PRIMARY OPHTHALMIC RHABDOMYOSARCOMA IN 33 PATIENTS*

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ABSTRACT

Purpose: To review the findings, management, and outcome in 33 cases of primary ophthalmic rhabdomyosarcoma.

Methods: The records of 33 consecutive patients from a single ocular oncology center were analyzed retrospectively for outcomes of final visual acuity, local recurrence, and distant metastasis.

Results: Rhabdomyosarcoma was primarily located in the orbit in 25 cases (76%), conjunctiva in 4 (12%), eyelid in 1 (3%), and uveal tract in 3 (9%). Findings had been present for a mean of 5 weeks and included proptosis in 10 patients (30%), eyelid swelling in 7 (21%), and blepharoptosis in 6 (18%). The initial diagnoses before referral to us included primarily rhabdomyosarcoma in 8 cases (24%), conjunctivitis in 5 (15%), cellulitis in 5 (15%), and pseudotumor in 4 (12%). Tumors were classified according to the Intergroup Rhabdomyosarcoma Study Group staging and treatment protocols as group I in 4 cases (12%), group II in 12 (36%), group III in 16 (48%), and group IV in 1 case (3%). Treatment included surgical debulking, chemotherapy, and radiotherapy. Local tumor recurrence was detected in 6 patients (18%), lymph node spread in 2 (6%), and distant metastasis in 2 (6%). Long-term visual outcome of the 28 patients who maintained their globe was 20/20 to 20/40 in 11 patients (39%), 20/50 to 20/100 in 5 (18%), and 20/200 or worse in 12 (43%). Mean follow-up was 8.3 years; tumor-related death occurred in 1 patient (3%).

Conclusions: Rhabdomyosarcoma can present in the orbit, eyelid, conjunctiva, and uveal tract. Following treatment, local tumor recurrence occurs in 18% of cases, metastasis in 6%, and death in 3%.

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INTRODUCTION

Over the past 25 years, the pediatric, oncologic, and radiologic literature has included several reports on the treatment and outcome of patients with rhabdomyosarcoma.[1-14] Through the collaborative efforts of the Intergroup Rhabdomyosarcoma Study Group, dramatic advances have been made in the understanding of the behavior and management of rhabdomyosarcoma.[1-14] The Intergroup Rhabdomyosarcoma Study Committee (as the group was originally known) was organized in 1972 to perform large collaborative randomized trials for treatment of rhabdomyosarcoma. Since the group's inception, 4 major trials (studies I through IV) have been done.[1-14] As a result of these trials, the survival rate following treatment of rhabdomyosarcoma at all sites has improved from 25% in 1970 to 70% in 1991.[15]

Orbital rhabdomyosarcoma has been recognized to have a better patient prognosis than rhabdomyosarcoma at other sites. Nearly 25 years ago, before the treatment trials were done, the survival rate of patients with orbital rhabdomyosarcoma was poor (about 30%).[16,17] Treatment generally consisted of orbital exenteration and various chemotherapy regimens. Following trials I and II, improved treatment regimens with chemotherapy and radiotherapy, usually avoiding exenteration, were successful, and the prognosis of patients with orbital rhabdomyosarcoma strikingly improved to a survival rate of 93% at 3 years.[13]

The published reports of the Intergroup Rhabdomyosarcoma Study Group trials focused on patient life prognosis following various treatment regimens; little description was given to the clinical spectrum and diagnostic features of rhabdomyosarcoma in the ocular region. These important reports emanated from pediatric oncology centers and not ocular oncology centers; thus the clinical ophthalmologic details were scant. Additionally, all sites of rhabdomyosarcoma involvement, including the head and neck, genitourinary system, extremities, trunk, and others, were included in most of the analyses of outcome, and only brief details were provided on the subset of ophthalmic rhabdomyosarcoma.[1-14] It appeared that patients with rhabdomyosarcoma in the ocular region were classified under the general heading of "orbital rhabdomyosarcoma" regardless of exact site of origin, whether in the orbit, conjunctiva, or eyelid. Thus, the goal of this report is to describe and define the

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clinical spectrum of ophthalmic rhabdomyosarcoma, giving particular emphasis to the various sites of origin, including the orbit, conjunctiva, eyelid, and globe.

MATERIALS AND METHODS

The computerized files of the Ocular Oncology Service at Wills Eye Hospital were reviewed, and all patients with the diagnosis of primary rhabdomyosarcoma were identified. The patients' charts were reviewed, and data on the patient, eye, and tumor were collected. The patient data included age, race, male or female sex, symptoms, duration of symptoms, and initial diagnosis. Data regarding the affected eye and orbit included visual acuity, intraocular pressure, ocular motility and proptosis, and specific ocular structures involved (eyelids, conjunctiva, intraocular contents). Data regarding the tumor included its management before patient referral and its location, size, color, configuration, and appearance on computed tomography (CT) and magnetic resonance imaging (MRI). The tumor management and histopathology, staging and management according to the Intergroup Rhabdomyosarcoma Study Group, and response to treatment were recorded. Final ocular outcome, local tumor control, and systemic outcome were determined.

RESULTS

Of more than 21,000 patients with ophthalmic tumors and pseudotumors evaluated on the Ocular Oncology Service at Wills Eye Hospital over the past 25 years, only 33 patients (0.2%) had primary ocular rhabdomyosarcoma. The mean patient age was 10 years (median, 7 years; range, 1 month to 68 years). At presentation, 8 patients (24%) were older than 10 years and 4 (12%) were older than 20 years. Twenty-three patients (70%) were male, and 10 (30%) were female; 27 (82%) were white, 4 (12%) were African American, 1 was Asian (3%), and 1 was Hispanic (3%). The right side was involved in 18 patients (55%) and the left in 15 (45%). The presenting clinical manifestations are listed in Table I. The mean duration of symptoms was 5 weeks (median, 4 weeks; range, 1 to 16 weeks). The initial diagnoses by the referring doctors are listed in Table II. Medical treatment of the lesion was performed in 12 cases prior to diagnosis of rhabdomyosarcoma; treatment and included corticosteroids in 4 (12%), antibiotics in 7 (21%), and antihistamines in 1 (3%). Surgical biopsy was performed in 9 cases (27%) prior to referral to us.

