NOWOTWORY Journal of Oncology • 2002 • volume 52
Number 5 • 389–393

Original contributions

The evaluation of results and late complications of radiotherapy in children treated for orbital rhabdomyosarcoma

Anna Skowrońska-Gardas, Katarzyna Pędziwiatr, Marzanna Chojnacka

Aim. To analyse treatment results and late complications of radiotherapy in children treated for orbital rhabdomyosarcoma.
Material and methods. Between the years 1980 and 2000 34 children (median age 7 yrs. range: 1-15) with orbital RMS, were treated in the 1st Department of the MCCMCC in Warsaw. All but two of the patients received induction chemotherapy; 3 children were treated after ablative surgery (exenteration); 6 children were irradiated due to recurrence after chemotherapy. All the children were treated with megavoltage radiotherapy from a Co-60 unit or linear accelerator. We applied individual lens and lacrimal apparatus shielding in 16 patients. Five children, treated between 1996-2000, received conformal radiotherapy, with CT and 3-D treatment planning system. To obtain information about late side effects, we developed a questionnaire, including questions about the status of the affected eye, appearance of the orbit and facial structures.
Results. Thirty one patients (91%) are still living (between 24 and 264 months – median 138 mos) after completion of radiotherapy and 28 (82%) with no recurrence. In six patients treated due to recurrent tumour OS and DFS was 80% and 60%, respectively. Late complications were evaluated in 24 patients. We observed lacrimal duct stenosis in 33%, cataract in 29%, enophtalmos in 20% of patients. Retinopathy developed in 2 children, glaucoma in 2 pts, and facial asymmetry in 3 pts. In one case enucleation of blind eye was performed. Thirteen children have preserved adequate vision in the treated eye. In children treated with conformal radiotherapy we did not observe any late complications.
Conclusions. Radiotherapy in orbital RMS allows to obtain good local control and excellent survival rate. Late complications could be limited with the application of individual treatment planning and conformal radiotherapy.

Ocena wyników i późnych powikłań radioterapii u dzieci leczonych z powodu mięsaka prążkowanokomórkowego oczodołu

Cel. Ocena wyników i późnych powikłań radioterapii u dzieci leczonych z powodu mięsaka prążkowanokomórkowego oczodołu.
Materiał i metody. W latach 1980-2000 w I Zakładzie Radioterapii Centrum Onkologii w Warszawie leczono 34 dzieci z rozpoznaniem mięsaka prążkowanokomórkowego oczodołu, w wieku 1-15 lat (mediana 7). Wszystkie dzieci z wyjątkiem 2 otrzymały wstępną chemioterapię, u 3 zastosowano okaleczający zabieg chirurgiczny (egzenterację). Sześcioro dzieci napromieniano z powodu nawrotu po chemioterapii. U wszystkich dzieci zastosowano chemioterapię megavoltową, za pomocą promieniowania z Co-60 lub akcelatora liniowego. U połowy pacjentów zastosowano indywidualne osłony soczewki i aparatu łzowego. Pięcioro dzieci, leczonych w latach 1996-2000, napromieniano z zastosowaniem technik konformalnych. W celu uzyskania informacji o późnych powikłaniach rozesłano kwestionariusz, z pytaniami dotyczącymi stanu leczonego oka oraz struktur oczodołu i wyglądu twarzy.
Wyniki. Trzydziestu jeden pacjentów (91%) żyje, od 24 do 264 miesięcy (mediana 138), po zakończeniu radioterapii i 28 (82%) bez objawów nawrotu. U sześciorga dzieci, napromienianych z powodu wznowy, przeżycie całkowite i bez nawrotu wynosiło odpowiednio 80% i 60%. U 33% pacjentów stwierdzono uszkodzenie aparatu łzowego, u 29% zaćmę, i u 20% wpadnięcie gałki ocznej. Retinopatia wystąpiła u 2 dzieci, jaskra u 2, u 3 znaczna asymetria twarzy. W jednym przypadku wykonano enukleację niewidzącego oka. Trzynaścioro dzieci zachowało zdolność widzenia w leczonym oku. U dzieci napromienianych za pomocą technik konformalnych nie stwierdzono późnych powikłań po leczeniu.

