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Comparison of sentinel lymph node biopsy and elective neck dissection for early oral cavity squamous cell carcinoma patients with clinically node-negative necks: systematic review and meta-analysis

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Review Article

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Abstract

Objective. This study aimed to compare the prognostic utility of sentinel node biopsy and elective neck dissection in early stage clinically node-negative oral cavity squamous cell carcinoma patients.

Method. PubMed, Scopus, Embase, Web of Science and Cochrane Library databases were searched up to March 2022. Hazard ratios, Kaplan–Meier curves, *p*-values and survival outcomes were extracted.

Results. Twelve studies involving 10 583 patients were included. No significant differences in overall survival between sentinel node biopsy and elective neck dissection groups were found. Heterogeneity was not detected in pooled overall survival, disease-free survival and disease-specific survival analyses (all I^2 less than 50). In subgroup analyses by follow-up period, sentinel node biopsy and elective neck dissection had similar prognostic value.

Conclusion. Sentinel node biopsy might be a valuable alternative to elective neck dissection for the management of early stage clinically node-negative oral cavity squamous cell carcinoma.

Introduction

Oral cavity squamous cell carcinoma (SCC) is the most common oral cancer, and many treatments have been evaluated.[1,2] However, the optimal method for evaluating neck nodes after removal of primary oral cavity lesions in patients with early oral cavity SCC (stage T_1 or T_2) free from lymph node metastasis (N_0) remains unclear. Neck node removal prevents clinical recurrence and significantly increases overall survival.[3,4] Metastasis to the cervical lymph nodes is very important in the prognosis, reducing survival by 50 per cent.[5] The risk of occult lymph node metastasis in oral cavity SCC patients of clinical stage N_0 is 20–30 per cent.[6,7]

Traditionally, elective neck dissection was considered for patients with early-stage oral cavity SCC. Several studies reported that this was better than watchful waiting (until metastasis developed).[8–10] Elective neck dissection improved survival and reduced the recurrence rate. However, elective neck dissection may be an unnecessarily invasive approach for patients at low risk of lymph node involvement.[8,9] As elective neck dissection can affect shoulder motility and cause persistent pain and scarring, an alternative is desirable.

Sentinel node biopsy represents a compromise between elective neck dissection and watchful waiting and has often been used to accurately detect occult neck node metastases.[11,12] Sentinel node biopsy involves the injection of a radiotracer or methylene blue dye to identify the lymph nodes that drain first from the primary cancer,[13,14] and sensitivity and accuracy are high.[15] However, long-term follow-up data are lacking, and the false-positive rate can reach 36 per cent.[15,16] Few reviews or meta-analyses have compared the utility of sentinel node biopsy and elective neck dissection, which we thus address herein. We also performed detailed subgroup analyses by follow-up period.

Materials and methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines[17] and recommendations for optimising literature searches for systematic surgical reviews.[18] The protocol was prospectively registered on the Open Science Framework (https://osf.io/agzkf/).

Relevant clinical studies were retrieved from PubMed, Scopus, Embase, the Web of Science and the Cochrane Central Register of Controlled Trials up to March 2022. The search terms were as follows: oral carcinoma, oral neoplasm, oral cavity neoplasms, neoplasm, oral cavity, oral cavity cancer, squamous cancer, sentinel node biopsy, elective neck dissection, prognosis, survival, hazard ratio, overall survival rate and disease-free survival. Reference lists were searched to ensure that no relevant studies were missed. Two independent reviewers removed irrelevant studies (i.e. those that did not discuss prognostic factors and survival rates) by reviewing the title, abstract and text.

The inclusion criteria were studies that had: comparison between sentinel node biopsy and elective neck dissection in terms of the prognosis of early stage (T_1 or T_2) oral cavity SCC patients; survival data and prognostic predictions including hazard ratios with 95 per cent confidence intervals (CIs) and/or overall survival, disease-free survival or disease-specific survival; human studies published in English; and exclusion of advanced oral cavity SCC (clinically confirmed staging (c)T_{3-4} or N_1) patients and those on drugs that might affect oral cavity SCC development.

The exclusion criteria were: reviews; case reports; studies on other head and neck cancers such as nasopharyngeal, oropharyngeal, hypopharyngeal or salivary cancer; and a lack of adequate prognostic data. The search strategy is shown in Figure 1.

