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Contemporary diagnostic and therapeutic possibilities in patients with adenoid cystic carcinoma of the head and neck

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ABSTRACT

Adenoic cystic carcinoma (SACC, ACC) in the head and neck area, occurring in small and large salivary glands are relatively rare tumors, usually undergoing slow progression. ACC is characterized by a different clinical course compared to other cancers, with a long latency period, a tendency to form late, initially asymptomatic metastases and a small percentage of responses to systemic treatment. This article presents current recommendations for diagnostic procedures and treatment possibilities.

Key words: adenoid cystic carcinoma, ACC, SACC, head and neck

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Introduction

Adenoid cystic carcinomas (ACC) in the head and neck area, occurring in small and large salivary glands (salivary adenoid cystic carcinoma [SACC]), comprise a relatively rare form of cancers, usually of slow progression. This type of cancer was described for the first time by Billorth in 1859 as a "cylindroma", due to the formation of specific structures resembling cylindromatosis. ACCs are characterised by a different clinical course compared to other cancers, with a long latency period, a tendency to form late, initially asymptomatic metastases, and a low response rate to systemic treatment [1, 2].

Epidemiology

ACCs account for about 1% of all malignant neoplasms of the head and neck region and 10% of all salivary gland tumours. ACCs develop more often in small than in large salivary glands. Locations outside the large salivary glands include the salivary glands of the tongue, paranasal sinuses, the palate, nasopharynx, or lacrimal glands. Adenoid cystic carcinomas extremely rarely develop in the secretory glands such as the bronchial tree, oesophagus, mammary glands, lungs, prostate, cervix, or Bartholin's glands [2–9]. ACCs in head and neck organs can occur at any age. Some authors indicate that in patients before 40 years of age and over 60 years of

age there are higher relapse rates. Many authors report that ACCs are more often diagnosed in women than in men. According to Dillon, this ratio is 60:40 and may be associated with more favourable prognosis in women, although this is not confirmed by the results of some other studies [1, 3, 9–11].

Pathomorphological characteristics

Originally, ACCs were called "cylindroma" due to their characteristic pathomorphological picture, consisting of cylindrical epithelial cells with the presence of hyaline stroma. ACC cell nuclei are hyperchromatic and contain a small amount of transparent or eosinophilic cytoplasm [1, 3, 4, 12, 13].

In the electron microscope image, two-phase differentiation of elements is visible in immunohistochemical studies — both myoepithelial and glandular secretory, with the former being dominant. Malignant cells can also produce glandular-like structures based on the glycosaminoglycan matrix and basement membrane elements.

Based on pathomorphological examination, three subtypes of cancer are distinguished: cribriform (most common), tubular, and solid (most clinically aggressive). Five-year and 15-year survival rates in patients with high- and medium-differentiated forms of ACC (pathomorphologically corresponding to cribriform and tubular types) are approx. 90% and 40%, respectively.

In the cribriform subtype islands of basaloid cells are visible, surrounded by cystic structures of varying sizes, similar in structure to "Swiss cheese" [14]. The tubular subtype has a cytological appearance similar to that of the cribriform subtype, but the tumour cells are located in nests surrounded by a variable amount of eosinophilic, often hyaline stroma. The cells of solid ACC are characterised by a cluster of basaloid cells without tubules or pseudocystic structures. The solid type is often diagnosed in advanced stage with the presence of distant metastases [3, 14, 15]. ACCs indicate a high tendency to spread along nerve structures [3, 14]. Myoepithelial tumour cells surrounding pseudocysts show a positive response for smooth muscle actin, S100, vimentin, and smooth muscle myosin heavy chains, as well as a strong reaction for c-KIT (CD117) and MYB tyrosine kinase receptors, regardless of the degree of malignancy. It is believed that the expression of c-KIT and vascular endothelial growth factor receptors (VEGFR) may correlate with an aggressive course of the cancer and unfavourable prognosis. It cannot be excluded that the interaction between Beclin-1 and p53 and Bcl-2 may play a role in the pathogenesis of cancer and that P53 expression is particularly pronounced during disease progression [3, 4, 6, 12, 16–18].

