Cervical lymph node metastasis in adenoïd cystic carcinoma of oral cavity and oropharynx: A collective international review


Instituto Universitario de Oncología del Principado de Asturias, Universidad de Oviedo, Oviedo, Spain
Fundación Investigación e Innovación Biosanitaria del Principado de Asturias, Oviedo, Spain
Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
Departments of Surgery and Otolaryngology – Head and Neck Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA
Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
Head and Neck Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Ocular and Maxillofacial Pathology, School of Dentistry, University of Liverpool and Cellular Pathology, Liverpool Clinical Laboratories, Liverpool, UK
University of Udine School of Medicine, Udine, Italy
Department of Anatomic Pathology, Hospital Clinic, University of Barcelona, Barcelona, Spain
Department of Surgery, Banner MD Anderson Cancer Center, Gilbert, AZ, USA
Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, São Paulo, Brazil
Division of Otolaryngology-Head and Neck Surgery, Southern Illinois University School of Medicine, Springfield, IL, USA
Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
Department of Otolaryngology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, The Netherlands
Department of Otolaryngology-Head and Neck Surgery, Radboud University Medical Center, Nijmegen, The Netherlands
Department of Otolaryngology – Head and Neck Surgery, Nottingham University Hospitals, Queens Medical Centre Campus, Nottingham, UK
European Salivary Gland Society, Geneva, Switzerland
University Pathologists, Providence, RI, USA
University Pathologists, Fall River, MA, USA
Department of Otolaryngology-Head and Neck Surgery, Philipp University, Marburg, Germany
Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia
Department of Radiation Oncology, University of Florida, Gainesville, FL, USA
Department of Otolaryngology – Head and Neck Surgery, Neurological Institute of New Jersey, Rutgers New Jersey Medical School, Newark, NJ, USA
Departments of Pathology and Otolaryngology-Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore, MD, USA

* This article was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).
* Corresponding author.
E-mail address: a.ferlito@uniud.it (A. Ferlito).

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1. Introduction

Minor salivary gland neoplasms arise from mucoserous glands that are widely distributed throughout the upper aerodigestive tract. While most parotid gland neoplasms are benign, most minor salivary gland neoplasms are malignant. Thus, in the parotid gland, approximately only 15% of tumors are malignant, while 30–40% are malignant in the submandibular glands, and in minor salivary glands as a group 45–50% are malignant. In the sublingual glands as much as 90% are malignant. Typically, there are between 500 and 1000 minor salivary glands that are most numerous in the mouth, particularly in the palate, and in the oropharynx at the base of the tongue. It is the presence of these widely dispersed minor glands that is responsible for the occurrence of the spectrum of salivary tumors at sites such as the oral cavity, oropharynx, larynx, nasal cavity and paranasal sinuses. The most common malignant histologic types are adenoid cystic carcinoma (AdCC) (24–70%) and mucoepidermoid carcinomas (11–39%). Other subtypes, such as adenocarcinoma, acinic cell carcinoma, myoepithelial carcinoma, and malignant mixed tumor (carcinoma arising from pleomorphic adenomas), occur less frequently [1–5] (Table 1).

Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>AdCC (%)</th>
<th>Mucoepidermoid carcinoma (%)</th>
<th>Other types (%)</th>
<th>Oral cavity (%)</th>
<th>Oropharynx (%)</th>
<th>Sinonasal (%)</th>
<th>Other locations (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. [1]</td>
<td>60</td>
<td>38 (63)</td>
<td>11 (18)</td>
<td>11 (18)</td>
<td>33 (55)</td>
<td>16 (27)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Jones et al. [2]</td>
<td>103</td>
<td>72 (69.9)</td>
<td>20 (19.4)</td>
<td>11 (10.7)</td>
<td>55 (53.4)</td>
<td>12 (11.6)</td>
<td>16 (15.5)</td>
</tr>
<tr>
<td>Zeidan et al. [3]</td>
<td>90</td>
<td>58 (64)</td>
<td>10 (11)</td>
<td>22 (24)</td>
<td>35 (39)</td>
<td>10 (11)</td>
<td>39 (43)</td>
</tr>
<tr>
<td>Iyer et al. [4]</td>
<td>67</td>
<td>16 (24)</td>
<td>26 (39)</td>
<td>23 (34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. [5]</td>
<td>103</td>
<td>48 (46.6)</td>
<td>37 (35.9)</td>
<td>18 (17.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AdCC, adenoid cystic carcinoma.
AdCC occurs more often in the minor salivary glands (43–80%) than in the major glands (20–49%), and is found mainly in the oral cavity, followed by sinonasal tract and oropharynx [6–19] (Table 2). The most frequent intraoral subsite is the palate, followed by the buccal mucosa and the floor of the mouth [11,12,20,21]. In the oropharynx, the base of the tongue and the soft palate are the most frequently involved sites [11,12,15,20] (Table 3).

