Chapter 7
Lacrimal Gland Tumors

Brent Hayek and Bita Esmaeli

Abstract This chapter outlines the clinical presentation and management of tumors that affect the lacrimal gland. Lacrimal gland tumors can be categorized as lymphoproliferative lesions, benign epithelial tumors, and malignant epithelial tumors. Lymphomas are the most common primary cancers of the orbit in adults, and the lacrimal gland is a frequent site of involvement. Benign epithelial tumors of the lacrimal gland include pleomorphic adenomas, oncocytomas, and spindle cell myoepitheliomas. Adenoid cystic carcinoma is the most common primary malignant epithelial tumor of the lacrimal gland; others include mixed tumor, adenocarcinoma, mucoepidermoid carcinoma, squamous cell carcinoma, oncocytoma, and acinic cell carcinoma. The American Joint Committee on Cancer staging system, which is used to classify many malignant epithelial tumors of the head and neck, can provide objective criteria for staging of lacrimal gland tumors. Because tumor stage at presentation may be associated with prognosis, it should be considered when treatment is planned.

7.1 Introduction

A wide variety of tumors can develop in the lacrimal gland and lacrimal gland fossa (Table 7.1). Lacrimal gland tumors can be categorized as lymphoproliferative lesions, benign epithelial tumors, and malignant epithelial tumors. Overlapping clinical presentations of mass lesions in this region are common, but findings on history as well as specific findings on clinical examination and imaging can help distinguish between different types of lesions [1–6]. Radiographic modalities, particularly computed tomography (CT) and magnetic resonance imaging, are useful in delineating the type of lacrimal gland lesion [7–9].

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B. Esmaeli (ed.), *Ophthalmic Oncology*, M.D. Anderson Solid Tumor Oncology Series 6, DOI 10.1007/978-1-4419-0374-7_7,

Table 7.1 Types of lacrimal gland lesions

Lymphoproliferative diseases
Benign lymphoid hyperplasia
Atypical lymphoid hyperplasia
Malignant lymphoma
Benign tumors
Pleomorphic adenoma (benign mixed tumor)
Benign fibrous histiocytoma
Oncocytoma
Myoepithelioma
Cystadenoma
Malignant tumors
Adenoid cystic carcinoma
Malignant mixed tumor (carcinoma ex pleomorphic adenoma)
Adenocarcinoma
Mucoepidermoid carcinoma
Squamous cell carcinoma
Acinic cell carcinoma
Malignant oncocytoma
Other localized lesions
Dacryops
Dermoid cysts
Hemangioma
Amyloid
Lung and breast metastases

This chapter will outline the clinical presentation and management of the various types of tumors that affect the lacrimal gland. The chapter will also review the American Joint Committee on Cancer (AJCC) staging system for lacrimal gland tumors.

7.2 Lymphoproliferative Lesions of the Lacrimal Gland

Lymphomas are the most common primary cancers of the orbit in adults, representing 20% of orbital masses [4, 10–12]. Almost all lymphomas of the orbit, lacrimal gland, or conjunctiva are of the non-Hodgkin B-cell types; the lacrimal gland is a frequent site of involvement and is estimated to be involved in about 50% of all cases of orbital lymphoma (Fig. 7.1a) [13]. Extranodal marginal-zone B-cell lymphoma (low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue type) is the most common histologic subtype seen in the orbit (Fig. 7.1b) [4, 5, 10, 13, 14]; the next most common subtypes, in decreasing order of frequency, are follicular lymphoma, diffuse large-cell lymphoma, and mantle cell lymphoma.

Clinically, both primary and secondary lymphoproliferative lesions of the lacrimal gland tend to grow slowly and be associated with minimal pain and minimal acute swelling [5, 6]. Most patients are elderly, have unilateral disease, and

