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ORIGINAL ARTICLE

45 GyRBE for group III orbital embryonal rhabdomyosarcoma

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ABSTRACT

Purpose: Despite widespread concerns of radiotherapy toxicity in children with head and neck tumors, recent Children's Oncology Group (COG) findings suggest that the use of 45 Gy results in an unacceptably high rate of local recurrences in patients with low-risk orbital rhabdomyosarcoma. We therefore evaluated outcomes in our pediatric patients who received 45 GyRBE using proton therapy.

Material and methods: To assess disease control and toxicity, we reviewed the medical records of 30 children (≤21 years old) with COG stage 1, group III embryonal orbital rhabdomyosarcoma enrolled on a prospective outcome study and treated with proton therapy between 2007 and 2018.

Results: Median age at the time of radiation was 4.8 years old. Twenty-one and nine patients received ifosfamide- and cyclophosphamide-based chemotherapy according to their respective cooperative group regimens. Median duration between the start of induction chemotherapy and radiation was 12 weeks. Two patients had a complete response to induction chemotherapy and two had stable disease. Twenty-six patients had a partial response to induction chemotherapy, with a median volume reduction of 66%. With a median follow-up of 4.0 years (range, 0.5–9.5 years), we observed 1 local failure 6 months following treatment in a patient who had a partial response to cyclosphophomide-based induction chemotherapy. The 5-year local control, progression-free survival, and overall survival rates were 97%, 97%, and 100%, respectively. Serious late toxicities included 18 patients with cataracts, 4 with exposure keratoconjunctivitis resulting in permanently reduced visual acuity, and 1 with chronic sinusitis.

Conclusion: 45 GyRBE offers effective local control for most patients with group III orbital rhabdomyosarcoma. The delivery of proton therapy to the postinduction tumor volume plus a small margin can mitigate early- and intermediate-term toxicity, but side effects still occur and long-term data are needed to demonstrate the dosimetric advantage of proton therapy.

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Introduction

Over the past two decades, the high cure rate for embryonal rhabdomyosarcoma of the orbit has prompted international efforts to de-intensify treatment. This effort has taken two broad forms in cooperative group studies via (a) reducing exposure to alkylating chemotherapy and (b) reducing exposure to ionizing radiation through lower prescription doses and smaller radiotherapy target volumes. A recent report from the Children's Oncology Group (COG) [1]; however, asserts that children with group III embryonal orbital rhabdomyosarcoma who receive lower cumulative doses of cyclophosphamide (4.8 g/m^2) and a lower radiation dose (45 Gy) to the tumor plus a 1-cm margin are at an increased risk of local failure compared to the historic Intergroup Rhabdomyosarcoma Study (IRS)-IV patients who received 26.4 g/m^2 cyclophosphamide and 50.4 to 59.4 Gy to the tumor plus a 2-cm margin [2,3]. Specifically, the 5-year local failure rate increased from 2% to 13%. Patients with tumors demonstrating a partial response to induction chemotherapy were shown to be at particular risk of failure—approaching 16%—following the de-intensified therapy regimen. These findings prompted many COG institutions to revert to a dose of 50.4 Gy for group III orbital rhabdomyosarcoma.

Beyond lowering prescription radiation doses and reducing target volumes, advanced technology can be used to further reduce patients' exposure to ionizing radiation. For example, proton therapy for orbital rhabdomyosarcoma reduces the integral radiation dose by 3.5 times compared to conventional radiation and is associated with significantly less radiation to developing facial bones, optic nerve, lens, lacrimal gland, temporal lobe, hypothalamus, and pituitary gland [4]. Such a dose reduction can result in improved survivor quality of life [5], which is critical in a young population with a long-term survival rate exceeding 90%. Based on this rationale, proton therapy has been the standard of care at the University of Florida for over a decade. While all patients have been treated with 45 GyCGE and ≤1-cm target margin, some have received low-dose cyclophosphamide

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(per COG ARST0331) and others have received standard-dose ifosfamide (per EpSSG RMS2005). In light of the recent COG report, we examined our outcomes to determine patterns of failure and whether our institutional treatment guidelines should be revised to ensure an optimal balance between efficacy and toxicity.

Material and methods

Between September 2006 and October 2018, 1657 pediatric patients (age $\leq$ 21 years) were treated with proton therapy at the University of Florida. Under an institutional review board-approved prospective study (IRB# 2006-153), 30 consecutive patients were identified with a group III embryonal rhabdomyosarcoma of the orbit with a minimum 6 months of potential follow-up since proton therapy. No patients were lost to follow-up. Patients who had received prior radiation were excluded.

