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Cervical lymph node metastasis in adenoid cystic carcinoma of the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal: a collective international review

INTERNATIONAL HEAD AND NECK SCIENTIFIC GROUP*

Abstract

Objective—To review reports of adenoid cystic carcinomas arising in the head and neck area outside of the major salivary glands, in order to enhance the care of patients with these unusual neoplasms.

Methods—An international team of head and neck surgeons, pathologists, oncologists and radiation oncologists was assembled to explore the published experience and their own working experience of the diagnosis and treatment of adenoid cystic carcinomas arising in the vicinity of the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal.

Results—The behaviour of adenoid cystic carcinoma arising in head and neck sites exclusive of the major salivary glands parallels that of tumours with a similar histology arising in the major

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salivary glands – these are relentless, progressive tumours, associated with high rates of mortality. Of 774 patients reviewed, at least 41 (5.3 per cent) developed documented regional node metastases.

Conclusion—The relatively low overall incidence of nodal metastases in adenoid cystic carcinomas arising in the head and neck region outside of the major salivary glands suggests that routine elective regional lymph node dissection might not be indicated in most patients with these tumours.

Keywords

Adenoid Cystic Carcinoma; Elective Surgical Procedures; Lymphatic Metastasis; Paranasal Sinus Neoplasms; Nasopharyngeal Neoplasms; Ear Canal; Lacrimal Apparatus; Neck Dissection; Lymph Nodes

Introduction

Adenoid cystic carcinoma is an uncommon head and neck tumour, representing 4–10 per cent and 7.5 per cent of all epithelial tumours and salivary gland malignancies respectively. It normally appears as an indolent, slow-growing mass, and is associated with late distant metastases and frequent local recurrences.[1]

Treatment protocols for adenoid cystic carcinoma are not firmly established and may lead to undesirable outcomes. This issue is especially pronounced when adenoid cystic carcinoma occurs in uncommon sites, such as the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal. As lymph node metastases are infrequent in adenoid cystic carcinoma, the need for an elective neck dissection is controversial.

This paper aimed to review published cases of adenoid cystic carcinoma in these unusual locations, to establish the frequency of lymph node metastasis and determine whether or not elective neck dissection may be warranted. The methods for establishing nodal status vary. Discussion of which imaging techniques should ideally be used for the detection or exclusion of lymph node metastasis, initially or in follow up, is beyond the scope of this review, but the techniques used should not be different from those deployed for other pathologies.

Materials and methods

A review was conducted of English-language publications on adenoid cystic carcinoma of the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal, for information on clinicopathological features, therapy and outcome. The Medline database was searched for articles published between 1966 and 2015.

Approximately 114 articles were identified, but most had to be excluded. The criteria for exclusion were: (1) specific diagnosis of adenoid cystic carcinoma could not be separated from other salivary gland tumours reported; (2) data regarding the primary tumour site were not specifically stated; (3) data regarding management could not be separated from generalised outcome information; (4) specific details about lymph node dissection were not

included; (5) information on lymph node status was not included (e.g. in ‘Quiz’ or ‘Case of the Month’ type reports); (6) tumours that arose primarily in the oral cavity, palate, alveolar ridge, upper lip, oropharynx or parotid gland with direct contiguous extension into the sites of interest; (7) age-limited reports (paediatrics only); and (8) information was too generalised and non-specific to meaningfully interpret the demographics, management or patient outcome. The remaining literature is included herein.

Sinonasal tract and nasopharynx

Adenocarcinomas arising in the paranasal sinuses and nasal cavity (sinonasal tract) and nasopharynx may be categorised into those arising from the surface (i.e. intestinal and non-intestinal-type sinonasal adenocarcinomas) and those arising from the mucoserous or minor salivary-type glands. While sinonasal tract carcinomas are uncommon overall, adenoid cystic carcinoma is the most common salivary-type adenocarcinoma in this anatomical location. Adenoid cystic carcinoma may arise in patients of a wide age range (mean age of 50–60 years), and affects men and women at similar rates.[2,3]

Adenoid cystic carcinoma in the sinonasal tract arises most often from the maxillary sinus, and presents as early stage (I or II) disease in approximately 50 per cent of cases.[2] Histologically, adenoid cystic carcinoma in this location is similar to what is encountered in salivary glands, growing as a biphasic population of luminal and non-luminal cells, arranged in tubules, cribriform structures and solid nests, with frequent peri-neural invasion. Adenoid cystic carcinoma can be mis-classified in this location, however, possibly because it may be unexpected.[2]

