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Original Research

Is selective neck dissection effective for N1 (Level I)? A systematic review

Nobuhiro Ueda^a, Daisuke Takeda^{b,*}, Hiroshi Hijioka^c, Masatoshi Adachi^d, Hidemichi Yuasa^e,
Narikazu Uzawa^f, Hiroshi Kurita^g

^a Department of Oral and Maxillofacial Surgery, Nara Medical University, 840, Shijo-cho, Kashihara, 634-8522 Nara, Japan

^b Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

^c Department of Maxillofacial Diagnostic and Surgical Science, Field of Oral and Maxillofacial Rehabilitation, Graduate School of Medical and Dental Sciences, Kagoshima University, 8-35-1 Sakuragaoka, Kagoshima 890-8544, Japan

^d Department of Oral and Maxillofacial Surgery, Akiru Municipal Hospital, Tokyo, Japan

^e Department of Oral and Maxillofacial Surgery, National Hospital Organization Toyohashi Medical Center, 50, Imure-cho Aza Hamamichi – Ue, Toyohashi, Aichi 440-8510, Japan

^f Department of Oral and Maxillofacial Surgery II, Osaka University Graduate School of Dentistry, 1-8 Yamadaoka, Suita, Osaka 565-0871, Japan

^g Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan



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ABSTRACT

Objective: This systematic review and meta-analysis aimed to compare the effectiveness of selective neck dissection (SND) and comprehensive neck dissection (CND) in patients with oral squamous cell carcinoma N1 (Level I).

Methods: Randomized controlled trials and prospective and retrospective non-randomized clinical studies were selected and evaluated for the certainty of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The statistical analysis was performed using Review Manager 5.4 software.

Results: We included one observational study. The analysis revealed no difference in survival rates (overall survival, disease-specific survival, and regional control) between SND and CND for oral squamous cell carcinoma N1 (level I) cases. In the included study, the risk of bias was high, total sample size was small, and certainty of evidence was rated as "very low."

Conclusion: This systematic review and analysis suggested no difference in effectiveness between SND and CND; however, a high certainty of evidence could not be determined. Such evidence needs to be established through future systematic reviews, including randomized controlled trials with larger sample sizes.

1. Introduction

The clinical treatment of oral squamous cell carcinoma (OSCC) with cervical lymph node metastasis clinically involves neck dissection (ND) along with simultaneous resection of the primary tumor. However, cosmetic, and functional defects such as shoulder syndrome and persistent neck and shoulder pain resulting from radical ND (RND), prompted the search for minimally invasive methods that can address neck metastases (cN+) while maintaining oncologic outcomes. These clinical challenges led to the development of modified RND (MRND) which preserves vital structures like the sternocleidomastoid muscle, jugular vein, or spinal accessory nerve (SAN). Consequently, selective neck dissection (SND) has emerged as a technique that conserves one or

more lymph node levels [1,2].

Traditionally, therapeutic ND has been advocated for patients diagnosed with cN+, typically involving RND or MRND [3]. Certain studies propose employing SND to excise lymph nodes commonly affected by metastases from the oral cavity, including those located above the hyoid muscle (levels I–III and possibly upper level IV) [4,5]. However, conflicting findings suggest that SND should be considered for cN+ patients regardless of N classification [6,7]. Cervical lymph node metastasis is the most important prognostic factor in oral cancer, and the treatment should vary depending on N classifications (cN+). Therefore, careful consideration is required when determining SND indication.

SND is increasingly being employed in cN1 (Level I) cases. Nonetheless, the adoption of SND remains contentious within the literature,

* Corresponding author.

E-mail address: dsktkd@med.kobe-u.ac.jp (D. Takeda).

