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ORIGINAL ARTICLE

Outcomes after eye-sparing surgery vs orbital exenteration in patients with lacrimal gland carcinoma

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Abstract

Background: This study examined whether eye-sparing surgery is associated with better or worse outcomes than exenteration for the treatment of lacrimal gland carcinomas.

Methods: Forty-six patients treated for lacrimal gland carcinoma were retrospectively reviewed and compared. A statistical analysis was performed using Kaplan-Meier plots.

Results: The overall survival rates for eye-sparing surgery were 52% and 37% at 5 and 10 years, and those for exenteration were 37% and 25% at 5 and 10 years, respectively ($P = .73$). The proportion of patients with local regional control at both 5 and 10 years after eye-sparing surgery was 0.75, and that for exenteration was 0.47 ($P = .30$). For eye-sparing surgery, the proportions of distant metastasis-free survival at 5 and 10 years were 0.51 and 0.39 for eye-sparing surgery and 0.29 and 0.14 for exenteration ($P = .50$).

Conclusion: Because the outcomes were not significantly different, the authors suggest that eye-sparing surgery can be proposed as a reasonable approach for lacrimal gland carcinomas in appropriately selected patients.

1 | INTRODUCTION

Malignant epithelial tumors of the lacrimal gland are rare carcinomas with an aggressive biological behavior and an incidence of 1.3 cases per 1 000 000 individuals per year.[1] These tumors can originate from all cell types that form the lacrimal gland. The most frequent type is adenoid cystic carcinoma (AdCC) (60% of cases), followed by pleomorphic adenocarcinoma (AC) (20%), and de novo AC (10%). Other types of lacrimal gland carcinoma are extremely rare. Overall, AdCC accounts for 2.1% to 3.8% of all primary orbital lesions.[1,2]

Aggressive local surgical treatments for lacrimal gland carcinoma do not lead to better long-term survival for patients.[3-5] Perineural and bone invasion are frequently observed, and the recurrence and metastasis rates are high.[3-11]

Multiple treatments for malignant tumors of the lacrimal gland have been developed since 1930. The first treatment proposed was radiotherapy, followed in the 1950s by eye-sparing procedures.[11] Because of concerns of local recurrence and potential ocular toxicity from delivery of high-dose radiation near the eye, orbital exenteration became the therapy of choice,[4,5,11-15] but this radical surgical procedure is associated with a high level of functional and psychological disability.[16] As a consequence, eye-sparing surgery followed by radiotherapy is now starting to be recognized as a possible alternative. Reports detailing

early preliminary positive results of eye-sparing surgery for AdCC have recently been published.[11,17,18]

In this retrospective report, we examined whether eye-sparing surgery followed by radiation has similar or different outcomes compared with orbital exenteration in terms of overall survival, disease-free survival, local regional control, and distant metastasis-free survival in appropriately selected patients.

2 | METHODS

The study was performed at the Department of Ophthalmology, Federico II University of Naples in Italy, after being approved by the Institutional Review Board of the Department of Surgical Sciences at the University of Naples. We retrospectively reviewed the medical records of all consecutive patients with a diagnosis of lacrimal gland carcinoma confirmed by histologic examination who were treated in our department between May 1976 and December 2018. All patients provided written informed consent and were assured that their confidentiality would be maintained. The data collected included age, sex, date of initial diagnosis, tumor size, histopathologic type (including the presence of perineural and bone invasion), date of diagnosis, evidence of local recurrence, time from diagnosis to local recurrence, presence and site of regional or distant metastasis, time from diagnosis to metastasis, type of surgery, radiation therapy administered and dosage, type of concurrent or adjuvant chemotherapy, type and grade of ocular toxic effects, date of last follow-up contact, and status at last follow-up (alive with no evidence of disease, alive with active disease, died of the disease, or died of other causes). Tumor staging followed the eighth Edition of the American Joint Committee on Cancer (AJCC) staging system.

2.1 | Multidisciplinary treatment

Forty-six patients were enrolled. Thirty-two (70%) patients had eye-sparing surgery, and 14 patients had exenteration (30%); both groups then received external beam radiotherapy (protocol: 60 Gy fractionated in 30 sessions with 200 cGy/5 days/week). Chemotherapy was suggested for all patients with metastatic disease, but compliance was very low.

