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Prognostic Significance of Extranodal Extension in HPV-Mediated Oropharyngeal Carcinoma: A Systematic Review and Meta-analysis

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Abstract

Objective. To determine the prognostic role of extranodal extension (ENE) among patients with human papilloma virus–positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) through a systematic review and meta-analysis of institutional studies.

Data Sources. MEDLINE, Embase, Scopus, and PubMed.

Review Methods. Two independent authors searched the databases on December 3, 2019, to identify studies of HPV+ OPSCC comparing prognostic outcomes stratified by ENE. The I^2 statistic was used to determine study heterogeneity. Fixed and random effects models were used to determine hazard ratios (HRs) with 95% CIs.

Results. Eighteen observational studies met inclusion criteria, yielding 3603 patients with HPV+ OPSCC (1521 ENE+ and 2082 ENE–) with a median follow-up of 49 months. The presence of pathologic ENE (pENE) and radiologic ENE (rENE) was associated with decreased overall survival (pENE HR, 1.89 [95% CI, 1.15-3.13], I^2 = 35%; rENE HR, 2.64 [95% CI, 1.46-4.78], I^2 = 75%) and distant recurrence (pENE HR, 3.23 [95% CI, 1.25-8.33], I^2 = 0%; rENE HR, 3.83 [95% CI, 1.88-7.80], I^2 = 0%). Neither pENE nor rENE was associated with locoregional recurrence (pENE HR, 0.75 [95% CI, 0.20-2.84], I^2 = 0%; rENE HR, 2.03 [95% CI, 0.86-4.79], I^2 = 0%). pENE was not associated with disease-specific survival (pENE HR, 1.45 [95% CI, 0.84-2.49], I^2 = 0%).

Conclusion. pENE and rENE are moderately associated with an increased risk of all-cause mortality and recurrence with distant metastasis in a cohort of patients with HPV+ OPSCC. These findings may be used to inform exclusion criteria for deintensification trials and assist in refined risk stratification.

Keywords

head and neck cancer, oropharyngeal squamous cell carcinoma, human papilloma virus, extranodal extension, prognosis

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Extranodal extension (ENE) in cervical lymph node metastases is regarded as an adverse prognostic feature in head and neck squamous cell carcinoma (HNSCC), being associated with increased rates of regional recurrence, distant metastasis, and decreased survival.[1,2] Additionally, ENE, with or without positive margins, was deemed to warrant postoperative concurrent chemoradiotherapy (CRT) in an unplanned pooled subset analysis of ENE and positive-margin cases from 2 landmark trials.[3-5] Consequently, the latter 2 variables represent the main indications for adjuvant CRT in head and neck oncology.[6] However, these analyses were carried out collectively for both adverse features, without testing or controlling for human papilloma virus (HPV)–mediated oropharyngeal squamous cell carcinoma (OPSCC). Hence, the analyses indicate neither any prognostic significance of ENE nor any benefit from adjuvant therapy as applied to HPV-mediated cases.[7]

Since then, inferior prognosis has been associated with ENE in multiple single-center studies within pooled-site HNSCC cases that included HPV– OPSCC.[8-10] Furthermore, ENE-associated upstaging of nodal category has been added to the staging of the American Joint Committee on Cancer (AJCC) for HPV– squamous cell carcinoma of the upper

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aerodigestive tract.[11] However, the absent prognostic significance of ENE among patients with HPV+ OPSCC in single-center studies[12,13] and in a pooled multicenter analysis[14] resulted in its absence from the current staging of HPV+ OPSCC (AJCC eighth edition).[15]

Clinical evidence of ENE is sometimes used to guide treatment toward definitive CRT in selected patients with locally advanced OPSCC, on the assumption that they will require adjuvant CRT postoperatively. Nevertheless, the benefits and increasing utilization of minimally invasive primary surgical treatments of OPSCC, such as transoral robotic and laser surgery, make more precise identification of patients requiring adjuvant CRT imperative.[16-18] Adjuvant treatment deintensification for patients with HPV+ OPSCC with ENE who are undergoing transoral primary tumor resection is being evaluated in current clinical trials.[19,20]

Until the results of these trials are available, research efforts evaluating the impact of ENE in HPV+ OPSCC are retrospective, with nonunanimous results. Some National Cancer Database (NCDB) studies with higher patient numbers (N = 1043-3952) indicate that ENE is associated with poorer overall survival,[21-24] while smaller, single-institution studies report divergent results.[25,26] Given this lack of clarity, we aimed to determine the prognostic role of ENE among patients with HPV+ OPSCC through a systematic review and meta-analysis of institutional studies.

Materials and Methods

This systematic review and meta-analysis adhered to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses; Supplement PRISMA Checklist).[27] No review protocol exists for this study.

Eligibility Criteria

Studies were considered eligible for inclusion if they met all of the following criteria: (1) retrospective or prospective observational cohort study, (2) histopathologic diagnosis of HPV-positive OPSCC, (3) histopathologic or radiologic cervical lymph node status available, (4) inclusion of comparison data of at least 1 prognostic outcome of interest between ENE+ and ENE– cases, and (5) publication in a peer-reviewed journal or as a stand-alone abstract.

Exclusion criteria included (1) missing information on survival or disease progression rate, (2) comparison between ENE+ and local disease only, (3) distant metastasis at presentation, (4) in vitro or animal studies, (5) articles not available in the English language, and (6) studies based on the NCDB only. The rationale for excluding NCDB studies included the inability to assess for cohort overlap with single-institution studies.

