Prognostic value of elective neck dissection in adenoid cystic carcinoma of head and neck: a meta-analysis

Suton, Petar; Lukšić, Ivica

Source / Izvornik: **International Journal of Oral and Maxillofacial Surgery, 2021, 50, 1403 - 1407**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.ijom.2021.01.010

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:091777

Prognostic value of elective neck dissection in adenoid cystic carcinoma of head and neck: A meta-analysis. A call for randomised trial and international consensus

Petar Suton[1], Ivica Luksic[2]

[1] Department of Radiotherapy and Medical Oncology, University Hospital for Tumours, University Hospital Center "Sisters of Mercy", Ilica 197, 10000 Zagreb, Croatia

[2] University of Zagreb School of Medicine, Department of Maxillofacial Surgery, University Hospital Dubrava, Ave. Gojko Susak 6, 10000 Zagreb, Croatia

University of Zagreb School of Medicine, Department of Maxillofacial Surgery, University Hospital Dubrava, Ave. Gojko Susak 6, 10000 Zagreb, Croatia

Corresponding author:

Prof. Ivica Luksic, MD, MSc, PhD

Department of Maxillofacial Surgery, University Hospital Dubrava

Ave. Gojko Susak 6, 10000 Zagreb, Croatia

Phone: +385 1 2903 431; Fax: +385 1 2864 250

E-mail: luksic@kbd.hr

Running heads: Elective neck dissection in adenoid cystic carcinoma of head and neck

ABSTRACT

Adenoid cystic carcinoma of head and neck (AdCCHN) is uncommon salivary gland cancer characterised for infrequent neck metastases, high rate of local and distant recurrence. The aim of this meta-analysis was to analyse significance of elective neck dissection (END) in terms of overall survival (OS) in patients with AdCCHN. A systematic literature search and meta-analysis was performed. Endpoint assessed by this meta-analysis included 5-year OS (death from any cause). Statistical heterogeneity was assessed using the Cochrane Q test and I^2 statistic. A pooled odds ratio (OR) was reported with 95% confidence interval (CI). There were 1934 patients in END arm and 3083 in the observation group. The pooled OR, calculated for END vs. observation, was 0.94. Patients receiving END had similar risk for death compared to observation cohort (P=0.76). No significant difference in final outcome after patient's stratification based on T stage was identified (OR for T1/T2 1.27, P=0.39; OR for T3/T4 0.95, P=0.90). Observation for cN0 neck is a reasonable option in AdCCHN. This findings suggest conduction of prospective trials on indications and extent of END in AdCCHN.

Keywords: head and neck cancer; carcinoma, adenoid cystic; neck dissection; neck metastases; survival

INTRODUCTION

Adenoid cystic carcinoma of head and neck (AdCCHN) is a rare, slow growing, malignant epithelial tumor, comprising about 1% of all head and neck malignancies and about 10-15% of all salivary gland neoplasms.[1] This tumor is known for its slow progression accompanied with perineural invasion (PNI), rare lymphatic spread to the neck, high rate of local recurrence and delayed occurence of distant metastases.

Whereas therapeutic neck dissection (TND) is performed in all clinically node-positive (cN+) patients, management of cN0 neck is still controversial and elective neck dissection (END) is not routinely carried out in patients with AdCCHN. While isolated lymph node involvement may not have significant effect on survival, it is a risk factor for subsequent development of distant metastases.[2] Recently, we reported largest systematic review on END in AdCCHN analysing important features of cN0 treated neck (incidence of occult neck metastases, lowest involved region, extranodal extension (ENE), the role of sublocalization with respect to regional metastases etc.).[3] The aim of this meta-analysis was to further address these important issues and to determine impact of prophylactic neck management in patients with AdCCHN with respect to survival. Additional effort was done in order to determine prognostic value of END based on the T stage of the primaries (early *vs* advanced disease). To our knowledge this is first meta-analysis of the role of END in AdCCHN.