Patients were treated according to our institution's pediatric treatment guidelines for rhabdomyosarcoma. The gross tumor volume (GTV) was defined by the gross disease at the time of radiation, following induction chemotherapy (Figure 1). The clinical target volume (CTV) was defined by the GTV + 5 mm, with further modification as necessary to encompass all surfaces originally in contact with the tumor and all soft tissue originally infiltrated by disease. The standard prescription dose was 45 GyRBE, delivered via two sequential phases. The initial planning target volume (PTV1), defined as the CTV + 3 mm, received 36 GyRBE followed by a 9-GyRBE boost to the PTV2, defined as the GTV + 3 mm. The primary goal when developing the radiation plan was to ensure that the entire CTV was encompassed by >99% of the nominal dose and that the entire PTV was covered by 95% of the nominal dose. Plans were optimized to minimize the dose to the retina, lacrimal gland, pituitary, hypothalamus, and brain tissue without compromising target coverage. All patients in this series were treated with double-scattered proton plans using 2 to 3 beams per phase. Each field was treated daily. The distal and proximal beam margins in millimeters were calculated through the empirically derived institutional formula of (2.5%×field range) + 1.5 mm. The aperture margin was 4 to 7 mm from the lateral PTV edge. The typical beam smearing margin was 5 mm. As part of the prospective component of the study, acute and late treatment toxicity information was collected during weekly on-treatment and follow-up visits. To assess disease outcomes, we calculated crude rates of local control, disease-free survival, and overall survival.

Results

Patient, tumor, and treatment characteristics

All 30 patients had COG stage 1, group III embryonal rhabdomyosarcoma of the orbit. The median age at the time of radiation was 4.8 years old (range, 1–11.4 years). Nineteen patients were male; 29 were white and 1 was Asian. One patient had a known germline p53 mutation. The median maximum tumor size at diagnosis was 3.4 cm (range, 2.2–6.1 cm) and the median tumor volume at diagnosis was 8.5 ml (range, 2.4–45.9 ml). Overall, 21 and 9 patients received ifosfamide- and low-dose cyclophosphamide-based chemotherapy according to their respective contemporary European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) and COG regimens. The median duration