The natural history of AdCC is characterized by slow, but relentless growth; multiple local recurrences; and distant hematogenous dissemination mainly to the lung, liver, bone and brain. Involvement of regional lymph nodes is relatively uncommon and has often thought to be the result of direct extension of tumor from an adjacent primary tumor site. Lymph node spread, in contrast, has been considered to occur infrequently. In practice, it is often difficult or impossible to distinguish between these two events and accordingly, the term “metastasis” as applied to cervical lymph nodes in this paper includes both possibilities unless stated otherwise. Although the long-term prognosis is poor, it is not uncommon for some patients to survive 10–15 years before succumbing to their disease. As late local and distant recurrences appear with some frequency, long-term follow-up is necessary to assess the effectiveness of treatment. AdCC also has a high propensity for perineural invasion, sometimes associated with remotely occurring lesions along nerve sheaths, which significantly increase the risk of recurrence after resection, even when negative margins are obtained.

Although elective neck dissection (END) generally has not been considered indicated in treatment of AdCC, there is some debate on its potential advantage in terms of a reduction of regional recurrence and distant spread. However, due to the relative rarity of these tumors, most studies report on small patient cohorts over extended periods, including all histologic types and at various locations in the head and neck, thus making it difficult to draw solid conclusions about therapeutic options. To further address this issue, we critically reviewed the literature on AdCC of the oral cavity and oropharynx to determine the frequency of cervical lymph node involvement and to suggest guidelines on how the neck should be managed.

On these purposes, we undertook a search of the English literature in the PubMed database (including Medline) using the search strategy “adenoid cystic carcinoma oropharynx”, “adenoid cystic carcinoma oral cavity”, and “adenoid cystic carcinoma head neck”. We excluded case reports, series with a small number of cases, and papers with no information on the neck status and/or outcomes.

2. Incidence and consequences of cervical lymph node metastasis

Metastasis to the cervical lymph nodes is uncommon in AdCC. The incidence of clinically evident metastases at
diagnosis of head and neck AdCC is variable depending on the series and site of origin of the tumor but usually ranges between 3% and 16% [1,2,4–6,8,10–13,15–20,22–29]. One of the reasons that overall reported occurrence of lymph node metastasis is rare for AdCC from different published series may be that the two most common sites for AdCC, the parotid gland and hard palate, have low propensity for nodal spread. Thus, Min et al. [12] studied 616 cases of head and neck AdCC, identifying 62 (10%) cases of AdCC with cervical lymph node metastasis, 38 cases at the time of surgery and 24 cases with late recurrence after initial surgery. When primary sites were compared, the reported incidence of cervical metastases was higher when primary tumor sites were located at the base of tongue (19.2%), followed by the mobile tongue (17.6%) and floor of mouth (15.3%), whereas the incidence of metastasis from primary tumors of the hard palate was only 8%. The reason for the high incidence from tongue base primary tumors may be due to their advanced stage at presentation, and the extensive lymphatic network in this site. The incidence of clinically positive nodes (cN+) for intraoral and oropharyngeal AdCC varies from 2% to 43% [4,5,12,20,23], and is low for AdCC of the palate and high for base of the tongue localizations [5,12,23].

