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Orbital Rhabdomyosarcoma: Current Perspectives

Review Article

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Abstract

Orbital rhabdomyosarcoma is mesenchymal tumor, presents 10-20% of all rhabdomyosarcoma are usually diagnosed in children. It presents clinically by rapidly progressive unilateral proptosis. Imaging is fundamental to assessing the extent of the tumor and the erosion of the bone, but only histology can confirm the diagnosis. The treatment involves a combination of chemotherapy, radiotherapy and surgery. The challenge is to choose a treatment with good cosmetic and functional results specially visual function and excellent survival.

Keywords: Orbital; Rhabdomyosarcoma; Histology; Radiotherapy; Chemotherapy; Surgery.

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Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in childhood, orbital RMS presented 8% of all soft tissue sarcoma of the head and neck. Improved treatment has allowed a significant change in survival rates from 30% in 1960 to 90% currently [1, 2]. The treatment is multimodal it included surgery, radiotherapy and chemotherapy. Here we presented a general overview of orbital RMS.

Epidemiology

Orbital RMS is the most common primary orbital malignancy in children with an annual incidence of 4.3 cases per million children, approximately 35 new cases per year in the United States [1, 3].

Most cases of orbital RMS were diagnosed before 16 years and the median age is between 5-7 years, however some cases were described in elderly patients [4]. RMS is localized in the orbit, conjunctiva, eyelid and more rarely in the uveal tract, or by extension from the nasopharynx and paranasal sinus or orbital can be site of metastasis [5].

The hereditary transmission in orbital RMS is not well known, however some genetic mutations have been described in association with orbital RMS like: li –fraumeni syndrome, neurofibromatosis, Beckwith-Wiedemann Syndrome, Costello Syndrome, retinoblastoma, Nevoid Basal Cell Carcinoma Syndrome [5-7].

Diagnosis

Orbital RMS manifested clinically by the appearance of a unilateral exophtalmos rapidly develop or slow growing mass, other signs may be associated like chemosis, swelling of the eyelids, painless, ophthalmoplegia, erythema and edema [3]. Imaging is important for diagnosis and evaluation of residual disease, CT scan showed a well-defined orbital mass with irregular albeit enhances after contrast injection. Also, MRI showed a well-circumscribed homogeneous orbital mass enhances with gadolinium, usually hypointense to orbital fact and isointense to extraocular muscles on T1-weighted imaging, but on T2-weighted imaging the orbital mass is hyperintense to orbital fat and extraocular muscles [8, 9].

CT or MRI may help in diagnosing by showing the location, size of the tumor, the extracranial extension and bone erosion and may assist the surgical planning, but only the histology with immunohistochemical study can confirm the diagnosis and differentiates it from other tumors like vascular tumors, schwanomma , inflammatory disease, orbital cellulitis, leukemia, Burkitt lymphoma, metastasis, and orbital pseudotumor [10].

Histology

There are four histological types: alveolar, embryonal, pleomorphic and botryoid. The embryonal subtype is the most common orbital RMS is associated with a good prognosis than others. Histologically, the RMS is characterized by the presence of rhabdomyoblastic cells forming elongated, spindle cell types with cross

striations representing cytoplasmic bundles in most cases by actin and myosin filaments. The diagnosis of RMS is made by immunohistochemistry, stains for myoglobin, myogenin, desmin and muscle specific actin [11, 12].

The use of cytogenetic is necessary to distinguish the alveolar RMS from the embryonal. The alveolar RMS is characterized by specific translocation, t(2;13)(q37;q14) or its variant t(1;13)(p36;q14) then to the embryonal subtype there is no specific chromosomal rearrangements or molecular markers [13].

Management

Treatment of orbital RMS is multimodal, including surgical excision with or without radiotherapy and chemotherapy.

Surgery

The standard of care for orbital RMS in the past was complete resection enucleation or exenteration of the tumor but due to the poor overall survival (OS) about 25-30% observed by sugery alone and in attempt to improve this outcome, the North American Intergroup Rhabdomyosarcoma Study Group (IRSG) and European cooperative groups add adjuvant chemotherapy and radiotherapy in cooperative group trials, the OS was improved to around 90% [14-17].

The diagnosis of orbital RMS is histopathologic following wide excision, incisional or excisional biopsy. It is preferable to perform incisional biopsy to avoid the risk of spread tumor cells. Thanks to its good prognosis after treatment by radiotherapy and chemotherapy, regardless of amount of tissue excised, some authors suggests that an incisional biopsy is sufficient. But some surgeons believe that complete excision with negative margins decreases tumor size which facilitates post-operative treatment [18, 19].

After biopsy of the tumor, orbital RMS can be staged according to the IRS post-surgical staging system [20-23].

Group I: localized disease completely resected.
Group II: microscopic disease remaining after biopsy.
Group III: macroscopic residual disease remaining after biopsy.
Group IV: distant metastasis.

This classification allows to adapt the treatment depending on stage of the tumor and its prognosis [20, 21].

Chemotherapy

RMS is a chemosensitive tumor, the goal of chemotherapy is to obtain tumor response and to reduce the use of local treatments. Many drugs was tested to treat rhabdomyosarcoma such as vincristine, dactinomycin, cyclophosphamide, doxorubicin, ifosfamide, etoposide and irinotecan. Various combination of this drugs was used. The most protocol used is association between vincristine, doxorubicin and cycophosphamde (VAC), this protocol improve complete response by 67% when used after surgery versus 25% in surgery alone [24]. Others combinations with other molecules were used to treat tumors with resistant to VAC combination.

