

RESEARCH ARTICLE

Multidisciplinary Collaborative Therapy for 30 Children with Orbital Rhabdomyosarcoma

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Abstract

Objective: To explore clinical experience and propose new ideas for treating children diagnosed with orbital rhabdomyosarcoma (RMS). **Methods:** We retrospectively analyzed the clinical data for 30 patients (16 males and 14 females, with a median age of 6.2 years) with primary orbital RMS who were enrolled in the Department of Eye Oncology and Pediatrics of our hospital from November 2004 to December 2012. International Rhabdomyosarcoma Organization Staging Standards indicated that among the 30 patients, 4 cases were in phase II, 20 were in phase III, and 6 were in phase IV. All patients underwent a multidisciplinary collaborative model of comprehensive treatment (surgery, chemotherapy, external radiotherapy, ¹²⁵I radioactive particle implantation, and autologous peripheral blood stem-cell transplantation). **Results:** Follow-up was conducted until March 2013, with a median follow-up time of 47.2 months (5 to 95 months), and 7 deaths occurred. The 2-year estimated survival rate reached 86.1%, the ≥3-year estimated survival rate was 77%, and the 5-year estimated survival rate was 70.6%. **Conclusions:** The multidisciplinary collaborative model can be a safe and effective approach to the comprehensive treatment of children with orbital RMS. It has clinical significance in improving the tumor remission rate.

Keywords: Orbit - rhabdomyosarcoma - children - chemotherapy - ¹²⁵I particle

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Introduction

Rhabdomyosarcoma (RMS) is a type of malignant tumor in the original skeletal muscle cells; in children, it is the most common malignant soft tissue sarcoma, which accounts for approximately 4% to 8% of pediatric malignant solid tumors (Oberlin et al., 2001). The orbit is the common primary site of RMS in children, and this condition accounts for about 35% to 45% of all cases (Breneman et al., 2012). With the development of combinative treatment that includes surgery, chemotherapy, and radiation, the prognosis of children has improved significantly. The two-year survival rate is approximately 70%, and the five-year survival rate is about 30% to 50% (Meza et al., 2006). In comprehensive treatment, complete tumor resection is the key to curing orbital RMS. However, in pediatric orbital RMS, the anatomical structure of the lesion is complex and the tumor growth is rapid, a condition that makes complete surgical resection difficult and leads to relatively high recurrence, metastasis, and mortality rates (Van Gaal et al., 2012). Achieving complete surgical resection to reduce recurrence, metastasis, and mortality rates has become a key research area.

Research data indicate that pediatric RMS is sensitive to chemotherapy drugs such as vincristine, actinomycin

D, cisplatin, and pirarubicin (Gosiengfiao et al., 2012). Preoperative chemotherapy can shrink the tumor, which cannot be completely resected. This finding has created an opportunity for complete tumor resection. Postoperative chemotherapy can improve the survival rate of children and decrease the tumor metastasis rate (Hawkins et al., 2013). Radiation therapy can also be used as one of the consolidation treatment methods for the complete remission of orbital RMS. Basing from clinical staging and condition assessment, this study focuses on selecting a reasonable chemotherapy, radiotherapy, and surgical treatment for pediatric orbital RMS.

A retrospective study was conducted on the clinical diagnosis and therapeutic efficacy of 30 children with first-episode orbital RMS in our hospital. The clinical characteristics, establishment of comprehensive treatment programs, and treatment principles for pediatric orbital RMS were analyzed preliminarily. The objective was to provide clinical experience to further enhance the curative effect of treatment options for orbital RMS.