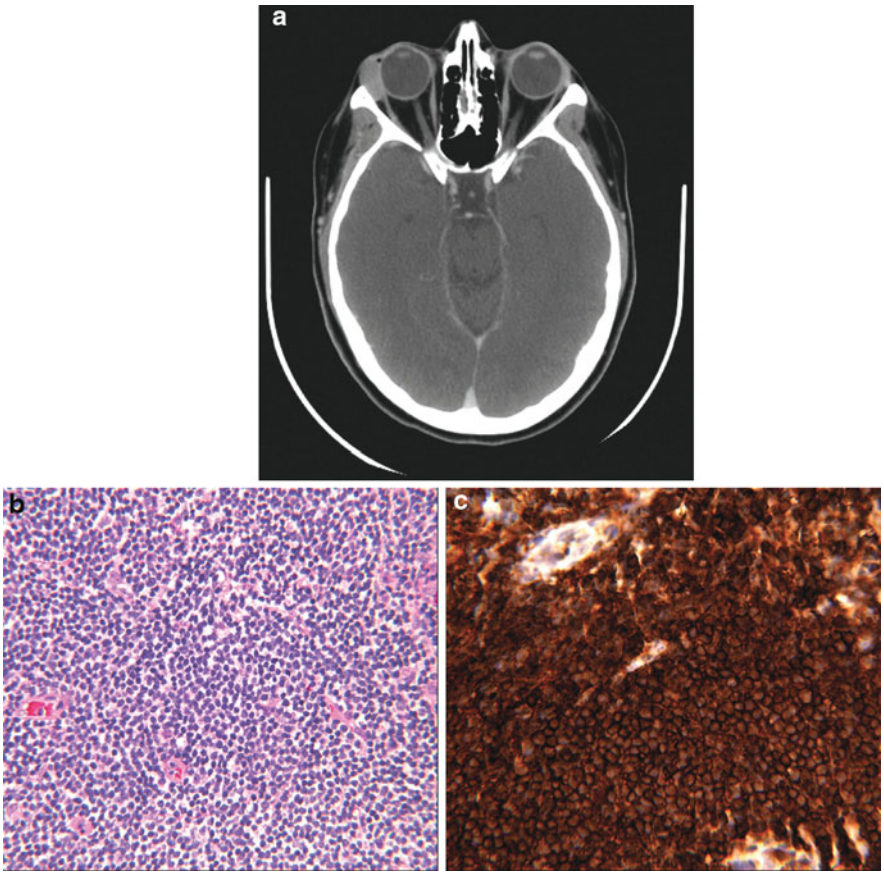

Fig. 7.1 Lymphoma of the lacrimal gland. (**a**) Computed tomography image of a 75-year-old patient with a right lacrimal gland lymphoma. (**b**) Histologic findings indicating low-grade non-Hodgkin B-cell lymphoma. (**c**) The lymphocytes are CD-20 positive, as shown in this photomicrograph. Figures courtesy of Dr. Bita Esmaeli

present with symptoms less than 1 year in duration. The overall rate of systemic involvement associated with orbital lymphoma is reported to be 30–50% [15]. Once the diagnosis of lymphoma of the lacrimal gland is established via a biopsy, a thorough workup is warranted to look for systemic sites of involvement. A total-body positron emission tomography scan is a way to rule out areas of hypermetabolic activity throughout the body and serves as a complement to conventional imaging for staging of lymphomas [15]. Positron emission tomography scans can also be used to evaluate response to therapy [16].

Treatment of lacrimal gland lymphoma depends on the histologic subtype and stage at diagnosis and may include radiation therapy, systemic chemotherapy, monoclonal antibody therapy, or a combination of these [11, 17].

7.3 Benign Epithelial Tumors of the Lacrimal Gland

7.3.1 Pleomorphic Adenoma

The most common epithelial tumor of the lacrimal gland is pleomorphic adenoma (a benign mixed-cell tumor) [18, 19], which accounts for approximately 50% of all epithelial lacrimal gland tumors [5]. Pleomorphic adenoma most commonly presents in the fourth to fifth decades of life and is rare in children [5, 19–21]. Actuarial estimates indicate that the risk of malignant transformation if pleomorphic adenoma is left untreated is 10% in 20 years and 20% in 30 years [19].

Pleomorphic adenoma commonly presents as a slowly progressive, painless mass in the lacrimal gland fossa. Most pleomorphic adenomas affect the orbital lobe, so the most common finding is axial proptosis with downward and medial displacement. However, pleomorphic adenoma may present solely with eyelid ptosis [3]. Patients may complain of diplopia from globe dystopia and restricted eye movement. This tumor affects males slightly more frequently than females and is usually symptomatic for more than a year before diagnosis [5, 19–21].

