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Koot, R.W.

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^{192}Ir STEREOTACTIC BRACHYTHERAPY FOR MALIGNANT GLIOMA

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Promotiecommissie:

promotores:	Prof. dr. D.A. Bosch
	Prof. dr. J.C.J.M. de Haes
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Faculteit der Geneeskunde

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Voor vier dames

Contents

1. Introduction

1.1 Literature on malignant glioma and irradiation

Epidemiology

Primary malignant tumours of the central nervous system are relatively rare, accounting for only 1.5% of all malignancies. Gliomas are central nervous system tumours originating from cells of glial tissue. The group consists mainly of astrocytomas, ependymomas, oligodendrogliomas and mixed gliomas (20;46). Glioma is the most common CNS tumour, accounting for 45-55% of the intracranial tumours. About 50% of gliomas is glioblastoma multiforme (GBM), the most malignant CNS tumour, with a cell cyclus of two to three days and a tumour volume doubling time of 30-45 days (43;71). Glioblastoma multiforme usually occurs in the sixth and seventh decade, shows a male predominance and may arise anywhere in the CNS, although in most cases supratentorially and unilocally.

Etiology

Radiation, viral infection and chemical agents have been mentioned as exogeneous mutagens in the aetiology of brain tumours. Although thorough epidemiological studies do not exist, there are numerous short reports of malignant gliomas, meningiomas and sarcomas arising five or more years after previous brain irradiation, as delivered in the cases for childhood brain tumours. Occupational exposure to chemical agents such as nitroso compounds (rubber industry) and polycyclic aromatic hydrocarbons are mentioned also as risk factors for gliomas (66;84). The BK-virus, SV virus and JC polyoma virus have all been mentioned as involved in the development of glioma, but solid evidence is still lacking.

Classification

The (classic) light-microscopic grading of gliomas, which correlates with survival time and which depends on cellular proliferation, anaplasia, microvascular proliferation and necrosis, was refined by Daumas-Duport and modified later on, leading to the WHO classification (20;47). The classification of astrocytomas consists of 4 grades, grade 3 (anaplastic) and 4 (glioblastoma multiforme) being considered as malignant. A problem remains the heterogeneity of gliomas; small biopsies carry the risk of nonrepresentative material, causing undergrading (17). Oligodendrogliomas can be divided into 2 groups, low grade and anaplastic oligodendroglioma. In these tumours, mitotic activity is not necessarily a sign of anaplasia, and corresponds therefore less with prognosis. In fact, this tumour is underdiagnosed (misinterpreted as fibrillary astrocytomas) and some malignant astrocytomas can be reclassified as oligo-astrocytomas, with a considerably better prognosis since oligodendrogliomas are chemo sensitive tumours (12;13). By this reclassification, the amount of oligodendrogliomas is estimated to increase from 5 to 30 % of all gliomas (18;21;22).

Apart from the classic morphology, gliomas can be divided in different subgroups according to their genetic heterogeneity with the aid of molecular biology (46). Changes in genetic material (loss of heterozygosity (LOH), deletions, mutations) have led to the classification of subgroups of glioma, of which some have better treatment options, particular true for oligodendroglioma. The problem of under-grading, due to small samples of a heterogeneous tumour, is also partly

solved with genetic analysis. Oligodendrogliomas frequently show for example LOH 1p and 19q, which is linked to chemosensitivity for a regimen of procarbazide, CCNU and vincristine. Molecular genetics has revealed two different types of GBM (48). One pathway is represented by an early p53 mutation leading to gradual development from low-grade astrocytoma, towards anaplastic astrocytoma and GBM. The second pathway leads to 'de novo' GBM and is characterised by loss of heterozygosity (LOH) of chromosome 10 (p or q) indicating the loss of expression of tumour suppressor genes and the over-expression, or amplification of oncogenes. This differentiation between two types of GBM has no relevance for clinical practice yet as the prognosis for these two types is still equally poor.

