual studies are summarized in the Appendix Tables A1–A4. The quality scores are summarized in the Appendix Tables A5–7. The demographic variables of gender and race were predominantly male and Caucasian, respectively, in both surgical and non-surgical studies; hence these variables were not included in the descriptive tables. Median follow-up was reported by 15 (79%) of the 19 surgical studies, and it ranged from 17 to 70.8 months. Median follow-up was reported by 38 (81%) of the 47 non-surgical studies, and it ranged from 9 to 111.6 months. In the surgical studies (n = 19), the variables of age, smoking, performance status, comorbidities, tumor site, T-stage, N-stage, recurrence site and rate, and Kaplan-Meier survival estimate at some time-point, and complications for HPV/p16-positive tumors were reported by 15 (79%), 11 (58%), 2 (11%), 2 (11%), 14 (74%), 13 (68%), 12 (63%), 13 (68%, estimated from text), and 10 (58%), respectively. In the non-surgical studies (n = 47), these variables were reported by 35 (74%), 27 (57%), 10 (21%), 1 (2%), 21 (45%), 33 (70%), 32 (68%), 20 (43%, 1 estimated from text), and 30 (64%), respectively. In the surgical studies, the method of HPV detection was p16 IHC in 6 (32%), HPV-DNA in 2 (11%) and both in 11 (58%). In the non-surgical studies, the method for HPV detection was p16 IHC in 25 (53%), HPV-DNA in 9 (19%) and both in 13 (28%). In the both-treatment modality studies, the method was p16 IHC in 3, HPV-DNA in 1, both in 4. Complications were reported by 3 [13,37,55] of 19 (16%) surgical studies (1 [13] stratified by p16/HPV status), and 16 of 47 (34%) non-surgical studies (9 [23,36,41,51,53,79,82,83,90] stratified by p16/HPV status).

Meta-analysis of both-treatment modality studies

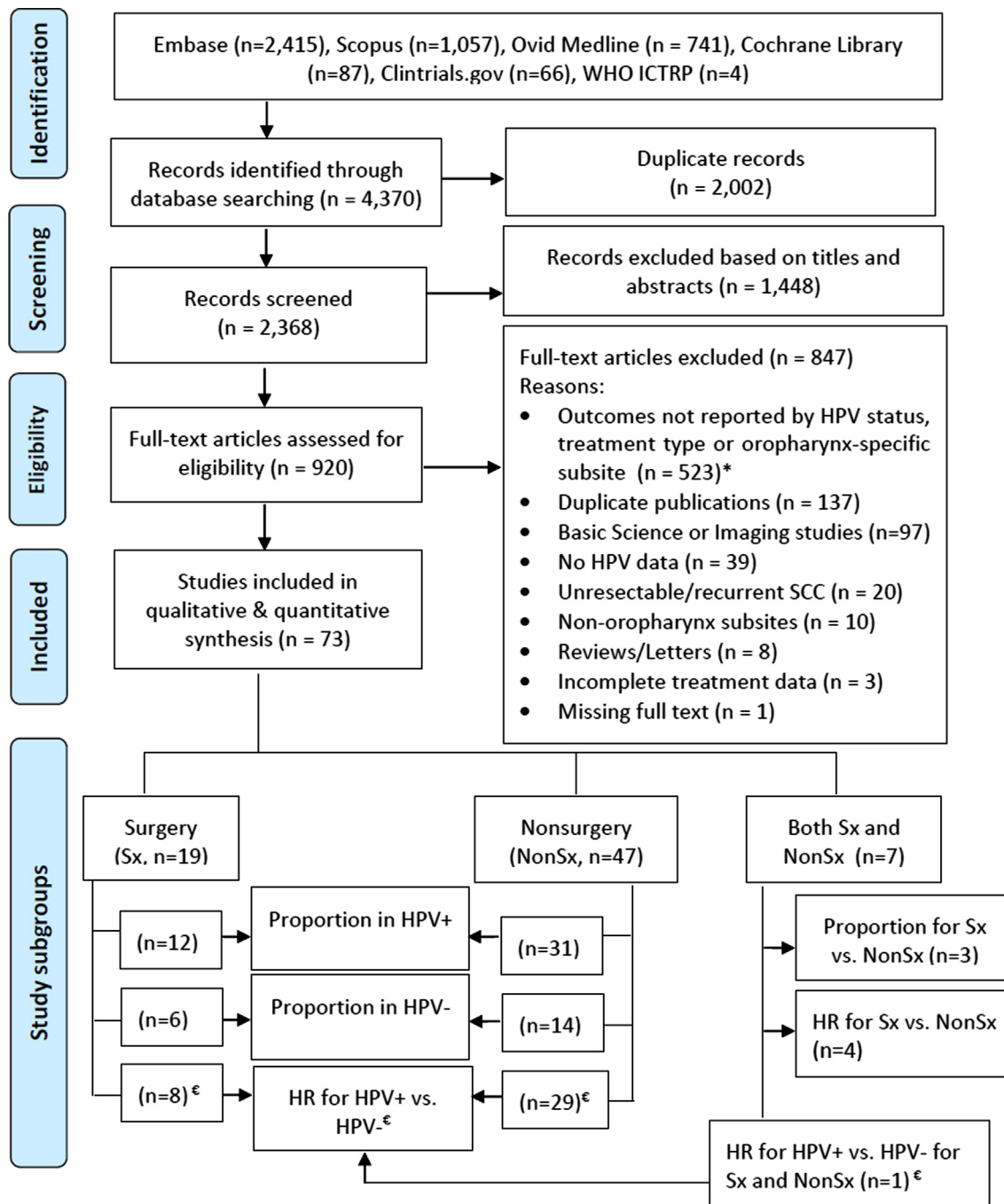
HR for OS in p16/HPV-positive cases with surgery versus non-surgery

