Cervical Lymph Node Metastasis in Adenoid Cystic Carcinoma of the Larynx: A Collective International Review

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ABSTRACT

Adenoid cystic carcinoma (AdCC) of the head and neck is a well-recognized pathologic entity that rarely occurs in the larynx. Although the 5-year locoregional control rates are high, distant metastasis has a tendency to appear more than 5 years post treatment. Because AdCC of the larynx is uncommon, it is difficult to standardize a treatment protocol. One of the controversial points is the decision whether or not to perform an elective neck dissection on these patients. Because there is contradictory information about this issue, we have critically reviewed the literature from 1912 to 2015 on all reported cases of AdCC of the larynx in order to clarify this issue. During the most recent period of our review (1991–2015) with a more exact diagnosis of the tumor...
histology, 142 cases were observed of AdCC of the larynx, of which 91 patients had data pertaining to lymph node status. Eleven of the 91 patients (12.1%) had nodal metastasis and, based on this low proportion of patients, routine elective neck dissection is therefore not recommended.

**Keywords:** Adenoid cystic carcinoma; Clinical protocols; Elective neck dissection; Larynx; Lymph node metastasis; Neck; Oncology; Treatment

**INTRODUCTION**

Adenoid cystic carcinoma (AdCC) is an uncommon tumor, accounting for about 1% of all head and neck malignancies [1]. It is typically a slowly growing but relentlessly progressive neoplasm characterized by perineural invasion, frequent local recurrences and late distant hematogenous dissemination to the lung, liver, bone and brain. In contrast lymph node metastasis, especially true embolic lymph node metastasis, is infrequent. Although the long term prognosis is poor, some patients may survive 10–15 years or more before succumbing to their disease.

In a recent international collaborative study involving nine cancer centers worldwide Amit et al. identified 270 patients with AdCC of the head and neck who underwent neck dissection and observed the overall incidence of neck metastasis to be 29% [2]. In the same year they also observed a 17% incidence of occult nodal metastasis among those patients who underwent elective neck dissections [3]. Because of its rarity, it is uncertain whether their data regarding the frequency of lymph node metastasis might also apply to AdCC of the larynx. To address this issue we critically
reviewed the world literature on AdCC of the larynx in an attempt to suggest guidelines for the management of the neck in patients with AdCC at this anatomic site. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

**REVIEW OF THE LITERATURE AND ANALYSIS**

Minor salivary-type glands are present in most of the laryngeal mucosa: abundantly in the subglottis, false cords/anterior commissure and usually absent from the true cords [4]. Yet despite their presence, glandular neoplasms are distinctly unusual. AdCC is one of the most frequent. Because of their rarity, no single institution has accumulated a large series of cases, and therefore, only single case reports or small series are available for review, which often results in widely conflicting data. Eschwege et al. [5] reported five cases of AdCC of the larynx and all were free of cervical lymph node metastasis as opposed to Spiro and Huvos [6] who also reported five cases and observed that four had associated positive lymph nodes (80%). Accordingly, to appreciate the potential biological behavior of AdCC of the larynx one often must rely on a composite review of published cases. However, this approach is also hampered by lack of quality data. Some cases are poorly documented with no histologic illustrations, and pertinent clinical and/or pathologic details are often not reported, including long term follow-up (more than 10 years). In addition, recent new histopathological entities have been described that may have been or continue to be confused with AdCC, such as basaloid squamous cell carcinoma, polymorphous low grade carcinoma, epithelial-myoepithelial carcinoma.

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basal cell adenocarcinoma, and cribriform adenocarcinoma.

With these limitations in mind, we undertook a literature search of PubMed (including Medline) using the search strategy “adenoid cystic carcinoma larynx” and “adenoid cystic carcinoma head neck” which resulted in 1292 articles, which were hand-searched for pertinent articles. Their reference lists were also searched for additional cases. We excluded cases without a definitive diagnosis of AdCC, cases where the location of the tumor was not definitely the larynx and cases which were included in previously published reviews (as stated in the table, see remarks). As stated above only a few cases reported include a complete staging procedure, the extent of neck dissections, histology images illustrating the definitive diagnosis, why the authors performed a neck dissection, follow-up of the patient, recurrence of the lesion and location of the recurrence. Our comprehensive review of AdCC of the larynx reported in the literature from 1912 to 2015 includes 252 cases as shown in Table 1 [3, 5–110] (excluded cases have been summarized in Table 2). Based on these data, our review indicates that AdCC of the larynx occurs in individuals averaging 52.3 years of age (range 12–84 years) and is more common in males (60.7%). The most frequent site of origin is the subglottis (58.2%) followed by the supraglottis (32.1%) and glottis (9.7%). Of the 252 cases, the status of the regional lymph nodes was specifically mentioned in 156, and of these 24 (15.4%) were associated with cervical lymph node metastasis. Due to the lack of sufficiently long term follow-up, the number of 47 cases reported to have had distant metastasis is probably underestimated.

Of the 24 cases with lymph node metastasis, information about the specific location of the tumor within the larynx was available in 16, and of these 9 arose in the supraglottis, 6 in the subglottis and 1 in the glottis.