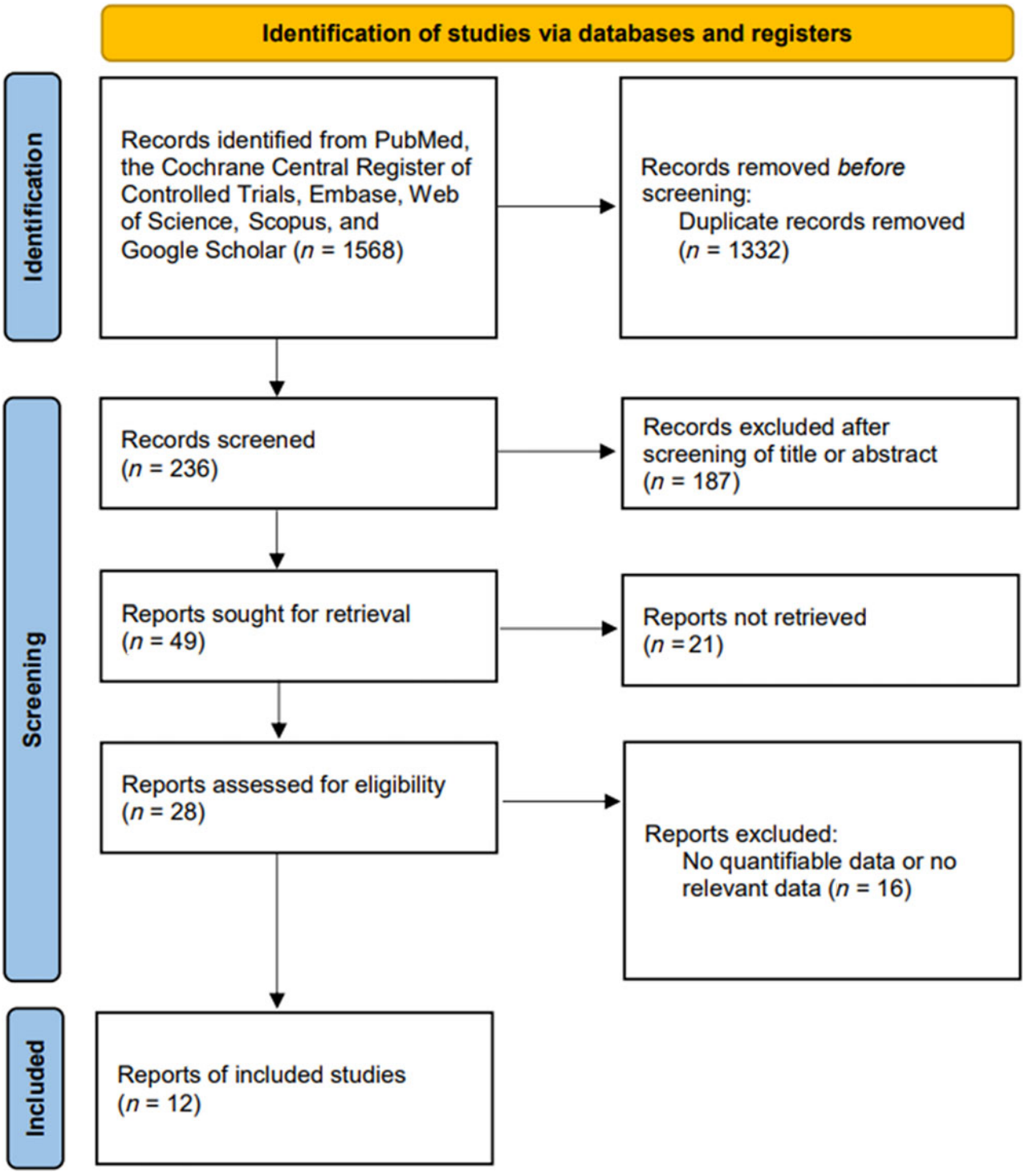

Fig. 1. Diagram of the selection of studies for meta-analysis.

