J Radiat Oncol (2012) 1:49–55
DOI 10.1007/s13566-012-0002-6

ORIGINAL RESEARCH

Experience using frameless fractionated radiosurgery for the treatment of orbital and ocular tumors

S. A. Morales · J. P. Lamond · S. Lally · S. O. Asbell · J. Yang · R. Lanciano · L. W. Brady

Received: 29 November 2011 / Accepted: 6 January 2012 / Published online: 10 February 2012

Abstract
Objective This study analyzes patients with orbital tumors who were treated with fractionated stereotactic radiosurgery to help maximize local control after surgery, or to more expeditiously treat radiosensitive tumors and palliative cases.
Materials and methods Thirty-one patients with tumors of the eye, orbit, or eyelid were treated using CyberKnife radiosurgery from June 2006 to June 2009. The 23 patients with at least 12 months of follow-up are included in this analysis. All patients had aquaplast mask immobilization with bolus if necessary. CT and MRI images were acquired and fused for treatment planning. Tumor contour and treatment planning was jointly performed by a radiation oncologist, ocular oncologist, and medical physicist. Total doses were lower for radiosensitive tumors (13.5–20 Gy in four to five fractions) than non-radiosensitive tumors (15–35 Gy in three to five fractions). Each fraction was delivered in 30–60 min with all treatments being delivered over 1–2 weeks. Patient ages ranged from 16 to 91 years old with a median age of 67. The majority (21 of 23) were treated with curative intent, including 9 radiosensitive tumors (all lymphomas), 17 with intact eye following limited surgery, and 3 after exenteration. Palliative patients included one metastasis and one lymphoma.
Results At a median overall follow-up of 34 months (range, 13–42 months), 21 patients (91%) exhibited local control. Complications included neovascular glaucoma (n=3), chronic dry eye (n=1), and osteomyelitis (n=1).
Conclusion Fractionated radiosurgery provided good local control with a low risk of side effects. Ocular oncology participation in target and normal tissue delineation was felt to be an important component of the treatment planning process.

Keywords Stereotactic radiosurgery · Ocular tumor · Orbital tumor · CyberKnife · Radiation therapy

S. A. Morales (✉)
Drexel University College of Medicine,
2900 W. Queen Lane,
Philadelphia, PA 19129, USA
e-mail: sam385@glink.drexel.edu

J. P. Lamond · S. O. Asbell · J. Yang · R. Lanciano · L. W. Brady
Philadelphia CyberKnife,
2010 West Chester Pike Suite 115,
Havertown, PA 19083, USA

S. Lally
Wills Eye Institute,
840 Walnut Street Suite 1440,
Philadelphia, PA 19107, USA

Introduction

Radiation therapy provides patients with eye and orbital malignancies the opportunity to preserve vision or improve local control after surgery; however, there are potential side effects. Standard conventional external beam radiation therapy (EBRT), although historically effective and readily available, has been particularly associated with several known toxicities when treated tumors reside in and around the eye [1–5]. Acute toxicities such as conjunctivitis and eyelid irritation are major complaints usually seen within 2 weeks of beginning standard radiation therapy. Late side effects can include damage to the optic nerve, retina, ocular surface, lacrimal gland, and lens resulting in optic neuropathy, retinopathy, severe dry eye, and cataracts [6]. Merriam and Focht have shown that post-irradiation cataract can be induced by as little as 2 Gy in a single fraction [7]. Other late side effects include corneal scarring, scleral atrophy, and atrophy of the iris. Specific dose ranges have also been recorded for particular side effects. For example, dry eye occurred after 30–45 Gy with a general 30%

risk even if doses were less than 30 Gy. Another common side effect is neovascular glaucoma (NVG), which is of particular risk when irradiating the eye. NVG was seen in 35% of those treated with standard radiation doses and treatment schedules [6, 8, 9].