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#	Search terms
1	Tongue Neoplasms"[Mesh] OR "Palatal Neoplasms"[Mesh] OR "Gingival Neoplasms "[Mesh] OR "Mouth Neoplasms"[Mesh] OR "Head and Neck Neoplasms"[Mesh:NoExp]
2	"diphosphonates"[MeSH Terms] OR "bisphosphonate"[Title/Abstract] OR "alendronate"[MeSH Terms] OR "clodronic acid"[MeSH Terms] OR "etidronic acid"[MeSH Terms] OR "ibandronic acid "[MeSH Terms] OR "pamidronate"[MeSH Terms] OR "risedronic acid"[MeSH Terms] OR "zoledronic acid"[MeSH Terms] OR "minodronic acid"[Title/Abstract]
3	"malignant"[Title/Abstract] OR "carcinom*"[Title/Abstract] OR "neoplas*"[Title/Abstract] OR "cancer"[Title/Abstract] OR "tumor" [Title/Abstract]
4	#1 OR (#2 AND #3)
5	"neck"[Title/Abstract] OR "necks"[Title/Abstract] OR "lymph"[Title/Abstract] OR "lymphs"[Title/Abstract]
6	"dissection"[Title/Abstract] OR "dissections"[Title/Abstract]
7	#5 AND #6
8	"lymph node excision"[MeSH Terms]
9	#7 OR #8
10	"modified*"[All Fields]
11	"select*"[All Fields]
12	"elect*"[All Fields]
13	"therapeuti*"[All Fields]
14	#10 OR #11 OR #12 OR #13
15	#4 AND #9 AND #14

Fig. 1. Search terms and results from MEDLINE databases.

particularly when evaluating its efficacy concerning oncologic outcomes in comparison to comprehensive neck dissection (CND). Systematic reviews (SR) or meta-analyses on the reduction of dissection extent with a guaranteed cure rate for cN1 (Level I) have not been conducted. Consequently, our objective was to conduct a systematic review and meta-analysis of the available data pertaining to the outcomes of CND and SND in patients with primary oral cancer classified as cN1 (Level I).

2. Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [8,9].

2.1. Eligibility criteria

The eligibility criteria for this review included the population, interventions, comparisons, outcomes, and study design (PICOS). The included populations were previously untreated, distant metastasis-free, histologically newly diagnosed patients with resectable oral cancer and N1 (Level I) metastases. The interventions involved SND, and comparisons were made with CND.

2.2. Literature selection criteria

Priority was given to clinical practice guidelines (CPG) or SRs that met the eligibility criteria. When no CPGs or SRs met the recruitment criteria, randomized controlled trials (RCTs) meeting the recruitment criteria were targeted, and SR was conducted. When no CPGs, SRs, or RCTs met the recruitment criteria, SRs were conducted for prospective and retrospective observational clinical studies, case reports, and case series.

2.3. Literature search

This review was conducted as an update to the Joint committee from the Clinical Practice Guideline for Oral Cancer Revision Committee of the Japanese Society of Oral Oncology & the Clinical Practice Guidelines for Oral Cancer Formulation Committee of The Japanese Society of Oral and Maxillofacial Surgeons previously ongoing Clinical Practice Guideline for Oral Cancer. A search was conducted for articles published since the search conducted in CPG for Oral Cancer 2019 [10]. The search was conducted using the MEDLINE databases and the Cochrane Central Register of Controlled Trials (CENTRAL), whereas the Ichushi web was used for literature published in Japan. The search strategy combined

medical subject headings (MeSH) words and search terms. In the literature search, CPGs/SRs, RCTs, prospective and retrospective observational clinical studies, case reports, and case series were selected in this order. The reports were in English or Japanese, and conference abstracts and reviews were excluded. Fig. 1 illustrates the search strategy. The literature search was completed on March 29, 2022.

2.4. Inclusion criteria

The inclusion criteria involved studies: (1) including patients aged 18 years or older, (2) focused on ND for delayed neck metastases, (3) focused on patients with cN1 (level I) cervical lymph node metastases confirmed on preoperative examination (regardless of the presence or absence of lymph node metastasis on postoperative pathology), (4) where preoperative lymph node metastases were evaluated using different diagnostic modalities (with or without fluorodeoxyglucose positron-emission tomography or fine-needle aspiration), (5) including at least 20 % of patients with oral cancer (even if less than 20 % of the patients had oral cancer, they were included if stratification was performed and only patients with oral cancer were identified), and (6) with at least 90 % of the patients having squamous cell carcinoma.

