Management of Lacrimal Gland Carcinoma: Lessons From the Literature in the Past 40 Years

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Purpose: To review the published literature on management strategies for lacrimal gland carcinomas.

Methods: Review of relevant articles in PubMed published in English from the year of 1970 through September 2014.

Results: A review of literature suggests that treatment strategies for adenoid cystic carcinoma of lacrimal gland are varied, but local control does not necessarily prevent future delayed distant relapse. Tumor size and histologic features of lacrimal gland carcinoma seem to be important prognostic features. With improved imaging modalities providing better tumor diagnosis and staging, and availability of more focused radiation delivery techniques, multimodality globe sparing management of lacrimal gland carcinomas may be possible in selected cases. The availability of targeted drugs based on the molecular signature of an individual lacrimal gland carcinoma may offer possible targeted treatments for patients with nonresectable or metastatic disease.

Conclusion: Given the rarity of lacrimal gland carcinoma, multi-institutional studies and consistent reporting of size and histologic type of tumors in the literature may be prudent. Particularly, multimodality globe-sparing treatment strategies should be studied further.

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The lacrimal gland fossa can harbor various pathologic lesions of epithelial and nonepithelial origin, and such lesions have been reported to account for approximately 9% to 35% of all orbital tumors and pseudotumors.[1–4] The overall incidence of lacrimal gland lesions was estimated to be 1.3 lesions per million individuals per year, and the incidence of neoplastic lesions was estimated to be 0.7 lesions per million individuals per year in a Danish report.[5] Epithelial neoplasms of the lacrimal gland account for 34% to 54% of lacrimal gland lesions according to the largest series to date.[2,6–8] Among the epithelial neoplasms of the lacrimal gland, pleomorphic adenoma is the most frequently diagnosed (accounting for 48–71% of epithelial lacrimal gland lesions), followed by adenoid cystic carcinoma (12–32%) and other types of carcinoma (9–20%).[6,9–11]

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Although lacrimal gland carcinoma is rare, it is an important subgroup because this disease is difficult to control locally and is associated with an overall guarded prognosis; the estimated rate of mortality at 5-year follow up is 50% regardless of the form of local treatment.[12] It is hard to determine the incidence of lacrimal gland carcinoma because of its rarity and because of referral biases that are inherent to reports from tertiary care centers.[5,6] The highest reported yearly incidence was 0.024 cases per 100,000 people aged 60 to 75 years in a Japanese study.[6] The low incidence of lacrimal gland carcinoma precludes a systematic approach to their management based on predicted prognosis. Most reports of lacrimal gland carcinoma are anecdotal experiences from a single center or small case series. Nevertheless, some general trends and information about this disease can be gleaned from the published literature. In this review, we attempt to arrive at some general insights regarding the prognosis and management of lacrimal gland carcinoma based on the literature published in the last 4 decades.

METHODS

On September 8, 2014, we searched the PubMed database for articles on lacrimal gland carcinoma that had been published since 1970 in English. Case reports were excluded with a filter in the search engine. Search details were ((lacrimal[All Fields] AND gland[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) NOT ((lacrimal[All Fields] AND gland[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields]) AND Case Reports[ptyp]) AND (("1970/01/01"[PDAT]: "3000/12/31"[PDAT]) AND English[lang]). Adenoid cystic carcinoma, adenocarcinoma, and mucoepidermoid carcinoma of the lacrimal gland were searched additionally for tumor-specific characteristics and management.

Articles with duplicate information or articles that did not contain information relevant to management options were excluded.

RESULTS

One hundred eighty-three articles were retrieved with the primary search; of these 183 articles, 92 articles were excluded because they were not focused on this study's purpose (n = 52) or they were a case report or small case series (n = 40), leaving 91 articles that were considered relevant to this study's purpose. These 91 articles were further reviewed. Of these 91 articles, 51 articles were not referenced because they were not focused on the lacrimal gland disease (n = 32); they were a review article (n = 7); they contained duplicated contents in another article (n = 6); or a full-text was not available (n = 6).

To evaluate the prevalence of lacrimal gland carcinoma, we used information from reports of 20 or more cases of lacrimal gland carcinoma (Table).

Adenoid cystic carcinoma was the most frequent histologic subtype, accounting for 51% to 76% (mean, 61.9%) of the lacrimal gland carcinomas; this was followed by malignant mixed tumor, accounting

Relative Frequencies of Various Histologic Subtypes of Lacrimal Gland Carcinoma in Series Published in the Literature Since 1970

		No. of Patients (%)							
Authors	Study Years	Adenoid Cystic Carcinoma	Malignant Mixed Tumor	Adenocarcinoma	Mucoepidermoid Carcinoma	Ductal Carcinoma	Undifferentiated Carcinoma	Other Carcinoma	Total
Forrest[13]	NA	20 (67)	—	—	—	—	—	10 (33)*	30
Font and Gamel[12]	NA	70 (54)	34 (26)	19 (15)	4 (3.1)	—	—	2 (1.5)	129
Ni et al.[9]	1953–1979	46 (66)	10 (14)	4 (5.7)	1 (1.4)	—	9 (13)	—	70
Janecka et al.[14]	1963–1983	11 (52)	4 (19)	1 (4.7)	—	—	—	5 (23.8)	21
Wright et al.[15]	1968–1990	38 (76)	6 (12)	4 (8.0)	1 (2.0)	—	—	1 (2.0)	50
Polito and Leccisotti[8]	1964–NA	11 (55)	7 (35)	1 (5.0)	1 (5.0)	—	—	—	20
Font et al.[7]	For 23 yr	12 (57)	7 (33)	2 (10)	—	—	—	—	21
Garrity and Henderson[16]	1948–1997	29 (51)	16 (28)	7 (12)	2 (3.5)	—	—	3 (5.2)	57
Weis et al.[11]	NA	38 (65)	9 (16)	3 (5.2)	2 (3.4)	2 (3.4)	2 (3.4)	2 (3.4)	58
Zeng et al.[10]	1961–2005	58 (68)	13 (15)	8 (9.4)	—	—	—	6 (7.0)	85
Shinder et al.[17]	1998–2009	18 (72)	2 (8)	—	1 (4)	—	—	4 (16)	25
von Holstein et al.[18]	1974–2007	15 (60)	4 (16)	2 (8.0)	2 (8.0)	1 (4.0)	—	1 (4.0)	25

NA, not available.
*Malignant lacrimal gland epithelial tumors, not specified.

for 8% to 35% (mean, 18.9%); adenocarcinoma, 5.0% to 15% (mean, 8.6%); and mucoepidermoid carcinoma, 1.4% to 8.0% (mean, 2.4%). Though the rates varied somewhat between studies, reflecting the small size of the case series, the relative frequencies were in the same order in most of the reports.

