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Review

Selective neck dissection in surgically treated head and neck squamous cell carcinoma patients with a clinically positive neck: Systematic review☆

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ABSTRACT

Adequate treatment of lymph node metastases is essential for patients with head and neck squamous cell carcinoma (HNSCC). However, there is still no consensus on the optimal surgical treatment of the neck for patients with a clinically positive (cN+) neck. In this review, we analyzed current literature about the feasibility of selective neck dissection (SND) in surgically treated HNSCC patients with cN + neck using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. From the reviewed literature, it seems that SND is a valid option in patients with cN1 and selected cN2 neck disease (non-fixed nodes, absence of palpable metastases at level IV or V, or large volume ->3 cm- multiple lymph nodes at multiple levels). Adjuvant (chemo) radiotherapy is fundamental to achieve good control rates in pN2 cases. The use of SND instead a comprehensive neck dissection (CND) could result in reduced morbidity and better functional results. We conclude that SND could replace a CND without compromising oncologic efficacy in cN1 and cN2 cases with the above-mentioned characteristics.

Introduction

Metastatic spread to cervical lymph nodes is considered the most important clinicopathologic prognostic factor in patients with head and neck squamous cell carcinomas (HNSCC) in the absence of distant metastases. Given the impact of neck metastasis on

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prognosis, the selection of adequate treatment is crucial to avoid or reduce regional failure in the neck. Neck dissection, with or without post-operative radiotherapy (RT) or chemoradiotherapy (CRT), is one of the fundamental therapeutic options in the treatment of neck metastasis.

The radical neck dissection (RND) represented the traditional surgical management of the clinically positive neck for many years, until the modified radical neck dissection (MRND), developed in the 1960s, progressively replaced the RND. These two forms of neck dissection were considered the only two suitable surgical options for the management of clinically positive necks (cN+) in patients with HNSCC [1,2]. However, in many cases of a clinically positive neck not all the palpable or radiologically detectable nodes are pathologically positive and not every neck level is involved. For this reason, RND or MRND may lead to an overtreatment in many cases, and the same rationale that became accepted using selective neck dissections (SND) for the elective treatment of cN0 necks could apply in the case of cN + necks [3].

Moreover, in the elective SND histologic specimens, metastatic lymph nodes are frequently found, and evidence of extracapsular spread has been identified in up to one third of cases with pathologically proven nodal metastasis. Therefore, SND is in fact being used routinely in cN0 necks already involved with lymphatic metastatic disease (pN+) [4]. We also know that HNSCC tends to metastasize in predictable pathways related to the primary tumor site. In a histopathological study by Shah in 1990 [5], which involved 1081 previously untreated patients who underwent 1119 elective and therapeutic classical RNDs for squamous cell carcinoma of the upper aerodigestive tract, lymph node levels I, II and III were found to be at greatest risk for nodal involvement from oral cavity tumors, while levels II, III, and IV seemed to be at risk for metastases from cancers of the oropharynx, larynx and hypopharynx. In this study, skip metastases were rare, and there were very few patients with metastatic disease at level V, all of whom had gross metastases at level III or IV. In cancer of the larynx and hypopharynx it has been shown that even in case of cN + disease most metastatic nodes were present at levels II, III, and IV, level I being involved in 7% and 10% and level V in 4% and 11% of the specimens, respectively [5]. In addition, a study by Kowalski et al. [6], which analyzed RND specimens of 164 patients with oral cavity cancer with a cN1 or cN2a neck, found a high false-positive rate (57.4% pN0) in patients with clinically palpable nodes at level I. Similarly, Simental et al. [7] reported a false-positive rate of 32% in patients who were initially staged as cN+. Therefore, in a further step to reduce treatment morbidity, pretreatment identification of lymph node metastasis is of utmost importance, as only reliable detection or exclusion of lymph node metastases can replace elective neck treatment. Diagnostic techniques, such as ultrasound-guided fine-needle aspiration cytology (USFNAC), are an option in selected patients in order to detect metastases at an early stage. USFNAC has the advantage of providing cytological evidence of the presence of metastatic cells in the lymph nodes. Specificity of the procedure is approximately 100% as false-positive results of cytology are exceedingly rare. With the use of USFNAC, unnecessary elective neck dissections can be avoided in the majority of patients without compromise of regional control of the neck and survival [8].

Various studies suggested that a comprehensive neck dissection (CND) may not be necessary in all cases with positive necks and selective procedures have progressively gained popularity. In the retrospective study of Byers et al. [9], including 517 SNDs mainly for patients cN0 or cN1, 50 patients had pathologic N1 disease (of these patients, 36 received postoperative RT and only one presented with a regional recurrence; in patients who did not receive irradiation, five of fourteen had neck failure). In a large retrospective review of 296 SNDs, Spiro et al. [10] reported a rate of regional failure of 6.5% in patients staged with a pathologically positive neck (most of these patients had postoperative RT). Schmitz et al. [11] reported a regional failure rate of 8% in pN1 necks treated with a SND, while the regional control rate was not improved with postoperative radiation therapy, suggesting that postoperative irradiation is not justified in pN1 neck disease without extracapsular spread. With the inherent limitation of retrospective studies, it appears that SND for patients with clinically positive neck disease is a safe procedure, if postoperative irradiation is given in the presence of risk factors for regional relapse. Also, a current Cochrane analysis by Bessell et al. [12] found no evidence that RND increases overall survival compared to more conservative neck dissection surgery.

