An Update on Tumors of the Lacrimal Gland

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Abstract: Lacrimal gland tumors are rare and constitute a wide spectrum of different entities ranging from benign epithelial and lymphoid lesions to high-grade carcinomas, lymphomas, and sarcomas with large differences in prognosis and clinical management. The symptoms and findings of a lacrimal gland lesion are a growing mass at the site of the lacrimal gland, including displacement of the eyeball, decreased motility, diplopia, and ptosis. Pain is the cardinal symptom of an adenoid cystic carcinoma. Radiological findings characteristically include an oval, well-demarcated mass for benign lesions whereas malignant lesions typically display calcifications, destruction of bone, and invasion of adjacent structures. The diagnosis ultimately relies on histology, as does the choice of treatment and the prognosis. In recent years, the understanding of the biology of various types of lacrimal gland neoplasia has improved and the choice of treatment has changed accordingly and holds further promise for future targeted therapies. Treatment of benign epithelial lesions is surgical excision whereas carcinomas often require adjuvant radiotherapy and/or chemotherapy. In contrast, the cornerstone in management of lymphoid lesions is chemotherapy, often including a monoclonal antibody. This article presents an update on the clinical, radiological, histological, and molecular features, along with treatment strategies for tumors of the lacrimal gland.

Key Words: lacrimal gland, carcinoma, lymphoma, treatment, prognosis

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Epithelial Tumors of the Lacrimal Gland

Distribution

Epithelial tumors are the most common tumors of the lacrimal gland, constituting approximately 50–60% of all benign tumors and 40–50% of all malignant tumors.1,3 Pleomorphic adenoma is the most common tumor encountered, representing ~20% of all lacrimal gland tumors. Other benign epithelial tumors include oncocytoma (see below), myoepithelioma, and Warthin tumor; however, these are extremely rare.4 The most common malignant epithelial tumor is adenoid cystic carcinoma, comprising ~20–30% of all malignant lacrimal gland tumors. Carcinoma ex pleomorphic adenoma accounts for ~10%, adenocarcinoma not otherwise specified (NOS) ~5–10%, and mucoepidermoid carcinoma ~2% of all malignant lacrimal gland tumors.5 Additional malignant epithelial tumors are rare and include, among others, ductal carcinoma, oncocytic carcinoma, and neuroendocrine carcinoma (see below).6 Other very rare epithelial malignant tumors of the lacrimal gland have been listed in Table 1.

Pleomorphic Adenoma, Carcinoma Ex Pleomorphic Adenoma, and Adenoid Cystic Carcinoma

Molecular and Genetic Characteristics

It has recently been demonstrated that epithelial tumors of the lacrimal gland are characterized by a recurrent tumor-specific pattern of genetic alterations that may be of use diagnostically but also in the future as targets for therapy.5,7 The most promising alteration is perhaps the fusion oncogene MYB-NFIB found in the majority of adenoid cystic carcinomas.8,9 The MYB-NFIB fusion arises as a consequence of a translocation between chromosome 6 and 9 t(6;9)(q22-23;p23-24).8 As a result of the fusion the MYB oncogene is activated. The proto-oncogene MYB is a transcription factor gene that regulates thousands of genes critical for cancer development including cell growth, transcription regulation, apoptosis, and cell cycle control.10 MYB is not expressed in normal glandular cells, but MYB RNA and protein is highly expressed in adenoid cystic carcinoma (Fig. 1).4,8 In addition, it has been demonstrated that a number of well-known MYB target genes are also highly expressed on the protein level.4 Taken together this strengthens the notion that MYB activation is a hallmark of adenoid cystic carcinomas and a key event in the oncogenic process. In the majority of cases, MYB activation is caused by the MYB-NFIB fusion; however, other mechanisms for MYB activation exist, such as selective gain at the MYB locus.4 Expression of MYB-NFIB is not only found in adenoid cystic carcinomas of the lacrimal gland but has been demonstrated in adenoid cystic carcinomas of many different anatomical locations.8,9 Studies of copy number alterations have confirmed additional similarities between lacrimal and salivary gland tumors, including recurrent gains involving regions at 6q, 8q, 11q, and 19q and losses involving...
regions at 6q12q and 17p along with aberrances in cytokine signaling.6,11–13 The target genes, and thereby functional consequence of these alterations, remain to be investigated.

Extensive studies of pleomorphic adenoma of the salivary glands have revealed that these tumors may be divided into 4 major subgroups based on their cytogenetic appearance.14 One group have alterations involving 8q12, corresponding to the oncogene PLAG1 (pleomorphic adenoma gene 1). The proto-oncogene PLAG1 is a transcription factor gene normally not expressed in adult tissue. Overexpression of PLAG1 has been demonstrated in a number of different tumors in addition to pleomorphic adenoma. In salivary gland tumors, the 8q12 rearrangement is typically involved in a translocation resulting in the creation of fusion oncogenes in which the PLAG1 gene is overexpressed due to promoter swapping with a number of different genes including CTNNB1, LIFR, TCEA1, CHCHD7, or FGFR1.14 Studies of pleomorphic adenomas of the lacrimal gland have demonstrated that these too have high expression of the PLAG1 protein and also translocations involving 8q12, but evidence of the specific involvement of the PLAG1 gene on this locus has not been reported.5,15 The second subgroup involves tumors with rearrangements of 12q14-15. These rearrangements typically result in similar fusions but this time it is the 3' end of HMG2A that is replaced by the 3' end of a number of different genes including WIF1, FHIT, and NFIB.14 Studies of lacrimal gland tumors have demonstrated that a small subgroup also have a high expression of HMG2A protein.3 The last 2 subgroups contain tumors with nonrecurrent changes and tumors with an apparently normal karyotype. Studies of copy number alterations in lacrimal gland pleomorphic adenoma have demonstrated similar large subgroups with none or very few genomic alterations.3

Much remains unknown regarding genetic alterations important for the oncogenic process in carcinoma ex pleomorphic adenoma. In salivary gland tumors, alterations such as amplification

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*Not all histological entities will be described in this review.
†This tumor is of myeloid origin despite its designation as a sarcoma and is listed under mesenchymal tumors due to its mesodermal origin.
of HER2 and 12q (MDM2 in particular), along with gains involving PLAG1 and MYC, have been suggested. Many authors have also pointed to loss of 17p corresponding to the well-known tumor suppressor gene TP53. In carcinoma ex pleomorphic adenoma of the lacrimal gland, recurrent gains involving NFIB and PDGFB have been demonstrated; however, more studies are needed before any clear conclusions can be drawn.

