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REVIEW

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Adenoid Cystic carcinoma of minor salivary glands (AdCCmSG): a multidisciplinary update

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ABSTRACT

Introduction: Adenoid cystic carcinoma of minor salivary glands (AdCCmSG) represents a 'rarity in the rarity,' posing a clinical challenge in lack of standardized, evidence-based recommendations. At present, AdCCmSG management is mostly translated from major salivary gland cancers (MSGCs). Ideally, AdCCmSG diagnostic-therapeutic workup should be discussed and carried out within a multidisciplinary, high-expertise setting, including pathologists, surgeons, radiation oncologists and medical oncologists.

Areas Covered: The present review provides an overview of epidemiology and pathologic classification. Moreover, the most recent, clinically relevant updates in the treatment of AdCCmSG (Pubmed searches, specific guidelines) are critically discussed, aiming to a better understanding of this rare pathologic entity, potentially optimizing the care process, and offering a starting point for reflection on future therapeutic developments.

Expert Opinion: The management of rare cancers is often hindered by limited data and clinical trials, lack of evidence-based guidelines, and hardly represented disease heterogeneity, which cannot be successfully tackled with a 'one-size-fits-all' approach. Our goal is to address these potential pitfalls, providing an easy-to-use, updated, multidisciplinary collection of expert opinions concerning AdCCmSG management as of today's clinical practice. We will also cover the most promising future perspectives, based on the potential therapeutic targets highlighted within AdCCmSG's molecular background.

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minor salivary gland cancer (mSGC); Adenoid Cystic carcinoma (AdCC); histotype; head and neck; radiation therapy; surgery; targeted therapy

1. Introduction

Adenoid cystic carcinoma of minor salivary glands (AdCCmSG) represents a 'rarity in the rarity' and, as such, its management is significantly hindered by the insufficiency of standardized, evidence-based recommendations.

In everyday clinical practice, the ideal management of AdCCmSG takes shape as a multifaceted, exquisitely customized decision-making process; as such, AdCCmSG's diagnostic-therapeutic workup should be discussed and carried out within a multidisciplinary, high-expertise clinical setting [1–3].

Building from these premises, there arises the clinician's need to integrate distinct fields of knowledge, with the challenge of merging the opinions of different professional figures, including pathologists, surgeons, radiation oncologists and medical oncologists.

This review provides some highlights in the current therapeutic strategies for AdCCmSG, with the aim of leading to a better understanding of this rare pathologic entity, potentially optimizing the care process and offering a starting point for reflection on future therapeutic developments.

First, we will focus on the descriptive aspects of AdCCmSG, including a brief overview on epidemiology and pathologic classification: we will discuss the rarity of this condition and report the most common sites of origin; we will illustrate the chief pathological aspects and compare the different histotypes which can be found in minor vs. major SG AdCC; we will mention the most significant and acknowledged pathological prognostic factors and describe the key challenges in the diagnostic/staging phase. Moving on, an integrated, interdisciplinary collaboration among maxillo-facial and ear-nose-throat (ENT) surgeons, radiation oncologists and medical oncologists will be simulated: we will stress the importance of a multidisciplinary approach and we will set out some key aspects concerning surgical management (e.g. open vs. endoscopic techniques, clinically node-negative patients, perineural invasion, surgical margins), radiotherapy (RT) techniques (e.g.

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Article highlights

- AdCCmSG management is mostly translated from major SGCs, in lack of specific data.
- Minor and major SGCs show a different distribution of histological subtypes.
- A high-expertise based pathology revision is recommended
- A case-by-case multidisciplinary management is advocated.
- New treatments (e.g. hadron RT, endoscopic surgery, targeted drugs) are developing.

target volumes, coverage of cranial nerves, particle radiotherapy), and systemic treatment (e.g. addition of chemotherapy (ChT) to post-operative radiotherapy (PORT), concomitant chemoradiotherapy (CRT) in the unresectable setting, treatment strategies in the recurrent/metastatic setting, with particular attention for anti-angiogenic drugs), including an overview on the current, most promising research lines in the field of molecularly targeted agents.

To sum up, the most recent, clinically relevant updates in the treatment of AdCCmSG will be critically discussed, also suggesting specific, patient-tailored treatment approaches across different proposed scenarios.

1.1. Epidemiology

Epidemiologic data specifically focused on AdCCmSG are still limited, in view of its rarity: RARECARENet, an EU-funded project coordinated by Fondazione IRCCS Istituto Nazionale dei Tumori (INT) of Milan, estimated the crude incidence rate of minor salivary gland cancer (mSGC) of the head and neck [years (y): 2000–2007] as 0.4 cases/100.000/y [4]. Indeed, mSGC is a rarer entity compared to major (M)SGC, which accounts for 0.9 cases/100.000/y: however, an exception to this statement is embodied by sublingual gland carcinoma, one of the three MSGC subtypes, which comprises < 1.0% of all SGCs [5]. The most reported histotypes include mucoepidermoid carcinoma (MEC), adenocarcinoma (ADC), and AdCC, with a prevalence of 29.4%, 24.6%, and 23%, respectively, as observed in a very large mSGC SEER dataset ($N = 5334$) [6]. As a whole, mSGC shows a slight predominance in males, while AdCCmSG is more often seen in females; in both cases, the highest incidence is reported among the elderlies (>65 y). Most of mSGCs (up to 90% of cases) arise from the SGs located in the oral cavity; the rest of mSGCs of the head and neck (i.e. pharynx, larynx, paranasal sinuses, and nasal cavity; see Figure 1) originate from seromucous glands, which do not produce saliva, but share an identical structure to SGs and, as such, are also considered within mSGCs. Only a minority originates outside of this anatomic district (i.e. upper aerodigestive, trachea and bronchi, breast, gynecological tract) [1]. For the scopes of the present review, we have chosen to focus on mSGC of the head and neck area. With regards to disease outcomes, the 5-y survival rate of mSGC of the head and neck has remained stable in time and, overall, it has resulted slightly better compared to MSGC (67% vs. 61%) [7].

1.2. Pathology

Not all histotypes of MSGC are equally represented in the context of mSGC. In other words, histology is closely related to anatomy, taking into consideration that the salivary duct is often much shorter – or even absent – in mSGs as compared