Information Source and Search Strategy

A senior medical librarian (J.S.) designed a comprehensive search strategy for published literature to identify studies examining the association of ENE and prognosis in HPV+ OPSCC. The MEDLINE, Embase, Scopus, and PubMed databases were searched for articles published from each database's earliest records up to December 3, 2019. The following key terms were used in the MEDLINE, Embase, and Scopus search:

> [(''carcinoma/squamous cell/head and neck neoplasms/oropharyngeal neoplasms/mouth neoplasms/squamous cell carcinoma of the head and neck'' AND ''papillomaviridiae/papillomavirus infections/human papillomavirus 16'') OR (''oropharynx cancer/oropharyngeal carcinoma/opscc/oropharynx tumor'' AND ''human papillomavirus/HPV/HPV-positive/p 16 positive'')] AND [''extranodal extension'' or ''extracapsular extension/extracapsular spread/ECS'' or ''perinodal spread/perinodal extension''] AND [(''neoplasm recurrence, local/neoplasm invasiveness/neoplasm grading/neoplasm staging/neoplasm metastasis/lymphatic metastasis'' or ''prognosis'' or ''treatment outcome/treatment failure'' or ''exp models, statistical/disease-free survival/survival analysis/survival rate'') OR ''(prognostic factors/prognosis/diagnosed/cohort/predictor/death'' or ''lymph node ratio/lymph node'')].

In PubMed, these terms were introduced into the Advanced Search Builder, yielding a similar query (Supplemental Methods, available online).

Study Selection

Following the initial search, duplicates were removed. In case of overlapping cohorts, the most recent or comprehensive study was used. Two authors (L.B. and S.J.T.) independently screened titles and abstracts of all potentially eligible articles and searched the reference lists of related reviews and all publications to identify additional articles. Eligibility criteria were then applied to consider the full text; disparities in article selection were resolved through discussion; and a final list of studies was built.

Data Extraction and Items

One investigator (L.B.) extracted data from the included articles, and a second (S.J.T.) validated the data extraction using standardized data forms. The following information was obtained from each study:

- *Study characteristics:* years, location, median follow-up, and methods of determining ENE and HPV status
- *Patient characteristics:* number, age, and sex
- *Disease and treatment characteristics:* ENE status, surgery, radiotherapy (RT), and CRT
- *Prognosis:* overall survival (OS), commonly defined as probability of survival from time of treatment initiation/diagnosis to death of any cause; disease-specific survival (DSS), defined as probability of survival from time of treatment initiation/diagnosis to death from OPSCC; locoregional recurrence (LRR) and distant recurrence (DR), defined as time from treatment to first LRR or DR, respectively

No attempt was made to contact authors of studies with missing information.

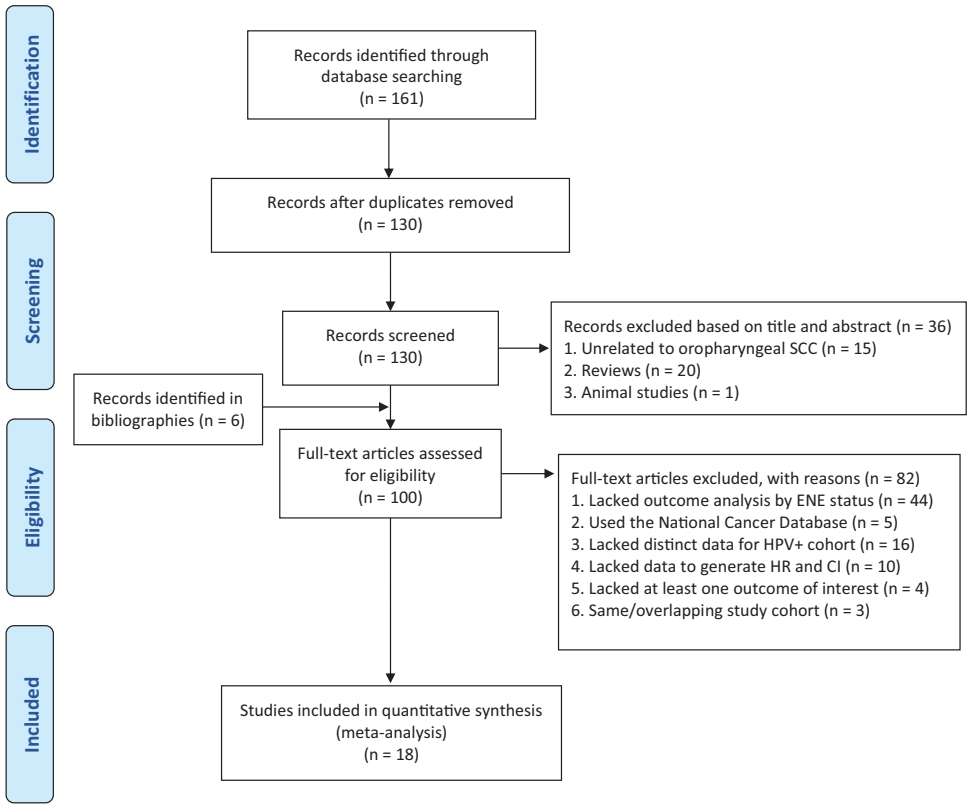

Figure 1. Flow diagram of PRISMA for the study selection (Preferred Reporting Items for Systematic Reviews and Meta-analyses). CI, confidence interval; ENE, extranodal extension; HPV, human papilloma virus; HR, hazard ratio; SCC, squamous cell carcinoma.

Assessment of Study Quality

The Newcastle-Ottawa Scale was used to evaluate study quality.[28] Two authors (L.B. and S.J.T.) completed the scale generating a methodological quality score up to 9 points. Studies receiving a score <6 points were considered high risk for bias and discussed by the 2 reviewers regarding the need of exclusion.