Molecularly, epithelial tumors of the lacrimal gland are very similar to epithelial tumors of the salivary glands. Because the tumors are so rare, extrapolating treatment regimens from tumors from other locations is often necessary in advanced stages of the disease. Knowing that the tumors are molecularly similar further validates this extrapolation. In addition, the fusion oncogenes such as MYB-NFIB and CRTC1-MAML2 represent diagnostic markers and potential therapeutic targets in the future.

**Clinical Characteristics**

All patients with a lacrimal gland tumor present with one or more symptoms relating to a growing tumor mass at the site of the lacrimal gland. The findings are displacement of the eyeball typically medially and downwards, decreased motility, diplopia, a palpable tumor mass, and ptosis (Figs. 1, 2). Pain is a cardinal symptom for patients with adenoid cystic carcinoma but uncommon for patients with other types of lacrimal gland tumors. The pain is caused by the perineural growth pattern characteristic of adenoid cystic carcinoma. The benign tumors typically have a history of symptoms lasting from 1–2 years before seeing a physician, whereas the malignant tumors have a more aggressive behavior and consequently a history of symptoms lasting approximately 6 months. In general, patients are middle-aged when diagnosed; however, pleomorphic adenoma may occur in children and in the elderly and the median age is 40 years. Median age for patients with adenoid cystic carcinoma is also 40 years, and for patients with other types of carcinoma it is approximately 50 years. As carcinoma ex pleomorphic adenoma is defined as a carcinoma arising in a pleomorphic adenoma, these patients may present with a history of a previous pleomorphic adenoma.

The presurgical diagnosis is made on image analysis (Figs. 1, 2). Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) can be used. Computed tomography is often preferred when evaluating a suspected pleomorphic adenoma, whereas MRI is preferred when evaluating a suspected adenoid cystic carcinoma owing to the ability of this modality to evaluate perineural spread. The typical appearance on image analysis of pleomorphic adenoma is a round to oval solid tumor with regular margins that occasionally causes bone remodeling and may have areas with calcification. Adenoid cystic carcinoma, in contrast, typically has irregular margins, appears nodular, infiltrates adjacent structures, and causes bone destruction. Characteristic features of all malignant tumors of the lacrimal gland on CT scans include irregular margins, bone erosion, and calcification. However, the final diagnosis is not made before a histological evaluation of the tumor has been performed.

**Histopathology**

Pleomorphic adenoma is characterized by epithelial and
modified myoepithelial elements that mix with mesenchymal components (Fig. 2). The epithelial component is a mixture of well-formed ductal structures and non-ductal cells that include spindle, round, stellate, plasmacytoid, oncocytoid, polygonal, and clear cells. The mesenchymal component may be myxoid, hyaline, cartilaginous, or osseous differentiation.

Carcinoma ex pleomorphic adenoma is defined as a carcinoma that shows histological evidence of arising in or from a pleomorphic adenoma (Fig. 2). Typically, residual benign pleomorphic adenoma is identified with zones of transition between the benign and malignant parts. In the majority of tumors, there is an infiltrative growth pattern and cytological atypia. The carcinomatous element can be any type of carcinoma; however, adenocarcinoma NOS and mucoepidermoid carcinoma are the most common.

Adenoid cystic carcinoma is a tumor composed of modified myoepithelial and ductal differentiated cells. It is characterized by 3 histologic growth patterns: the cribriform (“Swiss cheese”) (Fig. 1), solid, and tubular forms. The cribriform pattern is most common, whereas the solid pattern is the rarest. However, there is usually a mixture of patterns within each tumor. Adenoid cystic carcinoma is characterized by a perineural growth pattern that contributes to the symptoms and the challenges in treating the disease.

Prognosis

The prognosis for patients with pleomorphic adenoma is generally good; however, the tumors may recur locally if not removed completely. In rare cases, they may transform malignantly into carcinoma ex pleomorphic adenoma. The risk of malignant transformation has been associated with multiple recurrences and longstanding tumors, analogous to what is known from pleomorphic adenoma in the salivary glands. Traditionally, the prognosis for patients with carcinoma ex pleomorphic adenoma has been reported to be grave, but this depends on the type of the carcinoma component and the invasiveness and histological grade. Patients with adenoid cystic carcinoma continue to have a poor long-term prognosis despite many attempts to optimize treatment regimes. After 10 years, only 20–30% of patients are still alive. Patients die from distant metastasis and intracranial spread. Factors associated with a worse prognosis are a solid morphology and tumor size.