Dedifferentiation and/or high-grade transformation has been described in a variety of salivary gland carcinomas, including AdCC. A total of approximately 40 cases of AdCC with high grade transformation (AdCC-HGT) have been recognized in the literature to date [30–32]. AdCC-HGT is a highly aggressive tumor with a strong tendency to recur and metastasize to regional lymph nodes (57% in the review of Seethala et al. [31]) and to distant organs.

Min et al. [12] reported that minor salivary gland AdCC metastasized to only one neck level in almost 60% of cases. For the remaining patients, cervical lymph node metastasis was reported at two or more levels. Level II was the most frequently involved, with a reported incidence of 59.6%. Level III and IV regions were affected only in 22.5% of cases.

Neck node recurrence can occur after treatment in 0–14% of AdCC of minor salivary glands, and is highly dependent on the extent of the treatment. It is very rare in patients who received therapeutic or elective neck dissections [1,10,20], or postoperative radiotherapy (RT) to the neck [8,18].

Lymph node involvement with or without extracapsular spread at diagnosis in AdCC has been shown in most reports to be independently associated with decreased overall and causespecific survival [6,8,12–17,19,27,33–35]. Kakarala and Bhattacharya [36] reported that N status correlated with a higher odds ratio for poor survival, indicating the importance of regional metastasis in determining prognosis in oral cavity minor salivary gland tumors. Bianchi et al. [20] observed a distinct survival difference according to regional metastasis status in oral minor salivary gland AdCC. In their study, 5, 10, and 15-year survival rates were 44.4% in patients with regional metastasis, compared to 79.1%, 76.9%, and 76.9% respectively in patients without regional metastasis. Furthermore, Lee et al. [10] recorded, among 61 cases of head and neck AdCC, an overall survival rate of 85% at 5 years, 81.1% at 10 and 15 years in patients with negative status (N−), whereas in patients with positive N status (N+), the survival rate was 56.8% at 5 years and 28.4% at 10 years. Finally, Opletal et al. [13] have reported, from a cohort of 113 cases of head and neck AdCC that patients with regional cervical lymph node metastasis at the time of diagnosis had a mean survival of 46 months compared to a mean survival of 98 months for those without evidence of regional metastasis.

Lymphovascular invasion usually precedes spread to the lymph nodes that drain the tissue in which the tumor arose. On multivariate analysis, lymphovascular invasion was the only prognostic factor for overall survival [1] and was also an independent predictor of recurrence [13,37]. Other tumor-related histologic factors independently associated with decreased survival are perineural involvement of a major nerve [8,24] and solid histological subtype of AdCC [16,17,21,30,35].

Most authors have found that lymph node involvement is a risk factor for subsequent distant metastasis [1,6,27,38]. Thus, according to Ko et al. [14] 75% of patients with initial nodal involvement eventually developed distant metastasis. Even considering only the presence of histologic lymph node metastases in ENDs, Amit et al. [22] pointed out that the 5-year distant metastasis rate was significantly higher among patients with nodal metastasis than among those without (40% and 27%, respectively).

The characteristics of lymph node metastasis as related to the occurrence of distant metastasis in AdCC have been studied