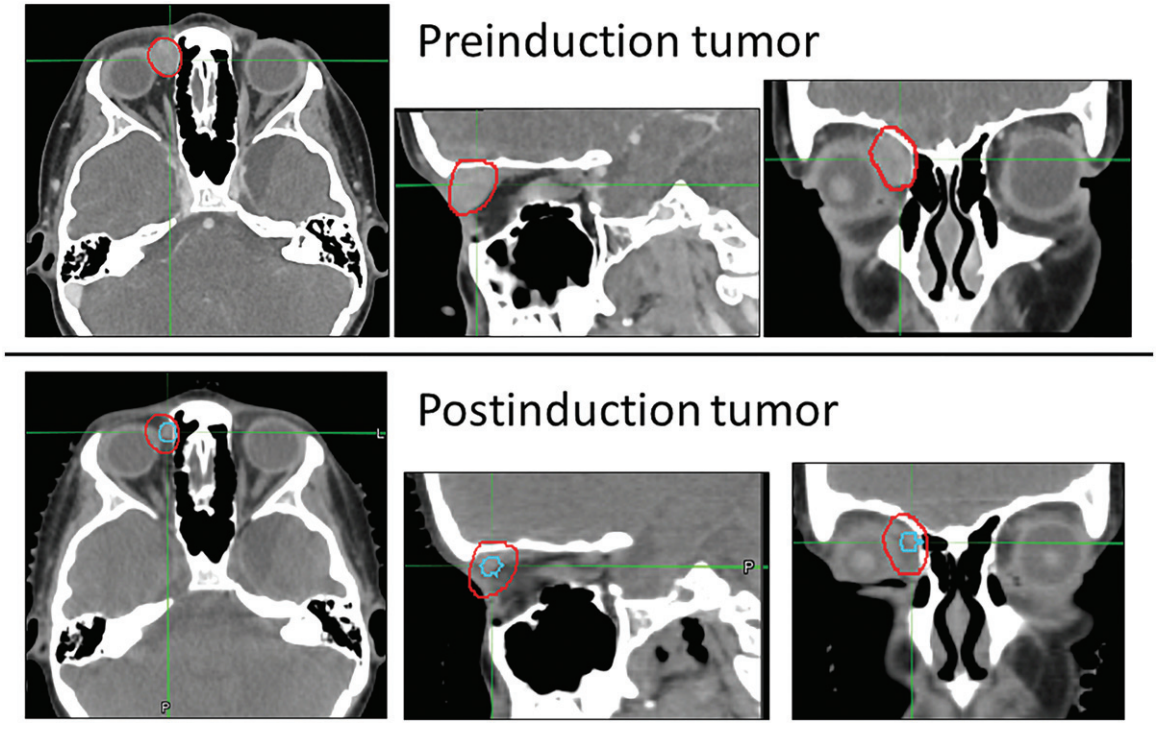

Figure 1. Imaging of a patient with a group III embryonal rhabdomyosarcoma of the medial orbit exhibiting the difference in gross tumor volume when using the original tumor volume (red) compared to the postinduction tumor volume (blue).

between the start of induction chemotherapy and radiation was 12 weeks (range, 6–20 weeks). The median maximum tumor size at the time of radiation was 2.3 cm (range, 0.1–4.0 cm) and the median tumor volume at the time of radiation was 2.6 ml (range, 0.4–13.4 ml). Two patients had a complete response to induction chemotherapy (>95% volume reduction) and two patients had stable disease (<5% volume reduction). Twenty-six patients had a partial response to induction chemotherapy, with a median volume reduction of 66% (range, 38–91%).

All 30 patients received 45 GyRBE to the PTV2 according to our guidelines outlined above. In 2 patients, the PTV1 was treated to 30.6 GyRBE (rather than the standard 36 GyRBE). In 2 other patients, the full dose of 45 GyRBE was delivered to the PTV1 (i.e., there was no boost volume). All patients received 1.8 GyRBE per day, 5 days per week. Due to cyclotron maintenance, 4 patients were treated with a component of 6-MV photon radiation (median 2 days; range, 2-3 days). The median treatment duration was 36 calendar days (range, 33–40 days). For the whole cohort, the median mean dose to the ipsilateral lens was 43.5 GyRBE (range, 19.3–52.2 GyRBE). The median mean dose to the ipsilateral lacrimal gland was 43.3 GyRBE (range, 5.5–50.4 GyRBE). On average, 2.9% of patients' supratentorial brain received between 1-20 GyRBE. A full detail of dose exposure to normal tissue is outlined in Table 1.

Disease control

With a median follow-up of 4.0 years (range, 0.5–9.5 years), we have observed 1 local failure, which occurred 6 months following treatment in a patient with a 3.4-cm tumor of the inferior orbital rectus who had a partial response to COG ARST0331 chemotherapy (Figure 2). The recurrence was addressed with an orbital exenteration followed by COG ARST0921 chemotherapy. At the time of the analysis, the patient was 22 months free of disease. We have observed no distant failures. The local control, disease-free survival, and overall survival rates in this group are 97%, 97%, and 100%. Two patients experienced post-treatment changes consistent with pseudoprogression: One patient had a documented finding on magnetic resonance imaging (MRI) 2 months following radiation that showed a slight increase in tumor volume and contrast enhancement, which resolved without intervention on a repeat follow-up scan 4 months later. The patient is currently 1.8 years from treatment with continued regression. Another patient had a similar documented finding on MRI 6 months following treatment, likewise demonstrating a slight increase in tumor volume with contrast enhancement. A biopsy was performed, but the pathology specimen was inconsistent with viable tumor. The decision was made to continue with close surveillance and the tumor has remained stable for 22 months.

Table 1. Doses to normal tissues in a cohort of 30 patients treated with proton therapy for orbital rhabdomyosarcoma.

Structure	Median (GyRBE)	Range (GyRBE)
Ipsilateral retina (max. dose)	46.5	45.5–54.1
Contralateral retina (max. dose)	1.3	0–22.2
Ipsilateral lens (mean dose)	43.5	19.3–52.2
Contralateral lens (mean dose)	0.1	0–3.1
Ipsilateral optic nerve (max. dose)	45.5	0–52.4
Contralateral optic nerve (max. dose)	0.2	0–11.8
Ipsilateral lacrimal gland (mean dose)	43.3	5.5–50.4
Contralateral lacrimal gland (mean dose)	0	0–0.1
Hypothalamus (mean dose)	0	0–16.8
Pituitary (mean dose)	0.7	0–27.4
Percent of brain receiving 1–20 Gy	2.90%	0.3–34.4%
Percent of brain receiving >20 Gy	1.60%	0–10.8%