Rare Epithelial Tumors

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma of the lacrimal gland is rare, in contrast to its large proportion of malignant tumors of the salivary glands. Histologically, mucoepidermoid carcinoma is composed of 3 cellular components: epidermoid-squamous, mucous-secreting, and intermediate cells. In addition, there may be admixed columnar, clear, and oncocytic cells. Mucous-secreting cells may be large, ovoid, or goblet-shaped, possessing an abundant foamy cytoplasm. In many tumors, intracytoplasmic mucin may only be evident with the use of special stains, such as mucicarmine or Alcian blue. The World Health Organization (WHO) has defined a scoring system for mucoepidermoid carcinoma dividing the tumors into low-, intermediate-, and high-grade tumors. Only the high-grade tumors have a poor survival. Mucoepidermoid carcinoma is characterized by a recurrent...
translocation between chromosome 11 and 19 (t(11:19)(q21;p13)) in the majority of tumors. This translocation results in a fusion oncogene CRTC1-MAML2. Studies have demonstrated that the CRTC1-MAML2 fusion protein is necessary for tumor cell growth in fusion-positive tumors. CRTC1-MAML2 fusion has been demonstrated in a great number of mucoepidermoid carcinomas of different anatomical locations including the salivary glands, lung, thyroid, cervix, and the lacrimal gland (Fig. 3).

Oncocytoma and Oncocytic Carcinoma

Oncocytoma is a benign and slowly growing tumor that frequently occurs in major and minor salivary gland, kidney, thyroid, and ocular adnexa. These tumors affect patients of all ages, and the symptoms and presentation resemble those of other benign lacrimal gland tumors (Fig. 4). Microscopically, oncocytes are characterized by large polyhedral cells with fine eosinophilic granular cytoplasm. The nuclei are round and centrally located. The cells are arranged in sheets, islands, or chords, and cysts may be present (Fig. 4). The granules are composed of excessive amounts of dysfunctional mitochondria, which is the hallmark of oncocytic lesions and the cause for their historical designation as “mitochondrioma” (Fig. 4). The pathogenesis is poorly understood, and few chromosomal aberrations have been identified. Mutations in the mtDNA component of the mitochondrial respiratory complex I have been observed in oncocytes. Cytogenetic studies have never been performed on lacrimal gland oncocytes. The prognosis of lacrimal gland oncocytomas is very good, as malignant transformation has not been observed. Few cases of lacrimal gland oncocytic carcinoma have been reported, and the prognosis of these tumors is poor due to distant metastases.

Ductal Carcinoma

Ductal carcinoma was described by Katz in 1996 and has a 4:1 male predominance, primarily affecting patients in their seventh decade. Preoperative imaging frequently reveals destruction of orbital bone (Fig. 5). Ductal carcinoma is an aggressive malignancy often presenting with locally advanced disease and a mortality of more than 40%. Metastases are only rarely present at diagnosis but subsequently develop in 50% of cases. Histologically, ductal carcinoma has been described in 2 morphologic variants; the most frequent is composed of large, rounded, irregularly shaped cystic nodules of carcinoma cells with prominent central comedonecrosis (Fig. 5). Carcinoma cells with centrally located nuclei line the cystic nodules in a cribriform pattern with frequent “Roman bridge” formation and prominent apocrine features analogous to their counterpart in the salivary gland and breasts (Fig. 5). The other variant has a scirrhous morphology dominated by dense fibrous stroma with small, infiltrating, solid nests of malignant tumor cells often with lymphocytic infiltrates and perineural invasion (Fig. 5). Regardless of morphology, ductal carcinomas are frequently positive for androgen receptor (83.3%) and HER2 (66.6%) and are always negative for estrogen and progesterone receptors (Fig. 5). Ductal carcinomas have shown amplification of the HER2 gene in 75% of cases investigated. The only case genetically characterized beyond HER2 had multiple genetic aberrations including deletion and inactivating mutations of PTEN and CDKN2A, and activating mutations of HRAS.

Neuroendocrine Carcinoma

Neuroendocrine tumors are exceedingly rare and arise from neuroendocrine cells of the “diffuse endocrine system.” All

FIGURE 3. Mucoepidermoid carcinoma of the lacrimal gland. A, A 73-year-old male presented with a swelling (arrow) progressing over 6 months at the site of the left lacrimal gland. B, A CT scan demonstrated a 20 x 15 mm tumor (asterisk) at the site of the left lacrimal gland. C, Histology showed a tumor characterized by cystic spaces lined by epidermoid, intermediate, and mucous-producing tumor cells (arrowheads) consistent with the diagnosis of a low-grade mucoepidermoid carcinoma (HE staining; scale bar = 100 μm). D, Immunostaining using a custom-made antibody directed at the CRTC1-MAML2 fusion oncogene as demonstrated by the brown staining in nuclei of tumor cells (scale bar = 100 μm).
reported cases are high-grade malignancies. Two cases of lacrimal gland neuroendocrine carcinoma have been reported, both of which metastasized to parotid lymph nodes and one also to the liver.\textsuperscript{35,36} Histologically, neuroendocrine carcinoma is characterized by highly proliferative, poorly differentiated tumor cells in a characteristic rosette-like growth pattern hinting at the neuroendocrine

\textbf{FIGURE 4.} Oncocytoma of the lacrimal gland. A, A 21-year-old male presented with 5 mm exophthalmos (arrow) and displacement of the globe on the left side. B, An MRI scan demonstrated a 30 x 20 mm mass (asterisk) at the site of the lacrimal gland. C, Histology showed a noninvasive tumor consisting of large, eosinophilic tumor cells without atypia in a ductal arrangement. D, Immunohistochemical staining for the mitochondrial protein MU213-UC showing abundant cytoplasmic mitochondria, consistent with a lacrimal gland oncocytoma.

