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# Evaluation of efficacy of indocyanine green enhanced transpupillary thermotherapy as a single treatment for recurrence of intraocular retinoblastoma

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## ABSTRACT

**Aim of the study:** Evaluation of efficacy of indocyanine green enhanced transpupillary thermotherapy (ICG-TTT) as a single treatment for recurrence of retinoblastoma.

**Material and methods:** Single-center, retrospective study of 18 procedures in 11 eyes of 11 retinoblastoma patients (12 tumors), with a mean follow-up of 31.94 months (range 1-44 months). Nine tumors had one procedure of ICG-TTT and 3 tumors had more than one procedure due to relapses. The technique involved applying thermotherapy (TTT) via an indirect ophthalmoscope 30 seconds after intravenous indocyanine administration at a dose of 0.6 mg/kg.

**Results:** During follow-up, tumor recurrence after ICG-TTT developed after 11 procedures. Taking into account cases where ICG-TTT was the only treatment for retinoblastoma relapse, the success rate was 26.7% (4 effective procedures out of 15). Overall, tumor control and globe salvage was achieved in all eyes with ICG-TTT alone or with other forms of therapy, e.g. systemic chemotherapy, ophthalmic artery chemosurgery, brachytherapy.

**Conclusions:** ICG-TTT as the only procedure for relapses of retinoblastoma has a moderate success rate. No ocular or systemic complications were noted.

**KEY WORDS:** retinoblastoma, indocyanine, treatment, thermotherapy, laser.

## INTRODUCTION

Focal treatments for retinoblastoma make an effective destruction of the tumor possible without causing serious, life-threatening, systemic side effects. Serious side effects may be generated by administering more complex methods of treatment such as systemic chemotherapy, external beam radiation and even selective intra-arterial chemotherapy [1]. The relatively small size of a tumor is the most important condition for effectiveness of any simple form of local therapy.

Laser transpupillary thermotherapy (TTT) has been used to treat intraocular tumors for about 30 years [2]. With this method, it is possible to successfully treat retinoblastoma tumors of a diameter of up to about 1.5 DD (DD – disc diameter) [3]. The target tissue for the energy associated with the infrared radiation of the diode laser is the retinal pigment epithelium, on which thermal energy is released, causing destruction to the adjacent tumor tissues. Thermal energy is delivered in a controlled manner to induce tissue hyperthermia, not coagulation. The tumor tissue is heated to a temperature of about 45-60°C, which causes necrosis of cancer cells and occlusion of blood vessels [4, 5]. Intravenous administration of indocyanine green (ICG) as a photosensitizer, with an energy absorption peak for electromagnetic wavelength of 805 nm, similar to the wavelength of a diode laser (810 nm), enhances the effect of laser thermotherapy, enabling treatment of larger tumors or tumors located on calcifications and areas of choroidal atrophy – with no contact with the retinal pigment epithelium [6]. Indocyanine green enhanced transpupillary thermotherapy (ICG-TTT) in the treatment of retinoblastoma has been performed in the world for more than 10 years [2, 3, 7, 8]. Previously, ICG-TTT was used in ophthalmology to treat choroidal melanoma and metastasis of breast cancer to the choroid [9, 10]. To our best knowledge, in Poland the aforementioned method was used for the first time – with

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regard to retinoblastoma treatment – in the Department of Ophthalmology of the Children's Memorial Health Institute in Warsaw.

## AIM OF THE STUDY

The aim of the study is to evaluate the efficacy of indocyanine green enhanced transpupillary thermotherapy as a single treatment for recurrence of intraocular retinoblastoma.

## MATERIAL AND METHODS

The single-center, retrospective analysis included 18 ICG-TTT procedures performed in the years 2016-2018. Informed consent was obtained from the parents of the children before the procedure. Analyzed data included patients' age, sex, race, tumor laterality (unilateral or bilateral), classification using the International Classification of Retinoblastoma (ICRB) (Table I), previous and following treatments, tumor location and diameter, complications, dates of diagnosis, therapy, recurrence and last visit.

In the years 2016-2018, 18 ICG-TTT procedures were performed in 11 patients in 11 eyes on 12 tumors (two independent tumors were treated in one eye). The total number of 18 procedures consisted of: 9 tumors with 1 treatment, 1 tumor with 2 treatments (two separate relapses of this tumor), 1 tumor with 3 treatments (three separate relapses of this tumor), and 1 tumor with 4 treatments (four separate relapses of this tumor).