Over the last century there have been advances in our understanding and classification of salivary tumors and new entities have been described some of which show histologic similarities to AdCC. Accordingly, one might question the authenticity of some of the cases labeled as AdCC of the larynx in the older literature. Considering the fact that basaloid squamous cell carcinoma was first described in 1986 [111], polymorphous low grade adenocarcinoma in 1983 [112], epithelial-myoepithelial carcinoma in 1972 [113], basal cell adenocarcinoma in 1988 [114] and cribriform adenocarcinoma in 1999 [115], all potential histologic mimickers of AdCC, we divided our review into two time periods, (a) 1912–1990 (we have further subdivided this into two time periods due to the description of epithelial-myoepithelial carcinoma in 1972) and (b) 1991–2015 (Table 3), in order to analyze whether the incidence of lymph node metastasis in AdCC of the larynx was higher before the description of these “new” tumors which may have been mistaken histologically for AdCC. Between 1912 and 1990, we identified 110 cases of AdCC of the larynx and, of these, 65 had data regarding lymph node status. Thirteen of these 65 patients (20%) had lymph node metastasis. For the period 1991–2015, 142 cases were observed and of these reports 91 patients had data pertaining to lymph node status. Eleven of the 91 patients (12.1%) had nodal metastasis. Possibly, this decline in the incidence of lymph node metastasis between the two time periods might in part be related as noted above to incorrect histological diagnosis prior to 1991, though the difference does not appear statistically significant ($\chi^2 = 1.75$, $df = 1$, $p > 0.05$).
Table 1  Review of reported cases of adenoid cystic carcinoma of the larynx

| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|----------------------------|-----------|-----|-----|----------|-------------------------------|-------------------|---------|
| Broeckaert (1912) [8]      | 1         | 57  | M   | SG       | Absent                        | Absent            |         |
| Bourgeois and Soulas (1931) [9] | 1         | 34  | F   | E        | Absent                        | Present           | Distant metastasis to lungs |
| Eigler (1932) [10]         | 1         | 45  | F   | E        | Absent                        | Present           | Distant metastasis to cervical spine |
| Lemaître et al. (1936) [11] | 1         | 34  | M   | E        | Absent                        | Absent            |         |
| Kramer and Som (1939) [12] | 1         | 36  | M   | SuG      | Absent                        | Absent            |         |
| Ide and Cahn (1948) [13]   | 1         | 52  | M   | SuG      | Absent                        | Absent            |         |
| McDonald and Havens (1948) [14] | 4        | NA  | NA  | 2 L      | NA                            | NA                | Data analyzed mixed with other locations and histologies |
| Pirodda (1951) [15]        | 1         | NA  | NA  | L        | NA                            | NA                |         |
| Berdal and Mylius (1954) [16] | 1         | 36  | F   | SuG      | Absent                        | Absent            |         |
| Putney and McStravog (1954) [17] | 1         | 55  | M   | SG       | Present                       | Absent            | Lymph node involvement due to invasion of extensive recurrent tumor |
| Abercromby and Rewell (1955) [18] | 1         | NA  | NA  | L        | NA                            | NA                |         |
| Ahued (1956) [19]          | 1         | 48  | M   | E        | Present                       | Present           | Cervical lymph node involvement due to direct invasion of the primary tumor |
| Murtagh and House (1956) [20] | 1         | 40  | M   | L        | Absent                        | Present           | Distant metastasis to lungs |


