# Does Multimodal Treatment Improve Eye and Life Salvage in Adenoid Cystic Carcinoma of the Lacrimal Gland?

*Fairooz P. Manjandavida, M.D., F.A.C.S.,*† Santosh G. Honavar, M.D., F.A.C.S., F.R.C.Ophth.,†‡ Ramesh Murthy, M.D., F.R.C.S.,†§ Sima Das, M.D.,†‖ Geeta K. Vemuganti, M.D.,†¶ Kaustubh Mulay, M.D.,†‡ and Vijay Anand P. Reddy, M.D.†‡*

*From the *Eye Cancer Service, Horus Specialty Eye Care, Bangalore, India; †Departments of Ophthalmic Plastic Surgery, Orbit and Ocular Oncology; and Ophthalmic Pathology, LV Prasad Eye Institute, Hyderabad, India; ‡Departments of Ophthalmic Plastic Surgery, Orbit and Ocular Oncology; and Ophthalmic Pathology, Centre for Sight, Hyderabad, India; §Department of Oculoplasty, Axis Eye Clinic, Pune, Maharashtra, India; ‖Oculoplasty and Ocular Oncology Services, Shroff's Charity Eye Hospital, Delhi, India; and ¶University of Hyderabad, Hyderabad, India.*



***Purpose:*** To evaluate the efficacy of multimodal treatment in adenoid cystic carcinoma (ACC) of the lacrimal gland.

***Methods:*** A retrospective comparative case series of 40 consecutive patients with ACC of the lacrimal gland without systemic metastasis at the initial presentation and primarily managed by one of the 3 treatment protocols—surgery + external beam radiotherapy (EBRT) (group 1), surgery + EBRT + adjuvant chemotherapy (group 2), and neoadjuvant chemotherapy + surgery + EBRT + adjuvant chemotherapy (multimodal treatment) (group 3) at a tertiary care ocular oncology center. Local tumor control, eye salvage, and systemic metastasis were the primary outcome measures.

***Results:*** The age ranged from 11 to 72 (mean ± SD, 36 ± 13; median, 36) years with 26 (65%) male and 14 (35%) female patients. Twelve (30%) patients belonged to group 1, 8 (20%) to group 2, and 20 (50%) to group 3. Primary surgery included tumor excision in 36 (90%) and orbital exenteration in 4 (10%). Chemotherapy composed of cisplatin + 5 fluorouracil (5FU) for 6 cycles in 28 (70%) patients. Extended-field stereotactic EBRT with a dose of 5,000–6,000 cGy included the entire pretreatment extent of the tumor with a 10-mm margin all around, superior orbital fissure, inferior orbital fissure, cavernous sinus, and temporal fossa. Mean duration of follow up after completion of treatment was 58 ± 26 (range, 29–180; median, 60) months. In all, local tumor recurrence occurred in 10 (25%) patients at a mean of 38 ± 23 (range, 12–120; median, 24) months. Local tumor recurrence was noted in 5 (42%) patients in group 1, 2 (25%) in group 2, and 3 (15%) in group 3. Overall, eye salvage was possible in 34 (85%) patients, with visual acuity >20/40 in 28 (82%). Systemic metastasis occurred in 10 (25%) patients at a mean of 53 ± 28 (range, 12–120; median, 43) months. Eight (67%) patients in group 1, 1 (13%) in group 2, and 1 (5%) in group 3 developed systemic metastasis. Six (15%) overall, 5 (42%) in group 1 and 1 (13%) in group 2, died with systemic metastasis.

***Conclusions:*** Multimodal treatment with sequential neoadjuvant chemotherapy, followed by surgery, extended-field stereotactic EBRT, and adjuvant chemotherapy seems relatively more effective in providing local tumor control and eye salvage and in minimizing the risk of systemic metastasis in ACC of the lacrimal gland.

(*Ophthalmic Plast Reconstr Surg* 2021;00:00–00)

Henderson considered adenoid cystic carcinoma (ACC) of the lacrimal gland the most-evil of all primary neoplasms of the orbit.[1] ACC of the lacrimal gland is indeed an aggressive tumor with suboptimal local tumor control and high mortality.[1–17] Although relatively rare, it is the most common malignant epithelial tumor of the lacrimal gland, accounting for about 2% of all orbital tumors, 5% of all primary orbital neoplasms, and 29% of all epithelial tumors of the lacrimal gland.[2–5]

Several studies have documented local tumor recurrence ranging from 55% to 88% following surgery and external beam radiotherapy (EBRT).[3–16] Complex regional anatomy and the proclivity for microscopic perineural, soft tissue, and bone infiltration makes it difficult to provide complete tumor clearance despite meticulous tumor excision, or orbital exenteration.[17] Radical orbital exenteration has failed to demonstrate a benefit over conservative eye-sparing procedures in improving the outcome.[8,10,18,22] Because of these well-known limitations of surgical modalities, postoperative adjuvant EBRT was advocated to potentially reduce the risk of local tumor recurrence.[17,22] Despite surgery and EBRT, systemic prognosis of these patients remains grim, with survival of ≤50% at 5 years and 20% at 10 years.[1,3–6,20–24] The dismal systemic prognosis has been attributed to aggressive biological behavior of this tumor and propensity to neural, hematologic, and lymphatic invasion.[1,3–6,14,25]

The role of chemotherapy in reducing the risk of systemic metastasis is not established.[5,16] Neoadjuvant chemotherapy with cisplatin for ACC of the salivary glands showed promising preliminary results.[26,27] Meldrum et al[16] used neoadjuvant chemotherapy before orbital exenteration, followed by combined EBRT and chemotherapy and noted improved survival. Recently, Tse et al[5] have reported the outcome of neoadjuvant

Accepted for publication October 20, 2021.

The authors have no financial or conflicts of interest to disclose.

Presented in part at American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) Fall Scientific Symposium 2016 at Chicago, IL, USA.