2.2 | Statistical methods

The baseline population characteristics were compared using the Chi-square test and Mann-Whitney-u test. Kaplan-Meier plots were generated to estimate the overall survival, local regional control, distant metastasis-free survival and disease-free survival, and log-rank tests were used to compare the groups. A P value $<.05$ was considered statistically significant. Statistical analysis was performed using Xl-Stat for Windows software (version 2018).

3 | RESULTS

Forty-six (27 males; 59%) patients fulfilled the inclusion criteria for the study. The mean age at diagnosis was 53 years (median 55 years; range 11-81 years). Table 1 shows the baseline characteristics of the two groups, which were not significantly different ($P > .05$).

The median follow-up time for the entire cohort was 2.7 years (1 month to 32 years). In the eye-sparing group, the median follow-up time was 3 years (1 month to 32 years), and in the exenteration group, the median follow-up time was 2.5 years (1 month to 27.5 years). Two patients were lost to follow-up.

All tumors were unilateral; 25/46 (54%) patients had AdCC, 13 (28%) had AC, 3 (7%) had mucoepidermoid carcinoma, 3 (7%) had squamous cells carcinoma, 1 (2%) had myoepithelial carcinoma, and 1 (2%) had acinic cell carcinoma. In the entire cohort, 34/46 (74%) tumors could be classified using the AJCC system. There were 22 (65%) $\leq$ T2 tumors and 12 (35%) $\geq$ T3 tumors. Among the 16 patients with AdCC and an AJCC tumor classification, 11 (69%) had $\leq$T2 tumors, and 5 (31%) had $\geq$T3 tumors.

A slight predominance of eye-sparing procedures was observed in the latter decades. Groups were not significantly different in terms of TNM tumor staging (Table 1).

3.1 | Survival and disease recurrence rates

The overall survival proportions at 5 and 10 years were 0.52 and 0.37 for the eye-sparing group and 0.37 and 0.25 for the exenteration group (Figure 1), and the difference was not statistically significant ($P = .73$). Death occurred in 17 patients (55%) in the eye-sparing group and in 8 patients in the exenteration group (53%). The cause of death was tumor-related in 53% of patients in the eye-sparing group and in 63% in the exenteration group. The cause of death was non-assessable in 35% of patients who died in the eye-sparing group and in 38% of the exenteration group.

Disease recurrence was observed in 16 patients (50%) in the eye-sparing group and in 10 patients (71%) in the exenteration group. Local recurrence was observed in 3 patients (9%) in the eye-sparing group and in 2 patients (14%) in the exenteration group. Distant metastasis was

TABLE 1 Baseline characteristic of the exenteration and eye-sparing groups

Age	Gender	TNM	Surgery
44	f	T3N0M0	Exenteration
75	m	T2N0M0	Exenteration
78	m	T4bN0M0	Exenteration
54	m	T2N0M0	Exenteration
55	f	T3N0M0	Exenteration
26	f	NA	Exenteration
52	f	T2N0M0	Exenteration
74	m	NA	Exenteration
11	m	NA	Exenteration
49	f	T2N0M0	Exenteration
68	m	NA	Exenteration
55	f	T3N0M0	Exenteration
61	m	T4bN0M0	Exenteration
53	m	T2N0M0	Exenteration
59	f	T3N0M0	Eye sparing
68	m	T2N0M0	Eye sparing
30	m	T1N0M0	Eye sparing
56	m	T2N0M0	Eye sparing
73	m	T1N0M0	Eye sparing
35	m	T2N0M0	Eye sparing
59	m	T3N0M0	Eye sparing
70	m	T2N0M0	Eye sparing
67	m	NA	Eye sparing
37	m	NA	Eye sparing
48	m	NA	Eye sparing
55	f	T2N0M0	Eye sparing
24	m	T2N0M0	Eye sparing
44	f	T2N0M0	Eye sparing
65	m	NA	Eye sparing
55	m	NA	Eye sparing
80	m	T4bn0m	Eye sparing
49	f	NA	Eye sparing
49	m	NA	Eye sparing
29	f	T2N0M0	Eye sparing
65	f	T2N0M0	Eye sparing
25	f	T3N0M0	Eye sparing
13	m	T2N0M0	Eye sparing
45	f	NA	Eye sparing
81	f	T3N0M0	Eye sparing
74	f	T1N0M0	Eye sparing
65	m	T2N0M0	Eye sparing
66	m	T4bn0m	Eye sparing
46	f	T2N1M0	Eye sparing
59	f	T1N0M0	Eye sparing
55	f	T3N0M0	Eye sparing
56	m	T2N0M0	Eye sparing