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**Table 4**

<table>
<thead>
<tr>
<th>No.</th>
<th>Clinical N+ HN AdCC (%)</th>
<th>Clinical N+ Oral/ oropharynx (%)</th>
<th>Neck recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. [1]</td>
<td>38</td>
<td>6 (15.8)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Jones et al. [2]</td>
<td>103</td>
<td>7 (6.8)</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td>Iyer et al. [4]</td>
<td>16</td>
<td>1 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>Li et al. [5]</td>
<td>48</td>
<td>1 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Lloyd et al. [6]</td>
<td>2286</td>
<td>183 (8)</td>
<td></td>
</tr>
<tr>
<td>Gomez et al. [8]</td>
<td>59</td>
<td>9 (15)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Lee et al. [10]</td>
<td>61</td>
<td>4 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Agarwal et al. [11]</td>
<td>76</td>
<td>6 (7.9)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Min et al. [12]</td>
<td>616</td>
<td>38 (6.2)</td>
<td>24 (3.9)</td>
</tr>
<tr>
<td>Opletal et al. [13]</td>
<td>99</td>
<td>7 (7.1)</td>
<td></td>
</tr>
<tr>
<td>da Cruz Perez et al. [15]</td>
<td>129</td>
<td>13 (10.1)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Fordice et al. [16]</td>
<td>160</td>
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<td>2 (1.2)</td>
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<td>vanWeert et al. [17]</td>
<td>105</td>
<td>11 (10)</td>
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<td>Balamuki et al. [18]</td>
<td>120</td>
<td>7 (6)</td>
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<td>Anderson et al. [19]</td>
<td>41</td>
<td>2 (5)</td>
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<tr>
<td>Bianchi et al. [20]</td>
<td>67</td>
<td>6 (9)</td>
<td></td>
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<tr>
<td>Amit et al. [22]</td>
<td>495</td>
<td>44 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Namazie et al. [23]</td>
<td>14</td>
<td>6 (43)</td>
<td></td>
</tr>
<tr>
<td>Garden et al. [24]</td>
<td>198</td>
<td>6 (3)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Spiro et al. [25]</td>
<td>242</td>
<td>17 (7)</td>
<td>18 (7.4)</td>
</tr>
<tr>
<td>Ettl et al. [26]</td>
<td>50</td>
<td>5 (10)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Douglas et al. [27]</td>
<td>151</td>
<td>20 (13)</td>
<td></td>
</tr>
<tr>
<td>Armstrong et al. [28]</td>
<td>55</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Sur et al. [29]</td>
<td>50</td>
<td>8 (16)</td>
<td></td>
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</tbody>
</table>

HN, head and neck; AdCC, adenoid cystic carcinoma.  
* Includes only isolated neck metastasis.
by Liu et al. [39] in 47 patients with neck node metastasis. They analyzed the number of lymph nodes involved, the positive lymph node ratio (percentage of positive lymph nodes to total lymph nodes examined), the neck level involved (I–V), and extracapsular spread. Whereas using the log-rank test, positive lymph node ratio, neck level involved, and extracapsular spread were strongly associated with lower metastasis-free survival, in the multivariate analysis, only the lymph node-positive ratio maintained its predictive value.

3. Treatment of the neck

3.1. Treatment of the clinically positive neck (therapeutic treatment)

Therapeutic neck dissection is performed as a matter of course in all patients with clinically evident nodal metastases. Conventional RT as a single modality primary treatment has a limited role in AdCC, due to evidence that the outcome of patients treated with surgery and RT is significantly better when compared to patients treated with RT alone [18]. The role of adjuvant RT has been much debated. Generally, patients treated with surgery and adjuvant RT showed comparable outcome with patients treated by surgery alone. Furthermore, regional recurrences are not usually identified in cN+ patients who undergo therapeutic neck dissection, whether or not adjuvant RT is administered [1]. The lack of a survival advantage for patients treated with surgery and RT is thought to be a result of the high rate of distant metastases observed in the patient population, and the relatively high likelihood of long-term survival after salvage therapy for patients who developed a local–regional recurrence [18].

3.2. Elective treatment of the neck

3.2.1. Neck dissection

Management of the cN0 neck is still controversial in AdCC because the reported incidence of regional metastasis varies widely. Thus, END is not routinely carried out in head and neck AdCC. Consequently, few published series contain a significant number of cases with sufficient statistical power to permit definitive conclusions. Results may also be biased since most END are probably performed on more advanced cases, or based on the surgeon’s preference, rather than according to established protocols. Prospective multicentric studies are lacking and it seems evident that such studies must be performed to establish the standard treatment for AdCC. In addition to the scarcity of information on occult metastasis in AdCC, most publications do not distinguish results according to the different locations of the primary tumor.