Toxicity

Non-hematologic acute toxicity in this cohort included mild periorbital edema, erythema, epiphora, photosensitivity, and conjunctival erythema. Serious late toxicity included 18 patients with cataracts at a median of 29.6 months following treatment (range, 23.8–51.6 months), 15 of whom required surgery or laser treatment. Despite surgery, 2 of 15 cataract patients still have significantly reduced visual acuity. In addition, 4 patients developed severe exposure keratoconjunctivitis. As a result, each has had corneal scarring or posterior capsule opacification causing permanent reduction in visual acuity and 4 have had severe dry eye requiring a protective shell implant to maintain conjunctival vitality. Another patient in the series with a rhabdomyosarcoma of the superior rectus developed chronic sinusitis with rhinorrea, possibly radiation-induced, and underwent tonsillectomy with adenoidectomy and a turbinate reduction with septoplasty. Other late toxicities observed in this cohort included 14 patients with chronic dry eye requiring artificial tears, 4 patients with recurrent epistaxis, and 3 patients with keratitis or conjunctivitis, now resolved (specifically exposure keratitis, papillary conjunctivitis, and conjunctival infection not otherwise specified). In 1 patient, dental imaging revealed shortened tooth roots. Two patients elected surgery for cosmetic sequelae related to the tumor and treatment: 1 patient underwent a fat pad implant for facial asymmetry and 1 patient had surgery to correct eyelid ptosis and entropion. Interestingly, we have observed 1 case of combined growth hormone and gonadotrophin deficiency and 1 case of isolated growth hormone deficiency. The radiation dose to the hypothalamus and pituitary gland was <0.1 GyRBE in both patients.

Discussion

Our prospective outcome data suggest that 45 GyRBE proton therapy to a small, postinduction target volume results in a 5-year local control rate of 97%. If validated in a larger patient cohort, this technique could represent a significant step in reducing radiation exposure in a young population at known risk of treatment toxicity. Our findings also suggest that the recent decline in local control observed in orbital rhabdomyosarcoma patients on COG ARST0331 may be more directly attributable to recent low-dose chemotherapy regimens than radiotherapy modifications.

The rationale for radiation de-intensification in orbital rhabdomyosarcoma is well-justified. Historic pooled data from the United States and Europe suggest that 51–82% of