Specific brain tumour features

Malignant gliomas consist of heterogeneous tumour cells. Subclones of genetically instable rapidly proliferating malignant cells can easily be selected. This heterogeneity not only hampers tumour-host interaction but also therapeutic efforts. Furthermore, cells of malignant gliomas are invasive by migration along fibre tracts, through perivascular Virchow-Robin spaces, and along cortical and ventricular surfaces. Because of this migration, malignant gliomas are difficult to cure. Finally, the immune response to (malignant) brain tumours is more limited than with solid tumours in other organs. The blood-brain barrier, the absence of a lymphatic system and the lack of both major histocompatibility complex antigen and tumour-specific antigen expression are responsible for an inadequate immune response (19).

These three features, heterogeneity, invasiveness, and lack of immune response, give malignant brain tumours a significant advantage as to tumour-host interaction compared to other tumours, leading to almost invincible problems with respect to their treatment.

Treatment

Surgery

Histopathological verification is essential for further treatment and thus for prognosis. Cytoreductive surgery and stereotactic biopsy are the available methods to obtain histological material, both with their own indications. Deep-seated small tumours in almost neurologically intact patients should be treated by stereotactic techniques. Peripherally located tumours causing mass effect and surrounded by a lot of peritumoural oedema should preferentially be treated with cytoreductive surgery. The 'in-between' group is in fact eligible for one of both options; many of these cases undergo cytoreduction with the aid of neuronavigation. For older patients, even when mass effect and oedema is present, the value of cytoreductive surgery is limited because of age-related poor prognosis, and stereotactic biopsy is then equally effective (44;63;67). On the other hand cytoreductive surgery in young patients should be carried out as radical as possible, as this treatment, if successful, has shown a small, but significant improvement in survival (28;67).

Radiation

External beam radiotherapy (EBRT) given with a linear accelerator is the primary adjuvant treatment for malignant glioma. Irradiation after surgery increases long-term survival for

anaplastic astrocytoma and GBM significantly, in particular for younger patients (11;14;68;87;88). Maximal standard treatment is 56-66 Gy in fractions of 1.8-2.0 Gy in 5-7 weeks. In elderly patients with a poor prognosis, an extreme hypofractionation scheme of 4 x 7Gy conformal radiotherapy should be considered as this provided equal palliation (40). Adjuvant radiation therapy is sometimes used as a 'boost', in which the total dose must be strictly focal, because of the already reached maximum tolerance of the brain and the unacceptable side effects when exceeding 60 Gy (89). In this respect brachytherapy (see paragraph 1.2) and stereotactic radiosurgery or stereotactic radiotherapy are mentioned (75). Stereotactic radiosurgery consists of many small beams of radiation delivered in a spherical mode to a stereotactically defined target, given in a high dose single fraction (SRS); when given in multiple fractions it is stereotactic radiotherapy (SRT). The best indications for SRS are small arteriovenous malformations, some skull base tumours (acoustic neurinomas) and some small (even multiple) metastases. SRS followed by conventional EBRT and chemotherapy (carmustine) did not show significant prolongation of survival compared to conventional EBRT and carmustine without SRS (79).

Chemotherapy

Unfortunately, the most common form of primary brain tumour (GBM) belongs to the relatively insensitive tumour types for chemotherapy. A recent meta-analysis to assess the effect of adjuvant chemotherapy for malignant gliomas, showed a small, but clear positive effect on survival (80). The most effective drugs in this field are the nitrosureas BCNU (carmustine) and CCNU (lomustine) supplemented in a triple agent regimen with procarbazine and vincristine (PCV) (41). Temozolamide appears to have a similar range of activity, although with less toxicity. Anaplastic oligidendroglioma, however, shows a high response rate to PCV, depending on its genetic composition (LOH 1p, 19q) (12).