Materials and Methods

Clinical information

A total of 30 patients diagnosed with primary orbital RMS were enrolled in the Department of Eye Oncology

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Table 1. Clinical Data of 30 Orbital RMS Patients

Group	Cases	Classification	Cases
Gender		IV metastasis section	6
Male	16	Intracranial & meningeal metastasis	5
Female	14	Lung metastasis	1
IRS Staging		Pathological Classification	
II	4	Embryo-type	26
III	20	Acinus-type	4
IV	6	Mixedtype	0

Table 2. Coronary Seed Implantation Dosage Form

Name	Volume	Minimum dose	Maximum dose	Average dose	D100	D90
Eyeball	4.7	1999.9	21815.9	6873.3	1999.9	3000
Optic nerve	0.1	2285	6904.9	3827.3	2285	2700
Target	1.4	9929.2	41483.4	22950.2	9929.2	15500

Prescription dose, 10000.0cGy; The maximum dose, 41593.9cGy; Particle types, I_125(6711_1985); Particle Activity, 0.90mCi

and Pediatrics of our hospital from November 2004 to December 2012. Among the patients, 16 were males and 14 were females, with male-female ratio of 1.2: 1. The median age was 6.2 years (4 month to 14.3 years old) (Table 1). Surgical resection combined with postoperative chemotherapy, radiotherapy, and/or autoperipheral blood stem-cell transplantation (APBSCT) was performed in 30 patients. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Beijing Tongren Hospital. Written informed consent was obtained from all participants.

Diagnosis and clinical staging

All cases underwent tumor biopsy or tumor resection and gained pathological diagnosis before chemotherapy. According to the surgical staging standards of the international RMS collaboration group (Burke et al., 2013) and clinical staging standards of the United States intergroup RMS study group (IRS) (Sandler et al., 2001). Phase I consisted of complete tumor resection through surgery and no tumor residual was observed in the cutting-edge microscopy. Phase II involved surgery along the resection margins, and the tumor residual could not be seen with the naked eye but could be seen under a microscope. Phase III consisted of tumor resection surgery, and the tumor was not completely removed or could not be completely removed, and the residual could be seen with the naked eye, and phase IV was characterized by the occurrence of distant metastasis. In this study, there were 4 cases in phase II, 20 cases in phase III and 6 cases in phase IV (Table 1).

Treatment methods

A multidepartment collaboration mode of treatment was applied, which involved preoperative chemotherapy + surgery + postoperative chemotherapy and/or local extra radiotherapy, radioactive particle implantation, and/or APBSCT. Based on the size of the primary tumor, the invasion extent, and the postoperative clinical stage, a comprehensive treatment plan was made, and the total course was set as two years.

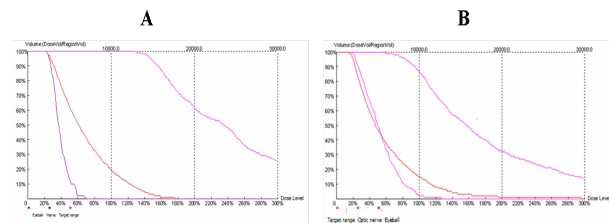


Figure 1. Diagnosis, Treatment and Follow-up Plan of Orbital RMS. A: Coronal seed implantation plan; B: Image verification of particle implantation

Chemotherapy: The conventional chemotherapy in this study referred to the three types of chemotherapy in US IRS diagnostic criteria (Crist et al., 1995; Walterhouse et al., 2006; Ballard et al., 2010), namely, AVCP (adriamycin + vincristine + cyclophosphamide + Cisplatin), IEV (ifosfamide + etoposide + vincristine) and DEV (actinomycin D + etoposide + vincristine), which were applied alternately. One patient with phase III orbital RMS underwent autologous peripheral blood stem cell transplantation (ASPBSCT). The child was a 14-year-old and male, and the primary position of the tumor was at the orbit and near the orbital apex. After standard chemotherapy and surgical treatment, the disease achieved partial remission (partial tumor residual). To preserve the eye and vision, high-dose chemotherapy with APBSCT was conducted with informed consent from the parents. IEV mobilization program (Ifos+Vp-16+VCR) + recombinant human granulocyte colony-stimulating factor was performed to mobilize and collect peripheral blood stem cells. After the collection, CEM program (carboplatin + etoposide+ melphalan) (Koscielniak et al., 1997) was applied for pretreatment. The hematopoietic reconstitution standard was settled as the nucleated cells $\geq 0.5 \times 10^9/L$, $PLT \geq 20 \times 10^9/L$, and $HB \geq 80 g/L$.