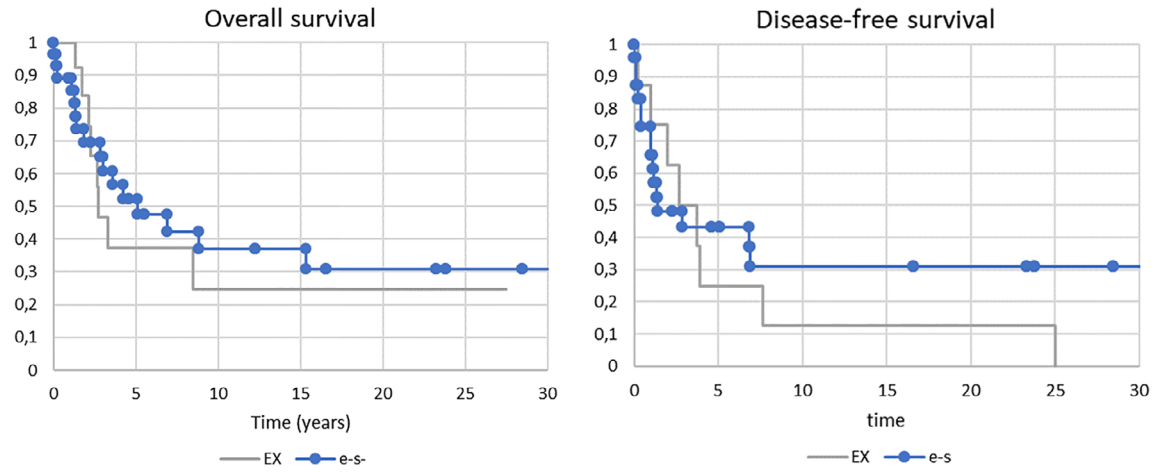

FIGURE 1 Kaplan-Meier curves of the probability of overall survival and disease-free survival. EX, exenteration; e-s, eye-sparing [Color figure can be viewed at wileyonlinelibrary.com]

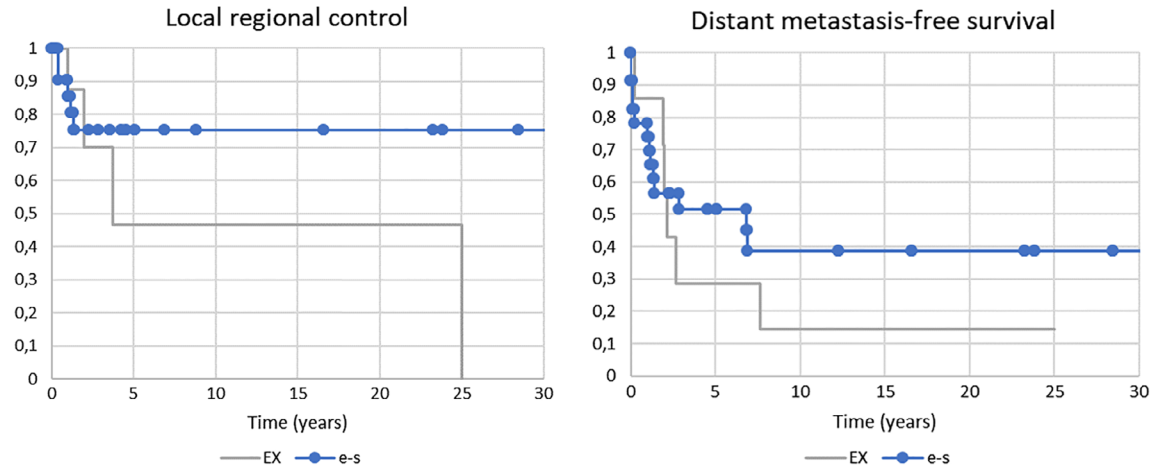

FIGURE 2 Kaplan-Meier curves of the probability of regional control and distant metastasis-free survival. EX, exenteration; e-s, eye-sparing [Color figure can be viewed at wileyonlinelibrary.com]