Prognosis and quality of life

Despite all new techniques and sometimes aggressive efforts, the overall survival of GBM patients has not increased over the last 20 years after the introduction of fractionated EBRT and the vast majority of patients die of their primary malignant brain tumour within 24 months. Local tumour recurrence in patients with malignant glioma is more than 90 % (16;36;37). The determination between recurrence and progression can in fact not be made, and is determined by clinical parameters. For malignant glioma important prognostic factors are age, performance status at the time of diagnosis and tumour grade (9;10;39;67;87;93). Median survival time in a retrospectively analysed large group of patients with GBM was 3 months without treatment, 6 months with surgery alone and 9 months with surgery and EBRT (69). On the basis of a 10 years experience in our centre, median survival was 7.7 months for surgery and EBRT(39). Survival times of about 10 months have also been reported in other series (23;86). Five years survival rate is less than 5% (57;69). With aggressive multimodality therapy, including sequential chemo-therapy regimens, median survival may be 12-15 months (70). By that time CSF dissemination is reported in up to 35 % of the GBM cases, and is significantly correlated with a decrease in survival rate (25).

For adults with malignant glioma, the side effects and complications of treatment, but also the influence of the brain tumour itself on neurological and cognitive function, have been demonstrated by several authors. Aggressive combined multimodality therapy of malignant glioma results in larger numbers of long-term survivors. The effects of treatment, however, suggest diffuse cognitive decline and problem-solving difficulties (3;30;31;38;42;45;58;82;83). In a pilot study, Archibald *et al* found verbal memory and sustained attention most impaired at 18 months after treatment (surgery, followed by irradiation with 40-60 Gy and BCNU chemotherapy), whith verbal learning and flexibility in thinking showing the greatest tendency to decline over time (follow-up 3-7 years). Only a few patients who were tumour recurrence free (CT/MRI scan proven) are capable of fully independent living (3).

1.2 Brachytherapy

History

Brachytherapy ('brachy' means 'short range') was successfully applied for the first time in 1903, for two cases of basal cell carcinoma of the face, five years after the discovery of Radium by Marie and Pierre Curie. Early radiation techniques consisted of surface application; Radium sources were mounted on wax or leather, which was moulded to the shape of the area of interest. Implantation of radioactive sources into a tumour was for the first time published and illustrated in medical literature in 1914. In the 1950s the practice of Radium brachytherapy became relatively uncommon, due to the rapid evolution of external radiotherapy and the problems caused with long term storage of used and/or obsolete Radium sources (half-live 1622 years). With the discovery of artificial radioactivity in 1933 radiochemistry was founded and with this research brachytherapy regained medical interest. Today, most commonly applied are ^{125}Iodine (^{125}I) and ^{192}Iridium (^{192}Ir) (62).

Dose rate considerations

Irradiation of tissue causes early and late effects. Tumour tissue, having a high cell proliferation, is in general more vulnerable for early effects, whereas healthy (surrounding) tissue responds in a later phase. The possibility to place radioactive sources within a tumour may lead to an optimal dose delivery strategy, applying high doses to target tissue and minimising radiation to normal adjacent tissue.

Important, however, is the fact that early and late responding tissues may react in a very different way to various dose rates (92). For a given dose, increasing the dose rate will increase late effects much more than it will increase tumour control. Thus, the therapeutic ratio (tumour control versus 'complications') will increase as the dose rate decreases. Low dose rate brachytherapy (LDR) therefore maximises the therapeutic effect, being the difference in effect between early and late responding tissues. In other words, the component of radiation damage (late effect) is dose rate dependent. However, radiation damage of adjacent tissue not only depends on dose rate, but also on volume of tissue irradiated. For interstitial implants, the dose rate tends to increase as the size of the implants increases, according to the Paris system of dosimetry (24).

Summarising, dose rate is a very important factor in determining the outcome of interstitial brachytherapy. Continuous LDR brachytherapy has similar biological advantages to hyperfractionation and seems therefore biologically most appropriate.
With the introduction of remote after-loading techniques (mechanically loading and removal of radioactive sources from a distance with minimal radiation exposure to doctors and nursing personal) fractionated high dose rate (HDR) brachytherapy became favourable from a logistic point of view. Although studies of HDR brachytherapy for malignant glioma do exist (15;61;94), LDR brachytherapy is to be preferred because of its higher therapeutic effect.