Of the 7 both-treatment modality studies, one did not report outcomes for surgery vs. non-surgery in p16/HPV-positive cases and was analyzed with the single-treatment studies (Fig. 1) [99]. Adjusted HR was reported by 3 studies [28,29,98] and unadjusted HR was extracted from 1 study [101]. In a meta-analysis of these 4 studies (n = 594, 306 surgery, 286 non-surgery), OS with surgical treatment (pooled HR 1.12; 95% CI 0.35, 3.57) was not significantly different from non-surgical treatment (Fig. 2). There was significant heterogeneity between ($I^2 = 82.4\%$) the studies, but no evidence of publication bias (Fig. 3). Three studies (n = 136, 81 surgery, 55 non-surgery) [10,100,101] reported number of deaths, and the pooled relative risk of mortality was 0.49 (95% CI: 0.32, 0.75) favoring surgery. Two of these three studies were performed only on T4 patients [100,101].

Meta-analysis of single-treatment modality studies

Mortality in p16/HPV-positive cases

Pooled analysis of mortality was performed individually for surgical (Fig. 4A) and non-surgical studies (Fig. 4B). A total of 14 studies reported the number of overall deaths in surgical studies, however, 2 were excluded [13,58] from meta-analysis since they were from the same institution. The pooled proportion of mortality in the 12 surgical studies (n = 1373) was 0.15 (95% CI: 0.09, 0.21) with significant heterogeneity ($I^2 = 89\%$). The pooled proportion of mortality in the 31



SCC- Squamous cell carcinoma; HPV- Human Papillomavirus; *30 were abstracts; [€] Outcomes not reported for Sx vs NonSx but for HPV+ vs HPV- within Sx and NonSx groups (Hong et al), hence this study was included in the meta-analysis of HR for HPV+ vs HPV- within the Sx group for a total of 9 and in the NonSx group for a total of 29 studies

Fig. 1. PRISMA flowchart (WHO ICTRP = World Health Organization International Clinical Trials Registry Platform).

non-surgical studies (n = 3301) was 0.20 (95% CI: 0.15, 0.24) with significant heterogeneity ($I^2 = 90\%$). For studies that reported outcomes for p16/HPV-negative cases, the pooled proportion for mortality was 0.48 (95% CI: 0.27, 0.69, $I^2 = 95\%$) in surgical studies (n = 6), and 0.59 (95% CI: 0.48, 0.69, $I^2 = 92\%$) in non-surgical studies (n = 14).

HR for OS in p16/HPV-positive versus p16/HPV-negative cases

The pooled HR estimate in the 9 studies (n = 889) from surgical group (including one both modality study that reported HR for HPV-

positive versus negative separately for surgical and non-surgical cohorts, Fig. 5A) was 0.26 (95% CI: 0.18, 0.38) with mild heterogeneity ($I^2 = 47\%$). The pooled HR estimate in the 29 non-surgical studies (n = 2682, Fig. 5B) was 0.36 (95% CI: 0.29, 0.44) with significant heterogeneity ($I^2 = 75\%$). Funnel plots for both surgical and non-surgical studies were symmetrical (Appendix Fig. A1).