Visual acuity at presentation was 20/20 to 20/50 in 23 patients (70%), 20/60 to 20/100 in 4 (12%), 20/200 or worse in none (0%), and "fix and follow vision" in the 6 preverbal children (18%). The mean intraocular pressure was 15 mm Hg (median, 14 mm Hg; range, 8 to 26 mm Hg).

TABLE I: MAIN PRESENTING FEATURE OF PRIMARY OCULAR RHABDOMYOSARCOMA IN 33 CONSECUTIVE PATIENTS

SYMPTOM	NO. (%)
Proptosis	10 (30)
Eyelid edema	7 (21)
Blepharoptosis	6 (18)
Conjunctival congestion	3 (9)
Visible mass	2 (6)
Blurred vision	2 (6)
Epistaxis	1 (3)
Nasal congestion	1 (3)
Leukocoria	1 (3)

TABLE II: REFERRING DIAGNOSIS IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

DIAGNOSIS	NO. (%)
Rhabdomyosarcoma	8 (24)
Orbital cellulitis	5 (15)
Conjunctivitis	5 (15)
Idiopathic inflammatory orbital pseudotumor	4 (12)
Capillary hemangioma	1 (3)
Orbital cyst	1 (3)
Stye	1 (3)
Allergic edema	1 (3)
Insect bite	1 (3)
Merkle cell tumor	1 (3)
Conjunctival papilloma	1 (3)
Conjunctival cyst	1 (3)
Scleritis	1 (3)
Iris juvenile xanthogranuloma	1 (3)
Retinal detachment	1 (3)

The primary tumor site was the orbit in 25 patients (76%), conjunctiva in 4 (12%), uveal tract in 3 (9%), and eyelid in 1 patient (3%) (Fig 1). The uveal tumors were located in the iris in 1 case and ciliary body in 2 cases (Table III). Of the 30 extraocular tumors, all had an orbital component, despite apparent tumor origin in the conjunctiva or eyelid, and the epicenter of orbital tumor location was superonasal in 11 cases (37%), superior in 10 (33%), inferonasal in 3 (10%), inferior in 3 (10%), nasal in 2 (7%), and inferotemporal in 1 (3%). No tumors were centered temporally or superotemporally in the orbit. Of the 4 conjunctival tumors, the location was upper fornix in 3 cases (75%) and lower fornix in 1 case (25%). No conjunctival tumors originated from the bulbar or limbal conjunctiva.

The ocular findings on presentation are listed in Table IV. The most common findings were proptosis (79%), paraxial globe displacement (79%), eyelid edema (64%), conjunctival congestion (61%), blepharoptosis

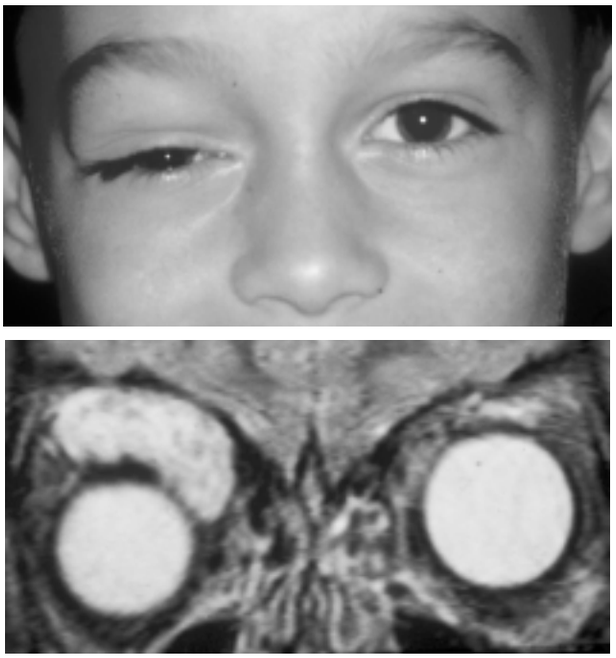

FIGURE 1A

Case 6. Top, Classic proptosis and eyelid edema from superonasal orbital rhabdomyosarcoma in 9-year-old boy. Bottom, MRI scan (T2-weighted image) demonstrating bright, moderately homogeneous signal of circumscribed superonasal tumor.

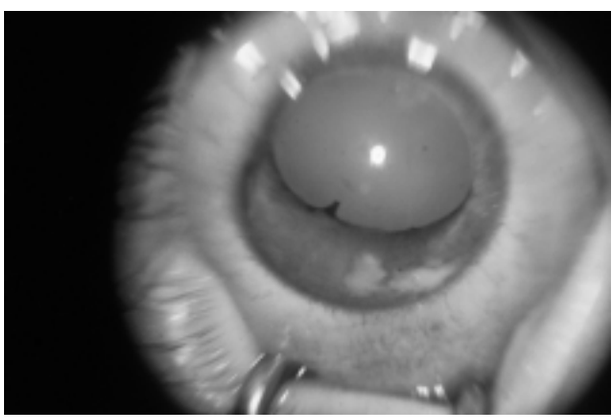

FIGURE 1C

Case 31. Fluffy white tumor in anterior chamber of 2-year-old child. At enucleation, tumor was confirmed to be intraocular rhabdomyosarcoma. Reprinted, with permission, from Elsas et al.[34]

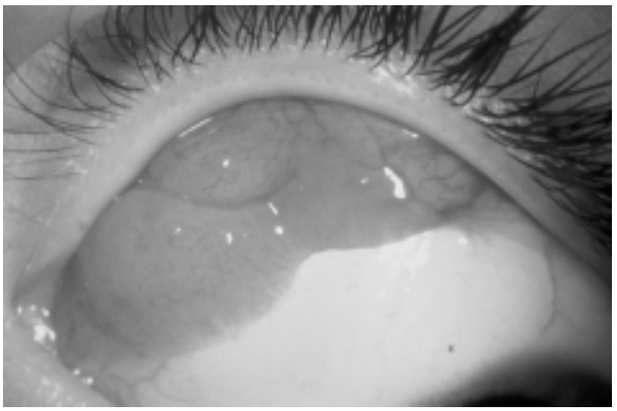

FIGURE 1B

Case 29. Pink subconjunctival rhabdomyosarcoma in superonasal fornix of 8-year-old child.