These findings have encouraged the use of SND for the management of the cN + neck, to provide the patient with a well-aimed surgical treatment which reduced morbidity without reducing oncologic efficacy. The first reports were on the cN1 neck, but the number of studies regarding SND application in cN2 necks increased considerably in the recent literature.

SND for the cN + neck has not only a therapeutic purpose, but may also be considered as a pathological staging procedure. In fact, the histopathological report can provide very valuable information for planning of adjuvant radiotherapy, with or without concurrent chemotherapy; dose levels, irradiation volume design, and addition of concurrent chemotherapy are based on the extent of disease in the neck (number, size, and location of positive nodes) and more importantly on the presence of extra nodal extension (ENE) of metastatic tumor [13,14]. But the more limited the neck dissection is, the more limited this information can be provided by histopathology.

However, although an increasing number of studies report the use of SND in patients with a cN + neck, these studies usually include a limited number of patients, and there is no consensus on the indications of SND in the cN + setting. Therefore, the aim of this study is to review the existing literature to analyze the regional control after SND for the treatment of cN + necks, and to compare those results with the results reported for the more extensive neck dissections, in an attempt to derive guidance for the selection of HNSCC patients with cN + neck that may indeed benefit from SND. As neck dissection is a fundamental component of surgical treatment of cN + cancers originated in different subsites within the head and neck, all subsites are included in this review, irrespective of the pattern of metastatic spread.

Materials and methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were used to conduct a systematic review of the current literature [15]. The search strategy aimed to include all articles concerning the use of SND in the management of clinically positive necks. A PUBMED internet search updated to March 7, 2017 was performed for English language publications between the years 1990–2016 using the following search criteria in the title or abstract: ‘selective neck dissection’, coupled with ‘positive’ or ‘therapeutic’. The search results were reviewed by two independent researchers (JPR and GG) for potentially eligible studies. When there was any statement in the abstract on follow-up data and outcomes of the use of SND in the therapeutic setting, the full text article was searched; all review articles were also checked in full. References from any full text articles were cross-checked to ensure inclusion in this review if appropriate (Fig. 1). Disagreements over the eligibility of an article were resolved by consensus.

Studies were selected if they met the following inclusion criteria: 1) patients with mucosal HNSCC not previously treated, 2) clinical or radiological evidence of neck node metastasis (cN + necks), which

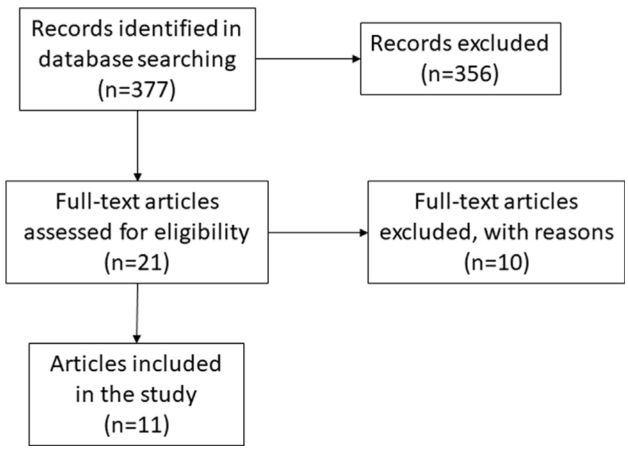

Fig. 1. Flow chart showing the process of the study selection for the systematic review.

were subsequently confirmed to be pathologically positive, 3) use of SND as a therapeutic approach, 4) statement of adjuvant treatment administered, and 5) clear description of regional control in the dissected neck. Subsites of primary head and neck SCC eligible for inclusion were the oral cavity, oropharynx, larynx, and hypopharynx. In the case of multiple series from the same institution, the most recent or largest series was selected. Those studies that had no information on the pathological nodal status, or the adjuvant treatment administered, or the studies with an insufficient follow-up (less than 24 months) were excluded from the analysis.

For the purposes of this review, the primary outcome measure analyzed was the disease control in the dissected neck. The disease control in the dissected neck in each study was calculated with the denominator being the number of patients that received a SND (either uni- or bilateral), and the numerator the number of patients that did not experience recurrence in the dissected side (or sides) of the neck (irrespective of the nodal levels involved by the recurrence). Recurrence rates were calculated on the proportion of patients with recurrent disease in the dissected neck(s) during the study period. Disease control rates were averaged for each group, and mean rates were compared within groups stratified with respect to postoperative treatment and pN-classification. For this comparison, we used the one-way anova test with the help of the IBM-SPSS 19.0 statistical software package.