1st Department of Radiotherapy
The Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology, Warsaw, Poland

Wnioski. Radioterapia, zastosowana u dzieci z rozpoznaniem mięsaka prążkowanokomórkowego oczodołu, pozwala na uzyskanie dobrych wyników miejscowych i wysokiego odsetka przeżyć całkowitych. Późne powikłania mogą zostać zminimalizowane przez zastosowanie indywidualnych metod planowania i radioterapii konformalnej.

Key words: orbital rhabdomyosarcoma, radiotherapy, late complications
Słowa kluczowe: mięsak prążkowanokomórkowy oczodołu, radioterapia, późne powikłania

Introduction

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood. RMS occurs in any anatomical location where there are skeletal muscles. More than 1/3 are located in head and neck sites, and in about 30% of patients from this group an orbital tumour is found. Historically, orbital RMS was treated with radical surgery, usually exenteration. With this method, about 40% 5-year survivals were obtained. Because it is difficult to remove a tumour of the orbit with wide, uninvolved margins and still preserve the eye and acceptable cosmesis, radiation therapy was used to obtain local control with the aim of preserving the eye [1]. This method allowed for better results and more than 60% of children survived 5 years. In the last two decades, multiagent chemotherapy with radiotherapy and, sometimes, conservative surgery allows to obtain about 90% > 5 year survivals and 80% disease free survival [2-7]. However, radiotherapy of the eye and orbital structures is usually connected with serious late side effects, such as cataract, lacrimal apparatus damage, retinopathy, glaucoma and, even, optical nerve injury [8]. Although one may find literature reports of complications of radiation of the eye in children with orbital RMS it was rather difficult to evaluate the real incidence and severity of ocular radiation morbidity [9, 10].

The main purpose of this study was to evaluate treatment results and late complications in 34 children with orbital rhabdomyosarcoma treated at the 1st Department of Radiotherapy at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. Our secondary aim is was to design future management strategies for these patients, basing upon our own experiences and published data.

Material and methods

From January 1980 until December 2000 34 children aged between 1 and 15 years (median age 7 yrs.) were treated in the 1st Department of Radiotherapy of the MSCMCC for orbital rhabdomyosarcoma. The clinical stage acc. to the IRS system was: I in 1 patient, II in 7 pts. and III in 26 pts. In 2 patients exenteration was performed before radiotherapy, in 7 – gross total excision, in 7 – partial excision, and in 18 – biopsy only. Thirty two patients were treated with multiagent chemotherapy regimes including cyclophosphamid, ifosphamid, vincristine, adriamycin, actinomycin immediately after surgery. Two children (1980 and 1982) were treated without chemotherapy. Chemotherapy and surgery were performed in paediatric oncology departments. Five patients were referred to radiotherapy because of recidival tumour after prior surgery and chemotherapy. All children were treated with megavoltage radiotherapy – Co60 or linear accelerator with photon and/or electron beams. We used individual shells and masks for patient immobilisation and reproducibility of treatment. In 29 patients treatment was performed with two-dimensional planning system and the entire orbit was included in planning treatment volume (PTV). In 5 children, treated since 1996, 3D conformal radiotherapy was applied, and PTV comprised residual tumour with 1 cm margin of normal tissue. In 18 patients we have spared the lens and lacrimal apparatus. The total doses of 50-55 Gy were applied in 31 patients, in 1 pt. – 40Gy and in 1 pt. – 60 Gy, in fractionated doses of 1.8-2.0 Gy. One patient had progression of disease during radiotherapy and did not complete treatment.

To obtain information about the late effects of treatment we developed a questionnaire involving the status of the affected eye and the appearance of the orbit and the facial structures.

