Intracavitary Irradiation of Malignant Brain Tumours*

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Undoubtedly, glioblastomas are a continuing discouraging problem. Surgeons have been content to remove the tumour incompletely and to resort to postoperative roentgen-ray therapy, which has not succeeded in destroying or restraining the residual tumour in any large degree. A few attempts have been made to increase the effective radiation by implantation of radon seeds or radium in the bed of the tumour,6,8,11 or by use of roentgen rays of high intensity directly in the operating room. Several long-term survivals have been reported with hemispherectomy, at a price, however, of severe neurological disability.3

Beginning in 1953, a further attempt was made to destroy the residual tumour with the more potent sources of radiation then becoming available. The disturbing feature about these tumours is that a large proportion lie deeply within the hemisphere and have even crossed to the other side when the patient is first submitted to treatment. This paper does not deal with this type of case, but rather with those few cases in which the tumour is near the surface and can be tilted easily out of its bed and in which the residual tumour might reasonably be expected to be destroyed if enough lethal radiation was directed to it. With the introduction of a source of radiation into the cavity remaining after gross removal of the tumour, it was planned to localize very large doses of gamma radiation to the bed of the tumour in such a way that destruction of all residual tumour to a depth of 2.5 cm. might be nearly certain. The sites of tumour were selected so that necrosis of intact brain to this depth should not produce serious neurological deficit. A method of shielding was introduced to protect the bone flap and scalp.

Only a few isotopes could reasonably fulfill the requirements of high- to medium-average energy of radiation, high rate of dose, small size and availability. At the time, Iridium192 proved suitable except for a relatively short half-life of 74 days. It could be produced in the form of a small metallic disc, 3 mm. × 0.5 mm., with a high specific activity and emitting a large number of gamma rays of average energy of 300 keV (Table 1).

It was possible to introduce directional radiation shielding, using mercury as absorber, by inserting the radioisotope into the centre of a hemispherical plastic applicator with a radius of 2 cm. The mercury shield (8 to 10 mm. thick) reduced the dose to the scalp and skull to about 1/10th of that delivered to the bed of the tumour. This design ensured that the dose 2.5 cm. from the surface of the applicator (and bed of the tumour) was about 20 per cent of the dose at the surface (Fig. 1). It was planned to give 5,000 r in 2 to 5 days at this depth, a presumed lethal tumour dose. The dose nearer the applicator was, of course, much greater, but a shallow layer of necrosis was to be accepted. At this rate of dose more eloquent areas of the hemisphere beyond 2.5 cm. from the applicator should have received amounts assumed to be within tolerance.

The applicator was placed in the cavity of the tumour at the initial (or subsequent) craniotomy and attached to the bone flap by means of a flange screwed to the shaft protruding through a central burr hole (Fig. 2). After closure of the wound the source was quickly inserted into the central channel of the applicator through a short overlying incision in the scalp. At the end of the period of treatment the source alone was withdrawn.

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through the small incision, although removal of the applicator required a second craniotomy. Careful records were kept of the exposure of radiation to the Operating Staff during the procedure. Special nursing instructions and isolation of the patient resulted in keeping the dose to all personnel well below permissible limits.

**Case Reports**

Over a 3-year period, beginning in 1953, 6 patients were treated by this method. The doses are given in two figures representing the dose at the surface of the bed of the tumour and at a depth of 2.5 cm.; e.g., 20,000 r to 5,000 r. The procedure was tolerated well in each instance. Epilation was restricted to the region of the bone flap. Radiation sickness was not a feature.

**Case 1.** R.F., a boy aged 17 years, had a solid, well circumscribed, malignant astrocytoma removed from his left frontal lobe. A dose of 20,000 r to 5,000 r was given to the bed of the tumour over a period of 182 hours. He is in good health with no evidence of recurrence 8 years after this treatment.