Sophisticated radiation techniques have been developed, including eye-specific radioactive plaques [10], which have been useful in treating smaller choroidal melanomas and retinoblastomas. Other forms of brachytherapy (radioactive seeds or catheters) have also played a role in treating ocular tumors and are mostly used in combination with some form of EBRT. Protons have also been used with encouraging results, but the relatively high doses to the anterior eye may lead to toxicity [11]. Conway et al. reported a 38% rate of NVG in those patients treated with proton therapy for large ocular tumors [12]. Neutron therapy has also been investigated as a potential treatment modality for refractive orbital tumors [11]. Radiosurgical techniques initially developed to treat brain tumors can also be used for tumors of the eye and orbit by providing highly focused radiation doses to the target volume while limiting the dose to peripheral tissue. The most specialized of these stereotactic radiosurgery units such as Gamma Knife and CyberKnife use multiple narrow photon radiation beamlets to create dose clouds that can closely conform to the target volume.

The CyberKnife (Accuray Inc. Sunnyvale, California) is a robotically controlled linear accelerator that uses the unique radiographic attributes of the patient's skull to guide treatment with submillimeter precision [13]. It does not require invasive immobilization, thus making fractionation more readily accessible. Typical ocular treatments are delivered in three to five fractions. The CyberKnife uses 50–250 pencil beams of radiation delivered from 50° to 90° angles to the lesion, which spreads out the entrance dose and helps to avoid high doses of radiation to anterior structures in the eye [14–17]. Treatment planning was designed to create a three-dimensional radiation dose cloud with a similar shape as the target, while allowing the dose to fall off rapidly to nearby normal tissues (Fig. 1). Based upon these properties, Zytkovicz et al. concluded that the CyberKnife might be a good option for treating large ocular lesions [18]. In this study, we present our experience using fractionated stereotactic radiosurgery delivered by the CyberKnife to treat select ocular and orbital tumors.

Material and methods

All patients were positioned supine with a customized immobilization aquaplast mask (WRF/Aquaplast Corp., Wyckoff, NJ) during pretreatment imaging and treatment delivery. A