Address correspondence and reprint requests to Santosh G. Honavar, MD, FACS, FRCOphth, Department of Ophthalmic Plastic Surgery, Orbit and Ocular Oncology, Centre for Sight, Hyderabad, Telengana 500034, India. E-mail: santosh.honavar@gmail.com.

**DOI: 10.1097/IOP.0000000000002108**

intra-arterial chemotherapy prior to orbital exenteration, adjuvant systemic chemotherapy, followed by EBRT.

The management of ACC of the lacrimal gland is still in evolution. There is no consensus yet on the role of various primary surgical procedures in providing local tumor control and that of adjuvant treatment in improving patient survival. We aimed to study the outcomes (local tumor control, eye salvage, and life salvage) of ACC of the lacrimal gland with sequential combination of neoadjuvant chemotherapy, surgery, radiotherapy, and adjuvant chemotherapy (multimodal therapy) and compare with it with conventional management modalities.

## MATERIALS AND METHODS

A retrospective review of medical records of all consecutive patients with ACC of the lacrimal gland managed at our Ocular Oncology Service from August 1995 to July 2015 (followed until July 2020) was performed. The ocular oncologist, medical oncologist, and the radiation oncologist were constant during the study period. Of the 1,280 biopsy-proven orbital tumors managed during the study period retrieved from the orbital tumor database, there were 48 (4%) cases of ACC of the lacrimal gland. Presence of systemic metastasis at the initial presentation or refusal to undergo the treatment were the exclusion criteria. Three patients with systemic metastasis at the initial presentation and 5 patients, who did not undergo the suggested treatment and were lost to further follow up, were excluded. Forty consecutive patients who completed the assigned treatment were included in the study.

The clinical variables studied included age, gender, presenting symptoms, duration of symptoms before diagnosis, presenting signs, radiological features, methods of treatment, local tumor recurrence, interval to local tumor recurrence, presence and location of systemic metastases, interval to systemic metastasis, and outcome at final follow up. We adopted the 8th American Joint Committee on Cancer—Tumor (T), Node (N), Metastasis (M) classification for staging the patients.

Initial evaluation composed of complete ophthalmic and regional examination and orbital imaging with CT scan and/or MRI. The diagnosis of ACC was considered based on clinical features along with radiological signs. Proptosis with inferior and nasal displacement of the eye caused by a firm to hard mass in the region of the lacrimal gland with accompanying features such as temporal ptosis, ocular motility restriction, diplopia, pain, and frontotemporal hypesthesia were the clinical clues. Imaging showed an ovoid hyperdense mass in the lacrimal gland area with irregular borders, crossing the midline, non-homogeneous contrast enhancement, intralesional calcification, cystic areas within the tumor and contiguous bone erosion on CT scan; and homogeneous isointense signals on T1 but variable (ranging from hyperintense to isointense and often mixed/patchy) signals on T2 on MRI. Baseline systemic evaluation by the oncologist included CT scan of head and neck, chest and abdomen, or whole-body positron emission tomography scan.

Management of ACC of the lacrimal gland has gradually evolved over time in our Ocular Oncology Service. Initially (from 1995 to 2002), surgery (complete tumor excision or orbital exenteration) followed by EBRT was the standard primary management (group 1). Complete tumor excision was performed if the tumor was well-defined and discrete on imaging. If the tumor was diffuse on imaging and involved contiguous orbital soft tissues or bone, a trans-septal incisional biopsy by a sub-brow incision was performed to confirm the diagnosis, followed by an orbital exenteration by the partial eyelid sparing technique. Surgery was followed by adjuvant fractionated stereotactic EBRT with a dose of 5,000 to 6,000 cGy 4 to 6 weeks later.

The addition of adjuvant chemotherapy to surgery and EBRT (from 2002 to 2006) was the next evolution in our clinical practice (group 2). Adjuvant fractionated stereotactic EBRT with a dose of 5,000 to 6,000 cGy was provided 4 to 6 weeks following tumor excision or orbital exenteration. Following surgery and postoperative EBRT, 6 cycles of 3-weekly adjuvant chemotherapy was provided with a combination of Cisplatin + 5FU.

Use of neoadjuvant chemotherapy to achieve chemoreduction, followed by surgery (tumor excision or orbital exenteration) as appropriate, EBRT and adjuvant chemotherapy (multimodal treatment) is our current (from 2006 onwards) preferred management (group 3). Following an initial trans-septal biopsy to histopathologically confirm the diagnosis, patients were initiated on neoadjuvant chemotherapy with 3 cycles of 3-weekly Cisplatin + 5FU. The decision to perform tumor excision or orbital exenteration was governed by the appearance of the tumor on imaging at 3 weeks after the third cycle of chemotherapy. Tumor excision was performed in cases where the tumor appeared well-defined on imaging without apparent involvement of contiguous orbital soft tissues. Orbital exenteration was planned in patients with a diffuse tumor involving contiguous orbital soft tissues. Tumor was excised en bloc along with the overlying periorbita by a direct sub-brow skin incision. Orbital exenteration was of the eyelid sparing type with transverse blepharorrhaphy to cover the exenterated orbit. Fractionated 5,000 to 6,000 cGy adjuvant stereotactic EBRT was provided 4 to 6 weeks following tumor excision or orbital exenteration. Extended-field EBRT comprised of the entire pretreatment extent of the tumor with a 10-mm margin all around, superior orbital fissure, inferior orbital fissure, cavernous sinus, and temporal fossa. Patients until 2010 received 3D conformal radiotherapy and later by intensity-modulated radiation therapy. Adjuvant chemotherapy included 3 cycles of Cisplatin + 5FU at 3-week interval following surgery and EBRT. Every patient in group 3 received 6 cycles of chemotherapy in all. Histopathological features studied included the predominant histologic pattern, mitotic count per 20 high power fields (40×), and presence of necrosis, hemorrhage, and neural, intraosseous, vascular, or leptomeningeal invasion.