Data Synthesis and Statistical Analysis

We used RevMan v5.3 (Review Manager version 5.3; The Nordic Cochrane Centre)[29] and STATA version 15 (StataCorp LLC, 2019) to perform the meta-analysis. Effect measures for the outcomes of OS, DSS, LRR, and DR were hazard ratios (HRs) with 95% CIs. HRs from multivariate models were used when provided; otherwise, values from univariate models were used. In studies with Kaplan-Meier log-rank data but no available HRs with 95% CIs, we used an accepted method for estimating HR and 95% CI.[30] When standard error of the mean (SEM) was not provided in the published articles, SEM was calculated from 95% CIs per the following equation: SEM = [ln(CI upper limit) − ln(CI lower limit)] / 3.92.[31]

Depending on heterogeneity, either the fixed effects model (Mantel-Haenszel method) or the random effects model (DerSimonian and Laired method) was applied to obtain a pooled HR estimate, 95% CI, and *P* value via the inverse variance method.[32] I^2 and χ^2 statistics were used to evaluate the percentage variability of the results attributed to heterogeneity among the studies.[33] If heterogeneity was denoted (χ^2 *P* value $\leq$0.1 or $I^2 > 0\%$), we used the random effects model; otherwise, the fixed effects model was applied. When data were available, as few as 2 studies were used for a meta-analysis.[34] Meta-analyses were first stratified by ENE determination method (pathologic [pENE] vs radiologic [rENE]) and subsequently combined for a full effect measure.

Finally, we inspected publication bias using a funnel plot generated via RevMan v5.3 and an Egger's regression test assessing plot asymmetry whenever >10 studies qualified for a meta-analysis.[31,35] In case of identified bias, an adjusted analysis was planned to remove the most extreme studies with recalculation of the effect size.[36]

Results

Search Results

As presented in **Figure 1**, the search strategy yielded 130 articles following the removal of duplicate publications. After the addition of 6 articles identified in the studies' reference lists, 100 full-text articles were assessed for eligibility. In total, 18 studies met inclusion criteria and were included in our meta-analysis.[12-14,25,26,37-49]

Of note, 2 excluded abstracts[50,51] were from the same institutions, involving overlapping periods and patients and identical outcomes as 2 full articles that were included in our analysis.[39,49] Although the 2012 study by Sinha et al[45]

analyzed a patient cohort overlapping that of the 2015 Sinha et al study,[13] the former was still included for its OS outcome, which was not available in the latter study.

Study and Patient Characteristics

Table 1 summarizes the characteristics of analyzed studies. Most studies (n = 15) were retrospective cohort studies, while the 3 studies conducted by Washington University[13,14,45] were prospective observational cohort studies. The studies spanned approximately 3 decades, from 1985 to 2016. The studies were conducted in North America (n = 13, 72.2%), Europe (n = 3, 16.7%), and Asia (n = 1, 5.6%). One study was conducted in North America and Europe (n = 1, 5.6%).[14] Overall, 3603 patients with HPV+ OPSCC (ENE+, n = 1521, 42.2%; ENE–, n = 2082, 57.8%) with a median follow-up of 49 months were included in the meta-analysis. Thirteen (72%) studies assessed pENE and involved surgery with or without adjuvant therapy as the primary treatment modality. The remaining studies (n = 5, 28%) assessed rENE and included definitive RT or definitive CRT as its mainstay treatment.

Additional study and patient outcomes are included in Supplement Table S1 (available online): 5 of 13 (38%) pENE studies reported adjusted outcomes, with a mean 3.75 variable adjustments. Of 5 rENE studies, 2 (40%) reported adjusted outcomes, including a mean 4 adjustments. HPV status was confirmed via p16 immunohistochemistry (IHC) in 17 (94%) studies. Polymerase chain reaction was used in addition to p16 IHC in 4 (22%) studies and alone in 1 (6%) study. In situ hybridization was added to IHC in 3 (17%) studies. pENE was most commonly defined as carcinoma spreading outside the lymph node capsule (4/13, 31%), although the majority of studies (8/13, 62%) did not report a specific definition. rENE had a unique definition in each of the 5 studies but commonly included ''tumor invasion into adjacent structures'' (4/5, 80%) and ''loss of nodal capsule integrity'' (2/5, 40%).

Meta-analysis Results for pENE

Results of the pENE meta-analysis are presented in **Figure 2**. Seven pENE studies reported OS outcomes (Supplement Table S1, available online); however, only 6 presented sufficient data for analysis, and 5 of the 6 demonstrated HRs that included 1.0 for OS (**Figure 2A**). The pooled HR was 1.89 (95% CI, 1.15-3.13), indicating that pENE was associated with decreased OS. Heterogeneity among studies existed (I^2 = 35%; P = .18); thus, a random effects model was used.

Five studies reported data on DSS, and all were analyzed (**Figure 2B**). The pooled HR was 1.45 (95% CI, 0.84-2.49), indicating no statistical significance in the association of pENE and DSS. Between-study heterogeneity was minimal (I^2 = 0%; P = .63), and a fixed effects model was used.

Two studies reported distinct data on LRR (**Figure 2C**). Pooled analysis yielded nonsignificant findings (HR, 0.75; 95% CI, 0.20-2.84). Heterogeneity among studies was nonsignificant (I^2 = 0%; P = .67), and a fixed effects model was used.

Finally, 3 studies contained distinct data for DR analysis (**Figure 2D**). The pooled HR was 3.23 (95% CI, 1.25-8.33), showing a significantly increased risk of DR associated with the presence of pENE as compared with no pENE. Between-study heterogeneity was nonsignificant (I^2 = 0%; P = .34); thus, a fixed effects analysis was conducted.

