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ORIGINAL RESEARCH

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Postoperative radiotherapy versus surgery alone in pN1 oral cavity cancer patients: A meta-analysis

Tsung-You Tsai MD[1] | Pin-Chun Chiang MD[1,2] | Wing-Keen Yap MD[3] | Yenlin Huang MD, PhD[4,5,6] | Anna See MMed, MPH[1,7] | Shao-Yu Hung MD[8] | Chueing-Yi Lu MD[8] | Chien-Yu Lin MD[3,9] | Tung-Chieh Joseph Chang MD[2,3] | Huang-Kai Kao MD[2,8] | Kai-Ping Chang MD, PhD[1,2]

[1]Department of Otolaryngology—Head and Neck Surgery, Chang Gung Memorial Hospital, Taoyuan, Taiwan

[2]College of Medicine, Chang Gung University, Taoyuan, Taiwan

[3]Proton and Radiation Therapy Center, Chang Gung Memorial Hospital-Linkou Medical Center, Department of Radiation Oncology, Chang Gung University, Taoyuan, Taiwan

[4]Department of Anatomic Pathology, Chang Gung Memorial Hospital at Linkou Branch, Taoyuan, Taiwan

[5]Institute of Stem Cell and Translation Cancer Research, Chang Gung Memorial Hospital at Linkou Branch, Taoyuan, Taiwan

[6]School of Medicine, National Tsing-Hua University, Hsinchu, Taiwan

[7]Department of Otorhinolaryngology—Head and Neck Surgery, Singapore General Hospital, Singapore

[8]Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital at Linkou Branch, Taoyuan, Taiwan

[9]Department of Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan

Correspondence
Kai-Ping Chang, Department of Otolaryngology—Head and Neck Surgery, Chang Gung Memorial Hospital & College of Medicine, Chang Gung University, No. 5, Fu-Hsing St. Kwei-Shan, Taoyuan, Taiwan 33305.
Email: dr.kpchang@gmail.com

Abstract

Objectives: The aim of this meta-analysis is to evaluate the potential benefits of postoperative radiotherapy (PORT) in patients with pN1 oral cavity squamous cell carcinoma.

Methods: A literature search through major databases was conducted until January 2023. The adjusted hazard ratio (aHR) or risk ratio (RR) with 95% confidence intervals (CIs) of different survival outcomes were extracted and pooled.

Results: Ten studies published between 2005 and 2022, with a pooled patient population of 2888, were included in this meta-analysis. Due to differences in study design and reported outcomes, the studies were categorized into distinct groups. In pN1 patients without extranodal extension (ENE), PORT was associated with a significant improvement in overall survival (OS) (aHR 0.76, 95% CI: 0.61–0.94). In pN1 patients without ENE and positive margins, PORT improved OS (aHR 0.71, 95% CI: 0.56–0.89) and was associated with a lower regional recurrence rate (RR 0.35, 95% CI: 0.15–0.83). However, in pN1 patients without ENE, positive margins, perineural invasion, and lymphovascular invasion, there were no significant differences observed between the PORT and observation groups in either 5-year OS (RR 0.48, 95% CI: 0.07–3.41) or 5-year disease-free survival (RR 0.37, 95% CI: 0.07–2.06).

Conclusions: The current study demonstrated that PORT has the potential to improve OS in pN1 disease. However, the decision of whether to administer PORT still hinges on diverse clinical scenarios, and additional research is necessary to furnish a more conclusive resolution.

Level of Evidence: 2.

KEYWORDS

adjuvant therapy, oral cancer, OSCC, PORT, postoperative radiotherapy, squamous cell carcinoma

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1 | INTRODUCTION

Oral cavity cancer remains a prevalent malignancy worldwide, with oral cavity squamous cell carcinoma (OSCC) accounting for approximately 90% of cases.[1,2] Lymph node metastasis of the neck is one of the most common features of OSCC and represents a critical prognostic determinant for patients.[3,4] Studies have shown that pathologically confirmed positive nodal disease may lead to a decrease of approximately 30%–40% of 5-year overall survival (OS) rate compared to those without neck metastasis.[5] Therefore, it is imperative to develop a comprehensive treatment plan for addressing neck metastasis and regional recurrence in OSCC patients.