Molecular disorders

Many researchers point to the inability to perform detailed analyses of ACC pathogenesis mechanisms due to the lack of verified cell lines. However, the available results of tests using primitive xenografts provide some interesting observations [3, 18]. Analysis of tumour RNA using microarrays revealed that the expression of genes responsible for myoepithelial ACC differentiation is associated with the presence of transcription factor SOX4 [3, 19]. Under physiological conditions, SOX4 regulates embryonic development and probably oncogenesis. Overexpression of casein kinase 1 (CK1), epsilon, and frizzled-7 is also observed, which may induce the Wnt/β-catenin signalling pathway and thus carcinogenesis. Expression of C-kit protein was also demonstrated in most ACC cells that correlated with the degree of cell proliferation [3, 20].

There was no correlation between bcl-2 protein expression, c-erbB-2 overexpression, transforming growth factor-alpha, epidermal growth factor receptor, and oestrogen and progesterone receptors and the degree of cancer differentiation and clinical progression [22–26]. A significant percentage of ACC patients have been found to have androgen receptor expression, which may be an important pathological marker of the disease [14].

The assessment of risk factors for overall survival (OS) and disease-free survival (DFS) in ACC indicates that one of them is perineural infiltration [9, 22]. There are few studies available explaining the pathomechanism of the molecular causes of this phenomenon. Some of them confirmed in vitro that the adhesion molecule of nerve cell is a basement membrane glycoprotein in ACC cell lines, and ACC cells stain evenly positively for the nerve cell adhesion molecule regardless of the degree of invasion. Kowalski demonstrated the expression of cytoplasmic protein BDNF (brain-derived neurotrophic factor) in ACC cells regardless of the degree of histological malignancy or perineural invasion. BDNF belongs to the neurotrophin family. These proteins have trophic functions and affect the proliferation, migration, differentiation, and integrity of many types of neurons. Neurons transport BDNF retrograde (target towards neuron) and anterograde (neuron to target), providing complex interactions between neurons and target tissues. The effect of BDNF on perineural invasion is attributed to the fact that indirect transport of BDNF protein from peripheral nerves is ultimately taken up by the target tissue, in this case ACC cells. An alternative hypothesis is that ACC may have a reverse function and spontaneously produce BDNF, creating a concentration gradient reached by peripheral nerves. The latter hypothesis undermines the findings to date that peripheral nerves are static entities actively infiltrated by cancer cells, which may be specific for ACC cells [22, 27, 28].

ACC is characterised by the presence of numerous somatic genetic mutations and characteristic chromosomal mutual translocations. One of the most important seems to be the translocation between chromosomes 6q and 9p ([6; 9] [q22–23; p23–24]), which is quite characteristic for this cancer and occurs in about 86% of patients. Persson was the first to demonstrate that this rearrangement results in the combination of *MYB* oncogene and nuclear transcription factor I/B (NFIB), which may result in the activation of MYB targets, affecting apoptosis, cell cycle control, and cell proliferation [3, 29–31]. Another significant demonstrated translocation was t (11; 19) causing the fusion of *CTRC/MAML2* genes. It has specific implications because clinical observations indicate that tumours in which fusions occur are less aggressive than those without fusion. Numerous studies are currently underway using new therapeutic targets, such as transcription factors and cancer fusion proteins [14, 32].

Distant metastases

A characteristic feature of ACC is not only slow local progression, but also relatively rare regional lymph node involvement. It is believed that a significant percentage of local recurrences and distant metastases seen after local treatment are associated with perineural infiltration, which results in a lack of microscopic radicality of surgery and a tendency to form haematopoietic metastases, even at early stages [9, 10, 15, 32, 33].