TABLE III: PRIMARY TUMOR LOCATION IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

TUMOR LOCATION	NO. (%)
Orbit	25 (76)
Quadrant location*:	
Superior	10
Inferior	3
Nasal	2
Temporal	0
Superonasal	11
Superotemporal	0
Inferonasal	3
Inferotemporal	1
Anteroposterior location*:	
Anterior orbit	11
Mid orbit	13
Posterior orbit	6
Eyelid	1 (3)
Upper	1
Lower	0
Conjunctiva	4 (12)
Upper fornix	3
Lower fornix	1
Intraocular	3 (9)
Iris	1
Ciliary body	2

*Total is 30 cases, including all orbital tumors, even those that arose primarily in the conjunctiva and eyelid and secondarily involved the orbit.

(55%), dilated episcleral vessels (42%), and ocular motility restriction (42%).

The mean largest tumor dimension by CT or MRI was 25 mm (range, 10 to 60 mm). Excluding the 3 cases of uveal rhabdomyosarcoma, the tumor location in the orbital soft tissues was extraconal alone in 26 (87%), intraconal alone in none (0%), and both intraconal and extraconal in 4 (13%). Bone erosion was present in 10 patients (30%). No tumors caused bone expansion or hyperostosis. Sinus invasion by the orbital tumor was found in the maxillary sinus in 6 cases (20%) (with additional involvement in the nasopharynx in 1 case and the ethmoid sinus in 1 case) and the nasal cavity in 1 case (3%). Intracranial invasion was found into the anterior cranium in 1 case (3%) and skull base in 1 case (3%). By imaging, the tumor was well defined in 21 cases (70%) and poorly defined in 9 (30%).

Orbital CT was available in 25 patients with orbital tumors and revealed a soft tissue, noncalcified mass with contrast enhancement of the tumor in all cases (100%), showing a pattern of generalized enhancement in 23 (92%) and peripheral "ring" enhancement in 2 (8%). The mass appeared cavitary in 2 cases (8%).[18] Orbital MRI was

TABLE IV: PRESENTING SIGNS IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

CLINICAL SIGN	NO. (%)
Proptosis	26 (79)
Displacement of eyeball	26 (79)
Superior	5 (15)
Inferior	8 (24)
Nasal	2 (6)
Temporal	3 (9)
Superonasal	1 (3)
Superotemporal	0
Inferonasal	1 (3)
Inferotemporal	6 (18)
Ocular motility restriction	14 (42)
Blepharoptosis	18 (55)
Edema	21 (64)
Both eyelids	8 (24)
Upper eyelid	12 (36)
Lower eyelid	1 (3)
Erythema	13 (39)
Both eyelids	4 (12)
Upper eyelid	8 (24)
Lower eyelid	1 (3)
Conjunctival congestion	20 (61)
Conjunctival chemosis	11 (41)
Dilated episcleral vessels	14 (42)
Retinal venous dilation	2 (6)
Retinal detachment	1 (3)
Choroidal folds	5 (15)
Disc edema	2 (6)

available in 10 cases, and T1-weighted images revealed a soft tissue mass with low signal in 4 cases (40%), intermediate signal in 5 (50%), and bright signal in 1 case (10%) (Fig 2). On T2-weighted images, the soft tissue mass showed low signal in 2 cases (20%), intermediate signal in 1 case (10%), and bright signal in 7 cases (70%). Gadolinium enhancement was documented in all 10 cases (100%); a pattern of generalized enhancement was shown in 9 cases and ring enhancement of the periphery in 1 case in which cavitary tumor was found[18] (Fig 3).

Histopathologically, the tumor cell type in the 30 cases of extraocular rhabdomyosarcoma was found to be embryonal in 27 cases (90%), alveolar in 3 cases (10%); no botryoid or pleomorphic types were found. The 3 intraocular tumors were too atypical to be classified into these groups. Frozen sections were performed in 15 cases and were found to be diagnostic in 13 (87%) and nondiagnostic in 2 (13%). Immunohistochemistry studies revealed immunoreactivity for desmin in all 16 cases (100%) in which it was performed. There was immunoreactivity for vimentin in 13 (94%) of the 14 cases in which it was performed. Immunoreactivity for myoglobin was detected in 6 (60%) of the 10 cases in which it was performed.

According to the Intergroup Rhabdomyosarcoma Study Group, the tumors were classified as group I in 4 cases (12%), group II in 12 (36%), group III in 16 (48%), and group IV in 1 case (3%) (Table V). Management was complex in these cases, involving various regimens of chemotherapy, radiotherapy, and even orbital exenteration

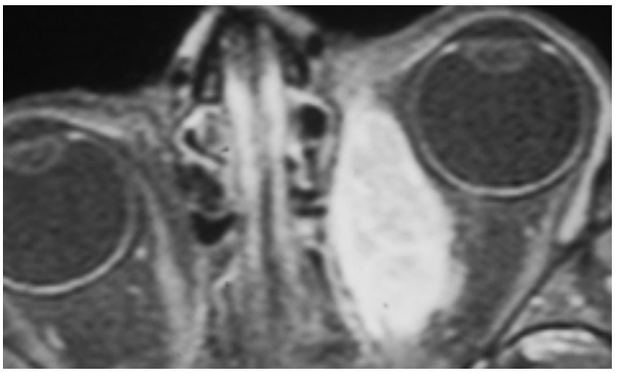

FIGURE 2A

Case 15. Oribital MRI scan (axial T1-weighted, fat suppression technique, gadolinium enhancement) showing fusiform moderately homogeneously enhancing rhabdomyosarcoma in superonasal orbit.

