

1 Introduction

Primary tumours of the brain represent about 1.5% of all cancers.

Patients presenting with malignant glioma will undergo local excision and/or external beam radiation therapy. Despite this initial therapy, nearly all tumours will recur. Furthermore, we have been shown that 90% of recurrences occur within 2 cm of the initial tumour site. This is mainly due to the poor radiosensitivity of gliomas, and to the fragility of normal brain tissue. There is however a good rationale for increasing the radiation dose, since a dose-response relationship has been demonstrated. This can be achieved with external beam radiation therapy, but pilot studies with conventional techniques or heavy particles were not encouraging. Brachytherapy, with its rapid dose fall-off, which offers the opportunity of sparing normal brain tissue, may consequently constitute an interesting option.

In the last two decades, the interest in brachytherapy for high grade gliomas has been increasing, because of the emergence of 3-D imaging (CT-scan and MRI) and the development of accurate stereotactic techniques. Stereotactic brachytherapy has been used to boost the tumour bed after wide-field external beam radiation therapy.

Brachytherapy may be considered at the time of recurrence. Most patients are then ineligible for further external beam radiation therapy because of previous radiation treatment. Radiosurgery is applicable in only a small number of patients, because of the volume of recurrent tumour to be treated, and results of reexcision with or without chemotherapy have been disappointing.

2 Anatomical Topography

Most brain tumours suitable for an implant are situated in the frontal, parietal, temporal and occipital lobes. Other areas are not suitable for implantation because of the high potential of serious complications.

3 Pathology

Gliomas (astrocytoma or oligodendroglioma) are the most common brain tumours, the vast majority of which are malignant (anaplastic oligodendroglioma, anaplastic astrocytoma, glioblastoma). Brachytherapy is mainly indicated in some selected anaplastic astrocytomas and glioblastomas, at presentation or at the time of recurrence.

4 Work Up

Every patient undergoing brain irradiation needs a detailed neurological examination as well as magnetic resonance imaging. Surgical or stereotactic brain biopsy is mandatory when tumour is

treated initially, but may in most cases be omitted at time of retreatment if there is sufficient evidence of local regrowth.

5 Indications, Contra-indications

Only a limited number of tumours are eligible for brachytherapy, because of the poor tolerance of normal brain to irradiation. Implantation techniques are indicated in patients with Karnofsky performance status of at least 70, presenting with biopsy proven anaplastic astrocytoma or glioblastoma, unifocal, supratentorial, peripheral, well circumscribed, and less than 5 cm in diameter or 30 cm³ in volume on contrast-enhanced CT or MRI. Tumours with a diffuse margin, corpus callosum involvement, or subependymal spread should be excluded.

6 Target Volume

Clinical target volume includes the contrast enhancing area on the MRI with or without a margin of 5 mm.

7 Technique

Implantation procedures are performed within one day. The first step is to carry out a virtual implantation in order to prepare the final implantation. Initial planning is achieved using magnetic resonance imaging (or CT-scan), obtained after contrast infusion with the stereotactic frame fixed to the skull under local anesthesia at four points. (Fig 29.1) Images are spaced at 1 - 2 mm. The frame is used to locate each point of the space in the frame coordinate system. The digital information from the MRI set is entered directly into the treatment-planning computer via the hospital network. Tumour volume and normal organs are outlined on each slice. The estimated dosimetry is performed using the treatment planning software, which includes virtual simulation software giving 3-dimensional image reconstruction. This system includes software algorithms for calculating tumour volumes as well as volumetric and surface dose distributions. Thus outlines can be visualized on the screen at various observation angles. The number of catheters, the source strength, and the catheter distribution are chosen in order to deliver 50 - 60 Gy to the periphery of the enhancing lesion. Dose-volume histograms are calculated for both the target volume and the surrounding non-target tissue. Coordinates for the placement of afterloaded catheters are determined in the frame coordinate system.

After the radiation oncologist and the neurosurgeon have approved the treatment plan, the patient is taken to the operating room for the stereotactic implantation. An afterloading catheter, welded at one end, is implanted through skull bore hole using local anesthesia, replacing the biopsy needle in exactly the same stereotactic frame coordinate system at the specified depth. The catheter is then stereotactically introduced through the hole to the specified depth. The catheter is glued to a plastic collar that is sutured to the scalp. The process is repeated for additional catheters as required.