Meta-analysis Results for rENE

While results differed numerically, rENE as reported in the nonsurgical studies (**Figure 2**) was prognostic for the same outcomes as pENE, except LRR, indicating that rENE was associated with worse OS (HR, 2.64; 95% CI, 1.46-4.78) and DR (HR, 3.83; 95% CI, 1.88-7.80) but not with LRR (HR = 2.03; 95% CI, 0.86-4.79). Heterogeneity was substantial only in the OS analysis (I^2 = 75%; P = .003), leading to the utilization of the random effects model. There were no rENE studies reporting sufficient data for DSS analysis, a common finding in nonsurgical studies.

Meta-analysis Results for Combined pENE and rENE

Combined results for pENE and rENE are also presented in **Figure 2**. Prognostic relationships were maintained such that ENE was associated with OS (HR, 2.36; 95% CI, 1.56-3.56) and DR (HR, 3.60; 95% CI, 2.04-6.36) but not with LRR (HR, 1.51; 95% CI, 0.74-3.12). Heterogeneity among studies was substantial only in the OS analysis (I^2 = 66%; $P < .0001$); thus, a random effects model was used. Meta-analysis forest plots with full values are available in Supplemental Figure S1, available online.

Publication Bias

Visual inspection of funnel plot symmetry was performed for the combined pENE-rENE outcome of OS, as it was the only meta-analysis including $\geq$10 studies (**Figure 3**). The funnel plot did not suggest publication bias, and an Egger's regression test (P = .0934) confirmed the result.

Study Quality

The median Newcastle-Ottawa Scale score was 7 (range, 6-8; **Table 2**). Many studies had comparability points deducted because adjustments were nonuniform and a detailed clinicopathologic comparison between ENE+ and ENE– groups was often missing.

Discussion

To the best of our knowledge, this is the largest systematic review and meta-analysis evaluating the prognostic significance of ENE among patients with HPV+ OPSCC. We analyzed 18 studies involving 3603 patients (1521 ENE+ and 2082 ENE–). Our analysis suggests that pENE and rENE (in nonsurgical cohorts) are associated with an approximately 1.7- and 2.6-fold increased risk, respectively, of reduced OS and a 3-fold increased risk of DR, as compared with ENE– disease. We did not find an association of ENE with DSS or LRR.

Two prior reports included meta-analyses addressing the prognostic value of pENE in HPV+ OPSCC.[52,53] Mermod

Table 1. Characteristics of Studies Included in the Meta-analysis.

Study	Location and years	No. of patients		Median age,[a] y	Male:female[a]	ENE status determination	Primary tumor treatment	Median follow-up,[a] mo
		Total	Included in analysis					
Beltz[37] (2019)	Germany (Mainz) 2008-2015	255	52	53 $\leq$ 60 52 $>$ 60[b]	72:33	Pathologic	Surgery $\pm$ aRT/aCRT	33.9
Haughey[14] (2016)	USA, UK, 1985-2015	704	660	57 (mean)	589:115	Pathologic	Surgery $\pm$ aRT/aCRT	43.9
Iyer[55] (2015)	USA (NY), 1985-2005	201	104	58	81:25	Pathologic	Surgery $\pm$ aRT	NA
Kaczmar[39] (2014)	USA (PA), 2010-2012	114	112	57	107:7	Pathologic	Surgery $\pm$ aRT/aCRT	17
Kharytaniuk[40] (2016)	Ireland (Cork), 1998-2015	83	45	54.6	35:10	Pathologic	Surgery $\pm$ aRT/aCRT	31
Klozar[57] (2013)	Czech Republic (Prague) 2001-2007	170	76	46 $\leq$ 58 52 $>$ 58[b]	79:19	Pathologic	Surgery $\pm$ aRT	NA
Kumar[58] (2016)	USA (OH), 2002-2012	296	222	57.8 (mean)	235:61	Pathologic	Surgery $\pm$ aRT/aCRT	NA
Lukens[42] (2015)	USA (MD), NA	174	174	NA	NA	Pathologic	Surgery + aCRT	38
Maxwell[56] (2013)	USA (PA), 1983-2009	351	76	57	113:20	Pathologic	Surgery $\pm$ aRT/aCRT	93
Park[43] (2019)	Korea (Seoul), 2005-2016	188	188	57.2	158:29	Pathologic	Surgery $\pm$ aRT/aCRT	61.8
Shevach[44] (2017)	USA (NY), 2005-2016	75	75	57.5	65:10	Pathologic	Surgery + aRT $\pm$ aCT	29
Sinha[45] (2012)	USA (MO), 1996-2010	152	152	56	134:18	Pathologic	Surgery $\pm$ aRT/aCRT	43
Sinha[13] (2015)	USA (MO), 1996-2012	220	199	56.7	191:29	Pathologic	Surgery $\pm$ aRT/aCRT	59
Bhattassali[46] (2019)	USA (CA), 2006-2015	238	238	61	206:27	Radiologic	dCRT	49
Huang[47] (2020)	Canada (Toronto), 2010-2015	558	517	59	442:75	Radiologic	dRT $\pm$ CT	61.2
Billfalk-Kelly[26] (2019)	Canada (Toronto), 2008-2015	280	279	58.1	238:42	Radiologic	dRT $\pm$ CT	57.6
Thompson[48] (2019)	USA (CA), 2006-2012	390	309	58	302:40	Radiologic	dRT $\pm$ CT	80.4
Tian[49] (2019)	USA (GA), 2008-2014	168	125	58	151:17	Radiologic	dRT $\pm$ CT	39.6

Abbreviations: aCRT, adjuvant chemoradiotherapy; aCT, adjuvant chemotherapy; aRT, adjuvant radiotherapy; CT, chemotherapy; dCRT, definitive chemoradiotherapy; dRT, definitive radiotherapy; ENE, extranodal extension; HPV, human papilloma virus; NA, not available.