2.5. Exclusion criteria

The exclusion criteria involved studies: (1) including patients younger than 18 years of age, except for studies that stratified patients and only included adults; (2) focused on surgery for recurrence in the surgical neck; and (3) with fewer than 20 eligible patients in each group.

2.6. Outcomes

The primary outcomes extracted were overall survival (OS), disease-specific survival (DSS), regional control, and treatment complications such as shoulder syndrome and chronic neck and shoulder pain. This meta-analysis was limited to human trials. Studies originating from the same institution reporting distinct populations at non-overlapping intervals and trials conducted by different authors were also incorporated.

2.7. Study selection procedure

The eligible studies were selected in two phases. In the first phase, two authors independently screened the titles and abstracts. In the second phase, the two authors independently evaluated the full texts of all potentially eligible studies identified in the first phase. Based on the

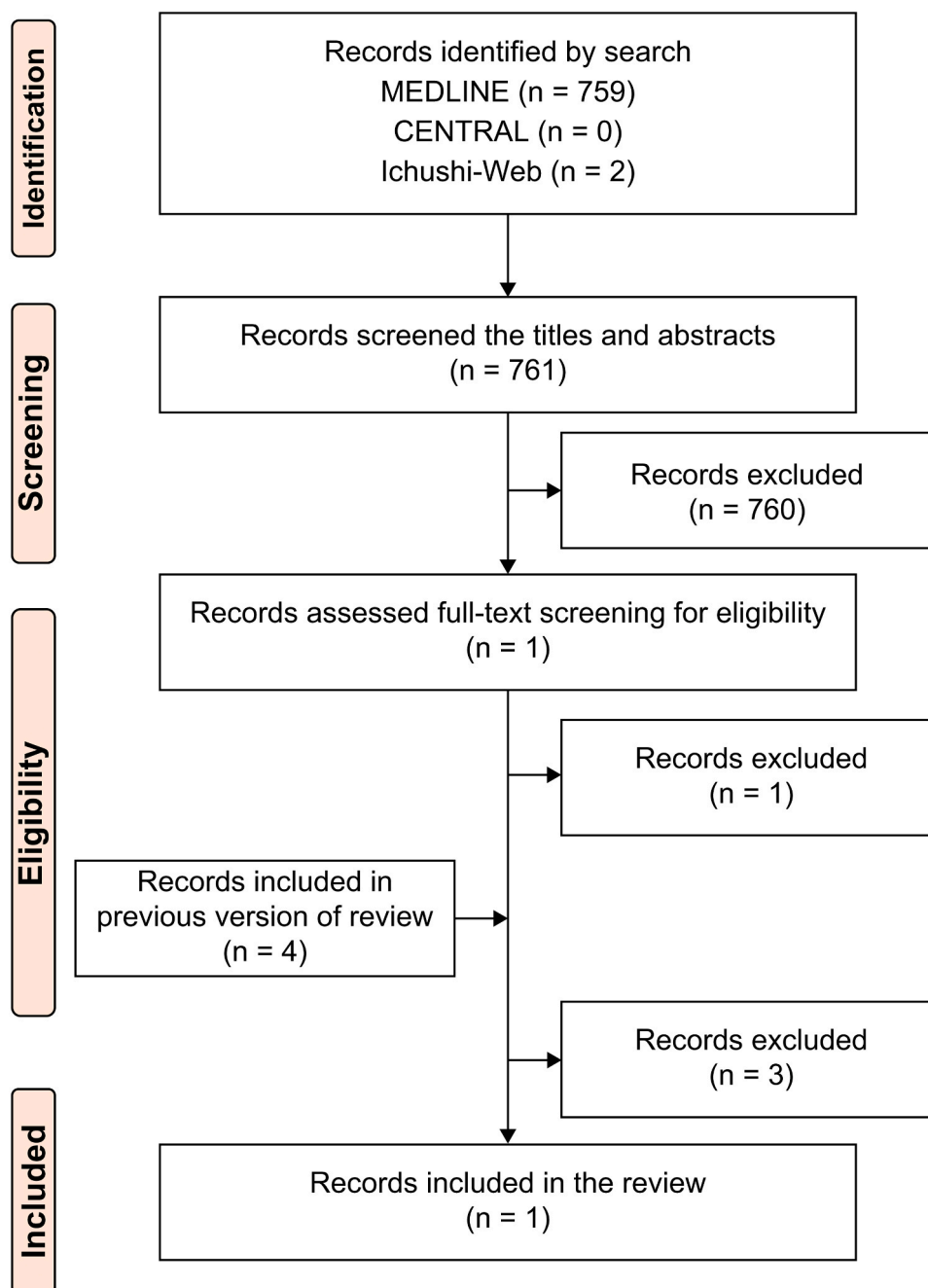


Fig. 2. Flowchart illustrating the study selection process for the systematic review.

inclusion and exclusion criteria, irrelevant studies identified during the full-text evaluation were excluded. In the case of a conflicting choice between the two authors, a third author was involved, and consensus was reached through discussion.

2.8. Statistical analysis

The statistical analysis was performed using the Review Manager 5.4 software [11]. Hazard ratios (HR) for OS and DSS were calculated, while risk ratios (RR) for regional control were determined and reported with 95 % confidence intervals (CI).

2.9. Certainty of evidence

The risk of bias in the included studies for the SR was evaluated using

a tool for assessing the risk of bias in observational studies [12,13]. In each domain, a quality assessment was performed to ascertain whether the bias was low risk (+), high risk (-), or if there were any concerns (?). Two independent reviewers conducted the evaluation, and when a choice was disputed, a third author was consulted to facilitate a consensus through discussions. Certainty of evidence was evaluated according to the procedures developed by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group [12].