\textbf{FIGURE 5.} Ductal carcinoma of the lacrimal gland. A, A 77-year-old male presented with complaints of 2 weeks of swelling of the left upper eyelid (arrow), diplopia, xerophthalmia, and progressive exophthalmos. B, A CT scan demonstrated a 32 x 20 mm mass (asterisk) at the site of the left lacrimal gland. C, Histology showed cystic spaces (asterisks) lined by bands of carcinoma cells in a cribriform architecture. Close up of the same specimen with “Roman bridge” formation and apocrine differentiation of the luminal cells (insert) (HE staining; scale bar = 100 µm). D, Other areas of the tumor are characterized by a fibrous stroma with small, infiltrating nests of malignant tumor cells. The malignant cells had amplification of the \textit{HER2} gene as demonstrated by fluorescent in situ hybridization (upper insert) and were intensely positive for \textit{HER2} protein by immunohistochemistry (lower insert) (scale bar = 100 µm).
origin. Application of neuroendocrine markers is necessary for the diagnosis, and the reported cases were indeed CD56-positive.\textsuperscript{35,36} The genetics of lacrimal neuroendocrine carcinoma is unknown, but the salivary gland counterpart has numerous gross chromosomal aberrations.\textsuperscript{37} Merkel cell carcinoma is caused by either sunlight or infection with Merkel cell polyomavirus (MCV) and the risk is increased in immunocompromised individuals.\textsuperscript{38} Histologically, Merkel cell carcinoma is infiltrative and is composed of uniform basophilic cells with scant cytoplasm growing in sheets, trabeculae, and/or a mixture of these.\textsuperscript{39} Neuroendocrine markers are positive (CD56, synaptophysin, and/or chromogranin), and MCV has been identified in a lacrimal gland Merkel cell carcinoma.\textsuperscript{40} In other sites, Merkel cell carcinoma has an aggressive course, but the prognosis in lacrimal gland cases is currently uncertain.\textsuperscript{39}

### Treatment of Epithelial Lesions of the Lacrimal Gland

Management of epithelial lacrimal gland tumors includes surgery, and in cases of malignancy additional adjuvant chemoradiation or neoadjuvant intra-arterial chemotherapy, depending on the stage of disease.

**Benign Tumors**

Management of benign epithelial tumors of the lacrimal gland involves complete surgical resection of the lacrimal gland mass, including pseudocapsule especially in pleomorphic adenoma. To avoid recurrence, incisional biopsies should be considered with caution when a diagnosis of pleomorphic adenoma is suspected based on clinical and radiographic findings. For pleomorphic adenomas, Font and Gamel reported a 5-year recurrence rate of only 3% for completely excised cases in contrast to a 32% recurrence rate for incompletely excised lesions.\textsuperscript{3} However, in a recent study by Lai et al\textsuperscript{41} there was no evidence of an increased rate of recurrence after biopsy of pleomorphic adenoma when the biopsy tract was subsequently excised. An anterior or lateral orbitotomy will allow for enough exposure to completely excise most pleomorphic adenomas (Fig. 6B). Long-term follow-up with repeat imaging of the orbit after surgery would be appropriate for at least 5 years to rule out local recurrence, which is unlikely to occur after 5 years if initial excision was complete including an intact pseudocapsule. In cases in which the pleomorphic adenoma is not amenable to surgery or with multifocal recurrences, radiation therapy is an option in doses of 70 Gray (Gy).\textsuperscript{4}

### Surgical Treatment of Lacrimal Gland Carcinoma: Exenteration vs Eye-Sparing Approaches

Local treatment of lacrimal gland carcinoma is an important first concern after a new diagnosis of lacrimal gland carcinoma is established. Historically, orbital exenteration with or without removal of the bony walls of the lacrimal gland fossa has been viewed as the most common “standard” surgical approach.\textsuperscript{3,18} This is mostly due to the fact that most cases of lacrimal gland carcinoma are infiltrative into the orbital soft tissue and also due to the relative lack of data and concern regarding toxicity from adjuvant high-dose radiation when delivered in close proximity to the sensitive components of the eye. However, more recently published data are accumulating for globe-preserving (“eye-sparing”) local excision, usually followed by radiation therapy. Adjuvant high-dose radiation therapy is recommended to begin 4–6 weeks after surgical resection of the lacrimal gland carcinoma both for eye-sparing surgery and exenteration because of the very high incidence of perineural invasion, especially for adenoid cystic carcinoma of the lacrimal gland. For more advanced cases, orbital exenteration may be appropriate (Fig. 6C), but given the...
lack of proven survival benefit in patients who undergo orbital exenteration, for smaller and more confined tumors eye-sparing surgery could be considered as long as comparable local control rates are achieved. Wright et al.\textsuperscript{18} reported that the disease-free survival rate was not related to whether cranio-orbital resection was performed. In a series of 7 patients with locally advanced lacrimal gland adenoid cystic carcinoma, 5 patients developed distant metastases and died of disease 12 to 32 months after surgery.\textsuperscript{43} These results reflect the potentially aggressive nature of lacrimal gland adenoid cystic carcinoma, and though extensive surgery may be appropriate to achieve local control in advanced cases, extensive surgery does not appear to impact the risk of distant metastasis and death from disease.

Several reports suggest that tumor size affects prognosis in patients with lacrimal gland adenoid cystic carcinoma. A multi-institutional study reporting on 53 patients with lacrimal gland adenoid cystic carcinoma, with MD Anderson Cancer Center as the main contributing and coordinating center, concluded that the sixth edition of the American Joint Committee on Cancer (AJCC) T category (which is mostly dictated by tumor size at presentation) correlated with prognosis.\textsuperscript{24} This report found that T categories of T3 or higher according to the sixth edition of the AJCC classification were associated with significantly higher risks of local recurrence, lymph node metastasis, and distant metastases and worse metastasis-free survival than tumors with lower T categories.\textsuperscript{24} Thus, this report concluded that for patients with T1 or T2 tumors (according to the AJCC sixth edition classification), less invasive surgical treatment may make sense.\textsuperscript{24} The authors suggested that for lacrimal gland carcinomas no more than 2.5 cm in greatest dimension, gross total tumor excision followed by radiation therapy can be considered as an eye- and vision-preserving procedure.