Stratified analyses for mortality

Stratified analyses showed no significant differences in the pooled

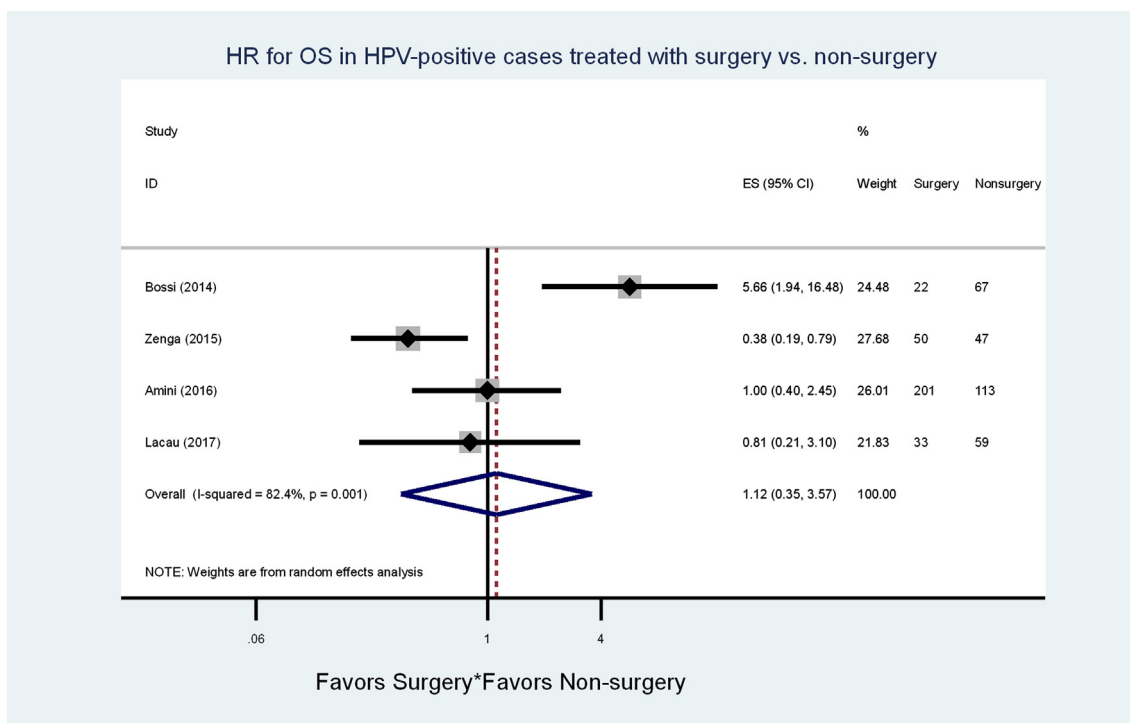


Fig. 2. Meta-analysis for overall survival in both-treatment modality studies in p16/HPV-positive OPSCC treated with primary surgical versus primary non-surgical approach.

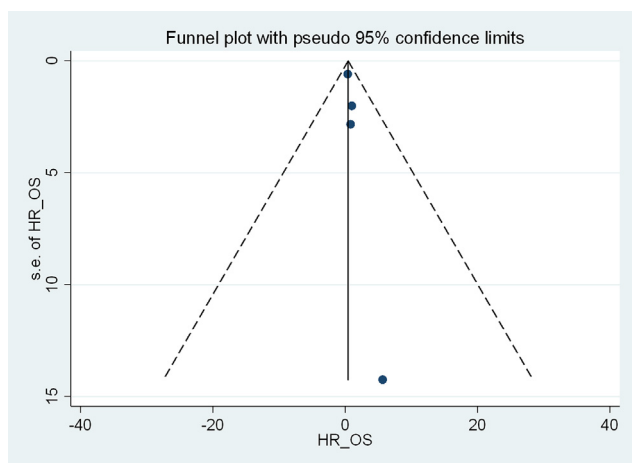


Fig. 3. Funnel plot showing no publication bias in both-treatment modality studies comparing overall survival for p16/HPV-positive OPSCC treated with primary surgical versus primary non-surgical approach.