Radiotherapy: Local extra radiotherapy applied irradiation to the primary site at a total dose of 40 Gy to 50 Gy. 10 patients (4 in Phase II and 8 in Phase III) underwent ^{125}I particle infra-tissue implantation (^{125}I radioactive particles were provided by Beijing Atom High-Tech Co., Ltd., China). Based on the lesion CT or MR image as the target reference, the image processing and the location and quantity of the implantation were set. A software was employed to verify the dosage curve and dose distribution, as well as to adjust the particle locations, which will cover more than 95% of the target area or volume within the prescription dosage range. This range was intended to reach the high-accordance requirements of the target dosage region and the lesion area while ensuring that the vital organs around the tumor were within the safe dosage range. Based on these considerations, the treatment plan was determined (Figure 1A and Table 2). All of the children with particles implanted underwent ^{125}I radioactive particle intra-tissue implantation individually, with activity from 0.7 mCi to 0.9 mCi and with periphery matching dosage from 120 Gy to 160 Gy. All of the surgeries were conducted in our hospital, and then postoperative CT was performed for verification.

Surgery: The one-stage surgery was directly conducted on patients competent of complete resection of tumor.

Table 3. Dose Verification of Particle Implantation

Name	Volume	Minimum Dose	Maximum dose	Average dose	D100	D90	D80	Conformal factor
Target	4.3	4148.2	50225.6	17488.6	4148.2	9400	10900	0.9
Optic nerve	0.4	1922.2	13395.9	5221.8	1922.2	2500	3200	0
Eyeball	6.9	1369.9	48578.8	5991.7	1369.9	2200	2700	0.2

Prescription dose,10000.0cGy; The maximum dose, 41593.9cGy; Particle types, I_125(6711_1985); Particle Activity, 0.90mCi

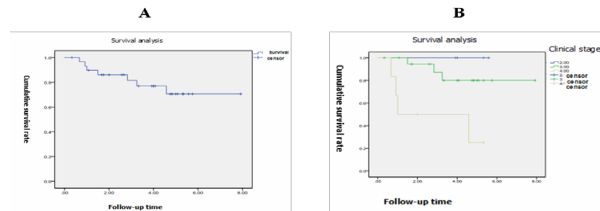


Figure 2. Analysis of the Survival Function. A: Survival function analysis of 30 patients; B: Survival function analysis of 30 cases with different clinical phases

For patients with large tumor invasion range not suitable for complete resection, the tumor biopsy was performed firstly. After pathological diagnosis, the chemical reduction was conducted to shrink tumor, followed by surgery. The tumor was resected as much as possible, with retention of organ functions.

Side-effect evaluation criteria

The criteria to evaluate side effects were as follows. (1) The evaluation standards for chemotherapy side effects were in accordance with the grading standards for chemotherapy side effects provided by the WHO. (2) The evaluation standards for radiotherapy side effects were based on the scoring criteria for acute radiation reaction (RTOG/EORTC) and anaphase radiation injury scoring criteria (RTOG/EORTC 1987). (3) The side effects of heart, bladder, kidney, liver, central nervous system, oral, and gastrointestinal acute toxicity after transplantation were evaluated and scored according to Bearmen standard (Bearman et al., 1988). Observation of the lungs was conducted 30 days after transplantation, and organ assessment was performed on the 60th day. A recheck was conducted every three months. (4) Surgical complications were observed, including blepharoptosis, eye movement dysfunction, decreased visual acuity and skin numbness.

Clinical follow-up

The prognosis of the children in this study was categorized according to integrated efficacy standards (Corrias et al., 2006): (1) complete remission (CR): the tumor disappeared completely after the treatment, and no evidence of tumor residue was observed in the imaging; (2) partial remission (PR): the tumor shrank by over 50%, and no new lesions were observed; (3) partial development (PD): the tumor volume increased by over 25%, and new tumor lesions appeared during the treatment; and (4) death. The first discharge date was set as the follow-up start time, with four rechecks conducted every three months after the end of chemotherapy, followed by two rechecks every six months, and then one recheck per year for three years. These rechecks included general physical examination, imaging check of the primary site, and hemogram. The

end of the follow-up period was March 2013.