**Case 2.** N.P. 451-57. R.T., a middle-aged farmer, had a large cystic tumour removed from his left frontal lobe less than 1 month after his first symptom. Histological sections showed the growth to be a malignant glioma. The majority of the tumour cells were astrocytes among which were multinucleated malignant giant cells. He was given only 10,000 r to 2,500 r over 40 hours into the tissue of the partially amputated left frontal lobe, because of the fear of damage from radiation to his anterior cerebral arteries and his left orbit. When the iridium applicator was removed a considerable amount of blood clot was found in the bed of the tumour which probably lowered the radiation to the residual tumour cells.

This patient survived only 5 months and post mortem the tumour, which had spread through the genu of the corpus callosum into the right frontal lobe (Fig. 3), was found to be almost completely necrotic. A few living residual tumour cells were found in the tissue of both frontal lobes. There was no necrosis from radiation in the white matter adjacent to this widespread necrotic tumour.

**Case 3.** N.P. 453-57. F.E., a man aged 37, was operated on 4 weeks after development of signs and symptoms of a tumour of the right frontal lobe. A glioblastoma multiforme was removed and

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**TABLE 1**

<table>
<thead>
<tr>
<th>Source</th>
<th>T 1/2</th>
<th>E  MeV</th>
<th>k cm² r me h</th>
<th>Me for 1000 r/h at 1 cm.</th>
<th>Integral Dose g r/me h</th>
<th>Mass of Applicator g</th>
<th>HVL</th>
<th>H₂O</th>
<th>Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ir⁹²⁹⁹ metal</td>
<td>74d</td>
<td>0.3</td>
<td>5</td>
<td>200</td>
<td>230</td>
<td>200</td>
<td>7 cm</td>
<td>2 mm</td>
<td></td>
</tr>
<tr>
<td>Cs³⁷³⁷ sulfate</td>
<td>30y</td>
<td>0.66</td>
<td>3.2</td>
<td>310</td>
<td>170</td>
<td>80</td>
<td>8 cm</td>
<td>5.4 mm</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 1.** The iridium and caesium applicators. The diagram shows half of each applicator only, for comparison. Isodoses are normalized to 100 per cent at 2 1/2 cm. from source.

**Fig. 2.** The applicator attached to bone plate.
20,000 r to 5,000 r were administered to the bed of the tumour over 111 hours. The applicator became detached from the bone flap, and, therefore, the exact distribution of the radiation in this case is unknown.

At necropsy 8 months later, viable, recurrent, glioblastoma multiforme was found extending into the cerebral cortex from the subarachnoid space over the right frontal lobe (Fig. 4). A second independent glioblastoma multiforme was found in the subcortical white matter of the left frontal lobe. No necrosis from radiation was seen in the white matter of either frontal lobe.

*Case 4.* N.P. 454-57, M.C., a woman of 46 years, had a malignant glioma removed from her right posterior frontotemporal region 16 days after her first symptoms. Irradiation of 36,000 r to 7,200 r was given to the bed of the tumour in 48 hours.

She lived for 14 months. Recurrent malignant glioma was found post mortem. The greater part of this recurrent tumour was necrotic, but living tumour cells were found in the more superficial part of the recurrence, where it was adherent to the overlying dura mater. In addition, there was severe necrosis from radiation in the tissues of the right cerebral hemisphere deep to the recurrent tumour. This extended backwards into the white matter of the right parietal lobe and inwards to involve the right thalamus.

*Case 5.* N.P. 280-57, F.D., a 50-year-old woman, had a malignant astrocytoma removed from the right temporal lobe for which 36,000 r to 7,200 r were given into the bed of the tumour in 54 hours. At postmortem examination, 9 months later, recurrent malignant gliomatous tissue was seen extending outwards into the tissues of the scalp in the right temporal region. Tumour cells also were found around the infundibulum of the pituitary gland, suggesting a metastatic spread through the subarachnoid space. Large areas of the recurrent neoplastic tissue were necrotic.

In addition, there was severe necrosis from radiation of the white matter of the right temporal lobe underlying the recurrent tumour (Fig. 5). Cerebral cortical tissue was remarkably well preserved even in areas where the subcortical white matter showed severe necrosis from radiation.

