

VISUAL ACUITY RESULTS AFTER MANAGEMENT OF RETINOBLASTOMA IN CHILDREN

ONDRÁČEK O., UNČOVSKÁ E.

Department of Paediatric Ophthalmology, Paediatric Teaching Hospital, Faculty of Medicine,
Masaryk University, Brno

Abstract

In this study we evaluated long-term functional results of different methods of retinoblastoma treatment including chemoreduction with carboplatine, etoposide and vincristine, chemothermotherapy, cryotherapy, diode laser thermotherapy, photocoagulation and external beam radiation. The group investigated involved 54 eyes of 43 patients treated in the period from 1985 to 1998. Thirty-two patients had unilateral and 11 had bilateral retinoblastoma. The mean follow-up was 8.6 years (range, 4 to 15). The visual acuity outcome was assessed in 31 eyes of 27 children because 23 eyes with Reese- Ellsworth stage IV to V retinoblastoma had to be enucleated. The mean visual acuity of the successfully treated eyes was 6/18. Fourteen eyes had a visual acuity better than 6/12, nine eyes had a visual acuity between 6/60 and 6/12 and eight eyes had a visual acuity less than 6/60. Maculopathy was observed in 11 eyes. Ten eyes were free from any treatment-related complications. It is concluded that chemotherapy combined with additional focal treatments resulted in good outcome in eyes with Reese-Ellsworth stage I to III retinoblastoma. Children with early and correctly diagnosed retinoblastoma now have a good prognosis for life.

Key words

Retinoblastoma, Chemotherapy, Focal treatment, Functional results

INTRODUCTION

Retinoblastoma is the most common primary intraocular tumour of childhood (1). It is highly malignant and, if left untreated, the mortality rate reaches 99%. The incidence is between 1 per 15.000 and 1 per 30.000 live births. One fourth to one third of all cases of retinoblastoma occur bilaterally, and more than 90% of patients have retinoblastoma before age 5 years (3,4). Bilateral retinoblastoma cases and large tumours have a very poor prognosis for saving the involved eye and for useful visual function (5,6). The most common manifestations of retinoblastoma are leucokoria and strabismus, but atypical manifestations such as uveitis or hyphaema are not unusual (7,8).

In the past, enucleation was the usual method of treatment because children developed retinoblastoma later in life, with large tumours often filling the entire globe. Survival was the obvious goal of treatment. Although a hundred years ago the mortality rate approached 100%, today more than 92% of the affected children

survive (2,3,4). Currently, each patient and each tumour receive specific treatment that may include enucleation, focal treatment with laser photocoagulation or cryotherapy, thermotherapy, plaque therapy, external beam radiation or systemic chemotherapy (9). The approach to treatment depends on the size, extent and location of the tumour, and the patient's systemic condition. Usually several different therapeutic modalities are necessary. The preservation of an eye can be achieved by external beam radiotherapy, which has been the reference treatment for many years. Because of the risk of second neoplasms in the radiation field (which is much more frequent after external beam radiotherapy in retinoblastomas associated with a gene mutation) and ocular and orbital side effects, over the past 5 years efforts have been made to avoid radiation in the conservative treatment of retinoblastoma.

In the mid-1960s, Ellsworth devised a quantitative system for evaluation of the response of different tumours to radiation treatment (2,10,11). The Reese-Ellsworth classification is still most widely used to stage intraocular retinoblastoma. This staging does not involve the macula and, therefore, the visual outcome is included in success evaluation. The relationship between tumour location and child's age at presentation as well as treatment response have been described (12,13). Long-term follow-ups of treated patients now available allow us to study the effects of treatment and tumour location on the final visual outcome. Using a retrospective study design, we evaluated the functional results of different treatment modalities in relation to tumour location in patients with retinoblastoma.

MATERIALS AND METHODS

A total of 54 eyes in 43 patients treated for retinoblastoma at the Department of Paediatric Ophthalmology, Paediatric Teaching Hospital, Faculty of Medicine in Brno in the period from 1985 to 1998 were included in the study. Of them, 32 patients had unilateral and 11 had bilateral retinoblastoma. The severity of disease was assessed according to the Reese-Ellsworth classification (stages I to V). Each eye was also examined for exact tumour location. Special attention was paid to tumours located most posteriorly (involving the macula and close to it) and to large tumours. The mean age at the time of treatment initiation was 2.8 ± 3.7 years (range, 9 months to 6.5 years).