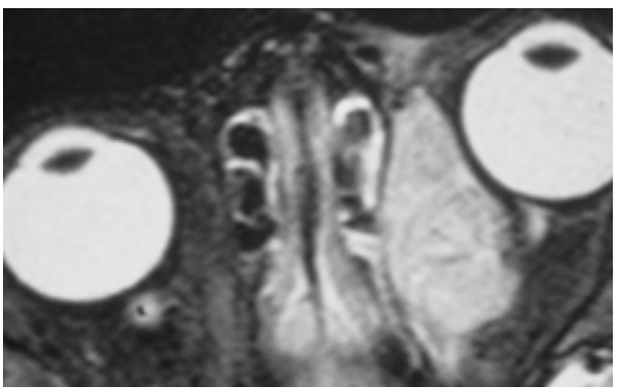

FIGURE 2B

Case 15. MRI scan (axial T2-weighted) showing bright signal of rhabdomyosarcoma with linear internal septations compared with orbital fat and normal muscle.

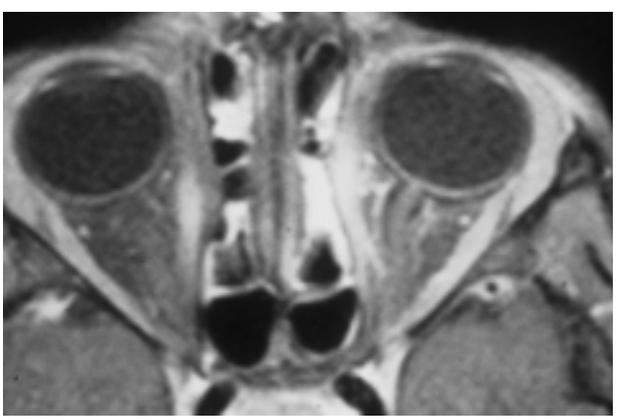

FIGURE 2C

Case 15. MRI (axial T1-weighted, fat suppression technique, gadolinium enhancement) performed 10 months after diagnosis and treatment of rhabdomyosarcoma, demonstrating lack of solid tumor and only mild enhancement at site of previous surgery.

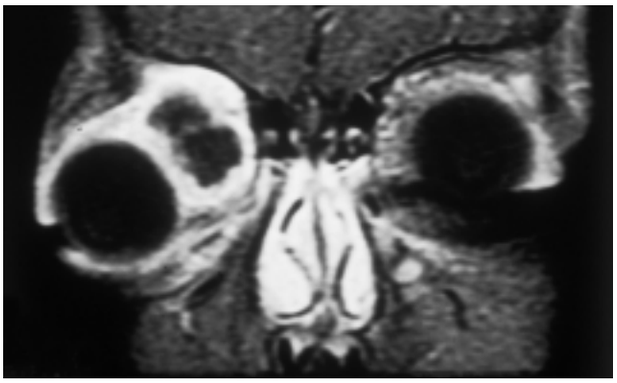

FIGURE 3
Case 17. Orbital MRI (axial T1-weighted, fat suppression technique, gadolinium enhancement) of atypical rhabdomyosarcoma, displaying central nonenhancing cavitation, simulating orbital lymphangioma.

Reprinted, with permission, from Fetkenhour et al.[18]

TABLE V: STAGING OF PRIMARY OCULAR RHABDOMYOSARCOMA IN 33 CONSECUTIVE PATIENTS ACCORDING TO THE INTERGROUP RHABDOMYOSARCOMA STUDY CLASSIFICATION

GROUP	DESCRIPTION	NO. (%)
I	Completely resected localized disease implying both gross impression resection and microscopic confirmation of complete resection and absence of regional lymph node involvement	4 (12)
Ia	Confined to muscle or organ of origin	4 (12)
Ib	Contiguous involvement outside muscle or organ of origin	0
II	Residual disease and/or regional lymph node involvement	12 (36)
IIa	Grossly resected localized tumor with microscopic residual disease and no evidence of gross residual tumor or regional lymph node involvement	11 (33)
IIb	Regional disease involving lymph nodes and completely resected*	1 (3)
IIc	Regional disease involving lymph nodes and grossly resected with microscopic residua*	0
III	Incomplete resection with biopsy or gross residual disease at site of origin or in regional lymph nodes	16 (48)
IV	Distant metastasis present at onset	1 (3)

*Regional disease implies involvement of regional lymph nodes.

TABLE VI: CURRENT RECOMMENDATIONS OF THE INTERGROUP RHABDOMYOSARCOMA STUDY GROUP IV FOR TREATMENT OF ORBITAL RHABDOMYOSARCOMA (GROUPS I, II, AND III)

GROUP	RADIATION THERAPY*	CHEMOTHERAPY
I	None	VA x 32 weeks (regimen 44, VA)
II	4,140 cGy CFI	VA
III	5,040 cGy CFI *or* 5,940 cGy HFI	VA+C x 52 weeks (regimen 41, VAI) *or* VA+I x 52 weeks (regimen 42, VAC) *or* VI +E x 52 weeks (regimen 43, VIE)

CFI, conventional fractionated irradiation; HFI, hyperfractionated irradiation; V, vincristine; A, actinomycin D; C, cyclophosphamide; I, ifosfamide; E, etoposide.
* Radiotherapy should begin at week 9.

Adapted from Lanzkowsky[20] *and Wexler and Helman.*[21]

TABLE VII: PRIMARY MANAGEMENT OF PRIMARY OCULAR RHABDOMYOSARCOMA IN 33 CONSECUTIVE PATIENTS

MANAGEMENT	NO. (%)
Surgical debulking + Chemotherapy + External beam radiotherapy*	28 (85)
Surgical debulking + Chemotherapy	1 (3)
Surgical debulking + External beam radiotherapy	1 (3)
Enucleation†	3 (9)

* Proton beam radiotherapy was performed in 1 case.
†All were intraocular rhabdomyosarcoma.

