• Review Article •

# Advances in treatment of adenoid cystic carcinoma of the lacrimal gland

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## Abstract

● Adenoid cystic carcinoma of the lacrimal gland (LGACC) is the most common type of malignant epithelial tumor of the lacrimal gland, which is characterized by a high recurrence rate, perineural invasion, and a propensity to metastasize to distant sites. Due to its unclear pathogenesis, LGACC has a poor prognosis and a high mortality rate. In recent years, a range of radiotherapy and chemotherapy have been clinically applied, leading to a shift in the treatment approach for LGACC. This article discussed the advances being made in the treatment of LGACC and provides readers with an overview of the impact of LGACC treatment modalities on patient survival and prognostic levels.

● **KEYWORDS:** lacrimal gland; adenoid cystic carcinoma; malignant epithelial tumor; chemotherapy; radiotherapy

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## INTRODUCTION

The most common primary malignant epithelial tumor of the lacrimal gland is adenoid cystic carcinoma of the lacrimal gland (LGACC), accounting for 3.8% of all primary orbital tumors and approximately 60% of all epithelial malignancies[1-3]. It is characterized by a high recurrence rate, perineural invasion, and a propensity to metastasize to distant sites, leading to a significant mortality rate. Since there is currently no universally accepted standard for treating LGACC, orbital exenteration is the most common treatment used to radical cure and lower the recurrence rate. However, this surgical method is controversial both locally and globally due to its negative impacts on the patient's quality of life and aesthetic appearance[2-3]. Therefore, exploring additional efficacious therapy strategies for LGACC is essential. This review aims to evaluate the development, effectiveness, and side effects of several treatment approaches for LGACC based on relevant literature (Figure 1).

## SURGICAL THERAPY

Patients with LGACC were treated with non-operative radiotherapy in the early 1930s, however, the therapeutic outcomes were unsatisfactory, and high radiation doses near the eye might be harmful. Consequently, eye-sparing surgery was undertaken in the clinic in the 1950s, but local recurrences were not adequately managed. Because of the very poor prognosis associated with LGACC, orbital exenteration was frequently employed as a conventional therapeutic approach[2-3]. However, with the advent of adjuvant therapy, eye-sparing surgery is being reconsidered as a surgical option that improves patients' quality of life in comparison to orbital exenteration. Still, long-term results of eye-sparing surgery combined with adjuvant radiotherapy require further investigation.

### Relationships Among Histologic Subtypes, American Joint Committee on Outcome, and Chosen Treatment Modalities

The TNM staging for LGACC primarily follows the Eighth Edition American Joint Committee on Cancer (AJCC) Cancer Staging Manual, which has established itself as the standard for categorizing cancer patients, establishing prognoses, and choosing the most effective treatment modalities (Table 1). This staging system helps create personalized treatment plans for patients with LGACC[4].

Han *et al*[3] reported 10 cases of LGACC confined to the orbit, with no evidence of spread to adjacent bone marrow or other organs. All patients underwent eye-sparing surgery. Over a median follow-up period of 89.5mo, one recurrence and one death (unrelated to LGACC) were observed, suggesting that eye-sparing surgery combined with adjuvant radiation therapy may be a viable option for orbit-confined LGACC. Additionally, the literature indicates that two patients who declined postoperative radiation had local recurrence, highlighting the significance of radiotherapy.