MATERIALS AND METHODS

Inclusion criteria were: (1) diagnosis of AdCCHN, (2) studies with patients undergoing primary surgical treatment including END group and those being observed for the cN0 neck, (3) information on OS rates among examined arms (END *vs* observation). Based on our previous article on END in AdCCHN,[3] preliminary analysis identified 1490 AdCCHN studies with five reports which met criteria mentioned above. Study by Lee et al.[4] was excluded due to fact that survival analysis was done comparing overall N+ rates vs N0 AdCCHN. Difference in OS between END vs no END group was not found (p=0.178), however there were no survival curves or absolute numbers on which analysis could be done. Also, additional search was done covering period between the date of last search (August 5, 2019) and July 25, 2020. One of the additionally identified studies (N=106) met these criteria. Therefore, five studies with 5017 patients were included in the final meta-analysis (**Table 1)**.[5-9]

Statistical analysis

Endpoint assessed by this meta-analysis included 5-year OS (death from any cause) Statistical heterogeneity was assessed using the Cochrane Q test and I^2 statistic. Statistically significant heterogeneity was considered present at $P<0.10$ and $I^2>50\%$. When homogeneity was minimal ($P\geq0.10$, $I^2\leq 50\%$), a fixed-effects model was applied for meta-analysis of disease outcome (OS); otherwise, a random effects model was used. Egger's test was used to estimate potential publication bias. A pooled odds ratio (OR) was reported with 95% confidence interval (CI). Analyses were conducted using statistical software Stats Direct version 3.0.165 (Stats Direct Ltd., Altrincham, United Kingdom).

RESULTS

This meta-analysis included four studies with a total of 5017 AdCCHN patients undergoing END in 1934 cases, while 3083 patients have been observed for cN0 neck. Included studies are presented in **Table 1**. There were 315 deaths from any cause in END group at 5-year follow-up, while 564 deaths were reported in the observation cohort at the same time period. **Table 2** shows patient's demographic and clinical characteristics.

5-year OS (all stages AdCCHN)

The analysis of pooled studies showed significant heterogeneity (I^2=74.3%, Cochran Q=15.59, P=0.004) without publication bias (Egger: bias= 0.21, P=0.93) (**Figure 1**). Therefore, the random effect model was used. The data from five studies were available for the analysis of 5-year OS (**Figure 2**). There were 1934 patients in the END group and 3083 patients in the observation group. The pooled OR, calculated for END vs. observation, was 0.94 (95% CI, 0. 63- 1.40; P=0.76).

5-year OS (early vs advance stage AdCCHN)

Early AdCCHN

The analysis of pooled studies showed significant heterogeneity (I^2=61.1%, Cochran Q=2.57, P=0.11). Therefore, the random effect model was used. Due to small number of patients bias indicator could not be calculated. The data from two studies were available for the analysis of 5-year OS (**Figure 3**). There were 579 patients in the END group and 1469 patients in the observation group. The pooled OR, calculated for END vs. no END, was 1.27 (95% CI 0.74 - 2.16; P=0.39).

Advanced AdCCHN

The analysis of pooled studies showed significant heterogeneity (I^2=79.6%, Cochran Q=4.89, P=0.03). Therefore, the random effect model was used. Due to small number of patients bias indicator could not be calculated.The data from two studies were available for the analysis of 5-year OS (**Figure 4**). There were 345 patients in the END group and 903 patients in the observation group. The pooled OR, calculated for END vs. no END, was 0.95 (95% CI 0.43 - 2.09; P=0.90).

DISCUSSION

AdCCHN accounts for 3-5% of all head and neck malignancies. It's characterized by intermediate grow rate, low probability of regional lymphatic involvement and frequent distant metastases/local recurrences.

Whereas TND is performed in all cN+ patients, management of cN0 neck is still contoversial and END is not routinely carried out in patients with AdCCHN. The decision regarding END performance should be based on both the incidence of occult lymph node metastases as well as expected impact of applied treatment on survival. Given the lack of data on incidence of neck metastases and it's influence on final outcome, the association between occult neck disease and OS remain inconclusive. The main objective of this study was to determine impact of END on survival in order to guide indications for prophylactic neck treatment in AdCCHN patient's.