American Society of Clinical Oncology practice guideline recommends postoperative radiation therapy (PORT) for patients with extranodal extension (ENE), multiple nodal metastasis, or contralateral node involvement, citing strong evidence to support its use.[6] However, the benefits of PORT for oral cavity cancer patients with a single pathologically positive ipsilateral lymph node ≤3 cm (pN1) without ENE remains contentious. American Society of Clinical Oncology guidelines for managing the neck in OSCC patients suggest that PORT should not be administered to pN1 patients without other adverse factors if a high-quality neck dissection has been performed (Recommendations 2.1a).[6] However, it is important to note that these recommendations are mainly based on expert opinion or retrospective studies with contradicting results. Despite previous attempts to investigate this issue using data from different institutions, the results remain heterogeneous regarding survival outcomes.[7–14] Although a meta-analysis focusing on pN1 patients was conducted previously, the review included some studies investigating oropharyngeal squamous cell carcinoma which has been known as a distinct disease entity from OSCC.[15] Hence, the current study aims to review and summarize the literature and investigate the potential benefits of PORT for pN1 OSCC patients. Specifically, we hypothesized that PORT may improve various survival outcomes in these patients.

2 | METHODS

The meta-analysis was conducted strictly following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[16] and had been registered on PROSPERO.

2.1 | Research question

In pN1 OSCC patients without ENE, does PORT improve the survival outcomes compared to surgery alone.

2.2 | PICO criteria

The following PICO criteria were applied to identify the studies:

1. Patients (P): pN1 OSCC patients without ENE.
2. Intervention (I): PORT.
3. Comparison (C): Surgery alone.
4. Outcome (O): Adjusted hazard ratio (aHR) for OS, disease-specific survival, disease-free survival (DFS), locoregional-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival; risk ratio (RR) for regional recurrence rate, RR for OS, RR for DFS.

2.3 | Search strategy

A systematic search was conducted in electronic databases, namely PubMed, EMBASE, and Cochrane Library, to identify studies published from inception until January 2023. The search strategy was developed using relevant keywords such as pN1, OSCC, radiotherapy, surgery, survival, recurrence, and metastasis, which were combined using Boolean operators. The search details are provided in Table S1. Subsequently, the full texts of the studies were meticulously screened for inclusion. In addition, the bibliography of previous systematic reviews and eligible studies was reviewed to identify potential eligible reports. To ensure the removal of duplicate articles, the retrieved studies were imported into a citation manager (Endnote, version X9.3.3, Clarivate Analytics, Philadelphia, PA).

2.4 | Eligibility assessment

The databases were independently searched by two reviewers who then evaluated the titles and abstracts of the identified studies. The process was conducted in a blinded manner, with each reviewer unaware of the other's evaluations. Following this initial screening, full-text assessments were performed based on the agreement reached by the two reviewers regarding the selected abstracts. In cases where doubts arose and a disagreement persisted, the final decision regarding eligibility was deferred to a senior author. Ultimately, eligibility was determined only when all reviewers were in agreement.

The following inclusion and exclusion criteria were employed to carry out the study selection.

Inclusion criteria:

1. Studies comparing outcomes of adjuvant radiotherapy versus surgery alone in pN1 OSCC patients.
2. Studies assessing the primary endpoints as different survival outcomes and regional recurrence rates.

Exclusion criteria:

1. Studies analyzing pN1 OSCC patients without excluding ENE.
2. Studies not published in the English language.
3. Studies not providing relevant information.

2.5 | Data extraction

Data extraction was also performed independently by the two researchers, and the following data were retrieved: first author, journal name, year of publication, patient recruitment period, study designs, sample size, age, sex, staging of cancer, country, aHR or RR with 95% confidence interval (CI) for the endpoints (OS, DFS, DSS, LRFS, RRFS, DMFS, regional recurrence rate), and follow-up time, and risk factors excluded for study designs.

2.6 | Data synthesis

Upon retrieval, the data underwent both qualitative and quantitative analyses. The demographic and interventional characteristics of all included studies were collated and presented in tabular form and subsequently subjected to a detailed analysis. Dichotomous outcomes, such as OS, DFS, DSS, LRFS, and RRFS, were expressed as aHRs with CIs, and the rates of regional recurrence and survival outcomes were expressed as RR. The aforementioned outcomes were then subjected to a meta-analysis. In cases where there was overlap in the study populations, preference was given to the more recent studies for the purposes of data synthesis.

2.7 | Appraisal of study quality

The risk of bias assessment was done using the Newcastle–Ottawa Scale for the included studies. The Newcastle–Ottawa Scale comprised three domains, namely selection, comparability, and outcome, which collectively comprised a total of eight questions. Based on the scoring system, studies were categorized into low-quality, fair-quality, and high-quality categories based on their respective scores. Specifically, studies with a score of ≤3 were classified as low-quality, those with a score between 4 and 6 were considered fair-quality, and studies with a score of ≥7 were deemed high quality.[17]

2.8 | Statistical analysis

The present meta-analysis was conducted using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA). To assess the effect of PORT on survival outcomes, aHR with a corresponding 95% CI was pooled using a random-effects model, which helped to distribute the effect of heterogeneity evenly among the various included studies. The presence of heterogeneity between studies was evaluated through both the Cochran *Q*-statistic and I^2 tests. Heterogeneity was deemed substantial if the *Q*-test $p < .05$ or if the I^2 value exceeded 50%. To determine the possibility of publication bias, funnel plots and Egger's linear regression test were employed, with a significance level set at $p < .05$. All statistical tests were two-tailed, with statistical significance defined as $p < .05$.