Because adenoid cystic carcinoma was by far the most common histologic subtype, most of this review will focus on that subtype. A brief discussion of other histologic subtypes follows the discussion of adenoid cystic carcinoma.

Adenoid Cystic Carcinoma. ***Unique Clinical Characteristics.*** Although it is difficult to compare the different histologic subtypes of lacrimal gland carcinoma because of their low incidence, it is clear that adenoid cystic carcinoma has several unique clinical characteristics.

Adenoid cystic carcinoma tends to be diagnosed at younger ages than other subtypes of lacrimal gland carcinoma: Ni et al.[9] reported a mean age at diagnosis of 37 years versus 56 years, and Wright et al.[15] reported mean age at diagnosis of 41 years versus 53 years. In Wright et al.'s study,[15] the difference in mean age at diagnosis was not statistically significant; however, all patients presenting under 30 years of age had adenoid cystic carcinoma, and the proportion of lacrimal gland carcinomas that were adenoid cystic carcinoma was significantly higher among patients younger than 30 years than among older patients.

Periocular pain is reported to occur more frequently and earlier with adenoid cystic carcinoma than with other lacrimal gland carcinomas.[9,12,15] Pain was present in 10 of 11 patients with adenoid cystic carcinoma and 8 of 13 patients with other lacrimal gland carcinomas in one report.[19] In another report, pain was reported in 30 of 38 patients with adenoid cystic carcinoma and 4 of 10 patients with other lacrimal gland carcinomas.[15] Pain might indicate perineural tumor infiltration with a more advanced stage of malignant disease; however, pain was unrelated to predominance of basaloid differentiation, the duration of symptoms, invasion of bone, loss of trigeminal nerve function, or whether recurrence was a first, second, or later recurrence or the timing of recurrence in relation to initial diagnosis.[15]

It is hard to draw firm conclusions regarding differences in survival between different subtypes of lacrimal gland carcinoma because most reports do not specify the tumor size or American Joint Committee on Cancer (AJCC) designation at presentation and do not normalize for types of treatment delivered; however, adenoid cystic carcinoma is notorious for slow growth, local recurrence despite therapy, and distant metastasis even after a several-year asymptomatic dormant period. In Brada and Henk's[20] report of radiation therapy after surgical intervention, 9 of the 11 deaths from tumor in patients with adenocarcinoma, malignant mixed tumor, and undifferentiated carcinoma in the lacrimal gland occurred within the first 2 years after diagnosis, whereas the 5 deaths from adenoid cystic carcinoma occurred evenly throughout the time of observation. The necessity of long-term follow up of patients with adenoid cystic carcinoma was clearly described by Font and Gamel[12]; in their series, the actuarial survival rate of patients with adenoid cystic carcinoma was 45% at 5 years, 23% at 10 years, but only 14% at 15 years.

Clinical and Pathologic Factors Affecting Patient Outcome. Local control of adenoid cystic carcinoma may be difficult to achieve because of perineural infiltration and bone invasion. Furthermore, distant metastasis occurs in about 50% of patients, and there is often a long latency period between treatment and development of overt metastasis.[7,15] Although many treatment modalities have been applied to manage adenoid cystic carcinoma, from extensive orbital surgeries to adjuvant therapies, the rarity of this cancer and the need for long-term follow up make it difficult to compare the efficacy of various different treatment strategies. Evaluation of management strategies for adenoid cystic carcinoma requires taking into consideration all the compounding factors potentially influencing the survival rate and prognosis.

Patient age is an important factor affecting the prognosis of patients with adenoid cystic carcinoma. In a study by Wright et al.,[15] children and adolescents had a better 15-year expected survival rate than older patients.[9,21] Tellado et al.[21] analyzed the survival rates of children and adolescents with adenoid cystic carcinoma and reported that patients younger than 19 years

tended to have low-grade tumors of nonbasaloid type and had better local control and survival rates than those previously reported in adults.

Histopathologic characteristics may also impact survival (Fig. 1A,B). According to several reports, presence of a basaloid or solid pattern had a statistically significant negative effect on survival.[11,22,23] In a report by Gamel and Font[22] of 54 patients with adenoid cystic carcinoma, the 5-year actuarial survival rate was 47% overall but 71% for patients with no basaloid component in their tumor and 21% for patients with any basaloid component. In the same report, the 15-year actuarial survival rate was 12% overall and 22% for patients with no basaloid component; for patients with any basaloid component, there were insufficient data to determine the actuarial survival rate because of poor survival.[22] In a report by Williams et al.[24] from The University of Texas MD Anderson Cancer Center, 11 of 18 patients with adenoid cystic carcinoma had a predominantly basaloid pattern; 7 of these patients developed distant metastases, and 6 of these 7 died of disease. In a report by Weis et al.,[11] the absence of a cribriform pattern and the presence of a solid (basaloid) pattern were significantly associated with death. In contrast, Lee et al.[25] reported that basaloid pattern or bone invasion was not associated with shorter survival, but that lower tumor grade and "Swiss cheese" pattern were associated with longer survival. Overall, adenoid cystic carcinoma with a basaloid (or solid) pattern was associated with a worse prognosis in most reports.

