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Long-term Outcomes of Globe-Preserving Surgery with Proton Beam Radiation for Adenoid Cystic Carcinoma of the Lacrimal Gland

EDITOR:

WOLKOW AND ASSOCIATES DESCRIBE THEIR RETROSPECTIVE experience in 18 patients with lacrimal gland adenoid cystic carcinoma (LGACC) who had globe-preserving surgery with high-dose mixed radiation beams of protons and photons.[1] The title is slightly misleading, since only 1 patient received proton therapy alone and the remainder received a combination of protons and x-ray therapy. The authors used passive scattering proton beams with x-ray therapy. The "modern" technique of proton therapy uses active scanning proton beam delivery and intensity-modulated proton therapy (IMPT) that eliminates the need for photon therapy for skin sparing. The ocular late toxicities can be reduced by limiting the radiation dose to 64 CGE, ensuring the cornea receives less than 35 CGE, limiting the maximum dose to the optic nerve to 60 CGE, and ensuring the optic chiasm remains less than 54 CGE. Although the timing of delivery of radiation, the exact radiation technique, the operating surgeons, and the approach to surgery were varied among the 18 patients collected over a 27-year period, the authors state that this is the "first," "largest," and "most uniform" series of patients with LGACC treated with eye-sparing multidisciplinary approach. Such claims are not necessary to make this manuscript worthy, nor are they accurate given all the other publications using a very similar approach.[2–4] We congratulate the authors on publishing their data with a relatively long follow-up time, which is additive to previous publications. The Discussion briefly mentions previous reports and downplays their significance but should instead emphasize just how similar the authors' findings are to all the other previous publications. The current report confirms the conclusions from previous reports that local control rates and disease-specific survival with eye-sparing surgery and radiation are very similar to same outcomes in patients with LGACC after orbital exenteration and radiation. Wolkow and associates report that 4 out of 18 patients experienced local recurrences (22%), very similar to the 18% local recurrence reported in 37 patients in Woo and associates' paper published in 2016.[4]

We thank the authors for referencing our data published in 2004 as one of their "historical data treated with conventional therapy"[5]; these data are historical indeed, but are also dated and also importantly limited to patients with locally advanced tumors, often with cranial involvement. The authors have failed to reference 2 more recent manuscripts from M.D. Anderson on outcomes in patients who had orbital exenteration followed by radiation (published in 2006 and 2010)[6,7]; these 2 later manuscripts contained a more diverse group of patients and showed much better survival rates than the paper published in 2004. It should be noted that we at M.D. Anderson Cancer Center started to offer eye-sparing multidisciplinary treatment to our patients with LGACC in 2007, and only to a subset of patients in whom we thought gross total resection of the lacrimal gland mass was possible without sacrifice of the eye and important orbital structures such as extraocular muscles and in whom the tumor had not already entered the central nervous system at presentation. At our center, eye-sparing surgery is usually followed by concurrent chemotherapy with weekly cisplatin and proton therapy to doses of 60-64 CGE (unless there are specific contraindications to chemotherapy). We published our data for the first 11 patients with lacrimal gland carcinoma using this approach in 2016[2]; the majority of patients had adenoid cystic carcinoma. We are pleased that since the publication of our manuscript, additional reports of a very similar approach have been surfacing from throughout the world, including this current report from Boston.[1,3,4]

One question for the authors: since you have so nicely provided both tumor size and AJCC T category at presentation in your table of 18 patients, why not report the correlation (or lack thereof) between tumor size and local recurrence, distant metastasis, and disease-free survival? Even with 18 patients it is possible to find significant trends (or lack of significance). Also, was there a correlation between T category at presentation and local recurrence, distant metastasis, and disease-free survival? Even a nonsignificant *P* value should be provided.

We agree with the authors that multicenter clinical trials are acutely needed for patients with adenoid cystic carcinoma of the lacrimal gland. However, we believe the main issue is not so much variations on the theme of eye-sparing surgery and radiation but rather finding effective treatments for metastatic disease for which we have nothing to offer at the moment. As data emerge on local/-regional control rates for eye-sparing approaches that seem to be at least as good as orbital exenteration, the next steps are to design clinical trials for treatment of patients with metastatic LGACC.

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Long-term Outcomes of Globe-Preserving Surgery With Proton Beam Radiation for Adenoid Cystic Carcinoma of Lacrimal Gland

REPLY

WE THANK DRS ESMAELI AND FRANK FOR THEIR CAREFUL reading of our article, in which we strove to describe our findings as accurately as possible and also to report scrupulously the complications and therapeutic limitations we encountered. We also endeavored to compare our results with those of other series. In comparing our outcomes to those of other studies, we focused primarily on studies with a globe-preserving approach, while also touching upon selected studies with long-term follow-ups in which exenteration was a primary treatment modality.

We sincerely appreciate Drs Esmaeli and Frank's mention of 2 papers that were not included in the final version of our Discussion section.[1,2] Our in-depth analysis of previous studies was significantly limited by the original reviewers, who stressed the need to shorten the paper, which precluded a well-deserved discussion of these other studies. Both of these papers focused on patients with adenoid cystic carcinoma of the lacrimal gland who were primarily treated with orbital exenteration with bone removal in combination with radiation. The earlier of these papers, which included mostly patients with larger tumors and basaloid histology, found that exenteration with bone removal and radiation did not decrease the risk of distant metastases.[1] The subsequent paper, which included 18 patients of whom 17 were treated with exenteration and external beam radiation, found that orbital bony invasion by tumor cells was present in most patients.[2] Both of these studies lend further support to the major points discussed in our paper[3]; specifically, that tumors with basaloid histopathology portend a poorer prognosis,[4] and that exenteration with bone removal does not prevent the development of metastatic disease.

With regard to correlations, using regression analyses we did not find any statistically significant relationships between tumor size and local recurrence ($P = .2375$), tumor size and metastases ($P = .3352$), tumor size and disease-free survival ($P = .1496$), T category and local recurrence ($P = .5397$), T category and metastases ($P = .8251$), and T category and disease-free survival ($P = .8642$). Caution is advised, however, in interpreting these results, as statistical analyses on small numbers of patients may be misleading. Significant relationships may become apparent with a greater sample size.

We have suggested in our paper, as have the present writers, that improvements in the design of radiotherapy portals and modalities are becoming more refined with time and should lead to improved results. We have straightforwardly addressed in our paper why photons were used in small doses; we do not believe that this feature seriously confounds our results. An important issue in comparisons of radiotherapy for lacrimal gland adenoid cystic carcinoma is provided in the study by Han and associates, which describes the exclusive use of photons with comparable results to proton beam therapy.[5] This will require additional study, as we have pointed out.

We are in complete agreement with Drs Esmaeli and Frank that, while our approach in treating localized orbital adenoid cystic carcinoma has shown progress, a salient but neglected area in need of further research and multicenter clinical trials is improving results for metastatic adenoid cystic carcinoma. Our belief is that collaborative efforts will lead to advances in the treatment of metastatic disease in the near future. Drs Esmaeli and Frank will certainly be central players in such investigations.

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