3. Results

3.1. Literature search and selection results

Fig. 2 depicts the PRISMA flow diagram. A search using MEDLINE,

Table 1
Characteristics of the studies included in the systematic review.

Author	Year	Population	Clinical N stage	Types of SND	Types of CND
Yanai	2012	68	cN1 (level I)	SMND	RND

Abbreviations: SND: selective neck dissection, CND: comprehensive neck dissection, SMND: submandibular neck dissection, RND: radical neck dissection.

CENTRAL, and Ichushi-web yielded 761 records with no duplicates (MEDLINE: 759, CENTRAL: 0, and Ichushi-web: 2). After screening the titles and abstracts of all 761 articles, 760 were excluded. The full-text screening was then performed on one study [14]. Subsequently, this study was excluded due to its inclusion of patients beyond the scope of N1 (Level I). The full-text screening was then performed on the four studies [15–18] extracted from the CPG for Oral Cancer 2019 search, and of these, three studies were excluded because the included patients did not meet our inclusion criteria. After completing the literature search, one retrospective observational clinical study was identified and included in the final analysis [16].

3.2. Data extraction

Tables 1 and 2 show the characteristics of the included studies. Each reviewer extracted data, collecting information such as author, year of publication, population, intervention, comparison, outcome, and prognosis. Notably, treatment complications were not described in the included RCTs.

3.3. Quality assessment of included studies

A retrospective observational study was included. Table 3 presents an assessment of the risk of bias. In the included studies, prognoses were calculated by excluding patients with positive surgical margins at the primary tumor site. Moreover, approximately half of the patients received neoadjuvant chemoradiotherapy, which is not a commonly indicated therapy. These factors may have influenced the quality of the evidence. Therefore, these results should be interpreted with caution.

