Adenoid cystic carcinoma of the head and neck – An update

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S U M M A R Y

This article provides an update on the current understanding of adenoid cystic carcinoma of the head and neck, including a review of its epidemiology, clinical behavior, pathology, molecular biology, diagnostic workup, treatment and prognosis. Adenoid cystic carcinoma is an uncommon salivary gland tumor that may arise in a wide variety of anatomical sites in the head and neck, often with an advanced stage at diagnosis. The clinical course is characterized by very late recurrences; consequently, clinical follow-up should extend at least >15 years. The optimal treatment is generally considered to be surgery with post-operative radiotherapy to optimize local disease control. Much effort has been invested into understanding the tumor’s molecular biological processes, aiming to identify patients at high risk of recurrence, in hopes that they could benefit from other, still unproven treatment modalities such as chemotherapy or biological therapy.

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Introduction

With a reported yearly incidence of 3–4.5 cases per million [1], adenoid cystic carcinoma (AdCC) is an uncommon tumor, accounting for about 1% of all head and neck malignancies [2] and about 10% of all tumors of the salivary glands [3]. It is the most commonly reported malignant tumor of the minor salivary glands (MSGs) [1] and is also one of the most common cancers of the major salivary glands (the parotid, submandibular and sublingual salivary glands) [4]. AdCC can also involve lacrimal and ce ruminous glands as well as other sites in the head and neck, including the nasal and paranasal sinuses, trachea and larynx [1,6–10]. AdCC was first described by Robin, Lorain and Laboulbene in two articles published in 1853 and 1854 reporting on one parotid and two nasal tumors. These authors described the characteristic cribriform arrangement of tumor cells on microscopy and noted the invasion of surrounding structures and the spread along nerves [11]. In 1856, Billroth suggested the term “cylindroma” for this tumor; the current name of “adenoid cystic carcinoma” was introduced by Spies in 1930. Despite the initial observations of Robin et al. the tumor was regarded as a variant of the benign mixed tumor. The malignant nature of this tumor was finally established by Dockerty and Mayo [12]. AdCC is a relentlessly growing tumor characterized by perineural invasion and multiple local recurrences. Regional lymph node metastases are conventionally regarded as rare, but these may be under-recognized due to potentially occult, clinically undetectable
cervical metastases, infrequent neck dissections for this tumor and arguably a lack of detailed pathological assessment of lymph nodes. In sharp contrast, hematogenous metastasis is common, especially to lung, bone and liver [11,13].

Clinically, AdCC is regarded a high-grade neoplasm, and consequently the treatment of choice is radical surgical resection and is almost always followed by postoperative radiotherapy [1,14]. Chemotherapy (both cytotoxic chemotherapy and targeted molecular therapies) has been extensively studied in patients with advanced AdCC, but the rather indolent course of the disease makes it difficult to observe clinical responses [15].

In the setting of incurable AdCC, the benefits and risks of treatment should be carefully weighed, as palliative chemotherapy for this often indolent malignancy may be associated with toxicity without known impact in disease course and patient prognosis [16]. Therefore, some asymptomatic patients with incurable disease may be observed without treatment, sometimes for years; chemotherapy is generally recommended when patients have demonstrated rapidly progressive disease or are symptomatic [17].

**Epidemiology**

AdCC is most frequently found in the parotid, submandibular and MSGs. A large Danish population-based study estimates that AdCC accounts for 27.9% of the overall incidence of salivary gland cancers (SGCs) ([11]/1,000,000/year), corresponding to an annual incidence of 3/1,000,000/year [1]. In Nova Scotia, the annual incidence raises to 4.5/1,000,000 cases [18]. It is important to note that these incidence estimates are certainly affected by challenges of histological diagnosis of SGCs, with reclassification rates ranging from 14% to 29% in several studies [1,19,20]. The cribriform pattern is easily recognized, but other patterns may be less familiar to non-specialists; epidemiological studies of SGCs should therefore consider the center from which the data has been collected.

The proportion of AdCC among SGCs varies according to the site/location of the primary tumor. In a Dutch nationwide study of parotid carcinoma, AdCC was the most frequent histology, accounting for 1 out of every 6 parotid cancers [21]. The likelihood of AdCC is even greater in the submandibular gland, where it accounts for 40% of SGCs [4,22]. AdCC is the most common cancer in MSGs, where the proportion of AdCC ranges from 32% to 71%. In MSGs, AdCC is most commonly found in the palate, followed by the paranasal sinuses (14–17%) and other sites of the oral cavity [10,22]. The tumor occurs in all age groups with a high frequency in middle-aged and older patients [24], the 5th and 6th decades being most commonly affected [1,11,20,25–27]. There are no distinct risk factors, and smoking is not known to affect the incidence [28].