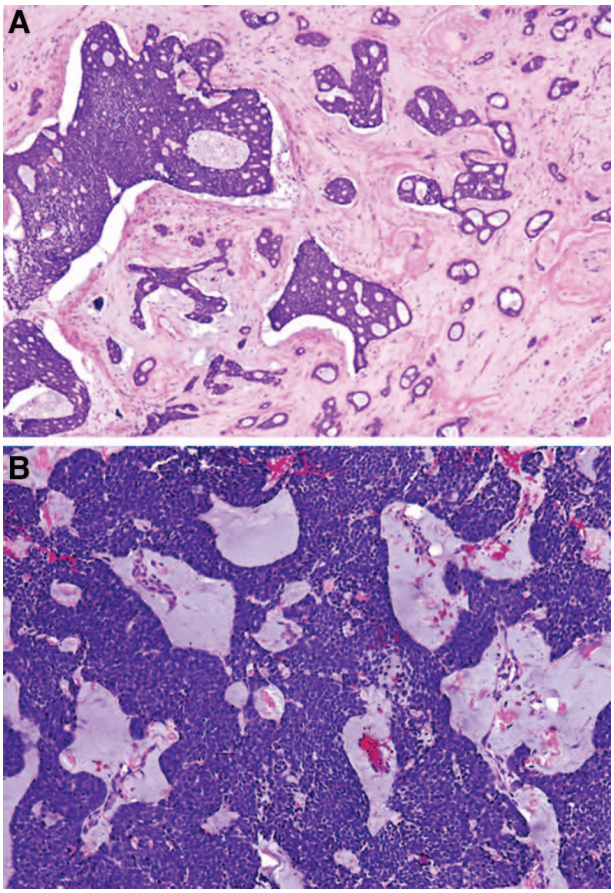

FIG. 1. **A**, Histologic section of a predominantly cribriform pattern of growth of adenoid cystic carcinoma of lacrimal gland. **B**, Histologic section of a predominantly solid (basaloid) pattern of growth for adenoid cystic carcinoma of lacrimal gland.

Perineural invasion is found in up to 85% of cases of adenoid cystic carcinoma (Fig. 2).[23,25–28] In a report by Ahmad et al.[26] of 53 patients, 14 of 38 patients (36%) with perineural invasion had local recurrence, and 14 of 15 patients (93%) with local recurrence had histologic evidence of perineural invasion in their initial surgical specimen. Perineural invasion is strongly associated with local tumor recurrence and skull base invasion.[24] In an analysis of histologic patterns, perineural invasion was reported not to correlate with mitotic activity, particular histologic pattern, or predominant histologic pattern.[11] Biologic factors or conditions possibly precipitating perineural infiltration of the tumor should be investigated to ensure good treatment outcome. Brain-derived neurotrophic factor, a growth factor, was found to be expressed in adenoid cystic carcinoma of the salivary gland and was considered to play a role in the neurotrophic nature of adenoid cystic carcinoma and its predilection for perineural invasion.[29]

Bone invasion is found on clinical or pathologic examination in a significant proportion of adenoid cystic carcinomas, especially those of high stage. Therefore, careful tumor evaluation to check for bone invasion is needed. Bone invasion was apparent clinically or pathologically in 81% of patients (21/26) with adenoid cystic carcinoma in a Mayo Clinic series and was apparent radiologically in 76% of patients (13/17) and pathologically in 82% of patients (14/17) in an MD Anderson Cancer Center series.[24,25] Henderson[30] advocated exenteration with cranio-orbital resection for adenoid cystic carcinoma, assuming that the tumor was almost always fatal because of early bone penetration during tumor growth.[31] This author considered that the tumor disseminated faster in bone because once the tumor penetrated bone, there were no tissue histiocytes or macrophages that might resist the spread of neoplasm along the marrow cavity of the bone.[30] Williams et al.[24] reported that bone invasion was present in all cases of adenoid cystic carcinoma with primary tumor larger than 2.0 cm and recommended that the lacrimal fossa wall be addressed surgically for cases with bony invasion.[24]

Tumor extent may also affect prognosis in patients with adenoid cystic carcinoma of the lacrimal gland. For adenoid cystic carcinoma occurring in other head and neck sites, Friedrich and Bleckmann[32] reported an excellent prognosis only for tumors detected early and radically resected. Similarly, 2 of 11 long-term survivors in Font et al.'s[7] series of patients with lacrimal gland carcinomas had been treated with early primary exenteration and local irradiation, which might indicate that

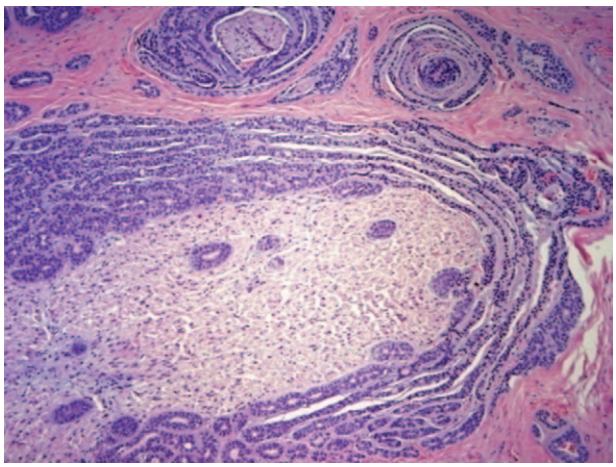

FIG. 2. Perineural invasion is a hallmark of adenoid cystic carcinoma.

good prognosis is associated with early detection and treatment. In a report on patients with salivary and lacrimal gland adenoid cystic carcinoma, Friedrich and Bleckmann[32] reported that neither tumor localization nor tumor histologic subtype had a statistically significant impact on prognosis, but that lower AJCC T category was associated with better prognosis. Perhaps the most comprehensive report attempting to correlate adenoid cystic carcinoma tumor size and stage at presentation with patient outcomes is the report published in 2009 based on a multi-institutional retrospective review of 53 patients with adenoid cystic carcinoma of the lacrimal gland from 8 institutions.[26] Patients' tumors at presentation were evaluated using the sixth edition of the AJCC classification. Local recurrence, lymph node metastasis, and distant metastasis were significantly more common, and overall survival and metastasis-free survival were significantly worse in patients with T3 (tumor 2.5–5 cm in greatest dimension) or more advanced tumors.[26]

During updating to create the seventh edition of the AJCC Cancer Staging Manual, the staging system for salivary gland malignancies was used as a guide to revise the T designations for lacrimal gland carcinoma.[33] The T designations corresponding to certain tumor dimensions were increased; however, the T designation corresponding to invasion to the orbital soft tissue was decreased. Bony invasion was considered a powerful prognostic factor, and the T designation was increased to T4 in the case of even periosteal bony involvement.[33] However, 2 reports to date suggest that the higher T designations in the seventh edition based on periosteal and bone involvement do not correlate with a greater risk of distant metastasis and tumor-related death for adenoid cystic carcinoma.[24,34] In a clinical review of 18 cases, Williams et al.[24] found that tumor size was a more adverse factor than bone invasion.[24] These authors observed that smaller tumors with bone invasion (T2, sixth edition) were less likely to metastasize than were larger tumors (T3b, sixth edition; 16.7% vs. 55.6%)[24]; however, tumors designated T2 or T3b in the sixth edition would be classified as T4 in the seventh edition based purely on periosteal and bony involvement regardless of size. The seventh edition of the AJCC staging system for lacrimal gland carcinoma should be revisited, and validation studies should be performed to help determine the appropriate size cutoffs for T designations. The eighth edition of the AJCC staging criteria is currently being developed and should be published by the end of 2015.

