



Nina Mikhailenko. *Karlou Most*. Oil on canvas, 16" × 20".

*The clinical, morphologic,  
and radiologic features of  
orbital rhabdomyosarcoma  
and its management are reviewed.*

## Orbital Rhabdomyosarcoma

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**Background:** Although rhabdomyosarcoma (RMS) is a rare tumor among the entire group of mesenchymal malignancies, it is a relatively common lesion and significant challenge for the ocular oncologist in terms of its diagnosis and management.

**Methods:** A comprehensive literature search of articles published over the past 30 years in PubMed was conducted.

**Results:** Orbital RMS usually presents as a space-occupying lesion in the orbit during the first decade and may mimic other neoplastic or inflammatory masses. The tumor has predilection for the superior nasal quadrant of the orbit. The clinical manifestations depend on the location of the tumor within the orbit and its rate of growth. The common histopathologic types are embryonal and alveolar varieties. CT and MR imaging are important in the evaluation of this tumor. Particular attention should be placed on the bone invasion and extension of the tumor into the intracranial cavity and paranasal sinuses. Treatment usually consists of a combination of chemotherapy and radiation therapy following excisional biopsy.

**Conclusions:** Survival of orbital RMS has improved due to advances in chemotherapy and radiotherapy. Posttreatment complications, including side effects of radiotherapy and secondary orbital malignancies, as well as visual dysfunction, occur more often and present new challenges due to improved long-term survival.

### Introduction

Rhabdomyosarcoma (RMS) is a rare tumor, with an annual incidence of 4.3 cases per million children.<sup>1</sup> The orbit is the primary site in approximately 10% of these

tumors.<sup>2,3</sup> Each year in the United States, an estimated 350 new cases of RMS are diagnosed, of which 35 cases are orbital RMS.<sup>4</sup> From the ophthalmologist's standpoint, however, RMS is the most common malignant orbital tumor of childhood.

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*Abbreviations used in this paper:* RMS = rhabdomyosarcoma; CT = computed tomography; MR = magnetic resonance; IRS = Intergroup Rhabdomyosarcoma Study; V = vincristine; A = actinomycin D; C = cyclophosphamide.

Rhabdomyosarcoma of the orbit usually appears in the first decade of life. The mean age at diagnosis is 8 years. Boys are affected more often than girls. A history of trauma may be associated with the clinical presentation of this tumor.<sup>5,6</sup>

## Morphologic Features

Although RMS was once believed to arise from extraocular muscles, it is now accepted that orbital RMS develops from undifferentiated mesenchymal cells that have the capacity to differentiate into striated muscle.

The histopathologic types of RMS include embryonal, alveolar, and pleomorphic. The embryonal form is the most common; the alveolar variety is less common and carries the worst prognosis. In a large series, 264 patients with orbital RMS were studied with light microscopy and immunohistochemistry in selected cases.<sup>7</sup> Embryonal RMS was diagnosed in 221 patients (84%). The 5-year survival rate for these patients is approximately 95%. In contrast, the 5-year survival rate for the 24 children with alveolar RMS was approximately 75%.<sup>7</sup> The pleomorphic type rarely occurs in the orbit.<sup>8</sup> Embryonal RMS is predominantly composed of elongated pleomorphic tumor cells with a centrally located hyperchromatic nucleus surrounded by a

considerable amount of eosinophilic cytoplasm (Fig 1). In embryonal RMS, the tumor cells differentiate along rhabdomyoblastic lines forming elongated, spindle cell types ("strap cells"). Longitudinal and cross striations are sometimes discernible, particularly with phosphotungstic acid-hematoxylin stain. The striations represent bundles of cytoplasmic actin and myosin filaments. The banding pattern may be accentuated with the use of immunohistochemical markers (eg, actin, desmin) or can be displayed with transmission electromicroscopy.<sup>9</sup> Alveolar RMS may present with a variety of histopathologic patterns. In the prevailing pattern, alveolar tumor cells are loosely adherent to a network of thin interstitial fibrovascular septa. The tumor cells are loosely attached to the connective tissue and in many areas become freely floating in the alveolar spaces.