Table 1 continued

| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|----------------------------|-----------|-----|-----|----------|-------------------------------|--------------------|---------|
| Pietrantoni and Leonardelli (1957) [21] | 2         | 42  | F   | L        | Absent                        | Absent             |         |
|                            | 2         | 49  | F   | L        | Absent                        | Absent             |         |
| Soboroff (1959) [22]       | 1         | 60  | F   | SuG      | Absent                        | Absent             |         |
| Leroux-Robert et al. (1961) [23] | 7         | 58  | M   | Left AEF, PS | Absent                        | Absent             | Some reservations about the correct identification of the oncotypes |
|                            | 55        | M   | Right PS | Absent                        | Present            |         |
|                            | NA        | M   | Right HL | Absent                        | Absent             |         |
|                            | NA        | M   | Right PS | Absent                        | Absent             |         |
|                            | 53        | M   | E, left AEF | Absent                        | Absent             |         |
|                            | 54        | M   | E     | Absent                        | Absent             |         |
|                            | 69        | M   | SuG   | Absent                        | Absent             |         |
| Ash et al. (1964) [24]     | 1         | 29  | M   | Right VC, FVC, V, T | NA               | NA      |         |
| Iosipescu and Manolescu (1965) [25] | 1         | 72  | M   | G        | Absent                        | Absent             |         |
| Rosenfeld et al. (1966) [26] | 3         | NA  | NA  | L        | NA                            | NA                 |         |
|                             | NA        | NA  | L     | NA                            | NA                 |         |
|                             | NA        | NA  | L     | NA                            | NA                 |         |
| Toomey (1967) [27]         | 1         | 68  | F   | SuG, T | Present                       | Absent             | Bilateral cervical nodes |
| Cady et al. (1968) [28]    | 3         | NA  | NA  | L        | NA                            | NA                 |         |
|                             | NA        | NA  | L     | NA                            | NA                 |         |
|                             | NA        | NA  | L     | NA                            | NA                 |         |
| Allachy (1969) [29]        | 1         | 58  | F   | SuG, Left L | Absent                        | Absent             |         |
| Berdal et al. (1969) [30]  | 1         | 36  | F   | SuG   | Absent                        | Absent             |         |
| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|---------------------------|-----------|-----|-----|----------|-------------------------------|-------------------|---------|
| Leonardelli and Pizzetti (1970) [31] | 4 | 38 | M | SuG | Absent | Present | Metastatic spread |
| | | 39 | M | SuG, Left VC | Absent | Absent | |
| | | 31 | M | Left FVC and V | Absent | Absent | |
| | | 51 | F | Left L | Absent | Absent | |
| Adams and Duvall (1971) [32] | 1 | NA | NA | Right FVC, AEF, E | Present | Present | Bilateral positive cervical nodes with histology illustration in text |
| Pincini and Mandelli (1971) [33] | 1 | 53 | M | SuG | Absent | Absent | |
| Jelínek (1973) [34] | 1 | NA | NA | SuG | NA | NA | |
| Spiro et al. (1973) [35] | 3 | NA | NA | 2 SG, 1 G | NA | NA | |
| Ackerman and Rosai (1974) [36] | 3 | NA | NA | L | NA | NA | Lymph node involvement due to embolic metastasis or contiguous infiltration? |
| | | NA | NA | L | NA | NA | |
| | | NA | NA | L | Present | Present | |
| Gross et al. (1974) [37] | 1 | NA | NA | VC, FVC | NA | NA | Distant metastasis to lungs |
| Muzaffar and Bolstad (1974) [38] | 1 | 47 | F | L | NA | NA | |
| Whicker et al. (1974) [39] | 9 | NA | NA | NA | NA | NA | One case with lymph nodes due either to direct infiltration or classic embolic metastasis |
| Eschwege et al. (1975) [5] | 5 | 46 | M | L | Absent | Absent | Distant metastasis to lungs |
| | | 52 | M | E | Absent | Absent | Distant metastasis to lungs; cancer of cervix associated |
| | | 53 | M | VC, PLW | Absent | Present | |
| | | 66 | F | SuG | Absent | Present | |
| | | 73 | M | SuG | Absent | Absent | |
| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|----------------------------|-----------|-----|-----|----------|-------------------------------|-----------------|---------|
| Gerard and De Gandt (1975) [40] | 1         | 71  | F   | SuG, G   | Absent                        | Present         | Distant metastasis to lungs |
| Sessions et al. (1975) [41] | 3         | NA  | NA  | NA       | NA                            | NA              | Clinical information are mixed with other glandular neoplasms |
| Houle et al. (1976) [42] | 1         | 52  | M   | Right AEF, FVC, arytenoid and PS | Absent          | Absent         | 20 lymph nodes histologically free |
| Kekidize (1976) [43] | 1         | NA  | NA  | L        | NA                            | NA              |                                    |
| Spiro et al. (1976) [44] | 3         | 57  | M   | G        | Present                       | Present         | Carcinomatosis                     |
|                         | 70        | F   | E   | Present  | Present                       |                 |                                    |
|                         | 38        | M   | E   | Absent   | Absent                        |                 |                                    |
| Olofsson and van Nostrand (1977) [45] | 4         | 26  | F   | SuG and T | Absent                        | Absent          | Three paraesophageal positive nodes, not palpated; distant metastasis to lungs |
|                         | 63        | M   | SuG, T, esophagus, pharynx, thyroid gland | Present | Present | | |
|                         | 66        | F   | Absent | Absent | | | |
|                         | 56        | M   | Right L SuG, left VC and FVC | Absent | Absent | | |
| Fleischer et al. (1978) [46] | 5         | 54  | M   | E, left AEF and PS | Absent | Absent | With histological illustration |
|                         | 41        | M   | FVC | Present | Absent | | Distant metastasis to lung and brain |
|                         | 35        | M   | SuG | Absent | Present | | |
|                         | 63        | F   | SuG | NA | NA | | |
| Marsh and Allen (1979) [48] | 1         | 50  | F   | SuG | Absent | Present | Distant metastasis to lung |
| Author (Year) | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|--------------|-----------|-----|-----|----------|--------------------------------|-------------------|---------|
| Donovan and Conley (1983) [49] | 3 | 42 | F | SuG, T, esophagus, paratracheal area | Present | Present | Distant metastasis to lungs, liver |
| | 70 | F | | SuG, T | Absent | Absent | Neck recurrence but not specified if it was on a lymph node |
| | 58 | F | | SuG, T | Absent | Absent | |
| Ferlito and Caruso (1983) [50] | 2 | 52 | F | E | Absent | Absent | |
| | 29 | F | | SuG | Absent | Absent | |
| Tewfik et al. (1983) [7] | 1 | 79 | M | SuG | Absent | Absent | |
| Cohen et al. (1985) [51] | 8 | NA | NA | 5 SG, 3 SuG | 3 Present | NA | Two patients with lymph nodes at diagnosis, one patient manifested lymph nodes 13 years after diagnosis |
| Stillwagon et al. (1985) [52] | 1 | 55 | M | E | Present | Present | AdCC-HGT |
| | | | | | Five cervical lymph nodes positive with extracapsular invasion (histological illustration) | Distant metastasis to liver, bone marrow, lymph nodes, brain, heart, lungs and kidneys |
| Gadomski et al. (1986) [53] | 2 | 68 | M | SG | NA | Absent | The first patient underwent modified neck dissection but the results are not available in the text |
| | | 54 | M | E | Present | Present | He is alive and free of disease |
| Jones et al. (1986) [54] | 1 | 34 | F | SuG | Absent | Absent | |
| Li (1988) [55] | 7 | NA | 5 M/2F | 3 SG, 3 G, 1 SuG | NA | NA | |
| Author (Year) | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|--------------|-----------|-----|-----|----------|-------------------------------|-------------------|---------|
| Ferlito et al. (1990) [56] | 6 | 52 | F | SG | Absent | Absent | Distant metastasis to liver, bones |
| | 29 | F | SuG | Absent | Absent | One incidental node free of tumor |
| | 72 | F | SuG | Absent | Present | 66 left cervical nodes free of tumor |
| | 58 | F | SuG | Absent | Absent | Positive resection margins; distant metastasis to lungs |
| | 48 | M | SuG | Absent | Absent | |
| | 76 | M | SG | Absent | Present | This series includes the two cases of AdCC reported previously by Ferlito and Caruso in 1983 [50] 
Case 3 distant metastasis prior to treatment |
| Paredes Osado et al. (1990) [57] | 1 | 52 | F | SuG, T | Absent | Absent | |
| Dueñas Parrilla et al. (1991) [58] | 1 | 65 | M | E | Absent | Absent | |
| Serafini et al. (1991) [59] | 2 | 62 | M | SuG | Absent | Absent | |
| | 54 | M | SuG | Absent | Absent | |
| Spiro and Huvos (1992) [6] | 5 | NA | NA | L | Present | NA | Incidence of cervical metastasis was reported as 60% which does not match with their data of 4 out of 5 positive lymph nodes = 80% |

