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REVIEW ARTICLE

Cervical lymph node metastasis in adenoid cystic carcinoma of the major salivary glands

INTERNATIONAL HEAD AND NECK SCIENTIFIC GROUP*

INTERNATIONAL HEAD AND NECK SCIENTIFIC GROUP

Abstract

Objective: To verify the prevalence of cervical lymph node metastasis in adenoid cystic carcinoma of major salivary glands, and to establish recommendations for elective neck treatment.

Methods: A search was conducted of the US National Library of Medicine database. Appropriate articles were selected from the abstracts, and the original publications were obtained to extract data.

Results: Among 483 cases of major salivary gland adenoid cystic carcinoma, a total of 90 (18.6 per cent) had cervical metastasis. The prevalence of positive nodes from adenoid cystic carcinoma was 14.5 per cent for parotid gland, 22.5 per cent for submandibular gland and 24.7 per cent for sublingual gland. Cervical lymph node metastasis occurred more frequently in patients with primary tumour stage T_{3-4} adenoid cystic carcinoma, and was usually located in levels II and III in the neck.

Conclusion: Adenoid cystic carcinoma of the major salivary glands is associated with a significant prevalence of cervical node metastasis, and elective neck treatment is indicated for T_3 and T_4 primary tumours, as well as tumours with other histological risk factors.

Key words: Adenoid Cystic Carcinoma; Parotid Gland; Submandibular Gland; Sublingual Gland; Cervical Lymph Node Metastasis

Introduction

Adenoid cystic carcinoma is an uncommon tumour, with a reported yearly incidence of 3–4.5 cases per million.[1] While, in most centres, mucoepidermoid carcinoma is the most common histological type of parotid cancer, a nationwide inquiry in Denmark reported adenoid cystic carcinoma to be the most frequent type of carcinoma arising in the parotid gland, representing approximately 25.2 per cent of cases.[1]

The natural history is that of a relentless, slowly progressive malignant tumour, characterised by frequent local recurrence and late distant haematogenous metastases (lung, liver, bone or brain), often preceded by one or more local recurrences. Although the long-term prognosis is relatively poor, this tumour tends to have a prolonged clinical course, and survival often exceeds 10–15 years.

When adenoid cystic carcinoma involves regional lymph nodes, it is often the result of direct extension from an adjacent primary tumour site, particularly the submandibular gland (see below). True embolic nodal metastasis has traditionally been regarded as a distinctly uncommon event. Recently, however, Amit *et al.*, in an international collaborative study involving nine cancer centres worldwide, have challenged the latter long-held concept.[2] In their retrospective study of 270 patients with adenoid cystic carcinoma of the head and neck who underwent neck dissections, they observed a 29 per cent overall rate of nodal metastases. The rate was highest (37 per cent) for tumours originating in the oral cavity, followed by those involving the major salivary glands (19 per cent). In the same year, Amit *et al.* reported a 17 per cent prevalence of occult nodal metastases among patients with adenoid cystic carcinoma who underwent elective neck dissection.[3]

The present study aimed to verify the reported prevalence of cervical lymph node metastasis in adenoid cystic carcinoma of major salivary glands based on a critical review of the literature, and to establish recommendations for elective neck treatment in adenoid cystic carcinoma of the parotid, submandibular and sublingual salivary glands.

Materials and methods

The US National Library of Medicine (PubMed) database was searched using the terms ‘adenoid cystic carcinoma and cervical lymph nodes’ and ‘adenoid cystic carcinoma and elective neck dissection’. Articles, with

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*See Authorship section for full list of collaborators.

data concerning regional metastasis in adenoid cystic carcinoma of major salivary glands, were selected from the abstracts, and the original publications were obtained to extract data. The electronic search was supplemented with papers obtained by crosschecking the bibliographies of relevant articles. Only original articles published in English language or with an abstract in English, involving human subjects, were selected for further review. Both recent and older studies were reviewed to determine if the reported prevalence and pattern of regional disease had changed over time.

Parotid gland

A precise histological diagnosis of parotid and other major salivary gland tumours, and the ability to evaluate particular risk factors, is often not possible pre- or intra-operatively, because an open surgical biopsy is rarely performed on these lesions. The diagnostic accuracies for malignancy and exact histological type with fine needle aspiration cytology, the usual pre-operative 'biopsy' procedure, have been reported as 86 per cent and 56 per cent, respectively.[4] Higher accuracy has been achieved in some centres. Postema *et al*. reported accurate diagnosis of adenoid cystic carcinoma in all 12 cases among a series of 388 salivary gland tumours treated at the Netherlands Cancer Institute, although a false positive diagnosis of adenoid cystic carcinoma was reported in 3 cases of monomorphic adenoma in the same cohort.[5] Zbären *et al*. noted that in about 55 per cent of parotid cancers, neither the exact tumour type nor the histological grade were ascertained by aspiration cytology or frozen section at the time of surgery.[6]

Therefore, as a practical matter, while parotid malignancy is often recognised pre- or intra-operatively, in almost half the cases it is not known whether the lesion is an adenoid cystic carcinoma, or other type of salivary gland cancer, and the presence of histological risk factors for lymph node metastasis cannot be evaluated pre-operatively. For this reason, and because the parotid gland is situated at the superior periphery of the neck, initial treatment often consists of parotidectomy alone in cases without clinically apparent metastasis. Elective neck treatment is often rendered after the initial surgery, unless there are strong indications to proceed with neck dissection at initial operation.