Tumor location within the orbit correlates to some extent with histology. Embryonal and differentiated types of RMS more commonly arise in the superior nasal quadrants, whereas the alveolar type usually originates within the inferior orbit.<sup>10</sup>

## Clinical Features

Orbital RMS can present insidiously, clinically and radiologically mimicking other space-occupying lesions. The most

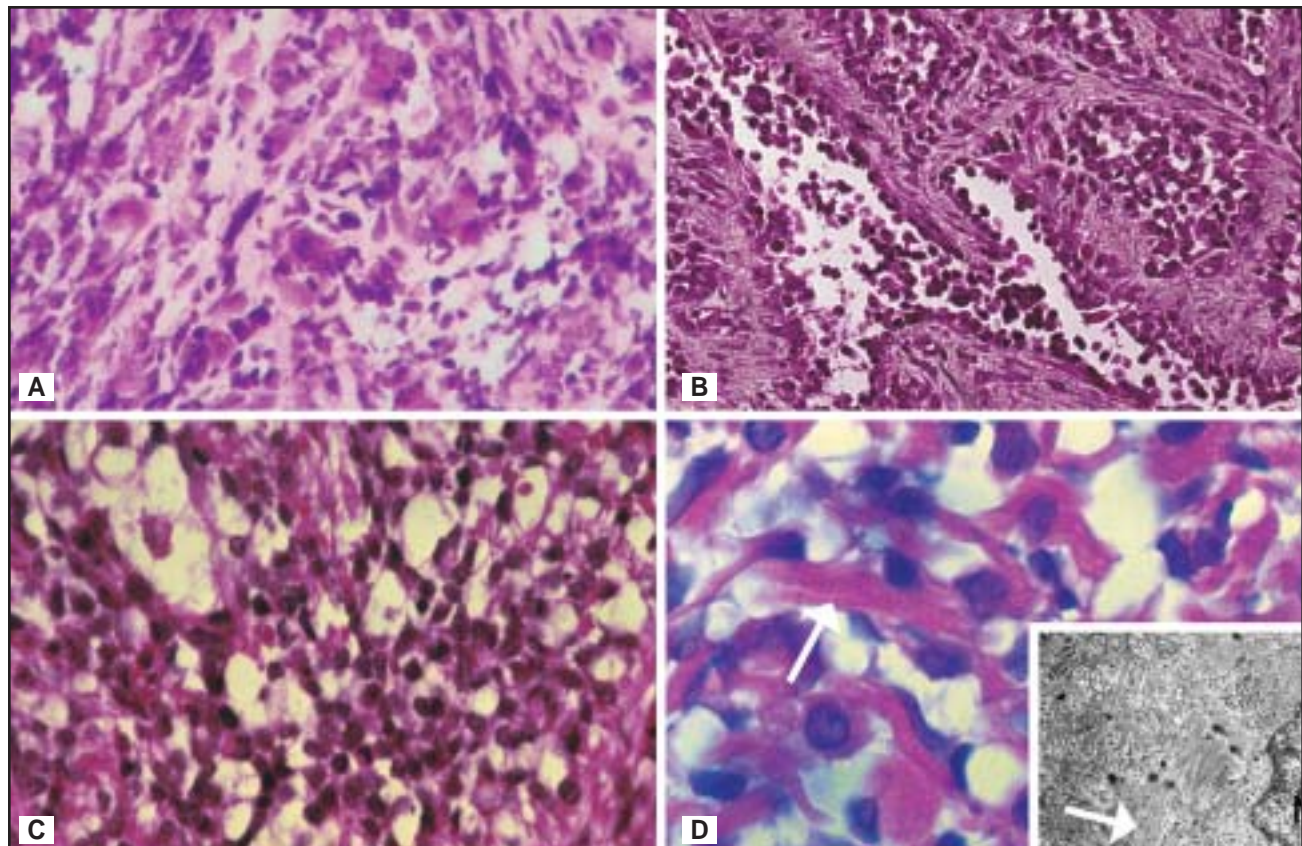


Fig 1A-D. — Light microscopic appearance of RMS: (A) poorly differentiated tumor, (B) alveolar type, and (C) embryonal type. (D) depicts the high-power magnification of a well-differentiated RMS, showing "strap" cells with cytoplasmic cross striations (arrow). The insert shows the electron microscopic appearance of a rhabdomyosarcoma cell with cytoplasmic microfibrils (arrow).