Sinonasal tract adenoid cystic carcinoma is often managed with surgery, with or without external beam radiation therapy. Survival rates are similar to those for major salivary gland tumours, with 5-year and 10-year overall survival rates of approximately 65 per cent and 40–50 per cent, respectively.[2–4]

Case reports of lymph node metastasis have been summarised in Table I.[2,3,5–13] Most papers reported up to 3 patients with lymph node metastases, except the article by Amit *et al.* which included 13 patients with lymph node metastases.[9]

In a recent report by Thompson *et al.*, all but 1 of 86 patients with sinonasal tract adenoid cystic carcinoma had clinically node-negative (N_0) necks at the time of presentation, while 70 patients were subjected to elective neck dissection (lymph node sampling, sentinel lymph node biopsy or modified radical neck dissection).[2] Of the 86 patients, only 3 presented with distant metastatic disease at initial clinical evaluation. Two of these three patients had disease to bone and one had disease to the lungs; all three patients had clinically staged N_0 necks. The one patient with a neck mass at presentation showed only benign reactive lymphoid hyperplasia of the lymph nodes sampled.[2,14] Two patients who developed high-grade transformation lacked lymph node metastasis at presentation, but both died with locally recurrent and metastatic disease less than one year after initial presentation.[2] In sinonasal tract adenoid cystic carcinoma, bone invasion ($p = 0.005$), perineural invasion ($p < 0.0001$) and lymphovascular invasion ($p = 0.006$) were all found to be statistically

significantly correlated with a worse patient outcome, but not with lymph node disease.[2] Similarly, even though many patients presented with a pathologically staged T_3 or T_4 (advanced stage) primary tumour, these patients did not present with lymph node metastases. Therefore, this group of patients presented with primarily local disease only (i.e. no lymph node or distant metastasis), a finding confirmed in other studies.[3,5] Nevertheless, local disease does not imply early stage disease. In fact, the majority of patients present with advanced stage disease according to pathologically staged T classification.

In a study reporting on outcomes of skull base surgery in patients with sinonasal tract adenoid cystic carcinoma, Pitman *et al.* found that 0 of 35 patients had regional metastases on presentation.[5] Six of the 35 patients subsequently developed 'regional recurrences', but additional details were not provided. Similarly, a 40-year review article by Wiseman *et al.* reported 1 patient with a 'neck recurrence' among 35 cases of adenoid cystic carcinoma, though further data are not provided.[6] Amit *et al.* conducted a meta-analysis of sinonasal tract adenoid cystic carcinomas.[9] Of the 41 patients subjected to neck dissection (from a cohort of 99 patients treated between 1985 and 2011 in 9 cancer centres worldwide), 13 (13 per cent) had regional lymph node metastases.[9]

Husain *et al.* conducted a meta-analysis of the literature on sinonasal tract adenoid cystic carcinoma published up to 2012, which included 88 individual cases and aggregated data on 366 patients.[15] The authors concluded that surgery of the primary tumour, with radiation and/or chemotherapy, is generally employed, and is possibly the most effective therapy. However, data regarding lymph node dissection or lymph node sampling were not included. Likewise, a large analysis of the Surveillance, Epidemiology, and End Results registry was conducted for sinonasal tract adenoid cystic carcinoma,[4] but does not include data regarding lymph node status or lymph node sampling.

Overall, the available information indicates that lymph node metastasis of adenoid cystic carcinoma from the sinonasal tract and nasopharynx is relatively uncommon, suggesting that elective neck lymph node dissection is not advisable.

Lacrimal gland

Tumours of the lacrimal gland are rare, but adenoid cystic carcinoma is the most common malignant epithelial neoplasm therein.[16–18] Adenoid cystic carcinoma generally affects adults (with a mean age of 40 years),[19] but can arise in children as young as 6 years.[18,20–22] Patients with adenoid cystic carcinoma of the lacrimal glands present with short histories of eye-related symptoms such as pain, diplopia and ptosis.[18,20,22] In this location, adenoid cystic carcinoma is essentially identical to what is encountered in the major salivary glands and other sites.[18,23] The majority of lacrimal gland adenoid cystic carcinomas are high-grade (solid/basaloid) phenotype which translates into a more aggressive clinical course and shorter median survival of only 2.5 years compared to other sites of origin.[24,25] Indeed, even with aggressive therapy including radical resection and/or external beam radiation, the recurrence rate is as high as 75 per cent.[18,22] Most patients eventually experience distant metastases, most frequently to the lung, and the 10-year survival is approximately 50 per

cent.[24–26] Outcomes are improved in children and in tumours that lack a component of solid growth.[18,21,23]