3 | RESULTS

3.1 | Literature search and study identification

The initial search of databases yielded 187 items, including 49 from PubMed, 11 from Cochrane, 127 from Embase, and 1 from additional resources (manual search from the reference of related articles). An

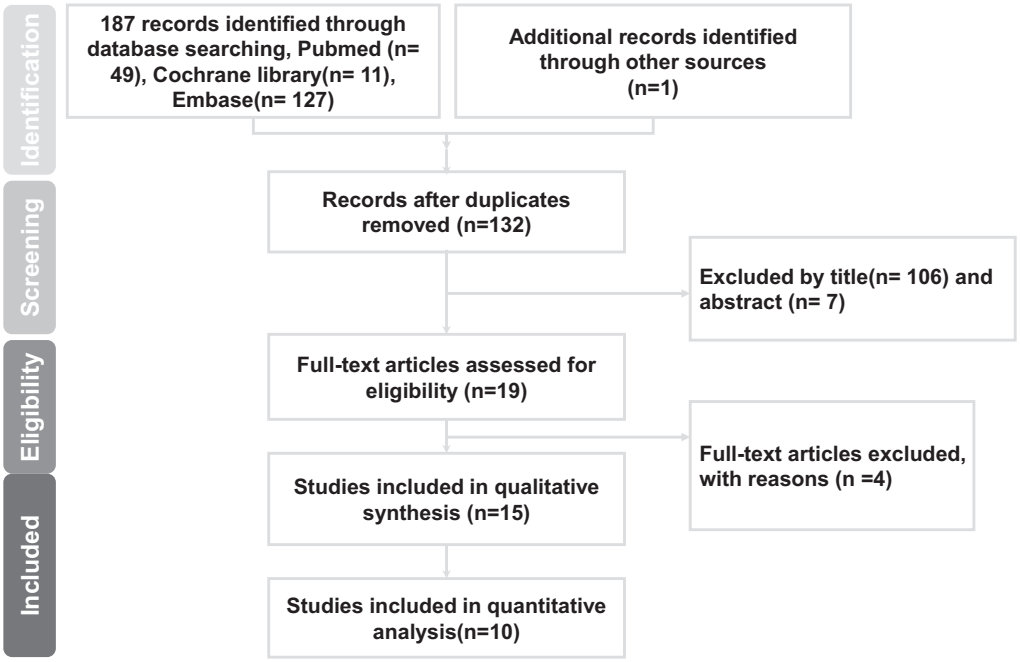

FIGURE 1 PRISMA flow diagram.

TABLE 1 Excluded studies.

Study	Year	Reason for exclusion
Kao[18]	2007	ENE not excluded in the study
Shrime[19]	2010	ENE not excluded in the study
Jäckel[20]	2008	No independent data of the OSCC patients in the study
Hasegawa[21]	2018	Only focused on single lymph node metastasis with ENE

Abbreviations: ENE, extranodal extension; OSCC, oral cavity squamous cell carcinoma.

overview of the selection process is illustrated in Figure 1; the search query and search algorithm are demonstrated in Table S1. After duplication removal, 106 studies were excluded by title, and 7 were excluded by abstract. Nineteen studies with full texts were reviewed, and four studies were excluded for specific reasons (Table 1).[18–21] Finally, 15 were eligible for the qualitative analysis, and 10 of which were eligible for the quantitative analysis.[7–14,22–28]

3.2 | Characteristics of the included studies

Table 2 presents a summary of the studies included in this meta-analysis. Of the 15 eligible studies (including studies for qualitative analysis), 14 were retrospective in design,[7–11,13,14,22–28] while 1 was prospective.[12] The studies were conducted in different countries, with the majority of contributions coming from Asian countries,[7–10,13,25,27] five from the United States (including three from the National Cancer Database and one from Surveillance, Epidemiology, and End Results, respectively),[11,14,22,24,28] two from Germany,[12,23] and one multicenter study from the United Kingdom and Australia.[26] These studies were published over a period of 18 years, ranging from 2005 to 2022. In total, 6609 patients were included in the analysis (2888 patients for data synthesis), with patient recruitment ranging from 1980 to 2019. The median age of the patients ranged from 50 to 62.1 years, and the male percentage ranged from 50% to 89.6%. Follow-up periods ranged from 36 to 80.7 months. While two studies focused on tongue tumors,[27,28] the remaining studies did not limit their subjects to specific subsites in the oral cavity. Five studies included OSCC patients with T1–T4 tumors,[7–9,25,28] one investigating T1–T3 tumors,[13] while the other nine studies focused on T1–T2 tumors.[10–12,14,22–24,26,27] Table 3 provides detailed information on the patients' clinicopathological characteristics in the eligible studies.