**Clinical behavior**

AdCC has been described as having an apparently indolent course; however, it has an aggressive long-term behavior, with persistent and recurrent growth pattern and late onset of metastases resulting in frequent eventual death [25]. It has been described as “one of the most biologically destructive and unpredictable tumors of the head and neck” [29].

The most common presenting symptom is a slowly growing mass, followed by pain attributed to its tendency for perineural invasion. The association between pain, facial nerve dysfunction and microscopic perineural invasion was emphasized in a Netherlands’ Cancer Institute cohort of patients with parotid carcinoma, where the majority of patients with these features had AdCC [30]. In the study of Nascimento et al. [24], 98% of patients reported a mass, 48% had pain, 30% had ulceration, and one patient had facial nerve paralysis; these symptoms had been present from 1 month to 4 years. The presenting symptoms of AdCC vary according to the site of disease. In major salivary glands the tumor produces a mass, and when located in the parotid, facial nerve palsy may occur; in the palate a mass is common, though ulceration or even oro-antral fistula may be seen; in the larynx dyspnea could be the first presenting symptom; in the nose and paranasal sinuses, nasal obstruction, deep facial pain, epistaxis and eye symptoms are at the forefront [5,10,31].

**Pathology and diagnosis**

On routinely-prepared histological sections of resection specimens examined with the naked eye and at scanning magnifications, AdCCs are asymmetrical tumors, with variously lobulated or invasive growth patterns (Fig. 1).

Morphologically, AdCC largely consists of non-luminal, basa-

lloid, hematoxyphilic cells, with small to moderate amounts of cytoplasm, and far fewer luminal, short cuboidal, eosinophilic cells (Figs. 2 and 3A). The nuclei tend to be relatively bland with small or inconspicuous nucleoli. The luminal cells may be inconspicuous, though immunohistochemical markers assist in their distinction (Fig. 3B).

Three distinct architectural patterns have been described: tubular (usually bilayered tubules lined by luminal cells surrounded by non-luminal cells that often show “clear” cytoplasm); cribriform (basaloid cells arranged in variable sized, oval/rounded masses punched-out by rigid, oval, cyst-like spaces (pseudolumina) that may contain “cylinders”/globsules of hyaline material and/or myxoid glycosaminoglycans, and occasional small true lumina lined by luminal cells]; and solid (largely basaloid tumor cells growing in sheets without lumina formation) (Fig. 2) [32,33].

AdCC is traditionally regarded as originating from the interca-

lated duct region – hence comprising a population of duct-like and purportedly myoepithelial-like cells [34]. Clearly, the luminal cells show duct-like phenotypes. Caution should be exerted before characterizing the basaloid cells as either neoplastic or modified myoepithelia. Smooth muscle actin (SMA) immunoreactivity has been described in AdCCs [35], but combined electron microscopy and stereology showed that typical myoepithelial cells are rare (3% of the tumor-cell population) [36]. Observations with special stains or immunohistochemical markers should also be carefully interpreted (Fig. 4).

Classic AdCC often shows a combination of cribriform and tubular patterns. In most studies, a solid growth pattern is associated with worse prognosis, advanced stage and development of distant metastases [30]. Szanto et al. [37] proposed a histologic grading scheme for AdCCs based on the degree of solid pattern. Three grades were suggested: Grade I, tumors with tubular and cribriform areas, but without solid components; Grade II, cribriform tumors that were purely or mixed with >30% of solid areas; and Grade III, tumors with a predominantly solid pattern.

