INTRODUCTION

Head and neck adenoid cystic carcinomas (ACCs) arise most commonly from the secretory epithelial cells of the salivary glands; however, sporadically, ACC can occur in other exocrine glands of the body, for example, breast, lacrimal glands, nasal passages, tracheobronchial tree, prostate, cervix, and vulva [1]. The tumor occurs in all age groups, children included, but it has a slightly
higher frequency in middle-aged patients (50s–60s). Lacrimal gland tumors are a very rare oncological entity that represent an incidence of 1 case per 1,000,000 persons per year and constitute approximately one-quarter of orbital space-occupying lesions with the majority being benign. These lesions are of epithelial origin in more than half of cases and of lymphoid origin in one-third of cases. Lacrimal gland ACC (LGACC) constitutes between 32% and 66% of the epithelial lacrimal gland malignancies and approximately 1.6% of all space-occupying orbital lesions. Despite the rarity of this disease, it is the most common malignant epithelial cancer of the lacrimal gland [2–4]. LGACCs are high-grade, slowly progressive, and aggressive tumors associated with a high mortality due to perineural invasion and dissemination not only to the regional lymphatic system but also to brain, lung, liver, and bones [5]. The 5-year survival rate is less than 50% and median overall survival only 7.6 years, due to early local, distant metastatic disease and delayed patient presentation [4]. The main factors related to locoregional recurrence or distant metastases are tumor size, TNM stage, perineural invasion, invasion of large trunk, incomplete resection, and lack of postoperative radiotherapy (RT) [6]. Currently, there is no standardized protocol for the management of LGACC and consensus regarding the optimal approach because of the rarity of the tumor. As a result, the effect of local resection, RT, or exenteration on the patient outcome still is unclear. The rarity of this tumor, lack of prospective studies, and the still debatable therapeutic approaches emphasize this article’s significance in understanding the disease behavior by reviewing the most relevant studies from the past decade’s literature.

**SIGNIFICANCE (IN-DEPTH ANALYSIS)**

**Signs and symptoms**

The median age for patients with LGACC is 40 years and the main clinical signs according to the tumor expansion at the time of diagnosis are superior temporal eyelid swelling with concurrent downward and medial globe displacement, ptosis, proptosis, and restriction of eye movements. Due to perineural invasion, pain and/or dysesthesia are the cardinal symptoms, followed by headaches, decreased visual acuity, and diplopia in some cases [7,8].

**Staging**

According to the eighth edition of the American Joint Committee on Cancer (AJCC) *AJCC Cancer Staging Manual* classification, primary tumor (T), lymph nodes (N), and metastasis (M) were subsequently defined (Table 1):

Studies have revealed that the AJCC classification might be able to guide the treatment planning and to help predict its outcome. Thus, patients with a disease stage under T3 at the time of presentation are associated with a more favorable outcome in contrast to patients with an advanced disease stage over T3 [9,10].

**Histopathology**

For a correct and complete assessment of LGACC and specific therapeutic management, incisional biopsy or fine-needle aspiration if done in order to
determine the histopathologic tumor type. LGACC consists of a dual population of small hyperchromatic differentiated ductal and modified myoepithelial cells. Regarding the growth pattern, 3 histologic forms have been described. The most common type is the cribriform pattern, followed by the tubular form, whereas the solid (basaloid) pattern is among the rarest and the most infiltrative form with a low survival rate. The cribriform type is known for the Swiss cheese aspect, given by islands of basaloid cells that surround cystlike spaces. Solid tumors also can present central necrosis as well as anaplastic and nuclear pleomorphic cells. With respect to mitosis, tubular LGACC and cribriform LGACC have low mitotic activity, specifically 2.9/10 high-power fields, whereas tumors with solid pattern evidence a higher mitotic activity with a median of 10.1 mitotic figures/10 high-power fields [8]. Immunohistochemical staining of luminal cells reveals positivity against CK 8/18, CD117, and AE1/AE3, whereas myoepithelial cells demonstrate positivity against CK 5/6, S-100, calponin, and p63. The recently described aggressive undifferentiated ACCs usually show an abrupt demarcation between areas of low-grade and high-grade carcinoma and present a higher proliferative rate, a high Ki67 positivity rate, and high incidence of p53 staining in high-grade areas compared with the low-grade ones [11].