3.4. Outcome evaluation of analysis

Fig. 3 displays the forest plots and statistical analyses regarding HR and RR. The analysis revealed no significant differences in OS (HR, 0.98; 95 % CI, 0.36–2.67, $p = 0.97$) (Fig. 3A) and DSS (HR, 0.90; 95 % CI, 0.21–3.86, $p = 0.88$) between SND and CND (Fig. 3B). The regional control results (RR, 1.13; 95 % CI, 0.40–3.14, $p = 0.82$) indicated no difference between SND and CND (Fig. 3C).

3.5. Certainty of evidence

The outcomes of OS, DSS, and regional control had very low certainty of evidence (Table 4). The absolute risk reductions were as follows: there were four fewer events per 1000 patients for OS (136 fewer to 267 more), 15 fewer events per 1000 patients for DSS (129 fewer to 339 more), and 22 more events per 1000 patients for regional control (100 fewer to 357 more).

Table 2
Characteristics of regional recurrences and survival.

Group	Population	Primary tumor site					Ipsilateral neck recurrence	Contralateral neck recurrence	Overall neck recurrence	Disease-specific death	Overall death
		Tongue	Lower gum	Upper gum	Buccal mucosa	Oral floor					
SND	32	14	11	3	1	3	4	2	6	6	7
CND	36	13	14	4	3	2	1	5	6	6	8

Abbreviations: SND: selective neck dissection, CND: comprehensive neck dissection.

*Although the number of events is not stated in the text, we obtained the information directly from the authors.

4. Discussion

This SR provide the latest comprehensive scientific evidence on SND for resectable oral cancer without distant metastasis (regardless of the primary site, cN1 [Level I]). The inclusion of a retrospective observational study did not yield any significant differences in OS, DSS, and regional control outcomes between SND and CND.

In OSCC, the risk of cervical lymph node metastases is high in levels I–III; hence, SND including those levels may be indicated [19,20]. Pantvaidya et al. conducted a prospective study on ND in 553 OSCC cases [21]. They reported that 91 % of positive lymph nodes were found in levels I–III, with 3.3 % metastasizing to level V. Multivariate analysis revealed that IIA positivity was an independent predictor of metastasis in IIB and V. A study of 129 SNDs in 106 head and neck squamous cell carcinomas included 57 N1 [22]. Five-year actuarial DSS in N1 was 88.1 %, and the five-year actuarial failure rate in the neck was 6.7 %, indicating favorable results for SND in N1. Kakei et al. [23] performed CND in 100 patients with cN1 oral cancer and discovered that two patients had metastasis to level IV, and none had to level V. These results may be attributed to the flow pattern from the oral cavity to the lymphatics in the neck; therefore, SND with the omission of the lower level of metastatic risk may be a suitable approach.

Two SRs on the adaptation of SND to cN+ were identified; however, they were not employed in this review because the patients were limited to those with N1 (level I) [6,7]. Both SRs lacked RCTs and were solely conducted on observational studies. The SR by Liang et al. [6] included only OSCC, and the SR by Rodrigo et al. [7] included squamous cell carcinoma of the head and neck. However, oral cancer accounted for approximately 80 % of the articles included in the SRs. The only

Table 3
Assessment of the risk of bias of the included observational studies.

Author, year	Outcome	Domain 1	Domain 2	Domain 3	Domain 4
Yanai, 2012	Overall survival	*1	*2	*4	
	Disease-specific survival	*1	*2	*4	
	Regional control	*1	*3	*4	

Domain 1: Failure to develop and apply appropriate eligibility criteria (inclusion of control population).

Domain 2: Flawed measurement of both exposure and outcome.

Domain 3: Failure to adequately control confounders.

Domain 4: Incomplete or inadequately short follow-up.

: Low risk, : Some concerns, : High risk.

*1: Cases of positive surgical margins at the primary tumor have been excluded.

*2: The evaluation event is death.

*3: Power Doppler ultrasound (US) and enhanced computed tomography (CT) are used in conjunction to diagnose metastatic lymph nodes.

*4: There are cases in which neoadjuvant chemoradiotherapy was performed.