mortality proportion by quality (0: $\leq 4/9$, 1: $> 4/9$) or sample size (0: < 50 , 1: ≥ 50) of the studies. In the surgical group, the pooled mortality proportion was similar for studies with low [n = 5, 0.10 (0.09, 0.21), $I^2 = 84\%$] and high-quality [n = 7, 0.19 (0.08, 0.29), $I^2 = 88\%$] scores (Appendix Fig. A2). The pooled estimate for mortality proportion was also similar for low [n = 7, 0.14 (0.05, 0.23)], $I^2 = 53\%$] and high sample [n = 5, 0.15 (0.07, 0.23), $I^2 = 95\%$] size studies (Appendix Fig. A3). In the non-surgical group, the pooled estimate was lower for studies with low [n = 15, 0.15 (0.09, 0.20), $I^2 = 87\%$] than high-quality [n = 16, 0.24 (0.18, 0.3), $I^2 = 91\%$] scores (Appendix Fig. A4). The pooled proportion for mortality was similar when studies were stratified by low [n = 14, 0.21 (0.11, 0.32), $I^2 = 82\%$] and high [n = 17, 0.19 (0.15, 0.24), $I^2 = 92\%$] sample size (Appendix Fig. A5).

Stratified analyses for overall survival in p16/HPV-positive versus p16/HPV-negative cases

The heterogeneity was reduced in surgical studies when stratified by quality and sample size. The pooled HR estimate was slightly higher for surgical studies with low quality [n = 2, HR = 0.34 (0.17, 0.72), $I^2 = 31\%$] compared to high-quality [n = 7, HR = 0.24 (0.15, 0.38), $I^2 = 51\%$] scores (Appendix Fig. A6). The HR estimate for low sample size surgical studies [n = 2, HR = 0.13 (0.06, 0.28), $I^2 = 0\%$] was lower than the pooled HR estimates for the high sample [n = 7, HR = 0.31 (0.22, 0.44), $I^2 = 37\%$] size studies (Appendix Fig. A7). Heterogeneity in the non-surgical studies was higher among low quality and low sample-size studies but the HR estimates were similar. The pooled HR estimate for non-surgical studies with low-quality [n = 12, HR = 0.34 (0.22, 0.53), I^2 of 82%] was similar to those with high quality [n = 17, HR = 0.36 (0.31, 0.43), $I^2 = 27\%$] non-surgical studies (Appendix Fig. A8). The pooled HR estimate was similar in low [n = 13, HR = 0.39 (0.25, 0.58), $I^2 = 67\%$] and high sample [n = 17, HR = 0.34 (0.29, 0.41), $I^2 = 32\%$] size studies (Appendix Fig. A9).

Discussion

This systematic review of the literature on oncologic outcomes in HPV-positive OPSCC showed an absence of high-quality studies that compare oncologic outcomes for patients treated with primary surgical versus non-surgical approach. A meta-analysis based on four observational studies that compared surgical versus non-surgical treatment in p16/HPV-positive OPSCC showed no statistically significant or clinically meaningful difference in overall survival with one treatment over another (1.12, 95% CI:0.35, 3.57). A meta-analysis for the proportion of mortality showed a 5% higher mortality in the non-surgical group compared to the surgical group (20% vs. 15%). Irrespective of the treatment type, overall survival was higher for p16/HPV-positive compared to p16/HPV-negative patients.

p16/HPV-positive OPSCC patients are considered to show favorable oncologic outcomes regardless of the treatment approach, surgical or non-surgical [4,7,10] but there is a lack of high-quality, prospective