Neural invasion can be seen even in early-stage tumors and has been regarded as an unfavorable prognostic factor, associated with distant metastasis and adverse final outcome (Figs. 1C, 2C, and 5) [26,38]. Recently, however, an analysis of 495 AdCCs from 9 international patient cohorts indicated that “while perineural invasion has no impact on survival, intraneural invasion is an independent predictor of poor prognosis” [39]. Another inference was that neural invasion did not predict hematogenous spread; distant metastases were related to age, primary site and nodal (N) classification. Teymoortash et al. [40] reviewed 22 cases of AdCC with documented perineural invasion and proposed a new classification scheme for AdCCs based on the presence of characteristic features in perineural invasion. They classified tumors as p1 when true perineural or endoneural invasion was observed (Fig. 5) and...
p2 when tumor was adjacent to nerves without invading them. Patients with p1 tumors had a higher recurrence rate in comparison with p2 patients. However, the number of cases analyzed was small, and it is recognized that perineural invasion is also a feature in polymophous low-grade carcinoma, a salivary gland malignancy associated with a different prognosis. Tumor size and growth (‘pushing’ or frankly infiltrative) pattern may be of greater influence.

Fig. 1. Note: Unless otherwise specified, the photomicrographs in this article are from sections of routinely processed tissue, which were stained with hematoxylin and eosin. It was not deemed necessary to give objective magnifications. Zooming on the electronic format of the photomicrographs would allow appreciation of detail, difficult to be seen on prints. (A) Scanned histological section of solid adenoid cystic carcinoma (T) of the floor of mouth; the hematoxylin (purplish) tumor is asymmetrical with a somewhat lobulated, advancing front. (E), oral epithelium; (M), skeletal muscle. (B) Invasion of salivary gland (G). (C) Highly invasive tumor penetrating soft tissues in the form of finger-like projections. Note the characteristic target-like arrangement around nerves (N). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. (A) Cribriform pattern. Hematoxyphilic material is present in cyst-like spaces (asterisks). Appearances simulating the Roman-bridge pattern seen in salivary duct carcinoma, but the strongly haemoxyphilic, basaloid cells preclude from considering that diagnosis. (B) Tubular pattern. Differences in tinctorial reactions between luminal and abluminal cells are discernible. (L), lumen. (C) Solid pattern. (Same case, as in Fig. 1A). Such tumors need to be differentiated from neuroendocrine carcinomas. Invasion of a nerve (N) is seen.

Fig. 3. Cribriform adenoid cystic carcinoma. (A) Compare the collapsed, true lumina (arrows) lined by eosinophilic, cuboidal cells with the cyst-like spaces (asterisk). (B) Selective p16 immunoreactivity of cells lining small collapsed lumina (arrows). The basaloid cells (arrowhead) surrounding the cyst-like spaces (asterisk) are unstained.
Contrary to popular belief, cervical nodal metastases in AdCC patients can be histopathologically detected when the primary tumor is surgically removed together with a neck dissection (Fig. 6). Metastases are often small, which may explain why clinical examination or imaging may fail to detect them. However, extensive information on pN status in AdCC is lacking because neck dissections are not commonly performed.

Fine needle aspiration cytology (FNAC) can be used for diagnostic purposes. The finding of large globules of extracellular matrix, partially surrounded by basaloid cells, suggests AdCC [41]. However, diagnosis of salivary cancers by FNAC is notoriously difficult and is often compromised by false negative evaluations [42]. Histopathological diagnosis remains the “gold standard” and is especially necessary when the planned therapeutic intervention involves radical surgery and possible sacrifice of the facial nerve [43].

Molecular biology

Current research in AdCC focuses strongly on the potential prognostic and therapeutic role of molecular markers. The molecular biology of AdCC has been recently reviewed [44]. The most relevant genetic and molecular alterations in AdCC are summarized in Table 1. We included only studies that were done in primary tumor tissues, as studies using only cell lines carry a high risk of contamination and thus false positive findings.

Cell cycle-based proliferation markers

These markers reflect the number of cancer cells going through the cell cycle towards division. Nordgård et al. [45] reported that assessment of the Ki-67 index, a nuclear antigen in proliferating cells, was an independent prognostic factor mirroring biological behavior. Cho et al. [46] suggested that high PCNA (proliferating cell nuclear antigen) expression is significantly associated with shorter disease-free and overall survival of patients with AdCCs. Minichromosome maintenance (MCM) protein expression has been found to be a novel marker for proliferating tumor cells and is diagnostically useful for the differential diagnosis of benign and malignant salivary gland tumors [47]. The expression of the argyrophyllic nucleolar organizer region (AgNOR) associated proteins were also an independent prognostic factor in these tumors [48]. Of these markers, the Ki-67 index is the least expensive and most widely applicable test for assessing tumor cell proliferation, which on multivariate analysis has been demonstrated as an independent prognostic factor [49].