The present series includes the cases reported previously by Spiro et al. [35] and Spiro et al. [44]
| Author (Year)                              | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks                                                                 |
|-------------------------------------------|-----------|-----|-----|----------|--------------------------------|--------------------|-------------------------------------------------------------------------|
| Bignardi et al. (1993) [60]               | 2         | 65  | F   | SG       | Absent                         | Absent             | No neck dissection; no RT; 6 years follow-up                            |
|                                           |           | 76  | F   | SuG      | Absent                         | Absent             | No neck dissection; postop RT; 4 years follow-up                        |
| Gierek et al. (1994) [61]                 | 2         | NA  | NA  | SuG, T   | Absent                         | Absent             | Data mixed with other location (hypopharynx) and other histologic types of tumors |
| Anderson et al. (1995) [62]               | 3         | NA  | NA  | SG       | NA                             | Absent             | Data mixed with other location                                         |
|                                           |           | NA  | NA  | SG       | NA                             | Absent             |                                                                         |
|                                           |           | NA  | NA  | SuG      | NA                             | Absent             |                                                                         |
| de Kerviler et al. (1995) [63]            | 1         | 52  | M   | AEF      | Present                        | Present            | Seven of the eight lymph nodes contained tumor, with ruptured capsule   |
|                                           |           |     |     |          |                                |                    | Bilateral cervical lymph nodes recurrence and lung metastasis           |
| Scott and Glover (1995) [64]              | 1         | 66  | F   | SuG      | Absent                         | Absent             |                                                                         |
| Lam and Yuen (1996) [65]                  | 1         | 56  | F   | SuG      | NA                             | NA                 | One case of AdCC among 451 cancers of the larynx                        |
| Parsons et al. (1996) [66]                | 2         | NA  | NA  | NA       | NA                             | NA                 | Two cases of laryngeal AdCC among 57 AdCC of the head and neck          |
|                                           |           | NA  | NA  | NA       |                                |                    | Data were analyzed together with other locations and histological subtypes |
| Spiro (1997) [67]                        | 5         | NA  | NA  | NA       | NA                             | 3                  | These data are not accounted at the end of the table because they are included in a previous article [6] |
| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|-----------------------------|-----------|-----|-----|----------|------------------------------|-------------------|---------|
| Srivastava and Bathia (1997) [68] | 1 | 30 | M | SuG | Absent | Absent | |
| Alavi et al. (1999) [69] | 5 | NA | NA | G | NA | NA | Data of different glandular carcinomas are mixed |
| | | NA | NA | SG | NA | NA | |
| | | NA | NA | SuG | NA | NA | |
| | | NA | NA | SuG | NA | NA | |
| | | NA | NA | SuG | NA | NA | |
| Damborenea Tajada et al. (1999) [70] | 1 | NA | NA | NA | NA | NA | |
| Fordice et al. (1999) [71] | 2 | NA | NA | NA | NA | NA | Data of AdCC of different locations analyzed together |
| Hogg et al. (1999) [72] | 1 | 72 | M | SuG | Absent | Absent | Patient with a goiter that confounded the diagnostic process |
| Morais Pérez et al. (1999) [73] | 1 | 26 | F | SG | Absent | Absent | No neck dissection |
| Veivers et al. (2001) [74] | 1 | 39 | M | SuG, anterior commissure | Absent | Present | Distant metastasis to lungs |
| Javadi et al. (2002) [75] | 1 | 12 | M | SuG | Absent | Absent | |
| Mahlstedt et al. (2002) [76] | 6 | NA | NA | SG | 1 patient was N1 | Absent | It is not specified in the article which patient was N1 |
| | | NA | NA | SG | Absent | Absent | Two patients underwent neck dissection |
| | | NA | NA | SG | Absent | Absent | |
| | | NA | NA | SG | Absent | Absent | |
| | | NA | NA | SuG | Absent | Absent | |
| Author (Year) [References] | No. cases | Age | Sex/Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|---------------------------|-----------|-----|--------------|-------------------------------|-------------------|---------|
| Lee et al. (2003) [77]   | 1         | 50  | M/E          | Absent                        | Absent            |         |
| Silverman et al. (2004) [78] | 4         | NA  | NA/NA        | NA                            | NA                | Data analyzed mixed with other locations |
| Gaissert et al. (2005) [79] | 9         | NA  | 9 SuG        | Absent                        | 3 present         | Three patients with AdCC died of distant disease |
| Ganly et al. (2006) [80]  | 10        | 45  | F/E          | Present                       | Present           | AdCC-HGT |
|                           | 40        | F   | E            | Absent                        | Present           | AdCC-HGT |
|                           | 54        | M   | E            | Absent                        | Absent            | AdCC-HGT |
|                           | 56        | M   | SuG          | Absent                        | Absent            |         |
|                           | 69        | F   | SuG          | Absent                        | Absent            | Distant metastasis to lungs and in patient 2 to lungs and bone (Grade classification following the M. D. Anderson Grading [81]) |
|                           | 74        | F   | SuG          | Absent                        | Present           |         |
|                           | 40        | F   | SuG          | Present                       | Absent            |         |
|                           | 53        | M   | SuG          | Absent                        | Absent            |         |
|                           | 54        | M   | SuG          | Absent                        | Absent            |         |
|                           | 55        | M   | SuG          | Absent                        | Present           |         |
| Haddad et al. (2006) [82] | 1         | 41  | M/SuG, G     | Absent                        | Absent            |         |
| Khan et al. (2006) [83]   | 1         | 30  | F/SuG        | Absent                        | Absent            |         |
| Wang et al. (2006) [84]   | 4         | 48  | M/G          | Absent                        | Absent            | Dead without disease |
|                           | 60        | M   | G            | Absent                        | Absent            | Dead without disease |
|                           | 69        | M   | SG           | Absent                        | Absent            | Alive without disease |
|                           | 58        | M   | SuG, G       | Absent                        | Present           | Dead of lung metastasis |
| Del Negro et al. (2007) [85] | 1         | 55  | F/SuG        | Absent                        | Absent            |         |
| Messaoudi et al. (2007) [86] | 1         | 49  | M/SuG        | Absent                        | Absent            |         |
| Aydin et al. (2008) [87]  | 1         | 16  | F/SuG        | Absent                        | Absent            |         |
| Author (Year) | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|--------------|-----------|-----|-----|----------|------------------------------|-------------------|---------|
| Moukarbel et al. (2008) [88] | 15 | NA | NA | NA | Absent | Present | No data available about lymph node status |
| | NA | NA | NA | Absent | Present | | Two patients suffered regional recurrences, but without specifications (showed in the table as NA in lymph node column) |
| | NA | NA | NA | Absent | Present | | |
| | NA | NA | NA | Absent | Present | | |
| | NA | NA | NA | Absent | Present | | |
| | NA | NA | NA | Absent | Present | | |
| | NA | NA | NA | Absent | Present | | |
| Moukarbel et al. (2008) [88] | 1 | 54 | F | SuG | Absent | Absent | |
| Zvrko and Golubović (2009) [90] | 1 | 55 | M | SuG | Absent | Absent | |
| Murray et al. (2010) [91] | 1 | 26 | M | L | NA | Present | Distant metastasis to lung and spleen |
| Nhembé et al. (2010) [92] | 1 | 54 | M | SuG | Absent | Absent | |
| Oplatek et al. (2010) [93] | 5 | NA | NA | NA | NA | NA | Data analyzed mixed with other locations |
| Zald et al. (2010) [94] | 1 | 60 | M | SuG, VC | Absent | Absent | |
| Lloyd et al. (2011) [95] | 26 | NA | NA | NA | NA | NA | |
| Author (Year) | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|--------------|-----------|-----|-----|----------|-------------------------------|-------------------|---------|
| Balamucki et al. (2012) [96] | 2 | NA | NA | NA | NA | NA | Data were analyzed mixed with other locations |
| Boland et al. (2012) [97] | 1 | 60 | F | L | NA | NA | Dead of disease |
| Calzada et al. (2012) [98] | 6 | NA | NA | Right VC | Absent | Absent | One of these patients had a modified radical neck dissection because of palpable nodal disease (although final pathology showed no evidence of metastatic AdCC) |
| Costa et al. (2012) [99] | 1 | 58 | F | L | Present | Absent | Present |
| Friedman et al. (2012) [100] | 1 | 67 | M | SG | Present | Absent | NA |
| Nielsen et al. (2012) [101] | 4 | 67 | M | SG | Absent | Absent | Distant metastasis to lung |
| Misiukiewicz et al. (2013) [102] | 24 | 73 | M | | Present | Absent | Absent |
| Testa et al. (2013) [103] | 1 | 61 | F | Left VC | Present | Absent | Patient had bilateral cervical lymph node hyperplasia, but histological examination was free of metastasis |
Table 1 continued