[a]Distribution of sex, age, and follow-up was reported for patients included in this analysis (HPV+ oropharyngeal cancer with known ENE status) unless entire cohort distribution was available.

[b]Age was provided as n (number of patients) less than or greater than certain numerical age in years (N $\leq$ age; N $>$ age).

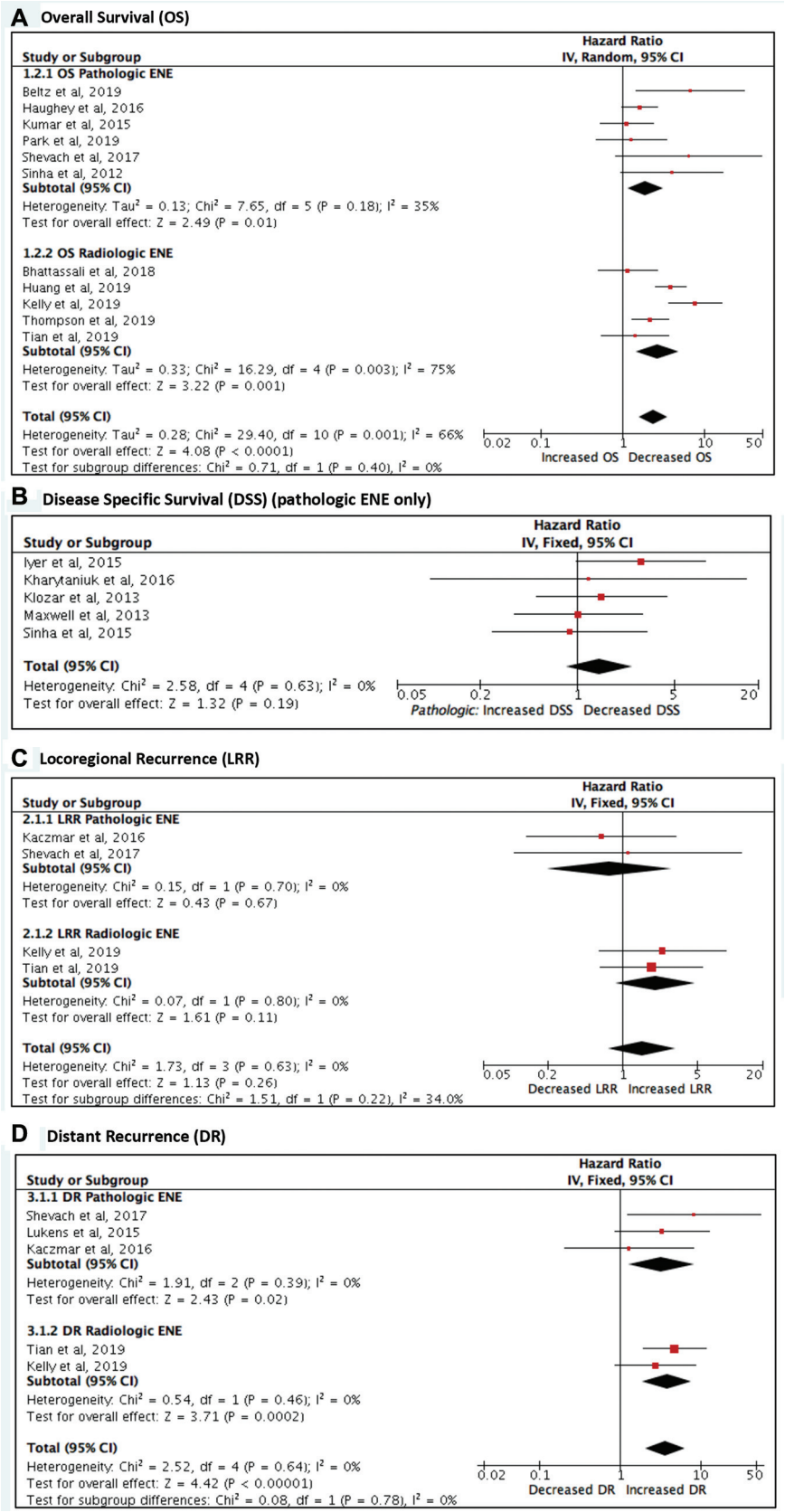

Figure 2. Meta-analysis forest plots among studies with pathologic and radiologic extranodal extension (ENE) showing association with (A) OS, (B) DSS, (C) LRR, and (D) DR. Error bars indicate 95% CIs.

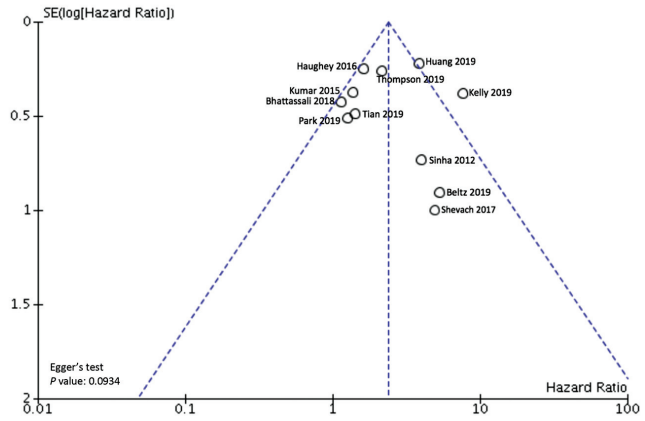

Figure 3. Funnel plot of risk of publication bias in overall survival analysis.

et al[52] analyzed 4 studies[13,40,45,54] totaling 561 pN+ cases (71% with ENE). ENE was not significantly prognostic for disease-free survival (HR, 1.39; 95% CI, 0.12-18.81). Surprisingly, however, 3 of the 4 analyzed studies had overlapping cohorts.[13,45,54] While the authors conducted an additional qualitative analysis of 3 studies (analyzed in our study as well),[40,55,56] no mathematical conversion was used to add the results to the quantitative meta-analysis. Tassone et al[53] performed a meta-analysis of 5 studies[12,13,53,57,58] totaling 588 patients. Given the small number of studies, they combined all outcomes (disease-free survival, DSS, and OS) to analyze event-free survival, which resulted in a nonsignificant prognostication for ENE (HR, 1.34; 95% CI, 0.82-2.18).