Specific genetic and epigenetic changes

At the basis of the deranged cell cycle lies an accumulation of genetic and epigenetic alterations that are also individually studied as “molecular markers”. For reporting on the investigated markers, we follow the structure used in the previous International Head and Neck Scientific Group (IHNSSG) review on parotid carcinomas [14]. A succinct overview is given in Table 1.

(1) Growth factor receptor proteins and ligands

This group includes the stem cell factor receptor (c-KIT); the family of human epidermal growth factor receptors EGFR (HER-1, ErbB-1), HER-2 (HER2/Neu, ErbB-2), HER-3 (ErbB-3) and HER-4 (ErbB-4); angiogenesis-related growth factor receptors (PDGF-R, VEGF-R, bFGF-R, PIGF, IL-8, TGFβ, EphA2); nerve growth factor (NGF); insulin-like growth factors (IGF–I/II) and receptor (IGF-1R); and hepatocyte growth factor (HGF) and its receptor tyrosine kinase MET.
c-KIT is detected in 80–94% of AdCC [50]. The relationship between high c-KIT expression (>50%) and histologic grade is debated. While Holst et al. [51] noted a significant association of c-KIT expression with grade III or solid pattern AdCC, Freier et al. [52] described a high expression only in cribriform and tubular AdCC.

Limited amounts of VEGF-C are produced in AdCC, which via a reduced interaction with VEGFR-3 may result in few lymphatic vessels; whether this relates to the purported low rate of cervical metastasis remains to be evaluated [53].

Data on angiogenesis-related growth factor receptors of salivary cancers generally suggest an association of VEGF expression with advanced stage and worse disease-specific survival [54]. Specifically for AdCC, overexpression of EphA2, a receptor tyrosine kinase involved in angiogenesis, and its ligand ephrin A1, have been recently reported. The overexpression is significantly greater in solid AdCC than in tubular and cribriform types and correlates with microvessel density, TNM staging and perineural and vascular invasion [55].

For the human EGFR family, EGFR/HER-1 has been identified in 82% of investigated patients with advanced AdCC. In patients expressing HER-1, treatment with cetuximab seemed to result in a higher proportion of stabilized disease [56]. In a study on 24 AdCCs, HER-1/CCND1/PIK3CA coamplification was the most consistently observed pattern (29%). HER-1 amplification correlated with distant metastasis, and the cases with the HER-1/CCND1/PIK3CA coamplification tended towards a reduced survival [57]. The observed HER-1 related biological aggressiveness, however, could not be confirmed by Lee et al. [58].

Increased expression of NGF is observed in 79% of solid type AdCCs (or 68% of all studied AdCC) and may relate to its neurotropism [59]. In this context, the overexpression of a cluster of neuronal genes grouped around Trkc/NTRK3 (a tyrosine kinase neurotrophic receptor associated with neurogenesis and cancer) suggests that AdCC expresses genes involved in neural stem cell differentiation [60].

(2) Cell cycle oncogenes

The growth factor–receptor interaction activates cell cycle oncogenes. For AdCC these include cyclin D1 [57]; sex-determining region Y-box 4 and 10 (SOX-4, SOX-10) [33,61,62]; nuclear factor kB (NFkB); phosphatidylinositol 3 phosphate kinase/serine-threonine protein kinase (PI3K); sarcoma signal transducer and activator of transcription 3 (STAT3); and mammalian target of rapamycin (mTOR) [63,64].

Cyclin D1 seems frequently overexpressed in AdCC tumors and correlates with prognosis [70].

Frierson et al. [33] found that SOX-4 was the most significantly overexpressed cell cycle oncogene in a microarray analysis of AdCC. Apoptosis increases following SOX-4 knockdown, suggesting that down-regulation of inhibitors of the NFkB pathway (inhibitor protein IκB-α) and up-regulation of apoptosis inhibitors such as survivin are the downstream effects [61]. Very recently, the transcriptional factor SOX-10, normally expressed only during salivary gland differentiation, was found markedly upregulated in a majority of AdCC cells [62].

The PI3K/AKT/mTOR axis is critical in oncogenesis; dysregulation of this pathway involves alterations of various upstream tumor-associated growth factors (EGFR, HER-2, PDGF and VEGF) as well as AKT, mTOR, and PTEN [63]. The PI3K/AKT pathway can be targeted by blocking mTOR with temsirolimus [65].