Local Treatment Options. Treatment strategies for adenoid cystic carcinoma should be focused on local control and prevention of distant metastasis, if possible. Appropriate treatment modalities for local control are still controversial.[14,31] Orbital exenteration has been a preferred treatment modality because the tumor lacks a capsule and marginal tumor infiltration is common; this along with the high prevalence of perineural invasion also indicates a need for postoperative adjuvant high-dose radiation therapy.[12,13,35–37] Adjuvant radiotherapy for lacrimal gland carcinomas is usually delivered at daily fractions of 2 Gy to a total dose of 60 Gy to 65 Gy (30–33 fractions).[20] More recently, many centers adopt intensity-modulated radiation therapy (IMRT) technique or intensity-modulated proton radiotherapy (IMPT) to deliver radiation more efficiently and to lessen adverse effects to important surrounding structures such as brain and pituitary axis.[37]

Factors that may contribute to local recurrence include perineural invasion, microscopically positive resection margin, and a larger tumor size.[24,26,27] In an MD Anderson series, 7 patients with locally advanced adenoid cystic carcinoma of the lacrimal gland were treated with surgery and radiation therapy (Fig. 3). All patients showed excellent local control at a median follow up time of 22 months; however, 5 patients had distant metastasis and died of disease at follow up times ranging from 12 to 32 months after surgery.[38]

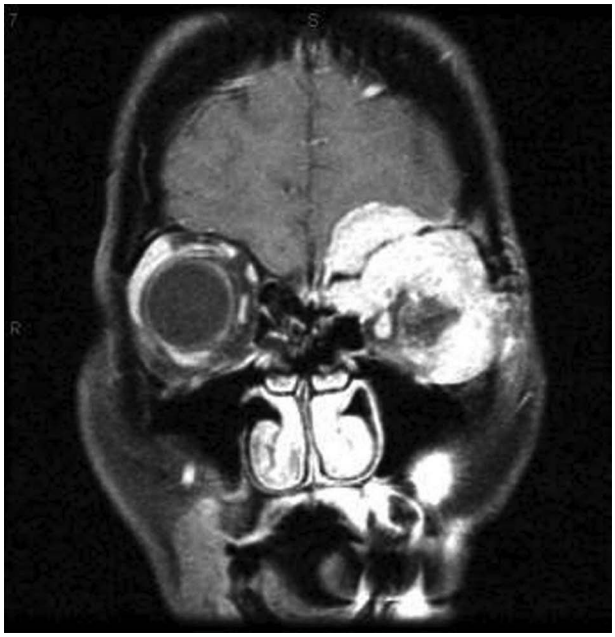

FIG. 3. MRI of a recurrent locally advanced adenoid cystic carcinoma of lacrimal gland with brain invasion.

There has been controversy about whether extensive surgery is indicated for adenoid cystic carcinoma of the lacrimal gland. Wright et al.[15] asserted that the rate of disease-free survival after treatment of adenoid cystic carcinoma appeared unrelated to whether cranio-orbital resection was performed though the patients who underwent such resection formed a greater proportion of those surviving for more than 10 years. Moreover, Polito and Leccisotti[8] reported that the median survival of patients with lacrimal gland carcinoma was 6.75 years in the 7 patients treated with extensive surgery and 9 years in the 12 patients treated with the eye-saving procedures of tumor excision and radiation therapy. Extensive surgery for lacrimal gland malignancies did not improve survival.

For cases with limited disease extent, globe-sparing tumor excision through lateral orbitotomy to allow for globe sparing surgery with or without adjuvant therapy has been performed in a small number of patients (Fig. 4A,B).[20,26,39–41] Ahmad et al.[26] proposed the possibility of more conservative treatment for early-stage tumors, including globe-preserving surgery followed by radiation therapy, after analyzing survival rates by AJCC stage. Adjuvant radiation therapy should be part of any globe-sparing approach because adenoid cystic carcinoma responds relatively well to radiation therapy compared with other lacrimal gland carcinomas and radiation therapy could decrease the overall recurrence rate.[20] Another important factor to consider when globe-sparing surgery and adjuvant radiation therapy is being considered is the lack of published studies to date detailing ocular toxic effects associated with high-dose radiation therapy after globe-sparing surgery for lacrimal gland carcinoma. Of note, in the surgical approach to the lacrimal gland fossa, a transfrontal approach via craniotomy is not recommended because it may not provide better exposure to the lacrimal gland region compared with other orbital surgical approaches, except for lesions with posterior orbital apical extension, and it might precipitate intracranial tumor spread in lesions that are incompletely excised.[8,12,42,43]