Three of the studies included in this review [24,27,33] made a retrospective comparison with patients who received a comprehensive neck dissection (CND) at the same institution. For these studies, a meta-analysis was undertaken using Review Manager 5.1. Heterogeneity was assessed using I^2 statistic and was found to be low to moderate ($I^2 = 34\%$) and not significant ($P = .22$). Then, we used the fixed effect model for the analysis. Forest plots and funnel plots were employed to test the overall effect and the publication bias, respectively. We also conducted subgroup analysis stratified by adjuvant treatment. All tests were two sided with a significance level of $p < .05$.

Results

According to our search criteria, 377 papers were initially identified. After sorting and removal of duplicates, all the remaining abstracts were reviewed, and 21 papers were retrieved and reviewed in detail [7,16–35]. The studies that did not fulfill all the inclusion criteria were discarded: one study included patients previously treated with RT [20], two studies included patients with cN0 necks [21,25], in one study the sternocleidomastoid muscle was systematically removed in the SND [23], one study did not provide information on adjuvant treatment [35], and the remaining discarded studies included cases that were pN0 [7,28,30,31,34]. This left 11 studies for the analysis (Fig. 1). All the studies included in this review were retrospective.

Table 1 summarizes the main features of the selected studies. All the patients included had a HNSCC with clinical nodal metastasis that were pathologically confirmed, and information about the pN classification, adjuvant treatment and disease control in the dissected neck. When available, information regarding adjuvant treatment and regional control by pN classification were also included. Typically, in the included studies, SND was performed in patients with clinical and/or radiological evidence of neck metastasis when there was no evidence of nodal fixation, no involvement of extra nodal structures, no lymph nodes at multiple levels, and no lymph nodes at level V. When it was specified, the most common indications for postoperative irradiation were (in addition to characteristics of the primary tumor) extra nodal extension and metastasis in multiple (>1) nodes. However, none of the studies described the irradiation fields, and only two mentioned the mean RT dosage (Table 1).

In the included studies, the regional control rate in the dissected neck ranges from 73 to 100% ($n = 764$). The mean (±SD) regional control rate (obtained from all the included studies) was 91 ± 6.51% (95% CI 87.15–94.39). It should be considered that nearly 60% of the included patients had a pN2 classification, and the extra nodal extension (ENE) rate was 28% (range 12%–50%). In 7 studies there were information about the sublevel of nodal recurrence, and we could observe that recurrence occurred in the previously dissected sublevels in most cases (34/44 recurrences, 77%). Recurrence rates in the dissected neck were lower than 15% in all, except in the study reported by Kolli el al [17] that shows a recurrence rate of 27%. However, among the subset of patients who received postoperative radiation therapy, the regional control rate of the Kolli study was 93%. This difference underscores the importance of appropriate postoperative treatment. In our review, the mean (±SD) regional control rate was 86 ± 17.5% (95% CI 78.87–98.12) in non-irradiated patients, and 93 ± 5.5% (95% CI 89.29–96.1) in patients who received adjuvant treatment, but these differences were not significant ($P = .45$).

By pN classification, the mean (±SD) regional control in pN1 cases was over 90% (95 ± 7.09%; range 78%–100%; 95% CI 90.6–99.39), either in cases treated only by surgery alone (91.5 ± 10.6%; range 71%–100%; 95% CI 83.5–99.3) or with adjuvant treatment (97 ± 4.33%; range 87.5%–100%; 95% CI 94.7–100.7) ($P = .15$). In pN2 cases, the regional control was 89.5 ± 9.3% (range 71%–100%; 95% CI 83.3–94.9), but in these cases the disease control was higher in the cases that received adjuvant treatment (94 ± 8.1%; range 76%–100%; 95% CI 86.7–97.9) than in the cases treated only with surgery (75.5 ± 32.9%; range 20%–100%; 95% CI 46.9–104.6), although the differences were not significant ($P = .19$). The study by Kolli et al. [17] had the highest recurrence rate in non-irradiated patients (50%), a rate that could have influenced the combined results. The differences in regional control between pN1 and pN2 patients were also not significant ($P = .17$).

Accordingly, SND (with appropriate postoperative treatment) is a valid procedure in controlling neck disease in selected patients with clinically and pathologically positive necks.

The added effects of adjuvant CRT therapy could not be assessed since only a portion of the patients in two of the 11 studies were treated in this manner without specific reporting of their outcome. Therefore, the influence of this treatment in regional control could not be addressed, although the overall regional control rates did not differ from those studies analyzed that did not include chemotherapy.

As mentioned, three of the studies included in this review [24,27,33] made a retrospective comparison of patients treated with

Table 1
Summary of the reviewed articles. All studies include patients with clinically and pathologically positive necks. Regional control in the dissected neck.