Adenoid cystic carcinomas have a long latency of distant metastases (up to 15 years), and the main metastatic sites are lungs and bones. In observation of 467 patients treated between 1963 and 2009, Gao reported distant metastases in 45 patients (31.0%); 20% of them had early disease progression and no local recurrence. The incidence of metastases has been shown to be dependent on the histopathological subtype and is 47.7%, 29.9%, and 27.3% in solid, cribriform, and tubular subtypes, respectively (16–35% on average) [34]. Other risk factors associated with unfavourable survival prognosis include the stage at diagnosis, advanced age, and lack of radical resection [4].

Due to the specific clinical course, particularly long-term follow-up is recommended in patients with solid subtype ACC, a significant proportion of whom have distant metastases. In 20-year follow-up, at intervals of 5, 10, 15, and 20 years, the overall survival rate in patients with distant metastases is 69.1%, 45.7%, 26.5%, and 14.3%, respectively, and in metastatic patients 85.6%, 67.4%, 57.6%, and 50.4%, respectively. More than half of patients with distant metastases have been shown to die within 10 years, and more than half without metastases survive for 20 years after diagnosis of ACC [34]. In a study by Sung, the median survival of ACC patients with distant metastases was 38 months (1–149 months), and in studies by Matsuba and Gao, 48 months and 36 months, respectively [34–36].

The Monterio study found that distant metastases were most often diagnosed in lungs (78.6%) as well as in liver and bones (21%), and less frequently in kidneys and brain (approx. 3.5%). It was observed that patients with limited lung metastases had a better prognosis compared to other patients with metastases [4].

Radical treatment

Surgery is the treatment of choice in the early stages of ACC. Indications for adjuvant radiotherapy include a narrow or positive surgical margin without the possibility of radicalisation, lymph node involvement, significant local advancement, or perineural infiltration. Although no prospective clinical trials have been carried out so far, the results of retrospective analyses indicate that patients benefit from such a procedure. For example, the results of a study by the Dutch Head and Neck Oncology Cooperative Group showed a lower rate of local recurrence after adjuvant radiotherapy [14]. British experience, based on the analysis of 50 cases of patients with salivary gland cancers, also confirmed a high rate of local cure, reaching 96% with adjuvant radiotherapy after surgical treatment with facial nerve sparing. In the Miglanico retrospective study, the percentage of cases without recurrence in the five-year follow-up in patients treated with adjuvant radiation was 78% compared to 44% after surgery alone [40]. In another historical study, Simpson reported that in patients either receiving adjuvant radiation therapy or undergoing surgery alone the 10-year local cure rate was 83% and 25%, respectively [3, 41]. Mendenhall et al. reported local cure rates for radiotherapy alone and surgery with complementary radiotherapy of 56%, 94% and 43%, 91%, respectively, and overall control rates of 77% and 69%, respectively. The five- and 10-year distant metastases-free survival rates were 80% and 73%, respectively. The five- and 10-year OS rates were: 57% and 42% for radiotherapy alone; 77% and 55% for surgery with complementary radiotherapy; and 68% and 49% for the whole observation. Tumour size ($p = 0.0043$) and clinical perineural invasion ($p = 0.0011$) were the most important factors affecting OS in multivariate analysis [42].

In the case of significant local advancement excluding the use of surgery, radiotherapy is the treatment of choice. In many clinical situations, radiation is a palliative method of treatment reducing cancer-related symptoms [14].

Treatment with radiotherapy using fast neutrons produced interesting results in patients with ACC.

In theory, this method has higher biological efficiency compared to conventional radiotherapy with photons or electrons. In a small, phase III study the local cure rate was 56% after neutron treatment and 17% after photon irradiation (p = 0.009) [14, 43].

Unfortunately, neutron radiation therapy is associated with more frequent late complications and a higher incidence of distant metastases, although the latter may be the result of longer survival. The results of subsequent studies confirm these reports. Currently, radiation therapy using neutrons is not recommended in ACC [14, 42, 43].

There are scarce data regarding the effectiveness of radiochemotherapy, both as independent treatment and as complementary treatment after surgery. Among others, this results from the limited activity of cisplatin, which is the most commonly used cytostatic in combination with radiation therapy in ACC patients. In a retrospective study evaluating the effectiveness of chemoradiotherapy (RADPLAT) with intra-arterial cisplatin administration, Samant noticed a therapeutic response in 14/16 patients (seven complete and seven partial responses). The overall percentage of responses, relapses, and local cures during the five-year follow-up was 87%, 39%, and 61%, respectively. Progression was found in eight patients, including eight in the form of distant metastases and three in the form of local recurrence [44].