*Case 6.* N.P. 261-57, R.W., a man of 48 years, had a 3-month history suggesting a right posterior frontal tumour. On removal, the tumour was found to be a malignant astrocytoma with areas of glioblastoma multiforme. He lived for 12 months following intracavitary radiation of 34,000 r to 7,000 r in 192 hours.

At necropsy recurrent glioblastoma multiforme was found to be confined to a nodule of tumour firmly adherent to the underlying surface of the right frontal bone flap (Fig. 6), and to the inner
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Fig. 5. Case 5. Vertical section through the temporal lobes. Below a mass of recurrent malignant glioma there is a well demarcated firm, white area of necrosis from radiation in the white matter, following radiation of 36,000 r given to a primary tumour in the right temporal lobe 9 months before death.

surface of the dura mater where it was adherent to the cortex of the right frontal lobe.

There was massive necrosis from radiation (Fig. 7) of the white matter of the right frontal lobe extending through the genu of the corpus callosum and backwards into the right basal ganglia. As in Case 5, the cortical tissue of the right frontal lobe was almost normal, histologically.

Analysis of Pathological Findings

The effects produced by intensive gamma radiation in the 5 fatal cases discussed above vary from case to case. The three main pathological findings were: (a) recurrence of tumour; (b) necrosis of residual tumour; and (c) necrosis from radiation of surrounding normal tissue.

(a) Recurrence of Tumour. Living tumour cells were found in all cases. In 4 of the 5 cases they were placed superficially (Figs. 4 and 5) which suggests that these cells may have been implanted during the surgical removal of tumour, and that they were protected from lethal radiation by the base of the applicator which is shielded to prevent necrosis of the overlying bone.

Fig. 6. Case 6. Right frontal bone flap removed post mortem. This shows a nodule of recurrent viable tumour attached to inner surface of the dura mater at site of operative removal of the tumour, 1 year before patient's death. (The position of the block removed for histological examination is visible.)

Fig. 7. Case 6. Horizontal section through cerebral hemispheres showing massive necrosis from radiation of white matter of atrophied right frontal lobe. The necrosis extends inwards through the genu of the corpus callosum and backwards into the anterior limb of the right internal capsule. There is considerable internal hydrocephalus, ex vacuo, of the anterior horn of the right lateral ventricle.
(b) Necrosis of Residual Tumour. Practically all of the cells in the deeply lying tumour were necrotic. This probably is the result of the gamma radiation, although it must be remembered that large necrotic areas are a usual finding in nonirradiated malignant gliomata.

(c) Necrosis from Radiation of Surrounding Normal Tissue. This was found in 3 of 5 cases studied (Cases 4, 5 and 6). The "dead"-white appearance and the firm texture of white matter which has undergone necrosis from radiation is well illustrated in Fig. 5 which may be compared with the necrotic tissue of the tumour in Fig. 3. As would be expected from its gross appearance, all cells of this tissue are dead, including those of the walls of the blood vessels. The lumina of many of the blood vessels are dilated passively and contain intact red blood corpuscles.

At the margin of such an area of necrosis from radiation the nerve fibres of the white matter showed degenerative changes, but there was evidence of reaction by astrocytes and histiocytes, many of the latter being filled with fat globules from the degenerating myelin sheaths. In these areas of incomplete necrosis the blood vessels appeared normal, histologically, and thrombi were not seen in their lumina. Many of the vessels showed cuffing, with lymphocytes in their Virchow-Robin spaces. The cortical tissue directly overlying partially necrotic subcortical white matter frequently was astonishingly normal, histologically.