The children were treated by one or several of the following procedures: primary chemotherapy (34 eyes), chemothermotherapy (38), cryotherapy (27), diode laser thermotherapy (11), photocoagulation (14) and external beam radiation (18). The chemoreduction treatment with intravenous administration of carboplatine, etoposide, and vincristine was introduced in our department for patients with grade IV or V retinoblastomas in 1995 and used since then. Cryotherapy was used in primary tumours less than 5mm in diameter. Tumours larger than 5 mm in diameter involving the posterior part of the retina were treated by photocoagulation and chemothermotherapy. The latter is a new method, first described in 1992, that avoids exposure of the patient to external beam radiation. It is based on the synergistic action of intravenous carboplatine infusion and thermotherapy delivered through the pupil precisely to the tumour, using diode laser via an operating microscope under general anaesthesia. The treatment was successful in 31 eyes and failed in 23 eyes with stage V retinoblastoma that had to be eventually enucleated.

The diagnosis of retinoblastoma and the evaluation of anticancer therapy were based on the following methods: funduscopy (indirect binocular ophthalmoscopy) including fundus photography,

slit lamp examination, ultrasonography, computed tomography, magnetic resonance imaging and fluorescein angiography. In children younger than 4 years of age, the examination was carried out under general anaesthesia. The frequency of examination was once a month in the first postoperative year and every 3 months thereafter.

According to the results of visual acuity measurements, the eyes were fell into one of the three groups characterised as follows: group 1, 6/6 to 6/12; group 2, 6/18 to 6/60; group 3, < 6/60. The results were statistically analysed using either the chi-square test or Fisher's exact test (for small-size samples).

RESULTS

VISUAL ACUITY ASSESSMENT

On the basis of the Reese-Eltsworth classification, five eyes were found to have stage I, seven eyes had stage II, 15 had stage III, 14 had stage IV and 13 had stage V tumours. Only 31 eyes in 27 children, at a mean age of 5.8 years, were examined for visual acuity because 23 eyes with stage IV or V tumours had to be enucleated, including bilateral enucleation in two children with bilateral retinoblastoma. The mean visual acuity in the 31 eyes of 27 children was 6/18. As shown in *Fig. 1*, the results of assessment were as follows: group 1, 14 eyes (45 %); group 2, 9 eyes (29 %); group 3, 8 eyes (26 %).

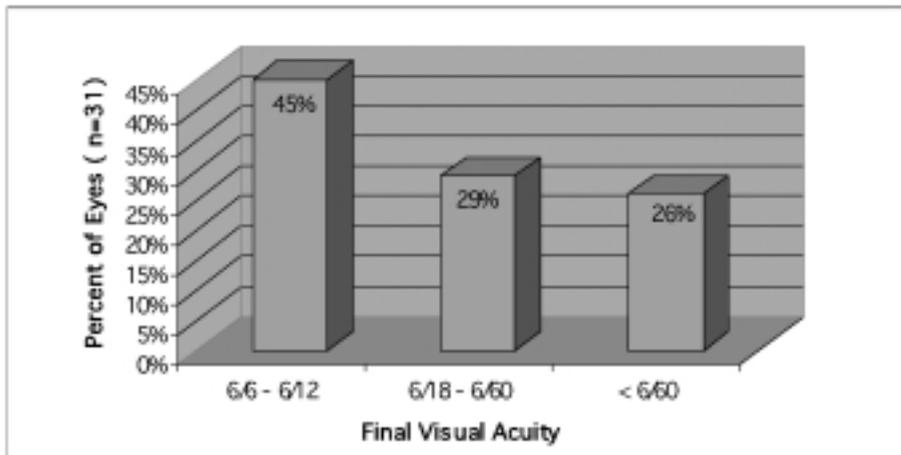


Fig. 1

Visual acuity outcome in 31 successfully treated eyes.

TUMOUR LOCATION AND DESCRIPTION

Nine eyes showed the most posterior tumour location, i.e., at the macula. In seven eyes, the tumour site was less than 3 mm from the macula and, in 15 eyes, it was more distant than 3 mm from the macula. Twelve of the 27 patients received 2 to 6 courses of carboplatine, etoposide and vincristine treatment to reduce tumour volume.

The primary chemotherapy resulted in tumour reduction to a size less than 3 mm in diameter in 6 eyes, to 3 to 6 mm in 11 eyes and, in 14 eyes, the tumour still remained more than 6 mm in diameter.