Due to the limited population of patients undergoing chemoradiotherapy using intravenous or intra-arterial cisplatin, data on the effectiveness of this method should be interpreted with caution, especially those regarding the control of distant metastases due to the specific kinetics of ACC cell growth and the long latency period of symptoms observed in this cancer. Nevertheless, it cannot be ruled out that this may be an effective therapeutic method for specific patient populations [43, 44]. There is currently a clinical trial ongoing dedicated to assessing the efficacy of complementary combined therapy compared to radiotherapy alone in patients with high-risk salivary gland cancer after surgery (RTOG 1008 — A Randomized Phase II/III Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors) https://clinicaltrials.gov/ct2/show/NCT01220583 [45]. It cannot be ruled out that the results of this study will greatly contribute to establishing the standard of adjuvant treatment in patients with ACC.

Chemotherapy

The effectiveness of standard chemotherapy in patients with ACC is limited, among others due to the slow proliferation of cancer cells. Many analyses assessing the activity of classic chemotherapy indicate its low effectiveness [46–48]. The subject of several studies has been a chemotherapy regimen combining anthracyclines with platinum derivatives (cyclophosphamide, doxorubicin, and cisplatin) [46, 49]. There was no significant advantage of the triple-drug scheme over monotherapy, but it should be noted that so far no large, prospective studies with random patient selection comparing multi- and single-drug regimens have been conducted [46]. In 2016, a summary of research conducted in the years 2001–2015 on the use of chemotherapy in salivary gland tumours, including ACC, adenocarcinoma not otherwise specified (NOS), and mucoepidermoid carcinoma (MEC), was published. This is one of the few large studies concerning the use of chemotherapy in patients with ACC [46]. It has been shown that in most studies, cisplatin or carboplatin was used in multi-drug regimens. Nearly 50% of analyses were dedicated to ACC. It was emphasised that the results of four studies may indicate the potential effectiveness of multi-drug regimens containing platinum derivatives. Airoldi in a small, randomised study reported higher therapeutic response rates in patients treated with cisplatin and vinorelbine compared to vinorelbine alone (44% and 20%, respectively). The objective response rate (ORR) as well as OS showed a trend towards statistical significance in favour of the combination arm [50]. In another analysis presented in this publication, regarding chemotherapy consisting of cisplatin and mitoxantrone, the objective response rate was 14% and median OS was 27 months [51]. In the analysis by the National Cancer Institute of Canada Clinical Trials Group, in patients with advanced salivary gland cancers, including ACC, treated with cisplatin and gemcitabine the objective responses rate was 24%. Four out of eight patients with adenocarcinoma had a partial response, and in one case it was complete response [52, 53]. The results regarding three-drug regimen published by Ross (cisplatin/carboplatin, epirubicin and 5-flurouracil) in eight ACC patients demonstrated low efficacy, and objective response was reported in a single case. However, the author emphasised the potential benefits in terms of median survival of 27 months. It should be critically noted that the naturally slow cancer course could have had a paramount influence on survival [53, 54].

The reports regarding efficacy of single-agent chemotherapy are also limited. In 2006, the results of the Eastern Cooperative Oncology Group study using paclitaxel showed 18% responses, but only for patients with adenocarcinoma or MEC (29% adenocarcinoma and 21% MEC); no objective responses were observed in patients with ACC. Overall survival was comparable for all subtypes, which only confirmed other observations that the use of systemic therapy does not translate into an increase in overall survival benefit in metastatic salivary gland cancer [46, 55]. No benefit was seen in a study with gemcitabine in patients with ACC.