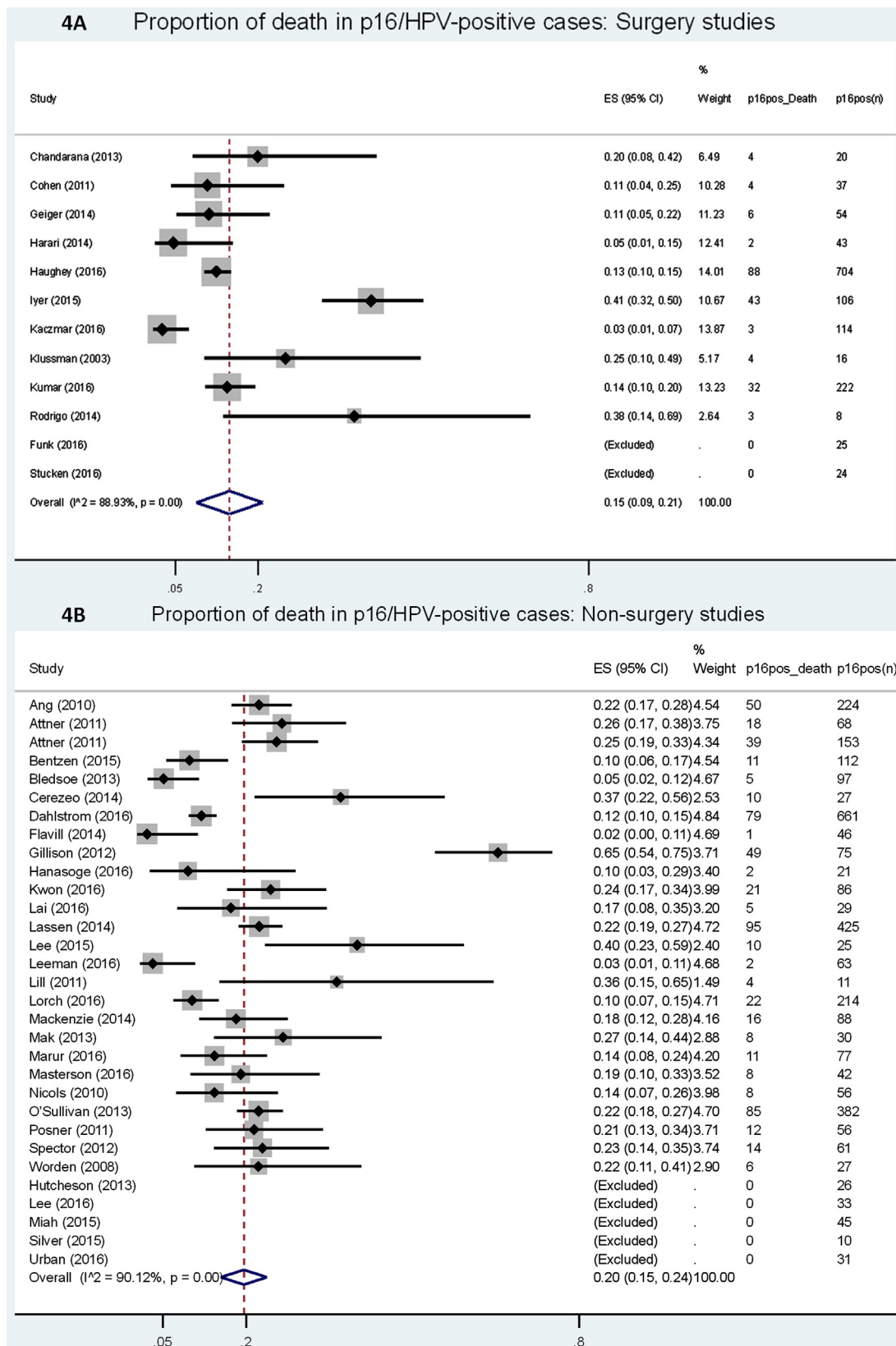


Fig. 4. Forest plot for proportion of mortality in p16/HPV-positive cases in single-treatment primary surgical (4A), and primary non-surgical (4B) studies.

studies that actually compare the two approaches as evidenced by this systematic review. In our meta-analysis based on the only four studies [28,29,98,101] for which data on HR for overall survival comparing primary surgical vs non-surgical was available (adjusted HR by 3,

unadjusted by 1), pooled effect estimates of HR did not show improved overall survival with either surgical or non-surgical treatment approach. Unadjusted estimates for the relative risk of mortality showed reduced risk with surgery (0.49, 95% CI:0.32, 0.75) but these were