Examination typically demonstrates a firm, mobile mass just inferior to the superolateral orbital rim. CT and magnetic resonance imaging often show a roundish mass of varying homogeneity, with evidence of bony excavation and remodeling correlating with the slow growth of this lesion. Bony excavation and remodeling is the classic finding on imaging but is not always present. In their review of patients with lacrimal gland pleomorphic adenomas, Garrity et al. [3] found that only 44% of patients had bony abnormalities. Also, atypical presentations of this tumor are not uncommon. Patients may present with signs mimicking orbital cellulitis, chalazion, or dacryoadenitis [22–26].

Pleomorphic adenoma is so named because of its mixed histologic features. The tumor is a lobular, grossly yellowish-white lesion with a thin pseudocapsule. It is solid when cut open (Fig. 7.2) but commonly has areas of cystic degeneration. Histologically, the tumor contains myxoid areas, benign epithelium in nests, and ductal structures. There may also be fibrosis and formation of hyaline cartilage and bone [26]. Immunohistochemical studies indicate that this tumor is derived from ductal epithelium and certain cells in the stroma and myoepithelium. Various reports have demonstrated increased S-100 and glial fibrillary acidic protein expression in pleomorphic adenomas [27–30]. Management involves complete resection of the tumor, the pseudocapsule, and a small margin of normal lacrimal gland/orbital tissue if possible, en bloc without a preliminary incisional biopsy or piecemeal excision (Fig. 7.2a and b) [1, 6, 31–33]. Therefore, the likelihood that the tumor is a benign pleomorphic adenoma must be determined on the basis of clinical and radiographic findings. The rate of correlation between the clinical and histopathologic diagnosis varies from 50 to 87% [3, 6, 34]. The pseudocapsule represents adjacent compressed lacrimal gland/orbital tissue and contains microscopic fenestrations, so excising a margin of normal tissue around the pseudocapsule is advised. In their 1978 series,

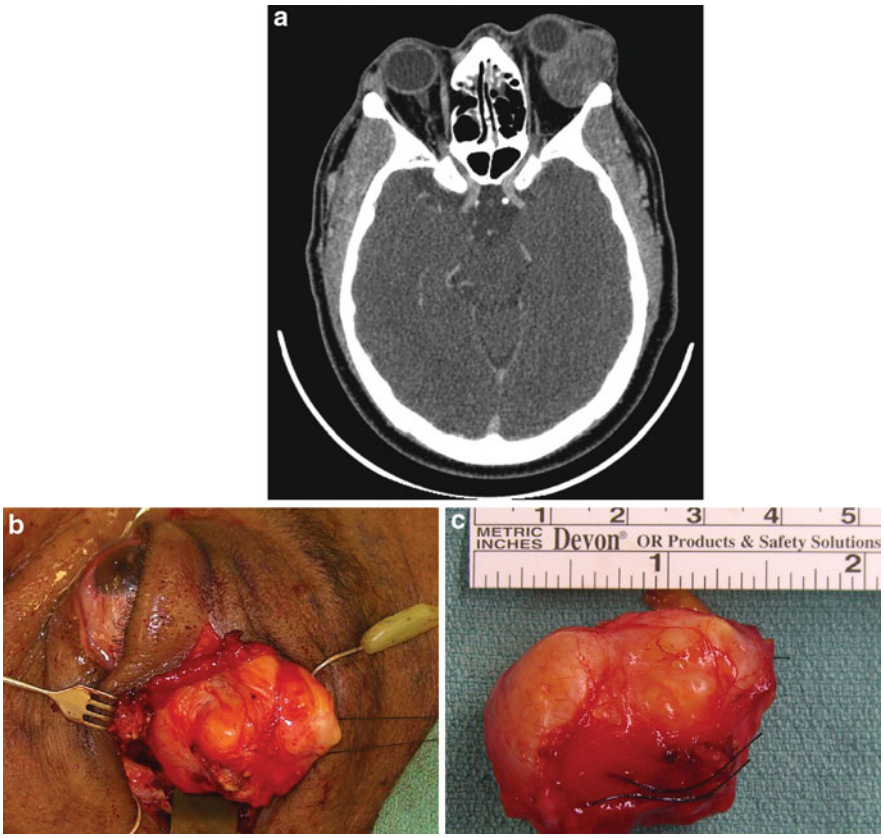

Fig. 7.2 (**a**) Computed tomography image of a patient with a large pleomorphic adenoma of the lacrimal gland. (**b**) En bloc surgical resection of a pleomorphic adenoma of the lacrimal gland through a lateral orbitotomy and bone flap. (**c**) The lesion was excised with its pseudocapsule intact. Figures courtesy of Dr. Bita Esmaeli

Font and Gamel [19] reported a 5-year recurrence rate of 3% for completely excised lesions and 32% for incompletely excised adenomas. An anterolateral orbitotomy will allow for enough exposure to resect the majority of these tumors. Ni et al. [35] reported that all 15 patients who underwent an anterolateral complete resection with a rim of adjacent lacrimal gland/orbital tissue were free of recurrence at a mean follow-up time of 9.7 years (range, 3–21 years).