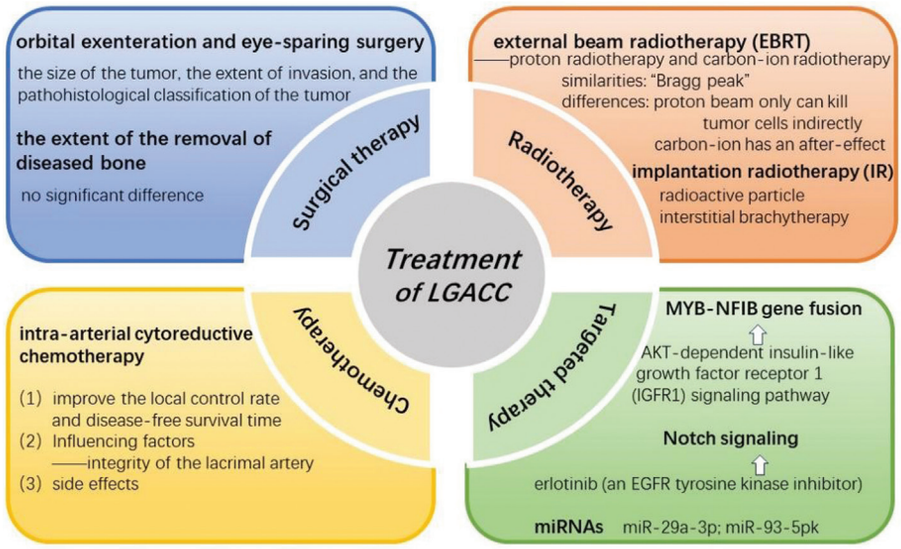


**Figure 1 Treatments of LGACC** LGACC: Adenoid cystic carcinoma of the lacrimal gland.

**Table 1 AJCC stage (8th edition) TNM stage of lacrimal gland carcinoma**

| T | Primary tumor |
|---|---|
| Tx | Primary tumors cannot be assessed |
| T0 | There is no evidence of a primary tumor |
| T1 | Tumor ≤2 cm in greatest dimension |
| T1a | No periosteal or osseous invasion |
| T1b | Tumor invades the periosteum |
| T1c | Tumor invades the periosteum or bone |
| T2 | Tumor larger than 2 cm but not larger than 4 cm in greatest dimension |
| T2a | No periosteal or osseous invasion |
| T2b | Tumor invades the periosteum |
| T2c | Tumor invades the periosteum or bone |
| T3 | Tumor larger than 4 cm in greatest dimension |
| T3a | No periosteal or osseous invasion |
| T3b | Tumor invades the periosteum |
| T3c | Tumor invades the periosteum or bone |
| T4 | Tumor invades adjacent tissues, including sinuses, temporal fossa, pterygoid fossa, supraorbital fissure, cavernous sinus, and brain tissue |
| T4a | Tumor ≤2 cm in greatest dimension |
| T4b | Tumor larger than 2 cm but not larger than 4 cm in greatest dimension |
| T4c | Tumor larger than 4 cm in greatest dimension |
| N | Regional lymph nodes |
| Nx | Regional lymph nodes cannot be assessed. |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| M | Distant metastasis |
| Mx | Distant metastasis cannot be assessed. |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

While evidence supports that eye-sparing surgery with adjuvant radiotherapy has lower mortality and recurrence rates, it is still not a substitute for orbital exenteration. Hung *et al*[5] followed 11 patients with LGACC for a long period over a median follow-up time of 7.2y. Of these, eight patients had T1 or T2 stage diagnoses, while three had T3 or T4 stage diagnoses. All patients received eye-sparing surgery as initial treatment, and most received adjuvant chemotherapy. The median disease-free interval was 23.5mo, and 6 patients experienced local recurrence, and 6 patients developed distant metastases. The 5- and 10-year overall survival rates were 81.8% and 68.2%, respectively. The study also revealed that patients in different stages showed significant differences in both overall survival and disease-free survival.

For T1 and T2 tumors, eye-sparing surgery offers comparatively optimal disease control while preserving the eye and maintaining psychological well-being. However, preventing metastasis and mortality remains challenging for T3 and more advanced tumors[5], and orbital exenteration reduces recurrence compared to eye-sparing surgery[6]. To determine whether the AJCC classification at presentation correlates with the type of treatment chosen, Ahmad *et al*[7] followed 53 patients with LGACC over a median of 94mo. None of the patients with <T3 tumors treated with eye-sparing surgery had local recurrence during the study period. In contrast, patients with ≥T3 tumors had a higher recurrence rate with eye-sparing surgery than orbital exenteration.

With advances in radiation techniques, chemotherapy, and targeted therapies, the recurrence rate of local tumor resection is decreasing. However, many patients are unwilling to accept the poor cosmetic outcomes of orbital exenteration. For patients with T3 and some T4 stages, eye-sparing surgery may be considered if the tumor can be resected in toto, optic nerve and extraocular muscle function are preserved, and the patient is willing to accept the high risk of recurrence.

Liu *et al*[8] found that the histological subtype of adenoid cystic carcinoma (ACC) was related to bone destruction and

prognosis in surgery combined with radiation therapy. Tumors with tubular or cribriform subtypes had a better prognosis, while basaloid subtype had a worse prognosis and were more prone to recurrence. Similar conclusions were made by Hung *et al*[5] regarding local recurrence, distant metastasis, and overall survival. These findings suggest that the histological subtype should be considered when deciding on surgery and its impact on prognosis.

