



Elective neck dissection in adenoid cystic carcinoma of head and neck: yes or no? A systematic review

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Abstract

Purpose Adenoid cystic carcinoma of head and neck (AdCCHN) is salivary gland malignancy known for its slow progression accompanied with perineural invasion, rare lymphatic spread to the neck, high rate of local recurrence and delayed onset of distant metastases. While local recurrence and distant metastases are most common patterns of relapse and cause of death in AdCCHN, it has been debated whether lymph node involvement affects the course of the disease. The aim of this systematic review was to address this important issue and to recommend guidelines on clinically node-negative neck management in patients with AdCCHN.

Methods A systematic review of the published literature on cases of elective neck dissection (END) among patients with AdCCHN was performed.

Results This analysis included a total of 5767 AdCCHN patients with 2450 ENDs, ranging from 10 to 1190. Elective lymphadenectomy was employed in 42.5% of patients with AdCCHN (range 9.2–100%). The overall rate of occult neck metastases in patients with AdCCHN was reported to range between 0 and 43.7%, the average being 13.9%.

Conclusions If performed, END should be limited to levels I–III of the ipsilateral neck since occult metastases are exclusively located within these neck regions. Although END is associated with a prolonged regional recurrence-free period, its influence on final outcome or survival is still controversial. This review strongly supports conduction of prospective trials on indications, prognostic significance and extent of END in AdCCHN.

Keywords Head neck · Adenoid cystic carcinoma · Elective neck dissection · Occult neck metastasis · Survival · Recurrence

Introduction

Adenoid cystic carcinoma of head and neck (AdCCHN) is a rare, slow growing, malignant epithelial tumor, with bidirectional differentiation towards luminal (ductal) and abluminal (myoepithelial and basal) cells [1, 2]. It comprises about 1% of all head and neck malignant tumours and about 10–15% of all salivary gland neoplasms [3]. AdCCHN is known for its slow progression accompanied with perineural invasion

(PNI), rare lymphatic spread to the neck (6–10%), high rate of local recurrence and delayed onset of distant metastases [4]. It can arise in a variety of sites in the head and neck including major salivary glands, as well as the minor salivary glands dispersed in the oral and oropharyngeal mucosa, paranasal sinuses, tracheobronchial tree and the oesophagus [3].

Although surgery is the gold standard of care for patients with AdCCHN, the role of adjuvant irradiation remains unclear. Whereas therapeutic neck dissection (TND) is performed in all clinically node-positive patients, management of cN0 neck is still controversial and elective neck dissection (END) is not routinely carried out in patients with AdCCHN. It has been debated whether lymph node involvement affects the course of the disease as local recurrence and distant metastasis have traditionally been identified as more important predictors of survival. Whereas isolated lymph node involvement may not have significantly

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altered survival, lymph node involvement is a risk factor for subsequent development of distant metastases [5]. To date, only few published series reports on END in AdCCHN. Furthermore, in these studies, there were not strict criteria or established protocols whether or not to perform END which can result in significant differences between published data. In addition, given the rarity of these tumors, most of the series include small cohorts, different histological subtypes of salivary gland malignancies and head and neck sublocalizations making it difficult to compare results and draw clear conclusions or suggestions on prophylactic neck treatment in these patients. The aim of this systematic review was to address this important issue and to recommend guidelines on clinically node-negative neck management in patients with AdCCHN. Additionally, other characteristics of prophylactic neck dissection specimen (distribution of occult neck disease, lowest involved region, and extranodal extension) and its potential influence on survival were analysed. To our knowledge, this is the largest study analysing the role of END in AdCCHN and the first critical review on all important features of occult neck disease in AdCCHN.

Materials and methods

The authors performed search of available scientific literature for creating systematic review regarding effect of END on patients with AdCCHN. Our search used terms: head neck, and adenoid cystic carcinoma as a primary endpoint. Inclusion criteria were: (1) AdCCHN, (2) primary surgical treatment including END, and (3) known data regarding occult neck disease rates. The criteria for exclusion were: (1) specific diagnosis of adenoid cystic carcinoma could not be separated from other salivary gland tumours reported (aggregated salivary gland histology subtypes); (2) no information on lymph node status (clinically and histopathologic); (3) END rates not stated; (4) tumours that arose primarily at extremely rare subsites (lacrimal gland, external auditory canal) and those with low incidence (<0.5% overall) of occult neck disease (laryngeal AdCC); (5) less than ten cases of AdCCHN treated with END. Relevant data were collected using following scientific databases: PubMed, MEDLINE, EMBASE, Web of Science, ScienceDirect, and Scopus. The search was completed on August 5, 2019. To increase the quality of performed search, every reference with the least indication for fulfilling the inclusion criteria was analysed. In addition, we performed a screening of a reference list of all analysed articles to increase the quality and broaden the scope of our search. Search was performed by two head and neck oncology experts (I.L. and P.S.) who included or excluded article by criteria presented in Fig. 1, independent of each other. Initial search resulted in articles, while the final number of articles included in this review fall