Local tumor control, eye salvage, and systemic metastasis were the main outcome measures. Kaplan-Meier analysis was performed for cumulative probability of local tumor recurrence and systemic metastasis at different time points until 10 years following primary treatment. Differences between survival curves in 3 groups were analyzed using log-rank test,

**TABLE 1.** Demographic profile, clinical features, and staging in 40 patients with ACC of the lacrimal gland

| Patient profile | Number (%) |
|---|---|
| Age in years | |
| Mean (range, median) | 36 (11–72, 36) |
| Gender | |
| Male | 26 (65) |
| Female | 14 (35) |
| Clinical presentation | |
| Proptosis | 38 (95) |
| Reduced vision | 10 (25) |
| Pain | 7 (18) |
| Hypoasthesia/parasthesia | 4 (10) |
| Bony deformity | 6 (15) |
| Compressive optic neuropathy | 4 (10) |
| TNM classification* | |
| T1N0M0 | 0 (0) |
| T2N0M0 | 6 (15) |
| T3N0M0 | 25 (62.5) |
| T4N0M0 | 9 (22.5) |
| Histopathological types | |
| Cribriform | 27 (67.5) |
| Basaloid | 6 (15) |
| Tubular | 4 (10) |
| Sclerosing | 3 (7.5) |
| Follow-up duration in months—mean (range, median) | 58 (29–180, 60) |

*Eighth American Joint Committee on Cancer (AJCC).
ACC indicates adenoid cystic carcinoma.

**TABLE 2.** Demographic features of patients of ACC of the lacrimal gland—Subgroup analysis of 40 patients

| Demographic features | Group 1 surgery + EBRT (n = 12) n (%) | Group 2 surgery + EBRT + adjuvant chemotherapy (n = 8) n (%) | Group 3 neoadjuvant chemotherapy + surgery + EBRT + adjuvant chemotherapy (n = 20) n (%) |
|---|---|---|---|
| Age in years, mean (median, range) | 28 (27, 11–47) | 37 (35, 15–60) | 39 (38, 26–72) |
| Gender | | | |
| Female (n = 14) | 3 (25) | 4 (50) | 7 (35) |
| Male (n = 28) | 9 (75) | 4 (50) | 13 (65) |
| Histopathology | | | |
| Cribriform (n = 27) | 8 (67) | 5 (63) | 14 (70) |
| Tubular (n = 5) | 2 (17) | 1 (13) | 2 (10) |
| Basaloid (n = 5) | 1 (8) | 1 (13) | 3 (15) |
| Sclerosing (n = 3) | 1 (8) | 0 (0) | 2 (15) |
| Perineural invasion (n = 14) | 3 (25) | 3 (38) | 8 (40) |
| Vascular invasion (n = 9) | 3 (25) | 1(13) | 5 (25) |
| AJCC 8 TNM staging | | | |
| T1N0M0 | 0 (0) | 0 (0) | 0 (0) |
| T2N0M0 | 1 (8) | 3 (37.5) | 2 (10) |
| T3N0M0 | 9 (75) | 2 (25) | 14 (70) |
| T4aN0M0 | 1 (8) | 1 (8) | 1 (5) |
| T4bN0M0 | 1 (8) | 2 (25) | 3 (15) |
| Follow-up duration in months, mean (median, range) | 75 (69, 36–180) | 47 (36, 30–80) | 52 (57, 29–72) |

ACC indicates adenoid cystic carcinoma; AJCC, American Joint Committee on Cancer; EBRT, external beam radiotherapy; TNM, tumor node metastasis.

with $p < 0.05$ considered statistically significant. Statistical analysis was performed with Stata version 13.1 (StataCorp, College Station, TX).

**Ethical Conduct of the Study.** The study was approved by the institutional review board and ethics committee. The principles outlined in the Declaration of Helsinki was followed for all subjects.

## RESULTS

Age ranged from 11–72 (mean ± SD 36 ± 15) years with 26 (65%) male and 14 (35%) female patients. Tables 1 and 2 provide an overview of patient demographics in 40 patients included in the study. The primary management was surgery with adjuvant EBRT in 12 patients (group 1), surgery with adjuvant EBRT and adjuvant chemotherapy in 8 patients (group 2), and neoadjuvant chemotherapy followed by surgery, adjuvant EBRT, and adjuvant chemotherapy in 20 patients (group 3) (Figs. 1 and 2). Follow up after completion of treatment was 58 ± 26, mean ± SD (range, 29–180; median, 60) months overall (Tables 1 and 2).

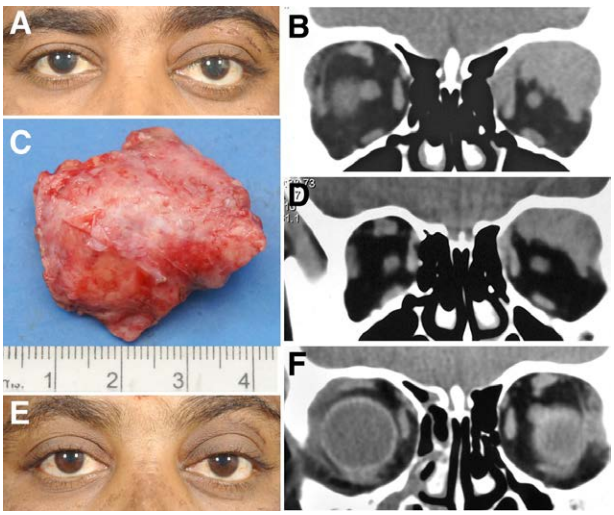


**FIG. 1.** A 60-year-old lady (group 3) with adenoid cystic carcinoma of the lacrimal gland in the left orbit (A) computed tomography scan in the coronal plane showing pretreatment appearance of the tumor involving the lacrimal gland (B); following neoadjuvant chemotherapy, the tumor was excised completely en bloc along with the overlying periosteum and it was well circumscribed (C). CT scan shows about 30–40% reduction in tumor volume (D) following neoadjuvant chemotherapy and before surgery; patient continues to do well 3 years thereafter with no local tumor recurrence (E) as confirmed by the CT scan (F).