The overall rate of occult neck metastasis in patients with head and neck AdCC is reported to range from 15% to 44% [4,10,11,18,24,35,40]. Although most of the reports do not include information on the relative rates according to the primary location, occult neck metastases from oral cavity/oropharynx (22–31%) seems to be higher than those in the sinonasal tract (17%) or in the major glands (11–23%) [1,4,9–11,18,24,35,40] (Table 5). Amit et al. [9] reviewed the results of END on 226 of 457 patients with AdCC of the head and neck, in a multinational study. The overall rate of occult nodal metastasis among the patients who underwent END was 17% (38/226). Subgroup analysis showed that the highest incidences of occult nodal metastases were among patients with oral cavity tumors (66% of all patients with positive nodes; 21.5% of 116 patients with tumors located in the oral cavity and oropharynx). The 5-year disease-specific survival was 74% for the patients who underwent END, compared with 81% for the patients who did not (no statistically significant difference). Furthermore, analysis of subgroups according to tumor site and disease stage suggested that even for patients at high risk of neck metastases (oral cavity and oropharynx) and with advanced T classification (T3–T4), END was not found to be correlated with patient outcomes.

Metastases are usually unilateral. Contralateral neck involvement was observed in only 2 of 18 patients with oral cavity tumors subjected to END (11.1%) [22]. In a cohort of 495 patients, 270 (55%) had undergone a neck dissection, elective or therapeutic. Regional metastasis presented in 55 of the 148 patients (37%) with oral cavity/oropharyngeal tumors, compared to 18 of the 95 patients (19%) with major salivary gland AdCC. The difference was highly significant. Eighty-five percent of the patients with oral cavity/oropharyngeal AdCC had lymph node metastasis restricted to levels I to III, meaning that END should be restricted to these areas [22].

The benefits of END in AdCC are not comparable to those in squamous cell carcinoma because the main cause of failure is

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Occult metastasis in elective neck dissection of adenoid cystic carcinoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Lee et al. [1]</td>
<td>16</td>
</tr>
<tr>
<td>Iyer et al. [4]</td>
<td>16</td>
</tr>
<tr>
<td>Amit et al. [9]</td>
<td>226</td>
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<tr>
<td>Lee et al. [10]</td>
<td>26</td>
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<tr>
<td>Agarwal et al. [11]</td>
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<tr>
<td>Balamucki et al. [18]</td>
<td>11</td>
</tr>
<tr>
<td>Garden et al. [24]</td>
<td>44</td>
</tr>
<tr>
<td>Bhayani et al. [35]</td>
<td>30</td>
</tr>
<tr>
<td>Nobis et al. [40]</td>
<td>16</td>
</tr>
</tbody>
</table>

\( ^{a} \) Includes oral cavity and oropharyngeal tumors.
not local-regional, but distant. Lee et al. [1,10] observed that regional recurrence was not identified in cN+ patients who underwent therapeutic neck dissection or in cN0 patients who underwent elective neck treatment, whereas regional recurrence was identified in four patients staged cN0 who did not have elective treatment of the neck. Although there was no significant difference in distant metastases or survival rates when END was performed in N0 necks, END could remove occult regional disease and provided patients with a regional recurrence-free life.

3.2.2. Neck irradiation

Elective neck treatment of AdCC also includes RT, but its use is controversial. Balamucki et al. [18] employed elective neck RT in 64 of 101 patients with undissected cN0; the remaining 37 were observed. The rates of neck control at 5 and 10 years were as follows: observation, 95% and 89%; elective neck RT, 98% and 98%. Multivariate analysis of neck control in these patients revealed that elective nodal irradiation significantly influenced this endpoint. In accord with these results, the authors recommend that although the overall risk of failure in the neck is relatively low, it would be prudent to electively treat the first echelon nodes, particularly in patients with primary tumors at sites that are rich in lymphatics, such as the base of the tongue and nasopharynx.