Previously, we have published an article on important features among AdCCHN patients undergoing END.[3] In the largest systematic review on the examined topic, we analysed 18 studies with a total of 5767 AdCCHN undergoing END in 2450 cases. According to our results elective lymphadenectomy was employed in 42.5% of patients with AdCCHN (range 9.2 - 100 %) and the overall rate of occult neck metastases was reported to range between 0% and 43.7%, the average being 13.9%. However, no meta-anaylsis on END and survival was performed due to high heterogeneity among examined studies. Also, there are no published meta-analysis on this topic: one meta-analysis combined both TNDs and ENDs as one clinical setting which makes these results and recommendations questionable,[10] while other analysed other features of this tumor (molecular mutations, chromosomal abberations, lympovascular and perineural invasion). Additionally, no randomised trial on this topic has been conducted to date.

Given the fact that OS is the single most important feature of any relevant trial in oncology when examining potential efficacy of therapy, we decide to explore this end-point in cohort of AdCCHN undergoing END. In this meta-analysis, control group was consisted of AdCCHN patients with identical disease stage (cN0) being observed for the neck.

According to the results of this meta-analysis, observation of the cN0 neck is a rationale option for AdCCHN patients with cN0 irresepective of T stage. It's seems that END is not associated with survival benefit in any subgroup of patients having this rare tumour.

Rational explanation for this findings could be found in biological behaviour of AdCCHN. While neck metastases in vast majority of head and neck carcinomas are the single most important prognosticator of poorer outcome, this survival disadvantage may be less prominent is AdCCHN due to indolent course of this tumour. Additonal explanation could be potential higher rates of elective neck irradiation in observation cohort resulting in similar neck control compared to those achieved by neck surgery. However, most historical data analysing postoperative irradiation showed that this modality reduces local recurrence rates without influencing final outocome.[5,11] Furthermore, in this study patients within END group underwent adjuvant radiotherapy more often (absolute difference 5.7%) compared to no END cohort. On the contrary, insufficient data on adjuvant radiotherapy features (included regions, dose distribution, whether field covered the neck electively in observation cohort, included field in END group with/without occult neck metastases) make it impossible to draw clear conclusions on its role in cN0 setting. Also, in this meta-analysis observation group had less favorable tumor/treatment releated characteristics (almost half of the cases were minor salivary gland AdCC and radiotherapy was less used), while other variables were comparable (age, gender and T1/T2 stage disease) which probably exclude possibility of selection more favorable patients in the group in which END was omitted.

The main weakness of the analysis is the non-randomised design of included studies. Due to the lack of randomisation, the groups could vary in terms of characteristics associated with outcomes. While our results (i.e. **Table 2**) show differences between groups for major salivary glands there could also be differences for other variables not reported by this study. As with any analysis of studies of this design, the size of differences between groups could be confounded by other variables.

Additionally, publication, availability, and selection biases are a potential concern for meta-analyses, but many reviewers neglect to examine or discuss them.[12] Reviewers should seek individual participant data from all studies identified by a systematic review; include, where possible, aggregate data from any studies lacking individual participant data to consider their potential impact; and investigate funnel plot asymmetry.[12]

Also, these results must be taken with caution due to high hetrogeneity of the data. Another weakness of this studywas no stratification among END and no END subgroup based to the T stage (only two studies had this information) or hystological subtype of the AdCCHN with respect to survival which could influence obtained results.

Also, AdCCHN is not a homogenous entity and it does behave differently in its propensity to metastasize to the neck from different sites. Although, survival was not associated with any subgroup of patients we were not able to subdivide patients by site due to insufficient data from individual studies. It's well known that there are subsites with higher risk of occult neck metastases which could potentially benefit from END (i.e. floor of mouth and tongue primaries with higher T stage). Whether in this subpopulation END actually affects survival may never be able to be proven given the small numbers from published series.

According to this meta-analysis, although END is reported to provide staging information and is associated with a prolonged regional control, it does not affect survival. Despite the fact that neck status is the most important prognosticator in vast majority of the head and neck

malignancies, commonest pattern of recurrence and death among AdCCHN patients are distant metastases and/or local recurrence. To date, only one study demonstrated survival benefit of END being observed in a cohort of patients with advanced stage major salivary gland (MSG) AdCC, with the effect being most pronounced in those undergoing adjuvant radiotherapy (8% difference in survival between END *vs* observation group and absolute improvement in survival of 11.5% at 5-year in those receiving adjuvant irradiation compared to END alone).[8] However, subgroup analysis showed that observation cohort had higher percentage of minor salivary gland primaries (56.5% vs. 24.8%) which is sublocalization associated with poorer survival compared to the similar stage MSG AdCC.