The questionnaire included questions about cataracts, visual acuity, keratitis, changes in other intraocular structures than the retina, presence of ptosis, facial abnormalities and other possible complications. The data was analysed to investigate correlations among the age of the patients, the dose of irradiation and the type of the complication noted.

Overall survival (OS) and disease free survival (DFS), measured from the onset of radiotherapy, were calculated using the Kaplan-Meyer method. The survival free of visual distributions was also estimated with the Kaplan-Meyer method.

Results

Mean follow-up was 138 months (range: 1-264 months). Minimum follow-up for a living patient was 24 months. At present 31 children are still alive, among them 28 with no evidence of disease. Local failure was observed in 6 children, 3 of them are alive after salvage surgery, 3 died due to the disease. All failures were local, with no evidence of metastases. Actuarial 5- year OS and DFS rates are 91% and 80%, respectively (Figures 1 and 2). In the

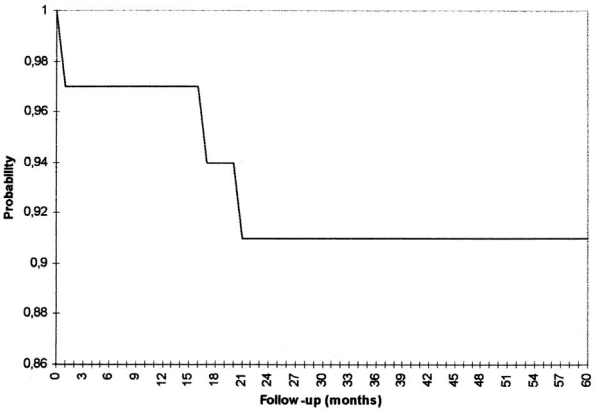

Figure1. Overall survival of 34 patients with orbital RMS estimated by the Kaplan-Meier method

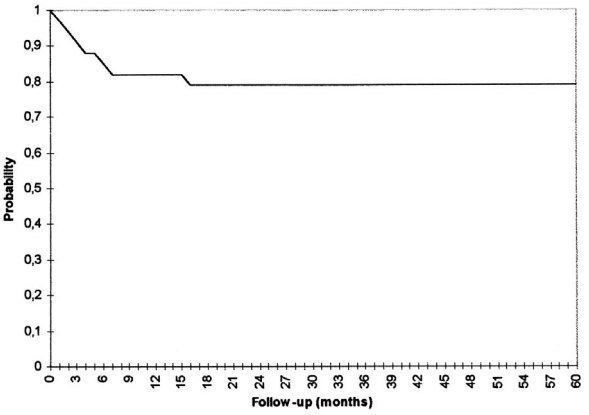

Figure 2. Disease free survival of 34 patients with orbital rhabdomyosarcoma estimated by the Kaplan-Meier method

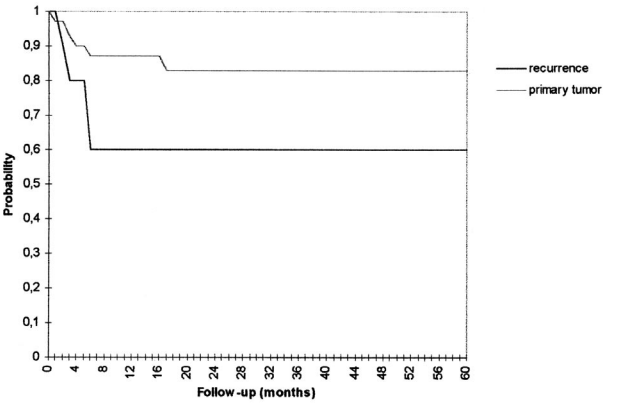

Figure 4. Disease free survival of 34 patients with orbital RMS according to treatment of reccurence after chemotherapy

group of patients irradiated immediately after neoadjuvant chemotherapy the actuarial 5-year overall (OS) was 93% and disease free survival (DFS) 82%. For patients irradiated due to recurrent tumour OS was 80% and DFS 60%. These results are presented in Figures 3 and 4. In order to evaluate late complications 3 children after orbital exenteration or enucleation before radiotherapy, and 6 children with local recurrence were excluded from the analysis. In the remaining 24 patients we obtained the information about their visual acuity and possible complications. In most of them we observed only mild complications, such as slight eye-lid asymmetry or minimal conjunctival teleangiectasies. Other late complications are presented in Table I.