In summary, the size of the tumor, the extent of invasion, and the histological subtype of the tumor should be considered when choosing between orbital exenteration and eye-sparing surgery to determine the extent of the surgical resection. Additionally, ocular side effects from radiotherapy should be monitored in patients receiving eye-sparing surgery followed by radiotherapy[5,7]. Post-surgery monitoring is essential to detect complications early and take appropriate actions.

**Whether the Bone Wall of the Lacrimal Fossa is Routinely Removed During Surgery** The wall of the orbital bone serves as both the most intrusive and frequent component of the LGACC and the natural barrier of the human body. The bony orbit is a cavity made up of seven bones. It is challenging to surgically remove tumor tissue that has invaded the bone wall, and the few remaining tumor cells will cause recurrence.

There has always been controversy about the extent of the removal of diseased bone. Some researchers believe that extensive removal of the lacrimal fossa bone flap is crucial in managing advanced LGACC[9], though others report that orbital enucleation combined with lacrimal fossa bone flap removal is ineffective in preventing recurrence and leads to extensive tumor infiltration of orbital structures[10]. The authors concluded that in cases where the orbital wall bone is unaffected, a lateral orbital wall incision may risk spreading to extra-orbital tissues post-surgery.

Rose *et al*[11] counted 53 cases of LGACC. Eight patients had orbital exenteration with the removal of the local orbital bone, and 32 patients had local tumor resection with radiotherapy. The results showed that there was no significant difference in overall survival, disease-free survival, recurrence, and metastasis rates between the two treatment modalities[11]. The authors propose that for patients with LGACC whose tumors infiltrate the orbital wall bone, the surgical management may involve administering radiotherapy prior to surgery to facilitate tumor reduction. During the surgical intervention, the visible tumor tissue, along with a margin of adjacent normal tissue, should be excised. Furthermore, a thorough examination of the adjacent bone wall is essential, and any suspected diseased bone should be occluded and cauterized. Postoperatively, local radiotherapy should be administered to diminish the risk of tumor recurrence.

## RADIOTHERAPY

Although surgical resection can be effective in certain scenarios, challenges such as postoperative complications and tumor recurrence underscore the increasing significance of radiation as a primary or adjunctive treatment option.

Previous studies have demonstrated that most ACC respond well to radiotherapy[12-18]. However, reliance solely on radiotherapy cannot effectively manage disease recurrence and metastasis. Therefore, the incorporation of radiotherapy as an adjuvant treatment following surgical resection is crucial for reducing the risk of tumor recurrence. There are mainly two types of radiotherapy for LGACC: implantation radiotherapy (IR) and external beam radiotherapy (EBRT). Both are employed as adjuvant treatments in clinical practice. During the treatment process, it's essential to monitor for complications such as eyelid erythema, retinopathy, and fundus hemorrhage[8].

**Proton Beam Radiation** A notable form of EBRT is proton radiotherapy, which utilizes a cyclotron or synchrotron to accelerate hydrogen nuclei, resulting in a significant release of energy that damages the DNA of target cells, ultimately leading to cell death. In addition, the proton beam possesses unique physical characteristics, slowing down abruptly upon reaching the cancer cells, creating a distinctive dose peak known as the "Bragg peak". This property allows for precise dose distribution, thereby protecting critical structures such as the optic nerve or eyeball[19].

Emma *et al*[17] detailed the methodology and outcomes of proton radiation therapy in this cohort, reporting a low recurrence rate and high survival rates during follow-up, suggesting its viability as an adjuvant treatment for epithelial tumors of the orbit and ocular appendages. Esmaeli *et al*[20] observed comparable ocular toxicity levels and local control rates.

Given the irregular shape of the target volume and the necessity for high doses amidst surrounding critical structures, LGACC presents an ideal clinical scenario for leveraging the advantages of proton irradiation. Previous studies have confirmed the efficacy of high-dose proton beam therapy[15]. Lesueur *et al*[1] reported favorable prognostic outcomes for 15 patients with LGACC, indicating that high-dose adjuvant proton beam radiation was well tolerated, associated with low levels of acute dermatotoxicity, and achieved good local control rates.