Our meta-analysis attempted to overcome some of the obstacles encountered previously by designing a comprehensive search strategy, maximizing the number of evaluated prognostic outcomes, and utilizing a previously described method[30] for obtaining HRs from Kaplan-Meier survival data when HRs were not directly reported.

Our finding of the prognostic association of pENE with reduced OS (HR = 1.89, $P = .01$) after pooling 1349 patients from 6 studies may elucidate the discordance between certain larger NCDB studies that, congruent with our analysis, reported reduced OS in patients with pENE[22-24,59] and smaller-scale single-center studies[12,40,45,55,57,58,60] in which

Table 2. Newcastle-Ottawa Scale for Quality Assessment of Nonrandomized Cohort Studies in Meta-analyses.

	Selection					Outcome			
First author (year)	Exposed[a]	Nonexposed[b]	Ascertainment[c]	Outcome of interest[d]	Comparability[e]	Death[f]	Follow-up[g]	Cohort[h]	Total[i]
Beltz[37] (2019)	*	*	*	*	–	*	*	*	7
Haughey[14] (2016)	*	*	*	*	–	–	*	*	6
Iyer[55] (2015)	*	*	–	*	–	*	*	*	6
Kaczmar[39] (2014)	*	*	*	–	**	–	*	–	6
Kharytaniuk[40] (2016)	*	*	*	*	–	*	–	*	6
Klozar[57] (2013)	*	*	*	–	–	*	*	*	6
Kumar[58] (2016)	*	*	*	–	**	*	*	–	7
Lukens[42] (2015)	*	*	*	*	–	*	*	*	7
Maxwell[56] (2013)	*	*	*	–	**	*	*	*	8
Park[43] (2019)	*	*	–	*	**	*	–	*	7
Shevach[44] (2017)	*	*	*	–	**	–	*	–	6
Sinha[45] (2012)	*	*	*	*	*	*	*	*	8
Sinha[13] (2015)	*	*	*	–	–	*	*	*	6
Bhattassali[46] (2019)	*	*	*	*	*	*	*	*	8
Huang[47] (2020)	*	*	*	–	**	–	*	*	7
Kelly[26] (2019)	*	*	*	–	**	*	*	*	8
Thompson[48] (2019)	*	*	*	*	**	*	*	–	8
Tian[49] (2019)	*	*	*	–	*	*	*	*	7

Abbreviation: ENE, extranodal extension.
[a]Representativeness of exposed cohort.
[b]Selection of nonexposed cohort.
[c]Exposure ascertainment. A star was awarded if ENE was assessed clearly with histopathology or radiology.
[d]Outcome of interest not present at study start: primary tumor.
[e]Cohort comparability based on design or analysis. Studies including a comparison of the cohort by ENE status and demonstrating comparability (≥1 variable, $P > .05$) were awarded 1 star. Studies that controlled for at least 3 factors in the multivariate outcome analysis for ENE status impact received 2 stars.
[f]Assessment confirmation of death.
[g]Adequate length of follow-up. Studies with follow-up >6 months were awarded a star. Studies with unstated median follow-up did not receive a star.
[h]Adequate cohort follow-up, including censoring (ie, accounting for people lost to follow-up).
[i]A study can be awarded a maximum of 1 star for each item—except for a maximum of 2 stars, which can be given for comparability. Each item's definition can be found at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

this association was not statistically significant. Increased power was possibly needed to arrive at a significant conclusion among institutional studies. Nevertheless, when compared with our HPV+ cohort, it is apparent that the prognostic impact of pENE is stronger in non–HPV-mediated HNSCC, with reported HRs ranging between 2.3 and 2.7.[8-10,58]

We identified rENE to be associated with worse OS (HR, 2.64; P = .001) after analyzing 1468 patients (307 with rENE) from 5 studies.[26,46,48,49,61] Notably, the prognostication of rENE was stronger than that of pENE. It is likely that more extensive ENE is required for radiologic versus pathologic diagnosis, correlating with a more aggressive disease, which corresponds with pathologic research identifying soft tissue metastasis of the neck as a negative prognosticator.[62] Another possibility is treatment effect, with surgical extirpation of ENE nodes mitigating their impact.