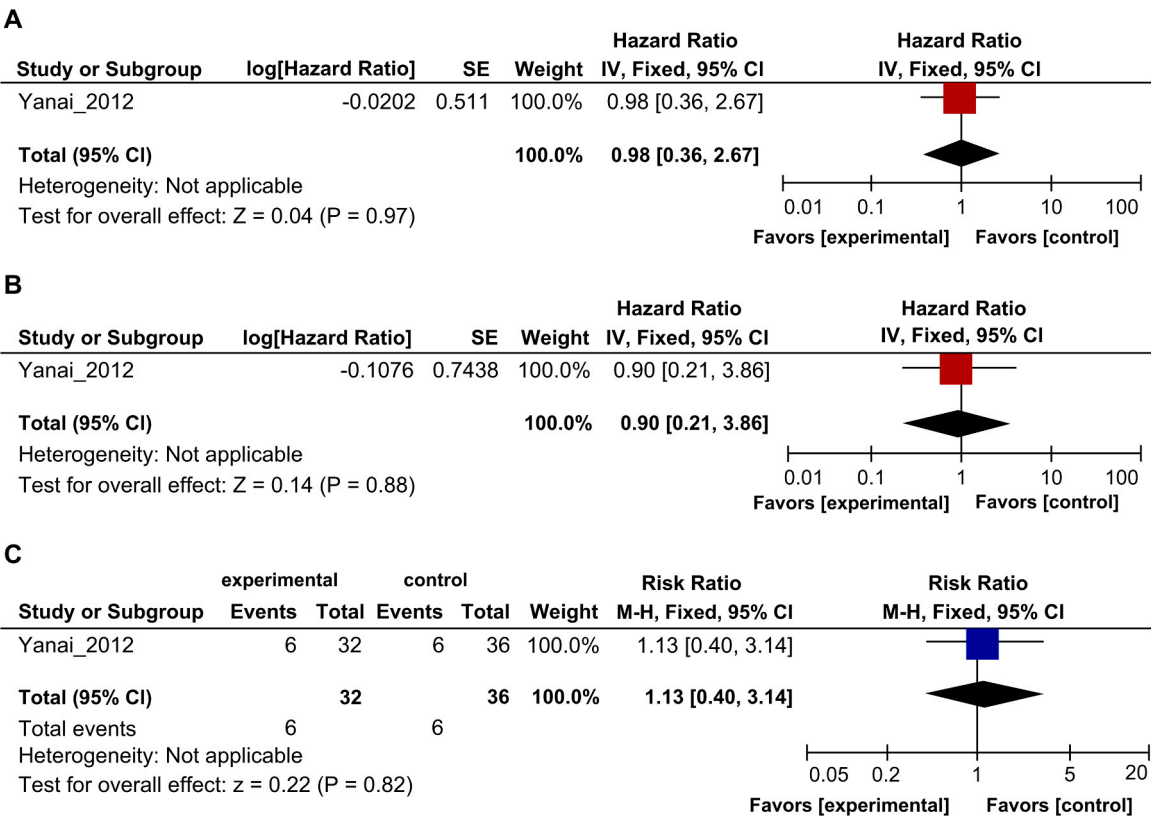


Fig. 3. Forest plots of the analysis. A. Forest plots of the analysis for overall survival using hazard ratios. B. Forest plots of the analysis for disease-specific survival using hazard ratios. C. Forest plots of the analysis for regional control using risk ratios.

Table 4
Summary of findings.