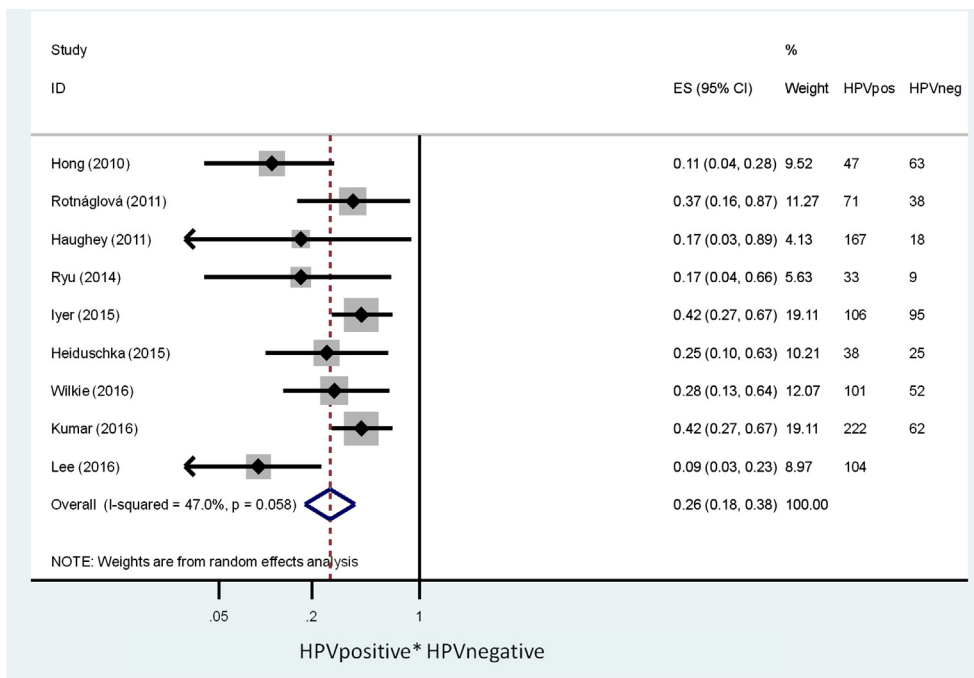


Fig. 5A. Forest plot for overall survival in p16/HPV-positive versus p16/HPV-negative in single-treatment modality primary surgical studies.

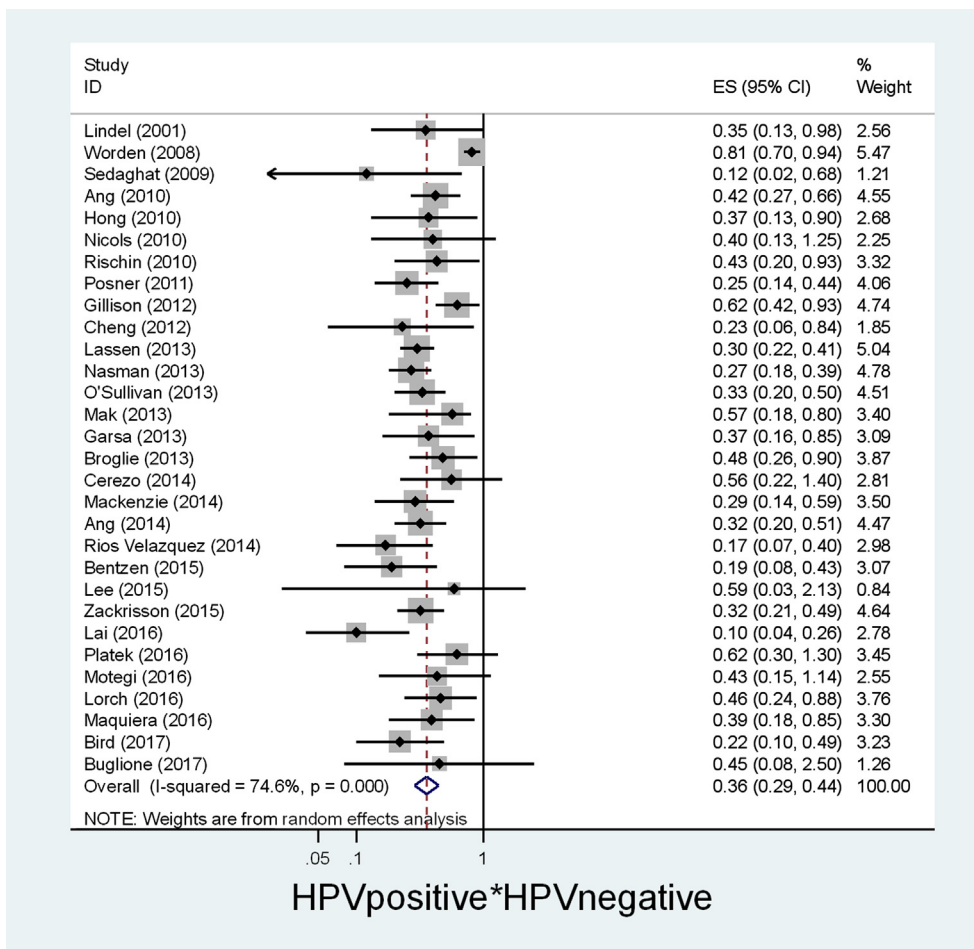


Fig. 5B. Forest plot for overall survival for p16/HPV-positive versus p16/HPV-negative in single-treatment modality primary non-surgical studies.