TABLE VIII: COMPLICATIONS OF MANAGEMENT IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

COMPLICATION	NO. (%)
Orbit	
Orbital hypoplasia	8 (24)
Strabismus	1 (3)
Restriction of ocular motility	1 (3)
Diplopia	1 (3)
Eyelid	
Blepharoptosis	3 (9)
Ocular surface	
Dry eye	12 (36)
Radiation keratopathy	1 (3)
Intraocular	
Radiation cataract	18 (55)
Radiation retinopathy	3 (9)
Phthisis bulbi	1 (3)
Face	
Second malignant neoplasm	1 (3)

as per the Study Group protocol at the time of patient entry over the past years (Tables VI and VII). All patients were managed by pediatric oncologists as part of the Intergroup Rhabdomyosarcoma Study Trials. The 3 patients with intraocular rhabdomyosarcoma were managed with enucleation alone.

Complications of management, listed in Table VIII, most commonly included cataract in 18 patients (55%), dry eye in 12 (36%), and orbital hypoplasia in 8 (24%). The orbital, globe, and visual outcomes are listed in Table IX. Two patients (6%) required orbital exenteration, 3 (9%) required enucleation (all cases of uveal rhabdomyosarcoma), and 12 (36%) had poor visual outcome (20/200 or worse).

The local and systemic tumor outcomes are listed in Table X. Local recurrence was discovered in 6 patients (18%), regional lymph node metastasis in 2 (6%), and distant metastasis in 2 (6%); 1 patient (3%) died. The mean

TABLE IX: OCULAR AND VISUAL OUTCOMES IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

OUTCOME	NO. (%)
Orbit	
No exenteration	31 (94)
Exenteration	2 (6)
Globe	
No enucleation	30 (91)
Enucleation	3 (9)
Visual acuity	
Good (20/20 – 20/40)	11 (33)
Intermediate (20/50 – 20/100)	5 (15)
Poor (20/200 or worse)	12 (36)
Enucleation or exenteration	5 (15)

TABLE X: LOCAL AND SYSTEMIC TUMOR OUTCOMES IN 33 CONSECUTIVE PATIENTS WITH PRIMARY OCULAR RHABDOMYOSARCOMA

OUTCOME	NO. (%)
Local tumor outcome	
Regression	28 (85)
Recurrence*	6 (18)
Regional outcome	
No lymph node spread	31 (94)
Lymph node spread†	2 (6)
Systemic outcome	
No distant metastasis	31 (94)
Distant metastasis‡	2 (6)
Final status	
Alive	32 (97)
Dead of metastasis	1 (3)

*Local recurrence was managed successfully with debulking + chemotherapy in all 6 cases, with additional external beam radiotherapy in 1 case, gamma knife radiosurgery in 1 case, and exenteration in 2 cases.

†Lymph node spread was documented at presentation in 1 case and upon follow-up after therapy in 1 case. Lymph node spread was successfully managed with debulking + chemotherapy in both cases and additional radiotherapy in 1 case.

‡Distant metastasis was documented at presentation in 1 case and upon follow-up after therapy in 1 case. Metastasis was successfully treated with debulking + chemotherapy + radiotherapy in 1 case. One patient with overwhelming lung metastasis died despite chemotherapy.

time from diagnosis to local recurrence was 16 months (median, 15 months; range, 7 to 26 months). According to Kaplan-Meier estimates, local recurrence was detected in 10% of patients at 1 year follow-up, 19% at 2 years, and 23% at 5 years. Regional lymph node metastasis was discovered at initial examination in 1 patient and 1 month following institution of treatment in another patient. In the 2 patients with distant metastases, metastasis to the scapula was diagnosed at initial visit in one patient and metastases to the lung and long bones, leading to death, was diagnosed 6 years following treatment in the other patient. Second cancers were found in 2 patients (6%) and consisted of nonfatal, completely resected facial basal cell carcinoma in the field of irradiation in 1 patient and fatal central nervous system glioblastoma occurring 10 years following complete control of orbital rhabdomyosarcoma in the other. In the 3 patients with uveal rhabdomyosarcoma, all of whom were treated with enucleation alone, no local recurrence, metastasis, or second cancer was found at mean follow-up of 29 months.

DISCUSSION

Rhabdomyosarcoma is the most common soft tissue sarcoma arising in the pediatric population. It accounts for about 5% of all childhood cancers.[6] About 250 new cases of rhabdomyosarcoma are diagnosed each year in the United States.[19] It can occur in any anatomic location of the body where there is skeletal muscle as well as at sites without skeletal muscle, such as the urinary bladder, common bile duct, and soft tissues of the orbit.[20,21] The primary sites of rhabdomyosarcoma are the head and neck (40%), genitourinary tract (20%), extremities (20%), trunk (10%), and other locations (10%).[20,21] Rhabdomyosarcoma of the head and neck can be further subdivided by location within the orbit (10% of all rhabdomyosarcoma); in the parameningeal region, such as nasopharynx, middle ear, paranasal sinuses, and infratemporal and pterygopalatine fossae (20%); and at other sites, such as larynx, oropharynx, oral cavity, parotid gland, cheek, and scalp (10%).[20,21]

The diagnosis and management of rhabdomyosarcoma have been refined over the past half century. In the 1930s and 1940s, improved understanding of the histopathologic features allowed reclassification of tumors as rhabdomyosarcoma that had been previously grouped into "round cell or spindle cell sarcomas."[22] Currently, rhabdomyosarcoma is classified into 4 major subtypes–embryonal (57%), alveolar (19%), botryoid (6%), and pleomorphic (1%)–with the remainder too undifferentiated (10%) or heterogeneous (7%) for specific classification.[22]

Over the past 30 years, several treatment trials by the Intergroup Rhabdomyosarcoma Study Group have stimulated interest in this tumor and provided important information regarding effective treatment regimens, leading to improved patient survival rates.[1-14] Currently, when all sites of rhabdomyosarcoma are considered, nearly 70% of patients survive.[15] Rhabdomyosarcoma shows a strong tendency for local invasion, local recurrence, and hematogenous and lymphatic metastases; thus treatment protocols involving both chemotherapy and radiotherapy have been used.[1-14,23,24] Patient survival from rhabdomyosarcoma at any site generally depends on several factors, including extent of disease at diagnosis (according to Intergroup