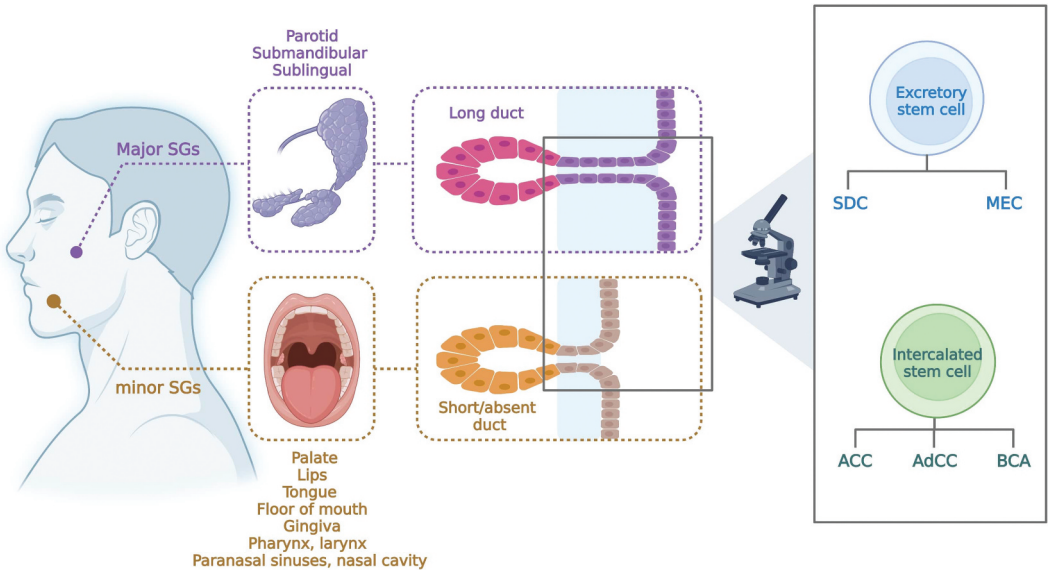

Figure 1. Relationship between anatomy and histology of major and minor salivary glands. Localizations, macroscopic and microscopic anatomy of major (purple) and minor (brown) salivary glands of the head and neck, respectively. The light blue boxes highlight the different length of the salivary ducts, which justifies the differences in relative percentages of distinct tumor histotypes (i.e., histotypes arising from the salivary ducts are more often seen in major salivary glands with respect to the minor counterpart). The histogenesis of the main malignant SG tumor types is also reported, according to the most widely accepted 'bicellular stem cell' theory of origin: this theory holds that excretory stem cells give rise to SDC and MEC, while intercalated stem cells give rise to ACC, AdCC and BCA. The variable representation of the two stem cell types (which is not necessarily correlated to the salivary glands' anatomic features) may also contribute to the different percentages of distinct tumor histotypes observed among mSGCs and MSGCs. SGs, salivary glands; SDC, salivary duct carcinoma; MEC, mucoepidermoid carcinoma; ACC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; BCA, basal cell adenocarcinoma. Created with BioRender.com.

to the major counterpart [8]. Therefore, within mSGC, a low percentage of salivary duct cancer (SDC) or of other cancers arising from salivary duct cells (i.e. intraductal carcinoma) is expected, while, as previously mentioned, the most reported histotypes include mucoepidermoid carcinoma (MEC), adenocarcinoma (ADC), and AdCC [6]. Another contributing factor to these differences may be found in the most widely accepted 'bicellular stem cell' theory of AdCC origin: this theory holds that excretory stem cells give rise to SDC and MEC, while intercalated stem cells give rise to acinic cell carcinoma (ACC), AdCC and basal cell adenocarcinoma (BCA) [9]. Therefore, the variable representation of the two stem cell types (which is not necessarily correlated to the salivary glands' anatomic features) may also contribute to the different percentages of distinct tumor histotypes observed among mSGCs and MSGCs (Figure 1). AdCC cytology is characterized by high cellularity with basalioid cells with a high nuclear-cytoplasmic ratio and hyperchromatic, angulated nuclei; atypia is often mild, making it challenging to perform a differential diagnosis from benign tumors with a cribriform pattern (e.g. cribriform subtype of basal cell adenoma). Giemsa staining shows discrete spheres and branching tubules of the acellular basophilic matrix. Concerning immunohistochemistry, pancytokeratin is strongly expressed in ductal cells and poorly expressed in myoepithelial cells; ductal cells are mostly positive for CK7 and KIT, while myoepithelial cells are positive for p63, p40, calponin, α-SMA. As far as molecular pathology, with regards to AdCCmSG, it is also worth noting that, as per the major counterpart, a solid growth pattern (>30%) as well as high-grade transformation (i.e. loss of myoepithelial markers) are associated with a poor prognosis. AdCC histotype exhibits biphasic differentiation of ductal and myoepithelial cells, and presents with tubular, cribriform, and/or solid architectural patterns [10–14].

1.3. Diagnosis, prognostic factors and TNM staging

In the context of AdCCmSG, performing prompt and correct histo-morphological diagnosis is often more challenging as compared to MSGs. In this respect, *Ihrler et al*. tried to summarize the most critical issues, which may be addressed as following: 1) pathological and biological considerations: i.e. mSGC frequently being low-grade lesions and displaying low/absent cell atypia 2) clinical and pathological correlations: i.e. mSGC being more frequently diagnosed on incisional biopsy/cytology, with a higher risk of misdiagnosis 3) difficulties related to the specific subsite of origin: i.e. tumors originating from the palate, where necrosis, ulceration, squamous metaplasia, pseudo-infiltration, early bone invasion, and fusion with palatal mucosa are often found [15].

All these aspects highlight the importance of a high-expertise, pathology-based revision, which is strongly recommended whenever lacking in the first instance.

Appropriate histological characterization is of paramount importance also because tumor histotype represents one of the most solid prognostic factors in this disease setting – along with solid growth pattern, AJCC TNM staging, margin status, and high mitotic index (defined as ≥5 per 10 high power fields) [16]. Specifically, the 5-y survival of AdCC is similar to that of ADC (i.e.: 5-y overall survival 55–89%, 15-y or 20-y survival 20–40%, rates of local recurrence and distant metastasis 16–67% and 8–46%), with both showing poorer prognosis as compared to MEC; however, projecting to a 10-y observation time span, the survival trajectory of AdCC significantly worsens, not only with respect to MEC, but also compared to ADC [6].

The primary subsite of origin also has a significant prognostic impact, with the worst outcomes expected for tumors arising in the nasal and paranasal sinuses [17].

Other well-established prognostic factors of mSGC include older age (>75 y), lack of surgery performed with primary curative intent, and advanced stage at diagnosis [7].

Differently from the major counterpart, mSGC, including AdCCmSG, is not described by a specific TNM system: specifically, the same TNM criteria of squamous cell carcinoma (SCC) is applied, according to the specific site of origin [18].

Given its propensity for locoregional invasion, magnetic resonance imaging proves essential to assess tumor submucosal extension and perineural spread at the time of AdCCmSG diagnosis [19].

2. Surgery

Surgery represents the mainstay of treatment in most of AdCCmSG cases. The key surgical aim is to obtain a wide resection with clear margins; however, the specific propensity of AdCC for perineural invasion and its frequent proximity to vital structures turn this goal into a real challenge. An overview of the available literature suggested that, in most cases, surgeons are faced with advanced stage tumors, especially when arising from the palate or the maxillary sinus – two of the most common localizations in the head and neck area [20,21]. Local recurrence is attributed in part to the proclivity of AdCC for perineural invasion. The neurotropism also contributes to the infiltrative nature of this neoplasm, with deep penetration of vital structures of the craniofacial region along major nerve trunks. Because of these clinical features, AdCC has been described as 'one of the most biologically destructive and unpredictable tumors of the head and neck' [22]. In this context, magnetic resonance imaging proves essential to assess tumor submucosal extension and perineural spread [19].

