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Transpupillary thermotherapy (TTT) by infrared irradiation of choroidal melanoma

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Abstract. We studied the destructive effect of hyperthermia at sub-photocoagulation level of 45–60 °C on melanomas. Optimal conditions for spreading of heat into tissue are a wavelength of 700–900 nm, a temperature of 45–60 °C, an exposure time of 1 minute or more, and a beam diameter of several millimeters. In hamsters with subcutaneous melanomas we obtained a tumour necrosis of 6 mm depth at 60 °C and one minute exposure time. We performed transpupillary thermotherapy (TTT) with a diode laser at 810 nm in patients with choroidal melanomas prior to enucleation. Treatment is based on the fortunate situation that irradiation at this wavelength combines optimal tissue penetration with a low absorption by clear ocular media of 5% or less. In 3 TTT-treated eyes histopathology showed a depth of necrosis of 0.9, 3.4, and 3.9 mm. TTT may become a new useful treatment modality for choroidal melanoma but its ultimate value has yet to be assessed.

Introduction

Conservative treatment modalities for choroidal melanoma currently in use include local excision, irradiation with charged particles or brachytherapy with Ru^{106} or I^{125} [1]. Irradiation treatment meets with failures and complications such as radiation retinopathy. To enhance its effect it has been combined with low range hyperthermia at 42–44 °C which in itself has no direct cell killing effect [2, 3].

In order to obtain a direct cell-destructive effect of hyperthermia it is imperative to use temperatures between 45 and 60 °C, which we coined intermediate range hyperthermia. At temperatures higher than 60 °C, high range hyperthermia, a white coagulation effect develops which reduces uptake of radiation [4, 5].

Penetration depth of radiation-induced hyperthermia can be optimized by selecting appropriate parameters: a tumour temperature of 45–60 °C, an exposure time of one minute or more, a beam diameter of several

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millimeters, and a wavelength between 700 and 900 nm [5]. Several studies have demonstrated a remarkable necrosis depth in non-ocular tissue after treatment by near infrared irradiation [6–11].

We investigated the depth of necrosis in relation to different exposure times and temperatures in the intermediate hyperthermia range in animal experiments and in human choroidal melanoma.

Animal experiments

Experiments were performed in Syrian Golden hamsters bearing pigmented melanomas measuring 7–12 mm in diameter. As light source we used a xenon photocoagulator provided with a red filter which permits transmission of 85% between 780 and 880 nm. Beam diameter was 4.5 mm, tumour temperatures were 45, 50, 55 and 60 °C, exposure times were 1.0, 2.5, 5.0 and 10.0 minutes.

Histopathology of the tumours, removed one day after hyperthermia, showed distinct cell necrosis. There was a sharp demarcation between the necrotic and the viable part of the tumour.

Depth of necrosis depended on both tumour temperature and exposure time (Fig. 1). Tumour necrosis was already observed at a temperature of 45 °C; at 60 °C 6 mm depth of necrosis was obtained after only 1 minute exposure [12].

The results of the hamster experiments induced us to start transpupillary thermotherapy (TTT) in human eyes containing choroidal melanomas. Heat propagation by transpupillary route at wavelengths of 700 – 900 nm may be a new useful technique for treating intraocular tumours. This is based on the fortunate situation that irradiation at these wavelengths combines an

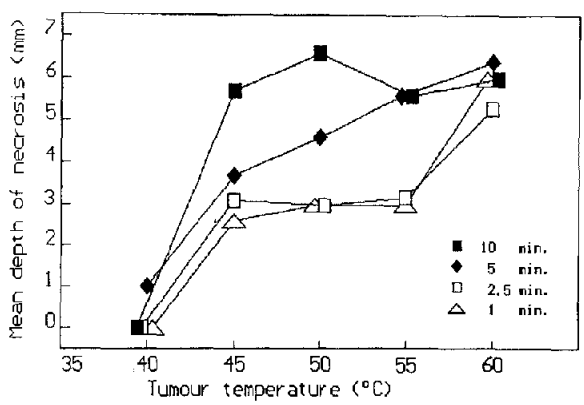

Fig. 1. Necrosis depth plotted as a function of temperature at exposure times of 1.0, 2.5, 5.0 and 10.0 min. Note the necrosis depth of 6 mm after hyperthermia at 60 °C for 1 min. (Courtesy Lasers & Light in Ophthalmology).

optimal tissue penetration with a low absorption of 5% or less by clear ocular media [13].