From 2007 to present, one of the authors (B.E.) has advocated eye-preserving surgery followed by radiation therapy (mostly proton radiation therapy) or concurrent chemoradiation for carefully selected patients. The preliminary results from this author’s experience suggest that control rates comparable to those with orbital exenteration can be achieved in selected patients.\textsuperscript{41} According to this published preliminary report, with a median follow-up time greater than 2.5 years, there were no local recurrences, and the ocular toxic effects associated with radiation therapy consisted of dry eye syndrome in all patients, which is expected given the loss of substantial parts of the lacrimal gland during surgery and the high radiation dose. Also, 3 instances of mild radiation retinopathy, which were responsive to anti–vascular endothelial growth factor (anti-VEGF) therapy, with visual outcomes better than 20/40 in more than 90% of patients. The updated and expanded data includes 1 case of local recurrence in a total of 17 patients treated to date with this eye-sparing multimodality treatment approach (B. Esmaeili, unpublished data, 2016), but long-term follow-up data will be required to determine local control rates and ocular toxicity.

**Neoadjuvant Intra-Arterial Chemotherapy Followed by Exenteration and Adjuvant Chemoradiation in Lacrimal Gland Carcinoma**

Tse et al.\textsuperscript{44} first reported the use of neoadjuvant intra-arterial chemotherapy in 2 patients with lacrimal gland carcinoma in 1998. The treatment regimen consisted of intracarotid administration of cisplatin and intravenous doxorubicin followed by orbital exenteration and postoperative orbital irradiation augmented by additional intravenous cisplatin and doxorubicin.\textsuperscript{44} In 2006, the same authors published the results of the same treatment regimen in 9 patients with lacrimal gland adenoid cystic carcinoma treated with the same protocol; these 9 patients were compared with 7 historical control patients treated with “conventional local therapies,” presumably orbital exenteration alone. The authors concluded that these 9 patients had improved local disease control and also overall disease-free survival compared with 7 historical controls presumably treated with orbital exenteration alone.\textsuperscript{44} The same authors published another report in 2013 using the same approach in 19 patients that included patients in all the previous reports. The authors retrospectively stratified these 19 patients into 2 groups; the first group that did remarkably well included 8 patients (group 1) compared with the rest of the 11 patients (group 2). The authors attributed the better outcomes in group 1 patients to an “intact lacrimal artery, no disruption of bone barrier or tumor manipulation other than incisional biopsy, and adherence to protocol.”\textsuperscript{46} The authors report 100% disease-free survival for group 1. There are several issues and precautionary notes regarding the conclusions of this report.\textsuperscript{47,48} First, groups 1 and 2 were not similar in terms of bone involvement and surgical resection margins (positive in 2 of 8 patients in group 1 vs 9 of 11 in group 2), and even more importantly, no information was given regarding tumor size at presentation, which is known to be of prognostic importance. Furthermore, the hypothetical explanation for the difference in outcomes between groups 1 and 2 is not supported by the presented data. The authors did not provide clinical or radiographic evidence of intact lacrimal artery for any of the 19 patients, and furthermore they presented data that suggested all 19 patients’ tumors responded nicely to an intra-arterial regimen, arguing against the importance of an intact lacrimal artery for chemoreduction and response to therapy. This is important, especially because intra-arterial chemotherapy is delivered through a branch of the external carotid artery. Furthermore, concluding a survival benefit from what is mostly a local/regional control regimen and based on retrospectively stratified data in only 19 patients is not well supported and should be interpreted with caution. Adverse effects from the treatment protocol could also be one of the reasons for the low compliance of group 2. There have been at least 3 documented cases of recurrence after neoadjuvant intra-arterial chemotherapy followed by surgery and high-dose radiation therapy that are in addition to the patients included in the studies by Tse et al.\textsuperscript{49,50} One patient who had the full course of treatment experienced massive diffuse metastases and died.\textsuperscript{49} Two additional patients required protocol modifications because of severe adverse effects and later experienced recurrent disease and died of metastatic disease.\textsuperscript{49,50}

Despite the concerns expressed in the preceding paragraph, the concept of delivering systemic chemotherapy to reduce the size of lacrimal gland carcinomas before surgical treatment, particularly if the goal is to preserve the eye and its function, may prove beneficial in terms of achieving local control, although survival benefit would be difficult to prove without larger scale studies that are at least controlled for tumor size and histological variants of adenoid cystic carcinoma at presentation. We are aware of data on 40 patients with locally advanced adenoid cystic carcinoma of lacrimal gland treated in India with intravenous administration of 5-fluorouracil and cisplatin followed by eye-sparing surgery and postoperative adjuvant chemoradiation therapy. Results from this group suggest successful chemoreduction achieved with...
intravenous chemotherapy (S. Honavar, unpublished data, 2016). Although such cytoreduction may facilitate eye-sparing surgical resection of lacrimal gland adenoid cystic carcinoma and it may especially make sense in larger tumors, proving a survival benefit from neoadjuvant chemotherapy would require randomized trials with strict stratification based on tumor size and histological grading and with many years of follow-up. We agree that neoadjuvant intravenous chemotherapy would be expected to have fewer side effects and is easier and less expensive to deliver compared with neoadjuvant intra-arterial chemotherapy.