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Table 1. The characteristics of the included studies

Study	Year	Design	Treated patients (*n*)	Sex (m/f)	Age (years, mean ± SD or median (range))	T-classification (T_1/T_2)	Control patients (*n*)	Sex (m/f)	Age (years, mean ± SD or median (range))	T-classification (T_1/T_2)	Tracer for sentinel node biopsy	Nation	Outcomes
Fan *et al.*,[20] 2014	2014	Retrospective cohort study	30	21/9	48	17/13	52	30/22	52	27/25	Lymphoscintigraphy, methylene blue	China	Disease-free survival (10 years), overall survival (3, 5, 10 years)
Chung *et al.*,[21] 2015	2015	Prospective cohort study	40	19/21	48.8 ± 14.1	29/11	21	6/15	55.9 ± 10.4	10/11	Lymphoscintigraphy, hand-held gamma probe	Korea	Disease-free survival (10 years), disease-specific survival (10 years), overall survival (10 years)
de Carvalho *et al.*,[22] 2016	2016	Retrospective cohort study	30	25/5	58.86	8/22	22	18/4	58.1	6/16	Lymphoscintigraphy, SPECT-CT scan	Brazil	Disease-free survival (10 years)
Hernando *et al.*,[23] 2016	2016	Prospective cohort study	32	23/9	65.8 (45–81)	17/15	41	28/13	66.7 (40–90)	19/22	Lymphoscintigraphy	Spain	Disease-free survival (5 years), overall survival (5 years), disease-specific survival (5 years)
Seferin *et al.*,[31] 2018	2018	Prospective cohort study	35	24/11	59.8 ± 10.4	27/8	35	28/7	61.9 ± 11.4	13/22	Lymphoscintigraphy with SPECT-CT, hand-held gamma probe	Brazil	Disease-free survival (5 years), overall survival (5 years), disease-specific survival (10 years)
Cramer *et al.*,[24] 2019	2018	Retrospective cohort study	240	133/107	NA	170/70	8088	4745/3343	NA	4039/4049	Not specified	USA	Overall survival (3 years)
Moya-Plana *et al.*,[25] 2018	2018	Prospective cohort study	179	151/78	56 (26–86) (total)	119/110 (total)	50				SPECT-CT, lymphoscintigraphy with a hand-held gamma probe	France	Disease-free survival (5 years), overall survival (5 years)
Sundaram & Subramanyam,[26] 2019	2019	Prospective cohort study	28	42/16	33–65 (total)	T_1 (25), T_2 (26), T_3 (7) (total)	30				Lymphoscintigraphy, hand-held gamma probe	India	Disease-free survival (5 years)
den Toom *et al.*,[27] 2020	2020	Retrospective cohort study	371	250/237	63 (55–69)	335/153	184	212/178	62 (53–70)	136/254	Lymphoscintigraphy with SPECT-CT, hand-held gamma probe	Netherlands	Disease-free survival (5 years), disease-specific survival (3, 5 years)
Garrel *et al.*,[28] 2020	2020	Randomised, controlled trial	140	88/52	60.8 ± 12.0	88/52	139	101/38	59.1 ± 10.9	91/52	Lymphoscintigraphy with transoral radiotracer injection	France	Disease-free survival (3, 5, 10 years), disease-specific survival (3, 5, 10 years), overall survival (3, 5, 10 years)
Hasegawa *et al.*,[29] 2021	2021	Randomised, controlled trial	134	89/45	63 (90–21)	26/108	137	90/47	63 (85–28)	25/112	Lymphoscintigraphy, hand-held gamma probe with or without single-photon emission computed tomography	Japan	Disease-free survival (3 years), overall survival (3 years)
Park *et al.*,[30] 2022	2022	Retrospective cohort study	91	59/32	51.27 ± 13.86	73/18	120	70/50	54.52 ± 13.34	138/73	Lymphoscintigraphy, hand-held gamma probe	Korea	Disease-free survival (5 years), overall survival (5 years)

m = male; f = female; SD = standard deviation; SPECT-CT = single-photon emission computed tomography–computed tomography; NA = not available

Table 2. Methodological quality of the included studies: Risk of Bias in Non-Randomized Studies of Interventions

Study	Confounding	Selection of participants	Classification of interventions	Deviations from interventions	Missing data	Measurement of outcomes	Selection of results
Fan *et al.*,[20] 2014	Low	Serious	Low	Low	Low	Low	Low
Chung *et al.*,[21] 2015	Low	Low	Low	Low	Low	Low	Low
de Carvalho *et al.*,[22] 2016	Moderate	Moderate	Low	Low	Low	Low	Low
Hernando *et al.*,[23] 2016	Moderate	Low	Low	Low	Low	Low	Low
Seferin *et al.*,[31] 2018	Low	Low	Low	Low	Low	Low	Low
Cramer *et al.*,[24] 2019	Low	Low	Low	Low	Low	Low	Low
Moya-Plana *et al.*,[25] 2018	Moderate	Moderate	Low	Low	Low	Low	Low
Sundaram & Subramanyam,[26] 2019	Moderate	Moderate	Low	Low	Low	Low	Low
den Toom *et al.*,[27] 2020	Moderate	Moderate	Moderate	Low	Low	Low	Low
Park *et al.*,[30] 2022	Serious	Moderate	Moderate	Low	Low	Low	Low