Clinical investigation

Material and method

Transpupillary thermotheraphy (TTT) was performed in 7 patients with choroidal melanomas prior to enucleation. Our aim was to study the effect of irradiation and not to destroy the tumour totally. Permission for the investigation was given by the Medical Ethical Committee of the Leiden University Hospital and informed consent was obtained from each patient after full explanation of the procedure. As irradiation source for the first 4 patients we used the Zeiss Oberkochen xenon photocoagulator modified for thermotherapy [14]; for the subsequent 3 patients we used a diode laser at 810 nm.* We started TTT at a relatively low level of irradiance of $3W/cm^2$ with a beam diameter of 3.5–4.5 mm and an exposure time of 1 minute. At this subthreshold level we did not see any effect on ophthalmoscopic control. On stepwise increase of the level of irradiance a greyish discoloration developed which finally became more or less white. The maximum irradiance used was $19W/cm^2$ for the xenon photocoagulator provided with a red filter and $9W/cm^2$ for the diode laser.

The interval between TTT and enucleation was one day in the first 4 patients, two days in 2 patients, and three days in 1 patient. After enucleation the eyes were fixated in buffered formaldehyde 4.0%, dehydrated and embedded in celloidin. Serial sections of 17 μm (Jung microtome, Heidelberg, Germany) were cut in a plane parallel to the light beam. Haematoxillin/eosin-stained and some depigmented ($KMnO_4$) sections were examined by light microscopy. The depth of tumour necrosis was measured with an ocular grid.

Results

The effect of TTT was evaluated by histopathologic examination of the eye after enucleation. The results in the first 4 patients treated with the red-filtered light of the xenon arc photocoagulator were rather disappointing. In one patient technical failures in the histopathological workup interfered with proper evaluation. None of the 3 other tumours showed distinct necrosis of melanoma cells. The only remarkable findings were slight swelling of the cytoplasm of the tumour cells and irregularities in the tissue near the tumour

* The diode laser was kindly provided by Nidek Ltd., Tokyo, Japan.

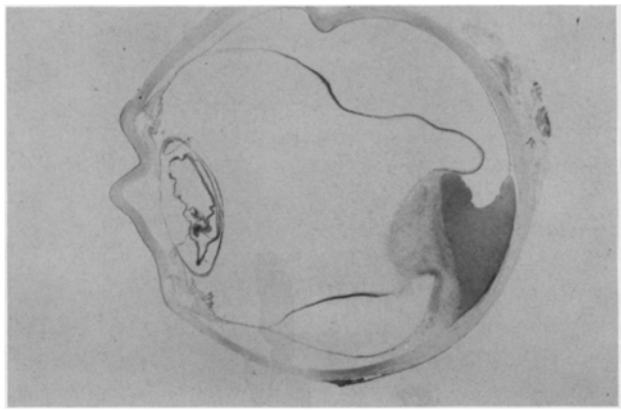

Fig. 2. Histopathological examination of a human choroidal melanoma after TTT shows a depth of necrosis of 3.4 mm.

surface in the area of irradiation, and slight hyperaemia. Damage to the retina and pigment epithelium was as found in non-treated uveal melanoma.

Three patients were treated with the diode laser at 810 nm. One patient treated with an irradiance up to $7W/cm^2$, radiant exposure $1020\,J/cm^2$, showed only a slight greyish discoloration of the tumour surface with a depth of necrosis of 0.9 mm. In the second and third patient treated by an irradiance up to $9W/cm^2$, radiant exposure $3620\,J/cm^2$, and irradiance $4W/cm^2$, radiant exposure $4203\,J/cm^2$, a whitish spot was found on ophthalmoscopy. Histological examination showed a tumour necrosis to a depth of 3.4 and 3.9 mm, respectively (Figs. 2, 3). The sclera had a normal aspect where it bordered on the necrotic part of the tumour. In the area of necrosis many blood vessels were occluded or even destroyed.