**Table I.** International classification of retinoblastoma [12]

| Group | Quick reference | Specific features |
|---|---|---|
| A | Small tumor | Retinoblastoma ≤ 3 mm in size* |
| B | Larger tumor<br>Macula<br>Juxtapapillary<br>Subretinal fluid | Retinoblastoma > 3 mm in size* or<br>Macular retinoblastoma location (≤ 3 mm to foveola)<br>Juxtapapillary retinoblastoma location (≤ 1.5 mm to disc)<br>Clear subretinal fluid ≤ 3 mm from margin |
| C | Focal seeds | Retinoblastoma with<br>Subretinal seeds ≤ 3 mm from retinoblastoma<br>Vitreous seeds ≤ 3 mm from retinoblastoma<br>Both subretinal and vitreous seeds ≤ 3 mm from retinoblastoma |
| D | Diffuse seeds | Retinoblastoma with<br>Subretinal seeds > 3 mm from retinoblastoma<br>Vitreous seeds > 3 mm from retinoblastoma<br>Both subretinal and vitreous seeds > 3 mm from retinoblastoma |
| E | Extensive retinoblastoma | Extensive retinoblastoma occupying > 50% globe or<br>Neovascular glaucoma<br>Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space<br>Invasion of postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber |

** Refers to 3 mm in basal dimension or thickness*

The study group consisted of 7 boys and 4 girls. The mean age of children at the time of ICG-TTT was: 24.72 months (median 21.5; range 8-50). Bilateral retinoblastoma was diagnosed in 7 patients, and unilateral in 4 patients. All patients were Caucasian. At the time of diagnosis of retinoblastoma, one eye was classified as ICRB Group A, five eyes – Group B, one eye – Group C, three eyes – Group D and one eye – Group E. The indication for 16 (out of all 18) procedures was an active tumor – recurrence after treatment with systemic (VEC – vincristine, etoposide, carboplatin) or intra-arterial (OAC – ophthalmic artery chemosurgery) chemotherapy or after local therapy including ICG-TTT (Figure 1). In the remaining 2 cases, ICG-TTT was a consolidation treatment for OAC or VEC. In most cases, tumors qualified for ICG-TTT were located on a white scar or on a calcification. In only 2 cases, the procedure was performed on tumors located directly on the retina (these tumors were relatively large: 4 DD and 2.5 DD).

Procedures were performed by two experienced ophthalmologists. Children underwent ophthalmologic examination under general anesthesia. During that examination both qualification for ICG-TTT and the treatment took place. The patient had pupils dilated prior to the procedure. ICG-TTT was performed during scheduled examinations and delivered via an Iridex Oculight SLx device coupled with an indirect binocular ophthalmoscope (diode laser emitting an electromagnetic wave in the infrared range of 810 nm). The laser beam was focused with the Volk Pan Retinal 2.2 lens. Indocyanine green (ICG Pulsion, Medical Systems) was administered intravenously as a photosensitizer, at a dose of 0.6 mg/kg. Laser thermotherapy was initiated about 30 seconds after ICG administration. ICG-TTT was performed by focusing the laser beam directly on the tumor. The power of the device was increased gradually from 300 mW to 1000 mW if needed, to achieve a desired effect of slow gray-white discoloration of the tumor tissues. The first follow-up visit was planned 4 weeks after ICG-TTT and subsequent examinations were scheduled every 4-12 weeks. The mean estimated tumor diameter before surgery was 1.69 DD (median 1.25; range 0.5-6).

The mean follow-up time of all patients (from ICG-TTT to last visit) was 31.94 months (median 35; range 1-44). Only one patient had a very short follow-up time of no more than 2 months. In this patient on the examination 3 weeks after ICG-TTT we noted lack of sufficient response to treatment. Then this patient received OAC with a good response but after OAC he left for another country to continue therapy. All other patients had follow-up time of more than 21 months.

## RESULTS

Out of 18 procedures, 7 were effective (Figure 1) and 11 were ineffective. A procedure was considered effective with no recurrence of activity of the tumor after ICG-TTT throughout the entire observation period. Of the 11 ineffective procedures, lack of sufficient response to ICG-TTT was noted in 5 cases (evidence of tumor activity on next examination), and in 6 cases recurrences were noted later. Recurrences were noted on average 5.17 months after ICG-TTT (median 4.5; range 2-11). Out of 7 successful treatments, in 1 case, two more local consolidation treatments for this tumor were performed with TTT (without ICG), and 2 other eyes received chemotherapy (VEC or OAC) as a continuation of the planned treatment. If the above 3 procedures are excluded, the efficacy of a single procedure of ICG-TTT as the only form of therapy for tumor recurrence is 4 effective procedures out of 15 (26.7%). Characteristics of tumors before ICG-TTT in relation to treatment outcome are shown in Table II.