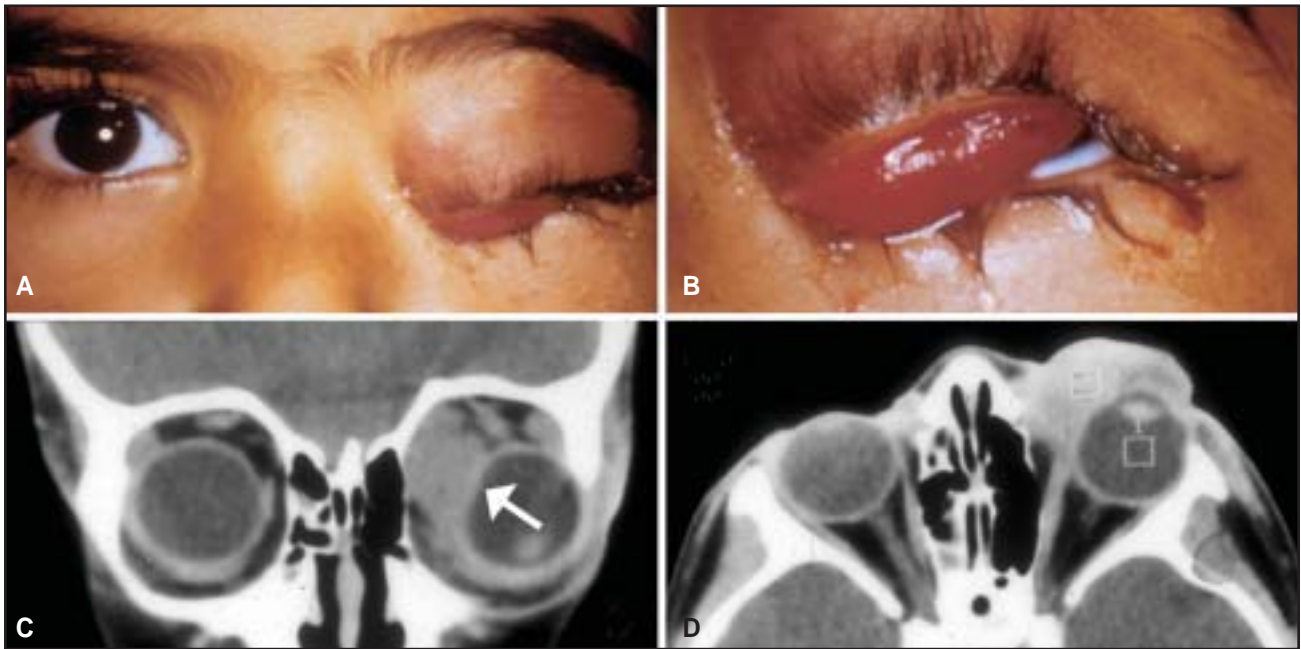


Fig 2A-D. — A 5-year-old child with superior medial RMS extending into the left upper eyelid and conjunctiva (A, B). Note that the well-delineated tumor pushes the globe laterally and inferiorly (C, D) and causes indentation of the sclera (arrow) without invading bony structures. The tumor respects even the thin medial wall of the orbit (C).

characteristic presentations, however, are the rapid onset and progression of proptosis and displacement of the globe.

RMS should be suspected whenever the clinical presentation of a rapidly progressive unilateral exophthalmos is observed in a child. Although the superior nasal quadrant of the orbit is the most common location of this tumor, it may also present as a palpable subconjunctival or eyelid nodule with edema of the lids and/or chemosis (Fig 2). Symptoms depend on the origin and site of the lesion. Posterior tumors tend to cause edema of the optic disk, choroidal folds, and some degree of ophthalmoplegia

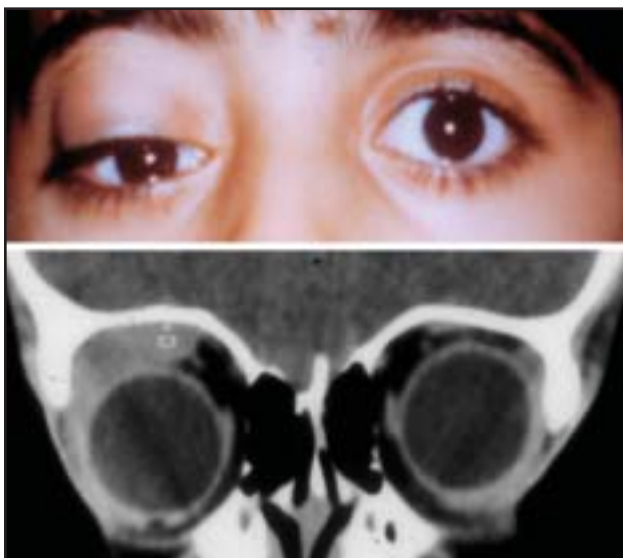


Fig 3. — Superior lateral RMS displacing the globe, inferiorly. Note that although the tumor is occupying the entire lacrimal gland fossa, it does not infiltrate into the bone of the lateral orbital wall and the roof.