However, potential side effects, including dry eye, severe corneal and conjunctival damage, cataracts, radiation retinopathy, radiation optic neuropathy, and radiation-induced brain necrosis, highlight the associated risks of this treatment modality[1,15]. To mitigate radiotherapy-related complications,

careful control of radiation doses is imperative, and patients may benefit from preventive medications aimed at enhancing microcirculation and nourishing nerves throughout the radiation therapy process.

**Carbon-ion Radiotherapy** Carbon ion therapy employs a heavy particle beam characterized by superior physical dose distribution, akin to protons, yet with a narrower Bragg peak width and steeper dose gradients. The greater biological efficacy confers significant antitumor effects, making it suitable for cancer treatment[21].

To evaluate the safety and efficacy of carbon-ion radiotherapy (CIRT) for locally advanced or postoperative recurrent epithelial carcinoma of the lacrimal gland, Mizoguchi *et al*[18] monitored 21 participants, 16 of whom had LGACC. Participants were categorized into three groups: a low-dose (LD) group, a high-dose minimal-margin (HDMM) group, and an extended-margin group (HDEM). Results indicated that HDEM is appropriate for treating epithelial carcinoma of the lacrimal gland concerning tumor control, although some patients experienced neovascular glaucoma.

Regarding normal tissue toxicity, while vision loss and neovascular glaucoma occurred in some patients, these complications were less burdensome than the morbidity associated with orbital exenteration. The eyeball preservation rate was 90.5%, suggesting that CIRT can maintain patients' appearance and enhance postoperative quality of life compared to orbital exenteration. These findings indicate that CIRT represents a promising approach for treating lacrimal epithelial carcinoma[18].

Due to fewer Coulomb interactions and sharper lateral penumbra, some researchers suggest that CIRT may offer superior protection for surrounding structures compared to proton therapy[16]. Conversely, proton beams primarily induce tumor cell death indirectly by disrupting DNA single strands, making them less effective for treating radiation-resistant and hypoxic tumors. In contrast, carbon ions possess substantial mass, allowing them to target hypoxic regions of tumors, a phenomenon referred to as the "after-effect"[22]. The prognostic implications of these two modalities for LGACC warrant further investigation, and some researchers aim to compare the prognostic impacts of carbon ion therapy with conventional radiotherapy for treating radiation-resistant tumors in the ongoing ETOILE trial[23].

**Iodine-125 Interstitial Brachytherapy** IR has become an increasingly utilized treatment modality for certain intraocular and orbital malignancies, employing radioactive particles such as strontium-90 (Sr-90), ruthenium-106 (Ru-106), or iodine-125 ($^{125}$I). Ocular malignancies were first treated with $^{125}$I ion radiotherapy in 1976 by Sealy *et al*[24]. Subsequent studies have explored the effects of these radioactive particles on various eye cancers. For instance, Wang *et al*[12] reported the successful use of $^{125}$I IR in four patients with malignant lacrimal sac tumors, including one case with ACC. All patients had disease control and maintained stable vision, supporting the efficacy of this treatment approach.

The technique of IR involves the implantation of small radioactive sources either permanently or temporarily into the tumor tissue or its vicinity. This source has the unique property that the radiation dose is inversely proportional to the square of the distance, allowing for maximum destruction and injury to the tumor tissues while minimizing damage to normal tissues. Compared to conventional external beam radiation, IR offers several advantages: it avoids recurrence caused by the radiation gaps between traditional therapy sessions and ensures more effective dose delivery, reducing the risk of insufficient irradiation that can lead to tumor recurrence or metastasis. As advancements in equipment and technology continue, IR is becoming more widely applied in clinical settings[25].

Regarding the comparison between IR and EBRT, the two radiation treatments for LGACC, multiple studies concluded that both modalities offer similar prognostic outcomes and do not differ significantly in effectiveness[13,26].

Liu *et al*[13] examined the results of $^{125}$I seed radiotherapy and localized γ-ray radiotherapy combined with surgical resection. With a median age of 42y and a mean follow-up period of 30mo following radiotherapy, the study examined the clinical records of 27 primary patients and 8 recurrent LGACC patients. Among these patients, 26 were treated with $^{125}$I seed radiotherapy, and 9 were treated with localized γ-ray radiotherapy. At the final follow-up, 8 patients (31%) in the $^{125}$I group and 3 patients (33%) in the γ-ray group experienced local recurrence, while 6 patients (23%) in the $^{125}$I group and 1 patient (11%) in the γ-ray group experienced distant metastasis. The finding showed that both radiotherapy methods have similar effects on preventing local recurrence and distant metastasis, but are associated with complications such as dry eye and vision loss, emphasizing the need for postoperative monitoring and management of side effects.