observed in 10 patients (31%) in the eye-sparing group and 5 patients (36%) in the exenteration group. Simultaneous distant and local recurrence was observed in three patients (9%) in the eye-sparing group and in three patients (21%) in the exenteration group. The median time to local recurrence was 13 months (mean 11.8; range: 5-16 months) in the eye-sparing group and 24 months (mean 77.2; range: 5-300 months) in the exenteration group. The median time to distant metastasis was 13 months (mean 21.2; range: 0-83 months) in the eye-sparing group and 28 months (mean 26.2; range: 3-92 months) in the exenteration group. Noticeably, one patient had distant metastasis at the time of diagnosis in the eye-sparing group.

The median disease-free interval was 12 months (mean 20; range 0-83 months) for the eye-sparing group and 28 months (mean 64; range 1-300 months) for the exenteration group.

The proportion of patients with local regional control at both 5 and 10 years in the eye-sparing group was 0.75, and the proportion in the exenteration group was 0.47 (Figure 2). This difference was not statistically significant ($P = .30$). The proportions of patients with distant metastasis-free survival at 5 and 10 years were 0.51 and 0.39 in the eye-sparing group and 0.29 and 0.14 in the exenteration group (Figure 2), resulting in no statistically significant difference ($P = .50$).

In the eye-sparing group, the probability of being disease-free was 0.43 at 5 years and 0.31 at 10 years. In the exenteration group, the probability of being disease-free was 0.25 at 5 years and 0.13 at 10 years (Figure 1), which resulted in no statistically significant difference ($P = .51$).

In the whole cohort, distant hematogenous metastases most commonly affected the lungs (5), liver (5), and brain (4). Nodal metastasis occurred in two patients who

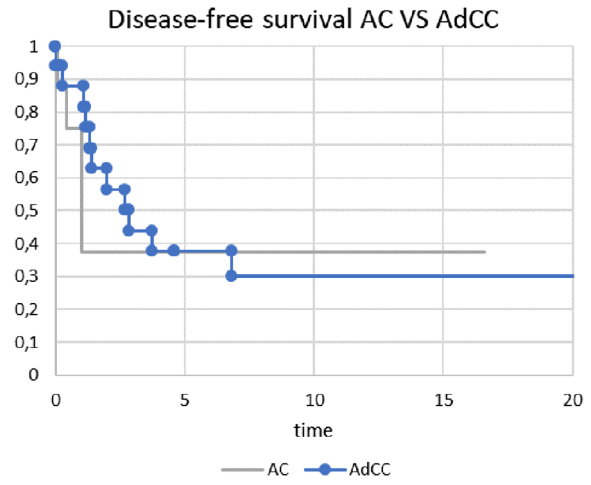

FIGURE 3 Kaplan-Meier curves of the probability of disease-free survival for AC, VS, and AdCC patients. AC, adenocarcinoma; AdCC, adenoid cystic carcinoma; e-s, eye-sparing; EX, exenteration [Color figure can be viewed at wileyonlinelibrary.com]

were treated with complete neck dissection (level I-V) carried out by the ENT team, followed by radiation therapy. Chemotherapy was suggested to 20 patients who developed metastasis, but compliance was very low; 6 patients in the exenteration group (AC 4, AdCC 1, and squamous cells carcinoma 1) and only 1 patient with AC in the eye-sparing group underwent chemotherapy. Unfortunately, results regarding local regional control, distant metastasis-free survival and disease-free survival were strongly influenced by the significant amount of missing data from the early decades (5/15 Not assessable (NA) in the exenteration group, 8/32 NA in the eye-sparing group).

