Title: Adjuvant Treatment Of Retinoblastoma.

Authors:
Khalid G. Ali ¹, Hoda T. El-Shiwy², Alaa M. El-Hadad ³.

1) Professor of Ophthalmology, Banha university
2) Lecturer of Ophthalmology, Cairo university
3) Professor of pediatric oncology, Cancer institute

Correspondent author: Khalid G. Ali, M.D.
Address: 5 El-Khatib street, Dokki, Giza, 12311 Egypt.
Tel: 02 3353182. Mobile: 012 2176395
Abstract

**Purpose:** To evaluate the results of trans-pupillary diode laser thermotherapy and exo-cryotherapy combined with systemic chemotherapy for the treatment of retinoblastoma.

**Methods:** Thirty-seven children with retinoblastoma received 2 to 6 cycles of systemic chemotherapy. Fifteen eyes with small- to medium- sized tumors were treated with thermotherapy and 5 eyes had additional cryotherapy. Thermotherapy was delivered for posterior tumors. Each tumor was treated separately with a continuous mode diode laser using an indirect ophthalmoscope delivery system. Peripheral tumors were treated by exo-cryotherapy.

**Results:** Posterior tumors less than 10 disc diameter in size responded well to thermotherapy. From one to four laser sessions were needed to control tumors. Two eyes with peripheral diffuse tumors relapsed after initial control. 83.78% of patients were treated without external beam radiation.

**Conclusion:** Trans-pupillary thermotherapy and exo-cryotherapy is an effective technique to treat small- to medium- sized posteriorly located retinoblastoma in children, avoiding external beam irradiation in many cases. Early treatment and close follow-up is recommended for these eyes.
**Introduction**

The treatment of retinoblastoma now includes a wide range of different techniques that can achieve good tumor control when used either alone or in combination. The current objective is to avoid external beam radiation whenever possible by using focal ocular treatment as cryotherapy, plaque radiotherapy, photocoagulation, thermotherapy (laser hyperthermia) and chemothermotherapy. External beam radiation increases the risks of a second malignancy, particularly soft tissue sarcomas, within the treatment field and may cause ocular problems like cataract, dry eye and radiation retinopathy. It may also cause cosmetic problems due to growth defect and bone deformity in the lateral wall of the orbit. The aim of this study was to evaluate the results of transpupillary diode laser thermotherapy and exo-cryotherapy combined with systemic chemotherapy for the treatment of retinoblastoma.

**Patients and methods**

Patients with newly diagnosed retinoblastoma presented to us from November 2002 to October 2003 were subjected to complete ocular examination including fundus examination and B-scan ultrasonography and to orbit and brain examination using computerized tomography (CT) scan or magnetic resonance imaging (MRI). Retinoblastoma tumors were classified according to Reese-Ellsworth classification system into five groups. Upfront enucleation will be done only for eyes that are not potentially salvageable with functional vision especially in unilateral cases. Patients with evidence of extraocular tumors or systemic metastasis, tumor extension at the cut end of optic nerve, any prior chemotherapy or radiotherapy will be excluded from the study. Otherwise patients will be assigned to receive 2 to 6 cycles of systemic chemotherapy and sequential local
treatment according to the clinical response. All patients will be followed-up by regular fundus examination, B-scan ultrasonography and CT scans if needed to assess the response. Treatment failure was defined as tumor progression, the need for further chemotherapy apart from the protocol and/or enucleation.

**Systemic Chemotherapy guidelines:**

All patients will receive 2 to 6 cycles of chemotherapy in the form of: Carboplatin 18.7 mg/kg in day 1, Vincrestine 0.05 mg/kg in day 1, Etoposid 5 mg/kg in days 1 & 2. Cycles are repeated every 21 days. All patients must have adequate organ functions defined as absolute neutrophilic count more than 1000, hemoglobin more than 8, and platelets more than 100000, Adequate kidney function tests: serum creatinine less than 1.5 of the normal or creatinine clearance of 0.60 ml/min/1.73 SA. Adequate liver function tests: total bilirubin less than 1.5 the normal, ALT and AST less three times the normal. Patients must have a performance status of 0 or 1.

**Technique of thermotherapy:**

Trans-pupillary thermotherapy is delivered under general anesthesia with fully dilated pupils. The pupil was dilated using tropicamide 1%, Cyclopentolate 1% and phenylephrine 2.5% one hour prior to treatment.

A continuous mode diode laser (wavelength: 810 nanometer) mounted on an indirect ophthalmoscope delivery system is used for treatment. Laser thermotherapy (hyperthermia) is applied using a 20 diopter lens with a special coating for diode laser. Each tumor is treated separately in a single session. The laser intensity is adjusted to the size of the tumor and the clinical response and it varies from 300 milliwatts to 500 milliwatts. The end point of treatment is pale gray color change of the tumor. Laser thermotherapy is stopped when the tumor
is surrounded by retinal edema and/or hemorrhages appearing on the surface of the retina or in the choroid. Small and medium sized tumors (Small: up to 4 DD, medium: up to 10 DD) that are situated at or behind the equator are considered to be eligible to this technique. For larger tumors more than 10 DD, thermotherapy was applied after 2 cycles of chemoreduction and only when the tumor decreased in size. Thermotherapy was applied one or two days before the chemotherapy.