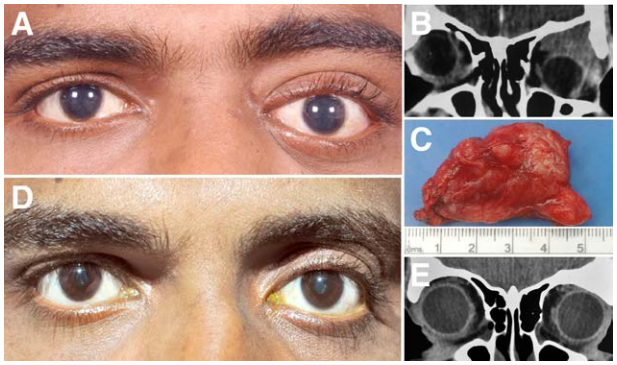


**FIG. 2.** A 32-year-old male (group 3) with adenoid cystic carcinoma of the lacrimal gland in the left orbit (A) with computed tomography scan showing bone involvement (B). The tumor was completely excised en bloc along with the overlying periosteum following 3 cycles of neoadjuvant chemotherapy (C). The patient has no evidence of local tumor recurrence 4 years following adjuvant external beam radiotherapy and 3 cycles of adjuvant chemotherapy (D), and CT scan shows complete remodeling of the involved bone (E).

Primary surgery composed of en bloc tumor excision in 36 (90%) and orbital exenteration in 4 (10%) patients. Histopathological details are shown in Table 2. Local tumor recurrence occurred in 10 patients at 38 ± 23, mean + SD (range, 12–120; median, 24) months after the primary treatment (Table 3). It was managed by cranio-orbital resection + EBRT + chemotherapy in 3, excision + after-loaded brachytherapy + chemotherapy in 3, excision + chemotherapy in 2, and orbital exenteration + chemotherapy in 2. All of them maintained local tumor

**TABLE 3.** Outcome of ACC of the lacrimal gland—subgroup analysis of 40 patients

| S. No | Features | Total number of eyes N = 40 n (%) | Group 1 (surgery* + EBRT) N = 12 n (%) | Group 2 (surgery* + EBRT + adjuvant chemotherapy) N = 8 n (%) | Group 3 (neoadjuvant chemotherapy + surgery + EBRT + adjuvant chemotherapy) N = 20 n (%) |
|---|---|---|---|---|---|
| 1 | Orbital exenteration | 6† (15) | 4† (33) | 1 (12.5) | 1 (5) |
| 2 | Eye salvage | 34 (85) | 8 (66) | 7 (87.5) | 19 (95) |
| 3 | Vision salvage ≥20/40 | 28 (87) | 6 (66) | 6 (85) | 16 (85) |
| 4 | Local tumor recurrence | 10 (25) | 5 (42) | 2 (25) | 3 (15) |
| 5 | Systemic metastasis | 10 (25) | 8 (67) | 1 (13) | 1 (5) |
| 6 | Mortality | 6 (15) | 5 (42) | 1 (13) | 0 (0) |

*Surgery includes local tumor excision and orbital exenteration.
†Includes 2 secondary orbital exenteration in patients who had local tumor recurrence in group 1.
ACC indicates adenoid cystic carcinoma; EBRT, external beam ratiotherapy.

control at the last follow up. Overall, 34 (85%) patients had eye salvage and 6 patients underwent orbital exenteration (Table 3). Final visual acuity was 20/40 or better in 28 of 34 (82%) patients who had eye salvage.

In all, systemic metastases occurred in 10 patients at a mean of 53 ± 28 (range, 12–120; median, 43) months, 7 to the brain and 3 to the lung. Systemic metastasis occurred in 8 patients in group 1, 1 in group 2, and 1 in group 3 (Table 3). While only 3 of 30 (10%) patients with local tumor control developed systemic metastasis, 7 of 10 (70%) patients with local tumor recurrence developed systemic metastasis. Six patients with systemic metastasis were treated with palliative chemotherapy, 5 of whom died, while 1 was alive with metastasis at the last follow up. Three patients with limited intracranial extension of the tumor underwent orbitocranial excision and stereotactic radiotherapy. Two of them were tumor free at the last follow up. One patient was managed with chemotherapy + EBRT; he was alive with metastasis at the last follow up at 18 months posttreatment.

The overall estimated 5-year failure free survival (FFS) for local tumor recurrence was 76% (95% CI, 59% to 87%). The overall estimated 5-year FFS for systemic metastasis was 84% (95% CI, 69% to 92%). FFS for local tumor recurrence at 3 years and 6 years was 92% (95% CI, 54% to 99%) and 62% (95% CI, 27% to 83%), respectively, in group 1; 75% (95% CI, 31% to 93%) at both 3 years and 6 years in group 2; and 85% (95% CI, 60% to 94%) at both 3 years and 6 years in group 3 (Fig. 3). The difference in the FFS for local tumor recurrence between the 3 groups was not statistically significant ($p = 0.59$). FFS for systemic metastasis at 3 years and 6 years was 83% (95% CI, 48% to 95%) and 46% (95% CI, 17% to 71%), respectively, in group 1; 87% (95% CI, 38% to 98%) at both at 3 years and 6 years in group 2; and 95% (95% CI, 69% to 99%) at both 3 and 6 years in group 3 (Fig. 4). FFS for systemic metastasis in group 3 was statistically significantly greater than that in group 1 ($p = 0.02$). FFS for systemic metastasis in group 2 was comparable to that in group 1 ($p = 0.2$) and group 3 ($p = 0.52$).