Author	Traynor, 1996 [16]	Kolli, 2000 [17]	Ambrosch, 2001 [18]	Andersen, 2002 [19]	León, 2004 [22]
Number of patients	29	26	254	106	29
Primary tumor site	Oral cavity (9) Oropharynx (8) Hypopharynx (8) Larynx (4)	Oral cavity Oropharynx	Oral cavity Oropharynx Hypopharynx Larynx	Oral cavity (42) Oropharynx (37) Hypopharynx (7) Larynx (20)	Oral cavity Oropharynx Hypopharynx Larynx
Type of SND	I–III, I–IV (include extended resections[a])	I–III	I–III, II–III (IV)	I–III, II–IV (do not include extended resections[a])	I–III, I–IV II–IV
Clinical neck classification			283 cN+, 254pN+		
-cN1					
-cN2	NA	NA	NA	NA	NA
Pathological neck classification					
-pN1	11 (38%)	9 (35%)	88 (35%)	58 (55%)	13 (45%)
-pN2	18 (62%)	17 (65%)	166 (65%)	47 (44%)	16 (55%)
Number of nodes harvested	NA	NA	NA	NA	21 (mean)
ENE	NA	NA	NA	36 (34%)	5 (17%)
Adjuvant treatment	20 (69%)	14 (54%)	158 (62%)	76 (72%)	26 (93%)
-RT	20 (69%)	14 (54%)	158 (62%)	76 (72%)	26 (93%)
-CRT	0	0	0	0	0
Indications of adjuvant treatment	NA	NA	NA	ENE Nodes at multiple levels	ENE >2 metastatic nodes
Mean RT dosis	NA	NA	NA	67.29 Gy	NA
pN1 adjuvant treatment					
-RT	2 (18%)	2 (22%)	40 (45.5%)	NA	10 (77%)
-CRT	0	0	0	0	0
pN2 adjuvant treatment					
-RT	18 (100%)	12 (71%)	118 (71%)	NA	16 (100%)
-CRT	0	0	0	0	0
Overall regional control	28 (96%)	19 (73%)	233 (92%)	100 (94%)	29 (100%)
-Surgery only	9 (100%)	6 (50%)	84 (87.5%)	NA	3 (100%)
-Adjuvant (C) RT	19 (95%)	13 (93%)	149 (94%)	NA	26 (100%)
pN1 regional control	11 (100%)	7 (78%)	84 (95%)	56 (96.5%)	13 (100%)
-Surgery only	9 (100%)	5 (71%)	45 (94%)	NA	3 (100%)
-Adjuvant (C) RT	2 (100%)	2 (100%)	39 (97%)	NA	10 (100%)
pN2 regional control	17 (94.5%)	12 (71%)	149 (90%)	44 (93%)	16 (100%)
-Surgery only	–	1 (20%)	36 (76%)	NA	–
-Adjuvant (C) RT	17 (94.5%)	11 (92%)	113 (96%)	NA	16 (100%)
Recurrence in the dissected levels	1/1	NA	17/21	6/6	0/0
Observations				One N3 case (no recurrence)	

a SND with patients who received a CND (Table 2). These studies showed similar rates of regional control in the dissected neck with both techniques (89%; range 86%–96% in the SND group, and 87%–94% in the CND group). However, it should be noted that patients submitted to a CND had in general a more advanced neck disease. In the meta-analysis there is no significant difference in regional recurrence between the SND and CND group. The pooled risk ratio (RR) in the fixed effects model was 0.93 (95%CI 0.47–1.84, P = .84) for overall neck recurrence in the dissected neck(s) (Fig. 2A). In addition, the regional control rate was not influenced by the administration of postoperative RT in these series. Subgroup analyses by postoperative treatment showed comparable results for neck recurrence in the dissected neck(s): 1.74 (95%CI 0.50–6.00, P = .38) in the surgically treated patients, and 0.98 (95% CI 0.45–2.13, P = .96) in the patients that received postoperative radiotherapy (Fig. 2B–C). The regional control was also similar when pN1 and pN2 patients were analyzed separately (Table 2). However, there was no enough data to perform a meta-analysis by pN classification.

Discussion

The first and most important observation to emphasize from the analysis of the collected data is the applicability of SND in patients with HNSCC and limited metastatic disease to the lymph nodes in the neck. In fact, the regional control rate in all but one study varies between 85% and 100% (with postoperative adjuvant treatment). These results are similar to those reported with the RND or MRND [3,8,11]. It is important to note that the studies with the greatest number of cases included patients with primary neoplasms originating from all the main head and neck sites and showed regional recurrence rates as low as 6%–8% [18,19,29]. Also, although all the identified studies were retrospective, those which compared SND with CND in patients treated at the same institution failed to show an advantage to CND in terms of regional control [24,27,33]. This was previously reported in a meta-analysis comparing these two types of neck dissections, but limited to the patients with oral cavity SCC [36]. This meta-analysis included five studies with a total of 443 patients, and no significant difference was found regarding regional recurrence, disease specific death or overall death between the SND and CND group. Three of these studies are included in this review, but two were excluded: either because some patients received neoadjuvant (chemo) radiation therapy in one study and because pN0 patients were included in the other.