Adjuvant Radiation Therapy for Lacrimal Gland Carcinoma
Postoperative adjuvant radiation therapy is a key component of the treatment regimen for management of lacrimal gland carcinoma, particularly the histological subtypes that have a propensity for perineural invasion such as adenoid cystic carcinoma. In general, radiation therapy is recommended for all epithelial malignancies and in cases of incomplete surgical resection; involvement of regional lymph nodes and presence of extracapsular spread dictates the dosage in non-adenoid cystic carcinoma. In a report published in 2015, 3-dimensional conformal radiation therapy was used in 10 patients with lacrimal gland adenoid cystic carcinoma; 8 patients underwent gross total excision followed by radiation therapy with median dose of 60 Gy, and 2 patients with locally advanced disease were treated with radiation palliatively after a biopsy. The authors report good local control in 8 patients with a median follow-up time of 21 months.

In another report published the same year, intensity-modulated radiation therapy was used in 22 patients with orbital carcinoma after an orbital exenteration. Local/regional control in the orbit was achieved in all cases with a median follow-up time of 43 months. In yet another report that was published in 2013, Gensheimer et al described 11 patients treated for lacrimal gland adenoid cystic carcinoma with neutron radiation therapy; 4 patients had an orbital exenteration, and 5 patients had eye-sparing local resections followed by adjuvant neutron beam radiation therapy. Six of 11 patients died of disease at a median follow-up of 75 months; 3 of these 6 patients had local recurrence in the orbit, and 4 also developed distant metastases. Overall 5-year local control rate was 80%, and in most cases good visual function was not achieved.

In the most recent report from MD Anderson Cancer Center, 11 patients with lacrimal gland carcinoma were treated with eye-sparing surgery followed by proton therapy with a median total dose of 60 Gy (relative biologic effectiveness). At a median follow-up time of 30 months, all 11 patients in this cohort had achieved eye preservation with better than 20/40 visual acuity and were without evidence of local recurrence. These recent preliminary data suggest that eye-sparing surgery followed by high-dose radiation therapy is feasible and associated with reasonable local control rates although longer follow-up is necessary to make definitive conclusions about local control rates with this treatment approach.

Mutational Signature of Lacrimal Gland Carcinoma and the Possibility of Targeted Therapy
A few recent reports have explored the molecular aberrations associated with lacrimal gland carcinoma. The genetic landscape of epithelial tumors of the lacrimal gland has been shown to include recurrent tumor-specific mutations and gene fusions which may serve as future targets for therapy. The most promising alteration is perhaps the fusion oncogene MYB-NFIB found in the majority of adenoid cystic carcinomas. Using next-generation sequencing, Bell et al found KRAS mutations in 46% (10/24) of primary lacrimal gland carcinomas tested, NRAS mutations in 8% (2/24), MET mutations in 13% (3/24), and PIK3CA mutations in 4% (1/24) of samples tested. The highest number of cancer-associated mutations were found among the 16 patients with adenoid cystic carcinoma included in this study. Eight cancer-associated mutations were found in 7 of the 16 patients with lacrimal gland adenoid cystic carcinoma, including KRAS mutations in 5 patients, a MET mutation in 1 patient, and an NRAS mutation in 1 patient. The finding of RAS mutations in lacrimal gland carcinoma suggests that the EGFR-RAS-RAF pathway could be targeted as a potential treatment strategy for patients with high-risk or metastatic lacrimal gland carcinoma. For ductal carcinomas of the lacrimal gland, overexpression of HER2 and androgen receptors is frequent and raises the possibility of targeted therapies (ie, HER2 blockade and androgen deprivation therapy). A single case report described a partial response to treatment with lapatinib, a HER2 tyrosine kinase inhibitor, in a patient with metastatic ductal carcinoma of the lacrimal gland. Lapatinib and other HER2-targeted agents, such as trastuzumab (Herceptin), ado-trastuzumab emtansine (Kadcyla), and pertuzumab (Perjeta), may be options for targeted treatment in patients with metastatic HER2-positive lacrimal gland ductal carcinoma. No reports on the effect of androgen deprivation therapy on lacrimal gland ductal carcinoma have been made.

LYMPHOID TUMORS
Distribution
Reactive lymphoid hyperplasia constitutes 6% of all lacrimal gland lesions (Table 1). Extramedullary marginal zone lymphoma (EMZL) is the most frequent lymphoma subtype of the lacrimal gland constituting approximately 40% of all lacrimal gland lymphomas. Follicular lymphoma (FL) accounts for up to 28% and diffuse large B-cell lymphoma (DLBCL) for 15%. Other subtypes, including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/ SLL), are rare.

Molecular and Genetic Characteristics
The most frequent translocation associated with ocular adnexal EMZL is the t(14;18)(q32;q21), which is detected in up to 25% of patients. Other less frequent chromosomal translocations include the t(14;18)(q32;q21) and t(3;14(p14.1;q32). The genetic hallmark of FL is the t(14;18)(q32;q21), which has been detected in 80% of primary ocular adnexal FLs. Diffuse large B-cell lymphoma is characterized by 3 molecular subgroups, termed germinal center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (PMBL). Prognostically, patients with ABC DLBCL have a worse prognosis compared with GCB DLBCL and PMBL. Mantle cell lymphoma is characterized by the t(11;14)(q13;q32) juxtaposing IGH and the CCND1 gene. However, MCL carries additional oncogenic alterations that involve DNA damage response pathways and regulatory cell cycle genes and are assumed to be necessary for malignant transformation.
Clinical Characteristics

Lacrimal gland lymphomas primarily affect elderly patients with a median age in the 60s and a predominance of females (female to male ratio, 2.4). In rare cases, EMZL has been associated with inflammatory disease such as reactive lymphoid hyperplasia, immunoglobulin G4-related disease, and Sjögren syndrome.

In general, the presenting symptoms are related to mass effect of the tumor. Thus, patients with lacrimal gland lymphomas complain of swelling, eyeball displacement, and diplopia (Fig. 7). Pain is rarely reported. The tumor is typically visualized on CT and/or MRI as a smooth homogeneous mass without invasion of adjacent tissue (Fig. 7). Symptom duration is on average 6 months before diagnosis. The diagnosis of lacrimal gland lymphoma depends primarily on the histological evaluation.