Treatment-related complications included dry eye needing tear supplements in all 34 (100%), radiation cataract in 6 (18%), radiation retinopathy in 4 (12%) of 34 patients who underwent EBRT. Transient bone marrow suppression during chemotherapy needed granulocyte colony stimulating factor support in 7 (25%) and blood or blood component transfusion in 10 (36%) of 28 patients who underwent chemotherapy.

Of 8 patients who were excluded, 3 had systemic metastasis at the primary presentation. Two of them managed by palliative chemotherapy succumbed to the disease at 6 and 8 months after the initial presentation. One patient who declined treatment survived for 3 months. Five patients, did not undergo the recommended treatment (2 in group 1, 1 in group 2, and 2 in group 3), were lost to further follow up and could not be contacted.

## DISCUSSION

ACC of the lacrimal gland, considered a "treacherous neoplasm," is characterized by a high rate of local tumor recurrence and systemic metastasis, and a dismal prognosis for survival.[1–22,28] Management of ACC of the lacrimal gland involves surgery, EBRT, and chemotherapy. Complete surgical clearance is difficult to achieve due to the infiltrative nature of the tumor, perineural invasion, soft tissue infiltration, and bone involvement.[3,17,24] Not surprisingly, orbital exenteration and radical cranio-orbital resection have not resulted in improved local tumor control or survival.[1–22,28] Logically, postoperative adjuvant EBRT may improve local tumor control and systemic chemotherapy may minimize the risk of metastasis.

The management of ACC of the lacrimal gland has evolved over time. We thus have a series of patients with long-term follow up, in which the initial set of patients were managed with surgery and adjuvant EBRT (group 1) and a few patients with surgery, adjuvant EBRT and adjuvant chemotherapy (group 2). Our current practice is to provide neoadjuvant chemotherapy, followed by surgery, adjuvant EBRT, and adjuvant chemotherapy, which we call multimodal therapy (group 3). We have analyzed the outcome in terms of local tumor control, eye salvage, and systemic metastasis in these 3 groups of patients.

The primary management for many years involved local tumor excision or orbital exenteration. Removal of the adjacent bone was attempted in recurrent tumors.[18,20] Radical surgery involving orbital bone resection was not routinely performed due to the high risk of meningitis and death.[1] Murray and colleagues proposed cranio-orbital resection for primary orbital disease.[19] Reported treatment protocols and outcome are summarized in Table 4. We performed en bloc tumor excision in 36 patients—10 (83%) in group 1, 7 (88%) in group 2, and 19 (95%) in group 3. Out of these, 10 (28%) developed local tumor recurrence. Local tumor recurrence occurred in 5 in group 1, 2 in group 2, and 3 in group 3. Seven of 10 patients with local tumor recurrence developed systemic metastasis. In all, 4 patients underwent primary orbital exenteration—2 (17%) in group 1, 1 (12.5%) in group 2, and 1 (5%) in group 3. Two of 4 (50%) patients who underwent primary orbital exenteration developed systemic metastasis and they belonged to group 1.

The role of adjuvant EBRT is debatable. In our series, 5 of 12 (42%) developed local tumor recurrence and 8 of 12 (67%) developed systemic metastasis with adjuvant EBRT alone following surgery. Lee reported that 88% of their patients received adjuvant EBRT with apparently no beneficial effect on patient survival.[9] Wright observed that tumor excision combined with adjuvant EBRT significantly delayed local tumor recurrence and was associated with longer survival.[8] Esmaeli used EBRT in 16 patients in their series, all of whom had perineural invasion. The median survival of these patients was lower (18 months) compared with the entire cohort (25 months). Recently, Han et al treated 10 patients with adjuvant EBRT after tumor excision and

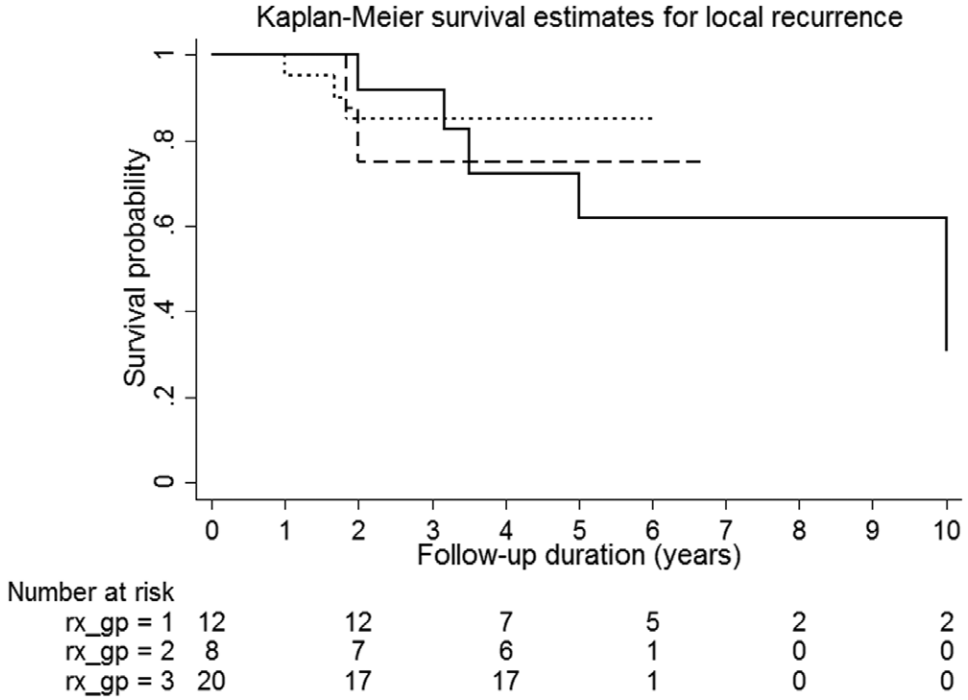


**FIG. 3.** FFS for local recurrence in group 1 (solid line), group 2 (dashed line), and group 3 (dotted line). FFS indicates failure free survival.