The types of SND used in the selected publications are heterogeneous: the most frequently spared levels were level IV in oral cavity neoplasms, sublevel Ia and Ib in cases of laryngeal tumors, and level V in all primary tumor locations. These findings suggest

Schiff, 2005 [24]	Santos, 2006 [26]	Patel, 2008 [27]	Givi, 2012 [29]	Allegra, 2014 [32]	Feng, 2014 [33]	Total
32	27	53	108	32	68	764
Tongue	Oral cavity (4) Oropharynx (1) Hypopharynx (5) Larynx (17)	Oral cavity (24) Oropharynx (12) Hypopharynx (9) Larynx (9)	Oral cavity (77) Oropharynx (25) Hypopharynx (5) Larynx (1)	Larynx	Oral cavity	Oral cavity Oropharynx Hypopharynx Larynx
I–III or I–IV	II–IV (V) I–III, I–IV	I–IV, II–IV (V)	I–III, I–IV II–IV, II–V	II–III, II–IV II–V	I–III or I–IV	I–III, I–IV II–IV, II–V
45 cN+, 32pN+				58 cN+, 32 pN+		
		26 (48%)	55 (51%)	12 (21%)		
NA	NA	28 (52%)	53 (49%)	46 (69%)	NA	NA
14 (44%)	7 (26%)	26 (50%)	39 (36%)	10 (31%)	40 (59%)	315 (41%)
18 (56%)	20 (74%)	26 (50%)	69 (64%)	22 (69%)	28 (41%)	447 (59%)
NA	NA	NA	32 (median)	NA	24 (mean)	–
NA	4 (14%)	16 (31%)	38 (35%)	11 (50%)	8 (12%)	118/424 (28%)
27 (84%)	27 (100%)	24 (46%)	95 (88%)	27 (84%)	68 (100%)	562 (74%)
27 (84%)	27 (100%)	24 (46%)	50 (46%)	16 (50%)	68 (100%)	506 (66%)
0	0	0	42 (39%)	11 (34%)	0	53 (7%)
NA	NA	ENE Multiple nodal involvement	NA	ENE Multiple nodal involvement (>1) Perineural or microvascular invasion	All pN+	–
NA	NA	NA	NA	NA	>60 Gy	–
			32 (82%)			
10 (71%)	7 (100%)	7 (27%)	NA	NA	40 (100%)	120/208 (58%)
0	0	0	NA	NA	0	0
			63 (91%)			
17 (94%)	20 (100%)	17 (65%)	NA	NA	28 (100%)	246/309 (80%)
0	0		NA	NA	0	
28 (87.5%)	23 (85%)	50 (96%)	102 (94.5%)	29 (91%)	56/65 (86%)	697/761 (91%)
5 (100%)	–	26 (89.5%)	10 (77%)	5 (100%)	–	148/172 (86%)
23 (85%)	23 (85%)	24 (100%)	92 (97%)	24 (89%)	56/65 (86%)	449/483 (93%)
14 (100%)	6 (86%)	24 (92%)	37 (95%)	10 (100%)	NA	262/275 (95%)
4 (100%)	–	17 (89%)	6 (86%)	NA		89/97 (91.5%)
10 (100%)	6 (86%)	7 (100%)	31 (97%)	NA		107/110 (97%)
14 (78%)	17 (85%)	26 (100%)	65 (94%)	19 (86%)	NA	376/419 (89.5%)
1 (100%)	–	9 (100%)	5 (83%)	NA		52/69 (75.5%)
13 (76%)	17 (85%)	17 (100%)	60 (95%)	NA		264/281 (94%)
NA	0/4	1/3	NA	NA	9/9	34/44
	All recurrences in T3-T4	One N3 case (no recurrence)	3 patients received adjuvant CT		3 patients lost to follow-up	

[a] ECM, IJV, IX. NA: Data Not Available. SND: Selective Neck Dissection. RT: Radiotherapy. CRT: Chemoradiotherapy. CT: Chemotherapy. ENE: Extra nodal extension.

that accurate recommendations on which cervical levels should be dissected for different primary sites of HNSCC are still needed. More systematic and homogeneous guidelines would allow better comparison between the results obtained in different studies. This heterogeneity could also have influenced the results, since not all the SNDs were comparable. However, except in the study of Kolli et al. [17], the recurrence rates were similar in all the studies, and most recurrences occurred in the dissected levels. This suggests that, despite the described heterogeneity, the levels at risk of nodal metastasis were adequately included in the SNDs in these studies.

All the authors emphasized the importance of careful selection of patients. From the reviewed articles, nodal fixation, gross extracapsular spread, multiple large nodes (>3 cm) or nodes at multiple neck levels, and history of previous neck surgery are considered as contraindications for SND. None of the reports describe the use of SND for neck metastases larger than 6 cm (cN3). Only two patients with cN3 disease in a single lymph node are included in the articles of Andersen [19] and Patel [27], resulting in insufficient information to support the applicability of SND for N3 disease. Therefore, the surgical gold standard for cN3 nodes remains at least CND, and extended CND is often required. Contraindications to SND in cN + necks, based on the opinion of the authors, are listed in Table 3. It should be emphasized the importance of an adequate preoperative imaging study before to select the surgical technique, not only to identify these adverse features but also to allow for a reliable detection or exclusion of lymph node metastasis [37]. As previously mentioned, reliable exclusion of lymph node metastases can replace elective neck treatment, and USFNAC is a useful tool to avoid false positive cases [8].