A CT scan is then obtained with the dummy sources in place to confirm that sources are positioned accurately and the final dosimetry is performed.

The patient is taken to the brachytherapy room. Nylon catheters containing the iridium-192 or iodine-125 wires are inserted into the afterloading catheters. A surgical clip holds the inner catheter in place within each outer catheter. The patient is then bandaged, given antibiotics, anticonvulsant medication, and corticosteroids.

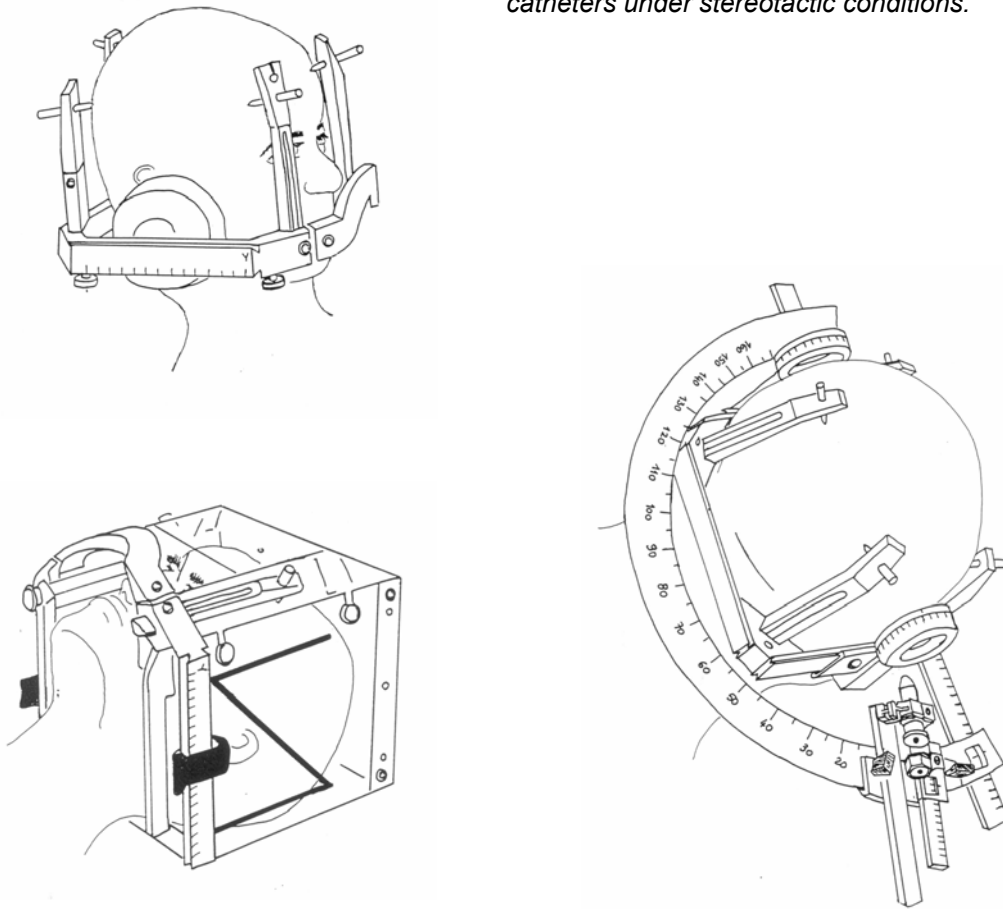


Fig. 29.1 The Leksell frame used for implanting the catheters under stereotactic conditions.

Sources and catheters are removed once the desired dose has been delivered, usually over a 7 - 12 days period. Radioactive wires are removed at the bedside, and catheters in the operating room. This procedure does not require anesthesia. The small scalp wound at each implant site is closed. Patients are observed overnight before discharge.

If iodine-125 seeds are used, the catheters can also be implanted through burr holes. Sources are then removed in the operating room.