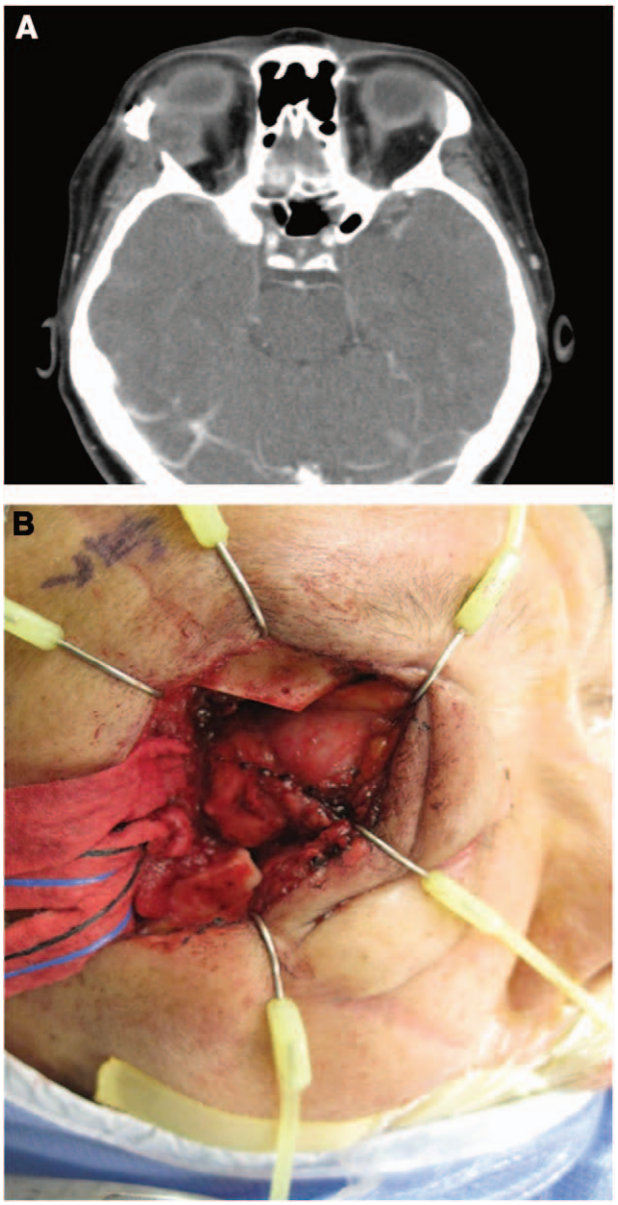

FIG. 4. **A**, CT axial image of lacrimal gland adenoid cystic carcinoma, which was excised through a lateral orbitotomy (**B**).

Several nonsurgical treatment modalities have been tried for patients with advanced adenoid cystic carcinoma of the lacrimal gland and for patients who wish to avoid surgical treatment. As adjuvant therapy, these include external beam radiation therapy,[20] plaque therapy,[39] proton therapy,[26,40,44] and neutron therapy.[41,45] Some of the reports of these treatments were limited to single institutions, and the numbers of patients enrolled and the follow up periods are not sufficient to permit any conclusions to be drawn. These therapeutic measures may prove effective in improving local/regional control rates for adenoid cystic carcinoma of the lacrimal gland, but further studies in larger cohorts of patients are needed to verify the efficacy and toxicity profiles of these measures.

The use of standard cytotoxic chemotherapy has had a limited role in treating head and neck adenoid cystic carcinoma. In patients with locally advanced adenoid cystic carcinoma, adjuvant chemotherapy after surgical treatment has not been considered a standard treatment but may be delivered concurrently with adjuvant radiation therapy to enhance radiation therapy's therapeutic effect.[26] Adjuvant chemoradiation with cisplatin, which is used as a radiosensitizer in head and neck cancers, such as squamous cell carcinoma, is occasionally applied in patients with adenoid cystic carcinoma with a high risk of local recurrence.[46–48] In patients with metastatic adenoid cystic carcinoma, clinical responses to cytotoxic chemotherapy were observed in the minority of patients and were generally short lived.[46,49] Combination cytotoxic regimens are known to produce higher response rates (28% in 100 patients) than monotherapy (6.8% in 117 patients) in patients with adenoid cystic carcinoma of the head and neck region[46]; however, the increased toxicity of combination regimens must be considered.[46,49]

Neoadjuvant Chemotherapy. Neoadjuvant intra-arterial chemotherapy followed by orbital exenteration followed by radiation therapy and several additional cycles of adjuvant chemotherapy has been employed as an investigational protocol by Tse et al. at one center in the United States.[50–52] In a series of 19 patients treated with this approach, the 8 patients (group 1) with an "intact lacrimal artery" or who "followed protocol" had a cumulative 10-year disease-free survival rate of 100%; this was significantly better than the 10-year disease-free survival rate of 50% for the 11 patients (group 2) who had an "absence of the lacrimal artery or deviated from the treatment protocol" and the 10-year disease-free survival rate of 14.3% for historical controls from the same institution treated conventionally in an earlier period.[52] The authors claimed that "an intact lacrimal artery," no disruption of bone barrier or tumor manipulation other than incisional biopsy, and protocol compliance were factors responsible for favorable outcomes.[52] However, no proof of an intact lacrimal artery in the 8 patients who did well (group 1) was provided in the report, no angiography was performed in any of the patients in the report, and no other radiographic evidence of an anatomical difference between patients in group 1 and group 2 was provided. Furthermore, all 19 patients in the study (whether with an "intact" lacrimal artery or not) reportedly had a clinical response to intra-arterial chemotherapy, making it difficult to understand why intactness of the lacrimal artery mattered. Furthermore, intra-arterial chemotherapy in this protocol was delivered through a branch of the external carotid artery, again making it difficult to understand the relevance of an intact lacrimal artery.

Other factors that might have contributed to the difference in survival observed between group 1 and group 2 include patient age, tumor stage at presentation, which was not reported in the article, and tumor surgical margin positivity.[50,51] Two of the 8 patients in group 1 (intact lacrimal artery) and 9 of the 11 patients in group 2 (absence of lacrimal artery) had bone involvement or positive surgical resection margins, which suggests that the 2 groups were different in disease stage and extent at the time of treatment. The poorer survival of group-2 patients could be explained by previous incomplete surgery and positive surgical margins, which were found in 10 of 11 group 2 patients. Furthermore, it is unclear which specific step in the protocol advocated by the authors is responsible for the reported "better outcomes" in group 1—the neoadjuvant intra-arterial cisplatin, the multiple cycles of postoperative intravenous chemotherapy, the uniform radical surgery (orbital exenteration) in all patients, or the postoperative concurrent chemoradiation? Could more than 1 step be essential or responsible for the better outcomes in group 1? Why not just use neoadjuvant intravenous chemotherapy in an attempt to shrink tumor? Intravenous chemotherapy is easier to administer with fewer side effects than intra-arterial chemotherapy.

The authors state that a low rate of protocol compliance had an unfavorable impact on prognosis in group-2 patients.[52]

Low compliance could have been due to substantial toxicity associated with intra-arterial chemotherapy. Several patients in Tse et al.'s[52] series had grade 4 life-threatening adverse events, including neutropenia (9 of 21 patients), blindness (1/21), and kidney damage necessitating renal transplant (1/21); in addition, there were numerous grade 3 adverse events, including anemia (5 of 21 patients), thrombocytopenia (12/21), and need to begin wearing a hearing aid (1/21), and other chemotherapy-related, local, catheter-related, and neurologic adverse events.[52] Tse et al.[51] recommended that their investigational treatment be implemented only in an environment "with considerable supportive care capabilities."