Another aspect to consider is the different options currently accepted as SND. As pointed out by Ferlito et al. [38], in a SND two points must be considered: how many levels are dissected, and how many and which non-lymphatic structures are removed? So, in some SND, the internal jugular vein or the accessory nerve or the sternocleidomastoid muscle can be removed for oncologic safety or because of involvement. The removal of those non-lymphatic structures is, of course, more frequent in N+ necks than in N0 necks. These procedures should be considered as extended SNDs [39].

Extra nodal extension (ENE) is the main factor influencing neck failure rate, even more than pN neck classification [40,41]. We could not analyze the influence of ENE in regional control due to insufficient data, but the regional control rates were very high in the reviewed studies despite a significant proportion of cases presented ENE (28%). The central role that the extent of nodal involvement and ENE play in selecting patients for SND was highlighted by 3-years survival rates reported by Woolgar et al. [42]: They report 33% survival in patients with macroscopic ENE, 36% in

Table 2
Summary of studies that made a retrospective comparison between SND and CND. Only patients with clinically and pathologically N1-N2 necks were included.

Author	Schiff, 2004 [24]		Patel, 2008 [27]		Feng, 2014 [33]		Total	
	SND	CND	SND	CND	SND	CND	SND	CND
Number of patients	32	17	53	122	68	75	153	214
Primary tumor site	Tongue	Tongue	Oral cavity Oropharynx Hypopharynx Larynx	Oral cavity Oropharynx Hypopharynx Larynx	Oral cavity	Oral cavity	Oral cavity Oropharynx Hypopharynx Larynx	Oral cavity Oropharynx Hypopharynx Larynx
Pathological neck classification								
-pN1	14 (44%)	2 (12%)	26 (50%)	48 (39%)	40 (59%)	31 (41%)	80 (52%)	81 (38%)
-pN2	18 (56%)	15 (88%)	26 (50%)	74 (61%)	28 (41%)	44 (59%)	72 (48%)	133 (62%)
ENE	NA	NA	16 (31%)	71 (58%)	8 (12%)	25 (33%)	24 (20%)	96 (49%)
Adjuvant treatment					68 (100%)	75 (100%)		
-RT	27 (84%)	16 (94%)	24 (46%)	59 (48%)	68 (100%)	75 (100%)	119 (78%)	150 (70%)
-CRT	0	0	0	0	0	0	0	0
pN1 adjuvant treatment								
-RT	10 (71%)	1 (50%)	7 (27%)	14 (29%)	40 (100%)	31 (100%)	57 (71%)	46 (57%)
-CRT	0	0	0	0	0	0	0	0
pN2 adjuvant treatment								
-RT	17 (94%)	15 (100%)	17 (65%)	45 (61%)	28 (100%)	44 (100%)	62 (86%)	104 (78%)
-CRT	0		0	0	0	0	0	0
Overall regional control	28 (87.5%)	16 (94%)	50 (96%)	106 (87%)	56/65 (86%)	58/64 (91%)	134/150 (89%)	180/203 (89%)
-Surgery only	5 (100%)	1 (100%)	26 (89%)	58 (92%)	–	–	30/34 (88%)	59/64 (92%)
-Adjuvant RT	23 (85%)	15 (94%)	24 (100%)	48 (81%)	56/65 (86%)	58/64 (86%)	103/119 (86%)	121/139 (87%)
pN1 regional control	14 (100%)	2 (100%)	24 (92%)	45 (93%)	NA	NA	38/40 (95%)	47/50 (94%)
-Surgery only	4 (100%)	1 (100%)	17 (89%)	NA				
-Adjuvant RT	10 (100%)	1 (100%)	7 (100%)	NA				
pN2 regional control	14 (78%)	14 (93%)	26 (100%)	61 (82%)	NA	NA	40/44 (91%)	75/89 (84%)
-Surgery only	1 (100%)	–	8 (89%)	NA			NA	NA
-Adjuvant RT	13 (76%)	14 (93%)	17 (100%)	NA			NA	NA
Observations					3 patients lost to follow-up	11 patients lost to follow-up		

SND: Selective neck dissection; CND: Comprehensive neck dissection; RT: Radiotherapy; CRT: Chemoradiotherapy. NA: Data not available.