Dose rate ranges have been broadly classified into 3 groups.

Low dose rate (LDR)	< 200 cGy/hr
Medium dose rate (MDR)	200-1200 cGy/hr
High dose rate (HDR	>1200 cGy/hr

Dose rates used for LDR brachytherapy boost in general are around 40-60 cGy/hr, but studies with much lower dose rates around 3cGy/hr have been reported (49).

Radioactive sources

Since the discovery of artificial radiotherapy about 2500 isotopes can be produced of which only 300 have half-lives between 10 days and 100 years. Approximately 10 sources have clinical applications in brachytherapy. The ideal radionuclide for brachytherapy emits photons in the form of X-rays and gamma-rays with energies of approximately 200 KeV and has a half-life of a few days for permanent implants and a much longer half-live (years) for temporary implants (85). The energy of the emissions determines the penetration of the radiation in tissue. Traditional sources such as ^{137}Ceasium (half-life time 30.07 yr, gamma 0.66 MeV, also beta), ^{60}Cobalt (half-life time 5.27 yr, gamma 1.2 MeV, also beta), ^{198}Gold (half-life time 2.7 days, gamma 0.41 MeV, also beta), ^{192}Iridium (half-life time 74 days, gamma 0.38 MeV, also beta) and ^{125}Iodine (half-life 60 days, gamma 30 KeV, no beta) have all their advantages and disadvantages.
The time interval between external beam radiotherapy and subsequent brachytherapy and finally the overall treatment time shows considerable variation. Intervals of 1-2 weeks are commonly used, but in fact the most appropriate interval depends on multiple parameters, including external beam dose, total dose delivered to the tumour periphery by brachytherapy, tumour clonogen doubling time, tumour regression rate constant and tumour size (62).

Brachytherapy and brain tumours

Because malignant brain tumours tend to recur locally, rather than diffusely (4;16;37;52;59) and EBRT is limited by the brain tolerance, focal radiation techniques such as brachytherapy have been considered the most suitable in the treatment of these tumours as improvement in local control is obtained with higher doses of radiation (89). Interstitial brachytherapy in the CNS may be delivered by stereotactic placement of temporary irradiation sources or permanently placed seeds. Brachytherapy is typically limited to unifocal tumours of <5-6 cm in diameter with well-defined margins on imaging studies. The lesion should be located away from functional areas,

and midline structures including the brainstem, midbrain, chiasm, or corpus callosum, so that tumour necrosis and associated mass effect are tolerated.

Multiple implant sources have been used. For brain implants, ^{125}I has been recommended, mainly based on its relatively low-energy photons, which should spare surrounding normal brain. The specific dose-rate factor of ^{125}I used for dosimetry is 1.32 cGy/hr. Other investigators have recommended ^{192}Ir because higher energy photons may yield improved dose distribution. The specific dose-rate factor of ^{192}Ir used for dosimetry is 4.55 cGy/hr. Although most authors use ^{125}I , there are no results available pointing to a more favourable outcome for either ^{125}I or ^{192}Ir in the treatment of malignant glioma.

For *recurrent* malignant gliomas, Scharfen updated one of the largest series of 66 glioblastomas and 45 with anaplastic astrocytomas, treated with ^{125}I interstitial implants (72). Median survival post-implant was 49 and 52 weeks respectively. In smaller studies similar results were found (5;6;32;33;51;64;72). Prognostic factors for survival time were younger age and lower histological grade, whereas Karnofsky performance score, extension of initial surgery, initial radiation therapy dose, implant dose, or volume at recurrence were not (72). Compared to re-operation (2;35) or chemotherapy (53;54), stereotactic brachytherapy did not improve survival in recurrent anaplastic astrocytoma (72). Other series confirm these observations; salvage therapies (including stereotactic brachytherapy) after recurrence may extend survival for nearly a year (6;65). All series are relatively small and randomised trials for recurrent anaplastic astrocytoma have not been published.