Much research is needed to elucidate prognostication arising from radiologic designations of a pathologic entity. Expert positions on the ability of imaging to correctly predict pENE are varied.[63-65] The Union for International Cancer Control and the AJCC express that rENE should be added to support unequivocal clinical ENE (cENE) findings on physical examination, such as skin invasion by tumor and nerve involvement, although rENE is not sufficient on its own to diagnose cENE.[15] They reference a 2014 study that evaluated the accuracy of computed tomography for anticipating pENE in 432 patients with HNSCC, calculating a sensitivity of 43.7%, specificity of 97.7%, positive predictive value of 82.6%, and negative predictive value of 87.3%.[66]

More recent studies are conflicting with higher sensitivity (61%) and, in one, specificity (95%) for contrast-enhanced computed tomography ENE diagnosis.[67] However, in a recent meta-analysis of rENE, the improved sensitivity at 77% was offset by poorer specificity (72%), PPV (69%), and NPV (81%), for an overall accuracy of only 64%.[68] Novel research is using artificial intelligence to standardize the grading and definition of rENE.[69] Additionally, overt physical examination ENE findings are not always present in moderate ENE cases, and despite the aforementioned findings, common practice continues to divert patients with head and neck cancer who are surgical candidates to definitive CRT treatment when preoperative imaging indicates rENE, in an effort to circumvent the toxicity profile associated with trimodality treatment.[70-77] In this context, it is emphasized that there is no prospective clinical trial evidence for the added benefit of adjuvant chemotherapy specific to HPV-mediated OPSCC surgical cases.[7]

DSS was available for analysis among only pENE studies and was not significantly prognostic (HR, 1.45; 95% CI, 0.84-2.49). The discordance between our findings for OS and DSS may be due to lower power in the pooled studies with available DSS outcomes (500 patients) as compared with OS outcomes (1349 patient). If so, this continues to imply a relatively weak effect of ENE overall when ENE is not in any way quantified. Comparing with HPV– head and neck cancer sites, ENE confers a significant 30% to 40% reduction in 5-year DSS in oral cavity cancers[78,79] and 32% to 59% reduction in 5-year OS in hypopharyngeal and laryngeal cancer.[9,80,81]

It is also possible that ENE is correlated with other risk factors, such as smoking or weakened immunity, predisposing patients to a higher all-cause mortality risk.[82,83] Another competing cause for mortality in ENE cases may be obesity, unaccounted for in most studies. It is well recognized in HPV+ OPSCC that patients first present with a neck mass, and the obese patient who exhibits the typical short, high-circumference neck may be subject to patient- and provider-related delays in diagnosis. Such physical masking may result in more advanced disease at presentation among the obese, who may be disproportionately represented among ENE+ cases. Patients who are obese are an increasingly prevalent and high-mortality group in the United States[84,85]—hence, the urgent need to incorporate comorbidity measures in overall survival studies, an important variable that we did not have available to control for in this study.

Pooling all DSS and OS studies revealed the HR of 1.63 ($P < .001$) and minimal between-study heterogeneity (I^2 = 5%; P = .40; Supplemental Figure S2, available online), suggesting that pENE is associated with decreased survival and that the variability of the results was not due to differences among study populations.

We did not find an association of LRR with either pENE or rENE. One possible explanation is the improved locoregional control conferred by the established practice of adding sensitizing chemotherapy to postoperative RT for patients with pENE.[86,87] Indeed, in our LRR articles, 90.6% of patients in pENE studies[26,49] and 81% of patients in rENE studies[39,44] received postoperative CRT and definitive CRT, respectively. While we maximized the number of included studies reflecting the currently available literature, the overall small number of studies precluded us from assessing publication bias among them, and additional studies will be needed to reach more definitive and generalizable conclusions.

After we pooled 361 patients assessed pathologically and 404 patients assessed radiologically for ENE, our analysis indicated a significantly increased risk of DR among patients with pENE (HR, 3.23; P = .02) and rENE (HR, 3.83; $P < .001$), as compared with patients without ENE. Similar to the LRR cohorts, the majority of surgical patients (97.5%) received adjuvant CRT,[39,42,44] and most patients (81%) in rENE studies were treated with definitive CRT.[26,49]

Our finding that patients with ENE were at higher risk of DR but not LRR may be representative of the more aggressive disease pattern conferred by ENE. Having tumor cells invade lymphatic pathways past their natural capsular barrier can increase the risk for occult micrometastasis. Since the main role of adjuvant cisplatin is to sensitize tumor cells to the locally administered RT, occult distant disease may be unaffected by administration of adjuvant chemotherapy. Moreover, both landmark trials that provided the basis for the current adjuvant CRT recommendation found that the addition of chemotherapy to postoperative RT reduced LRR, while DR remained similar in both treatment arms.[4,5] Additionally, while HPV positivity confers improved

locoregional control as compared with HPV– OPSCC, distant failure rates are similar and account for most of the relapses in the HPV+ population.[88,89]

Clinical nonsurgical treatment deintensification trials for patients with HPV+ disease do not often take ENE into account,[90] and according to our results, considering ENE could help identify patients who may benefit from higher versus lower chemotherapy doses. The ongoing transoral surgical Phase III PATHOS trial, however, tests the contribution of cisplatin to outcomes in the presence of pENE.[91]

Several reasons led us to conduct this meta-analysis even though large-scale NCDB studies[22-24,59]—aside from the first and smallest one that grouped ENE and/or positive margins in the Cox regression analysis (HR, 1.61; $P = .154$)[21]—showed a modest (HR range, 1.52-2.50) but significant association between pENE and reduced OS in the HPV+ OPSCC cohort. First, the NCDB is subjected to inherent selection bias brought on by substantially incomplete data, specifically variables critical to this analysis: HPV status, ENE status, staging, and follow-up. For instance, an article addressing ENE prognostication in HPV+ OPSCC that utilized the most recent NCDB data set (2010-2015) had a final population of 3622 patients.[59] The study, however, had to exclude >10,000 patients with unknown ENE status, unknown pathologic staging, or missing follow-up information.[59] Such exclusions, common to most NCDB analyses, inevitably result in significant selection bias, as previously suggested by several authors, and so preclude generalization of the findings.[92-94] Additionally, of the 5 NCDB studies analyzing ENE prognostication in HPV+ OPSCC, only the earliest (2016) and smallest NCDB study (991 patients but with an unknown proportion of confirmed ENE status) reported a sensitivity analysis to circumvent bias from excluding patients with unknown HPV status.[21]

Finally, OS is the only prognostic outcome available in the NCDB, thereby limiting the scope and application of the information that it generates. As a minimum requirement, cancer-related outcome research and national databases should report cancer-related outcomes. Nevertheless, our study's results are congruent with some of the NCDB studies, indicating a modest (HR, 1.89) but significant survival decrement associated with pENE. This leads to the tentative conclusion, given the aforementioned and following limitations, that decreased power was a reason for the unequivocally negative results in individual institutional studies examining pENE prognostication.