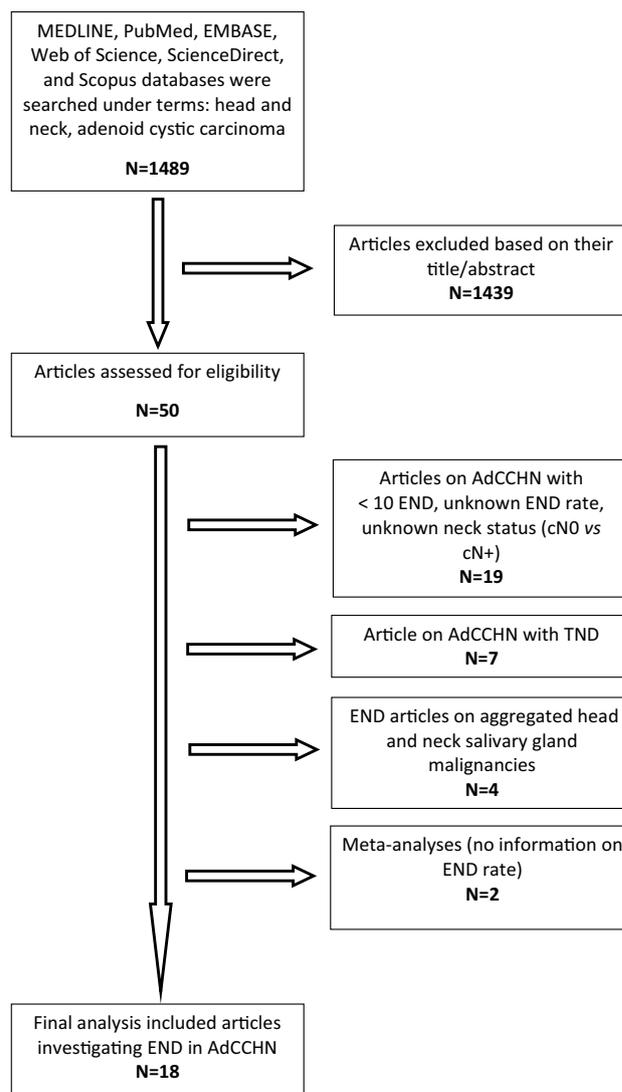


Fig. 1 Study selection flowchart

to, after application of exclusion criteria mentioned above. Articles included in this review had retrospective design, due to the lack of more quality evidences in a form of prospective randomised trials. In addition, during our search, we concluded that meta-analysis cannot be performed because of high heterogeneity present between the studies.

Results

Our initial PubMed search identified articles with patients with AdCCHN were analysed in this review. This review included 18 studies with a total of 5767 AdCCHN undergoing END in 2450 cases, ranging from 10 to 1190 [6–23]. Included studies are presented in Table 1. Elective lymphadenectomy was employed in 42.5% of patients with AdCCHN

Table 1 Occult neck metastases in patients with AdCCHN

Author (year)	No. of patients	No. of END (%)	No of pts. with occult neck metastases (%)	Oral cavity/oropharynx N (%)	Sinonasal N (%)	MSG ^a N (%)
Agarwal (2008)	76	29 (38.2)		9 (31)		
Ali (2017)	87	84 (96.6)	7 (8.3)			
Amit (2013)	99	15 (15.1)			1 (6.7)	
Amit (2015)	457	226 (49.5)	38 (17.3)	25 (21.5)	4 (16.7)	9 (10.6)
Balamucki (2012)	120	11 (9.2)	2 (18.2)			
Bhayani (2012)	60	30 (50.0)				7 (23.3) ^b
Cohen (2004)	22	17 (77.3)				0 (0) ^c
Cordesmeyer (2018)	59	34 (57.6)	7 (20.6) ^d			
Garden (1995)	198	46 (23.2)	16 (34.8)			
Iyer (2010)	67	16 (23.9)		4 (25)		
Lee (2013)	38	13 (34.2)	4 (30.8)			
Lee (2014)	61	26 (42.6)	4 (15.4) ^e			
Luksic (2016)	45	15 (35.6)	2 (13.3) ^f			
Nobis (2014)	19	16 (84.2)	7 (43.7)			
Qian (2019)	1504 ^g	1190 (79.1)				104 (8.7)
Stenner (2012)	10	10 (100)				2 (20) ^h
Wang (2012)	38	36 (94.7)	5 (13.9)			
Xiao (2019)	2807 ⁱ	636 (22.7)	85 (13.4)			