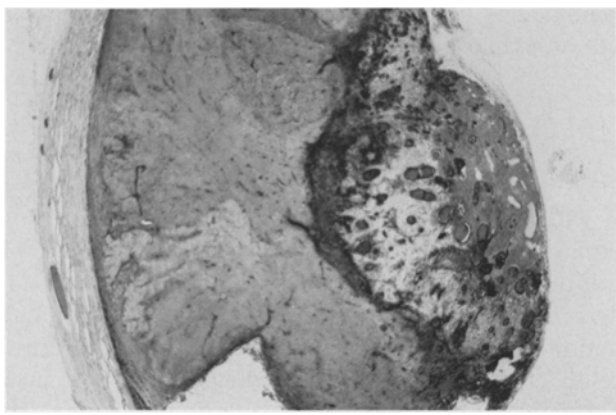

Fig. 3. Histopathological examination of a human choroidal melanoma after TTT shows a depth of necrosis of 3.9 mm.

In all patients subretinal fluid increased somewhat after hyperthermia. In one patient the peripupillary iris in one quadrant was for some time caught in the irradiation beam, which resulted in a slight iritis that regressed in two days and a localised cortical cataract along the pupillary margin in the affected area. Microscopy showed a necrotic zone of the iris near the pupillary margin, swollen lens epithelial cells, and local disruption of lens fibres.

Discussion

TTT is, as far as we know, a new technique for intraocular tumour destruction.

In 3 eyes treated with the diode laser we obtained a hyperthermia-induced necrosis of choroidal melanoma with depths of 0.9, 3.4, and 3.9 mm. In 4 patients we used the Zeiss photocoagulator provided with a red filter [14]. The radiant exposure which was effective in producing necrosis in hamster melanomas, was hardly effective in human choroidal melanomas. The absence of an evident necrosis may be related to the period of only one day between TTT and enucleation. When melanoma-bearing hamsters were sacrificed the day after hyperthermia, histopathology showed distinct cell necrosis. Hamster Greene melanoma is a fast growing tumour of high metabolic activity since a piece of implanted tumour tissue of about 1 mm^3 develops into a tumour of 1 cm^3 in about 10 days. Comparable growth in human choroidal melanoma may require many months or more. We assume that hyperthermia-induced necrosis develops more slowly in the choroidal melanoma than in hamster Greene melanoma. Laser-induced liver necrosis starting by the second day has been found to have its maximal dimension on the 7th day after hyperthermia [11]. Therefore, we extended the period between hyperthermia and enucleation to 2 or 3 days.

Histopathology of the effectively treated eyes showed a rather sharp demarcation between the necrotic and the viable part of the tumour, as also observed in our animal experiments [12].

Occasionally viable tumour cells were found around patent blood vessels in the necrotic part of the tumour near the demarcation zone as also seen in photodynamic therapy [15]. The cooling effect of blood circulation, which is the main way of heat drainage in hyperthermia, may have saved the cells from necrosis [6].

Diode laser TTT differs from laser photocoagulation both in technique and in pathophysiology. Argon and krypton laser therapy are performed at wavelengths in the spectrum of visible light with an exposure time of tenths of seconds and a small beam of up to 500 μ, prerequisites for obtaining a short time rise in tumour temperature with little tendency to spread beyond the treated area, resulting in a depth of necrosis of less than 1 mm [4, 5]. Foulds and Damato extended the exposure time to 10–30 sec [16]. In TTT

the conditions are optimal for penetration of heat into tissue: infrared wavelength at 810 nm, long exposure time of one minute or more, and a large beam diameter of 3–4.5 mm, resulting in a depth of necrosis of several millimeters.

Both modalities also differ in pathophysiology. In photocoagulation treatment the rise in temperature above 65 °C causes a direct necrosis due to coagulation. In TTT at subcoagulation temperatures cell necrosis takes one to several days and is mainly brought about by mitochondrial breakdown [17].

Transpupillary thermotherapy (TTT) has several advantages. The technique is not complicated, it does not require surgery, it can be repeated, and it does not affect the healthy structures of the eye.

The number of experiments is rather limited. For evaluation of TTT as modality for conservative treatment of intraocular tumours we have to extend our experience.

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