Noninclusion criteria for the technique are tumors larger than 10 DD not responding to chemoreduction or tumors associated with diffuse vitreous seeding, diffuse subretinal seeding, retinal detachment, and evidence of anterior chamber involvement, Rubeosis irides, Glaucoma, Cataract, and tumor involving optic disc.

**Technique of cryotherapy:** Trans-scleral cryotherapy was applied to peripheral tumors and the reaction was monitored by indirect ophthalmoscope. Freezing was stopped when the ice ball reaches the surface of the tumor.

**Follow-up:** follow-up fundus examination under general anesthesia was performed monthly for one year. When the child was more cooperative fundus examinations were performed without anesthesia. each tumor was assessed by indirect ophthalmoscope during examination. The main end points of the study were to assess local tumor control, describe relapses, and to assess the percentage of eyes not requiring enucleation or radiation.

**Regression of tumor:** the tumor was considered to have regressed when the scar was flat or contained a certain amount of calcification. Tumor persistence was defined as progression or no clinical change. Tumor relapse was defined by the appearance, during follow-up, of viable tumor on the previously regressed scar or localized or diffuse vitreous seeding facing the previously treated tumor.
Results

Thirty-Seven children were included in this study. There were 19 males and 18 females. The mean age at presentation was 16.35 months. Minimum age was 2 months and maximum age was 4 years. Twenty four patients (64.86%) had unilateral tumors, 15 eyes of these 24 eyes had large tumors occupying more than half the retina and accompanied with retinal detachment and vitreous seeding and were enucleated. Thirteen patients (35.14%) had bilateral tumors. 2 eyes of 26 eyes had large tumors and were enucleated.

The remaining Fifty-seven eyes of 37 patients were included in this study. The classification of tumors according to Reese-Ellsworth classification system at the start of the study and the details and results of treatment are shown in Table: 1.

Fifteen eyes were treated by thermotherapy. The number of laser sessions needed to control the tumors ranged from one to four laser sessions. Five eyes of these fifteen eyes had additional cryotherapy. Eight eyes regressed by flat scar (Figure: 1), five eyes regressed by calcified scar (Figure: 2), and 2 eyes regressed initially but still showing some activity and increased in size during follow-up.

Twenty-four eyes of 24 unilateral patients had no tumors at start of the study, one of these 24 patients had enucleation of one eye and the other eye was normal at the start of the study but developed a new equatorial tumor less than 4 Disc Diameter (DD) and was treated by thermotherapy and cryotherapy and regressed by flat scar and the eye could be saved.

Fourteen eyes of Thirty-three eyes with tumors were treated by thermotherapy. **Group 1:** Seven eyes had solitary tumor or multiple tumors less than 4 DD in size situated at or behind the equator were treated by thermotherapy. Two of them
had additional cryotherapy. Six of them regressed by flat scar and one regressed by calcified scar.

**Group 2:** Two eyes had solitary tumor or multiple tumors ranging in size from 4 to 10 DD situated at or behind the equator were treated by thermotherapy, one regressed by flat scar and the other regressed by calcified scar.

**Group 3:** Three eyes had tumors larger than 10 DD in size situated behind the equator and one of the tumors was extending anterior to equator. The tumors decreased in size after 2 cycles of chemotherapy and thermotherapy is started after the tumors decreased in size. One of these eyes had additional cryotherapy. Two tumors regressed by calcified scar and one tumor decreased in size initially and increased in size during follow-up and radiotherapy was performed for this eye.

**Group 4:** five eyes had multiple tumors with some of the tumors larger than 10 DD in size. The tumors were extending to the ora serrata in two eyes and localized vitreous seeding was present in one eye. After 2 cycles of chemotherapy, the tumors decreased in size in two eyes and thermotherapy was started in these 2 eyes and one eye had additional cryotherapy. The tumors in one eye regressed by calcified scar while in the other eye the tumors regressed initially but increased in size during follow-up and radiotherapy was performed for this eye. Three eyes in this group did not have any laser treatment because the tumors did not response well to chemotherapy. One eye was enucleated. The tumor increased in size in one eye and regressed but still active in one eye. Radiotherapy was performed in these 2 eyes.
Group 5: Sixteen eyes had tumors involving more than the half of the retina with vitreous seeding in twelve eyes. No laser treatment was attempt for these eyes. Eleven eyes of these eyes were enucleated.

Six patients of 37 patients were treated by additional external beam radiation (EBR). The indication of EBR was progression of tumor or residual activity after completion of 6 cycles of chemotherapy. 83.78% of patients (31 of 37 patients) were treated without EBR.