^aMajor salivary glands^bSix patients had ENE^cSubmandibular primaries^d57.1% (4/7) of all occult neck metastases occurred in oral cavity primaries^eNot including four patients (not receiving neck dissection initially) who experienced neck failure during follow-up period^fNot including two patients (not receiving neck dissection initially) who experienced neck failure during follow-up period^g314 patients had no lymph nodes sampled^hParotid gland AdCCⁱ1422 patients (50.7%) had major salivary gland primaries

(range 9.2–100%). The overall rate of occult neck metastases in patients with AdCCHN was reported to range between 0 and 43.7%, the average being 13.9%. Sublocalization of the primary tumor in relation to occurrence of neck micrometastases was reported by eight authors [6, 8, 9, 11, 12, 15, 20, 21], while other authors reported on aggregated head and neck subsites. The relative rates of neck micrometastases were the highest among oral cavity/oropharyngeal primaries (21.5–31%), followed by major salivary gland primaries (0–23.3%), with sinonasal AdCC affecting only 6.7–16.7% of patients submitted to END. These metastases were most often solitary unilateral metastatic deposits (pN1 disease) (94 of all neck dissection specimens) [9]. Anatomic distribution of occult neck metastases was reported by four studies being located in all cases within level I–III [9, 16–18]. Only one study reported on data with respect to lymph node capsule status. In this study, addressing prognostic factors in early-stage AdCCHN, authors proved that 85.7% (6/7) of patients with positive lymph node status experienced

extranodal extension (ENE) [11]. Histopathology subtype of the primary tumor in relation to regional metastases was reported by two studies with all three subtypes being associated with occult neck disease occurrence [16, 17].

Five studies reported on prognostic significance of END with respect to survival [9, 13, 17, 20, 23]. The data provided by previously mentioned studies reported conflicting results. In one of the largest study in the English literature examining the role of END, Amit et al. reviewed 457 patients of which 226 underwent prophylactic neck treatment [9]. The overall rate of occult neck metastases was 17.3% (38/226). Subgroup analysis showed that the highest incidence of micrometastases was among oral cavity/oropharyngeal primaries (66%, 25/38) and those with major salivary gland AdCC (24%, 9/38). The lowest incidence was among sinonasal AdCCs (10%, 4/38). These micrometastases were identified exclusively within levels I–III of the ipsilateral neck. The authors found no statistical difference in 5-year disease-specific survival (DSS) and overall survival

(OS) rates between patients who underwent END and those who did not (74% vs 81% and 72% vs 79%, respectively, $p=0.06$ and $p=0.08$). In addition, the 5-year regional and distant control rates did not differ between these two groups.

Similarly, three additional studies found no difference with respect to OS between patients who underwent END and those who did not [13, 17, 20].

On the contrary, Xiao analysed 2807 patients with AdCCHN treated surgically, of which 636 (22.7%) underwent END [23]. In this study, END was associated with extended OS for advanced stage AdCC of the major salivary glands (5-year OS 78.1% vs. 70.4%, $p=0.041$), while no difference in final outcome between the cohorts with early-stage disease was found (5-year OS 86.8% vs. 85.5%, $p=0.536$).

Discussion

AdCC accounts for 3–5% of all head and neck malignancies. It is characterised by intermediate grow rate, low probability of regional lymphatic involvement and frequent distant metastases.

Although surgical treatment is the gold standard of care for this patients, the role of adjuvant radiotherapy remains unclear. Whereas TND is performed in all cN+ patients, management of cN0 neck is still controversial and END is not routinely carried out in patients with AdCCHN. The decision regarding END is based on the incidence of occult lymph node metastases and expected impact of treatment on survival. Given the lack of data on incidence of neck metastases and its influence on final outcome, the association between occult neck disease and OS remain inconclusive. The main objective of this study was to determine incidence of lymph node metastases in elective settings and its potential impact on survival to guide more clearly indications for prophylactic neck treatment.

The only meta-analysis on cervical lymph nodes metastases in AdCCHN was published by Ning et al. [24]. According to the results on overall incidence of occult neck disease in AdCC of the minor salivary gland (25%), authors suggested that neck dissection may be applied in this subgroup of patients. However, these results must be taken with caution. Only four studies which were included in the meta-analysis had an information on END, while other studies ($N=14$) analysed frequency on neck disease from AdCC within TND settings.