Building from these premises, the following open questions regarding the surgical management of AdCCmSG are addressed:

2.1. Which is the ideal surgical approach? Open vs. endoscopic techniques

The feasibility of complete surgical resection relies on tumor size and site, proximity to vital structures and surgeons' experience. In this context, the ideal approach for tumor resection is currently debated: while AdCC of the oral cavity and other head and neck subsites is managed just as any other tumor histotype, particular attention should be given to AdCC of the paranasal sinuses, where growing evidence supports endoscopic resection techniques in high-expertise surgical settings. In detail, a review published by *Castelnuovo et al*. described comparable oncological outcomes with

endoscopic surgery as compared to the open counterpart, with several added benefits, including the sparing of facial incision, better post-operative management with less patient pain and discomfort, as well as shorter hospitalization. Moreover, the chief advantage of endoscopic approach is the high precision and the better visualization of surgical margins, especially at the level of the skull base and of the posterior sinuses [20,21]. Indeed, endoscopic-assisted resections of maxillary AdCCmSG are increasingly emerging, often applying to areas otherwise hardly manageable with standard, open approaches [23,24]. For instance, the medial and posterior walls of the maxillary sinus and pterygoid plates represent the ideal candidate for endoscopic-assisted resection: not only this technique spares facial incision, but it also allows high-accuracy in the section of pterygoid plates, improving bleeding control and increasing precision in the ideal height of section. The same authors fully outlined all absolute contraindications for endoscopic surgery – irrespective of tumor histology –, which include the infiltration of bony structures (i.e. hard palate, nasal bones, anterior plate of frontal sinus), and the massive involvement of the brain, lacrimal pathway and/or orbit (with or without dural invasion) [20].

Reconstructive considerations should also be made before choosing a pure endoscopic resection: not only wide resections are frequently required, but also patients are often young, carrying high expectations in terms of esthetic and functional outcomes. Therefore, a complex endoscopic surgery may miss its goal in case open conversion is required for following reconstruction, or if the attempt of avoiding more extensive approaches results in sub-optimal reconstruction.

2.2. Is neck dissection indicated in clinically node-negative (cN0) patients?

Another matter of discussion in the surgical management of AdCC are the indications for neck dissection in case of cN0 patients. In this respect, some compelling data derives from a few recent, large case series including AdCC of mSGs, as well as of MSGs.

Data revealed that a clinically positive node at diagnosis is quite rare, accounting for around 10% of cases both in the oral cavity and in the head and neck area. However, upon neck dissection, a positive node is detected in about 4% of MSGCs and in up to 30% of oral cavity AdCCmSG, with a rate of occult metastases reaching 25% of cases – as also seen in head and neck squamous cell carcinoma (HNSCC) [25]. All authors agreed that a positive neck node is one of the main negative prognostic factors and that, as such, the clinical and surgical focus should be on avoiding a missed diagnosis.

Based on these results, it could be reasonable to conclude that, at least for AdCCmSG of the oral cavity, a staging/prophylactic neck dissection could be indicated also in cN0 patients [25–31]. However, the need for nodal dissection for AdCC in the oral cavity of cN0 patients remains inconclusive, lacking strong support from literature. Retrospective studies, including those by *Amit et al*. and *Qian et al*., suggest limited survival benefits from nodal dissection in cN0 patients [29,32]. While the International Head/Neck Scientific Group advises nodal dissection at T3–T4 stages for most salivary gland tumors, it recommends against it for low metastasis risk areas like the sinus, lacrimal gland, and external auricular duct [33,34]. For AdCC of the oral cavity and oropharynx, considering the higher occult metastasis rate, nodal dissection is suggested for patients with negative prognostic factors not receiving PORT, as per a review by *Suárez et al*. [35]. Conversely, for laryngeal AdCC, which has a lymph node metastasis rate of 12%, nodal dissection is not recommended in cN0 patients, based on findings by *Coca-Pelaz et al*. [36].

2.3. What are the recommendations concerning perineural invasion (PNI)?

PNI is a well-known, disease-specific pathway of invasion in AdCC, as widely documented in literature. In this regard, a recently published review pointed out that, given the established awareness of surgeons concerning this issue, PNI should no longer be regarded as prognostic in terms of survival outcomes or of distant metastasis occurrence, whereas it should play a major role in treatment planning. Specifically, surgeons should extend their resection to neural structures, possibly with the aid of intraoperative frozen sections; furthermore, the presence of PNI must constitute a criterion for adjuvant treatment, as well as a target of RT volumes (see **Radiation therapy** paragraph) [37].

2.4. What are the recommendations concerning surgical margins?

Surgical margins are also matter of discussion in AdCCmSG, especially for nasal and paranasal sinuses malignancies. In these sites, surgery often results in R1 resections (i.e. microscopic residual tumor), due to the critical proximity to vital structures and the relatively early diffusion to neighboring areas – such as the dura, neural foramen, pterygopalatine fossa, as well as the brain.

On the other hand, in the management of AdCCmSG of the nasal and paranasal sinuses, *Amit et al*. underlined that tumors with positive/close margins or those originating from the sphenoid/ethmoid regions were linked to a poorer prognosis compared to those with negative margins or originating from the maxillary/nasal cavity area [38,39].

With a hazard ratio of 3.1, the association between positive/close tumor margins and reduced overall survival was significantly stronger than with negative tumor margins (69% vs. 27%, respectively). Comparable outcomes were observed for disease-specific survival, with 71% for positive margins vs. 30% for negative margins. Overall, the study by *Amit et al*. identified that the status of tumor margins and the location of the tumor significantly influenced patient outcomes [38].

As a result, the question of whether to proceed with surgery represents a thorny issue in the management of these patients.

In their review, *Castelnuovo et al*. underlined that pursuing complete resection of tumors in the nose and paranasal sinuses could often entail the removal of vital structures or could otherwise severely affect patients' quality of life [20]. In such instances, gross total or near-total tumor resection with close or positive margins may offer less morbidity, without jeopardizing survival

outcomes [38,39]. That being said, patients should always be referred to non-surgical treatment whenever an R2 resection (i.e. macroscopic residual disease) is expected. The key point remains the identification of areas at high risk for bone infiltration: while ongoing technical progresses in medical imaging will certainly aid at this purpose, to date the precise assessment of bone infiltration can only be described in the final histological examination, and it is a pivotal factor in the decision-making process concerning adjuvant treatment.

To sum up, our suggestions concerning AdCCmSG surgical management are as follows: i) choose the soundest surgical approach based on tumor size and site, using mini-invasive approaches (i.e. endoscopic resections) whenever feasible; reconstructive aims should be taken into account in the surgical approach selection; ii) consider neck dissection in case of cN0 AdCCmSG of the oral cavity and oropharynx; iii) PNI should be taken into account in the planning of the surgical procedure; iv) suboptimal (i.e. R1) resection could be taken into account in the surgical management of nose and paranasal sinuses AdCCmSGs.

3. Radiation therapy

Radiation oncologists participate in the management of AdCCmSG mainly in the adjuvant setting, as the optimal therapeutic strategy involves surgery plus post-operative radiation therapy (PORT). RT also has a role as definitive treatment in case of non-resectable lesions or for patients unfit for surgery, while it may offer longer survival and improved quality of life for patients with metastatic disease [2].