Table 3. Methodological quality of the included studies: Risk of Bias 2

Parameter	Randomisation	Deviations from interventions	Missing data	Measurement of outcomes	Selection of results
Garrel *et al.*,[28] 2020	Low	Low	Low	Low	Low
Hasegawa *et al.*,[29] 2021	Low	Low	Low	Low	Low

All data were extracted by two independent reviewers, who also assessed study quality. Differences were resolved by panel discussion. We recorded the first author, year of publication, country, type of cancer, and number, age, sex and T-stage of the patients. For overall survival, disease-free survival and disease-specific survival, hazard ratios (with 95 per cent CIs) were either described[19–31] or calculated as described by Tierney *et al.*[32] and Parmar *et al.*[33] If both multivariate and univariate analyses were used to evaluate overall survival, the hazard ratios and 95 per cent CIs generated by multivariate analysis were extracted.[34] The Risk of Bias in Non-Randomized Studies of Interventions ('ROBINS-I') and Cochrane risk of bias tool for randomised trials ('RoB 2') were used to assess study quality in line with the Grading of Recommendations, Assessment, Development, and Evaluations guidelines.[35,36]

R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was utilised for meta-analysis. Homogeneity was assessed using the Q statistic. The degree of heterogeneity was indicated by the I^2 value (76–100 per cent = high; 50–75 per cent = moderate; 25–49 per cent = low). Parameters with I^2 values less than 50 per cent were analysed using a fixed-effects model, whereas those with I^2 values more than 50 per cent were analysed with a random-effects model. Subgroup analyses were performed by follow-up period (3, 5 and 10 years). We used Begg's funnel plots and the Egger linear regression test to evaluate publication bias. For sensitivity analysis, we removed each item individually to assess its contribution to the observed effect.

Results

A total of 12 studies with 10 583 patients were included. Their characteristics and bias assessment results are shown in Tables 1, 2 and 3 in the supplementary material, available on *The Journal of Laryngology & Otology* website.

Overall, disease-free and disease-specific survival

We found no significant differences in overall survival (hazard ratio = 1.12; 95 per cent CI, 0.93 to 1.36), disease-free survival (hazard ratio = 1.08; 95 per cent CI, 0.88 to 1.33) or disease-specific survival (hazard ratio = 0.87; 95 per cent CI, 0.65 to 1.15) between sentinel node biopsy and elective neck dissection. Heterogeneity was not detected in analyses of pooled overall survival, disease-free survival and disease-specific survival data (I^2 less than 50) (Figure 2). Neither the Egger nor Begg's test showed any publication bias in terms of overall survival ($p = 0.84$) or disease-specific survival ($p = 0.76$) (Figure 3a and b). Although mild bias was apparently present in disease-free survival for sentinel node biopsy ($p = 0.00$; Figure 3c), the Duval and Tweedie trim and fill method showed no significant difference between the observed and adjusted values (hazard ratio, 1.08, $p = 0.47$ *vs* 1.04, $p = 0.71$). Thus, we concluded that the disease-free survival data were not biased. In the sensitivity analyses, the overall survival, disease-free survival and disease-specific survival data did not change on omission of any individual study (Figure 4).

Subgroup analyses

Most enrolled studies reported survival rates per different follow-up periods from 1 to 10 years and usually at 3, 5 and 10 years; we therefore performed subgroup analyses at these times. In all three subgroups, the survival outcomes (overall survival, disease-free survival and disease-specific survival) were consistently similar between sentinel node biopsy and elective neck dissection.