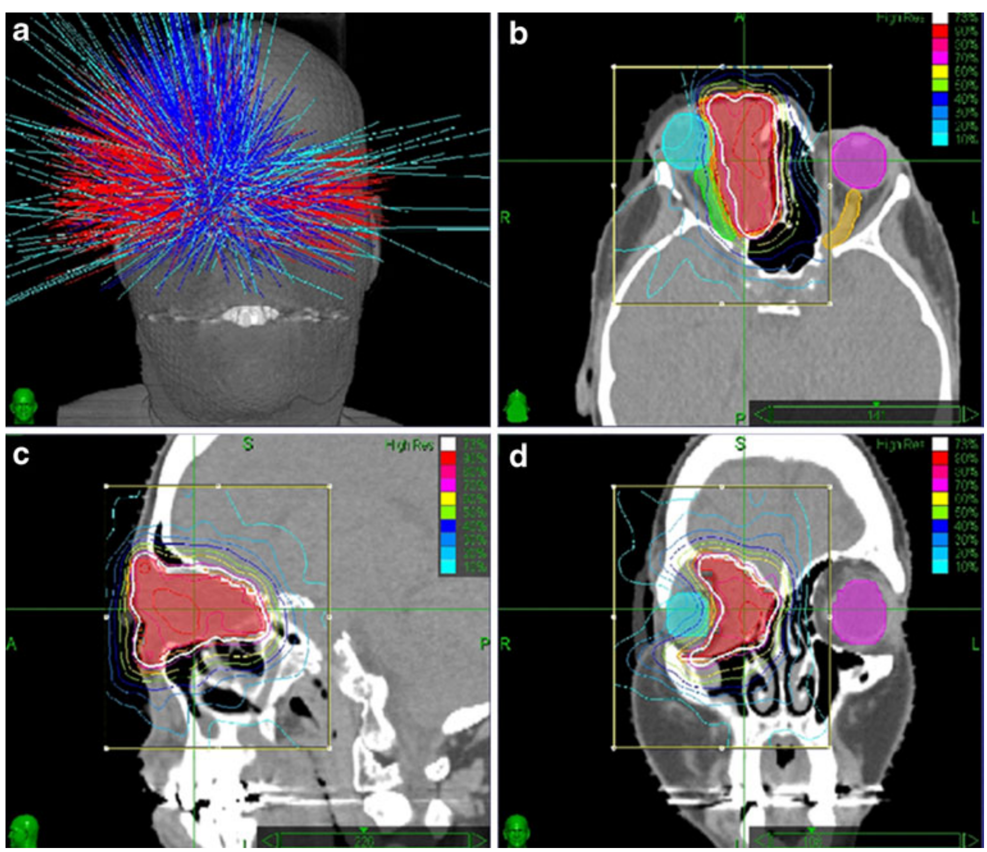

Fig. 1 Treatment planning images from a 46-year-old female with a history of a stage IIIA non-Hodgkin's lymphoma previously treated with chemotherapy, who presented with rapid onset of right proptosis and diplopia after being clinically free of disease for 1 year. MRI revealed a mass in her right orbit that on biopsy was consistent with recurrence. The right orbital mass was treated with a total dose of 16 Gy delivered in five fractions. **a** Three-dimensional coronal view representing the 188 CyberKnife beams delivered per fraction to the tumor within the right orbit, **b** axial view, **c** sagittal view, and **d** coronal view of the treatment plan showing the conformal dose distribution with steep dose fall off. Note the sparing of the right eyeball (*blue*) as well as the right optic nerve (*green*). The *white line* indicates the prescription dose to the 73% isodose line

wax bolus (0.5 cm thick) was attached to the aquaplast mask, if necessary. The wax bolus was felt to provide the best contact to the irregular surfaces of the orbit, particularly when surface doses were required. Non-contrast-enhanced CT and thin slice T1 MRI with IV contrast were also acquired before treatment (Fig. 2). Prior to the CT and MRI imaging, all patients were instructed to look straight forward and close their eyelids when the images were obtained. The MRI and CT images were then fused based on matching anatomy using the Multi-Plan (Accuray Incorporated, Sunnyvale, CA) treatment planning software. A radiation oncologist, ocular oncologist, and physicist jointly performed each treatment plan. Coronal and sagittal slices were generated from axial slices. Critical structures including the opposite eye, lacrimal glands, optic chiasm, optic nerves, brain, pituitary, and brain stem were delineated. Doses to the contralateral eye were kept to less than 1 Gy by eliminating any direct entrance or exit beams while the optic chiasm was kept below a 10-Gy single fraction equivalent. The participation of an ocular oncologist during treatment planning allowed for optimal target and normal tissue delineation, particularly in the postoperative cases.

In order to minimize ocular movement during treatment, patients with intraocular tumors were instructed to look straight ahead before closing their eyelids; this helped to ensure that the eyeball remained in a neutral position. In addition, a 2–3-mm treatment margin was added to the gross tumor volume of intraocular lesions to compensate for potential ocular movement. Prescribed total doses depended on the clinical scenario. For instance, total doses were lower for radiosensitive tumors (13.5–20 Gy) as compared to non-radiosensitive tumors (15–35 Gy). All treatments were delivered in three to five fractions (majority in five fractions) over a 1–2-week period, depending on patient preference. The median prescribed isodose line was 75% (range, 69–80%) with a median of 161 beams (range, 72–247). Prior to each treatment, the patient was positioned within the aquaplast mask that was created during the planning session. Prior to commencement of treatment, patients were reminded to keep their eyes closed in the same manner as they did during pretreatment imaging.

The skull was tracked using dual orthovoltage imagers located on the ceiling, with the detectors on the floor. The images were taken simultaneously, 90° apart, and were compared to the informational data from the planning CT in a process called six-dimensional (6D) tracking. Targets within the brain have been documented to possess an extremely low average treatment error of 0.57 mm when using 6D skull tracking [19]. During treatment, the patient's skull was typically imaged approximately every 30–60 s, and if a small movement of the skull was detected, the CyberKnife software was able to correct for the movement by either moving the patient's table position, or more frequently by the robot adjusting the position of the linear accelerator. If a larger movement was detected, the machine would stop until the patient was adjusted to the appropriate position. Each treatment session lasted 30–90 min, depending on the complexity of treatment. Local control was assessed by clinical and radiographic examination including ultrasound, X-rays, and clinical exam by an ocular oncologist, with whom they followed up with on a regular basis before, during, and after treatment.