(3) DNA damage repair proteins

p53 expression [66] and p53 mutations in AdCC appear generally associated with worse prognosis [67].

(4) Cell adhesion proteins

Loss of E-cadherin expression (due to promoter hypermethylation) is frequently found in AdCC, and has been correlated with poor prognosis [68].
adhesion molecule-1 (ICAM-1) may promote immune evasion and metastasis, resulting in poor prognosis in AdCC [69]. Increased expression of the membrane-cytoskeletal linker Ezrin, and its partner CD44V6, has been also associated with a more aggressive behavior [70].

A recently revealed association in AdCC links integrin-linked kinase (ILK) with epithelial-mesenchymal transition markers, where ILK plays a central role in cell-extracellular matrix interactions regulating cell proliferation, apoptosis, differentiation and migration. Expression of ILK correlates strongly with solid type AdCC, advanced TNM stage and increased risk of recurrence. Moreover, ILK over-expression and a neural invasive phenotype went along with downregulation of E-cadherin and upregulation of Snail and N-cadherin; by this mechanism ILK is believed to have a key role in progression and metastasis in AdCC [71].

The urokinase-type plasminogen activator receptor influences tumor invasion and metastasis by facilitating the destruction of extracellular matrices, so its expression seems to be a negative prognostic factor [72].

(5) Estrogen receptors

Estrogen receptors have been described in 17–92% of studied AdCC, suggesting a role for anti-estrogen therapy with tamoxifen [73] and supporting the plausibility of an earlier observed partial remission in a patient treated in this way [74].

(6) Markers for lymphangiogenesis

Podoplanin is a small mucin-like protein related to tissue development and repair. It is expressed in lymphatic endothelial cells and is used as a marker for lymphangiogenesis. It is also expressed in certain tumor cells and is associated with migration/invasion in cervical and oral squamous cell carcinomas. Recently, podoplanin was found overexpressed in a subset of salivary AdCCs (32.5% of tumors); overexpression was significantly associated with disease-free survival and distant metastasis, although it was not associated with recurrence and overall survival [75]. Despite this observation, caution should be exerted with this marker as podoplanin has been recently localized in nonluminal (myoepithelial-like) cells of pleomorphic salivary adenoma [76].

(7) Transcription factors

The reciprocal translocation t(6;9) (6q22–23; 9p23–24), resulting in fusion of the MYB gene on chromosome 6q22–q23 and the transcription factor NFIB on chromosome 9p23–p24, has recently been described in AdCC [77]. The fusion was shown to upregulate MYB protein expression, which is believed to be the oncogenic driver of this tumor. Mitani et al. confirmed this fusion, including MYB–NFIB translocations and somatic mutations in MYB-associated genes, solidifying the role of these aberrations as critical events in AdCC [78].

The expression of the transcription factor Engrailed Homeobox 1 (EN1) is silenced by hypermethylation in AdCC [81]. EN1 is important for development of the central nervous system. EN1 hypermethylation correlates with histologic tumor grade, tumor location and final patient outcome. EN1 protein expression seems typical for solid AdCC and implies a significantly lower survival rate. On these grounds EN1 could prove a potentially useful biomarker in AdCC.

Mutational profile of AdCC

Chan and colleagues reported on exome and genome sequencing of 60 AdCC tumor/normal pairs [82]. A low exon size somatic mutation rate (a mean of 22 somatic mutations per sample, corresponding to approximately 0.31 non-silent events per megabase) and wide mutational diversity was found. They identified potential driver mutations, including those in PIK3CA, TP53, PTEN, SMARCA2, KDM6A and CREBBP. Analysis of these driver genes demonstrated marked enrichment in pathways involved in chromatin remodeling, DNA damage, MYB, protein kinase A (PKA) signaling and PI3K signaling. In addition, they observed MYB–NFIB translocations and somatic mutations in MYB-associated genes, solidifying the role of these aberrations as critical events in AdCC. The discovery of genomic alterations in targetable pathways suggests potential avenues for novel therapies for a typically chemoresistant malignancy.

Diagnostic imaging

As is the case for all SGCs, preoperative diagnostic imaging of AdCC includes computed tomography (CT) and/or magnetic resonance imaging (MRI). This allows estimating the anatomical disease extent, which is crucial for accurate surgical planning. It is well accepted that CT is better at delineating bone invasion, whereas MRI superior for assessing soft tissue extension [83].