Li *et al*[14] reported similar findings, showing no significant differences between EBRT and IR regarding local control, regional lymph node metastasis control, or distant metastasis.

However, a study by Yan *et al*[26] indicated that IR might offer superior therapeutic outcomes compared to EBRT. This discrepancy may be due to the fact that IR studies typically focus on high-dose radiation, while EBRT involves both high-dose and LD radiation.

**Conclusion** All three radiotherapy modalities discussed in this article effectively managed disease prognosis. However, according to the literature, no significant difference was

observed in the prognostic impact of these modalities on LGACC. Future long-term follow-up studies should be undertaken to assess radiotherapy-related complications, which may potentially offer new insights.

## INTRA-ARTERIAL CYTOREDUCTIVE CHEMOTHERAPY

To improve the survival rate of LGACC, chemotherapy warrants consideration as an adjunctive therapeutic modality alongside radiation therapy in the comprehensive treatment paradigm. Chemotherapy is one of the most important modalities for the treatment of malignant tumors. Cisplatin and adriamycin are the predominant chemotherapeutic agents for LGACC, while apatinib and nedaplatin have demonstrated efficacy in select cases[27]. Intra-arterial cytoreductive chemotherapy (IACC) has emerged as a promising neoadjuvant chemotherapy strategy for LGACC, with literature indicating its effectiveness in enhancing local control rates and prolonging disease-free survival[28].

Meldrum *et al*[29] first introduced IACC as a neoadjuvant chemotherapeutic approach in clinical practice in 1998. This multimodal treatment regimen incorporates three key components: chemotherapy, orbital exenteration, and radiotherapy. The principal element is IACC, which involves administering high-concentration chemotherapeutic agents directly to the tumor *via* an intact lacrimal artery prior to surgical intervention, with the aim of reducing tumor bulk and optimizing surgical outcomes. Previous investigations have demonstrated that this therapeutic approach improves disease-free survival and local disease control[30]. IACC now represents an additional therapeutic option for patients with LGACC, particularly those at high risk for recurrence.

To evaluate the therapeutic efficacy of IACC, Costa *et al*[31] analyzed 99 LGACC cases, comparing 35 patients who received preoperative IACC with 64 who underwent conventional therapy. Their findings revealed a 40% reduction in mortality risk among patients receiving preoperative IACC, indicating substantial improvement in prognosis.

Following a long-term follow-up, Tse *et al*[28] subsequently corroborated these results, demonstrating superior outcomes in overall survival, disease-specific mortality, and recurrence results for patients receiving IACC compared to conventional treatment. Further stratification of IACC patients based on lacrimal artery integrity revealed that while disease-specific mortality rates remained comparable between groups, patients with intact lacrimal artery exhibited improved overall survival and reduced recurrence rates.

Yu *et al*[32] employed genome sequencing and apoptotic marker analysis before and after treatment to precisely assess IACC efficacy. Their data revealed reduced variant allele frequencies of mutated genes following therapy, further supporting IACC's clinical significance. Yan *et al*[26] reported similar findings, though the limited sample size necessitates cautious interpretation.

The high toxicity of chemotherapeutic agents necessitated vigilant monitoring for adverse effects during IACC administration. Yan *et al*[26] documented five cases of febrile neutropenia attributed to arterial cannulation, one case of blindness resulting from ocular arterial embolization, and one case of eyelid necrosis.

Liao *et al*[33] examined histopathologic changes in ocular structures post-treatment to evaluate IACC's potential for damaging the eye or critical extraocular structures. Their findings established that both orbital vasculature integrity and the method of chemotherapeutic drug infusion significantly influence prognostic outcome. An intact lacrimal artery facilitates maximal perfusion dosing and tumor volume reduction during preoperative IACC, while minimizing drug perfusion into branch arteries and reducing the risk of toxic complications, including ophthalmic artery occlusion, ophthalmoplegia, and choroidal and retinal hemorrhage.