A literature review reported the prevalence of lymph node metastasis in parotid carcinoma as ranging from 12.4 per cent to 24 per cent.[7] However, in one series reported by Stennert *et al*., of 139 patients who presented with clinically staged node-negative (N_0) major salivary gland malignancies, all cases underwent neck dissection, and 45 per cent had positive lymph nodes in their neck specimen.[8] One factor, easily determined pre-operatively, that does correlate with occult metastasis is primary tumour (T) stage, and several authors have noted that most cervical metastases occurred in patients with T_3 or T_4 tumours.[7–10] Tumours of 4 cm or more in size have a 20 per cent risk of occult metastases, compared with a 4 per cent risk for smaller tumours.[11] In the future, biomarkers of metastatic risk may aid in the decision making of such patients, particularly if an analysis could be performed on needle aspiration material obtained pre-operatively. For example, one study has identified that genetic aberrations of the molecular markers phosphatase and tensin homologue, and hepatocyte growth factor receptor, are powerful predictors of lymph node metastasis in salivary gland cancers.[12]

Regarding neck treatment, Cummings, in 1977, found that facial nerve involvement and pain attributed to perineural invasion (Union for International Cancer Control classification T_4) were strong indicators of poor prognosis.[13] Extensive resection of the parotid gland (including the facial nerve if involved), followed by external beam irradiation to the parotid area and upper neck, was considered to be the most rational treatment approach. Radical neck dissection (the standard neck treatment at the time) was felt to not be indicated, except in cases with clinically suspicious cervical nodes. Post-operative radiotherapy was recommended for all cases.

Pastore *et al*., in 1995, evaluated lymph node treatment strategies in 57 parotid gland carcinomas.[14] Thirty-three per cent of the cases were adenoid cystic carcinoma. Fourteen patients underwent a neck dissection (nine for clinically positive lymph nodes and five electively). There were no positive nodes found in the elective group. The authors recommended neck dissection for patients with clinically positive nodes, and post-operative irradiation for all N_0 necks, except in cases of acinic cell or mucoepidermoid carcinoma, for which they recommended a 'wait and see' policy. Armstrong *et al*. found that the lymph nodes involved in 90 per cent of major salivary gland carcinomas were located in levels II and III, suggesting that selective neck dissection of levels II–IV is appropriate.[11]

Régis de Brito Santos *et al*., in 2001, conducted a multivariate analysis of risk factors for lymph node metastasis in 145 patients with parotid cancer.[7] The authors noted the difficulty in evaluating specimens pre-operatively or even intra-operatively for the exact features and histology that would indicate high-risk tumours. Twenty per cent of malignancies in their study were mucoepidermoid carcinoma, which was the most frequent histological type. The number of adenoid cystic carcinoma cases was much lower, but the actual figure and percentage were not stated. Eighty patients underwent neck dissection (34 were therapeutic and 46 elective). The overall prevalence of lymph node metastasis in the study group was 23.5 per cent. Occult metastases were found in 17 (37 per cent) of 46 N_0 patients who underwent elective neck dissection. Thirteen of the 17 patients had T_3 or T_4 primary tumours. Multivariate analysis identified histological type, T classification (T_{3-4}) and desmoplasia as independent predictors of neck involvement. Histological types considered as high risk for cervical spread were undifferentiated carcinoma, salivary duct

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carcinoma, adenocarcinoma and squamous cell carcinoma. Adenoid cystic carcinoma was associated with a low risk for nodal metastasis, with a prevalence of 9.1 per cent.

Centers of the Dutch Head and Neck Society evaluated 498 patients with parotid cancer treated from 1984 to 1995.[15] Adenoid cystic carcinoma was the most frequently (28 per cent) diagnosed histological type. A rating scale was developed to score the risk of positive neck nodes in relation to T-status (score 1–3: $T_1 = 1$; $T_2 = 2$; $T_{3-4} = 3$) and histological type (score 1–3; adenoid cystic carcinoma = 1). By summation of scores, the authors reported the predicted risk of positive neck nodes for malignancies of the parotid gland. In the case of adenoid cystic carcinoma, the estimated risk was 4 per cent for T_1, 12 per cent for T_2 and 25 per cent for T_{3-4}.