In conclusion, it seems that initially cN0 neck should be rather observed for neck recurrence than treated "upfront" with prophylatic surgery of the neck. Most of the observed patients do not develop regional metastases during follow-up period making END questionable in terms of prognosis. This meta-analysis suggest conduction of prospective trial with balanced experimental and control arm in terms of other prognostic factors (age, gender, sublocalization of the primary, T stage, adjuvant radio(chemo)therapy, histological subtype of the AdCCHN etc.) and international consensus on the neck treatment in cN0 setting in order to assess it's role and treatment planning in AdCCHN patients.

Declarations

Funding: No funding

Competing Interests: Authors have no conflict of interest to declare.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research This is a meta-analysis of retrospective studies which were conducted on already available data for

which formal consent was obtained. Therefore, institutional ethical approval was not required according on the law and the national ethical guidelines.

Patient Consent: Patient consent was not required due to the fact that this is a meta-analysis of retrospective studies for which formal consent was obtained. Furthermore, personal details of patients are not known/available/included in any part of the paper and/or any supplementary materials.

REFERENCES

1. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. Am J Surg 1974;128:512-520.

2. Spiro RH. Distant metastasis in adenoid cystic carcinoma of salivary origin. Am J Surg 1997;174:495-498.

3. Luksic I, Suton P. Elective neck dissection in adenoid cystic carcinoma of head and neck: yes or no? A systematic review. Eur Arch Otorhinolaryngol 2019;276:2957-2962.

4. Lee SY, Kim BH, Choi EC. Nineteen-year oncologic outcomes and the benefit of elective neck dissection in salivary gland adenoid cystic carcinoma. Head Neck 2014;36:1796-1801.

5. Amit M, Na'ara S, Sharma K. Elective neck dissection in patients with head and neck adenoid cystic carcinoma: an international collaborative study. Ann Surg Oncol 2015;22:1353-1359.

6. Cordesmeyer R, Kauffmann P, Laskawi R, Rau A, Bremmer F. The incidence of occult metastasis and the status of elective neck dissection in salivary adenoid cystic carcinoma: a single center study. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:516-519.

7. Qian ZJ, Chen MM, Divi V, Megwalu UC. Impact of lymph node sampling on survival in cN0 major salivary gland adenoid cystic carcinoma. Head Neck 2019;41:1903-1907.

8. Xiao R, Sethi RKV, Feng AL, Fontanarosa JB, Deschler DG. The role of elective neck dissection in patients with adenoid cystic carcinoma of the head and neck. Laryngoscope 2019; 129:2094-2104.

9. Atallah S, Moya-Plana A, Malard O, Poissonnet G, Fakhry N, Bettoni J, et al. Should a neck dissection be performed on patients with cN0 adenoid cystic carcinoma? A REFCOR propensity score matching study. Eur J Cancer 2020 Jan 30. pii: S0959-8049(19)30894-9. doi: 10.1016/j.ejca.2019.12.026. [Epub ahead of print]

10. Ning C, Zhao T, Wang Z, Li D, Kou Y, Huang S. Cervical lymph node metastases in salivary gland adenoid cystic carcinoma: a systematic review and meta-analysis. Cancer Manag Res 2018;10:1677-1685.

11. Amit M, Binenbaum Y, Sharma K, Ramer N, Ramer I, Agbetoba A. Analysis of failure in patients with adenoid cystic carcinoma of the head and neck. An international collaborative study. Head Neck 2014;36:998-1004.