Because of the poor prognosis of malignant glioma, stereotactic brachytherapy was incorporated in the *initial treatment* of these tumours. After the very promising results in a highly selected patient group, reporting a median survival of 27 months (55), more recent studies by other authors showed that the increase in survival after brachytherapy is strongly influenced by age and Karnofsky Performance Score at the moment of implantation (65;78), factors already known as the most important parameters for the survival of patients with (malignant) brain tumors in general. Most of these studies report an increase in median survival of 4-8 months with additional stereotactic brachytherapy in primary GBM treatment (7;8;26;34;72;77;91). This increase is considerable for a tumour with a median survival of 4-6 months after surgery alone and 8-12 months after surgery and external beam radiation therapy (14;69;88). This increase was more than that obtained with any other single additional treatment regimen, although meta-analysis has shown that a combination of external beam radiation therapy with chemotherapy may also show some improvement in median survival (27;80). However, bias in patient selection is obviously responsible for at least part of the increased survival after stereotactic brachytherapy, although the amount of bias is difficult to assess (29). Recently, prospective randomised studies have become available, which failed to show a significant increase of survival for primary GBM patients treated with adjuvant brachytherapy (50;60;74;81).

Recurrence pattern after brachytherapy

Most malignant gliomas finally recur at the original site. After EBRT, recurrences are usually seen in the surgical bed (4;37;90). Loeffler *et al* (56) defined recurrence patterns after interstitial brachytherapy as local (extending in a contiguous fashion from the original implant edge to more

than 2 cm), marginal (> 2 cm, < 5 cm, no continuity with implant edge) or distant (> 5 cm from implant edge, no continuity). Only 4 out of 22 recurrences were local, 8 were marginal and 10 were distant. As 82 % of the recurrences were marginal and distant rather than local, Loeffler suggested that interstitial brachytherapy changed the recurrence pattern, indicating improved local control. Proliferation from peripheral parts of the tumour just outside the 100% isodose curve as well as tumour dissemination by the implantation might be responsible for this pattern of recurrence. More recent studies failed to confirm this difference in pattern of recurrence, reporting again 70-80 % local recurrences (contiguous spread) and only 10-20 % recurrences at distance (new focus more than 2 cm away from the implant edge) (1;73;76). It is therefore concluded, that despite very aggressive local radiation therapy (combined external and interstitial radiotherapy) with a cumulative dose of 100 Gy, local tumour progression is still the predominant pattern in recurrence. Schupak *et al* (73) studied the occurrence patterns in 47 patients in relation to the technical accuracy with which the implant had been placed. Patients with inadequately positioned implants had recurrence in both the central and peripheral (not defined) tumour region. Accuracy as such did however not affect the median survival, although inadequately implanted patients had more often reoperations and reoperations correlated with some increase in survival.

1.3 Outline of the thesis

This thesis is based mainly on a study of 27 de novo GBM patients treated primarily with cytoreductive surgery, external beam radiation therapy and additional 'boost' stereotactic brachytherapy. This study was initiated to investigate the additional value of brachytherapy in the up-front treatment of primary GBM. It was designed as a prospective, non-randomised study, with a historically matched control group, evaluating survival time and quality of life of patient and partner. Histopathology and emission tomography studies also belong to the core of this thesis.

The study

Selection criteria

The prospective study started in 1993 and had the approval of the Ethical Board of the AMC. All patients with a GBM who had undergone cytoreductive surgery and received 60 Gy (30x2Gy) external beam radiotherapy were potential candidates. They were included if they fulfilled the following criteria:

- GBM according to the histological classification scheme of Daumas-Duport (20) and the WHO classification (47)
- First presentation (de novo), supratentorial and not located in the midline.
- Diameter not more than 5 cm before implantation (CT and/or MRI confirmation) with clear demarcation from the surrounding tissue.
- The patient had no other serious illness and was at least 30 years of age (increased survival under this age).

- There was a technical restriction: Tumours near the os petrosum or the superior sagittal sinus are difficult to implant properly and had therefore to be rejected.
- The patient had a Karnofsky Performance Score of at least 70 % before implantation.
- The patient had to sign an "informed consent".