Table 1

Relationship between tumour location and visual acuity outcome

Visual acuity	Location of the tumour			No. of eyes
	At the macula	< 3 mm from the macula	> 3 mm from the macula	
<6/60	8	0	0	8
6/60 to 6/12	1	5	3	9
>6/12	0	2	12	14

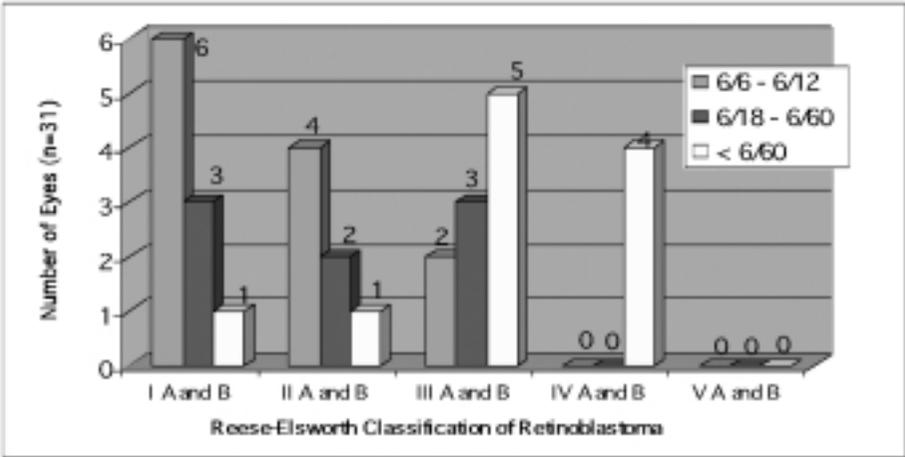


Fig.2

Reese-Ellsworth classification of retinoblastoma in relation to the visual acuity outcomes.

Neither tumour diameter nor the use of primary chemotherapy significantly influenced the outcome. In contrast, tumour location was a highly significant factor. As shown in *Table 1*, the visual acuity outcome was directly related to the tumour distance from the macula ($P = 0.037$).

There was a correlation between the Reese-Ellsworth classification and the visual acuity outcome (*Fig. 2*). Stage IV and V were associated with enucleation in a high proportion of the eyes (72 and 100 %, respectively).

Eighteen children underwent external beam radiation. The doses ranged from 30 to 45 Gy administered during 3 to 5 weeks (3-times per week). Some of the patients underwent additional treatment with laser photocoagulation, cryotherapy, plaque therapy or another radiation. Techniques for administration are discussed in papers published previously (2,9,12).

Ocular complications observed in 21 eyes included maculopathy or retinopathy in 11 eyes, peripheral lens opacity in 3 and localised vitreous haemorrhage in 7 eyes. Ten eyes undergoing additional focal treatment had no complications. Maculopathy was the most frequent complication and the cause of vision loss. When the tumour scar included the fovea, the visual acuity outcome was less than 6/60.

DISCUSSION

Most of the eyes studied received a combination of systemic chemotherapy and one or more local treatments. Some of them underwent additional external beam radiation.

The functional results of our study compare favourably with those reported after radiotherapy alone. *Migdal* reported 50% of eyes with a vision between 20/40 and 20/200 in a series of 116 patients (14). *Egbert et al.* (15) reported the same level of visual acuity in 22% of 22 eyes and *Hall et al.* (16) found it in 58% of 102 treated eyes.

In our patients treated without external beam radiotherapy, we did not include eyes with massive tumours or disseminated disease. Some of these patients had large tumours with many subretinal seeds; when chemothermotherapy was used, subretinal seeds were treated with laser at each session. However, some of the retinal seeds recurred after laser treatment and were successfully treated by subsequent cryotherapy.

The most frequent cause of visual loss was the development of tumour close to the macula. Previous papers reporting the results of radiotherapy have shown that good visual acuity can be preserved when the initial tumour does not involve the fovea (17,18,19,20). With the use of chemothermotherapy, it can be more difficult to preserve vision when a large tumour is situated very close to the fovea. The laser energy delivered by diode laser is absorbed by the retinal pigment epithelium (this temperature rise is synergistic with the action of carboplatine)

and may cause vitreous or retinal damage. In their initial description of this technique, *Murphree et al.* (21) have recommended treatment of each tumour for 20 min at 600 mW. When the tumour is situated close to the macula, it is very important to decrease laser energy and exposure time to avoid destruction of the fovea. We usually started with a spot of 400 to 500 mW according to the tumour size and carefully watched the retina around the tumour during the whole exposure time. We discontinued laser treatment when the retina became white; the exposure time was always adapted to the tumour volume. When these precautions are observed, chemothermotherapy can be delivered very close to the macula without causing any visual damage. Other authors have saved the eyes affected with retinoblastoma by chemotherapy and diode laser (22,23,24,25,26), but there are very few reports on the use of chemothermotherapy.