derived from only three studies [10,100,101], and two [100,101] of these three studies included only T4 tumors. All seven both-treatment modality studies were observational. Baseline characteristics stratified by HPV status were reported by only one [98] out of the seven both-treatment modality studies, thus limiting our ability to perform meta-regression to explore the causes for statistical heterogeneity. However, clinical heterogeneity was apparent among the method of HPV detection, tumor stage, follow-up period, and type of surgical resection or non-surgical treatment protocol.

Due to the very limited number of studies that reported adjusted HR (n = 3) for overall survival of p16/HPV-positive OPSCC treated with primary surgery versus non-surgery, we investigated and compared the pooled mortality estimate for single-treatment studies, acknowledging that these estimates will be unadjusted and the time to event will not be accounted. We were limited in pooling Kaplan Meier survival estimates as there was a wide variation in the time point at which the survival was reported, along with a lack in reporting of the 95% CI for survival or the number at risk for death at different time points. In our analysis of the mortality rate for p16/HPV-positive patients, we found a 5% difference between the two treatment modalities with a lower rate in the surgical studies. For the p16/HPV-negative OPSCC, there was a difference of 11% among the single-treatment studies with lower mortality in surgical studies. However, significant heterogeneity was noted among the pooled studies in both primary surgical and non-surgical groups. To further explore the heterogeneity due to the possible impact of study quality or sample size, we performed stratified analyses. These stratified analyses did not yield any widely different estimates of mortality for lower quality or lower sample size in both surgical and non-surgical studies, thereby, suggesting that the heterogeneity could be potentially related to other patient, tumor or treatment factors, for which the details were not completely or uniformly reported by the analyzed studies.

A comparison of the single-treatment modality studies included in the meta-analysis of mortality did not reveal any marked differences in the study design for patient accrual or HPV testing, demographic variables or quality scores (Table 1). However, among the studies which reported the T-category as early (T1-T2) versus advanced (T3-T4), a higher proportion of advanced tumors, 40%, were present in the non-surgical studies compared to 23% in the surgical studies. The maximum follow-up period was 227 months in surgical vs 158 months in non-surgical studies but the median follow-up was similar among those who reported the follow-up as median (min-max). Among studies that

reported the number of recurrences, the frequency rate was similar, 13.6% in surgical vs. 16% in non-surgical studies. Among studies that reported recurrence patterns, the rate of distant metastasis was 6% in surgical vs. 9% in non-surgical studies, while the rate of locoregional recurrence could not be determined due to incomplete data combined with lack of accounting for recurrences that occurred at multiple sites. In summary, it is difficult to accurately ascertain the comparability of the single-modality surgical versus non-surgical studies since reporting of the baseline characteristics, the tumor stage, follow-up and recurrence patterns was either incomplete or inconsistent across studies.

To date, only one systematic review [4] has evaluated outcomes of surgery versus non-surgery. In this review of 56 HPV-positive OPSCC studies from 2000 to 2014, Wang et al. [4] found that the outcomes may be better with primary surgery compared to radiation but the difference was not statistically significant. In this study [4], meta-regression analysis was performed and hazard rate for death, recurrence or disease progression was computed without making a distinction among the outcomes of overall, disease-free, progression-free or disease-specific survival due to author-acknowledged variability in reporting across various studies. However, the type of summary measure extracted from eligible studies, whether death rate, survival, odds ratio, HR or relative risk, was not clearly defined or represented by Wang et al. [4] The hazard rate was adjusted for the confounders of age, smoking, tumor site, stage and follow-up duration but as specified by the authors, no study reported all confounders, and hence HR was reported for one confounder at a time. Furthermore, it is difficult to interpret the findings since the distribution of confounders were not exclusively gleaned from within the HPV-positive OPSCC group. For studies that did not report the confounders specific for HPV-positive group, the analysis included confounder distribution from the overall, non-HPV stratified study cohort. Thus, to our knowledge, no previous study provides a comprehensive review of survival differences in HPV-positive OPSCC patients treated with surgical and non-surgical approaches adjusted for relevant confounders.