(Fig 3). When RMS is situated in the inferior and anterior portions of the orbit, it often causes obvious chemosis and swelling of the eyelids. Intracranial extension and invasion of the paranasal sinuses are uncommon at presentation, while changes in the adjacent bone frequently occur.<sup>11</sup>

The clinical differential diagnosis includes most causes of proptosis in childhood. Benign and malignant neoplasms need to be considered, along with inflammatory disease, vascular tumors, leukemia, Burkitt lymphoma, allergic sino-orbital aspergillosis, orbital pseudotumor, orbital cellulitis, histiocytosis, and metastatic neuroblastoma.<sup>12,13</sup>

Although imaging and clinical signs and symptoms are helpful in delineating the differential diagnosis, the decisive diagnosis is based on histopathologic confirmation. If the RMS is located within the posterior orbit, an open biopsy should be performed. Fine-needle aspiration biopsy can provide insufficient or misleading information.

## Radiologic Features

CT and MR images are fundamental in the preoperative evaluation to determine location and size, but they are also important in evaluating residual or recurrent disease. Particular attention should be given to the presence of bone erosion and intracranial extension.<sup>14</sup> CT demonstrates a moderately well-defined homogeneous orbital mass isodense to the extraocular muscles, which shows enhancement after contrast administration. Bone destruction is common (Fig 2).<sup>15,16</sup>

On T1-weighted MR images, the tumor may appear isointense to hyperintense to the extraocular muscles and

hypointense with respect to the orbital fat. On proton density and T2-weighted MR images, hypointensity, isointensity, and even hyperintensity may be appreciable with respect to both extraocular muscles and orbital fat (Fig 4).<sup>14,17,18</sup> On T1-weighted contrast-enhanced MR images, RMS shows moderate to marked enhancement, even though in some cases a highly vascular internal architecture mimicking a capillary hemangioma may be seen.<sup>19</sup>

## Staging

Following the biopsy, the tumor should be staged according to the classification systems of the Intergroup Rhabdomyosarcoma Study (IRS) and American Joint Commission on Cancer manual.<sup>3,20</sup> A simplification of the staging system developed by Shields et al<sup>21</sup> can be applied to orbital RMS. Since most orbital tumors are biopsied without an attempt at resection, there is gross residual disease (group III). Thus, most orbital RMSs are stage I/group III, a minority are stage I/group I or II, and rarely, a primary orbital RMS is stage IV.<sup>21</sup>

## Treatment

RMS is best managed with combination treatment of chemotherapy, external-beam radiation therapy, and surgery. At some centers, the therapeutic role of surgery is limited to excisional biopsy only, while in other centers, extensive surgery is performed to remove or debulk the tumor. The extent of surgical debulking should be planned according to the clinical and imaging findings. Our opinion is that tumor excision should be pursued if it

can be done without damaging the vital structures of the orbit. External-beam radiation therapy of 40 Gy in fractionated doses offers satisfactory tumor control (Fig 5).<sup>22</sup>

During the first half of the 20th century, the standard of care for RMS was to attempt complete resection of the tumor.<sup>23,24</sup> For orbital primaries, this meant enucleation and possible exenteration. Exenteration was the standard surgical treatment for orbital RMS up to the 1970s. The poor prognosis for children with orbital RMS following orbital exenteration led to the introduction of radiotherapy.<sup>25-27</sup> Chemotherapy was generally reserved for patients with recurrent or disseminated disease. Outcomes were poor, and many children had localized recurrence or distant metastasis. Beginning in the mid 1960s, higher doses of local radiation were used with chemotherapy, which was used for local control. Orbital exenteration is now confined to cases with recurrent disease.<sup>21</sup>

In the early 1970s, the IRS was formed to study large numbers of children with RMS in a short period of time. In the first study (IRS-I), all patients were treated with chemotherapy. Patients with group I disease (localized disease that is completely excised) were randomized to treatment with vincristine, actinomycin D, and cyclophosphamide (VAC) with or without radiation therapy. Patients with group II disease (microscopic residual or completely resected regional disease with positive lymph nodes) received vincristine and actinomycin D (VA) plus radiation therapy with or without cyclophosphamide. Patients with group III (gross residual) and group IV (metastatic) disease received VAC and radiation with or without doxorubicin.<sup>28,29</sup> Cyclophosphamide was given orally.