Usually one week after the cytoreductive operation, the neurosurgeon and radio-oncologist selected potential candidates according to histopathological diagnosis, postoperative CT or MRI scan and Karnofsky Performance Score. Apart from the patients in our institute, patients from the Leiden University Medical Centre were included. In the weeks thereafter, the schedule for external beam radiotherapy (EBRT) was carried out (60 Gy in 6 weeks). Halfway the EBRT, a CT-scan was made to see whether the patient was still a suitable candidate (no progression of the lesion), and an appointment was made at the outdoor clinic, where the patient was informed about the proposed additional brachytherapy. Two weeks after the end of the external radiation, a new CT-scan was made for the final decision. A ^{201}Thallium SPECT scan was also made, quality of life scores were filled in, and the patient was requested to sign the 'informed consent'.

Surgical procedure

^{192}Ir wires (0.12-0.23 mCi/mm, Amersham) were implanted temporarily. 40 Gy was given at a mean initial dose-rate of 61 cGy/hr (44-100 cGy/hr, 10.6 – 24 Gy/day). The Leksell stereotactic frame was used for implantation and treatment planning was done by combining the Nucletron (Plato) software data with the stereotactic coordinates. All catheters were implanted parallel to each other.

Under local anesthesia, a Leksell stereotactic frame was placed and the patient was transported to the MRI-scanner or CT-scanner. The stereotactic image data were downloaded on a terminal near the operating room. By means of 3-D visualization, the optimal angle and coordinates for parallel implantation in the tumor were calculated. According to the configuration of the tumor, a pre-planning was made to determine the number and stereotactic coordinates of the catheters. During these calculations, which took approximately one hour, the patient was brought under general anesthesia. Burr-holes (2 mm) were made with a high-speed twist-drill. Hollow catheters were introduced parallel to each other at the calculated depth and fixed to the skin. A CT-scan and plain X-rays were made to check the position of the catheters and to determine the length needed of the ^{192}Ir wires, followed by a definitive planning, to deliver 40 Gy at 5 mm around the contrast-enhancing zone. The interstitial radiation took place in a shielded room in which the patient was kept for 3-5 days, depending on the dose rate with a remote after loading system. The catheters were removed manually without anesthesia as soon as the total dose of 40 Gy was reached. Persistent leakage of cerebral spinal fluid was stopped by a stitch. Corticosteroids and antibiotics were given during the brachytherapy treatment. Total hospitalization time was approximately 10 days.

Follow-up

Patients were followed with 3 months intervals. Besides a general impression and neurological examination, a Mini Mental State Examination (MMSE), daily living activity examination (Barthel-index), and a quality of life score (Karnofsky Performance Score) were assessed. Moreover, patients and their partners were asked separately to complete a specially developed 'quality of live' questionnaire. CT or MRI scans were made every 3 months during the first year and every 6 months thereafter. If a recurrence was suspected, investigations were extended with a ^{201}Tl-SPECT and/or a ^{11}C-tyrosine PET scan, which results were used in the discussion to proceed to a re-operation or not.

The thesis

In chapter 2, an overview is given of the present state of the best treatment results including prognostic factors for GBM, over a 10 years period in the Academic Medical Centre. In chapter 3, two very different brachytherapy strategies for primary GBM are compared. Patients treated with brachytherapy at the University of Cologne in Germany and at the Academic Medical Centre are matched and compared. Chapter 4 deals with the quality of life during and after the brachytherapy treatment evaluated by the quality of life scores, completed by the patients and their partners. In chapter 5 we describe our experience with functional imaging such as ^{201}Thallium SPECT and ^{11}C-tyrosine PET scan in the follow-up of patients treated with brachytherapy. The scope of chapter 6 is the long-term effect of radiation on the human brain. We describe and illustrate the extensive vascular changes seen many years after irradiation by means of case reports. In chapter 7 interesting case material is presented. Finally, the main findings are summarized with some additional concluding remarks.