Evidence of sensory (pain or paresthesia) or motor nerve dysfunction (VII nerve paresis/paralysis) mandates MRI investigation to assess the corresponding nerves. Hanna et al. [84] evaluated the sensitivity and specificity of CT and MRI in detecting perineural spread of AdCCs along the base of the skull and concluded that MRI is clearly superior to CT for this purpose.

The main role of [18F] fluorodeoxyglucose positron emission tomography (18F-FDG PET), preferably in combination with CT, is to exclude gross distant disease for head and neck tumors in general and also more specifically for SGCs and AdCC [85]. Roh et al. [86] investigated the role of 18F-FDG PET in the management of patients with salivary cancers and found it helpful in initial staging, histologic grading and monitoring after treatment. However, 18F-FDG PET-CT is not helpful to rule out distant metastasis if the primary SGC does not show enhanced FDG uptake, a situation that is not infrequent in AdCC. Furthermore, AdCC with relatively low FDG uptake might be obscured by the normal physiologic FDG uptake of the salivary glands; conversely, salivary glands are frequently affected by inflammatory processes wherein increased FDG uptake might result in a false-positive result.

Treatment

Treatment of AdCC is influenced by location of the tumor, stage at diagnosis and biologic behavior as reflected in histologic grade [87]. The “gold-standard” treatment for AdCCs, that is deemed as potentially resectable after extensive workup is radical surgical resection, ensuring free margins, and postoperative radiotherapy. Mendenhall et al. [88] compared radiotherapy alone to radiotherapy combined with surgery and concluded that combination
treatment is preferable. AdCC has a high propensity for infiltrating into adjacent tissues, especially through perineural invasion so even in “resectable” AdCC the goal of “free margins” is often not achieved. Incomplete resection is typically a problem in AdCC arising in anatomical sites with difficult access. This is highlighted by a study indicating that 80% of skull base AdCC had positive surgical margins, despite the preoperative impression of experienced surgeons that resection with clear margins would be possible [89].

When AdCC arises in the parotid, the facial nerve should be preserved if it is not determined to be paralysed preoperatively and not intimately involved by tumor at the time of surgery; postoperative radiotherapy would be an effective adjuvant treatment for residual microscopic disease on a spared nerve branch [90–92].

Due to the historically low incidence of occult nodal metastasis, neck dissection is only performed in case of clinically positive lymph nodes. Clinically obvious lymph node metastasis is not frequent in AdCC, especially for parotid gland primaries [93]. However, for MSG subites the incidence of involved lymph nodes seems higher. Min et al. [94] described a general incidence of lymph node metastases in AdCCs of the head and neck of almost 10%, which was mainly attributed to sites such as base of tongue, mobile tongue and floor of the mouth. These authors noted that primary tumor site and peri-tumoral lymphovascular invasion were significantly associated with cervical lymph node metastasis.

On this basis, selective neck dissection should be considered for tumors of those sites showing lymphovascular invasion. It is, however, noted that lymphovascular invasion is more likely to be histologically detected in resection specimens rather than diagnostic biopsies, which are also expected to be small when taken from anatomically “difficult” sites. Lee et al. [95] recently reported that 15.38% of the patients who received elective neck dissection had occult metastases, and they recommend performing elective neck dissection for staging and achieving regional control. It remains unclear whether regional control, let alone survival, is improved by performing an elective neck dissection in these patients as compared to a strategy of primary radiotherapy of the neck nodes. For AdCC in locations like the submandibular gland, parotid and larynx, lymph nodes could also be involved by direct extension of the primary tumor [96,97].

Unfortunately, local recurrences occur despite combined treatment with surgery and radiotherapy. Some authors postulate that postoperative radiation may delay rather than prevent recurrence [98]. Other modalities of radiotherapy, particularly neutron irradiation, have also been studied. Huber et al. [99] retrospectively compared radiotherapy with neutrons, photons and a photon/neutron mixed beam in patients with AdCC of the head and neck. They postulated that the neutron-specific reduced oxygen enhancement factor, decreased variability of sensitivity through the cell cycle and lowered repair of sublethal cell damage explain the high 5 year local control in up to 75% in unresectable AdCC cases treated with this approach [100]. Unfortunately this does not result in a survival benefit, mainly because of unaffacted distant metastasis (in 2 out of 5 patients after 51 months). Furthermore, severe late side effects of this approach include necrosis of the soft tissues, mandible, temporal bone and the temporal brain lobe, as well as cervical myelopathy and sensorineural hearing loss [101,102].