Results

Outcomes

Between 2006 and 2008, 31 patients with eyelid, intraocular, orbital, or periorbital tumors were treated with the G4 CyberKnife system. The patients in this study were referred

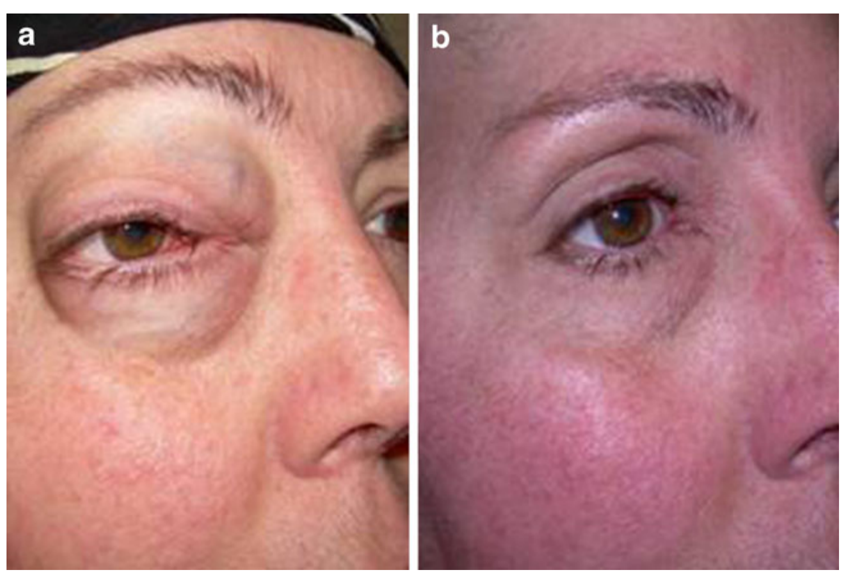

Fig. 2 Images of the patient in Fig. 1 taken just before (**a**) and at completion (**b**) of treatment. Note the near complete cosmetic response immediately following the completion of the fifth day of treatment. The patient maintained complete radiographic response up until her last follow-up at 14 months posttreatment. She subsequently succumbed to her systemic disease

from a busy ocular oncology practice with extensive experience in surgical and radioactive plaque techniques. Twenty-three patients with a minimum of 12 months follow-up were analyzed for this retrospective review (Table 1). The majority of patients (21 of 23) were treated with curative intent, including 9 radiosensitive tumors (all primary lymphomas), 17 with intact eye following limited surgery, and 4 after exenteration. Palliative patients included one metastatic breast cancer and one metastatic non-Hodgkin's lymphoma (Table 2). The patient population consisted of 22 Caucasians and 1 Hispanic; 13 were female and 10 male. Patients had a median age of 67 years (range, 16 to 91 years). Seven patients with radio-resistant tumors were treated with curative intent and had limited surgery with eye intact. Three patients received treatment after exenteration of the affected eye (two choroidal melanomas and one adenoid cystic carcinoma) (Fig. 3). At an overall median follow-up of 34 months (range, 14–42 months), 21 patients (91%) exhibited local control. CyberKnife treatments were generally well tolerated.

Adverse effects

Chronic complications, which included NVG in three patients, chronic dry eye in one patient, and osteomyelitis in one patient, were observed and managed by the ocular oncologists partnered with this study. Follow-up was comprised of a thorough ophthalmologic exam, which included ocular ultrasound and detailed retinography. Table 3 describes those patients who experienced chronic side effects from treatment.