| Author (Year) [References] | No. cases | Age | Sex | Location            | Cervical lymph node metastasis | Distant metastasis | Remarks                                                                 |
|---------------------------|-----------|-----|-----|----------------------|-------------------------------|--------------------|-------------------------------------------------------------------------|
| van Weert et al. (2013) [104] | 3         | NA  | NA  | 3 L                  | Absent                        | Absent             | Tumor site is referred as larynx/trachea                                |
|                           |           |     |     |                      |                               |                    | Author by personal communication indicate us that there are four cases, three larynx and one trachea |
| Qian et al. (2014) [105]  | 1         | 44  | F   | SG                   | Absent                        | Absent             | One patient had distant metastasis at diagnosis                        |
| Zhang et al. (2014) [106] | 9         | 84  | F   | SuG                  | Absent                        | NA                 | Seven patient dead of disease                                          |
|                           | 36        | M   | SuG |                      | Absent                        | NA                 |                                                                         |
|                           | 77        | M   | E, FVC |                      | Absent                        | NA                 |                                                                         |
|                           | 75        | M   | AEF, FVC |                      | Absent                        | NA                 |                                                                         |
|                           | 36        | F   | SuG |                      | Absent                        | NA                 |                                                                         |
|                           | 48        | M   | SuG |                      | Absent                        | NA                 |                                                                         |
|                           | 74        | M   | SuG |                      | Present                       | NA                 |                                                                         |
|                           | 74        | F   | SuG, esophagus, mediastinum | Present | NA                     |                     |                                                                         |
| Amit et al. (2015) [3]    | 6         | NA  | NA  | L                    | NA                            | NA                 | One case underwent neck dissection, but results are mixed with other locations |
| Carmel et al. (2015) [107] | 1         | NA  | F   | E, PS                | Absent                        | Absent             |                                                                         |
| Dubal et al. (2015) [108] | 69        | NA  | NA  | 5 G, 26 SG, 31 SuG, 7 L | NA                            | NA                 | Staging data were only available for 33 patients: 29 patients were N0, 1 N1, 2 N2 and 1 NX; 2 patients were M1 at the moment of diagnosis |
Table 1 continued

| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|----------------------------|-----------|-----|-----|----------|-------------------------------|-------------------|---------|
| Hsu et al. (2015) [109]    | 1         | NA  | NA  | L        | NA                            | NA                | NA      |
| Liu and Chen (2015) [110]  | 6         | 46  | M   | SG       | Absent                        | Present           | Four patients underwent modified radical neck dissection because of palpable cervical lymph nodes |
|                            | 61        | M   | SuG |          | Absent                        | Absent            | All the lymph nodes had reactive hyperplasia without evidence of metastatic AdCC |
|                            | 56        | F   | SG  |          | Absent                        | Present           |         |
|                            | 47        | F   | SuG |          | Absent                        | Absent            |         |
|                            | 15        | F   | SuG |          | Absent                        | Absent            | Patient 1 distant metastasis to lung, patient 3 to liver |
|                            | 39        | M   | SuG |          | Absent                        | Absent            |         |
| Total Data Available       | 252       | 52.36 | 82M | 96 SuG  | 53 F                          | 24^a              | 47      |
|                            |           | 53 F |      | SG       | (include E, V, FVC, AEF)      |                   | 47      |
|                            |           | 16   | G   |          |                               |                   |         |

AdCC adenoid cystic carcinoma, AdCC-HGT adenoid cystic carcinoma with high grade transformation, AEF aryepiglottic fold, E epiglottis, F female, FVC false vocal cord, G glottis, HL hemilarynx, L larynx, M male, NA not available, PLW pharyngolaryngeal wall, PS pyriform sinus, RT radiotherapy, SG supraglottis, SuG subglottis, T trachea, V ventricle, VC vocal cord

^a Status of regional lymph nodes available in 156 cases
**Table 2** Cases of AdCC of the larynx excluded in the analysis

| Author (Year) [References] | No. cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis | Remarks |
|--------------------------|-----------|-----|-----|----------|--------------------------------|-------------------|---------|
| Spiro et al. (1973) [35] | 3         | NA  | NA  | 2 SG, 1 G | NA                             | NA                | Different salivary gland tumors analyzed by location or by histology; These data are not accounted in Table 1 because they are included in a posterior article of the author [6] |
| Spiro et al. (1976) [44] | 3         | 57  | M   | G        | Present                        | Present           | Carcinomatosis; These data are not accounted in Table 1 because they are included in a posterior article of the author [6] |
| Ferlito and Caruso (1983) [50] | 2         | 52  | F   | E        | Absent                         | Absent            | These data are not accounted in Table 1 because they are included in a posterior article of the author [56] |
| Spiro (1997) [67]        | 5         | NA  | NA  | NA       | NA                             | 3 Present         | These data are not accounted in Table 1 because they are included in a previous article of the author [6] |
| Lloyd et al. (2011) [95] | 26        | NA  | NA  | NA       | NA                             | NA                | These data are not accounted in Table 1 because it is not possible to know if they are previously published cases (SEER Database) |
| Dubal et al. (2015) [108]| 69        | NA  | NA  | 5 G, 26 SG, 31 SuG, 7 L | NA                | NA                | Staging data were only available for 33 patients: 29 patients were N0, 1 N1, 2 N2 and 1 NX; two patients were M1 at the moment of diagnosis; These data are not accounted in Table 1 because it is not possible to know if they are previously published cases (SEER Database) |
DISCUSSION