12. Ahmed I, Sutton AJ, Riley RD. Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. BMJ 2012;344:d7762.

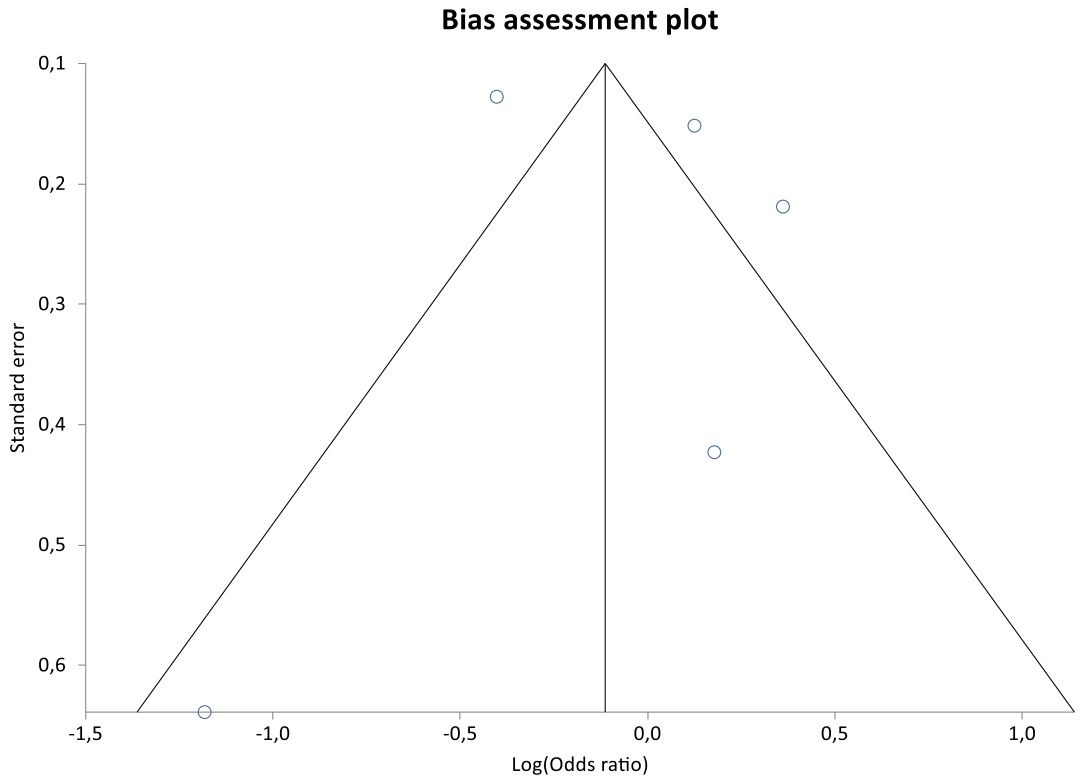
Figure legends

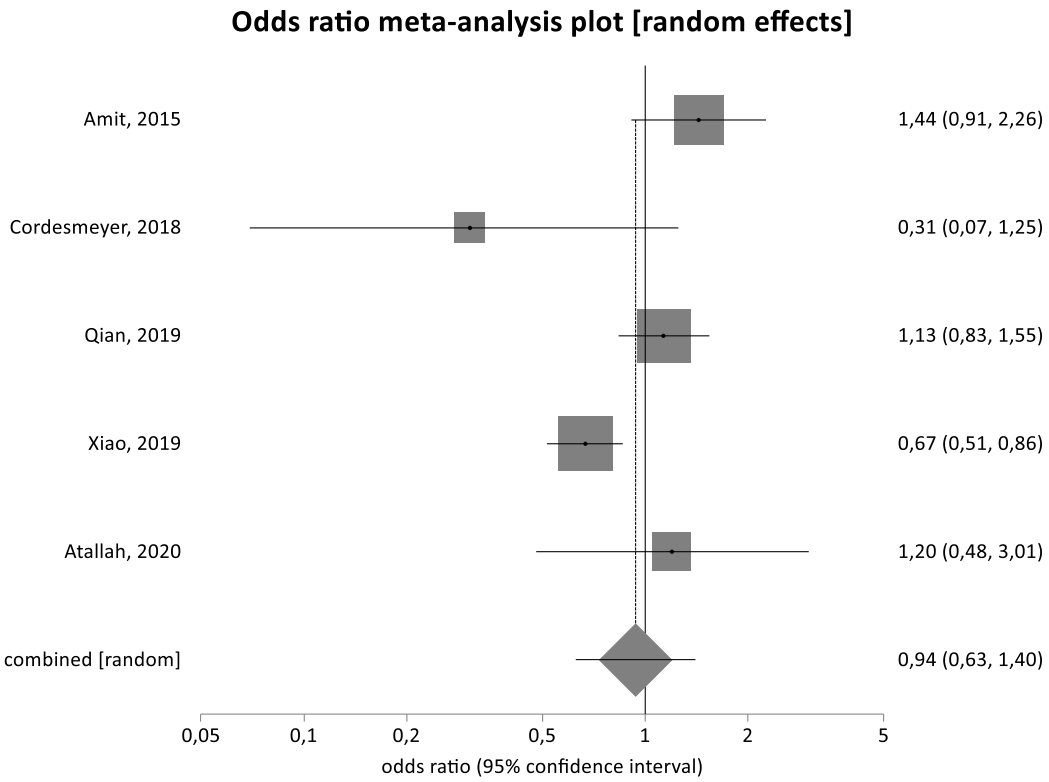
Figure 1. Bias asessment plot for five-year OS