According to the results of our analysis, neck treatment was employed 42.5% patients with AdCCHN. The overall rate of occult neck metastases in patients with AdCCHN was reported to range between 0 and 43.7%, the average being 13.9%. The relative rates of neck micrometastases were the highest among oral cavity/oropharyngeal primaries

followed by major salivary gland primaries, with sinonasal AdCC affecting lymphatics in smallest number of patients submitted to END. Occult neck metastases were most often reported as solitary unilateral metastatic deposits. Only one study reported on data with respect to lymph node capsule status. In this study, the authors proved that ENE is frequent event in early-stage AdCCHN [11]. Histopathology subtype of the primary tumor in relation to regional metastases was reported by two studies with all three subtypes being associated with occult neck disease occurrence [16, 17].

A special entity among AdCCs represents high-grade transformation (HGT) or “dedifferentiated” AdCC. First described by Cheuk et al. in 1999 [25] with histological criteria for diagnosis outlined by Seethala in 2007 [26], this form of AdCC is characterised by high propensity for lymph node metastasis (range 43–57%) and distant metastatic spread with mean survival being only 4.2 years [27]. If diagnosed after extirpative surgery of the primary, post-operative END or elective neck irradiation (ENI) seems an appropriate treatment option.

The retrospective design of the included studies represents the primary limitation of this study. In addition, this study included all available studies on AdCCHN from different time periods. During this time, diagnostic workup and treatment modalities have evolved. As such, the management of the study population is not homogeneous and may influence final outcome and the results obtained from statistical analysis. Furthermore, given the rarity of these tumors, series included in this review contain small cohorts, different histological AdCC subtypes and head and neck sublocalizations (different biological behaviours including propensity for regional lymphatics), and insufficient data on neck status (different diagnostics for cN0 status, no information on distribution of neck micrometastases and/or ENE, lack of information on extend of END, insufficient data on treatment of observation cohort (“no END” patients) and post-operative treatment (application of adjuvant radiotherapy, neck irradiation, doses and type of radiotherapy), making it difficult to draw clear conclusions on neck treatment and outcome in elective setting. Additionally, the study could not be strengthened by a meta-analysis due to the small number of cases and limited number of studies which analysed END in context of OS as most important primary endpoint of oncological trials.

On the contrary, this is the largest review on the topic (5767 AdCCHN patients with 2450 END specimens), providing more clear informations in which clinical scenarios END might be performed until data from randomised controlled trials on both indication and extend of neck surgery with mature follow-up in the context of survival are available.

According to this critical review, occult neck metastasis rate in AdCCHN is around 15%. Although END can

provide staging and prognostic information and is associated with a prolonged regional recurrence-free period, its influence on final outcome or survival remains unclear. Despite the fact that neck status is the most important prognosticator in head and neck cancers, most patient with AdCCHN die from distant metastases and/or unresectable local recurrence rather than regional recurrence. To date, only one study demonstrated survival benefit being observed in a cohort of patients with advanced stage MSG AdCC [23]. While there is no doubt that patients undergoing END benefit from prophylactic lymphadenectomy at the time of the surgery for primary tumor compared to TND counterparts, there is still a debate whether initially cN0 neck should be treated “upfront” with END or being observed for neck recurrence. Most of the latter patients do not develop regional metastases during follow-up period making END questionable both as staging and therapeutic procedure. If performed, END should be limited to levels I–III of the ipsilateral neck since occult metastases are exclusively located within these neck regions. It may be considered in selected cN0 patients with AdCCHN located in lymph-rich regions such as oral (floor of the mouth, anterior two-third of the tongue), oropharyngeal (tongue base) and submandibular area, cases of advanced stage major salivary gland AdCC, cases of lymphovascular invasion within the primary tumor, solid histopathologic subtype and rare cases of HGT-AdCC. Another possible treatment option is omission of END and performance of ENI which can provide regional recurrence-free period although without influence on final outcome. This review strongly supports conduction of prospective trial on the extend of surgical treatment of the neck in prophylactic settings to assess the role and prognostic significance of END in patients with AdCCHN. Until then, all patients with AdCCHN should be considered by a multidisciplinary team on a case-by-case basis to provide the optimal and most beneficial treatment strategy.

Compliance with ethical standards

Research involving human participants and/or animals All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This is a systematic review on retrospective studies which were conducted on already available data for which formal consent was obtained. Therefore, institutional ethical approval is not required according on the law and the national ethical guidelines.

Informed consent Informed consent was not obtained from individual participants due the fact that this review included retrospective studies for which formal consent was obtained.

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