Discussion

To the best of our knowledge, this is the largest meta-analysis (including subgroup analyses by follow-up period) to compare

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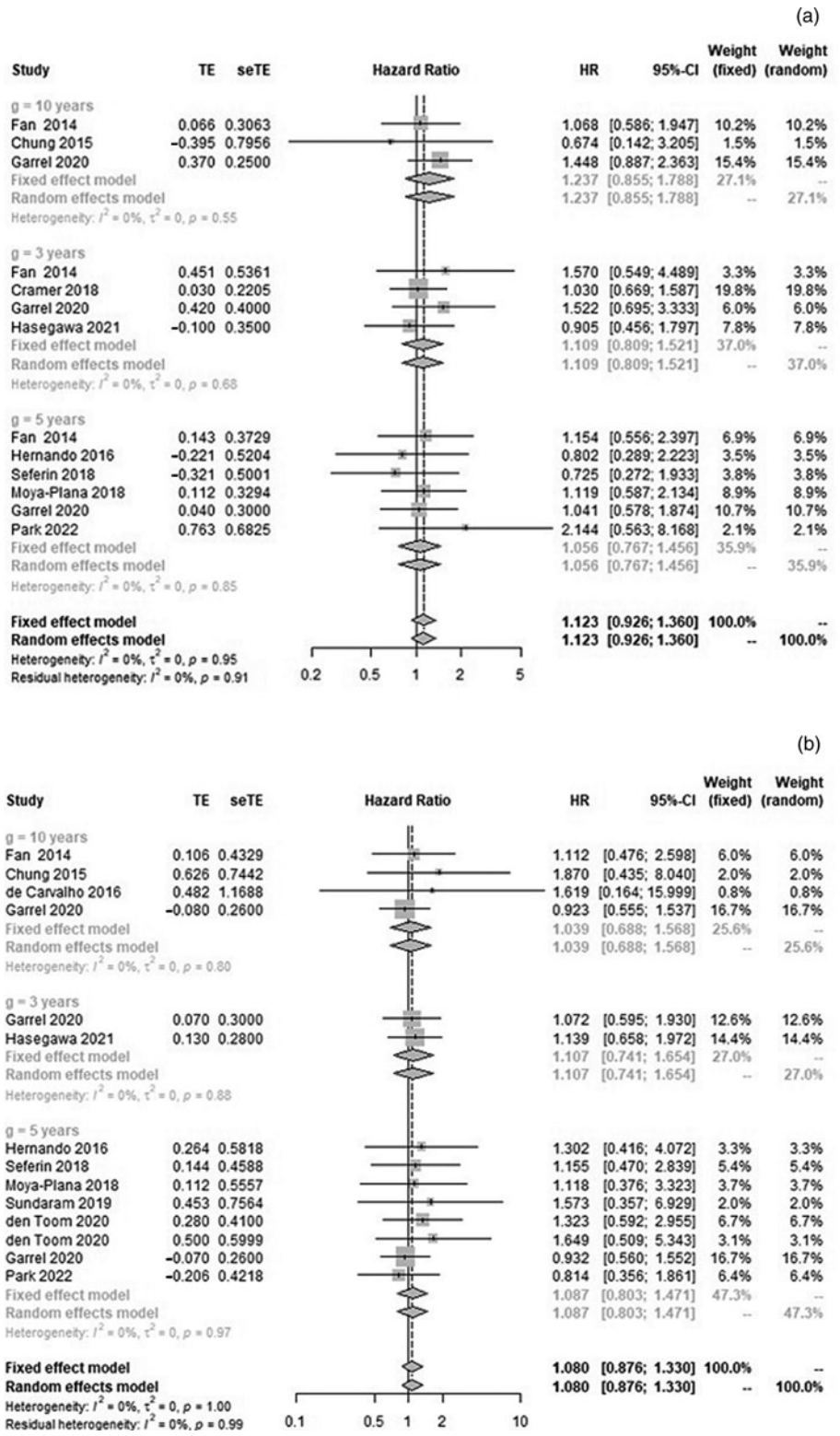

Fig. 2. Forest plots of (a) overall survival, (b) disease-free survival and (c) disease-specific survival. TE = estimated treatment effect; seTE = standard error of treatment estimate; HR = hazard ratio; CI = confidence interval

sentinel node biopsy with elective neck dissection for early-stage oral cavity SCC patients with clinically N_0 necks (no metastases). We found no significant difference in overall survival (hazard ratio = 1.12), disease-free survival (hazard ratio = 0.96), or disease-specific survival (hazard ratio = 1.08). Ding *et al.* reported similar five-year disease-free survival and overall survival in sentinel node biopsy and elective neck dissection groups in their review article.[9] However, they included only six prospective studies and did not discuss disease-specific survival. Saleem *et al.* found no significant difference in disease-free survival or overall survival between patients who underwent sentinel node biopsy and elective neck dissection.[37] However, unlike our study, their disease-free survival data were heterogeneous. Saleem *et al.*[37] included 10 studies in a meta-analysis, but one of those studies (Hiraki *et al.*[38]) compared sentinel node biopsy and no neck dissection groups. Recently, Gupta *et al.* found no significant difference in overall survival between sentinel node biopsy and elective neck dissection groups.[39] Isolated neck nodal and locoregional recurrences were compared, and there was no significant difference; however, only three studies were included.