We also performed a subgroup analysis to assess how overall survival outcomes differed for p16/HPV-positive versus p16/HPV-negative OPSCC treated with surgery versus non-surgery. In the surgical studies, the pooled estimate demonstrated 74% reduction in the hazard of death for p16/HPV-positive patients compared to p16/HPV-negative patients. In the non-surgical studies, there was a 64% reduction in the hazard of death. These findings again reiterate the observation of improved survival of HPV-positive OPSCC patients irrespective of the treatment

Table 1
Comparison of the key variable in single-modality studies eligible for the meta-proportion analysis in HPV-positive cases.

Variables	Categories	Surgical studies (n = 12, 1373)			Non-surgical studies (n = 31, 3301)		
		No. of studies (%) [*]	No. of patients	%	No. of studies (%) [*]	No. of patients	%
Accrual	Prospective	6 (50)	NA	50	17 (55)	NA	NA
	Retrospective	6 (50)	NA	50	14 (45)	NA	NA
HPV testing	Prospective	2 (17)	NA	17	5 (16)	NA	NA
	Retrospective	7 (58)	NA	58	20 (65)	NA	NA
	Both	3 (25)	NA	25	6 (19)	NA	NA
Age (y)	Median (min-max)	5 (42)	58 (37–91)	NA	19 (61)	57 (26–92)	NA
Gender	Male	8 (67)	1101/1231	89	23 (74)	2363/2840	83
Smoking	> 10 pack-years	5 (42)	316/544	58	9 (29)	475/1069	44
Site	Tongue base	8 (67)	489/1321	37	16 (52)	371/960	39
T-stage	T3-T4	7 (58)	281/1200	23	23 (74)	1094/2727	40
N-stage	N3	6 (50)	55/1203	5	15 (48)	146/1792	8
Recurrence	Yes	10 (83)	150/1097	13.6	19 (61)	327/1984	16
Recurrence pattern (distant metastasis)**	Yes	8 (67)	64/1038	6	16 (52)	167/1989	9
Follow-up (mo)	Median (min-max)	8 (67)	40 (2.4–227)	NA	26 (84)	43 (0–158)	NA
Quality	Score < 5	5 (42)	NA	NA	15 (48)	NA	NA

NA - not applicable.

* Number of studies that reported a particular variable.

** Isolated or with recurrence at local/regional sites; local, regional or loco-regional recurrences could not be determined due to incomplete reporting.

modality.

This systematic review is limited in drawing definitive inferences about adjusted survival estimates for surgery vs. non-surgery due to the small number of studies reporting such results as well as a significant heterogeneity among study variables including baseline tumor stage characteristics and treatment. For instance, when reported, within the group of surgical studies there were differences in the resection approach and type of adjuvant treatment, and within non-surgical studies, there were differences in both radiation technique (dose, schedules and fields treated) and chemotherapy regimen (drugs, schedules, doses). We were also not able to compare the adverse effects associated with either treatment approach due to lack of consistent reporting of treatment toxicity and complications. When reported, the toxicity information was most frequently not stratified by HPV status. Furthermore, the HR for overall survival reported in studies was mostly adjusted, but the mortality rate was not. Hence, the meta-analysis of proportions could be confounded by other prognostic factors but these factors were not well-delineated for the HPV-positive cohort in all of the original studies. In particular, exploration of the impact of tumor T-category was limited due to a relative predominance of low T-category in surgical vs. non-surgical studies as well as the variability in the manner that it was reported, such as clinical versus pathologic, T1-T3 vs. T4 or T1 vs. T2-T4. Furthermore, there was variation in the method of HPV detection.

In conclusion, there is an absence of high-quality studies that compare survival for patients treated with primary surgical versus non-surgical approach. Significant heterogeneity and inconsistency across studies in reporting baseline characteristics and outcomes, and lack of treatment toxicity, precludes definitive conclusions on how survival compares between surgical versus non-surgical treatment approaches. An individual patient data approach meta-analysis can be formidable to execute but will potentially allow more reliable comparisons given the marked heterogeneity. As also pointed out by Wang et al, authors of the only previous systematic review on this related topic [4], the quality of meta-analyses could be significantly improved if the reporting is more consistent across studies. Further research with oncologic and functional outcomes including patient-reported outcomes of quality of life in HPV-positive OPSCC cohorts treated with surgical vs. non-surgical approach will be desirable to generate higher-quality evidence to inform treatment practices and trial planning.

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Conflicts of interest statement

Nothing to declare for all co-authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.oraloncology.2018.09.018>.

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