Rhabdomyosarcoma Study groups I through IV), tumor burden at diagnosis, primary tumor site, patient age, histopathologic and cytologic type, cellular DNA content (ploidy), and therapeutic response.[20,21]

With regard to tumor burden at diagnosis, survival rates are 90% for patients with clinical group I disease, 85% for group II disease, 70% for group III disease, and 40% for group IV disease. Smaller tumor burden (< 5 cm) carries improved survival compared with greater burden (> 5 cm), and younger patient age at presentation (1 year to 7 years) is more favorable than older age (> 7 years). With regard to primary tumor site, 5-year survival is 80% to 90% for those with rhabdomyosarcoma of the orbit, 7l% for disease of the head and neck, 70% for parameningeal disease, 73% to 84% for genitourinary disease, 66% for disease of the extremity, and 60% for disease at other sites, such as retroperitoneum, trunk, pelvis, and paraspinal region.[20,21] Histopathologic features are important predictors of patient outcome; patients with embryonal cell type have the best prognosis, whereas those with alveolar cell type show the least favorable outcome. Additionally, prognosis is better with tumors whose DNA content is 1.5 times normal (hyperdiploid) than with those with normal diploid content. Finally, the most important prognostic variable is response to therapy: Patients who show a poor response or do not attain a complete pathologic response are less likely to survive.

In 1997, the Intergroup Rhabdomyosarcoma Study Group provided a comprehensive report on the subset of patients with orbital rhabdomyosarcoma.[10] Data were analyzed from 264 patients managed with treatment protocols from trials I, II, III, and IV. Tumor involvement was classified as group I in 3% of patients, group II in 20%, group III in 74%, and group IV in 3%. The tumor cell type proved to be embryonal in 80%, alveolar in 9%, botryoid in 4%, pleomorphic in 0%, undifferentiated in 4%, and other in 3%. Few details were given regarding patient clinical or imaging features because the report was focused on patient outcome. The average follow-up was 7.5 years. Overall, 18 patients (7%) died of rhabdomyosarcoma and 5 (2%) died of treatment-related complications. The 5-year survival rate was 74% for those with orbital alveolar rhabdomyosarcoma and 94% for those with embryonal rhabdomyosarcoma.

In our analysis of 33 patients with orbital rhabdomyosarcoma managed at an ocular oncology center in coordination with a major pediatric oncology center, we found similar results for tumor classification: group I in 12% of patients, group II in 36%, group III in 48%, and group IV in 3% (Table V). Likewise, we found a similar distribution of tumor cell type in the 30 tumors involving the extraocular structures: embryonal in 90%, alveolar in 10%, and botryoid or pleomorphic in none. Tumor-related death occurred in 1 patient (3%), treatment-related complications leading to death in no patients, and death from second cancer in 1 patient (3%). Therefore, our results are similar to those of the Intergroup Rhabdomyosarcoma Study. The important addition from our observations, however, is the analysis of the clinical variations of this malignancy within the ocular tissues and the identification of a minor group of patients with rhabdomyosarcoma within the globe.

Ophthalmic involvement of rhabdomyosarcoma generally occurs in children at an average age of 10 years, but this malignancy can develop in adults. In our group, 24% of patients were older than age 10, and 12% were older than 20; the oldest patient was 68 years.[25] The most common presenting clinical features were proptosis (30%), eyelid edema (21%), and blepharoptosis (18%) (Table I). Nasal congestion and epistaxis were also manifestations of ophthalmic rhabdomyosarcoma. Those patients with tumors in the uveal tract had symptoms of blurred vision or leukocoria.

Rhabdomyosarcoma can affect several ocular tissues. In our series, the tumor developed in the orbit in 76% of cases, conjunctiva in 12%, eyelid in 3%, and within the globe in 9%. Some degree of orbital involvement was found in all 30 cases of extraocular tumor, despite apparent tumor origin in the conjunctiva or eyelid. Of those 30 extraocular tumors, the tumor location within the orbit was superonasal or superior in 70% of cases, usually in the anterior orbit (Table III). Thus, this tumor has a tendency to occur in the superonasal anterior aspect of the orbit.[26]

The most frequent clinical findings in patients with ophthalmic rhabdomyosarcoma are proptosis (79%), globe displacement (79%), eyelid edema (64%), and conjunctival congestion (61%). Thus, the differential diagnostic considerations include inflammatory lesions such as orbital cellulitis, idiopathic inflammatory orbital pseudotumor, conjunctivitis, and allergic edema, and other tumors such as orbital capillary hemangioma, lymphangioma, Langerhan's cell histiocytosis.[27-31] Most of these conditions can be differentiated by clinical history taking and examination, but orbital lymphangioma may prove to be more challenging to differentiate from rhabdomyosarcoma. Rhabdomyosarcoma occurs in patients of the same age-group as those with lymphangioma, and both diseases cause painless, noninflammatory proptosis, occurring over a short time. Differentiation by orbital imaging is usually helpful and shows a solid enhancing mass with rhabdomyosarcoma versus a multicystic nonenhancing mass with lymphangioma. However, in rare cases, rhabdomyosarcoma can display cavitation appearing similar to lymphangioma.[18]

Intraocular rhabdomyosarcoma is particularly rare.

Because of our interest in intraocular malignancies, we have seen a disproportionate number of patients with intraocular rhabdomyosarcoma, skewing the true incidence of patients with tumor in this location. Two of the cases in our series have been previously published.[32,33] In the third case, the eye of a 34-year-old African American woman was enucleated for a ciliary body tumor at another institution, and the rhabdomyosarcoma was discovered on histopathologic examination. According to our cases and a few reported cases, intraocular rhabdomyosarcoma has appeared in the iris as a circumscribed or fluffy mass at a median age of 4 years and has also presented in the ciliary body.[32-35] Iris rhabdomyosarcoma can resemble iris juvenile xanthogranuloma.[33] Enucleation has been performed in all of these cases. In the 4 published cases of intraocular rhabdomyosarcoma,[32-35] no patients had developed metastasis at 1-, 3-, 4-, and 20-year follow-up examinations.