Long-term surveillance is advised since recurrence has been documented years after excision. Recently, Currie and Rose [36] retrospectively reviewed 72 patients who underwent excision of pleomorphic adenoma and had more than 5 years of follow-up. They stratified patients according to the degree to which the tumor was likely to seed the orbit and found that only one patient, who had a prior incisional biopsy, had a recurrence of benign disease, 12.5 years after excision.

7.3.2 Other Benign Epithelial Tumors

Other benign epithelial lacrimal gland tumors include oncocytoma and spindle cell myoepithelioma. Non malignant tumor lesions simulating clinical presentations similar to those of lacrimal gland lesions include congenital dermoid cysts, dacryops, and cavernous hemangioma.

Oncocytoma (oxyphilic adenoma) refers to a tumor of oncocytes. Oncocytes are found in numerous mucous membranes, including the caruncle, conjunctiva, lacrimal sac, and lacrimal glands. Oncocytoma of the lacrimal gland is rare and has been described as either malignant or benign in a few case reports [37–41]. Oncocytomas tend to grow slowly, have variable symptoms, and can be clinically mistaken for hemangiomas, nevi, or cysts [38]. Histologically, the large epithelial cells of oncocytomas contain a granular eosinophilic cytoplasm and small nuclei without atypia and can form cords and tubular structures [41]. Complete resection of oncocytomas is advised.

Primary spindle cell myoepitheliomas of the lacrimal gland are also rare, but numerous cases of this tumor have been reported in the literature since 1990 [42–44]. Grossniklaus et al. [44] were the first to report a case of non-spindle cell myoepithelioma, which was identified on the basis of immunohistochemistry and ultrastructural features. Myoepitheliomas of the lacrimal gland mimic benign pleomorphic adenomas in that they are associated with a long period of painless proptosis. Myoepitheliomas are encapsulated lesions, and complete resection is possible and advocated [3].

7.4 Malignant Epithelial Tumors of the Lacrimal Gland

7.4.1 Adenoid Cystic Carcinoma

The most common primary malignant epithelial tumor of the lacrimal gland is adenoid cystic carcinoma (ACC). It accounts for 1.6% of all orbital tumors and 20–35% of primary epithelial neoplasms of the lacrimal gland [1–3, 45]. This tumor presents most commonly in the fourth to fifth decades of life and is less common in children and teenagers. ACC has been histologically documented in individuals ranging from 6 to over 70 years, and a number of case reports have been published on this tumor occurring in children [46–50]. It occurs with equal frequencies in males and females. It is known to have an indolent and persistent course with a high risk of local and regional recurrence and late distant metastasis.

For ACC and other epithelial malignancies, the clinical history and presentation may include a palpable mass in the superior lateral quadrant, with associated pain or dysesthesia, and proptosis directed inferomedially. The duration of symptoms is typically less than 1 year. CT imaging may show bony erosion or destruction of the orbital roof and/or lateral wall. ACCs, similar to benign pleomorphic adenomas, are round or ovoid expansible masses (Fig. 7.3a), mainly originating in the orbital