Retinal tumor control in the eyes treated by thermotherapy was achieved in 86.67% (13 eyes of 15 eyes). The overall enucleation rate during the study in was found to be 39.19% (29 eyes of 74 eyes of 37 patients). In unilateral cases the enucleation rate was 45.83% (22 eyes of 48 eyes of 24 patients). In bilateral cases the enucleation rate was 26.92% (7 eyes of 26 eyes of 13 patients).

Complications of thermotherapy: 2 eyes developed hemorrhages on the surface of the retina which resolved completely. On eye developed choroidal hemorrhage which was stopped by compression on the globe for one minute. One eye had patch of iris atrophy. 3 eyes had chorioretinal scar encroaching on the macular area.

Discussion

This study shows that diode laser thermotherapy combined with chemoreduction achieves good retinal tumor control in selected cases of retinoblastoma. Tumor regression was obtained in 86.67% of treated eyes. Retinoblastoma patients with Reese-Ellsworth eye groups 1, 2, and 3 responded well to thermotherapy. Tumor relapsed in 13.33% of treated eyes with tumors reaching ora serrata at the start of therapy. In unilateral cases, enucleation was the main treatment line (45.83% of eyes) because the tumors were large in the majority of cases with no visual
potential. In bilateral cases more conservative treatment is considered and enucleation was performed only in 26.92% of eyes and bilateral enucleation was not performed in any case. Shields et al in 1997 showed that chemoreduction should be reserved for eyes with visual potential in which decreasing tumor size could allow use of a more conservative method of treatment. Those eyes with large retinoblastoma and no sign of vitreous or subretinal seeds and no subretinal fluid might benefit from chemoreduction plus adjuvant treatment to the regressed retinal tumor. They recommended at least 6 cycles of chemoreduction and adjuvant treatment to the retinal tumors and seeds in eyes with advanced disease, showing vitreous seeds, subretinal seeds, or subretinal fluid. In addition, those eyes with advanced disease with no hope for useful vision probably would benefit from enucleation.

Hamel et al treated 46 eyes of 35 patients affected with retinoblastoma. In their study small tumors less than 4 DD were successfully treated in 3 fewer sessions of 532-nm laser. Anterior small tumors were successfully treated with trans-scleral 810-nm laser or cryotherapy. Medium tumors, between 2.0 to 4.0 mm in thickness, required 2 to 9 treatments to achieve a good response and often required the addition of chemotherapy to reduce the size of the tumor before or during laser treatment. Large tumors required chemotherapy combined with many laser treatments for complete control. Complications of focal therapy can most often be avoided by using minimal effective laser power. Friedman et al treated 75 eyes of 47 children with retinoblastoma. Patients were treated with a six-cycle protocol of vincristine, etoposide, and carboplatin. Most (83%) also received ophthalmic treatment (cryotherapy, laser photocoagulation, thermotherapy, or plaque radiation therapy) during and/or after the chemotherapy.
They found that treatment of eyes with Reese-Ellsworth groups 1, 2, and 3 had excellent results with avoidance of EBR or enucleation in all 39 eyes. Treatment of groups 4 and 5 was less successful, with 33% of six eyes and 53% of 30 eyes, respectively, requiring EBR and/or enucleation. They\textsuperscript{5} concluded that more effective therapy is required for Reese-Ellsworth eye groups 4 and 5.

Lumbroso and coworkers\textsuperscript{6} treated 103 retinoblastoma tumors in 65 eyes of 51 children by chemothermotherapy. In these cases transpupillary thermotherapy was delivered shortly after intravenous injection of carboplatin. Tumor regression was obtained for 99 tumors (96.1%). Seven tumors relapsed after initial control (6.8%). Salvage treatment (EBR, iodine plaques, or enucleation) was necessary for a total of 11 tumors (10.7%). The only risk factor for relapse was the initial diameter of the lesion greater than 3.5%. Ninety-seven percent of treated eyes were able to be preserved, and 92% of cases were treated without EBR\textsuperscript{6}.

Shields el al\textsuperscript{7} concluded that tumor shrinkage with chemoreduction may allow treatment with less invasive measures, such as cryotherapy, laser photocoagulation, thermotherapy, or plaque radiotherapy, thereby avoiding enucleation and EBR. In a study by Levy et al\textsuperscript{8} EBR was avoided for 14 of the 17 eyes treated by thermochemotherapy\textsuperscript{8}.

Murfee et al\textsuperscript{9} showed that thermochemotherapy is successful primary treatment for Reese-Ellsworth group 1 and 2 retinoblastoma. For larger tumors in the absence of vitreous or subretinal seeding, 3 cycles of chemoreduction followed by local therapy eradicates residual viable tumor. Chemoreduction plus local therapy was not successful in eyes with diffuse vitreous or subretinal seeding\textsuperscript{9}.
References


**Legend for illustrations:**

Figure 1: Flat scar after treatment of retinoblastoma by thermotherapy.

Figure 2: Retinoblastoma tumor regressed by calcified scar.