Due to the differences in study designs and presented outcomes, the studies were categorized into different groups. The excluded possible confounding pathologic factors are presented in Table 1. Three studies further excluded intermediate pathological factors such as perineural invasion and lymphovascular invasion to investigate the sole effect of PORT on pN1 patients.[7,23,27] However, due to the strict inclusion criteria, the number of patients was limited, and the outcome comparison could not be presented in terms of aHR. Therefore, in this subgroup, we extracted the 5-year survival rate and calculated the pooled RR for meta-analysis.

3.3 | Quality assessment

The current meta-analysis included a total of 15 studies, all of which were assessed for their methodological quality utilizing the Newcastle–Ottawa Scale. The results showed that 13 out of the 15 studies scored higher or equal to 7 points, indicating that most of the studies were of high quality. The remaining two studies scored 6 points. For more information about the included studies, please refer to Table S2.

3.4 | Meta-analysis results

The meta-analysis was conducted in different groups based on the outcomes provided and the variables they excluded.

3.4.1 | pN1 patients excluding the cases with ENE only

First, all the included studies had claimed the exclusion of ENE patients in their study designs. Eight studies provided aHR for or OS, including 2740 patients in this group of analysis. Chen et al., Suresh et al., and Xiang et al. may have overlapping database (National Cancer Database), and thus the latest study was chosen for quantitative analysis.[11,22,24] The results of the meta-analysis indicated that PORT was significantly associated with better OS (aHR 0.76, 95% CI: 0.61–0.94, $p = .01$) (heterogeneity: $I^2 = 40.86\%$, random-effects model, $p = .13$; Figure 2). Funnel plots and Egger's test were conducted to examine publication bias (Figure S1). Egger's test showed no substantial publication bias in the analysis of OS ($p = .053$).

3.4.2 | pN1 patient excluding the cases with ENE and positive surgical margin

Considering that positive margins may be a significant confounding factor, we calculated the pooled adjusted HR for OS, focusing on studies that had addressed the results of pN1 patients with the exclusion of ENE and positive margins. In these studies (4 studies including 1525 patients),[9,10,12,22] PORT significantly improved OS (aHR 0.71, 95% CI: 0.56–0.89, $p = .004$) with lower heterogeneity (heterogeneity: $I^2 = 10.29\%$, random-effects model, $p = .34$; Figure 3A). Due to the significant decrease in I^2, the results of the subgroup analysis indicated that the inclusion of patients with positive margins might be the source of heterogeneity. Furthermore, PORT was also associated with a lower regional recurrence rate (RR 0.35, 95% CI: 0.15–0.83, $p = 0.02$) (heterogeneity: $I^2 = 0\%$, random-effects model, $p = .61$; Figure 3B).[9,12,28] On

TABLE 2 Eligible study characteristics.

Study	Year	Region	Database	Recruitment period	Prospective/ retrospective cohort study	Provided outcomes	Median follow-up (months)
Alsharif[12]	2022	Germany	Single institution	1992–2019	Prospective	aHR for OS, DSS, LRFS, RRFS; RR for regional recurrence	79.2
Tsai[13]	2021	Taiwan	Single institution	2007–2016	Retrospective	Qualitative analysis	69.5
Xiang[22]	2021	USA	NCDB	2004–2015	Retrospective	aHR for OS	36
Chen[9]	2021	Taiwan	Single institution	2010–2012	Retrospective	aHR for OS, LRFS, RRFS, DMFS	55.2
Chen[8]	2022	China	Single institution	2012–2016	Retrospective	aHR for OS, DSS	63
Tsai[10]	2021	Taiwan	TCR	2007–2015	Retrospective	aHR for OS, DFS	42.4 (mean)
Yang[14]	2021	USA	SEER	2004–2015	Retrospective	aHR for OS, DSS	NA
Tsai[7]	2021	Taiwan	Single institution	2009–2013	Retrospective	RR for 5-year OS, 5-year DFS	51.6
Weiss[23]	2019	Germany	Single institution	1986–2015	Retrospective	RR for 5-year OS, 5-year DFS	80.7
Suresh[11]	2019	USA	NCDB	2004–2013	Retrospective	aHR for OS	39.7
Chen[24]	2016	USA	NCDB	2004–2013	Retrospective	aHR for OS	62.4
Feng[25]	2017	China	Single institution	1996–2012	Retrospective	Qualitative analysis	NA
Barry[26]	2017	UK and Australia	Multicenter	1998–2013	Retrospective	Qualitative analysis	44.4
Chen[27]	2010	Taiwan	Single institution	1980–2002	Retrospective	RR for 5-year OS, 5-year DFS	46
Bradley[28]	2005	USA	Single institution	1980–1995	Retrospective	RR for regional recurrence	68.4