Five of the studies included in our meta-analysis had high weights because of their large sample sizes.[20,24,27–29] However, subgroup analyses showed minimal heterogeneity. Thus,

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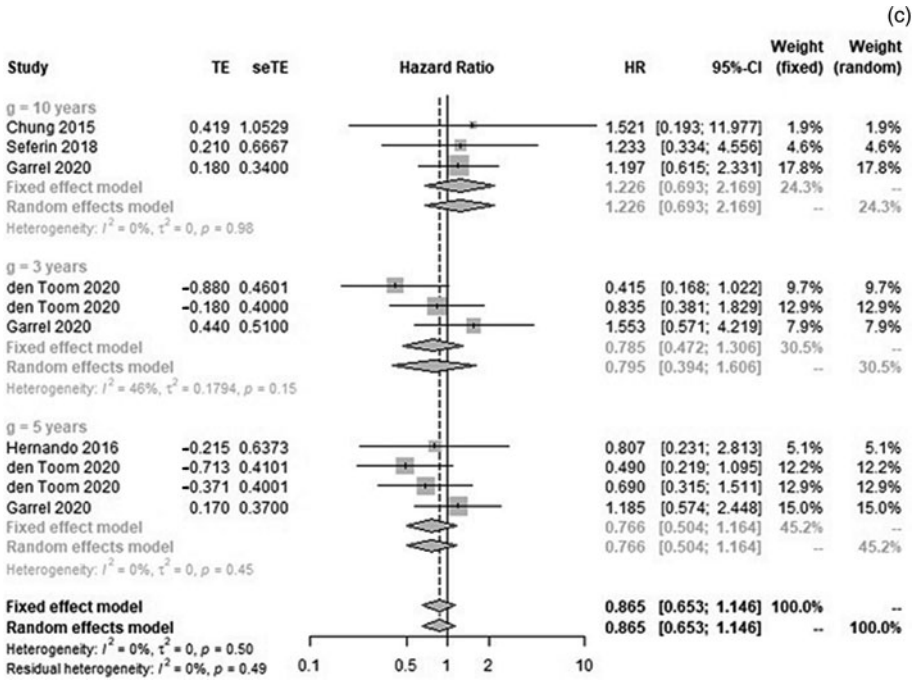

Fig. 2. (Continued).

although the studies varied somewhat in terms of design and quality, the variations did not affect the results, and the survival outcomes of sentinel node biopsy and elective neck dissection were similar. In contrast to Saleem *et al.*, we found no significant difference in overall survival, disease-free survival or disease-specific survival between sentinel node biopsy and elective neck dissection in any study (Figure 2), possibly because our subgroups were defined by follow-up period (3, 5 and 10 years).[9,37,39,40] Earlier meta-analyses did not perform subgroup analyses by follow-up period. In our analyses, the outcomes of sentinel node biopsy and elective neck dissection were similar. Also, we included three more papers than the largest previous meta-analysis.[37]

Sentinel node biopsy shows if there is a need for neck dissection; patients without neck node metastases can thus avoid unnecessary dissection. Elective neck dissection is associated with minimal complications.[41] The sensitivity of sentinel node biopsy for head and neck cancer was reported as 92 per cent[42]; in another study, it was 82.7 per cent, and the specificity was 98.1 per cent.[15,16,43] The Sentinel