Statistical analysis

SPSS 17 statistical package was used for statistical analysis. Kaplan–Meier method was employed to calculate the survival rates. Chi square test was performed for categorical data while t test was conducted for continuous data. $P < 0.05$ was considered as statistically significant.

Results

First symptom

The main clinical manifestations in the 30 cases of orbital RMS were eyelid swelling and proptosis, which accounted for 76.6% (23/30) of the cases, as well as eyeball (function and activity) disorders and vision loss, which accounted for 23.4% (7/30) of the cases. Frequency analysis of orbital RMS indicated that the primary diagnosed symptoms were mainly eyelid swelling and proptosis ($X^2 = 13.08$, $P = 0.0003$).

Pathological features

Histopathological examination indicated that the pathological types of the 30 cases included embryo type, which accounted for 86.7% (26/30), and acinus type, which accounted for 13.3% (4/30). Therefore, the histopathologic type of orbital RMS was mainly embryo type ($X^2=18.23$, $P = 0.0001$).

APBSCT effects

The lone case that underwent ASPBSCT was administered IEV program chemotherapy + rhGGSF for mobilization. The total number of collected mononuclear cells (MNC) was $4.43 \times 10^6/\text{kg}$, and the CD34 + cell count was $9.93 \times 10^9/\text{kg}$, which accorded with transplantation standards. High-dose chemotherapy combined with ASPBSCT treatment was then conducted. Hematopoietic reconstitution was conducted 14 days after the transplantation, and 20 days later, the patient left the laminar flow chamber. The patient experienced Class III adverse reactions, such as gastrointestinal bleeding and septic shock, during the transplanted hematopoietic reconstitution. After anti-infection and symptomatic treatment, the condition of the patient improved. The 31-month follow-up indicated that the patient achieved CR, with preservation of eye ball and vision. No obvious stunted growth or organ damage was observed.

¹²⁵I radioactive particle implantation effects

In this study, 10 patients were administered ¹²⁵I radioactive particle implantation by CT verification and image analysis, and activity was verified after the implantation. The activity and dose of radioactive particles

were calculated according to the different tumor locations (Figure 1B and Table 3), and then the average radiation area in the target area was calculated. The particle activities and particle radiation volume in all of the 10 patients were basically consistent with the plan, a result suggesting that the particles implanted were effective. The follow-up was conducted until March 2013, with an average follow-up duration of 48 ± 18.4 months and a median follow-up period of 55 months. Of the 10 cases, 8 achieved CR and 2 achieved PR. The overall survival rate was 100% (10/10), which indicated that ^{125}I radioactive seed implantation was effective in the topical treatment of RMS. The side effects experienced by the patients were corneal opacity, which accounted for 10% (1/10); eye pain, 10% (1/10); intensified blurred vision, 10% (1/10); and vision loss, 10% (1/10). Among the patients, 6 did not experience any partial side effect. Except for corneal opacity and vision loss with poor recovery, the other side effects were mitigated after treatment.