In three American studies for patients with complete resection the postoperative radiotherapy does not provide any benefit over VAC or VA protocols [25, 26]. To avoid the toxicity of cyclophosphamide SIOP developed MMT-84 protocol, they replace cyclophosphamide by high dose of Ifosfamide (VAI or VAC)[27], the response rate was higher with ifosfamide just in few study [28, 29]. The high dose of ifosfamide (9g/m²/course) is more effective in stage III this dose was tested in MMT-89 protocol. For the SIOP, ICG and CWS the standard regimen is IVA (Ifosfamide 6g/m²/course+VA) [30].

Doxorubicin has an antitumor activity in rhabdomysarcoma, it was tested in association to VAI in German study CWS-86 showed an improvement in objective response rate [31]. In metastatic disease the combination of doxorubicin and ifosfamide showed an improvement in objective response rate (63%) but no significant improvement in overall survival [32].

The use of cisplatin and etoposide in second line after failure of IVA showed an efficacy in MMT-84 protocol [27]. But in a randomized study comparing VAC versus VAC + cisplatin + doxorubicin versus VAC + cisplatin + etoposide in patient with macroscopic residual disease or metastatic disease, the combination does not improve overall survival comparing with VAC alone [33].

Topotecan seems to be effective in first line therapy; it showed a good response rate about 45% [34].

In aim to improve the results of chemotherapy in metastatic rhabdomyosarcoma, the high dose intensive chemotherapy followed by peripheral stem cell rescue did not showed any efficacy [35, 36].

Radiotherapy

RMS is radiosensitive tumor, its benefit was showed in 1960's with improvement in recurrence free survival with doses between 55 and 65 Gy [18] . In a pooled analysis of 306 orbital RMS patients showed 10 year EFS to be significantly better for patients receiving RT as part of their initial treatment compared to those who did not (82 vs 53%) however no statistical difference in OS [15]. The North American groups IRSG protocols used adjuvant radiotherapy systematically after surgical resection [25] but in the SIOP protocol they performed radiotherapy if high risk RMS like alveolar subtype or if persistent a residual disease after chemotherapy [33, 37].

Recently new technologies in radiation oncology are used including proton beam radiotherapy, intensity modulated radiotherapy (IMRT), 3-D conformational radiotherapy and implant brachytherapy, this therapies tend to offer an excellent survival, to reduce dose to normal tissue adjacent and to decrease the long term side effects of treatment [38].

IMRT for head-and-neck RMS was studied by Wolden et al, they showed that IMRT with image fusion gave a good results in local control by using a minimal dose to the normal adjacent tissue [39].

To test the possibility of organ-sparing particularly lens-sparing, a study conducted by Hein et al, comparing IMRT versus 3D conformational photon radiotherapy, they observed that although IMRT resulted in a reduced dose to the ipsilateral lacrimal gland and the lens, but against no significant difference was found for optic nerve and ipsilateral retina, with low dose radiation to the

brain compared to 3D conformal radiotherapy [40].

Brachytherapy

Brachytherapy has advantages over external beam radiotherapy EBRT by delivering a locally high dose while avoiding surrounding tissue, reducing time treatment and toxicity and improving functional prognosis especially visual prognosis. Blank et al, reported the use of brachytherapy it limited in case of complete tumor resection without intracranial extension and when the use of EBRT will be very toxic [41].

Recommendation

The treatment of orbital RMS is multimodal including surgery chemotherapy and radiotherapy based on risk as classified by IRS staging system. The European pediatric Soft tissue sarcoma Study Group (EpSSG) protocol (EpSSG-RMS-2005) proposes for each group [42, 43].

- Group I are treated with chemotherapy only VA (vincristine and actinomycin).
- Group II are treated with a combination of chemotherapy using VAC protocol and radiotherapy at 36 Gy.
- Group III are treated with a combination of chemotherapy (VAC) and radiotherapy (45 Gy), for group II and III the use of ifosfamide added to VA in the first four courses if complete response after three courses of chemotherapy but if not obtained complete response use radiotherapy at 45 Gy.
- Group IV are treated with a combination of intensive chemotherapy (IVA and doxorubicin) and radiotherapy, followed by one year of maintenance chemotherapy and radiotherapy to all involved sites.

Prognosis

The survival of patients with orbital RMS was improved over the years grace to advances in chemotherapy and radiotherapy. The overall 3-year survival was 95% for RMS localized to the orbit and 73% for RMS with parameningeal extension [44]. The prognosis depends on several factors age and anatomical site and histological type. Embryonal RMS has good prognosis versus alveolar RMS with a 5 year-survival of 94% versus 74% [18]. The prognosis was good for localized groups (I,II,III) 92% at 5 Year-survival and 87% at 10 years [8, 45, 46]. At recurrence, the prognosis also depends on histology, age, IRS group, and previous treatment [47, 48].

The perspective for the future is to identify patients who can be safely treated by only chemotherapy and to reserve local treatment (surgery and or radiotherapy) for patients at high risk of recurrence in goal to reduce side effects of treatment and to improve cosmetics and functional results.

Conclusion

Orbital RMS is a rare tumor, its diagnosis and management requires a multidisciplinary team. The treatment of orbital RMS should be based on international recommendations. The challenge in future it 'is the selection of patients according to risk of recurrence, to choose the less mutilating and most effective treatment.

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