Histopathological findings in human choroidal melanomas after transpupillary thermotherapy

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Abstract

Aims—The effect of transpupillary thermotherapy (TTT) on human choroidal melanomas was investigated by means of histopathology.

Methods—Before enucleation TTT was performed in 11 eyes with a xenon arc photocooagulator with a red filter or a diode laser at 810 nm. The exposure time was 1 minute; the estimated temperature at the top of the tumour was about 65°C. Results—Seven of 11 tumours developed necrosis to a maximum depth of 3.9 mm with a sharp demarcation between the necrotic and the viable part of the tumour. The depth correlated with penetration of heat into the tumour. Scattered small haemorrhages in the transitional zone between necrotic and viable tumours were observed in three eyes but large haemorrhages were absent. Ocular media were not affected owing to the low rate of absorption of radiation at 810 nm. TTT did not cause significant scleral damage. Intracranial tumour cells with a viable appearance were observed in one eye, where the tumour was almost totally necrotic.

Conclusion—Results show that TTT has potential as a conservative therapeutic treatment for choroidal melanomas.

Hyperthermia at a tumour temperature of 45°C or more can be designated as thermotherapy since after application for 1 minute it exerts an irreversible destructive effect on cells for which it does not require additional radiotherapy or cytostatic drug therapy. The application of thermotherapy at more than 45°C in clinical oncology is restricted since it affects both malignant and normal cells. In ophthalmology, however, thermotherapy by means of transpupillary infrared radiation can be used to treat choroidal melanomas because the rate of absorption at 810 nm is low for clear ocular media.

This paper deals with the histopathological findings in human choroidal melanomas enucleated after transpupillary thermotherapy.

Material and methods

Eleven patients with large choroidal melanomas underwent transpupillary thermotherapy (TTT) by infrared irradiation before enucleation. We did not aim for total destruction of the tumour. Permission for the investigation was given by the medical ethics committee of Leiden University Medical Centre and informed consent was obtained from each patient after full explanation of the procedure. Before treatment the pupil was dilated with phenylephrine hydrochloride 5% and tropicamide 0.25% eyedrops. Immobilisation of the eye and anaesthesia to make the treatment painless were achieved with a retrobulbar injection of 2 ml prilocaine hydrochloride 2% (Citanest).

TTT was performed in four patients with a modified xenon photocoagulator (Zeiss, Oberkochen, Germany) with a red filter permitting 85% transmission between 780 and 880 nm. In seven patients we used a continuous wave diode laser (Nidek, Tokyo, Japan) which produced radiation at 810 nm via a handheld fibre in front of the eye. Both methods yield a beam diameter on the surface of the tumour of 2–4.5 mm. For the laser lens we used the panfunduscope (Rodenstock, Munich, Germany) or the Mainster lens (Mainster, Ocular Instruments, Bellevue, WA, USA). Because of variations in beam diameter the energy output was calculated in W/cm² on the target area. We started the irradiation at the relatively low level of 3 W/cm² and an exposure time of 1 minute. In the absence of an ophthalmoscopic effect we increased the energy level stepwise until the tumour exhibited a greyish
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*Minimale (TTT) before enucleation

Table 1 Heat induced tumour necrosis in patients with choroidal melanoma treated with transpupillary thermotherapy (TTT)

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Height (mm)</th>
<th>Width (mm)</th>
<th>Equipment</th>
<th>Beam ø (mm)</th>
<th>Irradiance (W/cm²)</th>
<th>Radiant exposure (J/cm²)</th>
<th>Enucleation after TTT (hours)</th>
<th>Depth of necrosis (mm)</th>
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<tr>
<td>1</td>
<td>9</td>
<td>15</td>
<td>Xenon</td>
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<td>4-10</td>
<td>7 300</td>
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<td>10</td>
<td>13 +/-</td>
<td>Xenon</td>
<td>2.4</td>
<td>2-19</td>
<td>11 000</td>
<td>24</td>
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<td>Xenon</td>
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<tr>
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<td>6</td>
<td>12 +/-</td>
<td>Xenon</td>
<td>2.5</td>
<td>7-10</td>
<td>11 000</td>
<td>48</td>
<td>1.5</td>
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<tr>
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<td>13 +/-</td>
<td>Diode</td>
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<td>2-13</td>
<td>4 200</td>
<td>48</td>
<td>3.9</td>
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<td>5.3</td>
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<td>7-12</td>
<td>6 200</td>
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<tr>
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<td>9-11.5</td>
<td>3 150</td>
<td>240</td>
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*Minimal effect.
Figure 1  (A) Patient 7. Depigmented haematoxylin and eosin stained section showing transpupillary thermotherapy induced necrosis (N) in a choroidal melanoma with a depth of 3.4 mm, sharply demarcated from the viable part (V) of the tumour without haemorrhages. Retinal necrosis and atrophy correspond with the area of necrosis of the tumour. (B) Haematoxylin and eosin stained section of the same eye as shown in (A) at higher magnification. Sharp demarcation between necrotic (N) and viable (V) parts of the melanoma without haemorrhages.