Analysis of the survival function

All of the 30 patients were scheduled for follow-up until March 2013. The median follow-up time was 47.2 months (which ranged from 5 to 95 months), during which 7 patients died. Among the 30 patients, 12 received surgery + chemotherapy, 7 underwent surgery + extra radiotherapy (40 Gy to 50 Gy radiotherapy after surgery), 10 underwent surgery + chemotherapy + particle implantation, and 1 underwent surgery + chemotherapy + APBSCT. In all of the 30 patients, complete tumor resection was successfully performed in only 4 cases (postoperative stage II), and residual tumor was observed in the 26 other cases. In 4 patients with complete tumor resection, no ptosis, eyeball (function and activity) disorders, or visual acuity decrease was observed. During the follow-up period, 7 patients (4 cases in Phase IV and 3 cases in Phase III) died as a result of brain metastases. Among the death cases, 3 received no further treatment after 4 courses of chemotherapy and subsequently died on the 9th, 13th, and 14th months, respectively; 2 cases relapsed within 1 year after the surgery and extra radiotherapy, and then died on the 35th and 45th months after chemotherapy, respectively. The 2 remaining cases relapsed within 6 months of stopping chemotherapy, all underwent surgery and 6 cycles of chemotherapy, and then died on the 12th and 8th months, respectively. The total survival rate was 76.6% (23/30). From the statistical analysis of survival function, the average estimated survival time was 75.6 months, the 95% confidence interval was 63.24 to 88 months, the 2-year estimated survival rate reached 86.1%, the ≥ 3 -year estimated survival rate was 77%, and the 5-year estimated survival rate was 70.6% (Figure 2A).

Among the 30 patients, the survival rate of those in Phase IV was significantly lower than that of those in Phases II and III, with the Phase II survival rate at 100% (4/4), Phase III at 85% (17/20), and Phase IV at 33.3% (3/6). The 1-year estimated survival rate of those in Phase IV was 50%, and the 5-year estimated survival rate was only 25%. The survival rates for different clinical phases had a significant difference ($X^2=10.43, P=0.005$) (Figure 2B).

Discussion

RMS is a highly malignant soft tissue sarcoma with the trend of early invasion into local tissues. In the late stage, it exhibits distant metastasis through hematogenous and lymphatic pathways. The incidence rate of RMS is approximately 6% in children with malignant solid tumors (Maurer et al., 1988). The current study aims to retrospectively investigate the clinical diagnosis and therapeutic efficacy of 30 children with first-episode orbital RMS in our hospital. It also aims to preliminarily analyze the clinical characteristics, establishment of comprehensive treatment programs, and treatment principles of pediatric orbital RMS with the objective of providing clinical experience to further enhance curative effects. Our findings indicate that the characteristics of pediatric orbital RMS are consistent with those reported in other studies. A reasonable choice of chemotherapy, chemotherapy course, surgery time, and radiotherapy method and dose can improve the clinical remission rate and reduce the recurrence and mortality rates.

In this study, we found that boys were more susceptible to RMS than girls, with a male-to-female ratio of 1.2:1 and a median age of 6.2 years old for boys. These findings are consistent with those reported in the literature (Maurer et al., 1993; Rodeberg et al., 2005). Pediatric orbital RMS lacks characteristic clinical manifestations and often behaves differently on account of the different degrees of primary-site tumor compression and invasion onto surrounding tissues and organs. In this study, the children were brought to the hospital for treatment of unknown causes of eyelid swelling, exophthalmos, eye movement disorders, and vision loss. The doctors who first treated them often failed to recognize the disease, which led to delayed treatment. Therefore, the possibility of RMS should be considered if children exhibit the aforementioned symptoms.

With the current comprehensive treatment for RMS abroad, the five-year survival rate has increased to over 75% (Rodeberg & Paidas, 2006; Trahair et al., 2007; Gupta et al., 2012). For advanced orbital RMS, especially for stage IV patients, the total survival rate varies significantly, with the lowest at about only 20% (Pappo et al., 1995; Van Gaal et al., 2012). In this study, we applied a multidisciplinary treatment model for the diagnosis and treatment of pediatric orbital RMS; established joint diagnosis and treatment of eye oncology, children's medical oncology, imaging, pathology, and radiation oncology; assessed the diagnosis, staging, and surgical removal of orbital RMS; and discussed preoperative and postoperative chemotherapy to develop a reasonable treatment plan. The overall survival rate in this study was 86.1% (23/30), the 2-year estimated survival rate was 86.1%, the ≥ 3 -year estimated survival rate was 77%, and the 5-year estimated survival rate was 70.6%, all of which were similar to foreign levels (Kuru et al., 2013). A treatment mode that involved multidisciplinary collaboration was applied in this study, and the expected goal was basically achieved. However, the 1-year survival rate of stage IV patients was estimated at 50%, with a 5-year survival rate of only 25%. The stage IV

survival rate was significantly lower than that for stages II and III, which was different from reported results (Joshi et al., 2004). Early diagnosis and comprehensive treatment directly influenced the prognosis. Therefore, the multidisciplinary collaborative treatment mode should focus on advanced cases to explore reasonable diagnosis and treatment options.