In a review article published in 2011, Le Tourneau et al.[46] commented that the use of neoadjuvant chemotherapy should preferably be restricted to patients enrolled in clinical trials and suggested that further studies be focused on omitting specific steps in Tse et al.'s combination therapy protocol to reduce toxicity while still retaining efficacy. Additional controlled studies should be conducted to verify the influence of disease stage at the time of treatment and to distinguish essential parts of the treatment protocol from less significant steps to alleviate toxicity and improve patient compliance. Perhaps a chemoreduction trial using standard intravenous chemotherapy prior to surgery would make sense.

Molecular Insights. The molecular pathogenesis and phenotype of adenoid cystic carcinoma of the salivary and lacrimal glands have been studied to shed light on the relationship between tumor biology and prognosis. Highly metastatic cell lines have lower expression levels of extracellular matrix proteins, such as collagen Type IV and laminin, and adhesion molecules, such as cadherin 2, but higher expression of genes controlling extracellular matrix degradation, such as matrix metallopeptidase 9.[46] Vascular endothelial growth factor was also highly expressed in adenoid cystic carcinoma and showed positive correlations with the angiogenesis and clinical outcome.[53] Tumor expression of antiapoptotic proteins has also been associated with clinical outcomes: higher nuclear expression of survivin (BIRC5), a member of the inhibitors of apoptosis family, has been reported to be associated with higher expression of Ki-67, a solid histologic pattern in more than 30% of the tumor, and a shorter progression-free survival.[28,54]

Diverse molecularly targeted agents are currently under study in clinical trials for treatment of metastatic adenoid cystic carcinoma of the salivary gland.[46,49] Further investigations should be conducted on the underlying biology precipitating perineural invasion and distant metastasis of lacrimal gland adenoid cystic carcinoma and on disease-modifying therapeutic agents.

Other Lacrimal Gland Carcinomas. ***Patient Outcomes.*** The subtypes of lacrimal gland carcinoma other than adenoid cystic carcinoma are very rare, and the prognosis of patients with these other subtypes has been reported to be poor, but only on the basis of small case series.[12,36,55–58] In a series of 10 patients with squamous cell adenocarcinoma, undifferentiated carcinoma, or malignant mixed tumor of the lacrimal gland reported by Forrest[13] in the 1970s, 4 patients had biopsy as their only surgery, and 6 patients had exenteration. Seven patients died during the first year after surgery, while 1 patient lived for 4 years after exenteration.[13] In a series of 129 lacrimal gland carcinoma patients studied by Font and Gamel,[12] the reported overall mean survival time for all patients with lacrimal gland carcinoma was 5.0 years, the mean survival time for 34 patients with malignant mixed tumors of the lacrimal gland was 12.0 years, and the mean survival time for 19 patients with adenocarcinoma of the lacrimal gland was 3.5 years. However, no information was provided about tumor size or AJCC stage at presentation. Because of the small numbers of patients in series reported to date, the influence of therapy on the outcome of patients with lacrimal gland carcinomas other than adenoid cystic carcinoma is difficult to assess.

The biologic behaviors and prognosis of other lacrimal gland carcinomas may reflect those of salivary gland carcinomas, as the salivary gland carcinomas are histologically similar and more prevalent.[59] Terhaard et al.[60] found that histologic type of the salivary gland carcinoma of World Health organization (WHO) classification was an independent factor for the risk of distant metastasis; however, another study by Bjorndal et al.[61] showed no relationship between histologic type and survival. Age, latency, stage, microscopic margins, vascular invasion, and histologic grade were independent prognostic factors with regards to crude and disease-specific survival in 871 patients of primary salivary gland carcinomas in a national Danish series.[61]

Management Overview. In the management of other lacrimal gland carcinomas, lower stage at presentation, complete surgical resection, and use of adjuvant treatments such as radiation therapy are important factors related to good survival. Brada and Henk[20] suggested that radiation therapy was of little value as a salvage procedure for recurrent or incompletely excised adenocarcinoma, undifferentiated carcinoma, and malignant mixed tumor; however, these authors advocated radiation therapy as an adjuvant treatment following complete surgical excision. In a multivariate analysis of 565 patients with salivary gland carcinoma, postoperative radiation therapy was one of the independent factors affecting local and regional control rates.[60] The prognostic value of clinical stage at presentation and pathologic grade for patients with lacrimal gland carcinomas should be evaluated in larger patient cohorts.

Malignant Mixed Tumor. In malignant mixed tumor, the thinking about prognosis has evolved. Two categories of patients have emerged. Patients with primary malignant mixed tumor, which essentially is assumed to result from a spontaneous malignant transformation, are thought to have a worse prognosis than patients who experience a recurrence and malignant transformation after incomplete excision of a pleomorphic adenoma, which is thought to have a more indolent course. These 2 different patterns of clinical presentation may account for the variability in survival data reported for malignant mixed tumor.[36] From a pathologic standpoint, Font and Gamel[12] categorized malignant mixed tumor into adenoid cystic carcinoma and adenocarcinoma arising in benign mixed tumors; however, these authors did not observe a significant difference in patient survival. Henderson and Farrow[36] regarded the division of malignant mixed tumors into histologic subtypes as being of more academic than practical interest.

For malignant mixed tumor of the lacrimal gland, Henderson and Farrow[36] have suggested management with en bloc resection with surrounding bone (if involved) as a primary procedure. Other authors have recommended radical management because of the poor prognosis of these carcinomas; recommended strategies have included exenteration to include the biopsy tract and radical orbital bone resection with postoperative radiation therapy and cranio-orbital resection of the tumor.[14,36] As is the case for adenoid cystic carcinoma, most reports of malignant mixed tumor contain few patients and no information regarding tumor size, stage, or histologic grade.

Pathologic findings of malignant mixed tumor characteristically demonstrate an obvious contrast between the areas replaced with large malignant cells and the surrounding areas with benign cells. Malignant area may show high Ki-67 (MIB-1) index or HER-2/neu, p53, or androgen receptor overexpression.[62] These findings may be applied to distinguish the malignant from the benign components of a malignant mixed

tumor of lacrimal gland; however, caution is advised about interpretation these stains because benign pleomorphic adenomas can also express these markers to some degree.