Table 1
TNM staging

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>T0</th>
<th>No evidence of primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumors with a size &lt;2 cm with or without invasion of the soft orbital tissue moreover</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Absence of periosteal/bone involvement</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Presence of periosteal involvement</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>Both periosteal and bone involvement</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumors with a size between 2 cm and 4 cm</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Absence of periosteal/bone involvement</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Presence of periosteal involvement</td>
<td></td>
</tr>
<tr>
<td>T2c</td>
<td>Both periosteal and bone involvement</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumors greater in size than 4 cm</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>Absence of periosteal/bone involvement</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>Presence of periosteal involvement</td>
<td></td>
</tr>
<tr>
<td>T3c</td>
<td>Both periosteal and bone involvement</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor extension into adjacent structures</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Tumors with size &lt;2 cm</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumors with a size between 2 cm and 4 cm</td>
<td></td>
</tr>
<tr>
<td>T4c</td>
<td>Tumors with size &gt;4 cm</td>
<td></td>
</tr>
<tr>
<td>Regional lymph nodes</td>
<td>Nx</td>
<td>No assessment of regional lymph nodes</td>
</tr>
<tr>
<td>N0</td>
<td>No involvement of regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Presence of regional lymph nodes metastasis</td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>M0</td>
<td>Absence of distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Presence of distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from AJCC Cancer Staging Manual. 8th ed. Springer International Publishing; 2017: 1032.
Imaging

Imaging is crucial in assessing a lacrimal mass because in many cases the presenting symptoms are nonspecific. Magnetic resonance imaging (MRI) is preferred over computed tomography (CT) scans to evaluate a suspected LGACC due to its ability to detect perineural spread; however, bone assessment is superior on CT. On CT, the mass appears hyperdense with homogeneous enhancement and poorly demarcated margins extending along the orbital lateral wall up until the orbital apex, depending on the tumor size. Adjacent bone destruction and foci of calcification are common in large tumors. On MRI, the lesion is described as a well-defined nodular irregular mass that can infiltrate the adjacent orbital tissues and enhances moderately intense after contrast administration (Fig. 1). On T1-weighted images, the tumor has a hypointense signal to orbital fat, whereas on T2-weighted images it becomes hyperintense to fat with areas of central necrosis in some cases, giving a patchy aspect (Fig. 2). Foci of calcification appear as hypointense areas [8,12]. Contrast-enhanced T1-weighted images can reveal areas of cystic changes surrounded by a heterogeneous enhanced mass [13]. Additionally, MRI is helpful in demonstrating micro-serrations along the lesion border and in detecting perineural invasion or dura penetration. A study conducted by Williams and colleagues [14] reported evidence on imaging of bone involvement in 87.5% of patients who underwent both MRI and CT. A preoperative imaging assessment of the lacrimal fossa with positive bone invasion might indicate a more extended surgical approach with bony wall removal [14]. Recent studies have shown the utility of diffusion-weighted imaging in differentiating benign from malignant orbital tumors through measuring the apparent diffusion coefficient. Due to the hypercellularity of malignant lacrimal tumors, the diffusion of water protons is restricted; therefore, the mean apparent diffusion coefficient values are lower than in benign lacrimal tumors. Larger studies are fundamental, however, in order to raise the accuracy of diffusion-weighted imaging in discriminating the malignant tumors from the benign ones [15].