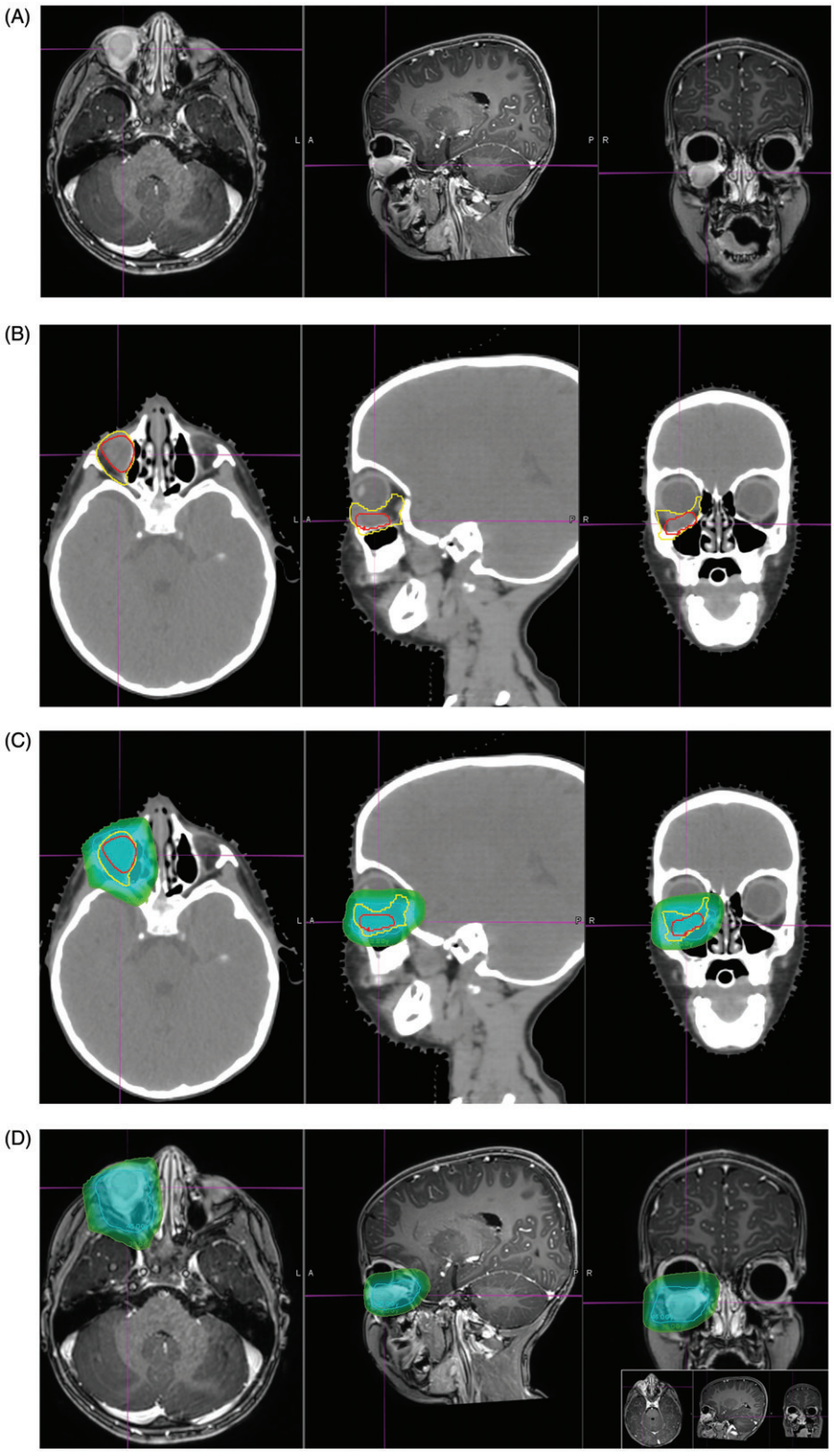

Figure 2. Imaging of the patient with group III embryonal rhabdomyosarcoma of the orbit who recurred, exhibiting (A) the tumor at diagnosis; (B) the tumor following partial response to ARST0331 induction chemotherapy; (C) target volumes, with the gross tumor volume shown in red and the clinical target volume in yellow; (D) the local recurrence at 6 months following radiation within the 45 GyRBE isodose line. Dosimetry: green colorwash, 36 GyRBE; blue colorwash, 45 GyRBE.

treated children develop cataracts, 29–59% develop orbital hypoplasia, and 54–70% experience reduced vision. As many as 11-14% may require enucleation for symptom relief [6]. Other common sequelae include ptosis, dry eye, keratitis, corneal ulceration, and dental abnormalities [7]. Efforts to reduce toxicity through the use of intensity-modulated radiotherapy have been largely unsuccessful [8–10], likely owing to similar dosimetric profiles [8]. Another explanation for persistent toxicity could be the practice of defining the target volume based on tumor extent at the time of diagnosis. In patients with a good response to induction chemotherapy, this might result in targets unnecessarily

encompassing parts of the lacrimal gland, tooth buds, and orbital bone. Our institutional guidelines instead use a post-induction chemotherapy volume, based on patterns of failure analysis from our institution [11] and elsewhere [12,13].

Theorizing that attenuated chemotherapy might lead to fewer hematologic, hepatotoxic, and fertility risks, while less radiation could reduce the damage to ocular and peri-ocular tissue, investigators of COG ARST0331 reduced the therapy for embryonal rhabdomyosarcoma by using a lower dose of cyclophosphamide and 45 Gy, as opposed to the 50.4–59.4 Gy used in IRS-IV. The radiotherapy target margin, although still defined by the extent of disease at diagnosis, was reduced from 2 cm to 1 cm. While it is too early to assess the impact of these treatment modifications on toxicity rates, the ARST0331 results were disappointing from a disease-control perspective: The 5-year local failure rate increased from 2% on IRS-IV to 13% on ARST0331 [1]. COG physicians have thereby questioned the impetus for this increase in local failures and deemed the use of 45 Gy 'insufficient,' particularly following an incomplete radiographic response to induction chemotherapy [14].