Most series of lacrimal gland adenoid cystic carcinoma have not specifically commented on the rate of documented regional lymph node metastases (including intraparotid gland lymph nodes), but these appear to be uncommon (Table II).[25,27–30] Interestingly, metastases to lacrimal glands from the parotid gland have been reported; thus, when encountering adenoid cystic carcinoma of the lacrimal glands, metastasis from a primary major salivary gland must be excluded.[31] Douglas *et al.* reviewed 151 patients with adenoid cystic carcinoma of the head and neck, including 32 cases of adenoid cystic carcinoma of the paranasal sinuses, 15 of the nasopharynx and 7 of the lacrimal glands.[32] They analysed all the locations together and concluded that 'at 5 years, 50 per cent of lymph node positive patients had developed distant metastases compared to 26 per cent ($p < 0.001$) of lymph node negative patients'.

External auditory canal

The external auditory canal, which spans the space between the auricle and the tympanic membrane, may give rise to a variety of both benign and malignant tumours. The great majority (over 90 per cent) of external auditory canal malignancies prove to be squamous cell carcinomas and basal cell carcinomas; less than 5 per cent are adenoid cystic carcinomas.[33,34]

Adenoid cystic carcinoma of the external auditory canal is presumed to arise from the apocrine-type ceruminous glands. It is regarded as one of the subtypes of 'ceruminous adenocarcinoma', comprising the glandular-derived malignant tumours of the external auditory canal.[35] These tumours most often present with ear pain, mass and/or hearing changes, with a mean age at presentation within the fifth decade of life. While the rarity of these lesions in this location limits analysis, there are rare instances of metastatic disease to cervical lymph nodes, with approximately 11 per cent of cases showing clinically occult disease.[33,36–39] Diagnostic criteria include exclusion of extension from a salivary gland (parotid gland) primary, by clinical assessment, imaging or gross examination.

Adenoid cystic carcinomas arising in the external auditory canal appear to be aggressive tumours and are usually treated by wide local resection, with possible adjuvant radiotherapy. Local recurrences have been reported in 40–60 per cent of patients, and have been detected as long as 15 years after initial diagnosis. Death from this disease is most often attributed to intracranial spread of tumour or distant metastasis (in particular, involving the lung),[33,36] rather than from metastatic disease to lymph nodes.

Conclusion

Adenoid cystic carcinoma is rare in the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal; furthermore, our review suggests that regional lymph node metastasis of this tumour is uncommon. Hence, elective neck dissection (including parotidectomy) seems unwarranted in most cases, but may be considered in some cases of: pathologically staged advanced disease, solid histological subtype or high-grade

transformation. Given the very low incidence of lymph node metastases in these locations, it is preferable to follow up the patients with careful, routine examination of the neck, possibly using ultrasound or ultrasound-guided fine-needle aspiration biopsy, computed tomography or magnetic resonance imaging (MRI). For the sinonasal tract, nasopharynx, lacrimal glands and external auditory canal, MRI is probably the most often used method in follow up, as it has higher sensitivity and specificity in detecting perineural spread to the skull base.[40]

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TABLE I

CASES OF PARANASAL SINUS, NASAL CAVITY AND NASOPHARYNGEAL ADENOID CYSTIC CARCINOMA WITH LYMPH NODE METASTASIS

Study (year)	Cases (*n*)	Lymph node metastasis cases (*n*)
Pitman *et al.*[5] (1999)	35	0 (6*)
Wiseman *et al.*[6] (2002)	35	0 (1*)
Sung *et al.*[7] (2003)	94	3
Rhee *et al.*[8] (2006)	35	2
Lupinetti *et al.*[3] (2007)	105	2
Amit *et al.*[9] (2013)	99	13
Choi *et al.*[10] (2013)	88	2
Gendeh *et al.*[11] (2013)	4	0
Michel *et al.*[12] (2013)	25	1
Seong *et al.*[13] (2014)	30	1
Thompson *et al.*[2] (2014)	86	0
Total	636	24

*‘Neck’ and ‘regional’ recurrences are presented (no further data are provided).

TABLE II

CASES OF LACRIMAL GLAND ADENOID CYSTIC CARCINOMA WITH LYMPH NODE METASTASIS

Study (year)	Cases (*n*)	Lymph node metastasis cases (*n*)
Friedrich *et al.*[27] (2003)	84	15
Esmaeli *et al.*[25] (2004)	20	1
Ahmad *et al.*[28] (2009)	16	0
Roshan *et al.*[29] (2015)	10	0
Sanders *et al.*[30] (2016)	8	1
Total	138	17