In the 2005, WHO classification of the salivary gland carcinoma, malignant mixed tumor was classified as follows: noninvasive (in situ, intracapsular), minimally invasive (≤1.5 mm), invasive (>1.5 mm) carcinoma ex pleomorphic adenoma (CEPA), carcinosarcoma (true malignant mixed tumor), and benign metastasizing pleomorphic adenoma.[59]

In the seventh edition of the *AJCC Cancer Staging Manual*, malignant mixed tumor of the lacrimal gland was divided into low-grade CEPA and high-grade CEPA (malignant mixed tumor), which includes adenocarcinoma and adenoid cystic carcinoma arising in a pleomorphic adenoma.[33] Rootman and White[33] also underscored the importance of tumor invasiveness; noninvasive CEPA not extending beyond the limits of the capsule was unlikely to cause future morbidity if excised without breach of the capsule. Therefore, clinical stage and histopathologic grade may influence the prognosis of patients with malignant mixed tumor. Our experience also suggests that the histopathologic grade and size of lacrimal gland carcinoma are key factors determining outcomes.

Adenocarcinoma. In Font and Gamel's[12] 19-patient series of patients with lacrimal gland adenocarcinoma, there was a male preponderance (3.7:1), and the actuarial 5-year survival rate was 34%. In a 13-patient series reported by Heaps et al.[56] from a multicenter study, orbital exenteration followed by radiation therapy was the most effective treatment for primary adenocarcinoma of the lacrimal gland; shorter duration of symptoms before treatment seemed to decrease the chance of metastasis and increase the chance of long-term survival.

Management of adenocarcinoma of the lacrimal gland has been evolving due to the knowledge of pathologic characteristics and clinical behavior of the salivary gland adenocarcinoma. Adenocarcinoma of the salivary gland has been subdivided into 10 subtypes with the change in WHO's classification.[59,63,64] Referring to the WHO's classification of the salivary gland tumors, the seventh edition of the AJCC classification categorized adenocarcinoma into low-grade tumors, such as basal cell adenocarcinoma, polymorphous low-grade adenocarcinoma, cystadenocarcinoma, and mucinous adenocarcinoma, and high-grade tumors, such as adenocarcinoma not otherwise specified, sebaceous adenocarcinoma, and ductal adenocarcinoma.[33,65,66] These subdivisions allow for a more precise diagnosis. Of note, complete tumor excision without intraoperative breach may be sufficient for some of the low-grade adenocarcinomas such as "cystadenocarcinoma."[65]

Mucoepidermoid Carcinoma. Mucoepidermoid carcinoma is considered to be the most commonly occurring major salivary gland carcinoma, although some differences exist across studies regarding frequencies of mucoepidermoid carcinoma of salivary gland.[61,63] In contrast, this particular cancer is very rare in the lacrimal gland, and this difference in incidence between salivary gland and lacrimal gland may be related to different embryologic origin for these 2 anatomical sites.[67] Eviatar and Hornblass[55] examined the prognosis of patients with mucoepidermoid carcinoma of the lacrimal gland in a cumulated case series. The prognosis could be predicted by the histologic tumor grade: prognosis was better for patients with low-grade tumors (grades 1 and 2) than for those with high-grade tumors (grade 3); the grading system is the same as that used for salivary gland carcinoma and as used for the seventh edition of the *AJCC Cancer Staging Manual*.[33,55] For early-stage and low-grade tumors, extirpation of the tumor with or without radiation therapy was suggested, and for high-grade tumors, exenteration and radiation therapy with additional excision of orbital bone was suggested.[35,55] These grade 3 tumors carried a poor prognosis despite aggressive multimodality treatment. For salivary gland mucoepidermoid carcinoma, prognosis is a function of the histologic grade, adequacy of excision, and clinical staging.[68] Additionally, a MIB-1 index greater than 10% correlated with high histopathologic grade, increased risk of recurrence and metastasis, and a decreased survival.[59] Complete surgical excision is the treatment of choice, and adjuvant radiotherapy is recommended in the case of high-grade tumors and presence of residual microscopic disease at the surgical margins.

Management Scheme for the Patients with Adenoid Cystic Carcinoma. An algorithmic approach to management of lacrimal gland tumors is summarized in Figure 5. Once a lacrimal gland mass is suspected, it should be further evaluated by an imaging study, either CT or MRI. Orbital imaging techniques have progressed significantly since the early reports by Wright et al.[69] in 41 patient who underwent CT scanning in 1975 for evaluation of their orbital mass lesions.[69–71] CT is superior to MRI for detection of bony invasion or lytic bony lesions. MRI is superior in delineating the soft tissue extension of tumor and more anatomical detail.[72] Furthermore, a technique of MRI sequencing as diffusion-weighted imaging (DWI) in a preliminary study has been suggested to potentially better distinguish pleomorphic adenoma from malignant lacrimal gland carcinoma.[73]

Once a diagnosis of lacrimal gland mass is established on imaging studies, the next consideration is whether to do an incisional biopsy or a total surgical resection of the mass. Font and Gamel[12] discouraged an incisional biopsy for epithelial lesions of the lacrimal gland stating that "Our data strongly suggest that if the tumor is of epithelial origin, the initial surgical procedure will have an immense impact on the patient's outcome." Wright et al.[43] recommended an approach based on duration of symptoms and bony change in radiographic finding to diminish the need for histologic diagnosis by frozen section and permits decisions on extensive surgical removal of the tumor. It could also be helpful to avoid unnecessary biopsy for pleomorphic adenoma and the potential risk of transformation after an incisional biopsy of a pleomorphic adenoma not followed by total surgical resection. An incisional biopsy is definitely appropriate when a lymphoproliferative or inflammatory lesion of lacrimal gland is suspected.[31,43] Once the diagnosis of lacrimal gland carcinoma is established based on an incisional or excisional biopsy, in the case of carcinoma of less than or equal to 2.5 cm in greatest dimension limited to the lacrimal gland or invading the periosteum of the lacrimal gland fossa, which is of T1 or T2 lesion in sixth AJCC classification, en bloc tumor excision can be cautiously considered as an eye and vision-preserving procedure.[26] An eyelid crease incision with bone flap is preferred by many oculoplastic surgeons for lateral orbitotomy approach for removal of a lacrimal gland carcinoma.[74] Careful meticulous tumors dissection is critical particularly in the case of multilobulated lacrimal gland carcinomas. As the lacrimal gland is adjacent to critical functionally important structures such as extraocular muscles, wide tissue margins are rarely obtained. Careful intraoperative inspection of adjacent orbital bone with biopsy or removal of any suspicious areas is warranted.[33]

When there is an obvious radiographic evidence of bony involvement or intraoperative clinical evidence of abnormal bone is encountered, bone removal needs to be performed.[30,38] All the resected bone should be decalcified and examined pathologically for accurate staging purposes. The pathologist should be alerted by the orbital surgeon about the presence of bone in the surgical specimen.