Histopathology

Reactive lymphoid hyperplasia is morphologically characterized by a dense infiltration of small lymphocytes with formation of reactive lymphoid follicles of different size reminiscent of normal lymph node architecture. Mitotic activity is restricted to the germinal centers. Within the germinal centers are numerous tangible-body macrophages displaying a starry-sky pattern. Immunohistochemically, the tumors consist of mixed B- and T-lymphocytes. B cells show polyclonality forκ and λ.

Extranodal marginal zone lymphoma is characterized by a diffuse infiltrating pattern of small cells with abundant cytoplasm and slightly indented nuclei without nucleoli resembling cells of the marginal zone (Fig. 7). A plasmablast differentiation, commonly with prominent Dutcher bodies, is often observed. Scattered immunoblast- and centroblast-like cells are typically present among the marginal cells. Immunohistochemically, EMZL is positive for pan B-cell markers such as CD79α and CD20. Furthermore, the majority of cases are BCL2 positive, whereas the tumor cells are negative for CD5, CD10, CD23, and cyclin D-1.

Follicular lymphoma is defined as a lymphoma of follicle center B cells displaying at least a partially follicular growth pattern with neoplastic cells in a closely packed pattern that lacks mantle zones. Immunohistochemically, FL is positive for CD79α and CD20, and for the germinal center markers CD10 and BCL6 in most cases. Approximately 90% of FLs demonstrate overexpression of BCL2. Follicular lymphoma stains negative for CD5. Furthermore, FL is categorized according to the number of centroblasts per high-power field (hpf): grade 1 (0–5 per hpf), grade 2 (6–15 per hpf), and grade 3 (>15 per hpf). Grade 3 is subdivided into grade 3A if centrocytes are present and grade 3B if solid sheets of centroblasts are displayed. Grade 3B is regarded as DLBCL clinically and biologically.

Diffuse large B-cell lymphoma encompasses a biologically, clinically, and histopathologically diverse set of diseases. The general definition of DLBCL describes a neoplasm consisting of a diffuse growth pattern of large B cells with a nuclear size either twice that of normal lymphocytes or equal to/larger than the size of normal macrophage nuclei (centroblastic morphology). Other common morphological variants include: the immunoblastic type with cells displaying a centrally located nucleolus and plenty of basophilic cytoplasm and the anaplastic type with large, oval, or polygonal cells with pleomorphic nuclei. Immunohistochemically, the tumor cells are positive for CD79α and CD20. Approximately 10% of the cells are positive for CD5 and up to 50% are positive for CD10. Expression of CD30 is characteristic in anaplastic DLBCL. The proliferative activity is high (>40%), expressed by Ki-67.

Mantle cell lymphoma arises from B cells of the inner mantle zone of the germinal center. Morphologically, the neoplasm displays a monotonous pattern of small- to medium-sized lymphoid cells with scant cytoplasm, irregular nuclei, inconspicuous

![Figure 7](https://example.com/fig7.png)
nucleoli, and absence of large transformed cells. The majority of the cases carry the t(11;14) (q13;q32) chromosomal abnormality, which causes cyclin D1 overexpression. Furthermore, immunohistochemically the cells are positive for CD20, CD79a, and BCL2, and negative for CD3, CD10, CD23, and BCL6.

**Prognosis**

All patients with biopsy-proven lacrimal gland lymphoma must be evaluated clinically to establish the choice of treatment. This includes bone marrow biopsy and one or more imaging techniques (positron emission tomography, full-body MRI, or full-body CT) to perform lymphoma staging according to both the Ann Arbor staging and the Tumor, Node, Metastasis-based staging system of ocular adnexal lymphomas. Likewise, patients should be evaluated according to lymphoma-specific prognostic clinical factors [ie, the International Prognostic Index (IPI) in DLBCL and EMZL, the FL International Prognostic Index (FLIPI), and the MCL International Prognostic Index].

**Treatment of Lymphoid Lesions of the Lacrimal Gland**

In contrast to epithelial tumors of the lacrimal gland, the cornerstone in the management of lymphoid lesions of the lacrimal gland is not surgical but rather various combinations of chemotherapy and radiotherapy.

**Benign Lymphoid Lesions of the Lacrimal Gland**

Reactive lymphoid hyperplasia is initially treated with high-dose steroids and/or external beam radiation therapy (EBRT) in the mid-20 Gy range. Rituximab is also an option in treatment-resistant cases.

**Malignant Lymphoid Lesions of the Lacrimal Gland**

The initial treatment of early-stage (stage I or II) EMZL and FL (grade 1, 2, and 3A) of the lacrimal gland is EBRT. Doses in the mid-20 Gy range provide excellent disease control with a 5-year overall survival rate of 100% in FL and 75% in EMZL. This is similar to early-stage FL and EMZL at other extranodal sites.

In FL patients with systemic symptoms or high tumor burden, current guidelines recommend the chimeric murine/human monoclonal immunoglobulin antibody rituximab (R) in combination with (1) cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP); (2) cyclophosphamide, vincristine, and prednisone (R-CVP); or (3) R-bendamustin, as equally beneficial first-line treatments with 3-year progression-free survival of 70–80%. Leukeran with or without rituximab is considered for elderly, weakened patients.

After rituximab-chemotherapy induction, treatment with rituximab maintenance for 2 years is generally recommended. Patients with EMZL of the lacrimal gland with concurrent systemic lymphoma are treated according to the same principles as FL patients.