In the absence of randomized trials, PORT recommendations are entirely based on retrospective clinical studies [40–44]. Generally, both in major and minor salivary gland tumors, target volumes delineation should be adapted to specific extensions based on the affected salivary gland, according to pre-surgical imaging prior and post-surgical pathological description [45]. As seen in Table 1, in almost all the included studies, tumor (T) and nodal (N) stage are independent prognostic variables for loco-regional disease control and for disease-related survival [40–44,46]. PORT plays a role in loco-regional control, reducing the risk of recurrence to 10%; whereas the distant failure rate remains high ≤ 30%) [42].

As per standard practice, in HNSCC PORT should start within 7 weeks after surgery to maximize treatment efficacy [3]. Interestingly, clinical data in SGC showed that this specific time window may not be so critical, as a surgery-PORT time interval of ≤12 weeks resulted in similar local control rates [47]. Conversely, a surgery-PORT time window of >12 weeks was associated with a significantly increased risk of local and distant failure in mSGC: therefore, in patients with AdCCmSG, PORT should be started as soon as possible after surgery [48].

Considering the long-term delay of distant metastatic dissemination (>10 y after curative treatment), the maximal local treatment should be offered, with the aim of providing prolonged local disease control and longer disease-free interval with minimal morbidity also to patients who will later experience metastatic recurrence [49].

While these results consistently support the relevance of PORT in this patient population, the following clinical questions remain to be addressed:

3.1. Which volumes should be included in the target?

Delineation of the clinical target volume (CTV) of mSGC depends on primary site of origin, disease extent and pathologic findings after surgery. Because of the high propensity of AdCC for PNI and intracranial extension, a deep anatomic knowledge of the inter-neural connections among cranial nerves is a fundamental requirement in CTV definition. PORT field should be appropriately expanded to cover the cranial nerve pathways at higher risk of perineural spread, to prevent further disease dissemination. In this respect, international consensus guidelines have been published to accurately delineate both primary tumor and nodal CTV (CTV-T and CTV-N, respectively), as well as to target cranial nerves [50–53]. As a detailed analysis of these guidelines is beyond the aim of this review, we will just briefly focus on the clinical scenario of AdCC with hard palate primary location as a relevant example. The hard palate region is characterized by the connection between the maxillary nerve (V2) – that largely supplies the hard palate –, the greater and lesser palatine nerves, and the facial nerve (VII) running via the Vidian canal, where the V2 and VII cranial nerves communicate. Consequently, for AdCCmSG of the hard palate (with asymptomatic, microscopic PNI), radiation oncologists should consider extending RT field to the V2 nerve up to the foramen rotundum, and the VII nerve up to the internal acoustic meatus [53].

The selection of CTV-N depends on the risk of occult metastasis, which is estimated through a scoring system (score: 0 to 4) including four clinicopathologic factors associated with risk of positive nodes: patient gender (male gender), tumor stage (T3 or T4 stage), site of origin (pharyngeal primary site), grade and histology (high-grade adenocarcinoma or high-grade mucoepidermoid carcinoma) [41]. The risk of positive nodes is 2% for score 0, 9% for

Table 1. AdCCmSG: prognostic factors.

		Prognostic factors	
Ref	Patient N (AdCCmSG)	LRC	OS
Beckhardt RN, 1995	43	Histology	T stage, margin status, grade
Parsons JT, 1996	95	T stage, N stage	T stage, N stage
Jones AS, 1998	72	T stage, N stage	T stage, PS
Chen AM, 2006	78	T stage, PNI, major nerve involvement	
Lloyd S, 2010	1022		T stage, grade, site, sex
Zeidan YH, 2013	58		T stage, N stage

AdCCmSG: adenoid cystic carcinoma of minor salivary glands; T: tumor; N: nodal; PS: performance status; PNI: perineural invasion; LRC: locoregional control; OS: overall survival.

score 1, 17% for score 2, respectively. A 41% and 70% risk of positive nodes is found for score 3 and 4, respectively. For a score ≥ 2, elective treatment of the neck lymph nodes is indicated. This prognostic index is based on a logistic regression analysis of a SEER database of a total of 2222 mSGC patients (including 252 AdCC cases), where PORT led to improved survival in patients with adverse clinicopathologic factors [54].

The authors developed a user-friendly version of this nomogram. According to this model, each patient is assigned a propensity score which represents the probability of receiving a specific treatment (surgery alone vs. PORT) based on the covariates of interest. For instance, a male patient with poorly differentiated T2N0 AdCC of the oral cavity has a median survival of 71 months with PORT vs. 26 months with surgery alone. Overall, oral cavity primary tumors have a more favorable prognosis than paranasal sinus tumors. This tool might be useful to guide decision-making and could assist in creating a tailored treatment strategy.

Regarding RT doses, the CTV-T should be associated to a dose level equivalent to 60 Gy (up to 66 Gy or 70 Gy in case of microscopic or macroscopic positive margin, respectively) in 2 Gy per fraction over 6 weeks. For the elective CTV-N, a dose level equivalent to 46–50 Gy (2 Gy per fraction) is recommended [53].

3.2. Which technique should be used?

Advanced RT technologies, such as intensity modulated RT (IMRT), volumetric arc therapy (VMAT) with image guided RT (IGRT) at least weekly, and proton beam therapy, should be used on a case-by-case basis: for an appropriate treatment selection, the clinician should consider several factors, including disease stage, primary tumor location, physician's training/experience, and available physics support.

More in detail, the charge and mass of protons allow lower exit doses as compared to photons – in other words, protons have the potential to limit RT dose to non-target tissues, potentially leading to further gains in terms of toxicity and quality of life. Therefore, proton therapy should be considered especially when normal tissue constraints cannot be met by photon-based therapy: for instance, protons may be preferred when tumor proximity to organs at risk – such as the optic chiasm, optic nerve, carotid arteries, brainstem, temporal lobe, and cochlea – may limit the adequate killing dose required for tumor cells [55,56].

Furthermore, carbon ions yield a higher relative biologic effect on tumor cells compared to photons. Hence, in view of the intrinsic radio-resistance of AdCC, carbon-ion RT may lead to superior local control rates in advanced, inoperable and/or recurrent AdCC, albeit without evidence of improved survival rates [57]. As the ACCO trial results are eagerly awaited, IMRT followed by a carbon ion boost to the macroscopic disease – the so-called 'bimodal therapy' – may represent a valid treatment option, when available [57,58].

We hereby summarize our suggestions with respect to RT techniques applied to AdCCmSG: i) coverage of the cranial nerve pathways is recommendable, especially in case of PNI; moreover, elective neck RT may be offered in a selected group of patients, according to their prognostic score; ii) patients with non-resectable or recurrent disease should be referred to specialized particle therapy centers; moreover, particle therapy's potential benefits should be carefully weighed over photon therapy also in the PORT setting.