Under the close oversight of our prospective outcome protocol, our approach has been to continue the use of 45 Gy and, by applying proton therapy and postinduction target margins, aggressively push forward with radiation toxicity reduction. In contrast to the ARST0331 data, our results suggest that such an approach does not compromise the therapeutic ratio. An important distinction, however, is that our cohort can be further divided by chemotherapy: approximately one-third received COG-based chemotherapy and two-thirds received EpSSG-based chemotherapy. The single local recurrence we observed was in a patient who received low-dose cyclophosphamide, for a crude recurrence rate of 11% (1/9), similar to the 13% observed on ARST0331. Although anecdotal, this finding supports other recent data indicating that lower cumulative cyclophosphamide dose and dose-intensity results in excessive treatment failures among patients with low-risk rhabdomyosarcoma [15–17].

Our findings raise important questions: First, if we establish that a lower cumulative dose of cyclophosphamide is impermissible in North America, is the next option a return to the higher-dose cyclophosphamide regimens of the past, a switch to the ifosfamide regimens used in Europe, or a replacement to alkylators altogether? Leukopenia and male infertility is the dose-limiting toxicity of cyclophosphamide, whereas ifosfamide may cause neurotoxicity and long-term tubulopathy resulting in Fanconi syndrome [18]. COG ARST1431, a phase 3 study for intermediate-risk rhabdomyosarcoma, was amended in early 2019 by the COG Soft Tissue Sarcoma committee to incorporate maintenance chemotherapy as a strategy to improve outcome without exposing all intermediate risk patients to a substantially higher cumulative cyclophosphamide dose. Second, despite the use of proton therapy, a dose of 45 Gy, and postinduction target margins, we continue to observe ocular and peri-ocular toxicity in our patients and these occurrences will only increase with time. The next incremental advancements in low-risk orbital rhabdomyosarcoma may need to take the form of risk-adapted therapy, wherein good responders receive even lower doses of radiation and complete responders forgo radiotherapy entirely. Off study, this has been the practice in many European countries for decades, and radiation avoidance was an option for some complete responders on EpSSG RMS2005. Risk adaptation may be further refined by advanced imaging and molecular subtyping. Finally, radiotherapy continues to evolve. Given a mean lens dose threshold of 7 Gy is necessary to keep cataract risk under 25% [19], it is unsurprising that 18 of 30 patients in our series developed cataracts given a mean lens dose of 43.5 GyRBE across the series. To mitigate this toxicity, we developed a system to fix the gaze of older patients in a reproducible manner that can reduce lens exposure. All the patients in this series were treated with double-scattered proton therapy. We can now use next-generation pencil-beam scanning to further shape the radiation dose to the lacrimal gland, and dose-painting to treat the PTV1 at $<$1.8 GyRBE/fx. Advances in brachytherapy also allow for treatment that does not sacrifice the globe. This approach provides particularly conformal dosimetry in cases where the brachytherapy can completely replace the use of external-beam radiation [20,21].

Despite provocative findings, this study has important limitations that should be considered. For example, although patients were treated according to standardized chemotherapy roadmaps, alkylator dose modifications were sometimes necessary to mitigate systemic toxicity according to normal clinical routine. If these dose modifications were implemented following the completion of radiation in a child who was referred from an outside center, the actual delivered chemotherapy dose may have deviated from the standard regimen. Furthermore, in the COG ARST 0331 study only 7% of patients received proton therapy. If any radiobiologic differences in proton therapy affect embryonal rhabdomyosarcoma beyond the common 1.1 cobalt-Gy modification, a straight comparison of 45 GyRBE might be inaccurate. Finally, late effects may manifest beyond the 4-year median follow-up described in our cohort. It is therefore important that we continue to follow this group of survivors to accurately characterize any differences in proton therapy-induced late toxicity relative to that reported in photon series.

Our data suggest that 45 GyRBE delivered to the postinduction tumor volume with a small margin remains an effective radiotherapy approach for most patients with group III orbital embryonal rhabdomyosarcoma. While this approach seems to mitigate early- and intermediate-term toxicity, side effects still occur and long-term data are needed to conclusively demonstrate the dosimetric advantages of proton therapy. To this end, our orbital rhabdomyosacoma patients have been offered co-enrollment on an international study examining cosmetic and facial morphologic effects in long-term survivors; this protocol also enrolls comparative cohorts of brachytherapy and photon patients. When mature, the findings will provide invaluable information from various perspectives. Finally, from a broader oncologic standpoint, we must urgently characterize the impact of reduced-dose cyclophosphamide on local control in this setting and among others with rhabdomyosarcoma.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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