Salivary gland carcinomas of the larynx are rare accounting for <1% of laryngeal malignancies [116] and it has already been noted that among these AdCC is one of the most common. Their rarity may be in part related to the paucity of accessory salivary (mucoserous) glands in this region [110]. It is reminded that the highest number of minor glands is localized in the subglottis; but they are also seen in the supraglottis and only infrequently in the glottis [80]. Moukarbel et al. [88], in a 40-year experience at the Princess Margaret Hospital of Toronto identified only 15 cases of AdCC of the larynx and observed the most frequent location to be the subglottis (60%). Others have also noted the predominant subglottic location of this tumor including Batsakis et al. [116] who found that 2 of their 3 tumors also arose in the subglottis as did 7 of the 10 tumors reported by Ganly et al. [80]. In our review of 252 cases of AdCC of the larynx, the exact location of the tumor was available in 165 and of these 58.2% arose in the subglottis, 32.1% in the supraglottis and 9.7% in the glottis.

AdCC has a distinct biological behavior as compared to other malignant tumors (slow growth, propensity to neurovascular invasion, high frequency of distant metastasis and long-term survival with tumor) [96]. Another characteristic of AdCC is that lymph node metastases are infrequent with a reported overall incidence of approximately 10%, but this frequency may vary depending on the location of the lesion [e.g. base of tongue (19.2%), mobile tongue (17.6%), floor of mouth (15.3%)] [117], and up to half of the patients with nasopharyngeal AdCC [118]. In our review of 252 cases of AdCC of the larynx, information regarding the status of the regional lymph nodes was available in only 156 cases and of these only 24 tumors (15.4%) were associated with lymph node metastasis.

The finding of enlarged cervical lymph nodes in patients with AdCC of the larynx is however not uncommon. Liu and Chen [110] reviewed six cases of AdCC of the larynx four of which underwent modified radical neck dissection because of palpable cervical lymph nodes (cN+) and all four showed no evidence of metastasis on pathologic examination (pN−). Calzada et al. [98] identified, over a 30-year period, 11 patients with AdCC of the airway, six of which had tumors of the larynx. One of these patients underwent a modified radical neck

| Period | No. of cases | Age | Sex | Location | Cervical lymph node metastasis | Distant metastasis |
|--------|--------------|-----|-----|----------|-------------------------------|-------------------|
| A      | 1912–1971    | 43  | 48.28 | 20M/10F | 11 SG, 2 G, 13 SuG | 3 Present<sup>a</sup> | 7 Present |
|        | 1972–1990    | 67  | 55.44 | 23M/18F | 17 SG, 6 G, 26 SuG | 10 Present<sup>a</sup> | 12 Present |
| B      | 1991–2015    | 142 | 52.50 | 39M/25F | 25 SG, 8 G, 57 SuG | 11 Present<sup>b</sup> | 28 Present |
| A + B  | 1912–2015    | 252 | 52.36 | 82M/53F | 53 SG, 16 G, 96 SuG | 24 Present<sup>c</sup> | 47 Present |

- G: glottis, SG: supraglottis, SuG: subglottis
- <sup>a</sup> Status of regional lymph nodes available in 65 cases
- <sup>b</sup> Status of regional lymph nodes available in 91 cases
- <sup>c</sup> Status of regional lymph nodes available in 156 cases
dissection due to palpable nodal disease, but the pathologic analysis of the neck dissection specimen reported only reactive lymph nodes. Testa et al. [103], also reported one case of a glottic-subglottic AdCC with bilateral cervical lymph node hyperplasia but with no evidence of metastasis. In a national study conducted in Denmark, Nielsen et al. [101] found four cases of AdCC of the larynx. All were staged N0, including the patient in whom a suspicious node was surgically removed.

In contrast, in 1977, Olofsson and van Nostrand [45] reported four cases of AdCC of the larynx and 1 of them had metastatic foci in three small paraesophageal lymph nodes. More recently, Dubal et al. [108] reviewed 69 cases of laryngeal AdCC of which 87.9% of the patients were N0. The remaining patients were staged N1 (one patient), N2 (two patients) and Nx (one patient) using the American Joint Committee on Cancer staging system. Amit et al. [2] in their international collaborative study of 270 patients who underwent neck dissection for AdCC, identified two cases of AdCC of the larynx, and one of them had positive lymph nodes. In a similar paper of Amit et al. [3] they reviewed the same series of 270 patients who underwent neck dissection for AdCC. This time, the authors identified six patients with AdCC of the larynx and only one of which underwent elective neck dissection. The definite pathologic result of this neck dissection is unknown because the results of all neck dissections were analyzed together.