Our findings are summarized as follows.

First, in the comprehensive treatment of pediatric orbital RMS, complete surgical resection has a decisive function; the feasibility assessment of whether the tumor has been completely resected is particularly significant in the prognosis (Dasgupta & Rodeberg, 2012). Unplanned tumor resection improves the tumor phase and increases the risk of local recurrence and distant metastases. The side effects of radiotherapy and chemotherapy strength become more pronounced than normal, and this condition results in a long-term decline in the quality of life. Therefore, the significance of preoperative assessment for each child with orbital RMS should be emphasized, such as undergoing various and comprehensive preoperative checks, determining the scope of the surgery and the presence of missing lesions, and identifying the possibility of surgical resection. For children with difficulty in preoperative assessment resection, we propose that biopsy pathological diagnosis be conducted first, and surgical resection be performed after chemotherapy. Before the surgery, doctors should cooperate closely with imaging physicians to obtain the lesion invasion range via CT, MRI, eye B ultrasonic examination, and other methods, as well as to determine the best surgical approach and treatment option. All of the Phase II patients in this study obtained complete resection without complications of blepharoptosis, eyeball (function and activity) disorders, or decreased vision. However, as a result of delayed treatment, huge tumors, special tumor positions, complete resection difficulty, and poor surgical timing, 26 cases had residual tumor and metastasis, which affected the prognosis significantly. Therefore, future research should focus on how to accurately conduct preoperative assessment to determine the best surgical timing and to guarantee complete resection while retaining most of the eye appearance or function.

Second, in accordance with WHO RMS histological standard, RMS can be classified into embryo, acinus, and multiformity types, among which the embryo type has relatively good prognosis (Eaton et al., 2013). In this study, embryo-type RMS accounted for 86.7% of the primary orbital RMS cases, a result that is consistent with the literature and is one of the reasons for the high three- and five-year survival rates.

Third, the application of conventional chemotherapy and high-dose chemotherapy combined with APBSCT in this study helped significantly improve the possibility of complete surgical resection, the clinical remission rate, and the survival rate. Chemotherapy has an irreplaceable role in the treatment of pediatric orbital RMS. The disease is extremely sensitive to chemotherapy, even in Phases III and IV. Patients can experience significant alleviation of their condition after surgical resection combined with chemotherapy and can even achieve

long-term survival. Preoperative chemotherapy can effectively reduce the tumor volume and clear potential metastasis, which provide a good foundation for radical surgery. Postoperative chemotherapy particularly has a significant function in preventing tumor recurrence. However, choosing the chemotherapy timing and determining the chemotherapy cycle are the difficulties faced in treating pediatric RMS and improving life quality. According to the treatment experience in this study, the preoperative chemotherapy (AVCP, IEV, and DEV) should be conducted for two to four cycles for stage III and IV patients, and the radiographic assessment should be conducted every two cycles to determine the surgery timing and postoperative chemotherapy. Doing so can enhance clinical efficacy and prognosis to a certain extent, and is one of the key factors for the total survival rate of 86.1%. In this study, a stage III RMS patient experienced recurrence after surgery and conventional chemotherapy. After the second chemotherapy and PR, high-dose chemotherapy with APBSCT was administered, which resulted in long-term event-free survival. Applying APBSCT to malignant tumors has become a widely recognized treatment option because it is easy to employ, involves few rejection reactions, and enables the bone-marrow blood-producing function to recover rapidly in a safer and considerably more effective way than allograft (Kim et al., 2012). However, high-dose chemotherapy combined with APBSCT in treating pediatric orbital RMS is rarely reported, and related clinical experience is lacking. Although APBSCT was administered to only one patient in this study, the treatment result led to long-term event-free survival. This finding provides a new treatment option for children with advanced RMS.