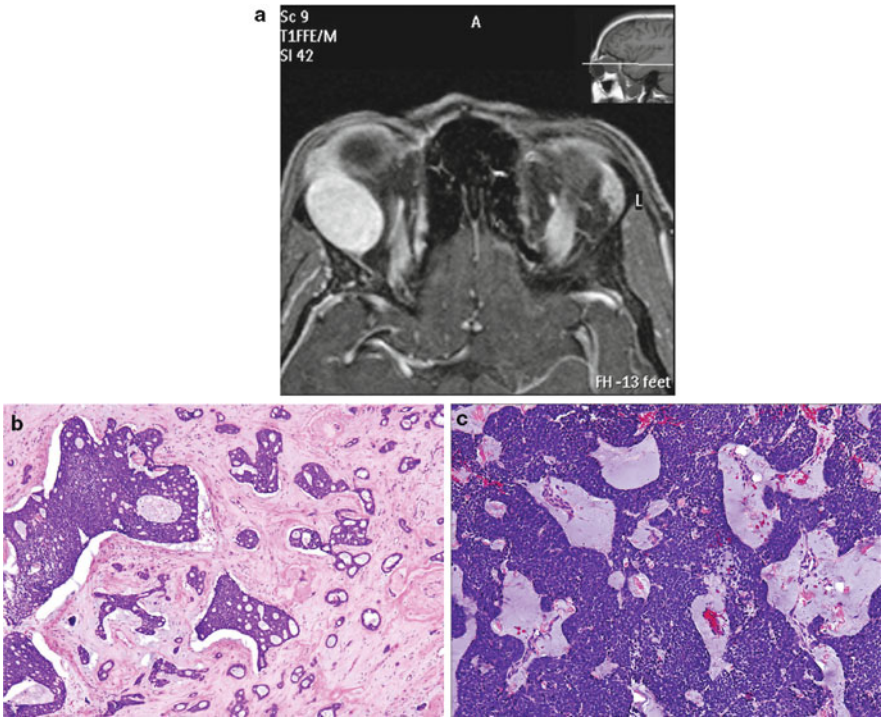

Fig. 7.3 Adenoid cystic carcinoma of the lacrimal gland. (**a**) Magnetic resonance imaging demonstrates a large lobular adenoid cystic carcinoma of the lacrimal gland. Typical histologic findings of adenoid cystic carcinoma of the lacrimal gland with predominantly cribriform pattern ("Swiss cheese" appearance) (**b**) and solid (basaloid) pattern (**c**). Figures courtesy of Dr. Bita Esmaeli

lobe, that displace and may indent the globe. Other signs noted on funduscopic examination may include choroidal striae and, less commonly, optic nerve swelling or decreased vision [6, 14, 26].

ACC of the lacrimal gland has a worse prognosis than ACC of the salivary glands. Lacrimal gland ACC has a tendency for early perineural spread and bony invasion. Even after treatment, rates of recurrence and distant metastasis are high, and death occurs in 50% of patients [51–58].

There are five histologic subtypes of ACC: cribriform ("Swiss cheese" appearance) (Fig. 7.3b), solid (basaloid), sclerosing, comedocarcinomatous, and tubular (ductal). Combinations of different subtypes are not uncommon, but typically one subtype predominates. The cribriform pattern is associated with a more favorable prognosis (particularly in children), and the solid subtype is associated with the worst prognosis [51, 52].

Treatment varies among different institutions, and standard treatments for different stages of the tumor are not well established [1, 52–57]. The most common surgical treatment is an orbital exenteration, usually with removal of the bony walls

of the lacrimal gland fossa, and this is usually followed by postoperative radiation therapy. Given the propensity for perineural invasion (seen in about 75% of cases), various forms of adjuvant postoperative radiation therapy have been advocated, including external-beam, proton, and brachytherapy [1, 49, 52–57]. More recently, a regimen of preoperative intraarterial chemotherapy, orbital exenteration followed by radiation therapy, and then intravenous chemotherapy has been employed at one center in an effort to enhance long-term overall survival [55, 56]. The preliminary results of this trial seem promising [56], although the historical control group in this study had an unusually high death rate (close to 100%), which makes the conclusions of this study potentially skewed. The other reason intraarterial chemotherapy and adjuvant chemotherapy have not been more widely used is that standard chemotherapy is quite ineffective in the treatment of metastatic ACC; thus, use of a drug or combination of drugs in the adjuvant setting is not well accepted by the majority of medical oncologists. Another approach that has been advocated at some centers is conservative surgery (globe-preserving surgery) followed by proton radiation therapy.

Given the rarity of ACC of the lacrimal gland, prospective trials comparing different treatment modalities are not practical. In addition, such trials would require long-term follow-up to be meaningful, as late recurrences and death have been reported [14, 52–57]. In a recent retrospective multicenter study, we concluded that AJCC stage at initial diagnosis of lacrimal gland ACC impacts the rates of local recurrence and survival [58]. In this study, we found that an AJCC classification of T3 or greater correlated with poorer survival outcomes in patients with ACC [58].