Considering these data, the incidence of lymph node metastasis seems to be very low, with anecdotal cases reported. There are however several reports that contradict this view. Spiro and Huvos [6] reported five patients with AdCC of the larynx, 4 (80%) of which had associated lymph node metastasis.

**TREATMENT SUGGESTIONS**

Specific data on neck dissection in AdCC of the larynx are scarce. Therefore, we analyzed mainly the incidence of clinically overt lymph node metastasis in laryngeal AdCC. However, it can be anticipated that when this incidence is about 15.4% and the sensitivity of modern diagnostic techniques to detect occult lymph node metastasis is similar to that for head and neck squamous cell carcinoma, the rate of occult lymph node metastasis after current diagnostic work-up would be around 7%–8%, probably too low to warrant elective neck dissection in this group. Moreover, patients will be more at risk for distant than cervical lymph node metastasis.

Adenoid cystic carcinoma with high grade transformation (AdCC-HGT), however, is another issue that requires special attention. High-grade transformation (previously referred to as dedifferentiation) is defined as the abrupt transformation of a tumor into high-grade morphology that lacks the original distinct histologic characteristics [119]. These changes may be focal within the tumor and, as a result, AdCC-HGT may not always be appreciated pre-operatively. AdCC-HGT is an aggressive tumor with a high tendency to recur and metastasize to the lymph nodes (at least 50% or higher) and distant organs [120], as illustrated by the supraglottic tumor reported by Stillwagon et al. [52], which metastasized to five cervical lymph nodes with extracapsular extension, as well as to the liver, bone marrow, brain, heart, lungs and kidneys. AdCC-HGT must therefore be treated aggressively with due consideration for neck dissection.

The best treatment of the “conventional” laryngeal AdCC remains controversial. Standard treatment recommends a surgical approach
with or without postoperative radiotherapy. Liu and Chen [110] reported six cases of laryngeal AdCC, all of which were treated with surgical resection and postoperative radiotherapy. They reported no local recurrences and only two patients had distant metastasis (lungs and liver) with a maximum follow-up of 6 years. With respect to cervical nodes, they did not recommend neck dissection in the absence of palpable lymph nodes (elective neck dissection), considering that four cases with palpable lymph nodes (cN+) were all free of tumor on histologic evaluation (pN−). Postoperative radiotherapy was recommended in view of the submucosal and perineural pattern of spread of this tumor. This explains why partial procedures or even total laryngectomy in AdCC may result in positive margins. For example, Moukarbel et al. [88] only achieved tumor-free margins in 5 of 15 patients. In three patients results were not available and seven had positive margins. Only three patients suffered local recurrence. In contrast, Calzada et al. [98] achieved tumor-free surgical margins in 5 of 6 patients (the sixth patient’s margin status was unavailable) including two patients who underwent partial surgery. All the patients received postoperative external beam radiotherapy. No cases of local recurrence were documented and only one patient had a distant failure.

In view of these data, neck dissection seems to be an overtreatment in patients with AdCC of the larynx. The reasons for not performing neck dissection are: very low incidence of cervical lymph node metastasis (probably under 15.4%), low probability of neck recurrence (published cases with lymph node recurrences are anecdotal), need of complementary radiotherapy after the surgery due to the pattern of spread of this tumor (submucosal and perineural) and the low possibility of undiagnosed positive lymph nodes. The reasons against not performing neck dissection are: the option of performing a neck dissection with a very low morbidity during the “open” surgery for the primary tumor and the observation that the appearance of enlarged lymph nodes in patients with AdCC is not uncommon, raising doubts to the surgeon about the correct diagnosis or the correct treatment.

LIMITATIONS

After commenting on this information, we would like to point out several limitations of this review: first of all, we have tried to be extremely accurate reviewing the cases published and we have tried to include “all” the cases from the literature. We appreciate that in the first period assessed (1912–1990) several cases with inexact histologic diagnosis could be found, but in order to be comprehensive, they were included in this review. There are a lot of cases with relevant information missing, but we had to include the data given by the authors although some of them did not give information about T stage, histologic grading, node levels involved, etc. As we have stated above the majority of the articles are case reports, and there are a lot of review articles mixing the data of AdCC of different locations in the head and neck.

CONCLUSION

Based on a thorough literature review, lymph node metastases in AdCC of the larynx are infrequent. In general, elective treatment of the neck is recommended for patients with squamous cell carcinoma of the upper aerodigestive tract when the anticipated risk of
occult metastasis is greater than 20%, based on a widely quoted decision analysis model like that proposed by Weiss et al. [121]. According to this, for the most recent period 1991–2015, with a more precise diagnosis of the tumor, 142 cases were observed of AdCC of the larynx and between them 91 patients had data pertaining to lymph node status. Only eleven of the 91 patients (12.1%) had nodal metastasis and in the previous period investigated (1912–1990) the incidence was also less than 20%. Therefore we think that elective neck dissection is not indicated, particularly if the neck is carefully examined by ultrasound and ultrasound-guided fine-needle aspiration biopsy in diagnostic work-up and follow-up.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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