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival;DSS, disease-specific survival; HR, hazard ratio; LRFS, locoregional recurrence-free survival; NA, not available; NCDB, national cancer database; OS, overall survival; RRFS, regional recurrence-free survival; SEER, Surveillance, Epidemiology, and End Results; TCR, Taiwan cancer registry.

the other hand, a meta-analysis on LRFS and RRFS were also performed, unfortunately, only two studies provided these outcomes in the current review.[9,12] No significant association was observed between PORT and LRFS (aHR 0.26, 95% CI: 0.02–3.33, $p = .30$) (heterogeneity: $I^2 = 88.05\%$, random-effects model, $p = .004$) (Figure 3C) or RRFS (aHR 0.29, 95% CI: 0.03–2.73, $p = .28$) (heterogeneity: $I^2 = 75.23\%$, random-effects model, $p = .04$) (Figure 3D).

3.4.3 | pN1 patients excluding the cases with ENE, margin positive, perineural invasion, and lymphovascular invasion

Three eligible studies reported the RR of OS and DFS, including 97 patients.[7,23,27] The results indicated that PORT was not significantly associated with OS (RR 0.48, 95% CI: 0.07–3.41, $p = .47$) (heterogeneity: $I^2 = 74.66$, random-effects model, $p = .01$) (Figure 4A) neither significantly associated with DFS (RR 0.37, 95% CI: 0.07–2.06, $p = .25$) (heterogeneity: $I^2 = 54.67\%$, random-effects model, $p = .08$) (Figure 4B).

4 | DISCUSSION

Adjuvant radiotherapy is commonly utilized in the management of oral cancer to mitigate locoregional failure and enhance survival rates. Nevertheless, the advantages of adjuvant radiotherapy for pN1 OSCC patients without ENE, characterized by solitary nodal involvement, continue to be a subject of controversy. The limited scope of previous studies may have contributed to this gap in understanding. A previous meta-analysis was conducted, which included studies investigating oropharyngeal squamous cell carcinoma, known as a distinct disease entity from OSCC.[15] In addition, the majority of the analysis performed in the meta-analysis was descriptive, with only two studies being eligible for inclusion in quantitative analysis.[27,29] As such, in the current meta-analysis, we are the first to focus on diagnosed pN1

TABLE 3 Patient clinicopathological characteristics of eligible studies.

Study	Age (year) median	Male (%)	Tumor site	T stage	Relevant case number	Case number (OBS)	Case number (PORT)	Exclusion of positive margin	Exclusion of PNI and LVI	Proportion of different types of ND	Proportion of adequate ND (LNY ≥ 18) (%)
Alsharif[12]	62	71	Oral cavity	1–2	51	26	25	Excluded	Not excluded	SND (18%)/MRND (82%)	NA
Tsai[13]	54	86.7	Oral cavity	1–3	105	53	52	Not excluded	Not excluded	NA	NA
Xiang[22]	61	58.87	Oral cavity	1–2	530	346	184	Excluded	Not excluded	NA	67.55
Chen[9]	50	88.1	Oral cavity	1–4	243	75	168	Excluded	Not excluded	NA	NA
Chen[8]	55	65.4	Oral cavity	1–4	107	18	89	Not excluded	Not excluded	SND (79%)/MRND (21%)	NA
Tsai[10]	51.9 (mean)	89.6	Oral cavity	1–2	701	196	505	Excluded	Not excluded	NA	NA
Yang[14]	60.9 (mean)	64.6	Oral cavity (subgroup)	1–2	1108	458	650	Not excluded	Not excluded	NA	67.5
Weiss[23]	57.2	81.54	Oral cavity (subgroup)	1–2	18	14	4	Excluded	Excluded	NA	NA
Tsai[7]	56.1	50	Oral cavity	1–4	40	20	20	Excluded	Excluded	NA	NA
Suresh[11]	62.1	57.57	Oral cavity	1–2	1909	1011	898	Excluded	Not excluded	NA	63.70
Chen[24]	61.3 (mean)	57.4	Oral cavity (subgroup)	1–2	1467	727	740	Excluded	Not excluded	NA	NA
Feng[25]	56	56	Oral cavity	1–4	141	64	77	Excluded	Excluded	NA	42.55 (LNY > 20)
Barry[26]	60	60	Oral cavity	1–2	90	45	45	Excluded	Not excluded	NA	NA
Chen[27]	50 (mean)	89.83	Tongue	1–2	39	19	20	Excluded	Excluded	SND (82%)/MRND (18%)	NA
Bradley[28]	NA	NA	Tongue	1–4	40	23	17	Excluded	Not excluded	NA	NA

Abbreviations: LVI, lymphovascular invasion; MRND, modified radical neck dissection; NA, not available; ND, neck dissection; PNI, perineural invasion; SND, selective neck dissection.