4. Systemic therapies

Solid data concerning effective systemic therapies in AdCC in general are very scant. All the concepts applied to MSGs can be translated to the minor counterpart, with the following highlights:

4.1. Should we add ChT to PORT in the adjuvant setting?

In the adjuvant, as well as in the unresectable setting (as previously described in the **Radiation Therapy** paragraph), according to ASCO and ESMO guidelines, the addition of ChT to PORT is not recommended in routine clinical practice (i.e. unless there is the opportunity of enrolling patients in specifically designed clinical trials) [1,2]. In this regard, *Patel et al.* have observed a significant increase in the addition of ChT concurrent to adjuvant RT among 33,262 patients with high-risk salivary gland malignancies (35% vs 21%, $p < 0.001$), especially in case of AdCC histotype (15% vs 8%, $p < 0.001$), despite the lack of a significant survival benefit associated to ChT addition [59]. Given this scenario, an international, multicenter, randomized phase III trial (RTOG 1008, NCT01220583) is ongoing, addressing the question of whether (or not) to add ChT to adjuvant PORT in radically resected AdCCs (Table 2).

4.2. Is there any role for concomitant CRT in the unresectable setting?

Although concomitant CRT is among the current standard approaches for locally advanced HNSCC in the curative setting, data supporting an analogous approach for AdCC of the head and neck area is limited.

Table 2. Radical concomitant CRT in AdCC of the head and neck.

Ref	Patient N (AdCC)	Treatment	Median FUP, mo	CRR (%)
Swain M, 2021	23	Platinum-based CRT	53	47.8%
Samant S, 2012	16	Platinum-based CRT	61	43.7%
Ha H, 2021	10	Platinum-based CRT		80%
Bhattasali O,2016	9	Platinum-based CRT	27	44%
Gomez DR, 2008	5	Platinum-based or CBDCA-PTX CRT		
Haddad RI, 2006	5	CBDCA-PTX CRT	36	100%

AdCC: adenoid cystic carcinoma; FUP: follow-up; CRR: complete response rate; CBDCA: carboplatin; PTX: paclitaxel; CRT: chemoradiotherapy; mo: months.

There is little evidence that concomitant CRT is superior to RT alone for mSGC, as randomized studies are ongoing (NCT02998385) in the context of SGCs – including, but not limited to AdCCmSG. Nonetheless, a few reported series of concomitant CRT in primary AdCC described encouraging outcomes, although limited by small sample size (Table 2) [60–65].

4.3. Recurrent/metastatic AdCcmSG

Owing to its frequently indolent clinical course and to the scarcity of strikingly effective and/or tolerable drugs, AdCCmSG is immediately managed with active systemic treatments only in a minority of instances. In accordance with the main international guidelines, in case of pauci-/asymptomatic disease and/or minor disease progression (i.e. no progression per RECIST and/or not potentially leading to any vital organ dysfunction), no active systemic treatment should be started [1,2].

As a pragmatic example, the presence of locoregional disease – irrespective of the presence of metastatic disease – can be a meaningful factor hindering vital organ function and, as such, can support the clinician in the decision to start systemic treatment, after having excluded the feasibility of local re-treatment (i.e. salvage surgery or re-irradiation).

In this respect, a particularly indolent disease biology may be defined in case of a prolonged disease free-interval (i.e. >36 months) and in case of ≤5 or single-organ metastases (especially pulmonary): in such settings, local therapies, including metastasectomy, radio-frequency ablation, stereotactic body RT, and trans-arterial (chemo)embolization, may be considered to limit the impact of disease on patients' quality of life and to potentially prolong progression-free survival (PFS) [66,67].

In case a systemic treatment is promptly indicated, ASCO and ESMO guidelines suggest that, in the lack of clinical trials, an antiangiogenic drug (AAD)-based monotherapy (e.g. lenvatinib) may be considered as first-line approach for recurrent/metastatic AdCCmSG [1,2]. Table 3 summarizes the most relevant phase II studies conducted across the last decade, investigating the use of multi-tyrosine kinase inhibitors (TKIs) with anti-angiogenic action in AdCC, including tumors originating from M/mSGs.

Regrettably, AADs are still characterized by limited activity in AdCC, with reported overall response rates (ORR) ranging between 0% and 15.1% and partial PFS benefits of no more than 5.7–17.5 months [68–71]. In lack of more compelling alternatives, AADs have raised growing interest and are being increasingly employed in everyday standard clinical practice, notwithstanding their poorly quantifiable and little predictable clinical benefit.

Furthermore, a few special concerns should be raised with regards to AADs use in AdCC: first, a close monitoring is needed in case of disease relapse within previous RT or surgical field, due to the higher risk of drug-related adverse events in such settings (e.g. bleeding and/or fistulae). Also, an adequate time interval should elapse between surgery and AAD start (i.e. at least 28 days or after full wound healing), to avoid wound complications [72].

In this regard, more encouraging, albeit preliminary, data seem to support the safety of AADs after particle beam RT: indeed, no concerning cross-interactions between lenvatinib and previous particle beam RT have been prospectively documented [73]; that said, larger, prospective studies are ongoing (Table 4) and real-world evidence is eagerly awaited to clarify the potential synergy – both in terms of activity and safety – of similar therapeutic combinations.

There is a strong biological rationale in the combination of AADs plus immunotherapy: however, *Ferrarotto et al*. have recently published the results of a phase II trial that demonstrated the activity of the combination axitinib + avelumab without any significant increase in response rate compared to axitinib alone, with the limits of cross-trial comparisons [74,75]. Such results did not come as a surprise, as, to date, all previous trials with single or combined immune-targeted agents (Table 5) failed to demonstrate any significant activity

Table 3. Antiangiogenic agents in AdCCmSG of the head and neck.

Ref	Phase	Patient N	Drug	Drug target	mPFS, mo	mOS, mo	ORR (%PR)	Toxicity ≥G3
Agulnik M, 2007	II	19	Lapatinib	HER2, EGFR	NA	NA	0%	NA
Thomson DJ, 2013	II	23	Sorafenib	multi-TKI (VEGF, PDGFR, RAF)	11.3	19.6	0%	57%
Locati LD, 2016	II	19	Sorafenib	multi-TKI (VEGF, PDGFR, RAF)	8.9	26.4	11%	29.7%
Ho AL, 2016	II	33	Axitinib	multi-TKI (VEGFR, c-KIT, PDGFR)	5.7	NR	9%	NR
Dillon PM, 2017	II	34	Dovitinib	FGFR	8.2	20.6	6%	63%
Tchekmedyian V, 2019	II	33	Lenvatinib	multi-TKI (VEGFR1,2,3)	17.5	NR	15%	78%
Locati LD, 2020	II	28	Lenvatinib	multi-TKI (VEGFR1,2,3)	9	27	12%	50%
Adeberg S, 2020	I/II	23	Cetuximab + IMRT, Carbon ion boost	EGFR	NA	54	35%	48%
Kang EJ, 2021	II	60	Axitinib	multi-TKI (VEGFR, c-KIT, PDGFR)	10.2 vs 2.8 (s)	NR vs 27.3	0 vs 11.5%	NR
Zhu G, 2021	II	65	Apatinib	VEGFR2	19.7	NA	46.2%	14.7%
Kang H, 2022	II	80	Apatinib	VEGFR2	9	NR	15.1%	80%
Van Boxtel W, 2022	II	15	Cabozantinib	multi-TKI (c-MET, VEGFR2, AXL, RET)	9.4	27.5	7%	24%
Ferrarotto R, 2023	II	28	Avelumab + Axitinib	PD-L1 + multi-TKI (VEGFR, c-KIT, PDGFR)	7.3	16.6	18%	26%*
Ye L, 2023	II	16	ATRA + Apatinib	VEGFR2	16.3	NA	19%	18.7%

*Also including other SGC histotypes.

mPFS: median progression-free survival; mOS: median overall survival; ORR: objective response rate; PR: partial response; mo: months; NA: not available; NR: not reached; IMRT: intensity-modulated radiation therapy; ATRA: all-trans retinoic acid; HER2: human epidermal growth factor receptor 2; PDGFR: platelet derived growth factor receptor; RAF: rapidly accelerated fibrosarcoma; FGFR: fibroblast growth factor receptor; RET: rearranged during transfection.