For larger tumors or those with infiltration into orbital soft tissue or significant posterior extension, an orbital exenteration would be the best alternative surgical procedure, and

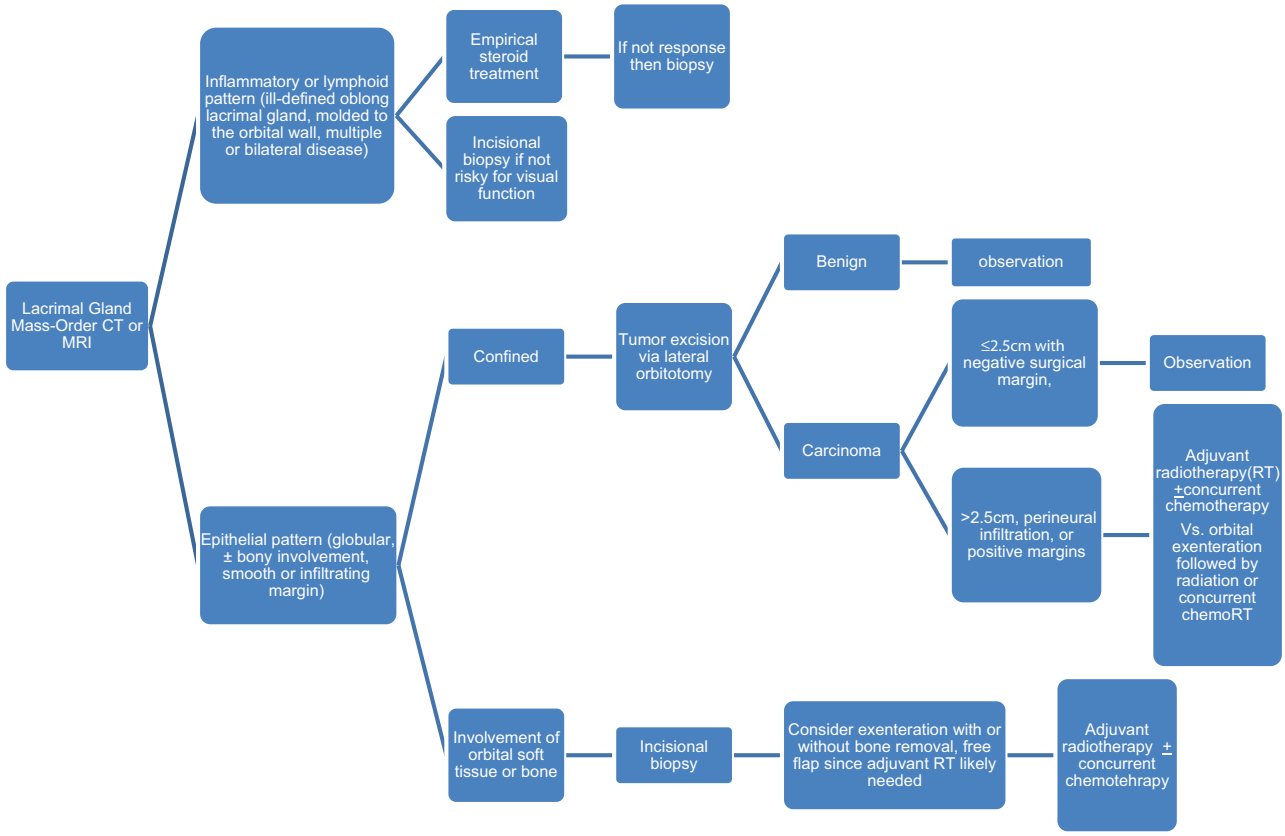

FIG. 5. An algorithm summarizing a proposed "decision tree" for management of lacrimal gland tumors.

in fact, historically, orbital exenteration is the most commonly performed surgical procedure for adenoid cystic carcinoma of the lacrimal gland. Henderson[30] introduced several techniques of bone resection during exenteration for adenoid cystic carcinoma. However, he was skeptical to perform such a radical surgery because of low rate of survival. For locally advanced cases of lacrimal gland carcinoma and those with extension through the superior orbital fissure or orbital apical structures or brain parenchyma or dural involvement, a radical orbitectomy procedure maybe necessary as described by Esmaeli et al.[38] This can be performed either through a craniotomy approach or fronto-orbito-zygomatic approach with removal of the bone of the superior and lateral wall.[38] Because of extensive dural exposure after removal of the bony roof of the orbit and the anticipated need for postoperative adjuvant radiation therapy, a vascularized free flap is usually needed as the optimal reconstructive option.[38]

FUTURE DIRECTIONS

In an article published in 1982, Wright[19] stated that the results of treatment of some epithelial lacrimal gland tumors had "improved greatly" during the previous 30 years. Conversely, in an article published in the mid-1980s, Lee et al.[25] asserted that the various therapeutic procedures did not significantly affect the duration of survival in patients with adenoid cystic carcinoma.[25]

Since the publication of these articles, improved imaging modalities such as high-resolution CT and MRI have improved diagnosis of lacrimal gland carcinoma. Furthermore, radiation delivery techniques and particularly techniques for organ-sparing delivery of high-dose radiation therapy, such as proton radiation therapy, have advanced significantly. Our understanding of the molecular signature of lacrimal gland carcinoma has improved, and the availability of newer targeted drugs based on the molecular signature of an individual lacrimal gland carcinoma opens the possibility of new drug treatments for patients with nonresectable or metastatic disease. Given the rarity of lacrimal gland carcinoma and the possibility of late distant relapse years after initial local therapy, there is a need for well-designed multi-institutional controlled clinical trials exploring multimodality management of lacrimal gland carcinoma through judicious use of surgery (including globe-sparing techniques in selected patients), radiation therapy, and adjuvant and neoadjuvant chemotherapy. Strict and standardized staging and histologic classification for lacrimal gland carcinoma will not only facilitate selection of treatment modalities but also improve data reporting and facilitate interpretation of data generated from various centers.

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