The limited data in some groups precluded analysis by histological subtype; therefore, statistical comparison was only performed for disease-free survival in patients with AdCC or AC. The probabilities of AdCC and AC patients being disease-free were 0.38 and 0.38 at 5 years and 0.30 and 0.38 at 10 years (Figure 3). This difference was not statistically significant ($P = .55$).

Regarding the ophthalmic status, in the eye-sparing group, the postoperative best corrected visual acuity was >20/25 in 11 patients, between 20/40 and 20/30 in 7 patients, and ≤20/200 in 4 patients. Data for the other 10 patients were not available. Dry eye symptoms were experienced by 70% of patients postoperatively. However, they were well managed with topical lubrication therapy.

4 | DISCUSSION

Historically, lacrimal gland carcinomas are neoplasms with a poor prognosis, and the most common treatment was exenteration surgery. Currently, an increasing number of publications[10,11,17-20] advocate local resection (eye-sparing) followed by radiation therapy. It is difficult to assess the superiority of exenteration vs eye-sparing techniques, mainly due to its rarity. The aim of our study was to compare the outcomes of exenteration vs eye-sparing surgery. Our findings suggested that overall survival, disease-free survival, local regional control and distant metastasis-free survival were not significantly different between the two groups. Our results seem to be particularly interesting due to the large cohort size and the length of follow-up.

The overall survival, local regional control and distant metastasis-free survival at 5 and 10 years were not significantly different between the two groups. Our results are in agreement with those reported by Rose et al.[17] Moreover, the median follow-up time of our cohort was similar to that reported by Esmaeli et al in a group of 11 patients treated with eye-sparing approach and adjuvant radiotherapy. Our recurrence rate is higher, but this difference could be related to the larger cohort of our study$_{18}$. Noticeably, in 2013, Tse et al published an interesting paper about the use of neoadjuvant intra-arterial cytoreductive chemotherapy in a subgroup of patients, reporting high efficacy outcomes. Our survival rates and disease-free rates are worse than the ones reported by Tse in the neoadjuvant chemotherapy group, but higher than those reported by Tse for the conventionally treated group.

Among the entire cohort (exenteration and eye-sparing procedures), the overall survival rate was slightly inferior to that reported by Skinner et al at 5 years (59% and 62%).[21,22] However, in their series, the authors included both lacrimal gland and lacrimal duct carcinoma patients, thus a direct comparison between the two studies is not possible. The mortality rate in our cohort was 43%, which is similar to that reported by Shields et al[19] and Woo et al[20] but higher than that reported by Ahmad et al (33%).[23] Interestingly, Han et al. recently published a paper with a mortality rate of approximately 0%, which was significantly lower than that of other authors. Perhaps this could be related to differences in the patient cohort (10 patients affected by lacrimal gland AdCC treated by eye-sparing tumor excision and postoperative radiotherapy (1 patient T1N0M0, 7 patients T2N0M0, 2 patients T3N0M0) with median follow up duration of 89.5 months).[11]

Despite the relevance of these results and the length of follow-up, our limits of our study should be considered. First, the size of the two groups was different. Second, a treatment-selection bias could have occurred during the early decades of the study when surgeons selected treatment based mainly on their experience and radiological evaluation. Third, some data were missing due to the long follow-up time of patients. Finally, the small numbers of patients

with different pathologic subtypes made a subgroup analysis unfeasible, which prevented a direct comparison.

In conclusion, according to the data presented, despite the limits of our study, our findings suggest that in appropriately selected patients, eye-sparing surgery followed by radiation therapy appears to have outcomes equivalent to those of exenteration. Arguably, exenteration surgery remains an appropriate option, particularly for patients with locally advanced disease for whom gross total resection of the tumor is not possible without removal of the eye or important orbital structures, such as the extraocular muscles, or for patients with recurrent tumors after previous eye-sparing surgery. Nonetheless, eye-sparing surgery followed by radiation therapy could be a valid choice for selected patients with localized disease when the concerns of radical surgery do not overcome the benefits.

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