Van Weert *et al*. reported on a series of 105 consecutive cases of adenoid cystic carcinoma, 27 of which were located in the parotid gland.[16] Among the entire group, the neck was pathologically staged N_1 in 3 per cent, N_{2a} in 1 per cent, N_{2b} in 5 per cent, N_{2c} in 2 per cent and N_3 in 0 per cent, resulting in a total prevalence of nodal involvement of 11 per cent.

Zhang *et al*. reported on a series of 218 cases of adenoid cystic carcinoma in the head and neck.[17] They provided detailed information on the N classification per tumour location. Overall, the prevalence of positive necks was found to be 13.3 per cent. None of the 21 patients with adenoid cystic carcinoma of the parotid were reported to have had lymph node metastasis. In the total series, lymph node metastasis correlated with disease-specific survival in univariate and multivariate analyses.

Fiorella *et al*. compiled a large series of parotid tumours from 28 Italian centres.[18] The results, which were similar to those of other reports, indicated that 14 per cent of tumours were malignant. Of the latter, 15.3 per cent were adenoid cystic carcinoma. Two-thirds of patients with an N_0 neck underwent either elective neck dissection or elective neck radiotherapy. Elective neck dissection was of the 'functional' (selective I–V) type in 54 per cent and selective (I–III or II–IV) in 46 per cent of cases. Sentinel node biopsy was performed in a few centres. The use of sentinel node biopsy is an interesting innovation, but no further information is given, and numbers and percentages of positive lymph node cases throughout the series are not stated.

Bhayani *et al*. studied 60 patients with clinical stage I and II adenoid cystic carcinoma of major salivary glands, including 19 parotid tumours.[19] Thirty patients had elective neck dissection. Of these, seven (23 per cent) had pathologically positive nodes, six with extracapsular spread. While survival was related to the presence of distant rather than lymph node metastasis, the presence of positive lymph nodes had a significant correlation with distant metastasis.

The prevalence of nodal metastasis in adenoid cystic carcinoma of the parotid gland, as reported in papers where the numbers were specified, is summarised in Table I.[6,8,11,17,20–24] The table shows that among 255 cases of parotid adenoid cystic carcinoma, 37 (14.5 per cent) had proven cervical metastases. Only four of the positive necks were clinically apparent. Of the 80 patients known to have undergone elective neck dissection, involving at least the 2 highest echelon node levels, 25 (31 per cent) had occult metastasis. Twenty-two (28.6 per cent) of 77 patients in the series, where all underwent elective neck dissection had pathologically positive nodes. Three patients who were chosen selectively for elective neck dissection based on characteristics of the primary tumour all had positive nodes.

External beam irradiation of the neck may provide a suitable alternative for elective treatment, as suggested by Armstrong *et al*.,[11] and others.[25] As post-operative irradiation to the primary site is indicated in most cases of adenoid cystic carcinoma, because of their infiltrating growth pattern, their tendency for perineural invasion and the difficulty of resection with ample tumour-free margins, it seems reasonable to also treat the neck with elective irradiation, after adequate surgery for the primary tumour.

Two recent studies, albeit retrospective, support this approach. Chen *et al*. studied 251 patients with salivary gland carcinomas and a clinically staged N_0 neck who were treated with surgery and post-operative radiation therapy, and who had not undergone previous neck dissection.[26] Post-operative elective neck irradiation reduced the 10-year nodal failure rate from 26 per cent to 0 per cent ($p = 0.0001$). In particular, there were no nodal failures observed among patients with adenoid cystic carcinoma. These authors concluded that elective post-operative irradiation effectively prevents nodal relapse and should be used for selected patients who are at high risk for regional failure.

The second study, by Herman *et al*., was conducted to determine whether patients with high-grade salivary carcinomas and clinically staged N_0 necks benefit from elective neck dissection prior to post-operative radiotherapy.[27] They studied 59 previously untreated patients with parotid cancer. The necks were treated with curative intent using elective neck dissection ($n = 41$, 10 had adenoid cystic carcinoma), or elective neck irradiation ($n = 18$, 4 had adenoid cystic carcinoma). Both groups underwent resection of the primary tumour followed by post-operative radiation therapy. Occult metastases were found in 18 (44 per cent) of the 41 patients in the elective neck dissection group. With a median follow-up period of 5.2 years (range, 0.3–34 years), there were 4 (10 per cent) recurrences in the elective neck dissection group and 0 recurrences in the neck irradiation group. The authors conceded that treatment regimens were affected by selection bias (more advanced primary lesions and unfavourable histologies in the elective neck dissection group), and that the slightly lower survival rates in the elective neck dissection group reflect this bias. They conclude, however, that the 0 per cent rate of neck

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TABLE I
PAROTID GLAND – NODAL METASTASIS IN ADENOID CYSTIC CARCINOMA