In the entire analyzed group of patients, no complications after the ICG-TTT procedure were noted. The normal reaction of the tumor consisting of small hemorrhages, pallor and edema was not counted as a complication. There were no lens opacities or cases of laser-induced iris atrophy. In the analyzed group, no eye treated with ICG-TTT was removed.

## DISCUSSION

Transpupillary thermotherapy is an established form of focal treatment of retinoblastoma. Its efficacy reaches 85% in the treatment of tumors smaller than 3-4 mm in diameter [4]. The effectiveness of the procedure considerably decreases when the tumor is located beyond the retinal pigment epithelium (calcification, choroidal atrophy, tumor diameter larger than 4 mm). The use of a photosensitizing substance – indocyanine green – makes it possible to bypass this problem. ICG molecules are relatively large and 98% are bound to blood albumins [6]. As a result, they do not diffuse rapidly from the blood vessels into the surrounding tissues. If the tumor has rich capillary vascularization, the laser energy, acting on ICG in the tumor's blood vessels, should allow for uniform tumor hyperthermia, regardless of the presence of melanin. Indocyanine green is safe, relatively inexpensive and commonly used in the diagnostics of eye diseases [6].

It is worth noting that most of the ICG-TTT treatments described in our article were used as the only treatment for tumor recurrence (15 out of 18 procedures). In the literature to date, most of the described ICG-TTT procedures were performed as adjuvant or consolidation treatments after or during OAC or VEC [2, 3, 7].

**Table II.** Characteristics of tumors before ICG-TTT in relation to treatment outcome. The table presents 15 procedures that were the only form of therapy for active tumor (effective treatments shaded green)

| Patients' initials | Date of ICG-TTT | No relapses after ICG-TTT | Tumor diameter before ICG-TTT [DD] | Location on calcification | Location on white scar | No vessels in tumor |
|---|---|---|---|---|---|---|
| KA | 10.07.2018 | | 1 | | + | + |
| KA | 09.08.2018 | | 1.5 | | + | |
| KA | 18.12.2018 | + | 1 | | + | |
| LD | 30.03.2017 | | 1 | | + | + |
| LD | 07.11.2017 | | 1 | | + | |
| LD | 24.04.2018 | | 1 | | + | |
| LD | 18.12.2018 | | 2 | | + | |
| MM | 21.06.2016 | | 1.5 | | + | |
| MM | 09.08.2016 | | 0.5 | | + | |
| StA | 27.03.2018 | + | 0.5 | | + | + |
| SzA Tumor 1 | 19.12.2017 | + | 1.5 | + | | + |
| SzA Tumor 2 | 16.01.2018 | + | 4 | | | |
| WK | 25.10.2016 | | 6 | + | | |
| ZF | 04.07.2017 | | 2 | + | | |
| RA | 14.11.2017 | | 1 | + | | |