Most institutes use temporary iodine-125 or iridium-192 sources, but HDR afterloaders have also been used. The advantage of remote afterloading is better radiation protection for personnel and easier optimisation of the dose distribution, but the disadvantage is the greater immobility of the patient. The experience with HDR brachytherapy in brain tumours is limited, and it is not possible to give time-dose-fraction recommendations. The dose per fraction should however be low, because of the fragility of normal brain.

8 Dosimetry

Dosimetry is based on the CT scan carried out with dummy sources. (Fig 29.2)

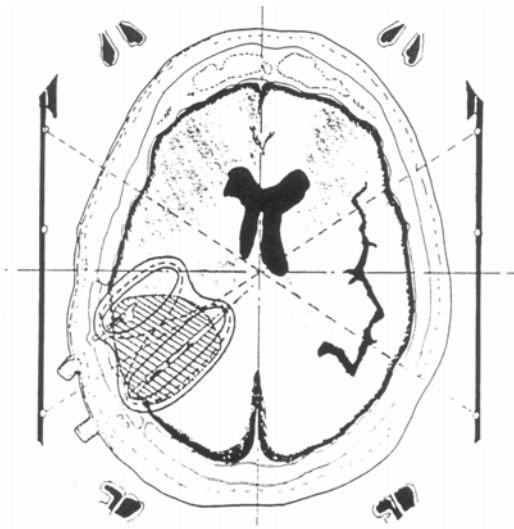


Fig 29.2: Distribution of dose with stereotactic iridium-192 implantation for glioblastoma multiforme recurring in previously irradiated territory.

9 Dose, Dose Rate, Fractionation

A dose of 50 - 60 Gy is prescribed on an isodose circumscribing the target volume. Whenever possible the dose rate ranges from 0.4 to 0.5Gy/h. HDR afterloaders have also been used, but there is at the moment no consensus on total dose and fractionation.

10 Monitoring

Monitoring is similar to invasive stereotactic procedures in neurosurgery.

11 Results

11.1 Recurrent malignant gliomas

Interstitial brachytherapy was initially used to retreat high-grade gliomas recurring after surgery and radiation therapy. In this situation surgery is disappointing with median survival not exceeding 7 - 8 months (3).

The University of California, San Francisco group, reported a median survival of 54 weeks for 45 patients with recurrent glioblastoma and 81 weeks for 50 treated for recurrent anaplastic astrocytoma treated with removable high-activity Iodine-125 implants and 3-year survival rates of 22% and 8%, respectively (7). Because of clinical deterioration, increasing steroid dependency, and increasing mass effect at the implantation site seen on CT-scans, necrotic tissue was excised from 47 patients (49%) at craniotomy; in some patients, tumour was mixed with necrotic tissue. Survival was significantly longer compared with patients who did not undergo this procedure. Serial determination of the Karnofsky Performance Score showed that there was no significant deterioration for the group

as a whole for the 6 months immediately after implantation. Mean Karnofsky Performance Score at 3 years was 79 and 53%, respectively.

Bernstein et al. reported the Toronto experience with 46 patients with recurrent malignant astrocytoma (32 with glioblastoma, 12 with anaplastic astrocytoma and 2 with low-grade astrocytoma) treated with high-activity temporary iodine-125 implants (1). The median survival was 46 weeks with 1- and 2-year survival rates of 46% and 10%, respectively.

From 1993 to 1997, 42 recurrent glioblastomas were implanted with iridium 192 at Salpêtrière Hospital (9). The probability of overall survival was 80% at 6 months, 48% at one year, and 11% at two years. Median survival was 50 weeks. Univariate analysis showed that both tumour volume ($T < 30 \text{ cm}^3$ or $T \geq 30 \text{ cm}^3$) and Karnofsky Performance Score were significant predictors of survival. Multivariate analysis showed that smaller tumour volumes were associated with a higher probability of survival ($p < 0.001$). Tumour volume less than 30 cm^3 was associated with a higher probability and quality of survival than larger lesions in patients reirradiated by brachytherapy for recurrent glioblastoma. A reoperation was carried out in 10 patients (24%) for decompression following clinical and radiological evidence of deterioration with mass effect. Eight of the 10-reoperation specimens were available for pathologic review in our institution. The histological findings were: identifiable tumour and radiation necrosis, 5 cases; radiation necrosis alone, three cases. Survival rates were not significantly different between patients who did or did not undergo reoperation. It was finally recommended that brachytherapy should be chosen for patients with a tumour volume $< 30 \text{ cm}^3$ and Karnofsky Performance Score > 70 .