Study (year)	AdCC cases (*n*)	Clinical node (cN) status (*n*)	Pathological node (pN) status (*n*)	Comments
Armstrong *et al.*[11] (1992)	55	$cN_+ = 1$ $cN_0 = 54$	$pN_+ = 1$ $pN_+ = 2$ (number of ENDs not stated)	In view of low frequency of occult N_+, the authors do not recommend routine END. END may be indicated on characteristics of the primary
Kelley & Spiro[20] (1996)	24	$cN_0 = 24$; 2 of 24 had END	$pN_+ = 2$ of 2 had END	Tumour grading best predictor of likely N_+ disease
Stennert *et al.*[8] (2003)	26	$cN_+ = 1$ $cN_0 = 25$	$pN_+ = 1$ $pN_+ = 10$	149 parotid & 11 submandibular gland malignancies of all histological types; all patients had END
Zbären *et al.*[6] (2005)	7	$cN_0 = 7$	$pN_+ = 1$ had END; no recurrence in others	N_+ patient was 84 years old with T_4 tumour. END should be performed for all parotid epithelial malignant salivary gland neoplasms
Min *et al.*[21] (2012)	68	$cN_+ = 2$	$pN_+ = 2$	616 cases, all sites. Necks evaluated by ultrasound. Neck dissection for cN_+
Stenner *et al.*[22] (2012)	10	$cN_0 = 10$	$pN_0 = 8$ $pN_+ = 2$	All patients had early-stage primary disease; all had END
Wang *et al.*[23] (2012)	38	$cN_0 = 36$	$pN_+ = 10$	Series of 219 MSG cases, 38 had AdCC; all cN_0 patients underwent END
Zhang *et al.*[17] (2013)	21	$cN_0 = 21$	$pN_+ = 0$ (number of ENDs not stated)	218 AdCC cases, all head & neck sites. In total series, lymph node metastasis correlated with disease-specific survival in univariate & multivariate analysis
Lim *et al.*[24] (2015)	6	$cN_0 = 6$	$pN_0 = 6$	All patients had END level II or III, 1 developed local recurrence

AdCC = adenoid cystic carcinoma; END = elective neck dissection; MSG = major salivary gland

relapses observed among patients who received elective neck irradiation strongly supports the efficacy of this treatment for controlling neck disease, and they suggest that patients with high-grade salivary carcinomas and a clinically staged N_0 neck who undergo surgery and post-operative radiation are not likely to benefit from elective neck dissection.

On the basis of the above information, we believe that elective post-operative irradiation of the neck is indicated for T_3 and T_4 parotid malignancy or in the presence of other known risk factors for metastasis. This indication applies to adenoid cystic carcinoma and to most other parotid malignancies. Elective neck dissection is not necessary if the neck is irradiated, usually in addition to post-operative irradiation of the primary tumour. Only the ipsilateral side of the neck should be treated. The occurrence of contralateral lymph node metastases in tumours of the major salivary glands is negligible.[20] Despite the traditional concepts that neither parotid tumours in general or adenoid cystic carcinoma in particular have a high tendency for neck metastasis, the findings of various studies involving elective neck dissection in adenoid cystic carcinoma of the parotid show that cervical metastasis does occur with reasonable frequency, although results are inconsistent. At this time, there is insufficient evidence to support a recommendation for elective neck treatment in all cases of parotid adenoid cystic carcinoma.

Submandibular gland

Although tumours of the submandibular gland are uncommon, a high percentage are malignant. While reports vary, adenoid cystic carcinoma is probably the most common malignancy therein. In a 1976 review of 217 patients with salivary neoplasms, conducted by Spiro *et al.*, only 9 per cent of tumours originated in the submandibular gland.[28] Fifty-six per cent of these, however, were malignant. The most frequent malignancy encountered was adenoid cystic carcinoma. Roh *et al.*, in a review of 62 submandibular gland carcinomas, found 19 adenoid cystic carcinomas and 11 mucoepidermoid carcinomas, with salivary duct carcinomas and carcinoma ex pleomorphic adenomas accounting for the others.[29] A Danish study of salivary gland carcinoma showed that only 12.2 per cent of primary salivary gland carcinomas originated in submandibular glands, and adenoid cystic carcinoma constituted 44 per cent of them.[1] These figures are consistent with other reports.[30] Furthermore, they reinforce the idea that while submandibular gland tumours occur infrequently, a high percentage are malignant, and adenoid cystic carcinoma is the histological type most frequently encountered. Nevertheless, because parotid tumours are overwhelmingly more frequent, the parotid is still the most common site of adenoid cystic carcinoma among major salivary glands.