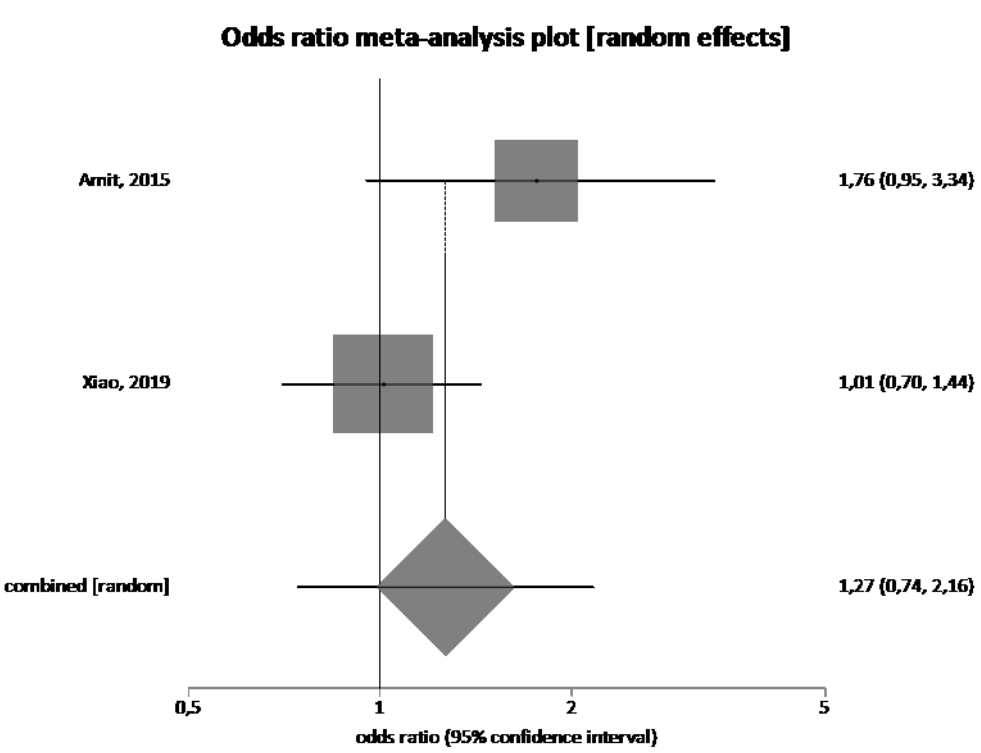
Figure 2. Meta-analysis of five-year OS (all-stages patients)

Figure 3. Meta-analysis of five-year OS (early-stage AdCCHN)

Figure 4. Meta-analysis of five-year OS (advanced-stage AdCCHN)


Bias assessment plot
0,1
0,2
0,3
0,4
0,5
0,6
Standard error
-1,5
-1,0
-0,5
0,0
0,5
1,0
Log(Odds ratio)


Odds ratio meta-analysis plot [random effects]
Amit, 2015
1,44 (0,91, 2,26)
Cordesmeyer, 2018
0,31 (0,07, 1,25)
Qian, 2019
1,13 (0,83, 1,55)
Xiao, 2019
0,67 (0,51, 0,86)
Atallah, 2020
1,20 (0,48, 3,01)
combined [random]
0,94 (0,63, 1,40)
0,05
0,1
0,2
0,5
1
2
5
odds ratio (95% confidence interval)


Odds ratio meta-analysis plot [random effects]
Amit, 2015
1,76 (0,95, 3,34)
Xiao, 2019
1,01 (0,70, 1,44)
combined [random]
1,27 (0,74, 2,16)
0,5
1
2
5
odds ratio (95% confidence interval)