Table I. Late complications in 24 children with orbital rhabdomyosarcoma

Complication	Number of patients	%
Enophtalmos	5	20
Cataract	7	29
Lacrimal duct stenosis	8	33
Retinopathy	2	8
Glaucoma	2	8
Retinal ulceration	1	5
Facial asymmetry	3	12

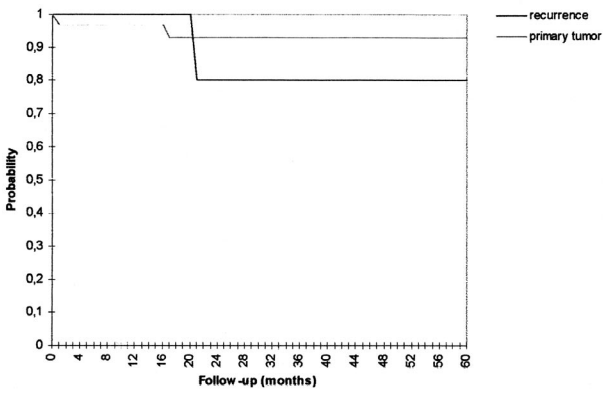

Figure 3. Overall survival of 34 patients with orbital RMS according to treatment of recurrence after chemotherapy

The lens is the most radiosensitive structure of the eye with an overt cataract developing after doses of 5-12 Gy. However, we observed cataract in relatively few patients, probably because in 18 patients we shielded the anterior part of the eye ball. In these patients the lens recieved doses of some 5-20 Gy. Lacrimal duct stenosis developed in 1/3 of our patients, the onset of symptoms being observed a few months after radiotherapy, but in a majority of cases the symptoms were mild. Enophtalmos was observed in 20% of cases, both among younger and older children. Serious facial asymmetry with maxillary hypoplasia was observed in 3 children, all of whom were under 6 years of age at the time of treatment. Retinopathy was diagnosed in 2 children, both irradiated due to recurrent tumour. These children were also treated with salvage multiagent chemotherapy, thus the retinopathy may have been brought on by both treatment methods.

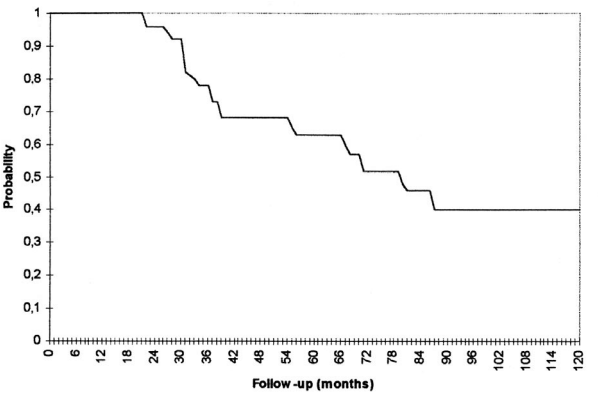

Figure 5. Survival free of cataract in 24 patients estimated by the Kaplan-Meier method

The most serious complications were glaucoma and painful retinal ulceration, leading – in one child – to eye ball necrosis. In this latter case enucleation of the blind eye was performed. Thirteen children have preserved good vision in the treated eve. Visual acuity disturbances were observed between 24 and 60 months after completion of radiotherapy, as is presented in Figure 5. Four

children, who were treated with 3D conformal radiotherapy have preserved good vision in the irradiated eye, with no evidence of serious complications related to radiotherapy. In one child we observed ptosis, but it appeared before radiotherapy and was caused by previous surgery.