Finally, the side effects of extra radiotherapy are more obvious in children than in adults, so local radiotherapy has become a common method of treating children with malignant solid tumors. Radioactive particle implantation into the lesion site with a small dose to continuously treat cancer has attracted much attention (Meng et al., 2012; Eaton et al., 2013). Because the primary site was the orbit, the focus of our investigation was how to prevent radiation-induced eye malformation while ensuring the efficacy of radiotherapy. Therefore, we cooperated with the Department of Nuclear Medicine, and basing from the lesion CT or MR image as the target reference, we conducted ¹²⁵I brachytherapy surgery on 10 patients for local radiotherapy. CT verification and image analysis indicated that the 10 cases of ¹²⁵I radioactive seed implantation succeeded because the activity of the particles and the target emission volume were consistent with the basic plan. Among the 10 cases, 8 achieved CR and 2 achieved PR, which resulted in an overall survival rate of 100% (10/10). Therefore, radioactive ¹²⁵I seed implantation can be used as an effective radiotherapy method for RMS in children.

In conclusion, pediatric cancer treatment is a collaborative effort that involves surgery, internal oncology, pathology, iconography, and radiation oncology. The lack of close coordination among various medical departments may cause inaccurate diagnosis, staging failure, and disjunction in treatment. This paper reported

only the collected data on orbital RMS in our hospital, and these data were single centered and characterized by a short collection time and follow-up period. Nevertheless, the results indicated that even though children with orbital RMS were the ideal type of subjects with a relatively high degree of malignancy, their clinical rate can be improved. Early diagnosis and a multidisciplinary collaborative approach combined with a comprehensive treatment plan that includes surgery, chemotherapy, radiotherapy, and auto-PBSCT are the key in improving the clinical rate of this patient population. However, in consideration of the special anatomical structure of the primary site, the aforementioned steps should be combined with early diagnosis, appropriate surgery timing, comprehensive treatment, and close follow-up to reduce recurrence and mortality rates and to improve the clinical remission rate.