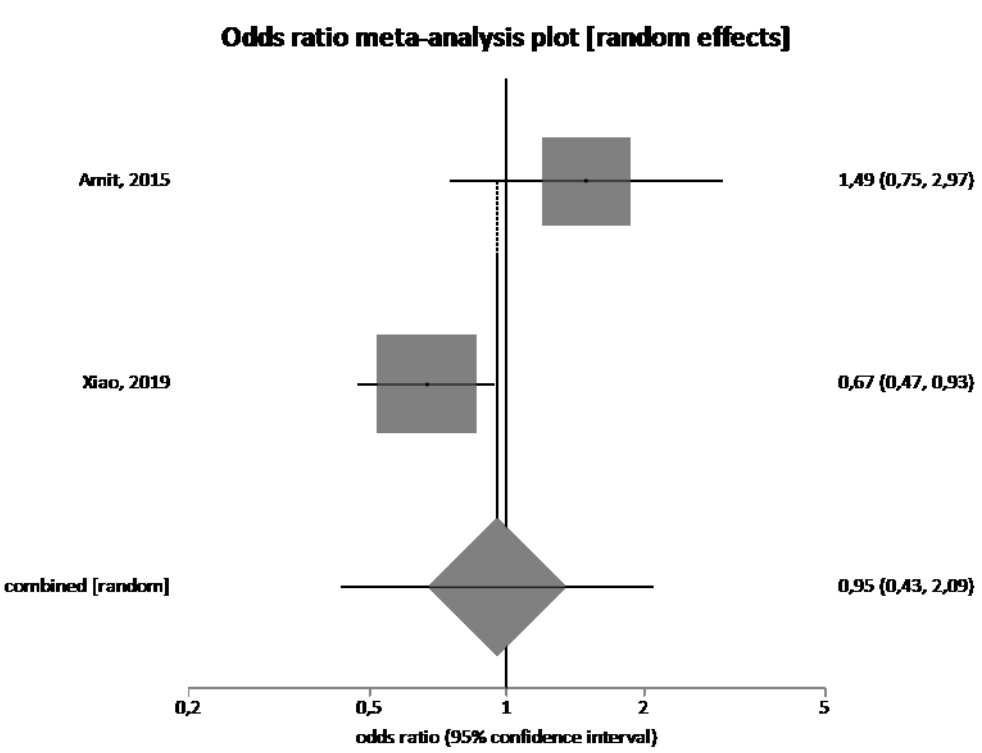

Odds ratio meta-analysis plot [random effects]
Amit, 2015
1,49 (0,75, 2,97)
Xiao, 2019
0,67 (0,47, 0,93)
combined [random]
0,95 (0,43, 2,09)
0,2
0,5
1
2
5
odds ratio (95% confidence interval)

Table 1. Occult neck metastases in patients with HNAdCC.

Author (year)	No. of patients	No. of END (%)	No of pts. with pN+ (%)	Oral cavity/Oropharynx N (%)	Sinonasal N (%)	MSG* N (%)
Amit (2015)	457	226 (49.5)	38 (17.3)	25 (21.5)	4 (16.7)	9 (10.6)
Cordesmeyer (2018)	59	34 (57.6)	7 (20.6)[†]			
Qian (2019)	1504[‡]	1190 (79.1)				104 (8.7)
Xiao (2019)	2807[§]	636 (22.7)	85 (13.4)			
Atallah (2020)	322	149 (46.3)[¶]	7 (4.7)	4 (57.1)	1 (14.3)	2 (28.6)

* major salivary glands

[†] 57.1% (4/7) of all occult neck metastases occured in oral cavity primaries

[‡] 314 patients had no lymph nodes sampled

[§] 1422 patients (50.7%) had major salivary gland primaries

[¶] after propensity score matching 96 patients were undergoing END submitted to survival analysis

Table 2. Patient's demographic and clinical characteristics.

	No END	END
Age, mean (y)	63.2	61
Female (%)	61.9	58.4
MSG* (%)	52.5	81.8
T1/T2 stage (%)	65.4	64.5
Adjuvant radiotherapy (%)	68.6	74.3

* major salivary glands