Based on current knowledge, it is advisable to recommend individual consideration of indications to chemotherapy, taking into account the naturally slow course of ACC in many cases. In asymptomatic patients, the implementation of chemotherapy should be deferred until the onset of symptoms or dynamic tumour progression. There are no reliable data showing the potential for any chemotherapy regimen to affect the survival in ACC patients.

Targeted therapy

The lack of satisfactory efficacy of standard chemotherapy, as well as the use of modern molecular diagnostic techniques, contributed to an increase in experience with the use of molecularly targeted treatment in ACC patients. The premise for the use of this type of therapy is the presence of numerous molecular abnormalities that are potential therapeutic goals. A theoretically attractive target appeared to be C-KIT overexpression occurring in a high percentage of ACC cells (65% to 90%) [3, 14, 46, 53]. Unfortunately, the results of studies using imatinib were unsatisfactory and only two of 42 patients in four phase II studies obtained objective responses. The addition of cisplatin did not increase the number of therapeutic responses. It cannot be excluded that the underlying phenomenon is the lack of molecular activity of C-KIT receptors, despite the overexpression. There was also no evidence of mutations in exon 9 or 11 of *C-KIT* gene in ACC cells, which were found in gastrointestinal stromal tumours [46, 56–59].

Attempts have also been made to use monoclonal antibodies and tyrosine kinase inhibitors such as cetuximab, gefitinib, and lapatinib [46, 60–62, 64–66]. There were no objective therapeutic responses after gefitinib or lapatinib use, but 79% of patients treated with lapatinib had disease stabilization, which in 36% lasted for six months or longer [64]. On the other hand, in a study with cetuximab and cisplatin the percentage of complete responses in patients with positive EGFR receptor was 22% (in 2/9 patients), and the proportion of partial responses was also 22% (2/9 patients) [57]. In patients with distant metastases, partial responses were recorded in 42% of patients (5/9 patients). Compared to gefitinib and lapatinib, cetuximab appears to be more effective, although the small number of treated patients requires caution in these types of claims [46, 64].

Multi-kinase inhibitors such as dovitinib, axitinib, sunitinib, sorafenib, and regorafenib have also been the subject of many studies. There were no complete responses in the study with sunitinib. Three further studies showed a partial response rate of approximately 10% [2/19 patients, 10.5% for dovitinib, 3/33 patients, 9% for axitinib and 2/19 patients (10.5%) in the sorafenib group] [59]. Sorafenib was evaluated in two studies — one limited to ACC patients and one in a mixed population. Thomson reported 11% of total responses and a median OS of 19.6 months in ACC patients. Similarly, Locati et al. reported an overall response rate of 16% with a difference observed in ACC patients compared to others (11 *vs*. 22%) [46].

During the American Society of Clinical Oncology (ASCO) Annual Meeting in 2018 the results of two phase II studies assessing the efficacy of another tyrosine kinase inhibitor — lenvatinib — with selective kinase inhibitory activity for VEGFR1–3, FGR 1–4, and PDGF in recurrent/metastatic ACC were presented.

Tchekmdyian showed that 15.6% of patients achieved partial remission, disease stabilisation was achieved in 75%, and the progression-free survival was 16.4 months. [67] In contrast, Locati showed a total percentage of partial and total responses of 27% [68].

Despite the presence a significant percentage of the mutation covering the FGF-PI3K-AKT pathway in the molecular analysis of ACC cells, no patients were found to benefit from treatment with the AKT inhibitor MK-2206 and the mTOR inhibitor everolimus [46]. Similarly, nelfinavir, a proteasome inhibitor that proved effective in inhibiting AKT, did not affect the objective responses in patients with ACC [46]. It cannot be excluded that the reason for this phenomenon is the lack of specific genetic changes on this pathway being the therapeutic target in each cell line.

There was no benefit from the use of vorinostat, a histone deacetylase inhibitor (response rate approx. 3%), although theoretically ACC should have abnormalities in epigenetic regulation [46].

Particularly promising results were related to treatment with an eribulin inhibitor with an objective partial response rate of 10% [46, 65]. It seems that the use of eribulin inhibitors in patients with advanced or metastatic ACC will be a very promising direction for further research. Other potential targets of the experiment are fusion transcripts, such as ETV6-NTRK3 [43, 46, 64, 65], which characterise some malignant tumours of the salivary glands and are likely to be further targets for specific inhibitors (NCT02576431).