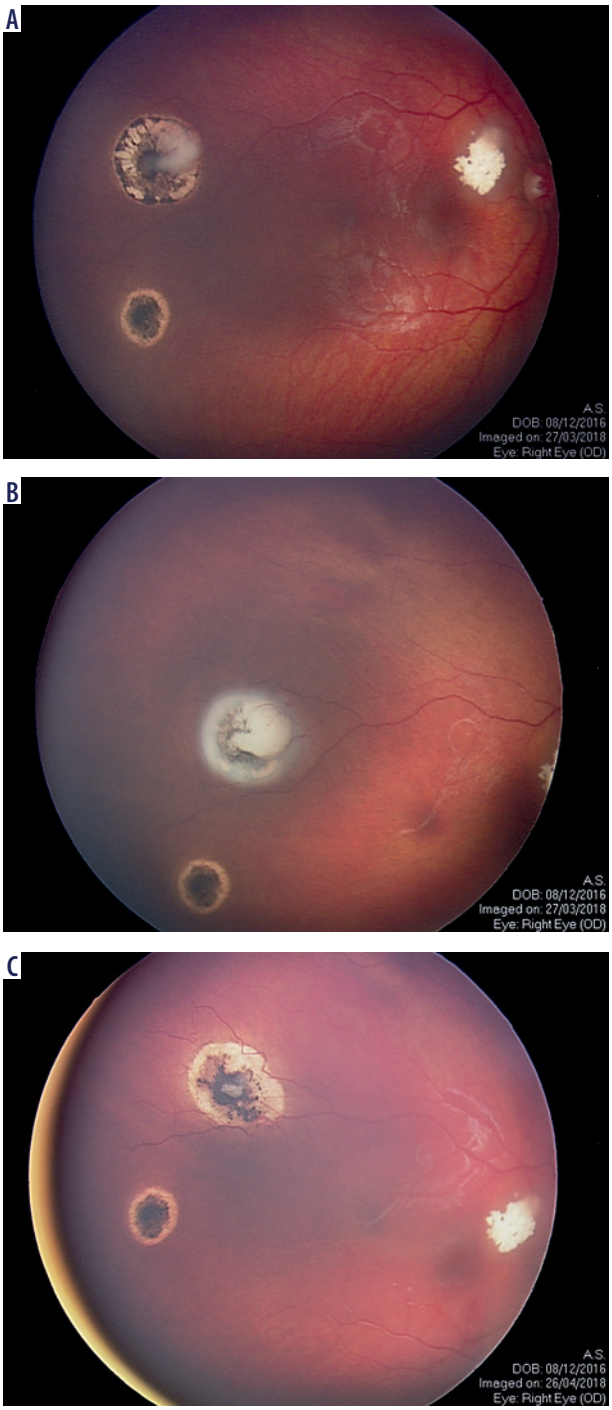


**Figure 1.** Patient StA. Tumor before and after ICG-TTT: A) active tumor on white scar just before ICG-TTT; B) the tumor minutes after ICG-TTT; C) the tumor 3 months after ICG-TTT

Tumor recurrence, after systemic treatment, seems to be an ideal indication for local forms of therapy, because it is usually a single, relatively small tumor. A particular indication for the use of ICG-TTT may be a recurrence on calcification or on choroidal atrophy. In our study, we found relatively low effectiveness of ICG-TTT as the only form of therapy in the treatment of retinoblastoma recurrences – 4 successful procedures out of 15 (26.7%). The reason may be that the tumors that we qualified for the ICG-TTT procedure were "difficult": located on a white scar or relatively large or located on a calcification. It should be emphasized that in 6 cases it was a subsequent relapse of a given tumor.

The most common indication for ICG-TTT in our study was a recurrence on a white scar (choroidal atrophy). The low effectiveness of the procedure in these cases may be caused by a lack of or very poor vascularization of the tumors located on the white scar and hence the poor inflow of ICG to the tumor. Most focal treatments performed on choroidal atrophy, except brachytherapy, seem to have low effectiveness. We analyzed the efficacy of a single procedure of ICG-TTT on an active relapse. It is probable that a series of 2 or 3 procedures of ICG-TTT would give better results (one ICG-TTT on the active tumor, followed by two or three consolidation ICG-TTT of the same already non-active tumor). Such treatment regimens may be more effective than a single treatment, by analogy to the commonly used 6 VEC or 3 OAC cycles. In the analyzed group such a treatment regimen was not followed; another type of adjuvant therapy was chosen due to the lack of blood vessels in the tumor. In one patient the procedure was effective despite the lack of visible blood vessels in the tumor and simultaneously lack of pigment (white scar). A very good effect was achieved in cases where ICG-TTT was a part of more complex therapy (with OAC or VEC or other focal treatments). In these patients, all 3 procedures were successful. Another reason for the relatively low effectiveness of ICG-TTT in our study may be the low melanin concentration in retinal pigment epithelium of the eyes of Caucasian patients. After TTT or especially ICG-TTT an avascular white scar remains on the sclera. It certainly to some extent hinders the penetration of the tumor by chemotherapeutic agents in the course of VEC or OAC. Therefore, use of ICG-TTT consolidation should be considered after completion of the above-mentioned therapies. It should be remembered that after intravenous administration of indocyanine green, there is a false reading of the pulse oximeter, indicating desaturation. This is due to the ICG absorption of the infrared radiation sent and measured by the pulse oximeter [11].

## CONCLUSIONS

In the case of treatment of recurrent retinoblastoma, in our group of patients, the efficacy of a single procedure of ICG-TTT as the only form of therapy was 26.7%.

ICG-TTT seems to be a relatively safe procedure, without serious local or systemic side effects.

Higher effectiveness of ICG-TTT is noted when it is combined with other procedures

## DISCLOSURE

The authors declare no conflict of interest.

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