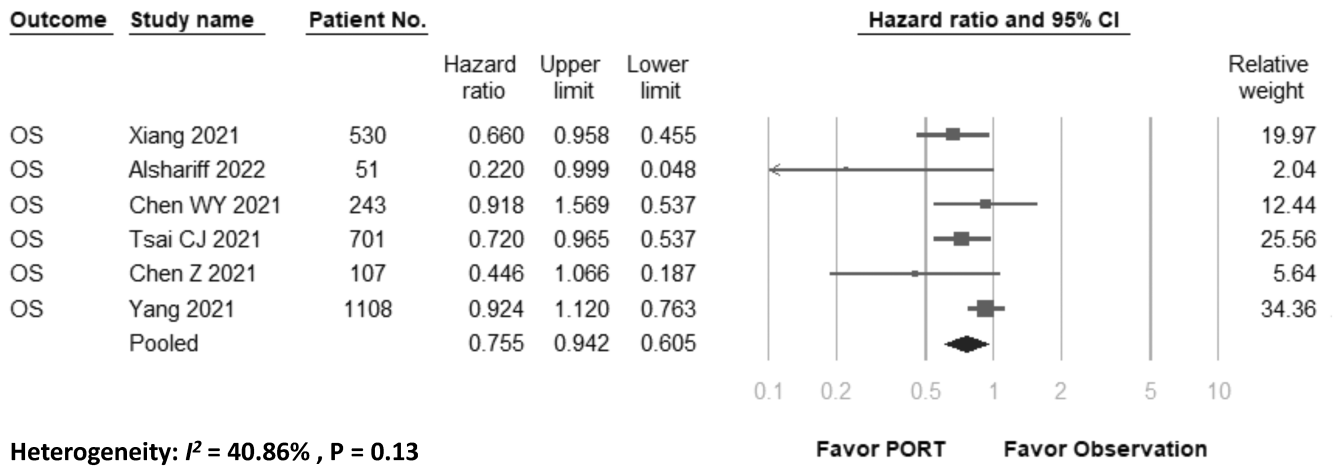

FIGURE 2 Forest plot of the meta-analysis regarding overall survival (OS) in studies related to pN1 patients, excluding the cases with ENE only. A random-effects model was applied.

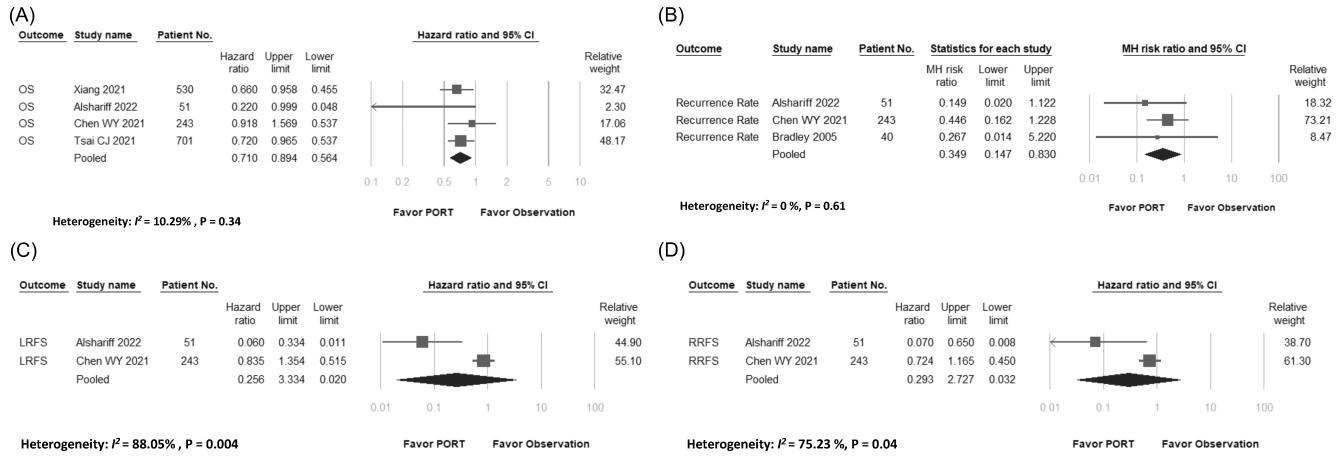

FIGURE 3 Forest plot of the meta-analysis regarding (A) overall survival (OS), (B) recurrence rate, (C) locoregional recurrence-free survival (LRFS), and (D) regional recurrence-free survival (RRFS) in studies related to pN1 patients excluding the cases with ENE and positive surgical margin. A random-effects model was applied.