First-line treatment for patients with DLBCL, even if only localized to the lacrimal gland, is R-CHOP. The subgroup of patients below age 60 and with a high-risk profile (age-adjusted IPI score ≥ 2 or elevated s-LDH) is treated with R-CHOP combined with the topoisomerase inhibitor etoposide (R-CHOEP). Furthermore, for the subgroup of patients with Ann Arbor stage IE lymphoma without constitutional B symptoms, EBRT is added to R-CHOP.

In MCL patients, the primary treatment is R-CHOP. The subgroup of MCL patients under age 65 is primarily treated with intensive R-CHOP and cytarabine therapy combined with stem cell transplantation.

**MESENCHYMAL TUMORS**

Mesenchymal tumors of the lacrimal gland represent a spectrum of rare entities with vascular lesions being the most common. The vast majority are benign, whereas malignant mesenchymal tumors are extremely rare.

**Vascular Tumors**

Angiolympoid hyperplasias with eosinophilia (histiocytoid-epithelioma-hemangiomia) along with Kimura disease seem to be the most common vascular proliferations of the lacrimal gland. Additionally, both intralacrimal capillary and cavernous hemangiomas have been reported. A single case describing an intralacrimal epithelioid hemangioendothelioma, a borderline malignant tumor arising from the endothelia of a vein, has been documented.

**Solitary Fibrous Tumor/Hemangiopericytoma**

Hemangiopericytoma and solitary fibrous tumor are rare in the lacrimal gland. They represent a group of collagen-rich and specialized fibroblastic tumors. Microscopically, a storiform pattern of tumor cells arranged in fascicles is seen and the intrallesional blood vessels form a characteristic “staghorn” configuration. Immunohistochemically, the tumor cells are positive in staining for CD34 and vimentin but will lack actin and S100. The definitive diagnosis is made with a positive stain for STAT6 protein, which is overexpressed due to a NAB2-STAT6 gene fusion. Although not reported in a lacrimal gland solitary fibrous tumor, malignant transformation has been described.

**Fibrous Histiocytoma**

Fibrous histiocytomas consist of a combination of fibroblasts and histioyte-like elements. These tumors are very rare in the lacrimal gland and only the benign variant has been documented in this location.

**Granular Cell Tumor**

Only 1 case regarding a lacrimal gland granular cell tumor has been reported. The tumor is characterized by a particular morphologic appearance with rounded tumor cells, prominent nucleoli, and granular cytoplasm. The granules are composed of excessive amounts of lysosomes.

**Neural Tumors**

Neurogenic tumors of the lacrimal gland are very rare. Benign schwannomas along with malignant peripheral nerve sheath tumors have been identified in the lacrimal gland. Plexiform neurofibroma of the lacrimal gland has been found in patients with von Recklinghausen disease (NF1). Histologically, the tumor presents with neural fascicles interposed between normal glandular acini.

**Synovial Sarcoma**

Two synovial sarcomas have been described, both in females. One case recurred after 3 years, but sufficient follow-up is warranted. Histologically, synovial sarcomas are composed of spindle cells arranged in fascicles with occasional mitoses and...
strong immunohistochemical expression of CD99 and Bcl2 in combination with negative stainings for CD34 and desmin.\textsuperscript{101,102}

**Granulocytic Sarcoma**

A case of lacrimal gland granulocytic sarcoma, also known as “chloroma” due to a high content of myeloperoxidase, has been described.\textsuperscript{103} Granulocytic sarcomas are frequently associated with the occurrence or recurrence of acute myeloid leukemia, making this a tumor of myeloid origin despite its name. Recurrence of acute myeloid leukemia was the case for the patient with lacrimal gland involvement.\textsuperscript{103}

**Treatment of Mesenchymal Lesions of the Lacrimal Gland**

Mesenchymal tumors are rare, and the management has similarities with that of epithelial tumors with certain important differences.

**Benign Mesenchymal Lesions of the Lacrimal Gland**

Benign mesenchymal lesions should be managed by complete surgical resection, preferably by lateral orbitotomy (Fig. 6). In contrast to some types of benign epithelial tumors, especially pleomorphic adenoma, mesenchymal tumors do not have pseudo-capsules and recurrences have not been reported.

**Malignant Mesenchymal Lesions of the Lacrimal Gland**

Experiences from synovial sarcoma and malignant peripheral nerve sheath tumor of other head and neck sites advocate complete surgical resection combined and adjuvant radiation therapy, in the range 60–65 Gy.\textsuperscript{104,105} The latter seems to improve local control but not long-term survival.\textsuperscript{104,105} In general, sarcomas do not spread to lymph nodes and the use of chemotherapy is controversial.

**METASTASES**

Due to the lack of lymph nodes in the lacrimal gland, metastatic lesions are rare and are believed to occur mainly by hematogenous spread. The most frequent origin of lacrimal gland metastases is the breast, but carcinoid tumors of the thorax and abdomen, renal cell carcinoma, neuroendocrine carcinoma, cutaneous melanoma, prostate carcinoma, thyroid carcinoma, and 1 case each of esophageal squamous cell carcinoma, hepatocellular carcinoma, salivary gland carcinoma, lung carcinoma, pituitary carcinoma, nasal carcinoma, and pleural mesothelioma have been described.\textsuperscript{106–110}

**PERSPECTIVE**

The rarity of lacrimal gland tumors in combination with the large spectrum of different types of lesions makes establishment of the optimal treatment for each individual entity difficult. Consequently, treatment regimens based on randomized controlled trials are nonexistent. However, as described above, numerous biological characteristics of lacrimal gland tumors are mutual to morphologically similar tumors of other anatomic sites, namely, from the salivary glands and breast for epithelial lesions and the lymph nodes for lymphoid tumors. The rapid evolution of treatments of these non–lacrimal gland sites lends hope for more rapid discovery of effective treatments of patients with lacrimal gland tumors.

**REFERENCES**

Tumors of the Lacrimal Gland


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