11.2 Newly diagnosed high-grade gliomas

The encouraging results obtained for high-grade gliomas recurring in previously irradiated sites led some institutions to propose brachytherapy as an adjuvant treatment after initial surgery and external beam radiation therapy. A dose of 50 - 60 Gy is typically delivered to the tumour bed after the completion of a 60 Gy conventional external beam treatment. The University of California, San Francisco group, had again the largest experience (2). The authors concluded from the phase II study that the combination was valuable for patients treated for a glioblastoma multiforme, with a median survival of 88 weeks, but not for those treated for an anaplastic astrocytoma, with a median survival of 157 weeks. Encouraging results obtained with unifocal well-circumscribed glioblastoma were obtained at the price of some severe side effects. Nearly half of the patients needed reoperation because of clinical deterioration, increasing steroid dependency, and increasing mass effect, after 46 weeks (median). Patients who had further surgery lived significantly longer than those who did not (median survival: 108 weeks versus 77, $p = 0.047$). The quality of life was moreover judged satisfactory with a Karnofsky Performance Score of 75% (60 - 100) at 2 years. About 90% of tumours recurred despite a total dose of 100 Gy or more, and only very few patients lived more than 5 years.

Two randomised trials were implemented in the late eighties. The initial results of Trial 8701 of the Brain Tumor Cooperative Group have only been published as a meeting abstract so far. After an external beam irradiation of 60.2 Gy patients were randomized to receive a temporary implant of 60 Gy at a dose rate of 0.4 Gy/h or not. A 3.5-month significant survival advantage was shown in the implant patients treated for glioblastoma multiforme. The Canadian trial included 140 patients presenting with malignant astrocytoma $\leq 6 \text{ cm}$ in size, not involving the corpus callosum or crossing the midline, and treated with surgery, external beam radiation therapy delivering 50 Gy in 25 fractions over 5 weeks, with or without a stereotactic iodine-125 implant of 60 Gy (6). The median survival for patients randomised to brachytherapy or not was 13.8 versus 13.2 months without ($p = 0.49$). The Cox proportional hazards model showed that randomisation to the brachytherapy arm was associated with a RR of 0.7 ($p = 0.07$).

Another randomised trial compared brachytherapy with or without hyperthermia, in patients presenting with newly diagnosed glioblastoma multiforme (11). Hyperthermia was associated with a significant improvement of median survival of 9 weeks.

Radiosurgery shows some similarity with brachytherapy in the treatment of high-grade glioma. A clinical retrospective comparison between brachytherapy and radiosurgery in newly diagnosed and recurrent tumours showed similar survival duration (10). The two groups were however not well balanced, because radiosurgery, due to its inherent technical characteristics, had been reserved for the smallest tumours.

11.3 Low-grade gliomas

In Germany, brachytherapy using permanent or temporary iodine 125-implants has been used for treating low-grade inoperable gliomas, which show signs of progression, do not exceed 5 cm in diameter, and do not infiltrate the corpus callosum. The 455 Patients reported had a Karnofsky index at least of 70 (5). A dose of 60 - 100 Gy was delivered to the outer limit of the target volume, at a dose rate preferably lower than 0.1 Gy/hr. The 5-year survival rates of patients presenting with pilocytic astrocytoma, grade II astrocytoma, oligoastrocytoma, oligodendroglioma, and gemistocytic astrocytoma, were 85%, 61%, 49%, 50%, and 32%, respectively. Radiogenic complications were observed in 8% of patients (4). The most important prognostic factor was the volume of the 200 Gy isodose. The technique was also used for implanting brainstem tumours (8). While no randomised trial has compared external beam and interstitial techniques, the results published seem comparable to those achieved with external radiation therapy.

12 References

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