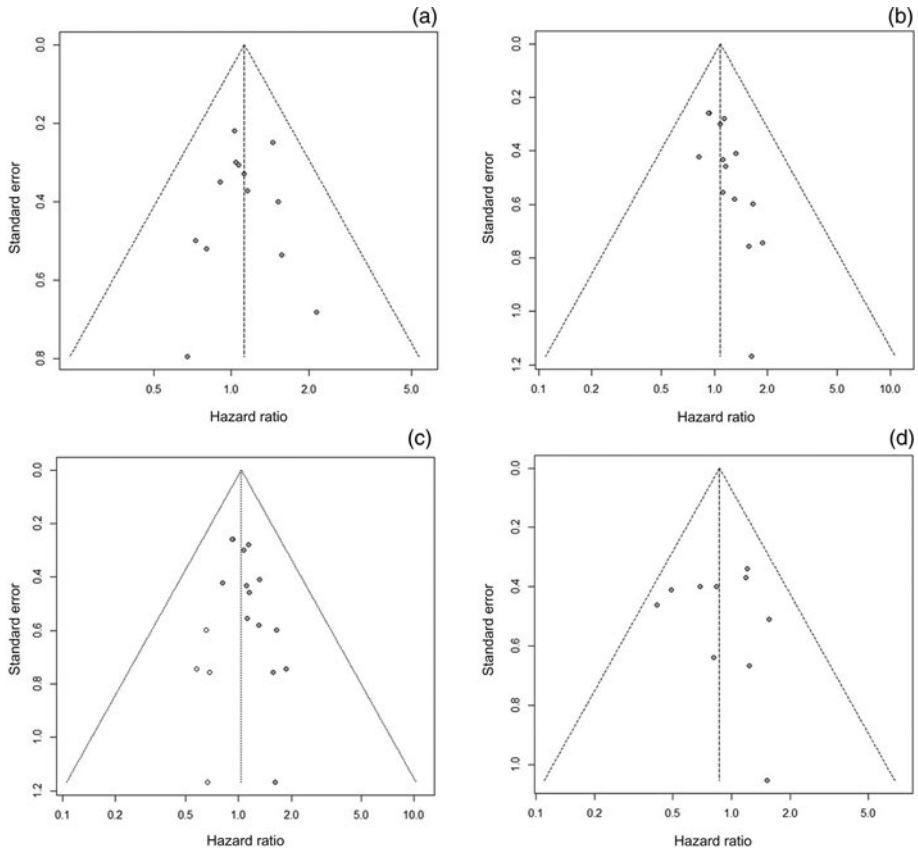

Fig. 3. Funnel plot of (a) overall survival, (b) disease-free survival, (c) trim filled disease-free survival and (d) disease-specific survival.

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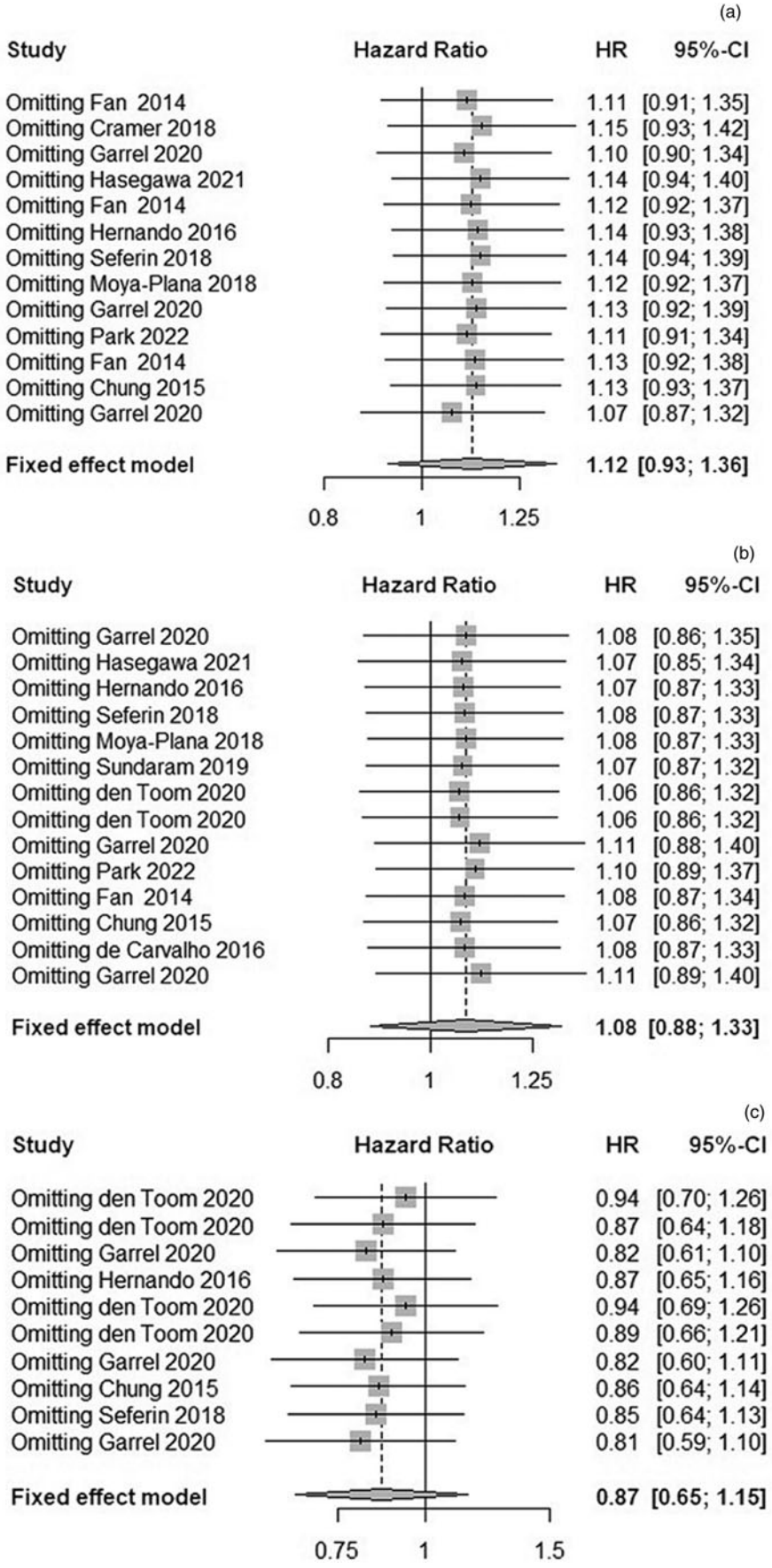