The most widely used staging for retinoblastoma is the Reese-Ellsworth classification. It places tumours into 5 groups depending on their size and location. The relation of the stage of tumour and photon radiation therapy to survival have been reported (27, 28). At present, gamma or beta radiation increases success in stage IV patients (3).

Many studies have explored trends in retinoblastoma treatment and management, but few have addressed visual outcomes. *Holbek and Ehlers* (29) reported visual performance in 18 patients with retinoblastoma treated with radiation. Fifty-four percent had visual acuity > 0.5. Several authors have included only patients treated for macular tumours and achieved surprisingly good vision outcomes (26,30,31,32). *Lueder* presented a case in which a tumour filled the area between the arcades, and functional vision was recovered after laser hyperthermia and chemotherapy (26).

Children with retinoblastoma currently have a good prognosis for life. Although there is a correlation with tumour location, the visual outcome is not easily predicted on the basis of the initial presentation.

The functional results after the management of Reese-Ellsworth stage I to III retinoblastoma by chemotherapy and focal treatment showed a vision of 6/12 and better in 45% of the eyes studied. The most important prognostic factor for visual acuity was the tumour site. The eyes with stage IV to V Reese-Ellsworth retinoblastoma had a very poor prognosis despite the initial regression of tumour mass by intravenous chemoreduction.

VÝSLEDKY ZRAKOVÝCH FUNKCÍ V LÉČBĚ DĚTÍ S RETINOBLASTOMEM

S o u h r n

Záměrem práce je zhodnocení dlouhodobých výsledků zrakových funkcí po různých postupech v léčbě retinoblastomu. Jsou hodnoceny alternativní metody lokální léčby retinoblastomu. V retrospektivní studii autoři analyzovali 54 očí u 43 dětí léčených na klinice dětské oftalmologie Lékařské fakulty Masarykovy univerzity v Brně v letech 1985 až 1998. Třicet dva dětí mělo jednostranný retinoblastom a 11 dětí mělo oboustranný retinoblastom. Od roku 1995 byla používána intravenózní chemoterapie v kombinaci carboplatina, etoposid a vincristin tzv. chemoredukce u pacientů se IV. a V. stupněm retinoblastomu podle Reeseho- Ellsworthovy klasifikace. Primární chemoterapie byla provedena u 34 dětí, chemoterapie ve 38 případech, kryoterapie u 27 očí, termoterapie diodovým laserem u 11 očí, fotokoagulace u 14 očí. Zevní radioterapie byla použita u 8 očí. Střední doba sledování po zahájení léčby retinoblastomu byla 8,6 roků v rozmezí 4 až 15 let. Výsledky zrakové ostrosti byly zhodnoceny u 31 očí 27 dětí s průměrným věkem 7,8 roku při poslední kontrole. Dvacet tři očí s rozsáhlým tumorem IV. až V. stupně muselo být primárně nebo následně enukleováno po selhání možných léčebných postupů. Průměrná výsledná zraková ostrost (vizus) 31 očí byla 6/18 na Snellenových optotypech. 14 očí mělo vizus lepší než 6/12, 9 očí mělo vizus v rozmezí 6/60 až 6/12 a 8 očí mělo vizus horší než 6/60. Makulopatie byla po léčbě přítomna u 11 očí, částečná katarakta u 3 očí, sklivcové hemoragie u 7 očí. Deset očí nemělo žádné komplikace související s lokální léčbou. Výsledky zrakových funkcí u dětí s retinoblastomem stupně I až III podle Reeseho-Ellsworthovy klasifikace po chemoterapii a adjuvantní fokální léčbě jsou úspěšné. Nejčastější komplikace lokální léčby tumorů v blízkosti žluté skvrny je makulopatie a sklivcové krvácení po kryoterapii. Děti s retinoblastomem zavčas správně diagnostikovaným mají velmi příznivou životní prognózu. Ačkoliv je korelace mezi lokalizací tumoru a výsledným vizem, není vždy možné výsledné vidění předpovědět jen na základě klinického nálezu při prvním vyšetření.

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