Similar conclusions have been drawn by Gomez et al. [8], who observed no neck failures in patients receiving radiation to the neck, whereas 7% of patients who were observed experienced a neck failure. Although postoperative radiation improved local-regional control with positive margins, it had no correlation with improved overall survival. Radiation therapy in combination with surgery produced excellent rates of local-regional control, although distant metastases accounted for a high proportion of failures.

Contrary results have been published by other authors. Chen et al. [7,41] compared the outcomes in a group of patients receiving neck irradiation and another group submitted to observation. There were no relapses in either group. In accordance with these results, their current policy is to not recommend elective neck irradiation routinely. Rather, treatment of the neck should be made on a case-by-case basis. Different reports agree that neck failures are uncommon with or without elective treatment [24,42,43].

4. Predictors of lymph node metastasis

The comparison of clinicopathological parameters with novel molecular markers for predicting cervical lymph node metastasis in salivary gland cancer is a promising field for the future. Ettl et al. [26] studied 316 patients with salivary gland carcinomas, including 50 AdCC of which 18% were N+. In addition, two patients with AdCC developed tumor recurrence as secondary lymph node metastasis. Neck dissection was carried out in 234 patients (74.1%). The results of a logistic multivariate regression analysis showed that the histological subtype of salivary duct carcinoma emerged as the strongest independent predictor of positive nodal disease. Further significant predictors of neck node metastasis were histology of adenocarcinomas, higher T classification, deletion of phosphatase and tensin homolog (PTEN), and aberration of hepatocyte growth factor receptor (MET). In contrast, age, histopathological grade (in AdCC solid vs tubular/c cribriform), epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER2) did not show any statistical significance for predicting neck node metastasis in the multivariate analysis. A total of 53.8% of patients who developed tumor recurrence as secondary lymph node metastasis despite primary neck dissection had aberration of MET and 41.7% deletion of PTEN. Aberration of MET seems to be highly important to lymphatic spread because 53% of the studied salivary gland carcinomas with a MET aberration had positive neck nodes. Multivariate analysis showed that aberration of genomic MET is a very strong predictor of lymph node metastasis, even stronger than the recognized criteria tumor size and grade. The investigation revealed a significant association between the deletion of genomic PTEN and the occurrence of neck node metastasis. Moreover, in multivariate analysis, loss of PTEN emerged as a strong predictor of lymph node metastasis (deletion in 10.6% of N0 and in 29.3% of N+).

Nevertheless, this is a preliminary report including different histologic types in addition to AdCC that has not yet been validated in other series. Thus, we cannot use this information in the treatment strategy of AdCC as a standard procedure, but it opens a new perspective to be considered.

5. Conclusions

For patients with head and neck squamous cell carcinoma, an END is indicated if the probability of occult cervical metastases is higher than 15–20%. Despite some discrepancies in the literature, occult nodal invasion in most of the primary locations of AdCC is less than 20%. Only in some oral and oropharyngeal locations does occult nodal involvement approach >20%, reaching the level normally used to justify END. On the other hand, correct N-staging by END could be important and may be a predictive factor for distant metastases in AdCC. Very few patients, who receive therapeutic or END with histologically involved nodes develop a regional recurrence. Nevertheless, in patients subjected to observation, the neck recurrence rate is notably lower than the rate of occult nodal involvement. It must be taken into account that the field of postoperative RT can include, in addition to that of the local site, the first echelon lymph nodes. Although there is some controversy about this point, neck recurrence after elective neck irradiation is uncommon. Most patients do not die due to neck relapse. Mortality is more frequently due to distant disease or, less often, to inoperable local recurrence. In summary, END should be considered in patients with a cN0 neck with AdCC in some high risk oral and oropharyngeal locations when postoperative RT is not planned, cases with lymphovascular invasion, or the rare AdCC-HGT. With patients in whom postoperative RT is recommended because of advanced T stage, perineural invasion, involvement of the skull base, etc., it appears advisable to irradiate the ipsilateral neck without additional neck dissection.
Conflict of interest

All authors declare that they do not have any financial support or relationship that may pose a conflict of interest.

References