Table 4. Ongoing trials with experimental treatments involving AdCCmSG of the head and neck.

NCT	Phase	Drug	Drug target	Primary outcome	Status
NCT01152840	II	Everolimus	mTOR	PFS	Completed
NCT03691207	II	AL101	γ-secretase	ORR	Unknown
NCT04119453	II	Apatinib	VEGFR2	ORR	Completed
NCT02942693	II	Proton + Carbon ion boost RT ± Apatinib	VEGFR2	ORR	Unknown
NCT01417143	II	Dovitinib	FGFR	PFS	Completed
NCT02098538	II	Regorafenib	VEGFR2, TIE2	PFS, ORR	Active, not recruiting
NCT04973683	I	AL101	γ-secretase	Toxicity, changes in NICD1 levels	Recruiting
NCT03639168	II	Chidamide + CDDP	Histone deacetylase	ORR	Completed
NCT04209660	II	Lenvatinib + Pembrolizumab	multi-TKI (VEGFR1,2,3) + PD-1	ORR	Recruiting
NCT00886132	II	Sunitinib	multi-TKI (PDGFs, VEGFRs, c-KIT)	ORR	Completed
NCT01678105	II	Dovitinib	FGFR	ORR	Completed
NCT02883374	II	Chidamide	Histone deacetylase	DCR	Unknown
NCT00180921	II	Imatinib	multi-TKI (CSF1R, ABL, c-KIT, FLT3, PDGFR-β)	PFS	Unknown
NCT05074940	II	Amivantamab	EGFR, MET	ORR	Recruiting
NCT04974866	II	EGFR TKI	EGFR	PFS	Recruiting
NCT00077428	II	Bortezomib + Doxorubicin	NA	ORR	Completed
NCT00017498	II	Gemcitabine	NA	ORR	Completed
NCT04883671	NA	SBRT	NA	PFS, LRC	Recruiting
NCT04214366	II	Carbon ion RT	NA	LRC	Recruiting
NCT05733910	NA	Carbon ion RT	NA	Toxicity	Not yet recruiting
NCT05774899	I/II	CB-103 ± Venetoclax	pan-NOTCH ± BCL2	PFS	Recruiting
NCT05010629	II	9-ING-41 + CBDCA	GSK3β	ORR	Recruiting
NCT03291002	I	CV8102 ± anti-PD-1	PD-1	Toxicity	Active, not recruiting
NCT03172624	II	Nivolumab + Ipilimumab	PD-1 + CTLA-4	ORR	Active, not recruiting
NCT03146650	II	Nivolumab + Ipilimumab	PD-1 + CTLA-4	PFS	Unknown
NCT03781986	I/II	APG-115 ± CBDCA	MDM2	Toxicity, ORR	Recruiting
NCT01637194	I	Everolimus + Cetuximab	mTOR + EGFR	Toxicity	Completed
NCT01586767	NA	Proton RT or IMRT	NA	LRC	Recruiting
NCT04249947	I	p-PSMA-101 CAR-T cells + Rimiducid	PSMA	Toxicity, ORR	Active, not recruiting
NCT00045669	II	Imatinib	multi-TKI (CSF1R, ABL, c-KIT, FLT3, PDGFR-β)	Toxicity, ORR	Completed
NCT04973683	I	AL101	γ-secretase	Toxicity, changes in NICD1 levels	Recruiting
NCT02775370	II	Apatinib	VEGFR 2	PFS	Unknown
NCT02780310	II	Lenvatinib	multi-TKI (VEGFR1,2,3)	ORR	Active, not recruiting
NCT05930951	I	OBT076 ± Balstilimab	CD205 ± PD-1	ORR	Not yet recruiting
NCT01192087	I/II	Cetuximab + IMRT + Carbon ion RT	EGFR	Toxicity	Unknown
NCT04433169	II	ATRA, VEGFR inhibitor, chemotherapy	VEGFR	ORR	Unknown

PFS: progression-free survival; ORR: objective response rate; DCR: disease control rate; LRC: locoregional control; RT: radiotherapy; CDDP: cisplatin; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; SBRT: stereotactic body radiotherapy; PSMA: prostate-specific membrane antigen; CBDCA: carboplatin; IMRT: intensity-modulated radiation therapy; CAR-T: Chimeric antigen receptor T; VEGFR: vascular-endothelial growth factor receptor; HER2: human epidermal growth factor receptor 2; PDGFR: platelet derived growth factor receptor; RAF: rapidly accelerated fibrosarcoma; FGFR: fibroblast growth factor receptor; RET: rearranged during transfection; m-TOR: mechanistic target of rapamycin; CSF1R: colony stimulating factor 1 receptor; FLT3: fms-like tyrosine kinase 3; BCL2: B-cell lymphoma 2; GSK3β: glycogen synthase kinase 3β; MDM2: mouse double minute 2; NA: not applicable.

in AdCC. In this regard, one phase II study (NCT04209660) is currently testing the combination of lenvatinib + pembrolizumab in advanced AdCC.

Given the above-described limits of AADs, as the available therapeutic armamentarium of AdCCmSG remains scant, a platinum-based ChT doublet (e.g. platinum compound plus doxorubicin) may be offered in selected cases for which the ChT-induced disease shrinking activity (which ranges between 20–25%) is needed [76].

Our suggestions regarding systemic approaches in the treatment of AdCCmSG are as follows: i) the addition of adjuvant ChT to PORT is not the current standard of care for AdCCmSG; ii) as part of primary curative treatment of unresectable disease, the addition of ChT to RT should not be routinely offered; iii) in presence of indolent disease presentation, systemic treatment should be started only in case of symptomatic disease, of disease progression per RECIST or of AdCC localizations in potentially critical areas; systemic therapies for recurrent/metastatic AdCCmSG are largely translated from the major counterpart: in the first line setting, AADs may be considered also outside of clinical trials; in more selected cases (e.g. fast tumor shrinkage needed, AADs contraindicated), a platinum-based ChT doublet may be offered.

5. Other systemic approaches

To date, several studies are ongoing, evaluating further possible therapeutic weapons both in locally advanced and metastatic AdCCmSG settings (Table 4). Among other projects, a phase II

Table 5. Immunotherapy agents in AdCCmSG of the head and neck.