Discussion

Primary malignancies of the eye and orbit are uncommon, consisting of less than 1% of all malignancies. Patients commonly travel long distances for diagnosis and surgical treatment with an ocular oncologist. Patients who require radiation treatment, which can commonly span a time frame of more than a month, typically return to their homes for radiation therapy. Community radiation oncologists may have less experience treating patients with ocular tumors and do not have direct access to ocular oncology specialists. It has been our anecdotal experience that joint involvement of an ocular and radiation oncologist in targeting and treatment planning is beneficial. The ocular oncologist commonly makes changes to the target volume that is not apparent from simple review of the patient's previous diagnostic studies, pathology, and operative notes alone. As a result, we found this team approach and level of expertise proved

Table 1 Description of the diagnosis and treatment regimen of the 23 patients analyzed in this study

Patient #	Age	Sex	Pathology	Dose (Gy)	Fractions	Primary or Mets
1	16	M	Adenoid cystic carcinoma	26	5	Primary
2	80	F	MALT lymphoma	16	5	Primary
3	62	F	Metastatic breast choroid	15	3	Mets
4	69	M	Metastatic melanoma	30	5	Mets
5	80	F	Conjunctival melanoma	30	5	Mets
6	54	M	Choroidal melanoma	30	5	Mets
7	91	F	Conjunctival/eyelid melanoma	30	5	Mets
8	68	M	Ocular lymphoma NOS	16	5	Primary
9	63	M	Choroidal melanoma	30	5	Primary
10	65	M	Conjunctival MALT lymphoma	16	5	Primary
11	72	F	Retinal/vitreous lymphoma NOS	17.5	5	Mets
12	46	M	Apocrine adenocarcinoma	18	4	Primary
13	68	M	Retinal/vitreous lymphoma NOS	20	4	Mets
14	46	F	Non-Hodgkin's lymphoma	16	5	Mets
15	56	F	Conjunctival/orbital lymphoma NOS	16	5	Primary
16	59	F	Ocular lymphoma NOS	13.5	3	Primary
17	69	F	Orbital squamous cell carcinoma	21.25	5	Primary
18	65	M	Ocular melanoma	30	5	Primary
19	76	F	Sebaceous carcinoma	25	5	Primary
20	40	F	Orbital basal cell carcinoma	19	5	Primary
21	82	F	Ocular lymphoma NOS	17.5	5	Primary
22	71	M	Ocular melanoma	30	5	Mets
23	67	F	Ocular melanoma	30	5	Primary

NOS not otherwise specified, *Mets* metastasis

Table 2 Treatment details grouped by those treated with curative versus palliative intent

Treatment intent	Number of patients	Mean dose (range) Gy	Number of fractions	Prior exenteration	Mean follow-up (range) months
Curative intent	21	21.25 (13.5–30)	–	3	34 (14–42)
Lymphoma	9	17.22 (13.5–20)	3–5	0	33 (23–38)
Melanoma	7	30[a]	5	2	27 (14–42)
Basal cell carcinoma	1	19	5	0	34
Adenoid cystic carcinoma	1	26	5	1	41
Apocrine carcinoma	1	18	4	0	37
Sebaceous carcinoma	1	25	5	0	20
Squamous cell carcinoma	1	22.5	5	0	14
Palliative intent	2	15.5 (15–16)	–	0	18
Metastatic non-Hodgkin's lymphoma	1	16	5	0	18
Metastatic breast cancer	1	15	3	0	18
Overall	23	20 (13.5–30)	3–5	3	33 (14–42)

Patients represented in this table had a minimum follow-up time of 12 months

[a] All melanoma patients received a total dose of 30 Gy

beneficial to our patients. Despite having a collaborative effort from a team of experts, there still exist challenges when attempting to deliver radiation to the eye and orbit. Foremost of which is that the location of the tumors in reference to nearby critical structures plays an important role in treatment planning, so as to spare healthy tissue unnecessary radiation exposure.