Fig. 4. Sensitivity analysis of (a) overall survival, (b) disease-free survival and (c) disease-specific survival. HR = hazard ratio; CI = confidence interval

European Node Trial recommended sentinel node biopsy for patients with clinical N_0 oral cavity SCC.[43] Sentinel node biopsy is also recommended by the National Comprehensive Cancer Network.[44] Sentinel node biopsy is also effective in patients with other cancers and is widely used to evaluate breast cancer patients without metastases.[12] However, sentinel node biopsy has certain disadvantages. The node closest to the injection site may be too bright, which can lead to error.[45]

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Also, radiotracers may reduce sentinel node biopsy effectiveness. In patients with other cancers, the use of methylene blue dye was associated with high false-negative rates. When methylene blue was combined with indocyanine green or a technetium-based radiotracer, sentinel nodes were effectively detected.[46] Sentinel node biopsy accuracy was enhanced by dynamic lymphoscintigraphy and the use of a same-day protocol.[47,48] Sentinel node biopsy tracers require further study.

The main strength of our meta-analysis is that it included 12 studies with 10 583 patients and showed publication bias in terms of overall survival or disease-specific survival (Figure 3). Some bias in terms of the disease-free survival for sentinel node biopsy was initially suggested, but the Duval and Tweedie trim and fill method indicated otherwise. Therefore, we concluded that the studies were not biased and the data are thus clinically relevant.

Our meta-analysis had some limitations. First, most of the included studies were non-randomised, so patient characteristics and tumour subsites may have differed among the groups, which would have slightly affected the results. However, few survival studies are randomised.[49] Garrel *et al.* included mainly early stage oral cavity SCC patients with no clinical lymph node metastases, but also a small number of oropharyngeal cancer patients (less than 13 per cent).[28] Patients with human papillomavirus-positive oropharyngeal cancer have good prognoses and should be analysed separately.[50] Sundaram and Subramanyam included mainly T_1 and T_2 patients but also a small number of T_3 patients (less than 13 per cent).[26] Second, the tracers differed among the included studies. Several studies used tracers detectable by single-photon emission computed tomography–computed tomography,[22,25,27,31] but Hasegawa *et al.* used a tracer evident on single-photon emission–computed tomography.[29] Third, we lacked data on smoking history and co-morbidities, which may affect survival.

Conclusion

Our meta-analysis addressed the problems of previous meta-analyses and also included more studies. The overall survival, disease-free survival and disease-specific survival did not differ significantly between early-stage oral cavity SCC patients without clinical neck metastases undergoing sentinel node biopsy and elective neck dissection. Sentinel node biopsy, which has no life-threatening side effects, is preferable to elective neck dissection for patients with early stage clinically node-negative oral cavity SCC.

Competing interests. None declared

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S0022215122002043

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