Ref	Phase	Patient N	Drug	mPFS, mo	mOS, mo	ORR (%PR)	Toxicity ≥G3
Fayette J, 2019 (NISCAHN)	II	98 (47% ACC)	Nivolumab	NR	NA	8.7%	7.1%*
Cohen RB, 2018 (KEYNOTE-028)	Ib	26 (8% ACC)	Pembrolizumab	4	NA	12%	12%
Marabelle A, 2020 (KEYNOTE-158)	II	109 (54.1% ACC)	Pembrolizumab	4	NA	4.6% (3.7% PRs)	0.1%*
Tchekmedyian V, 2021 (NCT03172624)	II	32 ACC + non-ACC (60% SDC, ACC)	Nivolumab + Ipilimumab	2.3 non SDC vs. 2.19 SDC	NA	6%	NA
Rodriguez CP, 2019	I/II	12	Pembrolizumab + Vorinostat	6.9*	14*	0.08%	36%*
Mahmood U, 2021	II	20	Pembrolizumab ± RT	4.5 (Pembro + RT); 6.6 (Pembro)	NR (Pembro + RT); 27.2 (Pembro)	0%	0%

*Also including other SGC histotypes.
mPFS: median progression-free survival; mOS: median overall survival; ORR: objective response rate; PR: partial response; mo: months; NA: not available; NR: not reached; RT: radiotherapy; AdCC: adenoid cystic carcinoma; ACC: acinic cell carcinoma; SDC: salivary duct carcinoma.

study tested Lutetium-177-PSMA radioligand therapy in advanced SGC patients, in line with the relevant PSMA-ligand uptake previously observed in AdCC (up to 94% of cases) and SDC patients [77]: regrettably, treatment efficacy was limited, with only 3/10 AdCC patients reaching stable disease as best response [78]. Another promising alternative, as previously described, is represented by particle beam RT: this is being pursued in trials evaluating it alone (NCT04214366, NCT05733910), as well as in a phase II trial with proton beam RT + carbon ion boost ± apatinib (NCT02942693).

Hopefully, the foreseeable therapeutic scenario of AdCC will be enlightened by a more comprehensive knowledge of the underlying disease molecular biology. In this context, *Ferrarotto et al*. have described two distinct AdCC proteogenomic clusters: ACC-I (37%) and ACC-II (63%). These are potentially characterized by distinct tumor histology (solid in ACC-I vs. cribriform/tubular in ACC-II), immunohistochemical profile (MYC+/p63- in ACC-I vs. MYC-/p63+ in ACC-II), mutational profile (higher mutational burden in ACC-I) and drug sensitivity (NOTCH/BRD4 inhibitors in ACC-I vs. TKIs in ACC-II), with marked differences in prognostic outcomes (mOS: 3.4 y in ACC-I vs. 23.2 y in ACC-II, $p < 0.001$) [79]. Similar results were reported by *Romani et al*. who applied a molecular-based approach to link specific pathway alterations with histopathological and prognostic features of AdCC (i.e. enrichment of mitotic and transcriptional genes in p63-, aggressive AdCC) [80]. ACC-I tumors were also found to overexpress the immune checkpoint B7-H4, which independently correlated with poorer survival outcomes; this co-signaling molecule is known to play a crucial role in T cell activation and is often expressed on tumor cells and on tumor-associated macrophages (TAMs) [81,82]. At present, a phase I trial (NCT05194072) testing a drug active against this potential therapeutic target (SGN-B7H4V) is open for recruitment of patients with advanced solid tumors, including AdCC.

Within this framework, across the last decade, research has been focusing on NOTCH1 activating mutations, which are present in up to 25% of recurrent/metastatic AdCC cases: NOTCH1 alterations are especially enriched in the ACC-I phenotype, often exhibiting downstream MYC upregulation, and they have been associated with a solid growth pattern and worse clinical outcomes [83]. These premises fueled great expectations on NOTCH1 as a potential target for selective inhibitors. However, discouraging results were obtained both in terms of suboptimal responses and unfavorable toxicity rates [84–87]. Limited efficacy results were recently presented from phase II ACCURACY trial (NCT03691207) evaluating the γ-secretase inhibitor AL101, which showed an ORR not exceeding 7%, with aclinically relevant toxicity profile (i.e. 51-61% serious adverse events) [88]. Further strategies to better clarify the therapeutic potential of NOTCH1 inhibitors include dual targeting of overexpressed proteins (e.g. NOTCH1 + BCL2 inhibitors) and window of opportunity trials allowing in-depth analysis of the effects of NOTCH1 inhibitors on the microenvironment in pre-treated AdCC surgical specimens (NCT04973683) (Table 4) [89].

Another area of expanding molecular knowledge concerns transmembrane glycoprotein Trophoblast Cell Surface Antigen 2 (TROP-2), which is expressed in over 95% of AdCCs arising from salivary glands [90]. This may prove particularly relevant considering the availability of specific agents. Among them, the antibody–drug conjugate sacituzumab govitecan has already demonstrated significant activity and efficacy across different tumor entities, leading to Food and Drug Administration (FDA) approval of its use in triple-negative and, more recently, hormone-receptor positive, advanced, pre-treated breast cancer [91,92].

Furthermore, fusions involving the MYB protein family also participate in AdCC oncogenesis, involving NFIB as a partner in approximately 60% of AdCC cases; moreover, MYB/MYBL1 oncoprotein is overexpressed in most of AdCC – including fusion-negative tumors [13,93,94]. To date, several studies have attempted to exploit this potential therapeutic target, yet without achieving any clinical applications [95]. In this regard, a first-in-human phase I clinical trial is currently testing a DNA vaccine, TetMYB, based on the pVAX1 plasmid vector carrying a fusion construct consisting of the universal tetanus toxin T-cell epitopes flanking an inactivated MYB gene (NCT03287427).

Finally, it is worth mentioning that epithelial-mesenchymal transition (EMT) has been shown to play a critical role in AdCC tendency for local growth and distant metastatization, as well as for its overall poor responsiveness to standard ChT. In this respect, several phase I and II trials are currently investigating different agents (largely TKIs, see Table 4) targeting the EMT axis – which involves, among others, c-KIT, MYB, epidermal growth factor receptor (EGFR), vascular endothelial growth

factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), glycogen synthase kinase 3β (GSK3β) [96].

Based on these captivating, although preliminary and hypothesis-raising results, further larger and prospective, preclinical and clinical investigations are warranted to better refine treatment tailoring and hopefully improve patient outcomes in AdCCmSG.

6. Conclusions

We provide an update on the current understanding and difficulties of AdCCmSG clinical management. For sure, complete surgery (ensuring free margins) followed by PORT plays a vital role in the treatment of this disease. Despite this combined approach, long-term clinical outcomes remain rather poor. Optimizing systemic therapy, while preserving quality of life, represents a high priority, mainly considering the indolent growth seen in many patients. Indeed, treatment strategies should be dictated by patient characteristics and preferences, comorbidities, toxicity concerns, and costs, always keeping in mind the possibility of enrollment in dedicated clinical trials, when available and feasible. In this regard, the scientific community's efforts should be invested into further unraveling the tumor molecular and biological profile. While specific, selected trials are ongoing, further research is still needed, with the support of adequate funding to accelerate the development of deeper scientific understanding and, as a consequence, of better treatment and care for AdCCmSG patients [97].