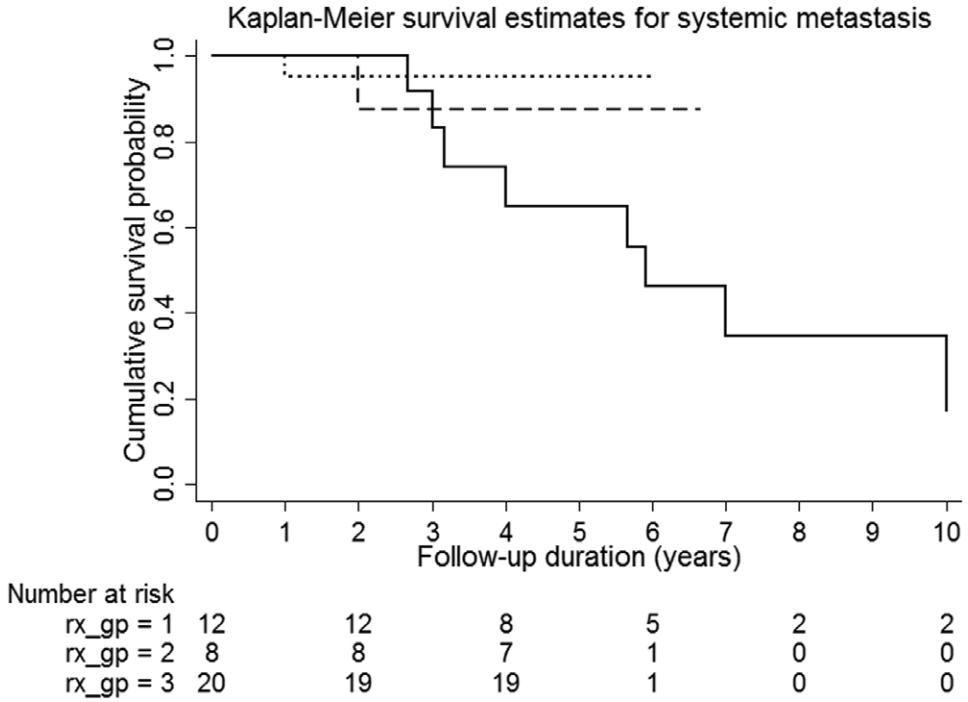


**FIG. 4.** FFS for systemic metastasis in group 1 (solid line), group 2 (dashed line), and group 3 (dotted line). FFS indicates failure free survival.

found recurrence in 1 patient and no metastasis-related death.[6] Wolkow et al used adjuvant proton beam radiotherapy in 18 patients with recurrence in 4 and metastasis in 3 patients.[29]

Chemotherapy has not been extensively used in the primary management of ACC of the lacrimal gland. However, cisplatin and doxorubicin have been used in the management of malignant epithelial tumors of the parotid and salivary glands with good success.[5,16,17,26,27] Intra-arterial chemotherapy aims to achieve a higher drug concentration in the target area while minimizing systemic side effects.[5,26,27] Neoadjuvant intra-arterial cisplatin combined with intravenous doxorubicin, followed by orbital exenteration and EBRT has shown promising results.[5,16] Meldrum reported favorable outcome of neoadjuvant chemotherapy using cisplatin and doxorubicin in 2 patients.[16] Both

**TABLE 4.** Review of treatment outcome in ACC of lacrimal gland

| S. no | Author | Year | Sample size | Treatment groups | No. of eyes (%) | Recurrence (%) | Metastasis (%) | Mortality (%) |
|---|---|---|---|---|---|---|---|---|
| 1. | Wright JE | 1979 | 38 | Local resection | 2 (5) | 1 (50) | 1 (50) | 1 (50) |
| | | | | En bloc cranio-orbital resection | 6 (16) | 3 (50) | 3 (50) | 3 (50) |
| | | | | EBRT | 12 (32) | 6 (50) | 6 (50) | 6 (50) |
| | | | | Local resection + EBRT | 10 (26) | 2 (20) | 2 (20) | 2 (20) |
| | | | | En bloc cranio-orbital resection + EBRT | 2 (5) | 0 (0) | 0 (0) | 0 (0) |
| | | | | EBRT + en bloc cranio-orbital resection | 4 (11) | 2 (50) | 1 (25) | 1 (25) |
| | | | | EBRT+ chemotherapy | 1 (3) | 1 (100) | 0 (0) | 0 (0) |
| | | | | Local resection + EBRT+ en bloc cranio-orbital resection | 1 (3) | 0 (0) | 0 (0) | 0 (0) |
| 2. | Esmaeli B | 2004 | 20 | Local resection | 2 (10) | 1 (50) | 2 (100) | 2 (100) |
| | | | | Orbital exenteration | 1 (5) | 1 (100) | 1 (100) | 1(100) |
| | | | | Orbital exenteration+ bone excision | 1 (5) | 1 (100) | 0 (0) | 0 (0) |
| | | | | Local resection + EBRT | 3 (15) | 1(33) | 2 (67) | 2 (67) |
| | | | | Orbital exenteration + EBRT | 8 (40) | 1(12.5) | 4 (50) | 4 (50) |
| | | | | Orbital exenteration + bone excision + EBRT | 5 (25) | 3 (60) | 4 (80) | 4 (80) |
| 3. | Han J | 2017 | 10 | Tumor excision + EBRT | 10 (100) | 1 (10) | 0 (0) | 0 (0) |
| 4. | Wolkow N | 2018 | 18 | Tumor excision with bone removal+ PBR+ photon | 12 (67) | 2 (16.5) | 3 (25) | 2 (16.5) |
| | | | | Tumor excision without bone removal + PBR + photon | 4 (22) | 2 (50) | 1 (25) | 1 (25) |
| | | | | Tumor excision with bone removal + PBR | 1 (5.5) | 0 (0) | 0 (0) | 0 (0) |
| | | | | Tumor excision without bone removal + PBR + CT | 1 (5.5) | 0 (0) | 0 (0) | 0 (0) |
| 5. | Present study | 2018 | 40 | Orbital exenteration + EBRT | 2 (5) | 2 (100) | 2 (100) | 2 (100) |
| | | | | Tumor excision + EBRT | 10 (25) | 3 (30) | 6 (60) | 3 (30) |
| | | | | Orbital exenteration + EBRT + adjuvant chemotherapy | 1 (2.5) | 0 (0) | 0 (0) | 0 (0) |
| | | | | Tumor excision + EBRT + adjuvant chemotherapy | 7 (17.5) | 2 (28.5) | 1(14) | 1 (14) |
| | | | | Neoadjuvant chemotherapy + orbital exenteration + EBRT + adjuvant chemotherapy | 1 (2.5) | 0 (0) | 0 (0) | 0 (0) |
| | | | | Neoadjuvant chemotherapy + tumor excision + EBRT + adjuvant chemotherapy | 19 (47.5) | 3 (16) | 1(5) | 0 (0) |