Specialized radiation techniques have been used to treat the most common adult primary eye malignancy, choroidal melanoma. Radiation has allowed many to spare their eye and to maintain useful vision, while maintaining the same survival rates as radical surgery. One modality that has been studied in the radiosurgical setting has been the Gamma Knife system (GKS); however, it is important to

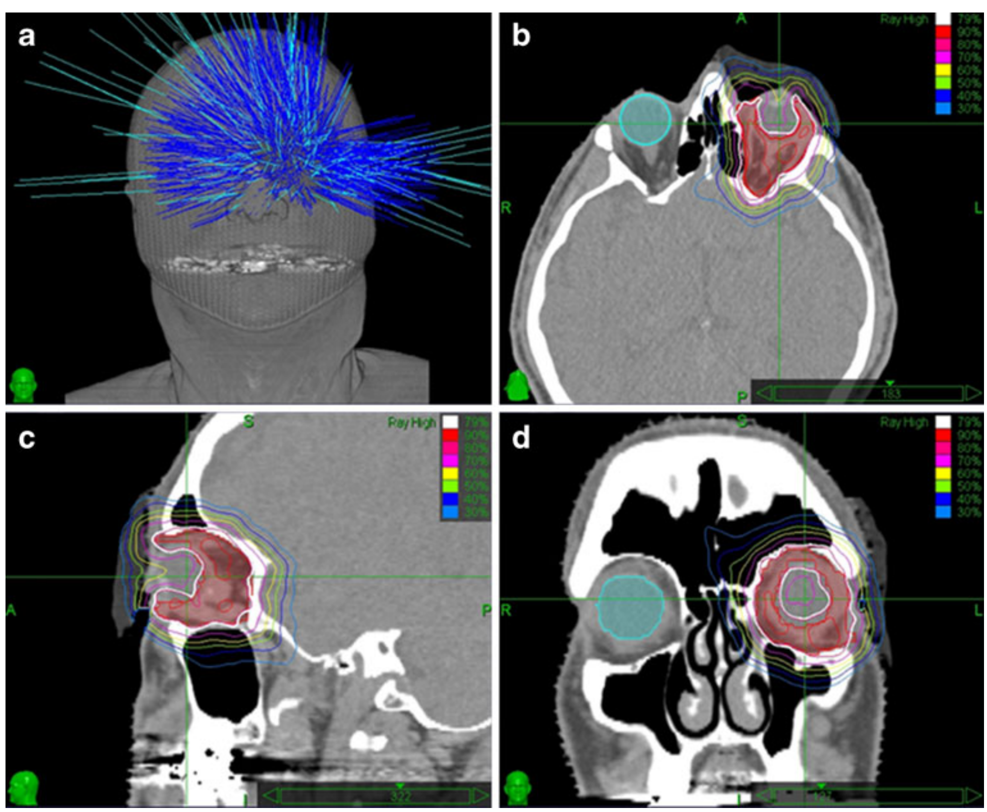

Fig. 3 Treatment planning images of a 54-year-old male with a recurrent left choroidal melanoma previously treated with iodine-125 radioactive plaque 3 years earlier. The recurrence was treated with a total dose of 30 Gy delivered in five fractions. **a** Three-dimensional coronal view representing the 163 CyberKnife beams delivered per fraction to the tumor, **b** axial view, **c** sagittal view, and **d** coronal view of the treatment plan showing the dose distribution. Note sparing of the right eyeball (*blue*) as well as the right optic nerve. The *white line* indicates the prescription dose to the 70% isodose line. He remains disease free at 41-month follow-up

Table 3 Observed complications and treatment prescriptions for those patients with reported adverse side effects

Patient #	Pathology	Prescription	Side effect
6	Choroidal melanoma	6 Gy×5=30 Gy	NVG
17	Squamous cell carcinoma	4.25 Gy×5= 21.25 Gy	NVG
9	Choroidal melanoma	6 Gy×5=30 Gy	NVG
18	Ocular melanoma	6 Gy×5=30 Gy	Chronic dry eye
19	Sebaceous carcinoma	5 Gy×5=25 Gy	Osteomyelitis

note that the vast majority of the literature reported has been on using GKS for ocular melanomas. While good results have been shown for local control, GKS does appear to have its limitations in the form of necessary invasive immobilization of the eyeball. A report from the *Journal of Neuroscience* in 2000 described this technique of immobilization in which patients were required to have local nerve block in the form of injectable anesthetic applied before tethering sutures were inserted to keep the eye fixed during treatment. While not a limitation for the use of GKS, it is important to note that the authors also used a 40-Gy dose prescribed to the 50% isodose line, as compared to our study, which used a lower dose, 30 Gy, to a median 74% isodose line [20].