In patients with adverse prognostic factors, chemoradiotherapy using various agents may be considered, and preliminary evidence suggests its usefulness [103]. In a series of SGCs (43% AdCC), Schoenfeld et al. [104] explored the use of carboplatin or paclitaxel as a radiosensitizer, and trastuzumab in HER2/Neu-positive tumors.

The role of palliative systemic therapies (including cytotoxic and targeted therapies) has recently been extensively reviewed [105]. Only level-3 evidence (case-control or cohort studies) exists, and the available trials have only involved small patient numbers with heterogeneity regarding histology, many having had prior systemic therapies and a proportion of patients with locoregional recurrence versus distant metastasis. Moreover, the majority of AdCCs have a slow growth pattern, making it difficult to assess the efficacy of the particular systemic therapy, as objective tumor responses are uncommon [106]. Several studied targeted therapies for the disease are presented in Table 2 [105,56,105–113]. For an overview of ongoing or planned clinical trials of targeted therapies for AdCC, the reader is referred to the recent publication of Dillon et al. [114]. The latest efforts combine cytotoxic and targeted treatments: in patients with EGFR-expressing AdCC, the efficacy of cetuximab plus cisplatin-based chemoradiotherapy (for locally advanced tumors) or chemotherapy (for systemic disease) appeared encouraging and was associated with manageable toxicity [115].

One may conclude that to date, systemic treatment employing cytotoxic chemotherapy or targeted molecular therapies does not yet result in patient cure with advanced (locally recurrent or metastatic) AdCC. At best, temporary partial disease response or stabilization may be achieved. Chemotherapy therefore should be reserved as a palliative treatment for patients with poorly controlled disease or affected with symptomatic metastases [114].

### Prognosis

In general, prognosis of AdCC of the head and neck is rather poor, and this is the reason why many authors consider AdCC a “clinically high grade” neoplasm. Reported prognosis varies widely, mainly because different reports have different quality and length of follow-up. In a large European study on AdCC of the head and neck, the 10-year survival rate was 65% [116]. Van Weert et al. [23] reported 5-, 10- and 20-year survival rates of 68%, 52% and 28%, respectively, on a series of 105 patients. Huang et al. [38] reported that overall and recurrence-free survival rates at three years were 84.6% and 58.2%, respectively, while the rate of survival with recurrence was 26.4%. After 15 years, the overall survival rate was 24.5%, and the recurrence-free survival rate was 22.6%.

Many clinicians assume that “cure is never achieved” in AdCC. Optimistic 5-year survival rates are occasionally reported (e.g., 92% in an Australian series) [117], but 10- and 20-year survival rates continuously drop. In a UK series, 40% of AdCC patients were alive at 20 years and survival continued to drop until 30 years; the actuarial primary site recurrence rate at 30 years in that study was 100% [118], and it was 54% in the Australian series.

The low long-term survival rate of AdCC patients is uniformly linked to the failure to control distant disease. These distant metastases occur most frequently in the lung. Spiro [97] suggested that the incidence of distant metastasis to other anatomical sites is likely higher than previously recognized, because once lung metastases are detected no further investigations are performed. Van der Wal et al. [119] found that the average time between the

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AdCC = adenoid cystic carcinoma.

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occurrence of lung metastases and death was 32.3 months, and that between the occurrence of metastases elsewhere and death was 20.6 months; it was hypothesized that metastases outside the lungs may be detected later in the course of the disease or interfere with vital functions more rapidly. Umeda et al. [120] found that the estimated doubling time of pulmonary metastasis in AdCC ranges from 86 to 1064 days with an average of 393 days. These findings suggest that metastasis at the cellular level could occur prior (average, 227 months) to clinical presentation of primary cancer.

Conclusion

Advances in therapeutic modalities have not had a significant impact on the natural history of AdCC of the head and neck. The preferred treatment for the majority of the patients is radical surgery with postoperative radiotherapy. The frequent development of distant metastases continues to determine treatment outcome. Currently, the only options for patients with metastatic disease at best supportive care, palliative systemic therapy or inclusion in clinical trials in order to establish effective and evidence-based treatment strategies.

Conflict of interest

None declared.

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References