An important finding of this large study was that patients with localized orbit primaries fared well regardless of the extent of initial resection (group II or III). Sur-

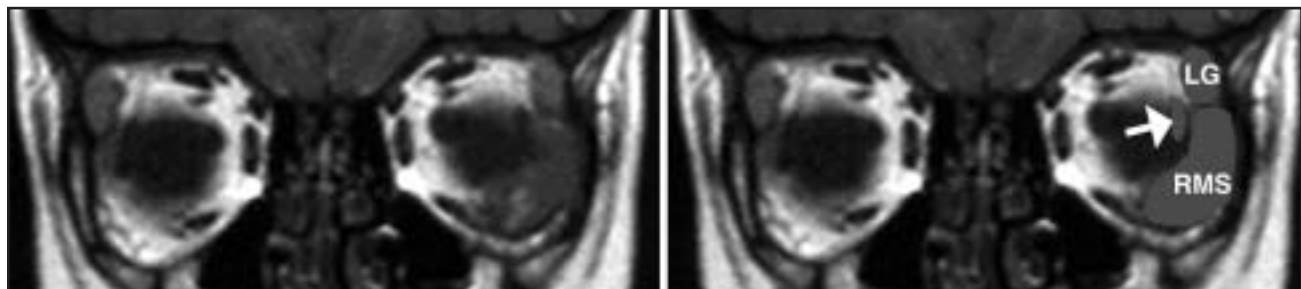


Fig 4. — T1-weighted coronal MR image depicting an inferior lateral RMS pushing the lacrimal gland (LG) superiorly and the lateral rectus muscle (arrow) medially. The tumor signal is homogenous and slightly hypointense to intraocular muscles.

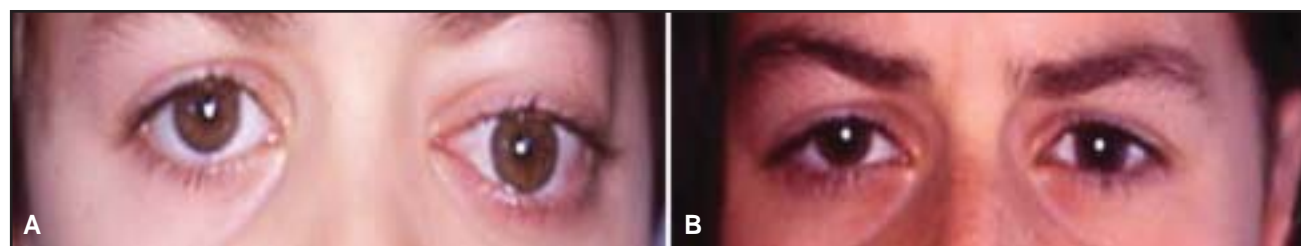


Fig 5. — Superior orbital embryonal RMS at presentation when the patient was 4 years of age (A). The appearance of the same patient following combination treatment with surgical debulking, radiation, and chemotherapy at 12 years of age (B).

vival of 6 to 12 years from diagnosis was seen in 15 (94%) of 16 patients with group II disease and in 33 (85%) of 39 patients with group III disease.<sup>29</sup> The 5-year overall survival rate for all patients with orbital primary disease was 89%. Importantly, of the 6 deaths that occurred within the first 3 years, 2 were due to infection and 1 was related to a secondary leukemia. The other deaths were related to recurrent disease. Because of the excellent outcome in patients with group II or III disease, the initial attempt at complete or partial surgical excision of orbital RMS ceased to be recommended as the standard of care.<sup>28-30</sup>