### Patients Treated with Caesium$^{137}$

After having gained some experience with the Iridium$^{192}$ sources, Caesium$^{137}$ began to be available in quantity. Because of the much longer half-life of Caesium$^{137}$, a single source will last for many years and there is no need to remeasure the rate of dose as was necessary with the short-lived Iridium$^{192}$. A more compact source applicator was designed (Fig. 1) so that it could be fitted into and removed through a 1-inch burr hole without the necessity of reopening the bone flap. Tungsten alloy shielding was used to protect the bone flap and scalp. A rubber-sponge space was necessary to keep the brain from entering a region of low dose close to the junction of the applicator and the bone flap. The powdered caesium sulphate, in a doubly sealed capsule a half-inch in diameter, was again inserted last or removed first from the applicator.

In 1959 3 patients were treated using Caesium$^{137}$ in the new applicator (Table 2). There were no untoward reactions during the period of treatment or early thereafter, but the relief from symptoms was brief and death occurred after 5, 7, and 9 months, respectively.

The pathology was similar in each case. On gross examination there was no definite mass of recurrent tumour. Instead, the hemisphere showed tremendous swelling with shift of the midline structures to the opposite side. The bed of the tumour was necrotic. There was evidence of increased intracranial pressure.

### Table 2

<table>
<thead>
<tr>
<th>Source</th>
<th>Dose</th>
<th>Time</th>
<th>r/hr.</th>
<th>Survival</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iridium$^{192}$</td>
<td>10,000r</td>
<td>2,500r</td>
<td>40 hrs.</td>
<td>62</td>
<td>5 mos. Recurrence</td>
</tr>
<tr>
<td></td>
<td>20,000r</td>
<td>5,000r</td>
<td>111 hrs.</td>
<td>45</td>
<td>8 mos. Necrosis &amp; recurrence second primary</td>
</tr>
<tr>
<td></td>
<td>30,000r</td>
<td>7,000r</td>
<td>132 hrs.</td>
<td>38</td>
<td>12 mos. Dural recurrence, with deep necrosis</td>
</tr>
<tr>
<td></td>
<td>36,000r</td>
<td>7,200r</td>
<td>48 hrs.</td>
<td>150</td>
<td>14 mos. Superficial recurrence with extensive deep necrosis</td>
</tr>
<tr>
<td>Caesium$^{137}$</td>
<td>38,000r</td>
<td>5,050r</td>
<td>72 hrs.</td>
<td>70</td>
<td>5 mos. Scattered tumor cells in massive oedema</td>
</tr>
<tr>
<td></td>
<td>30,000r</td>
<td>2,600r</td>
<td>37 hrs.</td>
<td>70</td>
<td>6 mos.</td>
</tr>
<tr>
<td></td>
<td>37,500r</td>
<td>3,350r</td>
<td>48 hrs.</td>
<td>70</td>
<td>9 mos.</td>
</tr>
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</table>
by herniation of the hippocampal uncus and widening of the temporal lobe of the affected hemisphere.

Microscopic preparations of the white matter immediately surrounding the bed of the tumour showed severe necrosis from radiation with complete death of all tissues, including the blood-vessel walls. The deep white matter showed partial demyelinization with astrocytic gliosis. There was occasional fibrinoid necrosis of the walls of the vessels which was associated with exudation of fibrin into adjacent tissues. In each case residual clumps of tumour cells were found. The majority appeared to be necrotic. The viable cells were found in the depth of the hemisphere, in the insular white matter, the internal capsule, the corpus callosum, and, in 1 case, the fornix. These deep structures also showed partial breakdown of the myelin sheaths, in between which there was a moderate astrocytic proliferation producing a fine fibrous reticulum. The adjacent cortex showed severe astrocytic gliosis and only occasional recognizable nerve cells. The cortical blood vessels contained red blood corpuscles, and there were a few fresh perivascular haemorrhages.

In contrast to the "Iridium" patients, in whom no clear-cut cause of death could be named, the "Caesium" patients died as a result of massive swelling of the radiated hemisphere 5 to 9 months after treatment.

Discussion

These cases are of great interest in showing the effects of gamma radiation applied to the brain from within the cerebral hemisphere in a single massive dose of 40 to 192 hours' duration. The roentgens delivered to the bed of the tumours varied from 10,000 to 58,000 r at the surface to between 2,500 and 7,200 r at a depth of 2.5 cm. during these short periods.