Treatment approach

Controversy remains regarding the appropriate local therapy for LGACC. The rare nature of this malignancy is the reason for a lack of prospective randomized trials on different forms of treatment. As a result, clinical practice patterns are based mostly on anecdotal experience. Although the most common surgical treatment is orbital exenteration followed by various forms of postoperative RT, recent studies on eye-sparing surgery with adjuvant RT reported good local control similar to orbital exenteration and a good long-term survival in patients with early-stage tumors and locally advanced LGACC [16,17]. Management strategies include orbital exenteration, globe-sparing resection followed by plaque brachytherapy, proton beam RT, neutron radiation and concurrent systemic or neoadjuvant intra-arterial chemotherapy, however, without any clear conclusion [18].

At first, in the early 30s, RT alone without surgery was recommended for ACC. Over time, it became evident that RT alone was ineffective as a curative
treatment modality for ACC [19]. Later, the eye-sparing procedures with complete tumor excision (without RT) became more common. Because this approach was not effective in controlling local recurrence, radical orbital exenteration (without RT) with bone removal was selected in some patients despite the high mortality and low survival rates of 20% [20–25].

Historically, orbital exenteration with or without removal of the bony walls of the lacrimal gland fossa has been viewed as the most common “standard”

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**Fig. 1.** Axial (upper) and coronal (lower) CT scans in a 78-year-old male patient with left intraorbital soft tissue mass at the level of lacrimal gland with both extraconal and intraconal components with irregular margin. The mass cannot be delimited from the lacrimal gland, superior rectus, lateral rectus, and superior oblique muscles.
Fig. 2. MRI in the same patient (T1W [upper]; T2W [middle], T1W with contrast [(bottom (left/right))]). T1w, T1 weighted image. Undelineated soft tissue mass at the level of the lacrimal gland with and isointense signal on T1W sequence and a hypointense signal on T2W images. Intense and inhomogeneously enhancement after contrast. Enhancement is present up until the orbital apex but no signs of perineural extension or intracranial metastasis are noted.
surgical approach, despite the uncertain evidence of survival benefit. This most likely was because of concern regarding toxicity from adjuvant high-dose radiation when delivered in close proximity to the sensitive components of the eye. With more experience, it was evident that the radical surgical approach did not reduce rates of recurrence, metastasis, and mortality but decreased patient quality of life due to functional disability and disfigurement [2,26]. Thus, the idea of adjuvant RT treatment began to gain more interest.

In the mid-1980s, Lee and colleagues [27] embraced the eye-sparing procedure with en bloc excisional biopsy via anterolateral orbitotomy in cases of small, localized tumor. Wright and colleagues [28] reported that disease-free survival may not be improved after cranio-orbital resection in patients with clinically and radiologically localized tumors, and extensive surgery does not appear to have an impact on the risk of distant metastasis and mortality.

Recent literature on LGACC focuses on eye-sparing local excision followed by radiation therapy. Adjuvant high-dose radiation therapy is initiated 4 weeks to 6 weeks after surgical tumor resection due to the very high incidence of perineural invasion. A retrospective cohort analysis reported favorable outcomes of eye-sparing tumor excision combined with adjuvant RT or chemoradiotherapy for 37 patients with lacrimal gland carcinoma, specifically 32 patients were tumor-free, 3 patients presented distant metastasis, and 1 patient died after treatment. The 5-year recurrence-free survival rate was worse in patients who were not treated with adjuvant RT compared with those who underwent RT [16,17]. Moreover, Han and colleagues [29] presented their cohort results of 9/10 patients treated with eye-sparing surgery followed by adjuvant RT without any local recurrence during their study period, and the only patient with local recurrence was treated successfully with orbital exenteration.

These studies support the point of view that in LGACC patients, eye-sparing surgery with adjuvant RT is associated with a favorable visual and functional outcome and the postoperative adjuvant RT seems to improve local control rates. The treatment of a patient with LGACC is approached stepwise by a multidisciplinary team consisting of an orbital surgeon, radiation oncologist, radiologist, and oncologist. Patients are considered eligible for the combined approach of eye-sparing surgery with RT when the tumor is considered grossly resectable without sacrifice of the eye or extraocular muscles. Nonetheless, the risks of local recurrence and secondary exenteration are acknowledged and agreed on by the patient.