A concept that prevailed for a long time, regarding the pathogenesis of lymph node metastases from

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adenoid cystic carcinoma of the submandibular gland, was expressed by Allen and Marsh in a 1976 report of 34 cases observed between 1946 and 1974.[31] Lymph node involvement was found in three cases of adenoid cystic carcinoma of the submandibular gland, and all of the affected lymph nodes were in the immediate vicinity of the primary tumour. Tumour was present in the soft tissue surrounding each involved node, and extended therein. The nodes were found during local excision of the primary tumour. Neck dissections were conducted in two of the three patients subsequent to the primary tumour removal; no metastatic tumours were observed in either case. The third patient died 20 years later after developing local and distant recurrence, but with no regional node metastasis. The authors concluded that adenoid cystic carcinoma only invades lymph nodes in the immediate vicinity of the primary tumour, and that when lymph node involvement occurs, it does not result from embolic lymph node metastasis, but, rather, from direct tumour invasion of the perinodal soft tissue.

Spiro and Huvos, in a 1992 review of 164 cases of adenoid cystic carcinoma, found 22 cases in the submandibular gland, of which 5 (23 per cent) had lymph node metastasis.[9] Thirty-two cases were classified as 'parotid/sublingual', of which only two (6 per cent) had lymph node metastasis.

Some papers deal with adenoid cystic carcinoma of all sites, with findings and conclusions that apply to the submandibular and other major salivary glands, without distinguishing results for each gland. Stell *et al*., in 1985, reported that the prevalence of enlarged lymph nodes at presentation of patients with adenoid cystic carcinoma was 15 per cent (8 out of 52), and found that T stage and primary site of tumour were not important factors affecting the metastatic rate.[32] Twenty of the 52 tumours were in major salivary glands. Lymph node metastases at presentation or later occurred almost exclusively in men, and the five-year rate of 'node-free' survival was 62 per cent for men and 95 per cent for women. Node metastases were more common in poorly differentiated tumours. The authors were unable to confirm that embolic metastases did not occur in this disease. Several of their patients had metastatic nodes low in the neck, some distance from the primary tumour, although they found that surgery for node disease had little effect on survival.

In 1986, Matsuba *et al*., in a study of 71 cases of adenoid cystic carcinoma, found that long-term survival was related to development of distant metastasis, despite local control of the tumour.[33] Patients with cribriform and tubular varieties (grade I) had similar rates of distant metastasis. The cribriform variant demonstrated a significantly higher local recurrence rate, while patients who had a solid histological pattern (grade III) had an overall worse prognosis in terms of distant metastasis and long-term survival. Seethala *et al*. reported on 11 cases of high-grade transformation (previously known as dedifferentiation) of adenoid cystic carcinoma.[34] This rare phenomenon should not be confused with the solid variety, and does not fit into the traditional grading schemes for adenoid cystic carcinoma. Submandibular gland adenoid cystic carcinoma accounted for 4 of the 11 cases.[34] The authors noted a 51 per cent incidence of lymph node metastasis in cases with high-grade differentiation.

The conclusions and findings regarding lymph node metastasis of adenoid cystic carcinoma in submandibular glands seem to have evolved with time, with a higher prevalence of an occult embolic type of metastasis reported in some more recent publications. Bosch *et al*., in 1980, found positive nodes in 4 of 10 cases with adenoid cystic carcinoma of the submandibular gland.[35] A review of the slides in three cases showed direct extension of tumour from surrounding soft tissue, although the possibility of true embolic metastasis could not be excluded. Seaver and Kuehn, in 1979, reviewed 93 cases of adenoid cystic carcinoma, of which 80 were in major salivary glands.[36] High recurrence rates in parotid glands (20 of 47) and submandibular glands (20 of 33) were attributed to inadequate surgery. Cases with recurrence had a high frequency of perineural lymphatic involvement, suggesting local extension along the nerves. Radical neck dissection, when performed, was felt to have contributed to improved survival rates when the primary site was the submandibular gland.

Munir and Bradley, in a 2008 review of neoplasms of the submandibular triangle, found a relatively high prevalence of malignant tumours in this region: 58 of 107 tumours (54 per cent) were malignant.[37] Forty-eight of the malignant lesions were primary and 10 were metastatic. There were nine adenoid cystic carcinomas and nine mucoepidermoid carcinomas, comprising the most frequent primary epithelial malignancies. These tumours were treated either by extracapsular excision, or by selective level I, II and III neck dissection, with the submandibular gland included in the block of resected tissue. The authors concluded that the adequacy of primary surgery is crucial, and supported the approach of a more radical initial excision by performing selective level I, II and III neck dissection that includes the submandibular gland. This avoids the risks of tumour spillage associated with more limited excision, while removing the primary echelons of lymph nodes at risk of metastasis, without a significantly higher morbidity in comparison with extracapsular gland excision alone.