Moreover, Tse *et al*'s[34] research highlighted concerns regarding ocular thrombosis risk with internal carotid artery (ICA) infusion, which Liao *et al*'s[33] study suggested advantages of external carotid artery (ECA) infusion over ICA delivery. Researchers postulate that administration *via* the lacrimal artery through ECA circulation minimizes ocular adverse effects.

Overall, evidence supports the efficacy of IACC in improving patient prognosis, though it is associated with additional prognostic complications. Preservation of orbital blood vessels and optimal delivery of chemotherapeutic agents contribute to minimizing side effects. Therefore, to mitigate the risk of side effects, patients undergoing IACC require diligent monitoring and long-term follow-up. Further research on the treatment and prognosis of IACC is needed.

## TARGETED THERAPY

Research into the molecular mechanisms of LGACC suggests the possibility of utilizing molecularly targeted therapies to reduce mortality from the disease.

A key feature of ACC is the fusion of the proto-oncogene MYB with the transcription factor NFIB. This specific genetic alteration is useful diagnostic evidence for ACC[35]. The MYB fusion protein exhibits pronounced oncogenic potential due to the elevated expression of MYB resulting from this fusion event. This upregulation is believed to drive the oncogenic processes in ACC. Figure 2 illustrates the MYB-NFIB gene fusion and its downstream biological consequence[35].

The most common MYB-NFIB fusion involves the t (6; 9) (q23; p23) translocation, which has been suggested by several studies as a possible therapeutic target. However, due to the

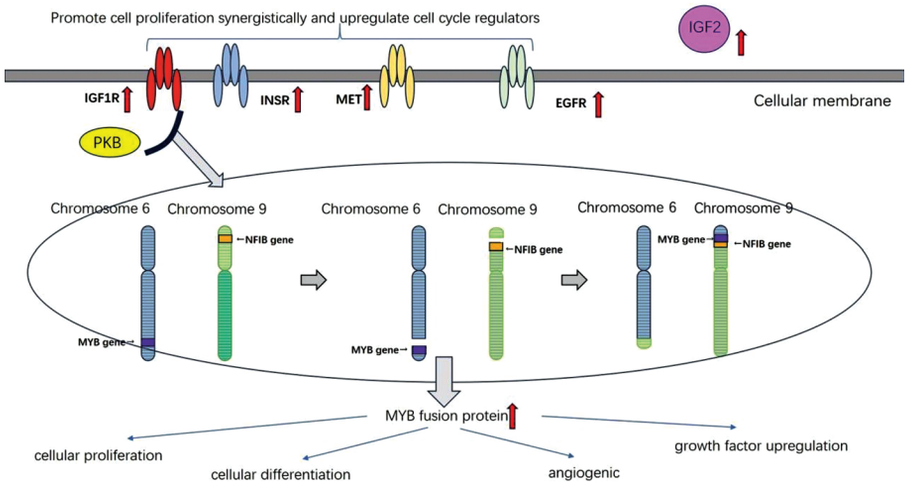


**Figure 2 The ACC cell line exhibits high activation of IGF2, IGF1R, INSR, MET, and EGFR** Targeting EGFR, MET, and IGF1R/INSR together can upregulate cell cycle regulators and synergistically enhance cell proliferation. IGF1R regulates MYB-NFIB in an AKT-dependent way. The fusion causes the MYB fusion protein to be significantly upregulated, which in turn triggers several carcinogenic processes. EGFR: Epidermal growth factor receptor; ACC: Adenoid cystic carcinoma; IGFR1: Insulin-like growth factor receptor 1; PKB: Protein kinase B.

lack of well-characterized ACC cell lines with MYB-NFIB fusions, research in this area remains limited[35]. Andersson *et al*[36] found that the protein kinase B (PKB)-dependent insulin-like growth factor receptor 1 (IGFR1) signaling pathway regulates the MYB-NFIB fusion, offering a potential therapeutic target to block the IGF1R/PKB signaling pathway (Figure 2).

Furthermore, Notch signaling is crucial for the normal development of the lacrimal gland. Four transmembrane receptors (Notch1, 2, 3, and 4) and two types of Notch ligands [Jagged-1, 2 and Delta-like (DLL-1, 3, 4)] make up Notch signaling. Cell-to-cell contact *via* interaction between notch receptors and their ligands is necessary for the activation of notch signaling[37]. Sant *et al*[38] employed whole-exome sequencing to identify mutations in LGACC and found that Notch mutations were present in 31% of patient samples. Mutations in the NOTCH gene were observed in the heterodimerization structural domain, the intracellular structural domain, and epidermal growth factor (EGF)-like repetitive sequences[39]. Nie *et al*[40] applied erlotinib (an EGFR tyrosine kinase inhibitor) to the clinic with efficacy has further supporting that the Notch signaling pathway is a potential therapeutic target for LGACC.