Discussion

The experience derived from the co-operative trials of the Intergroup Rhabdomyosarcoma Study and the trials of International Society of Paediatric Oncology clearly indicates that radiotherapy is the essential method for local control of orbital sarcoma. The results obtained with combined treatment are excellent, with 5-year OS 90-100% and DFS 80-90% [11, 12]. The results obtained in our study – 91% OS and 80% DFS confirm these patients' good prognosis. Because of a possibility of serious side effects of radiation on the treated eye, investigators in Western Europe have chosen to give initially chemotherapy to patients with orbital sarcoma in order to postpone radiotherapy, indefinitely or until evidence of failure. 38% of their patients were never treated with radiotherapy and had a low rate of orbital complications. But at least 45% of the initially non-irradiated patients suffered local recurrence. Local recurrence usually requires surgical intervention, sometimes mutilating, while it still may call for irradiation. Only 70% of the initially non-irradiated patients survived the recurrence, 30% died due to uncontrolled disease. Two patients suffered cardiac and renal failure after toxic chemotherapy, and one of them died of doxorubicin cardiotoxicity [13]. In our study we also observed worse outcome in children treated due to local recurrence of an initially non-irradiated tumour, with 5-year OS and DFS rates 80% and 60%, respectively.

Few authors have reviewed the late sequelae of radiotherapy in patients with orbital sarcoma [9, 10]. However, recently, two large studies focusing on the late effects of therapy in children with orbital RMS have been presented. The Italian authors have described a group of 19 children, treated between 1980 and 1995, with an excellent survival rate of 95% and continuous local control of 81%. These patients received a total dose of as much as 60 Gy. The most common complications were enophtalmos, lacrimal duct stenosis and facial asymmetry in half of the patients. In the eye ball structures corneal changes, lens opacities and iris damage were observed. These complications caused a decrease in visual acuity in 37% of the patients. Lens alterations have been registered in a relatively small number of subjects (47%), probably due to eyeball shielding [14]. Raney et al. have presented the results of a recent review of 94 survivors of localised orbital sarcoma treated acc. to the IRS-III protocol between 1984 and 1991. 96% of their patients are alive and in 86% the eye has been preserved. 82% of the patients have developed cataract, but 66% of them have undergone cataract surgery. 70% had varying degrees of diminished visual acuity, but only 6% were blind in the affected eye. Corneal and conjunctival changes and lacrimal duct injury were observed in 1/3 of the patients. Orbital hypoplasia was described in 60%, but only 9% had maxillary hypoplasia, and 1 patient was said to have significant facial disfigurement [15]. In our study the late complications were similar. The relatively low rate of cataract is probably the effect of shielding of the anterior part of eyeball in some patients. The evaluation of height and hormonal status was not the focus of our study, but we have not observed significant deviations in growth and puberty status in our patients. Similar results have been reported by the Italian authors [14]. In the IRS study decreased statural growth was observed in 24% of children. These authors have also reported school difficulties in 14% of patients [15]. In our study one child had problems at school, but it was more likely brought on by mental retardation caused by microcephalus.

We must stress that radiation side effects have to be carefully considered – parallel to the therapeutic goal. Five children in our study were treated with 3D conformal radiotherapy. One patient, treated due to recurrent tumour, relapsed and died. Four are living with no recurrence, and we have not observed any late side effects, except ptosis caused by previous surgery in one girl.

In our opinion the conformal or stereotactic radiotherapy with inclusion of the residual tumour only in PTV should be appllied in children with orbital rhabdomyosarcoma.

Further studies are needed to investigate other possible radiotherapy techniques in order to minimise late complications of irradiation in this group of patients [16, 17].

Conclusions

1. Our study confirms previous reports of good results obtained in children with orbital rhabdomyosarcoma treated with chemo- and radiotherapy.
2. Late side effects of radiotherapy are observed in some patients, but application of individual methods of treatment planning allows to preserve useful vision in the treated eye in 50% of the patients.
3. 3D conformal radiotherapy techniques may result in further reduction of radiation-related sequelae.