The predicted risk of positive neck nodes for adenoid cystic carcinoma of the submandibular gland, as proposed by the study of Terhaard *et al*., is 0 per cent for T_1, 33 per cent for T_2 and 57 per cent for T_{3-4}.[15] In the study by Zhang *et al*., 3 (15 per cent) of the 20 patients with adenoid cystic carcinoma of the submandibular gland had lymph node metastasis.[17]

Beppu *et al*., in 2003, reviewed 27 patients treated surgically for submandibular gland cancer.[4] Thirteen

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patients had adenoid cystic carcinoma, six had mucoepidermoid carcinoma and nine had other types of cancer. Sixteen patients underwent elective neck dissection. Six (46.2 per cent) of the 13 patients with adenoid cystic carcinoma had occult lymph node metastasis. All pathologically positive nodes were situated at levels II and III of the neck. Similar findings were reported with other tumour types. The authors recommended elective selective level I, II and III neck dissection for primary malignant tumours of the submandibular gland because of: the significant rate of metastasis to levels II and III, the poor prognosis of patients with positive lymph node metastasis, and the fact that the neck dissection can be performed through the same incision used for the primary tumour.

Other recent publications report different results. Cohen *et al*. found no occult metastasis in 17 patients with submandibular gland adenoid cystic carcinoma who underwent elective neck dissection; 2 patients were clinically and pathologically staged N_+.[38] Han *et al*. reported no occult neck metastasis or regional recurrence in all 17 of their patients with submandibular gland adenoid cystic carcinoma, regardless of histological grade (solid, or tubular or cribriform).[39]

Thus, the results in various reports have been mixed regarding the prevalence of metastasis in adenoid cystic carcinoma of the submandibular gland. Table II summarises eight series where the exact number of cases of adenoid cystic carcinoma of the submandibular gland and the number of cases with proven lymph node metastasis are stated.[4,9,17,31,35,38–40] Of 147 cases, 33 (22.5 per cent) were pathologically staged N_+. Among 35 patients who underwent elective neck dissection beyond level I, 10 (28.6 per cent) had occult positive nodes.

The discovery of metastasis may be related to pre-treatment diagnosis, which has improved during the past decades. Moreover, more intense histopathological examination of the neck dissection specimen may reveal more occult lymph node metastases when compared to routine histopathological examination. The acceptance of selective neck dissection as the procedure of choice has encouraged the employment of elective neck dissection for the detection of occult metastasis, particularly when the primary tumour can be removed through the same incision. Inconsistency in reported results between various series and over time may be related to the relatively small number of cases reported in each series, and to the variation in and the evolution of techniques employed for the diagnosis and treatment of the neck.

The ease of inclusion of the submandibular gland in a level I, II and III selective neck dissection, as suggested in the above cited reports, would indicate that when the diagnosis of malignancy has been established prior to surgery, the operation performed should be a level I, II and III neck dissection in continuity with the submandibular gland, rather than an extracapsular excision of the gland alone. This has been referred to as en bloc resection,[41] and would seem to apply well

TABLE II
SUBMANDIBULAR GLAND – NODAL METASTASIS IN ADENOID CYSTIC CARCINOMA

Study (year)	AdCC cases (*n*)	Clinical node (cN) status (*n*)	Pathological node (pN) status (*n*)	Comments
Allen & Marsh[31] (1976)	6	$cN_0 = 6$	$pN_+ = 3$ (in proximity of primary tumour)	Nodes found during primary tumour resection. 2 patients had completion RND with negative nodes
Bosch *et al.*[35] (1980)	10		$pN_+ = 4$	5 RNDs & 5 SNDs at initial surgery – 3 occult positive & 1 positive at recurrence
Weber *et al.*[40] (1990)	37		$pN_+ = 10$; total number of ENDs not clear	Only elective removal of nodes in level I, except for massive tumours
Spiro & Huvos[9] (1992)	22	$cN_+ = 5$	$pN_+ = 5$	Only therapeutic neck dissections
Beppu *et al.*[4] (2003)	13	$cN_0 = 6$ had END	$pN_+ = 6$	All positive nodes situated at levels II & III
Cohen *et al.*[38] (2004)	22	$cN_0 = 20$ $cN_{2b} = 1$ $cN_{2c} = 1$	$cN_0 = 17$ had END, all pN_0; all cN_+ were pN_+	Entire series was AdCC of submandibular gland – evaluation of treatment results
Han *et al.*[39] (2012)	17	$cN_0 = 17$	$pN_0 = 17$; total number of END not clear	No regional recurrence in cN_0 cases. Only level I END in all cases. Levels I, II & III for larger & more invasive tumours
Zhang *et al.*[17] (2013)	20		$pN_+ = 3$	cN status not reported. Node stage predicted survival in entire group of AdCC, all sites

AdCC = adenoid cystic carcinoma; RND = radical neck dissection; SND = selective neck dissection; END = elective neck dissection

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to submandibular gland malignancies. This also allows for more precise dosimetry of post-operative radiotherapy, which could be administered based on the number and location of positive neck nodes.