Several studies suggest that miRNAs play an important regulatory role in tumor progression. Xu *et al*[41] reported that miR-29a-3p can specifically downregulate the expression of the Quaking protein, thereby inhibiting the proliferation, migration, and epithelial-mesenchymal transition of LGACC cells. In contrast, Hao *et al*[42] reported that miR-93-5p could regulate the Wnt signaling pathway, thereby specifically down-regulating the expression of the *BRMS1L* gene and promoting epithelial-mesenchymal transition, migration, and invasion of LGACC cells. These findings suggest the potential application of miRNAs as therapeutic targets in the study of LGACC.

Other related molecules, such as hypoxia-inducible factor-1α, vascular endothelial growth factor[43-44], along with various signaling pathways, may also serve as potential therapeutic targets.

## DISCUSSION

This paper provides a comprehensive review of the therapeutic strategies and prognostic outcomes associated with LGACC, aiming to inform the selection of clinical treatment options (Table 2). While conventional treatment involving surgery combined with radiotherapy has demonstrated favorable prognoses in early-stage patients, it falls short in controlling recurrence and metastasis in advanced-stage cases. Given the high mortality and poor prognosis of LGACC, novel treatment strategies are urgently needed. IACC and targeted therapies may present new avenues for management, necessitating close follow-up to monitor patient outcomes and manage potential side effects. A deeper understanding of the molecular mechanisms underlying LGACC is also critical. The limited prevalence of LGACC constrains the existing literature, which is marked by small sample sizes and low levels of evidence. Therefore, multicenter randomized controlled trials with larger cohorts are warranted to establish more definitive treatment guidelines.

Currently, there is no standard treatment protocol for LGACC; thus, a multidisciplinary approach is essential for improved outcomes. Researchers are encouraged to better align their findings with clinical challenges to tackle the complexities of diagnosing and treating lacrimal gland malignancies, ultimately striving for patient-centered, personalized, and precise interventions to enhance survival rates.