Anna Skowrońska-Gardas M.D. Ph.D.
1st Department of Radiotherapy
The Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology
Wawelska 15, 00-973 Warszawa

References

1. Halperin E, Constine L, Tarbell N, Kun L *Paediatric Radiation Oncology*, 3rd ed. Philadelphia: Lippincott Wiliams and Wilkins; 1999, 223-46.
2. Flamant F, Rodary C, Voute P A et al. Primary chemotherapy in the treatment of rhabdomyosarcoma in children: Trial of the International

Society of Paediatric Oncology (SIOP) preliminary results. *Rad Oncol* 1985; 3: 227-236.
3. Mauer HM, Beltangedy M, Gehan EA et al. The Intergroup Rhabdomyosarcoma Study I. *Cancer* 1988; 61: 209-20.
4. Mauer HM, Gehan EA, Beltangady M et al. The Intergroup Rhabdomyosarcoma Study II. *Cancer* 1993; 71: 1904-22.
5. Crist W, Gehan EA, Ragab AH et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995; 13: 610-630
6. Florillo A, Migiliorati R, Grimal.di M et al. Multidisciplinary treatment of primary orbital rhabdomyosarcoma. *Cancer* 1991; 67: 560-3.
7. Skowrońska-Gardas A, Dramińska D. The value of irradiation in the combined treatment of orbital rhabdomyosarcoma in the children with the aim of vision preservation. In: *Progress in Radio-Oncology*, edit: Kogelnik HD. Bologna: Monduzzi Edit; 1995, 257-60.
8. Parsons J, Fitzgeral.d C, Hood C et al. The effects of irradiation of the eye and optic nerve *Int J Rad Oncol Biol Phys* 1983; 9: 609-33.
9. Heyn R, Ragab A, Ranev B et al. Late effects of therapy in orbital rhabdomyosarcoma. *Cancer* 1986; 57: 1738-43.
10. Paulino A Simon J, Zhen W, Wen B. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Rad Oncol Biol Phys* 2000; 48: 1489-95.
11. Wharam M, Hanfelt J, Tefft M et al. Radiation therapy for rhabdomyosarcoma: local failure risk for clinical group III patients on Intergroup Rhabdomyosarcoma Study III. *Int J Rad Oncol Biol Phys* 1997; 38: 797-804.
12. Crist W, Anderson J, Meza J at al. Intergroup Rhabdomyosarcoma Study IV: results for patients with nonmetastatic disease. *J Clin Oncol* 2001; 19: 3091-102.
13. Rousseau P, Flamant F, Quintana E et al. Primary chemotherapy in rhabdomyosarcomas and other malignant mezenchymal tumours of the orbit: results of the International Society of Paediatric Oncology MMT 84 Study. *J Clin Oncol* 1994; 12: 516-21.
14. Florillo A, Migliorati R, Vasello P et al. Radiation late effects in children treated for orbital rhabdomyosarcoma. *Rad Oncol* 1999; 53: 143-8.
15. Raney RB, Anderson J, Kollath J et al. Late effects of radiotherapy in 94 patients with localised rhabdomyosarcoma of the orbit: report from the Intergroup Rhabdomyosarcoma Study (IRS) -III 1984-1991. *Med Ped Oncol* 2000; 34: 413-20.
16. Hug E, Adams J, Fitzek M et al. Fractionated, three dimensional planning assisted proton radiation therapy for orbital rhabdomyosarcoma:a novel technique. *Int J Rad Oncol Biol Phys* 2000; 47: 979-84.
17. Mirabell R, Cella L, Weber W. Lomax A Optimising radiotherapy of orbital and paraorbital tumours: intensity modulated X-ray beams vs intensity modulated proton beams. *Int J Rad Oncol Biol Phys* 2000; 47: 1111-9.

Paper received: 25 July 2002
Accepted: 26 August 2002