Sublingual gland

Sublingual gland tumours are rare and are usually malignant. Individual instances of adenoid cystic carcinoma of the sublingual gland are quite scarce, and it is difficult to generalise from the small number of reported cases. Zhang *et al*., in their 2013 report, found lymph node metastasis in 4 (22 per cent) of 18 patients with adenoid cystic carcinoma of the sublingual gland.[17] In 2011, Zdanowski *et al*. reported on 13 patients treated at a single institution between 1995 and 2007: 95 per cent of the tumours were malignant.[42] Adenoid cystic carcinoma was the most common malignancy, comprising 66.7 per cent. Elective neck dissection was performed in 69.2 per cent of (all) cases of malignancy, with no metastasis detected. Distant metastases were diagnosed in three (25 per cent) patients.

In 1969, Rankow and Mignogna reported on seven cases treated at their institution, and reviewed another eight treated elsewhere, between 1920 and 1968.[43] The authors pointed out the difficulty of precise pre-operative histological diagnosis, even when incisional biopsy was attempted. All 15 cases were malignant. In total, there were six patients (40 per cent) with adenoid cystic carcinoma, and among the seven patients treated by the authors, three had adenoid cystic carcinoma. All were clinically staged N_0. One developed a cervical node metastasis three years after local excision of the tumour. Two patients who underwent elective neck dissection were found to have negative nodes. The authors warned against attempts to perform incisional biopsy, and recommended total removal of the gland once the presence of a neoplasm has been established.

Sun *et al*., in 2010, reported on a series of patients with sublingual gland tumours.[44] Of 21 malignant cases, 18 were adenoid cystic carcinoma. Nodal involvement was identified in three cases; two necks were clinically staged N_0 and one was clinically staged N_+. All patients treated surgically underwent selective neck dissection.

Results from eight series in which the exact number of cases of adenoid cystic carcinoma of the sublingual gland and the number of cases with cervical node metastasis were reported are summarised in Table III.[17,42–48] Pathologically positive nodes were found in 20 (24.7 per cent) of 81 patients with sublingual gland adenoid cystic carcinoma. Twenty-eight underwent elective neck dissection and positive nodes were found in eight (23 per cent) of them.

The small numbers of sublingual gland tumours in general, and of sublingual gland adenoid cystic carcinoma in particular, make it difficult to generalise about treatment protocols. Of note, large sublingual gland malignancies often have to be treated surgically with a combined oral and cervical approach, possibly

TABLE III
SUBLINGUAL GLAND – NODAL METASTASIS IN ADENOID CYSTIC CARCINOMA

Study (year)	AdCC cases (*n*)	Clinical node (cN) status (*n*)	Pathological node (pN) status (*n*)	Comments
Rankow & Mignona[43] (1969)	3	$cN_0 = 3$	$pN_0 = 2$ had END; 1 patent with no ND developed a late metastasis	Total of 5 MSL of all histological types
Andersen *et al*.[45] (1991)	3		$pN_0 = 3$	Total of 6 MSL of all histological types
Spiro[46] (1995)	9		$pN_+ = 1$ had END	Total of 18 MSL of all histological types
Perez *et al*.[47] (2005)	4	$cN_0 = 4$	$pN_0 = 4$	Total of 6 MSL of all histological types; 3 AdCC cribriform, 1 AdCC tubular
Yu *et al*.[48] (2007)	18	$cN_0 = 11$	$cN_0 = 4$ had END, all pN_+	Total of 29 MSL of all histological types; 11 patients had ND, 5 had N_+ proven intra-operative frozen sections & 6 had N_+ post-operative findings
		$cN_1 = 6$	$cN_+ = 7$ were pN_+	
		$cN_2 = 1$		
Sun *et al*.[44] (2010)	18	$cN_0 = 15$	$pN_0 = 15$	Total of 25 MSL of all histological types
		$cN_0 = 2$	$pN_+ = 2$	
		$cN_+ = 1$	$pN_0 = 1$	
Zdanowski *et al*.[42] (2011)	8	All neck masses were primary tumour	$pN_0 = 8$	Total of 13 MSL of all histological types; 8 AdCC cases, no ENDs. Nodes treated according to cN stage. No nodal recurrence
Zhang *et al*.[17] (2013)	18		$pN_+ = 4$	Node stage was related to survival

AdCC = adenoid cystic carcinoma; END = elective neck dissection; ND = neck dissection; MSL = malignant sublingual gland tumour

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involving mandibulotomy or mandibulectomy. In such cases, elective neck dissection of levels I, II and III would seem reasonable and appropriate. Smaller tumours, excised entirely through an intraoral approach, should receive evaluation of cervical nodes by the modalities available, with the decision as to a subsequent neck treatment based on the total information obtained. Considering the excellent results obtained with prophylactic neck irradiation in adenoid cystic carcinoma at other locations, this seems a reasonable alternative in cases where no neck incision would otherwise be required, particularly if the primary site is to be irradiated.