The existing data analyses available at the time on ENE prognostication in HPV+ OPSCC logically led to its absence from the new AJCC eighth edition staging. Pathologic nodal staging was based on a multicenter retrospective cohort analysis by Haughey et al,[14] which identified a prognostic cutoff at >4 metastatic nodes among 704 patients with HPV+ OPSCC treated with primary surgical resection and adjuvant therapy. pENE was close but did not reach prognostic significance (HR, 1.61; $P = .060$) at the univariable level for OS and was therefore not included in the multivariable analysis. Metastatic node maximum size was also not significantly prognostic, again possibly related to the treatment effect of surgical excision. Consequently, the refined staging system includes pN1 (1-4 lymph nodes), pN2 (>4 lymph nodes), and no pN3.[14,15,95] Clinical staging for HPV+ OPSCC was based on a study performed by the International Collaboration for Oropharyngeal Cancer Network for Staging,[96] whose analysis of 661 patients treated with definitive CRT lead to 3 cN categories based solely on lymph node size and laterality. Conversely, ENE was included in the clinical and pathologic upstaging of HPV– OPSCC.[15,95]

A more nuanced distinction of ENE prognostication in HPV+ OPSCC may involve ENE extent rather than its absolute presence or absence, as suggested by several studies evaluating pENE[45,59,62,97,98] and rENE.[61,99] The ongoing Eastern Cooperative Oncology Group 3311 clinical deintensification trial for surgically treated cases of HPV+ OPSCC acknowledges the possible prognostic difference conferred by ENE extent and stratifies pENE into 3 groups: low risk (no ENE), intermediate risk (≤1-mm spread), and high risk (>1-mm spread).[20] Imaging-based ENE stratification will prove to be more challenging, given the absence of histologic signaling. The inconsistent ENE extent definitions and variably evaluated outcomes across studies precluded us from properly analyzing the prognostic impact of ENE extent.

Limitations and Strengths

The current systematic review and meta-analysis have limitations. First is the retrospective observational cohort nature of the majority of studies, as well as their relatively small sample sizes and variable definitions for pENE and rENE. This latter, significant limitation applies to reporting on ENE, with a 2012 study identifying a low interobserver kappa value of 0.42 pertaining to agreement of pathologists on the presence of neck node ENE.[100]

In addition, while most studies included a statement reassuring a baseline-level similarity of clinicopathologic characteristics between the ENE+ and ENE– cohorts, only half of the studies presented a characteristics table allowing us to assess this similarity. To that end, a small proportion of the studies adjusted their outcomes for confounding variables. All of these decreased the quality of the reports and somewhat increased between-study heterogeneity. Given the missing data and the fact that a meta-regression should be performed only for analyses with at least 10 studies,[31] we did not pursue further adjustments. An example of this is our lack of control for metastatic node number, shown to be prognostic in most HPV+ OPSCC pathology-reporting publications.

While the evidence for OS appeared comprehensive, since it included 6 pENE and 5 rENE studies, data for DR and LRR were more limited. The propensity of HPV-mediated OPSCC to develop recurrences much later than what was previously observed for HPV– HNSCC[101] may contribute to the observed difference. Hence, follow-up beyond 5 years may or may not reveal a stronger negative prognostic impact of ENE on DR and LRR, since late recurrences are rare.[102] The impact of longer follow-up on OS is not clear, as

DR and LRR could correlate with other health decrements, such as weakened immunity,[103] leading to reduced survival.

Some of our analyses resulted in wide CIs. This was partly due to a low event rate, as well as the need to estimate the number of patients at different time points in cases when the studies presented survival percentages and Kaplan-Meier curves but not HRs and 95% CIs. It is conceivable that more robust patient and outcome data would have narrowed the CIs.

Our analysis was strengthened by an experienced librarian who designed a comprehensive literature search strategy, allowing us to assess a relatively large number of studies as well as their reference lists. Additionally, we strictly followed the PRISMA guidelines and refrained from analyzing overlapping cohorts.

Conclusion

Our results indicate that pENE and rENE are moderately associated with an increased risk of all-cause mortality and distant metastasis but not LRR in a cohort of patients with HPV+ OPSCC. These findings may be used to guide research, inform exclusion criteria for deintensification trials, and assist in refined risk stratification.

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Author Contributions

Liliya Benchetrit, conceptualization, methodology, project administration, resources, data gathering and analysis; writing—original draft, critical review and editing; final approval of the submitted version; accountability for all aspects of the work; **Sina J. Torabi**, conceptualization, methodology, project administration, resources, data gathering; writing—critical review and editing; final approval of the submitted version; accountability for all aspects of the work; **Babak Givi**, conceptualization, methodology, project administration, resources; writing—critical review and editing; final approval of the submitted version; accountability for all aspects of the work; **Bruce Haughey**, conceptualization, methodology, project administration, resources; writing—critical review and editing; final approval of the submitted version; accountability for all aspects of the work: **Benjamin L. Judson**, conceptualization, methodology, project administration, resources; writing—critical review and editing; final approval of the submitted version; accountability for all aspects of the work.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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