Imaging of periocular rhabdomyosarcoma is critical in establishing the diagnosis, as well as the extent and location of the tumor, for surgical planning.[36,37] Mafee and associates[36] reviewed 11 cases of orbital rhabdomyosarcoma and found that these tumors on CT were isodense compared with normal muscles, generally with homogeneous internal qualities and well-defined margins, and lacking adjacent bone destruction. Moderate to marked enhancement with contrast agent was a feature of all tumors. However, larger tumors were less well defined, sometimes with bone destruction and heterogeneous internal qualities related to hemorrhage. Sohaib and coworkers[37] further refined these observations and noted that orbital rhabdomyosarcoma was intraconal in 40% and extraconal in 60%. Bone erosion was found in 17% and bone thinning in an additional 23%. MRI of orbital rhabdomyosarcoma demonstrated isointense or slightly hypointense signal compared with normal brain on T1-weighted images and increased signal on T2-weighted images.[36] All tumors showed enhancement with contrast agents. Areas of hemorrhage appeared as focal increased signal on T1- and T2-weighted images. In our series, similar features were found on imaging. All of the tumors in our series were extraconal, but some showed partial intraconal component. There were no tumors with intraconal involvement alone. The findings on MRI were more variable than those described by Sohaib and associates,[18] in that low or intermediate signal was found on T1-weighted images in 90% of cases and bright signal on T2-weighted images in 70% of cases. In 1 case, cavitary changes within the mass displayed ring enhancement.

Treatment protocols for rhabdomyosarcoma have evolved over the past 25 years according to the recommendations of the Intergroup Rhabdomyosarcoma Study Group.[4,6,10,13,38] Currently, according to the results of trial IV, the recommended treatment includes both chemotherapy and radiotherapy as listed in Table VI, with the exception of completely resected orbital tumors, where only chemotherapy without radiotherapy is advised. Current management of group IV orbital rhabdomyosarcoma depends on the location and extent of disease and generally consists of combination chemotherapy and radiotherapy delivered to the orbit and all involved sites of tumor.[20] Recurrent tumors in the orbit usually are treated with orbital exenteration, sometimes supplemented with chemotherapy and radiotherapy.[39]

Several investigators have focused on late effects of therapy in orbital rhabdomyosarcoma in children.[12,40,41] In 2000, Raney and coworkers[12] reported on late effects of therapy in 94 patients with orbital rhabdomyosarcoma from the Intergroup Rhabdomyosarcoma Study III. Data were gathered by questionnaire from numerous oncology institutions involved in following the clinical course of the children. The investigators reported that exenteration or enucleation was necessary in 14% of patients for tumor control or treatment complications. Other late effects included cataract (82%), decreased visual acuity (70%), orbital hypoplasia (59%), dry eye (30%), chronic keratoconjunctivitis (27%), and retinopathy (6%). In our series, we were able to accurately record the late effects, since all patients were examined by our team of ocular oncologists. Overall, enucleation was necessary for all 3 patients with intraocular rhabdomyosarcoma, and orbital exenteration was performed for 2 (7%) of the 30 patients with extraocular rhabdomyosarcoma in order to achieve tumor control. Of the remaining 28 eyes, late effects included cataract (55%), dry eye (36%), orbital hypoplasia (24%), blepharoptosis (9%), and radiation retinopathy (9%), as listed in Table VIII. Consequently, current treatment of periocular rhabdomyosarcoma can lead to substantial local late effects.

In the late effects study, the visual acuity was reportedly decreased in 70% of patients, ranging from 20/30 to 20/400.[12] The details regarding visual outcome were not provided. We can add to these data and state that visual acuity following treatment in the 30 patients with periocular rhabdomyosarcoma was good at 20/20 to 20/40 in 37%, intermediate at 20/50 to 20/100 in 17%, and poor at 20/200 or worse in 47%. These results reflect primarily the long-term effects of radiation on the function of the eye.

The prognosis for patients with orbital rhabdomyosarcoma has greatly improved in recent years. Orbital rhabdomyosarcoma represents about 10% of all rhabdomyosarcoma cases, and it is recognized that patients with tumors at this site carry the best prognosis.[12] On the basis of Trials I, II, III, and IV, the survival rate of patients with orbital rhabdomyosarcoma is now 93%.

Tumor morphology is an important predictor of death: those patients with alveolar cell type have a 74% 5-year survival rate, whereas those with embryonal cell type demonstrate a 94% 5-year survival rate.[10] This favorable prognosis may be directly related to the tumor site and perhaps earlier detection with smaller tumor burden, but it could also be related to the fact that more orbital tumors display embryonal cell type (80%) when compared with rhabdomyosarcoma at any site (54%).[10] Despite the overall good prognosis, the seriousness of this malignancy should be realized. From another perspective, 44% of children who die of orbital rhabdomyosarcoma displayed alveolar cell type.[10] Even though age at diagnosis did not prove to be a predictor of tumor-related death, infants under 1 year of age with orbital rhabdomyosarcoma show particularly poor prognosis, with death in 46%.[10] The reason for more aggressive behavior of rhabdomyosarcoma in infancy is unknown.