7. Expert Opinion

Navigating the complexities of rare cancers, such as AdCCmSG, presents as a clinical challenge for today's medical oncologists. The nature of these cancers is distinctive, as they are exquisitely characterized by limited data availability, by the lack of dedicated clinical trials, and by considerable heterogeneity – which is, inevitably, poorly represented. For instance, a significant percentage of these patients (15–20%) exhibits a 'born-to-be-bad' disease, with an intrinsically aggressive behavior from the very beginning of its biological history and with a tendency to metastasize soon (e.g. NOTCH1 mutated AdCC): these patients deserve a more aggressive and prompt active therapeutic strategy with respect to their more indolent counterpart (e.g. MYB/MYBL1 rearranged AdCC). All these challenges underscore the need for a nuanced and better individualized approach, which proves particularly challenging when building from these premises. In the attempt of addressing these unmet needs, our goal is to provide the present review, summarizing a number of key, practical and implementable suggestions that could positively and pragmatically impact the clinical management of AdCCmSG.

To begin with surgery, we emphasize the importance of choosing the soundest surgical approach, which should always aim to radical tumor resection; when technically feasible, mini-invasive techniques may be applied, yielding reduced morbidity and faster recovery times. Also, we stress the value of anticipating during early surgical planning all considerations on elective neck dissection, PNI, surgical margins, and reconstructive concerns, aiming to the best balance between sound oncological outcomes and satisfactory aesthetic and functional results for patients' quality of life.

Moving to radiation therapy, we highlight the relevance of appropriate volume planning, including cranial nerve pathways to minimize the risk of local recurrence, while maximizing treatment efficacy. Moreover, we endorse referral to specialized particle therapy centers, with careful consideration of the potential benefits and logistical challenges associated with this treatment modality.

Finally, talking about systemic treatment, we acknowledge the limited efficacy of ChT both in the adjuvant setting with PORT and in the unresectable setting with concomitant RT, and we recommend to carefully observe each peculiar AdCCmSG's biological and clinical behavior (which is fostered by the molecular disease milieu) to build a tailored strategy for the initiation of systemic treatment. In this respect, as on one hand we face the limited efficacy of standard agents (ChT, AADs), on the other hand we are witnessing a growing number of different, potential therapeutic approaches, which spring from the developing knowledge of the deeper pathological and molecular aspects of this rare disease entity.

In view of the above, at the heart of the issue of AdCCmSG management lies the inadequacy of a 'one-size-fits-all' strategy in dealing with rare cancers. This approach inevitably fails to account for the diverse manifestations and complexities inherent to diseases like AdCCmSG. A virtuous example of an attempt to address this matter could be exemplified in the 'hub-and-spoke' model, which seeks to centralize expertise, while extending its reach to everyday oncological practice. This model was first designed to democratize knowledge and proficiency, ensuring that insights gained from experts were disseminated effectively across a spectrum of healthcare settings. One of the aims of the present work is, in some way, to reenact the 'hub-and-spoke' model, simulating an interdisciplinary, collaborative effort among expert and dedicated professionals, including surgeons, radiotherapists, and medical oncologists. Along the previous lines, these experts bring their unique perspectives to the table and collectively tackle the clinical challenges surrounding AdCCmSG. Through this proposed collaboration, we aim to establish a sound foundation for AdCCmSG practical management strategies, that could be applied throughout diverse healthcare environments, spanning from high-expertise, high-volume centers, to more peripheral, day-to-day clinical realities.

In this scenario, an example of a current critical challenge is the formalization and standardization of a 'Head and Neck Cancer Unit:' indeed, our multidisciplinary discussion chiefly included surgeons, radiation oncologists and medical oncologists; however, when we imagine the codification of a pragmatic multidisciplinary team for this setting, we cannot spare from also involving other key professional figures, such as pathologists, radiologists, and several other professionals which could be identified.

Another hindrance in the 'hub-and-spoke' model regards, for instance, the pathological diagnosis of rare cancers, which is hampered by an extreme centralization of high-expertise knowledge. The limits related to the inevitably scant number of 'expert' pathologists in rare cancer settings could be

addressed by the application of digital pathology techniques: these would allow easier data collection, harmonization, and dissemination, improving the diagnostic-therapeutic workflow across the spectrum of diverse healthcare settings (i.e. from centers to peripheries).

Moving forward, our exploration also extends to the potential future shifts in AdCCmSG management. In this respect, the integration of minimally invasive surgical techniques and RT approaches involving particle therapies are already being implemented into current practice, while also holding promise for more precise and effective future treatment developments. Furthermore, when considering the potential forthcoming paradigms of AdCCmSG care, we cannot spare from delving into the realm of targeted therapies, which are a current object of research, and which bear the potential of further developing through an evolving comprehension of the crucial molecular pathways involved in AdCCmSG pathogenesis. Indeed, the future of oncology envisions, among others, a flourishing paradigm of precision medicine, driven by increasingly refined molecular profiling techniques, in the attempt of yielding more effective therapeutic strategies. Such shift bears the potential to further clarify the intricate molecular pathways of AdCCmSG, paving the way for more personalized treatment strategies. These could be increasingly tailored to the specific characteristics of each patient, thus moving away further from older, traditional, and more generic therapeutic approaches.

In conclusion, the journey toward better care of rare cancers, including AdCCmSG, begins with a collective commitment to innovation and cooperation, as we pursue better patient outcomes and more effective resource utilization. This requires a dynamic and adaptable approach that acknowledges the rarity and complexity of the disease, while also seeking to encourage the dialogue between peripheral settings and those holding centralized expertise. By fostering collaboration and embracing emerging knowledge and technologies, we may usher into a new era of better refined, precision-based approaches, tailored to the unique challenges posed by AdCCmSG.

Abbreviations

Adenoid cystic carcinoma of minor salivary glands (AdCCmSG), major salivary gland cancer (MSGC), minor salivary gland cancer (mSGC), salivary duct cancer (SDC), mucoepidermoid carcinoma (MEC), adenocarcinoma (ADC), acinic cell carcinoma (ACC), squamous cell carcinoma (SCC), head and neck squamous cell carcinoma (HNSCC), perineural invasion (PNI), plus post-operative radiation therapy (PORT), tumor clinical target volume (CTV-T), nodal clinical target volume (CTV-N), intensity modulated RT (IMRT), volumetric arc therapy (VMAT), image guided RT (IGRT), concomitant chemoradiotherapy (CRT), chemotherapy (ChT), progression-free survival (PFS), antiangiogenic drug (AAD), tyrosine kinase inhibitors (TKIs), overall response rates (ORR), tumor-associated macrophages (TAMs), Trophoblast Cell Surface Antigen 2 (TROP-2), Food and Drug Administration (FDA), epithelial–mesenchymal transition (EMT), ear-nose-throat (ENT), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), glycogen synthase kinase 3β (GSK3β).

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