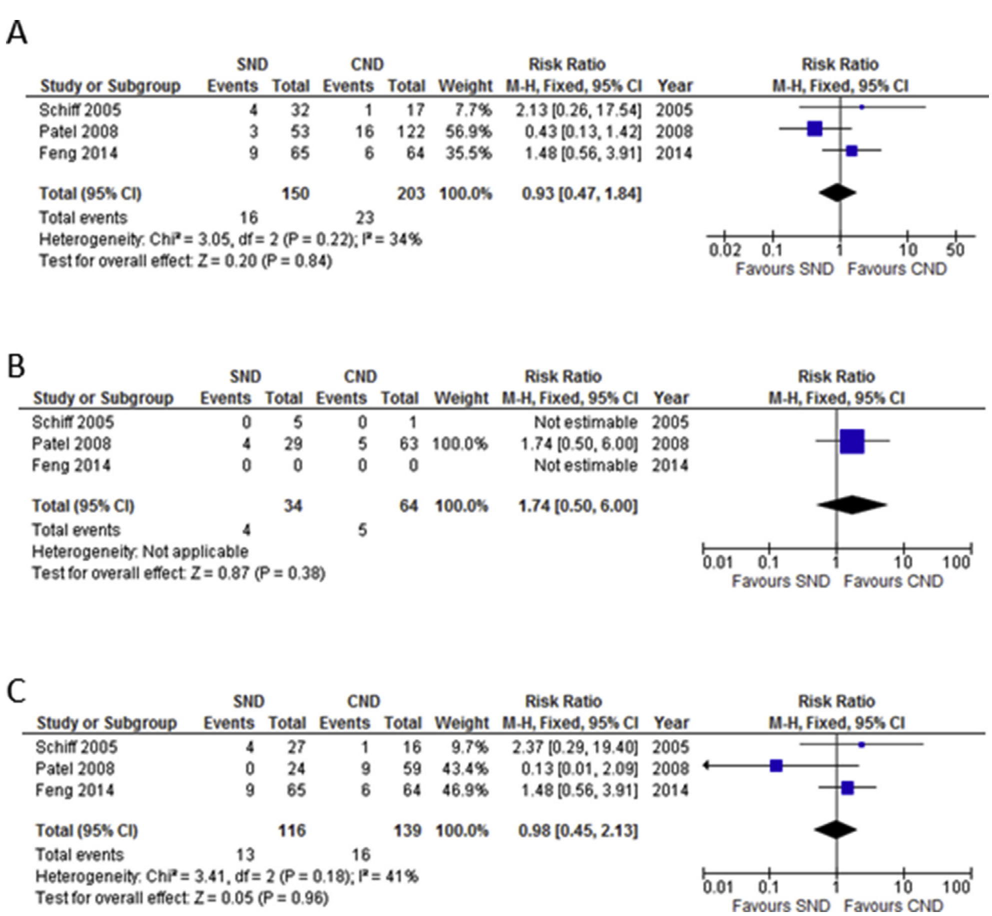

Fig. 2. Forest plots showing the relative risk of recurrence in the dissected neck for the complete series of patients (A), in non-irradiated (B), and irradiated patients (C).

Table 3
Contraindications to SND for cN + neck disease in surgically treated patients.

- Palpable metastases at level IV or V
- Metastatic lymph node >6 cm.
- Large volume (>3 cm) multiple lymph nodes at multiple levels
- Gross extra nodal extension involving sternocleidomastoid muscle or carotid sheath
- Metastatic disease in lymph nodes other than expected first echelon lymph nodes
- Recurrent disease after previous neck surgery

patients with microscopic extra nodal extension, 72% in metastases limited to lymph nodes without ENE, and 81% in absence of nodal metastases.

Despite the poorer prognosis in patients with ENE, SND has been used by some authors in the treatment of clinically positive necks with involvement of non-lymphatic structures [43]. In that study 18 SNDs were performed as part of the primary treatment and 25 for salvage following (C)RT. Although most patients (84%) had nodal disease $\geq$N2, 91% had disease clinically confined to $\leq$2 neck levels. Primary treatment and salvage cases showed respectively 0% and 13% regional recurrence rates. Although these results are very encouraging, this is the only study which analyzes this application of selective neck dissection and needs to be supported by additional experience from other investigators. Due to the unique features that distinguish this work from the others we did not include it in the general comparative analysis.

Postoperative RT or CRT play a central role in the oncologic outcomes after SND for cN + necks in patients that are primarily surgically treated. Every single study analyzed in this review relies on adjuvant postoperative treatment to achieve satisfactory local and regional control rates after surgery in higher risk patients (mainly pN2 patients and patients with ENE). RT alone or with concurrent chemotherapy are required to achieve better regional control rates. This is due to the inclusion of the undissected levels of lymph nodes in the radiation ports, which covers the entire neck for postoperative radiotherapy. The importance of adjuvant postoperative RT was highlighted in a study by Kolli et al. [17], who reported a regional recurrence rate of 27% in the group of patients who had SND alone compared to a recurrence rate of 7% in patients who received postoperative RT after SND, and by the better regional control rate (although not significant) in the combined series of patients that received postoperative treatment, especially in pN2 cases (94% vs. 75.5% in non-irradiated patients). Moreover, the development of improved radiation delivery techniques with IMRT has allowed more accurate dose delivery and selective and accurate dose distribution to the different neck nodal levels. This has resulted in reduced morbidity and more specific dosimetric evaluation level by level in relation to the probability of the presence of residual tumor cells [44]. Addition of concurrent chemotherapy, further improves tumor control, and potentially compensates for the less extensive surgery. In two of the reviewed studies not only RT, but also adjuvant CRT was administered to some patients [30,33]. However, the benefit of the addition of chemotherapy in these studies could not be analyzed due to insufficient data. But the overall regional control rates reported by these authors was similar to that reported in the other studies that used only RT, suggesting that the addition of chemotherapy might not be necessary in these patients.