Conclusion

Although not often the cause of mortality, cervical lymph node metastasis does occur in major salivary gland adenoid cystic carcinoma. Despite wide discrepancies in the prevalence reported by some authors, the overall number of reported instances justifies addressing the neck electively, certainly for larger tumours or tumours with known histological risk factors. The reported prevalence of neck involvement in parotid adenoid cystic carcinoma is lower than with submandibular and sublingual carcinomas. The overall prevalence of pathologically positive necks in adenoid cystic carcinoma of major salivary glands found in our survey was 90 (18.6 per cent) of 483 patients, which corresponds to that (19 per cent) reported by Amit *et al.*[2] Of 143 patients with major salivary gland adenoid cystic carcinoma known to have undergone elective neck dissection, 43 (30 per cent) had pathologically positive nodes. This figure includes patients selected for elective neck dissection because of risk factors and patients from series where all clinically staged N_0 patients underwent elective neck dissection.

In the case of parotid tumours, elective irradiation of the neck has been shown to afford the same benefit as elective neck dissection. Thus, elective post-operative irradiation of the neck should be employed for parotid malignancies, including adenoid cystic carcinoma cases that have known risk factors for cervical metastasis, such as large size (T_{3-4}), desmoplasia or lymphovascular invasion. Because of the efficacy of post-operative irradiation, elective neck dissection is not necessary at the time of the parotidectomy unless gross disease is encountered in the operative field. In some cases, limiting factors, such as skull base invasion, may render the question of elective neck dissection irrelevant to the patient's prognosis. Neck irradiation should be strongly considered in cases where post-operative irradiation to the primary tumour site is indicated.

For submandibular gland carcinoma, the same problems often exist with regard to pre- or intra-operative knowledge of exact tissue diagnosis and risk factors. The location of the gland within the domain of a level I, II and III selective neck dissection, and the known occurrence of lymph node involvement, either by direct extension or by the embolic route, indicate that elective removal of lymph node groups in these regions, along with the excision of the primary tumour, should be the initial surgical approach for submandibular gland adenoid cystic carcinoma and other malignancies of the submandibular gland when the diagnosis is known pre-operatively.

Elective neck dissection of levels I, II and III should be performed for rare sublingual gland cancers, including adenoid cystic carcinoma, that are large enough to require a combined oral and cervical approach. In cases where no neck incision has been required for removal of the primary tumour, elective treatment of the neck by either radiation or surgery should be considered for primary tumours that present risk factors for node metastasis, or if the primary tumour site must be irradiated post-operatively for other reasons.

Authorship

This article was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com): C E Silver, Department of Surgery, University of Arizona College of Medicine, Phoenix, Arizona, USA; P J Bradley, Department of Otolaryngology – Head and Neck Surgery, Nottingham University Hospitals, Queens Medical Centre Campus, UK, and European Salivary Gland Society, Geneva, Switzerland; L Barnes, Department of Pathology, University of Pittsburgh School of Medicine, Pennsylvania, USA; R de Bree, Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands; M Hamoir, Department of Head and Neck Surgery, Head and Neck Oncology Program, St Luc University Hospital and King Albert II Cancer Institute, Brussels, Belgium; J E Medina, Department of Otorhinolaryngology, University of Oklahoma Health Sciences Center, Oklahoma City, USA; P Strojan, Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia; W M Mendenhall, Department of Radiation Oncology, University of Florida, Gainesville, USA; L P Kowalski, Department of Head and Neck Surgery and Otorhinolaryngology, A C Camargo Cancer Center, São Paulo, Brazil; V Vander Poorten, European Salivary Gland Society, Geneva, Switzerland, and Otorhinolaryngology – Head and Neck Surgery and Department of Oncology, Section Head and Neck Oncology, University Hospitals Leuven, KU Leuven, Belgium; J A Eloy, Department of Otolaryngology – Head and Neck Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, USA; K T Robbins, Division of Otolaryngology – Head and Neck Surgery, Southern Illinois University School of Medicine, Springfield, USA; A Triantafyllou, Oral and Maxillofacial Pathology, School of Dentistry, University of Liverpool and Cellular Pathology, Liverpool Clinical Laboratories, UK; A Teymoortash,

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Department of Otolaryngology – Head and Neck Surgery, Philipp University, Marburg, Germany; A Rinaldo, University of Udine School of Medicine, Italy; K T Pitman, Department of Surgery, Banner MD Anderson Cancer Center, Gilbert, Arizona, USA; and A Ferlito, Co-ordinator of the International Head and Neck Scientific Group, Padua, Italy.

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Address for correspondence:
Prof Alfio Ferlito,
Via Firenze 11,
35031 Selvazzano Dentro,
Padova, Italy

E-mail: a.ferlito@uniud.it

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