Several reports suggest that tumor size affects prognosis in patients with LGACC. A multi-institutional study of 53 LGACC patients concluded that the sixth edition of the *AJCC Cancer Staging Manual* T factor (which is dictated mostly by tumor size at presentation) correlated with prognosis. This report found that tumors categorized as T3 or higher were associated with significantly higher risks of local recurrence, lymph node metastasis, distant metastases, and lower disease-free survival rate than tumors with tumors below T3. Thus, this report concludes that patients with T1 or T2 tumors might be suitable candidates for less invasive surgical treatment. In cases of lacrimal gland
carcinomas, no more than 2.5 cm in dimension, gross total tumor excision (eye
sparing) followed by radiation therapy can be considered [10].

Adjuvant RT is the standard of care after surgery for local control. Various
types of RT have been reported, including external beam radiation (EBRT)
therapy, proton beam therapy (PBT), and plaque brachytherapy. Being the
most affordable and accessible, EBRT is the most common technique. The me-
dian total dose is 60 Gy (59.4 Gy to approximately 70 Gy) with daily fractions
ranging from 2.0 Gy to 2.3 Gy. Based on small series, plaque RT appears to be
a reasonable alternative to external beam irradiation. In contrast to EBRT, pla-
que RT can be completed in 4 days rather than 4 weeks to 5 weeks. It does,
however, require a surgical procedure, usually with local anesthesia. The sur-
gical placement sometimes can be difficult because of scar tissue from the pre-
vious orbital surgery [30]. Another treatment approach is intensity-modulated
radiation therapy (IMRT), which uses multiple small photon or proton beams
of varying intensities to irradiate the tumor mass precisely. The radiation inten-
sity of each beam is controlled, and the beam shape changes throughout each
treatment. The goal of IMRT is to conform the radiation dose to the target and
to avoid or reduce exposure of healthy tissue to limit the side effects of treat-
ment. Investigators showed high control rates and low side effects by using
IMRT in head neck ACC [31,32]. PBT is considered another local RT treat-
ment choice for ACC after primary excision. Linton and colleagues’ [33] and
Lesueur and colleagues’ [34] reports emphasize that PBT is a safe and efficient
treatment and should be considered an adjuvant irradiation modality for pa-
tients with LGACC after conservative or radical surgery [33,34].

New therapeutic options, such as intra-arterial neoadjuvant chemotherapy
(IANC) consist of chemotherapy administered before any definitive surgical
procedure in patients without evidence of metastatic disease but at high risk
for such. The rationale of the neoadjuvant regional treatment is to administer
a high concentration of a chemotherapeutic agent to the lacrimal gland tumor
through the vascular system, prior to surgical excision of the tumor, in order to
enhance tumor cell apoptosis [35]. Thanks to the drug’s intra-arterial route de-
elivery, its concentration is considerably higher than that with intravenous de-
ivery. The higher drug concentration increases its cytotoxic effect while
preserving the therapeutic levels for chemotherapy to the systemic circulation.
The authors demonstrated that IANC was effective in achieving preoperative
cytoreduction by down-staging the disease and enhancing the ability to resect
the entire lesion for local disease control. Controversy still remains, however,
regarding the optimal local therapy for lacrimal gland. The reluctance of many
orbital surgeons and oncologists to integrate IANC into the primary treatment
is based on the lack of long-term survival data, chemotoxicity, and the desire to
preserve the globe. In addition, fewer data are available regarding systemic
therapy in the locally advanced setting, with less than 10% of patients receiving
any type of chemotherapy in the largest series to date. The only evidence to
support such practice comes from case reports and is insufficient to recommend
the routine use of adjuvant chemotherapy for LGACC. Furthermore, adjuvant

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chemotherapy has not been shown to bring additional benefits in other types of head and neck cancer [36–38].