ACC indicates adenoid cystic carcinoma; CRT, chemoradiation with doxorubicin; CT, chemotherapy with carboplatin; EBRT, external beam radiotherapy; GK, gamma knife radiotherapy; PBR, proton beam radiotherapy.

the patients subsequently underwent orbital exenteration and achieved a long-term survival of 9.5 and 7.5 years, respectively.

Intravenous neoadjuvant chemotherapy with a combination of 5FU and Cisplatin was used in 20 patients in our series. Of those, 19 (95%) underwent local tumor excision and 1 underwent orbital exenteration following 3 cycles of neoadjuvant chemotherapy. Local tumor recurrence in this subgroup was seen in 3 (15%) and systemic metastasis in 1 (5%). In contrast, local tumor recurrence was noted in 7 (35%) and systemic metastasis in 9 (45%) in patients who did not receive neoadjuvant chemotherapy.

Theoretically, adjuvant chemotherapy following surgical management may have the potential to eradicate occult micrometastasis and help improve patient survival.[7,9,14] Of the 28 patients who received adjuvant chemotherapy in our series, 5 (18%) developed local tumor recurrence and 2 (7%) developed systemic metastasis. In contrast, 5 (42%) of 12 patients who did not receive adjuvant chemotherapy developed local tumor recurrence and 8 (67%) developed systemic metastasis. Adjuvant chemotherapy may thus have a protective role in preventing local tumor recurrence and systemic metastasis.

On histopathological evaluation, cribriform pattern was predominant (65%) in our series. Four (13%) of these patients developed local tumor recurrence. In our series, 3 of 5 patients with basaloid pattern developed local tumor recurrence, and 2 of them developed systemic metastasis. This may indicate aggressive behavior of the tumor in relation to basaloid pattern on histopathology. Wright noted that ≥50% basaloid differentiation was associated with local tumor recurrence and a reduction in the estimated disease-free survival.[8]

ACC of the lacrimal gland is characterized by a high rate of local tumor recurrence. The cumulative 5-year local recurrence in this study was 24% following primary treatment, while Esmaeli and Wright, who did not perform the formal survival analysis, reported 25% and 47.3% recurrence noted at a median interval of 24 months and 26 months, respectively.[4,10] Font and Gamel noted that all their patients had local tumor recurrence at a mean interval of 3.5 years.[7]

Systemic metastasis (7 to brain and 3 to lung) occurred in 10 (25%) overall (67% in group 1, 13% in group 2, and 5% in group 3) in our series at 58 ± 26 months following initial treatment. Font and Gamel[7] and Lee[9] reported systemic metastasis in 50% of cases, most commonly to the lung and lymph nodes. Esmaeli noted systemic metastasis in 80% of their cases, most commonly to the lung, bone, and liver, and at a mean interval of 51 months.[1]

ACC of the lacrimal gland is reported to have a dismal prognosis for survival. Esmaeli reported that 65% of patients in their series died of the disease and the 10-year survival rate was 49%.[10] Font and Gamel noted that 60% of their patients died with a mean survival of 5 years.[7] Henderson reported 11 patients, 9 (81.8%) of whom died at a mean interval of 3 years and 7 months following initial diagnosis.[30] Our mean follow up was 58 months. At the final visit, 32 (80%) patients were alive and well, 2 (5%) were alive with systemic metastasis, and 6 (15%) were dead with systemic metastasis.

This study has the limitation of being retrospective, with a small number of patients with different disease severities included in each group. Being a relatively rare tumor, it is difficult to perform a prospective comparative study over a longer follow-up duration. However, our study reports on a relatively larger set of patients as compared to the prior published literature, with adherence to a common treatment protocol during each specific time frame. Although radiotherapy was planned and delivered by the same radiation oncologist all through the study period, changing techniques of radiotherapy over time

(3D conformal radiotherapy until 2010 intensity-modulated radiation therapy from 2011 onwards) may impact the outcome. The potential role of variable follow-up intervals with respect to results, particularly given that late recurrence or metastasis are common with ACC of the lacrimal gland is one of the limitations of a study of this sort.

Our study reiterates the aggressive nature of ACC of the lacrimal gland, and high chance of local tumor recurrence and systemic metastasis with the conventional treatment approach (surgery followed by adjuvant EBRT). We have observed relatively beneficial effect of multimodal treatment (intravenous neoadjuvant chemotherapy, followed by surgery, extended-field stereotactic EBRT, and adjuvant chemotherapy) in reducing the risk of local tumor recurrence and systemic metastasis and in improving eye salvage in this retrospective case series. A prospective randomized multicentric study with long follow up may further help standardize the treatment protocol.