7.4.2 Other Malignant Epithelial Tumors

Other primary malignant epithelial tumors of the lacrimal gland include malignant mixed tumor (carcinoma ex pleomorphic adenoma), adenocarcinoma, mucoepidermoid carcinoma, squamous cell carcinoma, malignant oncocytoma, and acinic cell carcinoma [1, 19, 38, 59–62].

A malignant mixed tumor of the lacrimal gland may arise out of a long-standing or incompletely resected benign pleomorphic adenoma. Malignant mixed tumors represent 4–19% of lacrimal gland epithelial neoplasms and can be further subclassified on the basis of the malignant elements predominant in the tumor [1–3, 45, 63]. The four most often encountered malignant subtypes are adenocarcinoma, ACC, squamous cell carcinoma, and spindle cell carcinoma. An epithelial–myoepithelial carcinoma subtype has also been described [64]. The adenocarcinoma subtype may be more common in men, and the ACC subtype may be more common in women [19]. Imaging may reveal both benign- and malignant-appearing components [65]. All subtypes of malignant mixed tumors are highly malignant tumors. In light of this fact and the reality that malignant mixed tumors can arise from pleomorphic adenoma, when a benign pleomorphic adenoma is resected, it is critically important

to perform a complete resection with an intact capsule and a margin of surrounding normal tissue.

Adenocarcinomas occur with about the same frequency as malignant mixed tumors and are also very malignant [66]. Adenocarcinoma most often affects men in their fourth to sixth decades and is prone to recurrence and early lymphatic and distant metastatic spread [19]. Because of the possibility of early dissemination, it is prudent to perform sonography of the neck and chest radiography at presentation. The clinical presentation and CT appearance of adenocarcinoma are similar to those of ACC. Management of lacrimal gland adenocarcinoma is challenging because of the rarity of this tumor. On the basis of retrospective reviews, some authors advocate orbital exenteration with postoperative radiation therapy for high-grade tumors, whereas others suggest en bloc craniofacial orbitectomy combined with regional lymph node dissection [3, 66]. In cases of low-grade adenocarcinoma of the lacrimal gland, complete surgical resection with preservation of globe and postoperative adjuvant radiation therapy may also be a reasonable option. Four cases have been reported of a subtype of adenocarcinoma of the lacrimal gland, termed primary ductal adenocarcinoma [67–71].

Mucoepidermoid carcinoma of the lacrimal gland is rare [59]. Histologically, the tumor is composed of epidermoid and mucous-secreting cells. Eviatar and Hornblass [59] subclassify these tumors as either low grade (grade 1 or 2) or high grade (grade 3) on the basis of histopathologic features. On the basis of histopathologic review and follow-up of 14 patients, they recommend simple resection with or without radiation therapy for low-grade tumors and orbital exenteration with radiation therapy for high-grade tumors [59].

Primary lacrimal gland squamous cell carcinoma is also a rare tumor and represents fewer than 2% of primary lacrimal gland carcinomas [67]. Most squamous cell carcinomas of the lacrimal gland are the subtype associated with malignant mixed tumors. It is thought that squamous cell carcinoma of the lacrimal gland can also arise from preexisting metaplasia in a dacryops or from choristomatous epithelium-lined cysts [72, 73].

Malignant oncocytoma and acinic cell carcinoma of the lacrimal gland are very rare, and there are only a few case reports in the literature [19, 62].

7.5 AJCC Staging for Lacrimal Gland Tumors

Until recently no uniform classification system had been used to classify lacrimal gland tumors for purposes of reporting outcomes or for selecting treatment algorithms. The AJCC staging system is used to classify many malignant epithelial tumors of the head and neck and can provide objective criteria for management of such tumors [74]. However, there is little information in the literature on the value of AJCC staging for orbital tumors. Most studies and textbooks on orbital tumors make no mention of AJCC stage as a predictor of outcome for cancers of the orbit and ocular adnexa.

In a retrospective analysis of ACC of the lacrimal gland at our institution and several other centers, we found that a tumor size of T3 or greater is associated with a higher rate of local recurrence and poorer prognosis [58]. Thus, incorporation of AJCC stage at presentation as the basis for choosing treatment modalities in multi-institutional clinical trials for epithelial tumors of the lacrimal gland may make sense. This might ultimately lead to a more selective approach to surgical treatment of epithelial tumors of the lacrimal gland, including the use of more conservative surgery with globe preservation followed by radiation therapy for selected patients with smaller tumors and less aggressive histologic subtypes at presentation.

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