Current reports from prospective clinical trials indicating increasingly long disease control in ACC provide the basis for the further search for effective molecularly targeted therapies. This seems to be the most effective direction for clinical experience.

Hormonal therapy

Although no prospective studies have been conducted to assess the efficacy of hormone therapy in ACC patients to date, the presence of androgen receptor expression may be a potential therapeutic target.

Data from a retrospective study using bicalutamide and triptorelin show a therapeutic response of 65% [46]. In the Locati et al. analysis, the percentage of complete responses was 20% [43, 44, 46]. Second-line hormone therapy with abiraterone, a CYP17 inhibitor, has also been shown to be effective after first-line androgen deprivation failure [46]. Currently, EORTC is conducting a randomised, multicentre phase II study in Europe to assess the effectiveness of androgen deprivation in salivary gland cancer with positive androgen receptor expression (NCT01969578) [45].

Immunotherapy

Immunotherapy is one of the most promising trends in the development of systemic treatment in oncology. Clinical trials are also being carried out to assess the effectiveness of immunotherapy in patients with ACC. Previous preclinical experience suggests that programmed death ligand-1 (PD-L1) expression is associated with unfavourable disease-free survival and possibly with overall survival [56]. The preliminary data of the phase 1b KEYNOTE-028 study presented at ASCO 2016, which concerned patients with non-ACC, showed disease stabilisation in 12 patients (46%) and a time to progression of 20.7 months. In ACC patients, anti-cancer vaccines and adoptive immunotherapy using lymphopine-activated cells (LAKs) and cytokines were tested in a small number of clinical studies [59].

An *in vitro* study of immunotherapy on ACC cell line by a Chinese group of researchers confirmed that LAK cells showed cytotoxicity to ACC cells. The authors also concluded that both TNF-α and IFN-γ may enhance this cytotoxic process. It was previously reported that these cytokines induced differentiation and apoptosis. CTLA4 and PD-L1 receptors are other therapeutic targets that are under investigation, but available data are limited. It is necessary to conduct clinical trials dedicated exclusively to ACC [59].

Summary

Surgery combined with radiotherapy remains the standard radical treatment of ACC patients. The unsolved problem is still the management of distant metastases or inoperable relapses, which is associated with ACC resistance to conventional systemic treatment. The application of modern methods of molecular and genomic diagnostics and molecularly targeted therapy to clinical practice has significantly increased the percentage of total cures and has prolonged the survival in patients with cancer. The results of clinical trials obtained so far allow us to believe that also in the case of such a distinctive cancer as ACC it will be possible to obtain satisfactory clinical responses that will translate into the extension of overall survival in advanced stages. The most promising direction of research seems to be the analysis of the effectiveness of eribulin, an inhibitor of dynamic microtubule instability in ACC. Preliminary results are very encouraging.

Another attractive research direction is the use of immunotherapy in ACC. Due to the rarity of the cancer and its different biology, it is most justified that this group of patients should be treated in reference centres with access to the experimental base, including diagnostic laboratories using high-tech molecular and genomic techniques. Patients with advanced forms of ACC should have an opportunity to participate in clinical trials. In the case of heterogeneous cancers such as ACC, the "unisize" approach must be avoided. When selecting a therapy, one should be guided by stage, performance status, the presence of comorbidities, and, above all, the patient's preferences regarding optimal management. In classic advanced ACC forms of slow course, especially in cribriform and tubular subtypes, observation may be considered.

Adenoid cystic carcinomas are still a challenge for the oncologist. They require experience and a multidisciplinary approach to the patient. Despite the application of innovative diagnostic methods to clinical practice and progress in treatment, ACC still remains a complex problem for the diagnostician and therapist, often called the "paradox" of oncology. It is hoped that interdisciplinary cooperation using translational medicine will change the face of this rare and still mysterious disease.

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