Our results should be interpreted with caution. First, we maintain a tertiary referral practice, and some of our patients had initial biopsy or therapy elsewhere and were then referred to us following diagnosis or failure of treatment; thus, our series may represent cases with an expected worse prognosis. Second, tumors in the conjunctiva may be difficult to distinguish from those in the anterior orbit, leading to imprecision in pinpointing exact tumor origin in the periocular tissues. Additionally, the patient outcomes were gathered from data over 25 years with use of multiple treatment protocols. Our goal was to present details of the ocular spectrum of rhabdomyosarcoma, since this information was not available in the major reports from the Intergroup Rhabdomyosarcoma Study Group. We did not intend to compare one treatment with another, since this had already been accomplished by the previously mentioned studies.[1-14] Finally, our series represents only primary ocular rhabdomyosarcoma; secondary cases such as those that occur following radiotherapy for retinoblastoma were excluded.[42]

SUMMARY

Primary rhabdomyosarcoma in the ophthalmic area can originate in the orbit, conjunctiva, or eyelid or within the globe. Most patients present with classic findings of proptosis, globe displacement, or eyelid edema. Orbital exenteration is necessary in 6% of patients for tumor control. Life prognosis is favorable, with a survival rate of greater than 90%.

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DISCUSSION

DR GEORGE B. BARTLEY. I very much appreciate the opportunity to initiate the discussion of this fine paper by Dr Shields and her colleagues. The clinical features that they summarize complement those published by the Intergroup Rhabdomyosarcoma Study in 1997.[1] The clinical outcomes are consistent with that report and confirm that orbital radiation therapy is cruel to the eye.[2] To frame your discussion of this tumor and its treatment, I'd like to summarize the 150-year story of rhabdomyosarcoma in approximately 150 seconds. It is a tale that includes raisins and bubble gum, tadpoles and FISH.

Although a case identifiable as a rhabdomyosarcoma was described by Weber[3] in 1854, the first notable descriptive series was not published for nearly another century, namely, Stout's[4] seminal paper in 1946. The lesions were included among the small blue round cell tumors primarily affecting children and initially were thought to develop from striated muscle. Soon, however, it was recognized that the tumor could originate from a more primitive, undifferentiated precursor and in 1958 the light microscopic categories that are now familiar to all of us were formally proposed by Horn and Enterline.[5]

The embryonal subtype constitutes about 60% of all newly diagnosed cases and accounts for more than 90% of orbital involvement. The histopathologic appearance has been memorably described by Dr Morton Smith as "raisins in bubble gum." Mature rhabdomyoblasts may resemble tennis racquets or tadpoles. About one-fifth of cases are categorized as alveolar because of a structural resemblance to pulmonary tissue. The remaining 20% demonstrate a pleomorphic or undifferentiated histiotype.

Diagnostic accuracy improved in the 1960s as immunohistochemical techniques to recognize myosin were used to complement light microscopy.[6] The prognosis for affected patients, however, remained nasty, brutish, and short. The momentum shifted in 1972 with the formation of the Intergroup Rhabdomyosarcoma Study Committee, whose collaborative recommendations now form the "standard of care" for the treatment of this rare tumor.

The future of rhabdomyosarcoma, in a sense, began in 1982, with the discovery that most alveolar tumors contain a translocation between chromosomes 2 and 13.[7] What results is the fusion of the PAX3 gene from chromosome 2 (band 2q35) with the FKHR gene from chromosome 13 (band 13q14). PAX3 is thought to be a transcriptional regulatory protein that contributes to the formation of myoblasts from mesenchymal precursors. Dysregulated cell growth and tumor transformation occur when the mutation's chimeric product (PAX3-FKHR) functions as an oncogene and activates PAX3's targets.[8]

Embryonal tumors do not demonstrate tumor-specific translocations, but they may show a loss of heterozygosity for several loci that are closely linked on the short arm of chromosome 11. This implies that a tumor suppressor gene, yet to be identified, is inactivated.

In addition to the *structural* genetic abnormalities that I've just described, *numerical* anomalies also have

been identified in rhabdomyosarcoma. For instance, some embryonal tumors with a hyperdiploid DNA content appear to be more sensitive to chemotherapy and radiation therapy than are tumors with a normal DNA content. The correlation, however, is inconsistent.

It is hoped that future studies, perhaps using fluorescence in situ hybridization (or FISH), will evince specific genetic abnormalities for each histologic subtype of rhabdomyosarcoma and suggest avenues for more precise means of therapy. This is important because neither vincristine nor actinomycin D is tumor-specific.[9] In the meantime, there is optimism that some patients may respond favorably to decreased doses of radiation therapy, shorter courses of chemotherapy, or possibly even to chemotherapy alone,[10] decreasing the treatment-related side effects noted in this paper and others. Thank you.

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DR CAROL L. SHIELDS. I would like to thank my discussant, Dr George Bartley. Dr Bartley made several important points regarding rhabdomyosarcoma, including tumor genetics, DNA ploidy, and radiotherapy complications.

With regard to tumor genetics, I agree that it is critical to evaluate fresh tumor tissue for genetic abnormalities, especially tumors that occur in children. It is our policy to save fresh tumor tissue on all patients with pediatric ocular cancers, whether it be rhabdomyosarcoma, retinoblastoma, or others. This tissue is immediatly evaluated by genetic researchers or snap frozen for future research. Evaluation of tumor genetics can be useful for diagnostic and therapeutic reasons as well as for future genetic counseling.

With regard to DNA ploidy, it is recognized that rhabdomyosarcoma with hyperdiploid DNA content show different features and responses than those tumors with normal DNA content. In fact, DNA ploidy is a factor important in patient prognosis. Patients with hyperdiploid DNA content show more favorable prognosis than those with normal DNA content. However, there are several additional factors that affect prognosis in the patient with rhabdomyosarcoma including extent of disease at diagnosis as graded by Intergroup Rhabdomyosarcoma Study grouping I to IV, tumor burden at diagnosis, primary tumor site, patient age, histopathologic and cytologic type, and therapeutic response. Thus, the combination of these features with DNA ploidy is important for speculating on prognosis.

With regard to radiotherapy complications, there are efforts using newer methods of radiotherapy and lower doses to minimize treatment side effects. Even despite these therapeutic efforts radiation complications still occur but radiation-induced dry eye, cataract, and retinopathy are more effectively managed today than in the past.

In summary, we have come a long way with regard to tumor control of orbital rhabdomyosarcoma. Future efforts will focus on genetic investigations, therapeutic innovations, and minimizing side effects of treatment.