Ten thousand r to 2,500 r delivered over 40 hours (Case 2) appeared to have been sufficient to have caused almost complete necrosis of the residual tumour tissue, but a few living tumour cells were found post mortem.

With 20,000 r to 5,000 r given in 111 hours (Case 3), there was well marked recurrent tumour invading the cerebral cortex from the subarachnoid space (Fig. 4). A similar dosage of gamma rays given in 132 hours appeared to cure the patient in Case 1. These 2 patients may, perhaps, suggest some individual variability in the effects of gamma rays on similar gliomatous cells. As would be expected, massive necrosis from radiation was found in the 3 "Iridium" patients (Cases 4, 5 and 6) who received the highest doses.

The cause of the rapid deterioration and death of these 5 patients is unexplained by the pathological findings, except perhaps in Case 3, in which an independent second tumour in the opposite frontal lobe may have killed the patient by increasing intracranial pressure. In the remaining 4 cases the amount of recurrent tumour found post mortem was insufficient to have caused death. This suggests that the radiation may have produced more widespread pathological lesions than those observed. It is of interest in this connection that in Case 4, necrosis from radiation was found in the thalamic tissue. In some contrast, the death of the "Caesium" patients was explained more readily by the massive delayed swelling of the radiated hemisphere.

The cause of necrosis from radiation of normal brain tissue is undetermined. As suggested above, it has its maximum effect on white matter in the path of gamma rays. An interval of a number of months of good health following the removal of the tumour was well illustrated by these cases, and return of the symptomatology with the rapid decline of the patient was not accompanied by papilloedema or other evidence of increased intracranial pressure, except in those patients treated with Caesium. It must, therefore, be postulated that necrosis from radiation of the white matter is a "delayed" reaction. This delayed effect of gamma radiation has been considered to be caused by a progressive ischemia related to severe degenerative and obliterative alterations of the small blood vessels. The striking escape of the cortical cells has been attributed to the abundant vascularity of this layer. However, in the cases studied above, no convincing
arterial or arteriolar thrombosis was found in the white matter. Furthermore, in the marginal seminecrotic tissue where more recent thrombosis would have been expected in a “progressive” lesion, the blood vessels appeared normal, histologically. Similarly, Russell et al.¹⁹ in a study of radioneurosis in the brain of rabbits, found the vascular changes to accompany the parenchymal lesions, but not to precede them, and they became striking in only the more advanced stages. Several authors¹,²,³,⁴,⁵,¹² have considered the necrosis of the white matter to be a consequence of direct effects of the gamma energy on neurones and glial cells. Degeneration of oligodendroglia would result in myelonecrosis, but this has been described only as an acute phenomenon following high doses of cathode rays.⁶ Lampert et al.⁷ noted that a “delayed” effect of radiation upon oligodendroglia has not been proved and that the absence of these cells might be either primary or secondary to the degeneration. These investigators found no satisfactory “vascular” or “direct-effect” basis for the radionecrosis, but noted a strong resemblance of the lesions to those of acute demyelinating diseases. With his colleagues Lampert postulated that the radiation might have produced a primary alteration of the myelin sheaths, with the release of an antigenic substance, and that the subsequent demyelination might be viewed as the expression of an autoimmune reaction.

Summary

Massive gamma radiation was directed to the bed of the tumour in 9 patients with malignant gliomas using the isotopes, Iridium²¹² and Caesium¹³⁷, in special applicators. Useful life was not prolonged except in 1 patient who has now survived for 8 years without recurrence. In 3 cases it was possible to destroy the deeply placed residual tumour, at a price, however, of a degree of necrosis from radiation that ended the patients’ lives in much the same fashion as recurrence of tumour. It is believed that the reason for viable tumour cells remaining in these 3 cases was the result of failure to irradiate tumour-containing dura mater overlying the shielding of the applicator.

References