## REFERENCES


1. Henderson JW, Farrow GM. Past, present, and future surgical management of malignanat epithelial neoplasms of the lacrimal gland. *British J Ophthalmol* 1986;70:727–731.
2. Bonavolonta G, Strianese D, Grassi P, et al. An analysis of 2,480 space occupying lesions of the orbit from 1976 to 2011. *Ophthal Plast Reconstr Surg* 2013;29:79–86.
3. Woo KI, Yeom A, Esmaeli B. Management of lacrimal gland carcinoma: lessons from the literature in the past 40 years. *Ophthalmic Plast Reconstr Surg* 2016;32:1–10.
4. Mulay K, Puthyapurayil FM, Mohammad JA, et al. Adenoid cystic carcinoma of the lacrimal gland: role of nuclear survivin (BIRC5) as a prognostic marker. *Histopathology* 2013;62:840–846.
5. Tse DT, Kossler AL, Feuer WJ, et al. Long-term outcomes of neoadjuvant intra-arterial cytoreductive chemotherapy for lacrimal gland adenoid cystic carcinoma. *Ophthalmology* 2013;120:1313–1323.
6. Han J, Kim YD, Woo KI, et al. Long-term outcomes of eye-sparing surgery for adenoid cystic carcinoma of lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2018;34:74–78.
7. Gamel JW, Font RL. Adenoid cystic carcinoma of the lacrimal gland: the clinical significance of a basaloid histologic pattern. *Hum Pathol* 1982;13:219–225.
8. Wright JE, Rose GE, Garner A. Primary malignant neoplasms of the lacrimal gland. *Br J Ophthalmol* 1992;76:401–407.
9. Lee DA, Campbell RJ, Waller RR, et al. A clinicopathologic study of primary adenoid cystic carcinoma of the lacrimal gland. *Ophthalmology* 1985;92:128–134.
10. Esmaeli B, Ahmadi MA, Youssef A, et al. Outcomes in patients with adenoid cystic carcinoma of the lacrimal gland. *Ophthalmic Plast Reconstr Surg* 2004;20:22–26.
11. Wright JE, Stewart WB, Krohel GB. Clinical presentation and management of lacrimal gland tumours. *Br J Ophthalmol* 1979;63:600–606.
12. Tellado MV, McLean IW, Specht CS, et al. Adenoid cystic carcinomas of the lacrimal gland in childhood and adolescence. *Ophthalmology* 1997;104:1622–1625.
13. Perzin KH, Gullane P, Clairmont AC. Adenoid cystic carcinomas arising in salivary glands: a correlation of histologic features and clinical course. *Cancer* 1978;42:265–282.
14. Font RL, Smith SL, Bryan RG. Malignant epithelial tumors of the lacrimal gland: a clinicopathologic study of 21 cases. *Arch Ophthalmol* 1998;116:613–616.
15. Kaplan MJ, Johns ME, Cantrell RW. Chemotherapy for salivary gland cancer. *Otolaryngol Head Neck Surg* 1986;95:165–170.
16. Meldrum ML, Tse DT, Benedetto P. Neoadjuvant intracarotid chemotherapy for treatment of advanced adenocystic carcinoma of the lacrimal gland. *Arch Ophthalmol* 1998;116:315–321.
17. Goldberg RA. Intra-arterial chemotherapy: a welcome new idea for the management of adenocystic carcinoma of the lacrimal gland. *Arch Ophthalmol* 1998;116:372–373.
18. Reese AB, Jones IS. Bone resection in the excision of epithelial tumors of the lacrimal gland. *Arch Ophthalmol* 1964;71:382–385.
19. Murray JE, Matson DD, Habal MB, et al. Regional cranio-orbital resection for recurrent tumors with delayed reconstruction. *Surg Gynecol Obstet* 1972;134:437–447.
20. Natenegara IA, Koornneef L, Veenhof K, et al. An alternative approach for the management of adenoid cystic carcinoma of the lacrimal gland. *Orbit* 1990;9:101–105.
21. Douglas JG, Laramore GE, Austin-Seymour M, et al. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;46:551–557.
22. Polito E, Leccisotti A. Epithelial malignancies of the lacrimal gland: survival rates after extensive and conservative therapy. *Ann Ophthalmol* 1993;25:422–426.
23. Tse DT, Neff AG. Recent developments in the evaluation and treatment of lacrimal gland tumors. *Ophthalmol Clin North Am* 2000;13:663–681.
24. Honavar SG, Singh AD. *Ocular Adnexal and Orbital Tumors*. In: Williams C, ed. *Evidence-Based Oncology.* London BMJ Books, 2003:586–595.
25. Hemprich A, Schmidseder R. The adenoid cystic carcinoma. Special aspects of its growth and therapy. *J Craniomaxillofac Surg* 1988;16:136–139.
26. Scheel JV, Schilling V, Kastenbauer E, et al. [Intra-arterial cisplatin and sequential radiotherapy. Long-term follow-up]. *Laryngorhinootologie* 1996;75:38–42.
27. Sessions RB, Lehane DE, Smith RJ, et al. Intra-arterial cisplatin treatment of adenoid cystic carcinoma. *Arch Otolaryngol* 1982;108:221–224.
29. Wolkow N, Jakobiec FA, Lee H, et al. Long-term outcomes of globe-preserving surgery with proton beam radiation for adenoid cystic carcinoma of the lacrimal gland. *Am J Ophthalmol* 2018;195:43–62.
28. Tsukuda M, Kokatsu T, Ito K, et al. Chemotherapy for recurrent adeno- and adenoidcystic carcinomas in the head and neck. *J Cancer Res Clin Oncol* 1993;119:756–758.
30. Henderson JW, Farrow GM, ed. *Orbital Tumors*. New York: Brian C Decker, 1980.


 