OSCC patients and investigate the potential of PORT to enhance neck control and improve survival outcomes.

First, we extracted hazard ratios that were adjusted for important covariates from each study for meta-analysis. Our findings showed that PORT significantly improved OS in pN1 patients of most reports, which did not exclude any other pathological risk factor. As positive margins can be a profound confounding factor, the results further obtained after excluding them are less biased and more aligned with the answer in our clinical circumstances. Four studies focusing on pN1 OSCC cases without ENE had specifically excluded positive margins, and we found that the role of PORT on posttreatment outcomes based on our meta-analysis results remained significantly helpful in this subgroup, while the heterogeneity became relatively low compared to our first analyses without excluding the cases with positive surgical margins. Furthermore, in the current study, a significant difference in the regional recurrence rate was also found between the PORT and observation groups, indicating that PORT may reduce the rate of regional recurrence. However, the current study also attempted to present the results of LRFS and RRFS, but unfortunately, only two studies reported these specific outcomes, to makes it quite challenging to draw a definitive conclusion.

Three studies focused on even more specific clinical scenarios to investigate the role of PORT in pN1 OSCC patients after excluding the pN1 OSCC cases with positive pathological findings of surgical margins, perineural invasion, and lymphovascular invasions. Unfortunately, due to the relatively small case numbers, it was difficult to perform multivariate Cox regression model analysis, and therefore aHRs were not provided in these studies. RRs were extracted instead, and the meta-analysis shows no significant differences in OS neither DFS between the PORT and observation groups. However, caution must be exercised when interpreting such results. First, some heterogeneity existed in this analysis. In the study by Chen et al., which focused only on tongue OSCC patients and there were significant differences between the two groups in both survival outcomes, while the other