Figure 2  (A) Patient 5. Transpupillary thermotherapy induced necrosis (N) with a depth of 3.9 mm in a choroidal melanoma sharply demarcated from the viable part (V) of the tumour. Different histological features of cell damage in the superficial and deeper layers of the necrotic zone. All tumour vessels in this area are dilated and occluded by thrombi. Scattered small haemorrhages are present in the transitional zone between the necrotic and the viable part of the tumour (asterisks). Retinal necrosis is seen in the target area. (B) Detail of (A). Blood vessels in the most superficial layer contain red blood cell ghosts (arrow). (C) Detail of (A). The transition area (T) between necrotic (N) and viable (V) parts of the tumour contains scattered haemorrhages (arrows) and tumour cells with dense pyknotic nuclei (asterisks). (D) Histological section of a different part of the tumour as shown in (A). Large dilated blood vessel crossing the area of necrosis became thrombotic but did not bleed. (V) viable part, (N) necrotic part of the tumour, (bv) blood vessel.
Figure 3 Patients. Sharp lateral demarcation of transpupillary thermotherapy induced effect in a melanoma (arrowhead), and in retinal (arrows) and subretinal exudate (asterisks).

Figure 4 (A) Patient 11. Transpupillary thermotherapy induced tumour necrosis with a depth of 2 mm. Different histological features of cell damage in the superficial layers of the tumour. Haemorrhages (H) developed along the periphery of the necrotic part of the tumour. Retinal necrosis is present in the target area (arrows). (B) Same patient as in (A). Necrotic tumour borders on the sclera. The inner scleral layers are oedematous (O); the lamellar structure of the collagen remained intact. Intrasceral tumour cells (arrows) have a viable appearance but scleroocytes in this area have disappeared.

Figure 5 Patient 10. Depigmented haematoxylin and eosin stained section of the tumour. Different histological features of transpupillary thermotherapy induced cell damage in the superficial and deeper layers of the tumour. Irregular but sharp demarcation of the area of necrosis as cones of necrotic tissue (arrows) are located in between segments of viable tumour tissue. (V) viable part, (N) necrotic part of the tumour.
moste

Figure 6 Schematic drawing of ‘sandwich therapy’, transpupillary thermotherapy being most effective at the top of the tumour, and brachytherapy at the base of the tumour.

subcutaneously in hamsters. The heat induced necrosis is caused mainly by a direct cytotoxic effect, not by ischaemia as is evident from our light and electron microscopic findings after thermotherapy.

Thrombosis of tumour vessels may explain the low tendency to bleed, which was also observed clinically and in animal experiments.

The transition between the necrotic and the viable part of the tumour was about perpendicular to the direction of the radiation beam. The rather sharp demarcation may be attributed to a steep decrease in temperature in the tumour. During TTT the maximum temperature at the apex of the tumour will be about 65°C, at or just below the threshold for an ophthalmoscopically visible coagulation effect. The temperature in the demarcation zone is estimated to be about 45°C, the lowest temperature which causes irreversible tissue damage.

Thus the decrease in temperature in a tumour with necrosis measuring 3 mm in depth will be about 5°C per mm tumour tissue, as was also calculated by Svaasand (personal communication).

Bleaching of erythrocytes in the most superficial tumour vessels is caused by heat damage during stasis of the circulation caused by thrombosis developing during TTT (Fig 2B).

The temperature in these vessels was increased above 57°C, the critical clotting temperature where fibrinogen is converted into fibrin.

Signs of tumour cell damage were absent in one patient (No 1) despite a rather high irradiance of 4–10 W/cm² and radiant exposure of 7300 J/cm²; in another patient (No 3) an even higher irradiance resulted in only slight cell damage in the superficial tumour layers. The xenon photocogulator converted for thermotherapy was diode laser converted for thermo-laser damage in the superficial tumour layers. The higher irradiance resulted in only slight cell damage.

The rather sharp demarcation may be attributed to the direction of the radiation beam. The thermal alterations induced by heat are not an impediment to clinical thermotherapy; the inner layers of the sclera became oedematous and sclerocytes disappeared but the lamellar structure of the scleral collagen remained intact. The sclera is fairly heat resistant since temperatures of 52.2°C for 45 minutes and 65°C for 1 minute did not cause significant damage.

In one eye intrascleral tumour cells with a viable appearance were located only 36 μm from a totally necrotic tumour (Fig 4B). The distance is too short to explain this viability by a decrease in temperature. Moreover, the heat was sufficient to destroy the sclerocytes in the inner scleral layers. If we assume that the tumour cells were located intravascularly, then their viability could be explained by a cooling effect of the blood circulation, as also observed in animal experiments.

Since viable intrascleral tumour cells may be the source of tumour recurrences we usually combine TTT with ruthenium-106 brachytherapy. The two treatments, together coined as ‘sandwich therapy’, are complementary since the impact of the transpupillary infrared laser is maximal at the top of the tumour and that of the trans-scleral brachytherapy is maximal at its base (Fig 6).

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