FUTURE AVENUES
Guidelines defining therapeutic approaches are lacking, due to the rarity of these tumors. Surgery followed by postoperative RT in a majority of cases seems to be the mainstay of treatment to date, although there is not yet consensus on the type of surgery and postoperative RT. Several studies have shown equal survival outcome for patients treated with eye-sparing surgery compared with exenteration. Some investigators have pleaded for postoperative EBRT with photons or protons after eye-sparing surgery, whereas others advocate brachytherapy or neoadjuvant plus adjuvant intracarotid chemotherapy with cisplatin and doxorubicin in combination with exenteration and postoperative RT.

Due to morphologic and embryologic similarities, lacrimal gland tumors are treated analogously to salivary gland tumors. Lacrimal and salivary gland tumors have been treated bimodally with carbon ion RT (CIRT) in combination with IMRT or with CIRT alone based on prior experiences with high linear energy transfer RT for malignant salivary gland tumors. This approach is well known for more accurate tumor targeting due to superior dose distribution compared with photons or protons and increased biological effectiveness as well as better preservation of surrounding tissue and less toxicity. Although superior results for CIRT in the treatment of malignant salivary gland tumors of the head and neck have been shown in recent years, for lacrimal gland tumors this remains challenging, possibly due to histopathologic differences and locoregional challenges regarding surrounding organs at risk. Further studies are necessary in order to determine the outcome of this treatment approach with regard to recurrence rate and late toxicity [39].

Because approximately 50% of LGACCs have oncological mutations (such as MYB-NFIB fusion gene transcript abnormalities), gene-targeted therapies might represent an alternative option in the future [40]. Despite efforts, no viable agent targeting MYB was efficient. There is evidence, however, that targeted agents against receptor tyrosine kinases (sunitinib and dovitinib), epidermal growth factor receptor (cetuximab), and histone-deacetylases (vorinostat) may extend survival rates and have limited responses against the tumor in a small proportion of patients. There is hope that current or future studies of targeted agents may reveal clinically relevant antitumor activity to locally and systemically control the disease by preventing metastatic spread [41].

SUMMARY
Today, more orbital malignancies, such as ACC, are discovered at an earlier stage by orbital imaging studies, which allow for eye-sparing, near-total surgical excision. In cases of patients who have only minor residual tumor and good visual function of the affected eye, attempts at further excision, orbital exenteration, or external beam irradiation may be undesirable, particularly because
there is no firm evidence that they improve prognosis. There is no doubt that orbital exenteration can cause functional and psychological disability for patients. Consequently, patients often are inclined to refuse such radical surgery despite the possible risk to life. At this time, there is debate about the treatment of LGACC with regard to the survival benefit, but this review suggests that, in selected patients with lacrimal gland carcinoma, an eye-sparing approach with surgery and adjuvant RT or concurrent chemoradiotherapy may be both safe and effective while preserving cosmesis and visual function. This approach has gained traction in the recent years due to the positive impact on the quality of life of patients. Eye-sparing surgery followed by RT, however, is appropriate only for patients with less than T3 tumors, whereas patients with greater than or equal to T3 tumors have a surgical indication of orbital exenteration with bone removal and RT [29]. Various publications have reported that the ocular toxicity profile after eye-sparing surgery and RT was reasonable with good visual acuity (<20/40). Radiation retinopathy and keratitis were the most serious adverse events. Close follow-up after surgery should be undertaken to evaluate both local recurrence and radiation-related complications.

The global strategy to cure lacrimal ACC has yet to be determined. If a patient proceeds with preservative surgery and adjuvant RT, the irradiation modality and the role of IANC can be discussed. Future clinical trials with longer follow-up time, however, are fundamental to better understand the risks of locoregional recurrence and ocular adverse events associated with eye-sparing multimodality treatment of LGACC and to validate the safety and efficacy of eye-sparing approach over radical orbital exenteration.

**CLINICS CARE POINTS**

- Orbital exenteration followed by various forms of postoperative RT.
- Radical orbital exenteration (without RT) with bone removal.
- Targeted agents against receptor tyrosine kinases (sunitinib and dovitinib).

**References**