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References

- Ballard KS, Tedjarati SS, Robinson WR, Homesley HD, Thurston EL (2010). Rhabdomyosarcoma adjuvant and ex vivo assay directed chemotherapy. *Int J Gynecol Cancer*, **20**, 561-3.
- Bearman SI, Appelbaum FR, Buckner CD, et al (1988). Regimen related toxicity in patients undergoing bone marrow transplantation. *Clin Oncol*, **6**, 1562-8.
- Breneman J, Meza J, Donaldson SS, et al (2012). Local control with reduced-dose radiotherapy for low-risk rhabdomyosarcoma: a report from the Children's Oncology Group D9602 study. *Int J Radiat Oncol Biol Phys*, **83**, 721-6.
- Burke ME, Lyden ER, Meza JL, et al (2013). Does body mass index at diagnosis or weight change during therapy predict toxicity or survival in intermediate risk rhabdomyosarcoma? A report from the Children's Oncology Group Soft Tissue Sarcoma Committee. *Pediatr Blood Cancer*, **60**, 748-53.
- Corrias MV, Haupt R, Carlini B, et al (2006). Peripheral blood stem cell tumor cell contamination and survival of neuroblastoma patients. *Clin Cancer Res*, **12**, 5680-5.
- Crist W, Gehan EA, Ragab AH, et al (1995). The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol*, **13**, 610-30.
- Dasgupta R, Rodeberg DA (2012). Update on rhabdomyosarcoma. *Semin Pediatr Surg*, **21**, 68-78.
- Eaton BR, McDonald MW, Kim S, et al (2013). Radiation therapy target volume reduction in pediatric rhabdomyosarcoma: implications for patterns of disease recurrence and overall survival. *Cancer*, **119**, 1578-85.
- Gosiengfiao Y, Reichel J, Walterhouse D (2012). What is new in rhabdomyosarcoma management in children? *Paediatr Drugs*, **14**, 389-400.
- Gupta AA, Anderson JR, Pappo AS, et al (2012). Patterns of chemotherapy-induced toxicities in younger children and adolescents with rhabdomyosarcoma: a report from the Children's Oncology Group Soft Tissue Sarcoma Committee. *Cancer*, **15**, 1131-7.
- Hawkins DS, Spunt SL, Skapek SX (2013). Children's Oncology Group's 2013 blueprint for research: Soft tissue sarcomas. *Pediatr Blood Cancer*, **60**, 1001-8.
- Joshi D, Anderson JR, Pappo AS, et al (2004). Age is an independent prognostic factor in rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *Pediatr Blood Cancer*, **42**, 64-73.
- Kim NK, Kim HS, Suh CO, Kim HO, Lyu CJ (2012). Clinical results of high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in children with advanced stage rhabdomyosarcoma. *J Korean Med Sci*, **27**, 1066-72.
- Koscielniak E, Klingebiel T, Peters C, et al (1997). Do patients with metastatic and recurrent rhabdomyosarcoma benefit from high-dose therapy with hematopoietic rescue? Report of the German/Austrian Pediatric Bone Marrow Transplantation Group. *Bone Marrow Transplant*, **19**, 227-31.
- Kuru TH, Roethke MC, Nyarangi-Dix J, et al (2013). Pediatric case report on magnetic resonance imaging/transrectal ultrasound-fusion biopsy of rhabdomyosarcoma of the bladder/prostate: a new tool to reduce therapy-associated morbidity? *Urology*, **81**, 417-20.
- Maurer H, Beltangady M, Gehan EA, et al (1988). The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer*, **61**, 209-20.
- Maurer H, Gehan E, Beltangady M, et al (1993). The Intergroup Rhabdomyosarcoma Study-II. *Cancer*, **71**, 1904-22.
- Meng N, Jiang YL, Wang JJ, et al (2012). Permanent implantation of iodine-125 seeds as a salvage therapy for recurrent head and neck carcinoma after radiotherapy. *Cancer Invest*, **30**, 236-42.
- Meza JL, Anderson J, Pappo AS, Meyer WH (2006). Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: The Children's Oncology Group. *J Clin Oncol*, **24**, 3844-51.
- Oberlin O, Rey A, Anderson J, et al (2001). Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment—results of an international workshop. *J Clin Oncol*, **19**, 197-204.
- Pappo AS, Shapiro DN, Crist WM, Maurer HM (1995). Biology and therapy of pediatric rhabdomyosarcoma. *J Clin Oncol*, **13**, 2123-39.
- Rodeberg D, Pappo AS, Crist WM (2006). Childhood rhabdomyosarcoma. *Semin Pediatr Surg*, **15**, 57-62.
- Rodeberg D, Arndt C, Breneman J, et al (2005). Characteristics and outcomes of rhabdomyosarcoma patients with isolated lung metastases from IRS-IV. *J Pediatr Surg*, **40**, 256-62.
- Sandler E, Lyden E, Ruymann F, et al (2001). Efficacy of ifosfamide and doxorubicin given as a phase II "window" in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. *Med Pediatr Oncol*, **37**, 442-8.
- Trahair T, Andrews L, Cohn RJ (2007). Recognition of Li Fraumeni syndrome at diagnosis of a locally advanced extremity rhabdomyosarcoma. *Pediatr Blood Cancer*, **48**, 345-8.
- Van Gaal JC, Van Der Graaf WT, Rikhs B, et al (2012). The impact of age on outcome of embryonal and alveolar rhabdomyosarcoma patients. A multicenter study. *Anticancer Res*, **32**, 4485-97.
- Walterhouse D, Meza JL, Raney RB, et al (2006). Dactinomycin (A) and vincristine (V) with or without cyclophosphamide (C) and radiation therapy (RT) for newly diagnosed patients with low risk embryonal/botryoid rhabdomyosarcoma (RMS). an IRS-V report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group [abstract]. *J Clin Oncol*, **24**, 18S.