Although not evaluated in our review because most included studies did not address this issue, cosmetic and functional outcomes are the two main reasons for proposing SND over CND in cN + necks. In the study reported by Feng et al. [33], the SND group showed significantly fewer complications and faster recovery compared with the MRND group (7.3% vs. 20%). Impairment of shoulder function associated with persistent pain due to XI cranial nerve damage or sacrifice is considered to be the most morbid iatrogenic consequence of RND or MRND for the patient. The function of the accessory nerve is more likely to be spared in SNDs compared to more comprehensive neck dissections [45]. However, although the spinal accessory nerve is preserved during SND, the nerve function may still be affected due to circumferential dissection around the nerve, to clear sublevel IIB, leading to ischemia or neurapraxia from stretch injury to the nerve due to retraction of that segment of the nerve [45]. In this way, in a recent systematic review, the prevalence rates of shoulder pain after a SND range from 9 to 25% in the included series [46]. As expected, these rates were higher in RND (range, 10–100%) and MRND (range, 0–100%). In this review, the type of neck dissection (including nerve sparing approaches) was the most frequently identified risk factor for undesirable outcomes including shoulder pain [46]. It is generally accepted that removal of lymph nodes from sublevel IIB is not necessary in patients with clinically N0 necks, while its dissection is required in patients with gross metastases at sublevel IIA, or when the neck is clinically positive either unilaterally or bilaterally. However, some authors report that not dissecting sublevel IIB during SND does not necessarily retain superior functional results [47]. For these reasons it is important not to overestimate the hypothetical advantages of preserving spinal accessory nerve function during a SND when sublevel IIB is not dissected, particularly if there is a risk of occult metastases in these nodes, which may more likely be the case in patients with cN + necks. Although shoulder morbidity is often present after non-surgical treatment of the neck, radiotherapy seems to add no shoulder morbidity to neck dissection [48], making SND with adjuvant radiotherapy an attractive option. However, other toxicities associated with the administration of RT must be also considered (e.g. xerostomia, late toxicities such as carotid stenosis).

Another way of helping to identify optimal treatment in complex decisions such as on treatment of the neck, may be the use of decision analysis. This has been used for decades for decisions on the treatment of the N0 neck [49,50] and can potentially be helpful in the decisions on extend of neck dissection in the cN + neck as well [51].

In addition to the retrospective nature of all the studies, the main weakness of this review is that the number of patients enrolled in the different studies included in this analysis is variable, but in general quite small: only 3 of 11 studies included more than 100 patients. The cumulative data however strongly suggest the feasibility and safety of SND in cN + patients and stimulate the need for further prospective studies with larger number of patients comparing the oncologic (and functional) outcomes after SND and CND for some subsets of patients with cN + disease such as cN2 or even cN3 when some neck levels are not involved. Another limitation is that there is no data in any of the papers regarding HPV/p16 status of oropharyngeal SCC. SND may well be sufficient even for advanced neck disease in this biologically distinct disease. Papers including an unknown number of HPV-related oropharyngeal SCC may be skewed towards low rates of regional recurrence in SND cases.

The use of SND for cN + neck disease raises several questions. How to select patients with cN2 neck disease for SND? Besides size of lymph node metastases also number and levels involved may be important. Is it always necessary to irradiate the non-dissected levels as well? Previously mentioned studies showed that the risk of occult lymph node metastases is low. However, the lymph node status of these levels is not known for sure and the morbidity of radiation limited. What to do when histopathological examination of a SND specimen reveals only one single lymph node metastasis? If only one lymph node metastasis without extra nodal extension is found after MRND in most centers no adjuvant radiotherapy is indicated. Analogously, adjuvant treatment would be unnecessary in pN1 necks without ENE. However, the lymph node status of the non-dissected levels is not completely known. In pN1 necks, SND with adjuvant radiotherapy may even increase morbidity as compared to CND only. These questions can only be answered if studies report their findings in detail and in a similar way allowing for meta-analysis.

Conclusions

The articles analyzed in this review suggest that SND offers an effective and oncologically safe surgical procedure in selected patients with clinically positive metastatic nodes in the neck. Current literature supports the role of SND in HNSCC patients with cN1 and in cN2 necks when the nodes are not fixed, there are no palpable metastases at level IV or V, the nodes are <3 cm in diameter, and when there are no multiple lymph nodes at multiple levels in the neck. The use of preoperative imaging studies to adequately address the presence and characteristics of lymph node metastasis are mandatory to select cN + cases candidates for a SND. In this regard, USFNAC could be used to confirm the presence of nodal metastasis, combined with MRI staging in selected cases for an early detection of ENE. Postoperative RT or CRT improves regional control in more advanced neck disease (>pN1). However, it is important to underscore that, even though most of the reported results are encouraging, some studies do report relatively high regional failure rates, which may reflect undertreatment. Since prospective trials comparing SND to CND are unfeasible due to practical and ethical reasons, in the absence of such trials, the results of this review should serve as a guide to select patients with cN + necks for a SND.

Conflict of interest statement

The authors have nothing to disclose.

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