Outcomes	Number of participants	Certainty of the evidence (GRADE)	Relative effect (95 % CI)	Anticipated absolute effects	
				Risk with comprehensive neck dissection	Risk difference (per 1000 patients) (95 % CI)
Overall survival (HR)	36 (one retrospective study)	⊕○○○ Very Low ^{a,b,c}	HR 0.98 (0.36–2.67)	222 per 1000	4 fewer per 1000 (136 fewer to 267 more)
Disease-specific survival (HR)	36 (one retrospective study)	⊕○○○ Very Low ^{a,b,c}	HR 0.90 (0.21–3.86)	167 per 1000	15 fewer per 1000 (129 fewer to 339 more)
Regional control (RR)	68 (one retrospective study)	⊕○○○ Very Low ^{a,b,c}	RR 1.13 (0.40–3.14)	167 per 1000	22 more per 1000 (100 fewer to 357 more)

Selective versus comprehensive neck dissection for cN1 (level I) oral cancer.
Populations: patients with previously untreated, distant metastasis-free, resectable N1 (Level I) oral cancer.
Interventions: selective neck dissection.
Comparisons: comprehensive neck dissection.
Abbreviations: HR, hazard ratio; CI, confidence interval; RR, risk ratio; GRADE, grading of recommendations, assessment, development, and evaluation.

^a Downgraded once due to risk of bias.
^b Downgraded once due to indirectness.
^c Downgraded once due to imprecision.

retrospective observational study [16] incorporated in this review was one that was included in a previously conducted SR; however, it was excluded by the others because it involved more preoperative treatment. Liang et al. [6] discovered no significant difference in OS, DSS, and regional control between SND and CND. Rodrigo et al. [7] observed no significant difference in regional control outcomes between SND and CND. They concluded that SND is a valid option for patients with cN1 and selected cN2 neck diseases (non-fixed nodes, absence of palpable metastases at level IV or V, or large volume >3 cm multiple lymph nodes at multiple levels).

Furthermore, SND is adapted to reduce long-term complications due to CND, with the most frequent complication being shoulder syndrome due to dissection or injury to the SAN. Shoulder syndrome is primarily

characterized by pain, limited shoulder abduction, full passive range of motion, and anatomical deformities such as scapular flaring, droop, and protraction, which reduce patients' quality of life [24,25]. The SAN emerges from the skull base and traverses through levels two and five of the neck before entering the trapezius muscle. Recent SR [26] have reported a 1.3–81.8 % rate of SAN injuries after MRND, with an estimated prevalence of 33.0 %. However, this complication is greatly reduced by SND indication, which omits level-five dissection. Recently, preserving level 2b in cN0 patients with OSCC further reduces the shoulder syndrome considering that latent metastases at level 2b are rarely observed in these patients [27,28].

Furthermore, besides ND level, other factors, such as need for transcervical (pull-through) resection of the primary tumor, need to be

considered with regards to patient survival. The intervening floor of the mouth must be sacrificed to reduce recurrence in the area between the primary site and the neck. Hence, reconstruction is often required, and functional morbidity is high. Therefore, indications are often debated. In addition, resection of the lymph nodes at the root of the lingual artery, which is beyond the limits of cervical dissection, should also be considered [29,30]. Additionally, researchers agree that combining ND and adjuvant radiotherapy improves survival [31]. However, there is ongoing debate regarding the circumstances under which patients with OSCC should receive adjuvant radiotherapy or chemoradiotherapy to the dissected neck. In addition to the considerations of this review, high-quality research in various areas is required to obtain good survival and high quality of life in OSCC management.

4.1. Limitation

This review had some limitations. Only one retrospective observational study of cN1 (level I) was recruited for this SR. The study included many cases in which neoadjuvant chemoradiotherapy was performed and excluded cases with positive surgical margins. Therefore, the quality assessment had limitations regarding bias risk, indirectness, and imprecision. Another limitation is that the study could not examine harm-related outcomes commonly known as shoulder syndrome and chronic neck and shoulder pain.

5. Conclusions

Our SR suggests no significant difference in survival rates between SND and CND. However, the quality of evidence was very low, providing little confidence in the estimated effects. Therefore, the results may not be applicable to all cN1 (level I) oral cancers. In the future, conducting RCTs with larger sample sizes becomes imperative to more comprehensively evaluate the effectiveness of SND in this patient population.

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Declaration of Interest statement

All authors have no conflicts of interest.

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