The IRS-II study was conducted from 1978 to 1984. Patients with group I disease were treated with VA or VAC (no radiation). Patients with group II disease received local radiation and intensive VA or VAC, and patients with group III disease received radiation and intensive VAC with or without doxorubicin. There was no improvement in any of the more-intensive arms when compared with the less-intensive regimen. However, all arms did better than the comparable group on the IRS-I protocol. When the patients from IRS-I and IRS-II are combined, local control was achieved in 93% of patients who did not undergo exenteration. However, 11% of patients with group III disease in the IRS-II study had local failure.<sup>31</sup> Following local recurrence, many of the patients could still receive salvage therapy. Long-term complications were common. Infectious complications were more likely in patients who had initial exenteration. Most patients developed some degree of unilateral visual loss, primarily due to cataract related to radiation therapy. In addition, second primary malignancies occurred.<sup>32</sup> Thus, there was a strong incentive to decrease therapy in patients who had a good prognosis in order to reduce these risks.

In the IRS-III study, the anticipated number of patients with orbital group II or III tumors was not large enough to design a randomized study due to the good response seen by the end of the IRS-II study. Therefore, all patients with group II and III disease with orbital RMS were treated with a 1-year regimen of VA and local radiation. They were then compared with patients in the IRS-II. There was no statistically significant difference in outcome between the patients treated on IRS-III vs IRS-II.<sup>3</sup>

The IRS-IV study enrolled patients from 1991 to 1997 and continued the use of VA for all group I and II orbital primaries. Conventional radiation therapy was given to patients with group II disease. Patients with group III disease were randomized to receive one of three regimens: (1) VAC, (2) VA and ifosfamide, or (3) vincristine, ifosfamide, and etoposide. In addition, these patients were randomized to receive either conventional radiation therapy or hyperfractionated radiation therapy at a higher dose (presumed equitoxic dose). For 22 patients with group I and II disease, the 3-year failure-free survival rate was 91%, and the 3-year overall survival rate was 100%. This represents no change compared to IRS-III, as would be expected. For the 59 patients with group III disease,

the 3-year failure-free survival rate was 94% and the overall survival rate was 98%. There was no difference in the three chemotherapy groups or two radiation groups. However, when compared with the failure-free survival rate on IRS-III (80% for the group III orbit primaries), patients with group III primary tumors benefited from the three-drug regimen compared with the VA regimen.<sup>33</sup>

Because of concerns about complications associated with alkylating agents (cyclophosphamide and ifosfamide) and etoposide, there seems to be a trend to decrease the use of these drugs. In a prospective study, 34 children with nonmetastatic RMS of the orbit were treated with VA plus ifosfamide without initial radiation therapy. Radiation therapy was reserved for patients who did not achieve complete response to the primary chemotherapy. The authors concluded that although higher incidence of local recurrence was encountered, early survival rates were not compromised; 10 children avoided the late effects of radiation.<sup>34</sup> Other investigators studied the effectiveness of radiotherapy alone for the treatment of RMS. Notis et al<sup>35</sup> retrospectively reviewed the medical charts of 24 patients who were treated with radiotherapy alone. They reported a 12.5% tumor recurrence rate and a 4.2% tumor-related death rate. When these results were compared to the IRS, chemotherapy did not appear to offer an advantage over treatment with radiotherapy alone.

The currently ongoing IRS-V study uses standard doses of VA combined with a decreased dose of radiation therapy (45 Gy compared with 50 Gy) for patients with low-risk RMS, including group III orbital RMS. Further reduction in radiation sequelae may result from the use of 3-dimensional conformal radiation therapy techniques by minimizing the inclusion of normal structures in the treated volume.<sup>36</sup>

## Conclusions

Advances in chemotherapy and radiotherapy have improved survival rates of patients with orbital RMS. The excellent survival has allowed observation of the late effects of radiotherapy, on both facial growth (eg, bony hypoplasia of the orbit, facial asymmetry) and visual function (eg, cataract, keratopathy, retinopathy).<sup>37,38</sup> New modalities of radiation therapy such as external-beam proton radiation therapy tend to offer improved sparing of the normal ocular and orbital tissues while maintaining conformal target dose coverage.<sup>39</sup> Although radiation therapy and surgery may lead to undesirable cosmetic and functional outcomes, new agents need to be developed before these treatment modalities can be omitted.

The challenge for the future is to identify patients who can be safely treated only with chemotherapy and to reserve radiotherapy and radical surgery for patients at risk of recurrence in an attempt to reduce undesirable effects.<sup>40-42</sup>

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