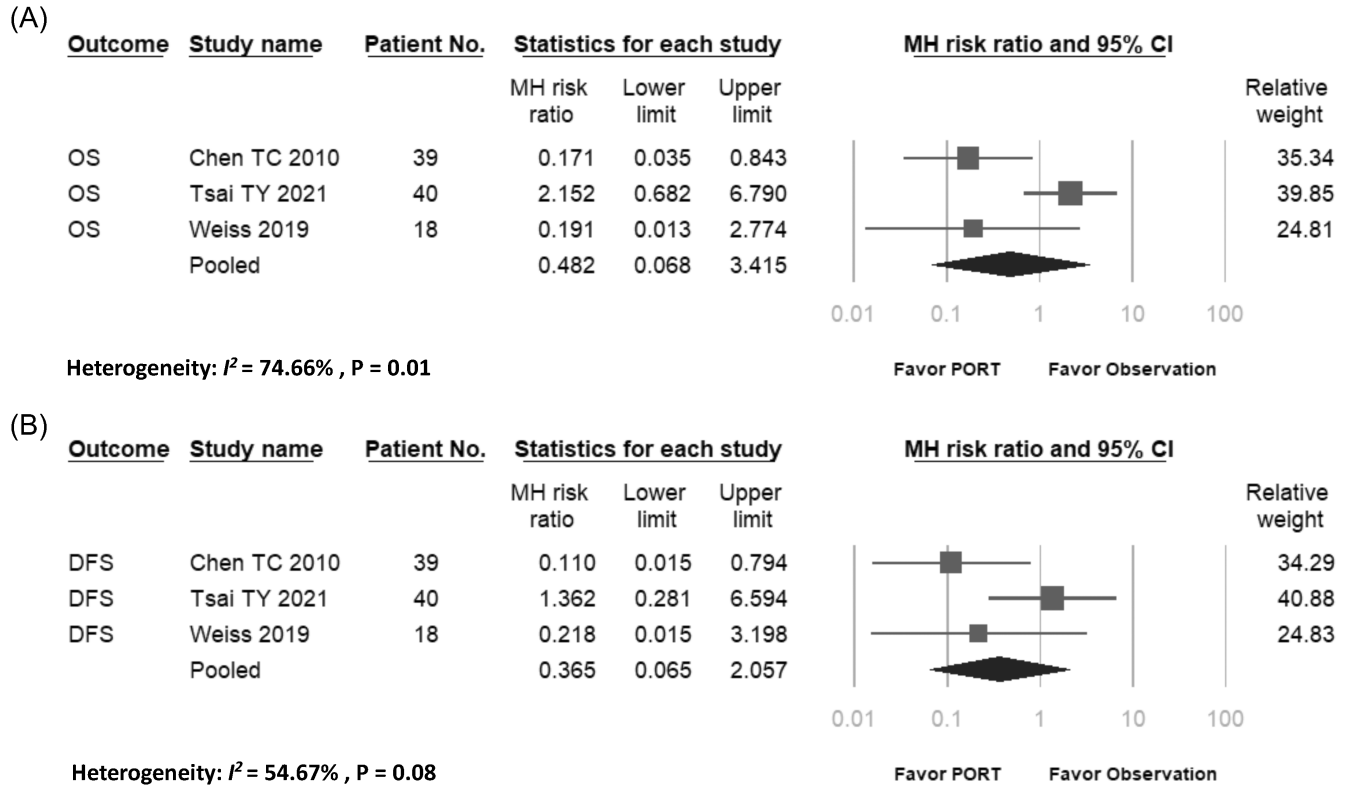

FIGURE 4 Forest plot of the meta-analysis regarding (A) overall survival (OS), (B) disease-free survival rate (DFS) in studies related to pN1 patients excluding the cases with ENE, margin positive, perineural invasion, and lymphovascular invasion. A random-effects model was applied.

two studies not specifically focusing on any subsite of the oral cavity showed no significant differences between the two groups.[7,23,27] The metastatic behavior of tongue OSCC tumors, such as more contralateral cervical metastasis or skip metastasis, may contribute to the divergent results.[30,31] Second, the number of studies and pooled case numbers were relatively limited. Therefore, although PORT seems to have no significant benefit on the survival of pN1 patients in the meta-analysis, it is still inconclusive whether such patients could be spared from PORT after surgery.

It is noteworthy that several studies included in the current meta-analysis have advocated the benefits of PORT for certain subpopulations of pN1 patients. Chen et al. recommend PORT for pN1 patients with histological Grade II or III tumors.[8] Feng et al. suggest that pN1 tongue OSCC patients without any other adverse histopathologic feature may also benefit from adjuvant radiotherapy if a lymph node yield was smaller than 20 at Levels I–III neck dissections.[25] In addition, the extent of the neck dissections was found to be another issue for pN1 OSCC patients. The prospective study conducted by Alshariff et al. indicated that completing the neck dissection to include all relevant cervical levels (I–V) does not influence OS or relapse-free survival, supporting the hypothesis that the removal of uninvolved lymph node stations does not improve the treatment outcome and is unnecessary.[12] Similarly, Chen et al. suggest that selective neck dissection may be appropriate for cN1 OSCC patients.[8] Taken together because most of the studies were retrospective in nature, there are still some differences with regard to the treatment recommendations for pN1 patients. We hope that in the future, more clinical trials or prospective studies could be conducted to provide more compelling evidence in the treatment of diverse clinical scenarios.

4.1 | Limitations of the study

It is important to acknowledge certain inherent limitations in the current study. The observed heterogeneity among the studies may be attributed to the fact that all of the eligible studies were retrospective, which may have led to some levels of variation in the quality of recorded clinicopathological factors. For example, the mean or median number of nodes removed with neck dissection, which reflected the quality of neck dissection, were only recorded in two eligible studies.[22,25] The pattern of regional failures, including in/out of field or unilateral/bilateral regional recurrences, was investigated in one study but not specific to the population of pN1 patients without ENE.[27] Furthermore, due to the limited number of eligible studies, a meta-regression to identify the source of heterogeneity could not be conducted. Finally, there may still be a presence of publication bias, as positive results are more likely to be published or reported in the literature. Given the limited number of studies included in our meta-analysis, although we still provided a funnel plot in the analysis regarding pN1 patients excluding ENE only, we refrained from performing

funnel plots and Egger's tests in accordance with the guidelines set forth by the Cochrane Collaboration.[32]

5 | CONCLUSIONS

In the present meta-analysis, PORT has been observed to improve OS significantly in pN1 OSCC patients. However, the efficacy of PORT in pN1 patients without ENE, positive surgical margins, more intermediate risk factors, such as close surgical margins, perineural invasion and lymphovascular invasion, remains uncertain, and further investigations with higher methodological rigor or prospective design are warranted to provide a more definitive answer to this inquiry.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Tsung-You Tsai https://orcid.org/0000-0002-2486-7317
Yenlin Huang https://orcid.org/0000-0002-9647-1135
Anna See https://orcid.org/0000-0003-2126-4665
Tung-Chieh Joseph Chang https://orcid.org/0000-0003-4227-0546
Kai-Ping Chang https://orcid.org/0000-0003-1777-9578

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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