When considering enucleation versus radiation therapy for treatment, it is important to mention the Cooperative Melanoma Study (COMS), which demonstrated similar 5-year survival rates for both scleral plaques (82%) and enucleation (81%) [21]. In those patients whose tumors were too large or located in an area of the eye not technically amenable to plaque treatment, there have been promising reports using protons or stereotactic radiosurgery. Although protons have less low dose radiation scatter to other parts of the brain and body, a particular advantage in children and younger adults, there is concern that higher doses to the anterior eye may lead to a higher risk of NVG. NVG is difficult to treat and potentially leads to severe eye pain and visual problems and may require enucleation.

Radiosurgical techniques can better spare anterior structures, but a recent report from Fernandes et al. reported NVG despite no pathological evidence of damage to the anterior chamber in those patients that required enucleation [9]. Fernandes et al. suggest that NVG is caused by late effects of radiation to the posterior aspect of the eye rather than to the anterior aspect as was historically thought; however, the true cause remains unknown [9]. Our patients treated with stereotactic radiosurgery would typically be treated with external radiation and not other specialized techniques. The literature for such patients is more scant. A recent study by Bianciatto et al. showed a 100% local control rate in 13 patients with ocular lymphomas of several different histopathologies treated with CyberKnife with a mean follow-up time of 23 months [22]. External radiation techniques continue to evolve, using intensity modulation and more sophisticated means of tumor targeting, blurring the lines between what is stereotactic radiosurgery and external radiation.

It is quite difficult to directly compare all of these treatment modalities. In our circumstance, patients who were appropriate candidates were treated with scleral plaques based on the phase III evidence presented in the COMS trial [21]. We used the CyberKnife to help maximize local control after more limited surgery, to maximize chances of local control after radical surgery, or to more expeditiously treat radiosensitive tumors or palliative cases. We were able to treat patients with irregularly shaped dose clouds that spared nearby normal structures. Our study shows promising local control rates, with 91% local control with a mean follow-up of 33 months. In addition, despite using higher radiation doses per fraction, CyberKnife treatments were well tolerated, with a low risk of chronic side effects. Our results demonstrate that frameless fractionated radiosurgery has promise in the treatment of orbital and ocular tumors (Table 4).

Conclusion

Our data demonstrates that frameless robotic stereotactic radiosurgery is an effective modality for the treatment of orbital and periorbital tumors. It offers the convenience of noninvasive radiation treatment over 1–2 weeks with sophisticated dose-shaping capability needed to spare nearby critical structures. Future studies are needed, particularly to compare various sophisticated techniques such as plaques, protons, and fractioned radiosurgery in the treatment of ocular tumors.

Table 4 Local control rates for those patients with a minimum of 12 months follow-up denoting whether they were curative intent or palliative intent

	Local control
Curative intent (*n*=21)	19 (95%)
Lymphoma (*n*=9)	9 (100%)
Melanoma (*n*=7)	6 (86%)
Other pathologies (*n*=5)	4 (80%)
Palliative (*n*=2)	2 (100%)
Metastatic non-Hodgkin's lymphoma (*n*=1)	1 (100%)
Metastatic breast cancer (*n*=1)	1 (100%)
All patients (*n*=23)	21 (91%)

Follow-up time ranged from 14 to 42 months

Conflict of interest We certify that regarding this paper, no actual or potential conflicts of interests exist; the work is original, has not been accepted for publication nor is concurrently under consideration elsewhere, and will not be published elsewhere without the permission of the Editor and that all the authors have contributed directly to the planning, execution, or analysis of the work reported or to the writing of the paper.

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