**Table 2 Reported case series of systemic therapies for LGACC**

| Author | Year | Sample size | Mean age, y (range) | Treatment | Outcomes | Median follow-up (mo) |
|---|---|---|---|---|---|---|
| Bonavolontà *et al*[2] | 2020 | 46 LGACC | 53 (11–81) | Orbital exenteration for 14 pts<br>Eye-sparing surgery for 32 pts | 8 deaths in orbital exenteration group (63% related to LGACC)<br>17 deaths in eye-sparing surgery group (53% related to LGACC)<br>10 recurrences in the orbital exenteration group<br>16 recurrences in the eye-sparing surgery group | 2.7y |
| Han *et al*[3] | 2018 | 10 LGACC | 42.4 (17–67) | Eye-sparing surgery with radiation | 1 recurrence<br>1 death (unrelated to LGACC) | 89.5 |
| Hung *et al*[5] | 2019 | 11 LGACC (8≤T2; 3≥T3) | 43.6 (20–86) | Eye-sparing surgery | 6 recurrence, 6 distant metastases<br>5-year overall survival 81.8%<br>10-year overall survival 68.2% | 7.2y |
| Ahmad *et al*[7] | 2009 | 38 LGACC (≥T3) | 40.4 (10–79) | Orbital exenteration for 26 pts<br>Eye-sparing surgery for 12 pts | 7 recurrences in the orbital exenteration group<br>8 recurrences in the eye-sparing surgery group | 94 |
| Rose *et al*[11] | 2019 | 79 lacrimal gland carcinoma (53 LGACC ) | 48 (13–84) | Orbital exenteration for 9 pts<br>Eye-sparing surgery for 44 pts | There was no significant difference in overall survival, disease-free survival, recurrence, and metastasis rates between the two treatment modalities. | 4.7y |
| Holliday *et al*[17] | 2016 | 7 ACC | Not given | Orbit-sparing surgery and proton therapy | No local recurrence | 27.1 |
| Esmaeli *et al*[20] | 2016 | 7 LGACC (4≤T2; 3≥T3) | 49.7 (24–65) | Eye-sparing surgery with radiation | Disease free | 33 |
| Wolkow *et al*[15] | 2019 | 18 LGACC | 40 | Surgical resection and proton beam radiation | 3 deaths (from metastatic disease)<br>4 local recurrences | 12.9y |
| Lesueur *et al*[1] | 2020 | 15 LGACC | 43 (23–68) | High-dose adjuvant proton irradiation | 3y overall survival 78%, 8 recurrences | 67.4 |
| Damico *et al*[19] | 2021 | 17 patients with tumor epicenters within 2 cm of the eye and optic apparatus | 67 | Surgical resection and proton beam radiation | The 18-month cumulative incidence of local failure was 19.1%<br>1-year overall survival was 80.9% | 19.7 |
| Mizoguchi *et al*[18] | 2015 | 16 LGACC | Not given | Carbon-ion radiotherapy | The three-year overall survival rate was 82.2%<br>The three-year local control rate was 79.0% | 42 |
| Hu *et al*[21] | 2025 | 28 LGACC | 35 (16–74) | Eye-preserving treatment and particle beam radiotherapy | 5-year disease-specific survival, local control rate, distance metastasis control rate, progression-free rates were 89.3%, 60.1%, 66.3%, 52.9% | 40.7 |
| Wang *et al*[12] | 2020 | 1 LGACC | - | $^{125}$I interstitial brachytherapy | Disease free | - |
| Liu *et al*[13] | 2021 | 35 LGACC | 42 (17–61) | $^{125}$I seed radiotherapy for 26 pts<br>localized γ-ray radiotherapy for 9 pts | 8 recurrences, 6 distant metastases in the $^{125}$I seed radiotherapy group<br>3 recurrences, 1 distant metastasis in the localized γ-ray radiotherapy group | 36 |
| Li *et al*[14] | 2021 | 114 primary ACC of the oral and maxillofacial region | 48 (18–74) in Group 1<br>45 (26–76) in Group 2 | Group 1: brachytherapy for 75 pts<br>Group 2: EBRT for 39 pts | The prevalence of local control at 3y and 5y:<br>Group 1: 90% and 78.8%<br>Group 2: 91.5% and 84.8%<br>The prevalence of control of regional lymph node metastasis at 3y and 5y:<br>Group 1: 94.3% and 89.2%<br>Group 2: 94% and 94%<br>Distant metastasis:<br>Group 1: 20%; Group 2: 53.8%<br>Overall survival at 3y and 5y:<br>Group 1: 86% and 79.6%<br>Group 2: 84.4% and 74.9% | 66.1 in group 2<br>46.8 in group 1 |
| Costa *et al*[31] | 2024 | 99 LGACC | Not given | IACC for 35 pts<br>excision therapy for 64 pts | The 5- and 10-year disease-specific survival rates for patients treated with IACC were 84% and 76%<br>The 5- and 10-year disease-specific survival rates for the population-based cohort were 72% and 46% | Not given |
| Tse *et al*[28] | 2022 | 19 LGACC | Not given | IACC | Group 1 (intact lacrimal artery):<br>cumulative proportions surviving at 10 and 15y are 87.5% and 87.5%<br>Group 2 (incomplete lacrimal artery):<br>cumulative proportions surviving at 10 and 15y are 63.6% and 34.1% | Not given |
| Manjandavida *et al*[30] | 2022 | 40 LGACC | 36 (11–72) | Group 1: surgery+EBRT for 20 pts<br>Group 2: surgery+EBRT+adjuvant chemotherapy for 8 pts<br>Group 3: neoadjuvant chemotherapy+surgery+EBRT+adjuvant chemotherapy for 20 pts | Failure-free survival for local tumor recurrence at 3y and 6y:<br>Group 1: 92% and 62%<br>Group 2: 75% and 75%<br>Group 3: 85% and 85%<br>Failure-free survival for systemic metastasis at 3y and 6y:<br>Group 1: 83% and 46%<br>Group 2: 87% and 87%<br>Group 3: 95% and 95% | 60 (29–180) |

LGACC: Adenoid cystic carcinoma of the lacrimal gland; ACC: Adenoid cystic carcinoma; IACC: Intra-arterial cytoreductive chemotherapy; EBRT: External beam radiotherapy.

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