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2. Prognostic factors in glioblastoma multiforme; 10 years experience of a single institution

MCCM Hulshof , RW Koot , EC Schimmel, F Dekker, DA Bosch, D González González†

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Summary

Background: To analyse prognostic factors in patients with a glioblastoma multiforme (gbm) treated in an academic institute over the last ten years.
Methods: From 1988 to 1998, 198 patients with pathologically confirmed glioblastoma multiforme were analysed. Five radiation schedules were used mainly based on pre-treatment selection criteria: (1) 60 Gy in 30 fractions followed by an interstitial Ir-192 (Ir-192) boost for selected patients with a good performance and a small circumscribed tumour, (2) 66 Gy in 33 fractions for good performance patients, (3) 40 Gy in 8 fractions or 28 Gy in 4 fractions for poor prognostic patients and (5) no irradiation.
Results: Median survival was 16 months, 7 months, 5.6 months, 6.6 months and 1.8 months for respectively the group treated with Ir-192, 66 Gy, 40 Gy, 28 Gy and the group without treatment. No significant improvement in survival was encountered over the last ten years. At multivariate analysis patients treated with a hypofractionated scheme showed a similar survival probability and duration of palliative effect compared to the conventionally fractionated group. The poor prognostic groups receiving radiotherapy had a highly significant better survival compared to the no-treatment group. Patients treated with an Ir-192 boost had a better median survival compared to a historical group matched on selection criteria but without boost treatment (16 versus 9.7 months, n.s.). However, survival at two year was similar. Analysis on pre-treatment characteristics at multivariate analysis revealed age, neurological performance, addition of radiotherapy, total resection, tumour size post-surgery and deterioration before start of radiotherapy (borderline) as significant prognostic factors for survival.
Conclusion: Despite technical developments in surgery and radiotherapy over the last ten years, survival of patients with a gbm has not improved in our institution. The analysis of prognostic factors corresponded well with data from the literature. A short hypofractionated scheme seems to be a more appropriate treatment for patients with intermediate or poor prognosis as compared to a conventional scheme. The benefit in median survival for patients treated with an interstitial boost is partly explained by patient selection. Since there were no long-term survivors with this boost treatment, its clinical value, if there is one, is still limited.

Introduction

Glioblastoma multiforme (gbm) is one of the most devastating primary tumours in oncology. Median survival of all patients with a gbm after surgery and radiotherapy is less than one year with hardly any patient surviving more than 2 year (2;26). In the last decennium new techniques in diagnostics as well as treatment have entered the clinic for neuro-oncology patients. The use of MRI, CT-simulation, conformal radiation techniques, interstitial boost therapy and hypofractionation became standard over the last 10 years in our institute. These innovations can have an influence on treatment results and prognostic factors. Generally accepted favourable prognostic factors for gbm are low age, good performance, normal mental status, totally resected tumours and dexamethason independence (2;4;15). The purpose of this retrospective analysis of all gbm patients presented at an academic radiotherapy department is to provide an update of prognostic factors over the last ten years including the results of modern radiation schemes.

Patients and Methods

Patient population

Between 1988 and 1998, 198 patients with primary histological proven gbm were referred to the radiotherapy department. Patients with an anaplastic astrocytoma (WHO) or grade III (Daumas-Duport) astrocytoma as well as recurrent tumours were not entered in this study. All patients were operated at the same neurosurgical department. Standard policy was complete resection of macroscopic tumour preserving neurological functions in eloquent areas. For patients in a poor neurological condition or with deep-seated tumours, surgery was confined to a stereotactic biopsy. All patients were discussed with representatives of the radiotherapy department. Radiotherapy (RT) was the standard postoperative treatment except for older patients in poor neurological condition. However, when these patients expressed a strong wish for treatment they were accepted for irradiation. None of the patients received systemic chemotherapy as part of the primary treatment.

All patients were followed until death or until 1st September, 1998 and none of them was lost to follow-up for survival analysis. A CT-scan was mostly performed at 3 months after radiotherapy and/or at clinical deterioration. An in-field recurrence was defined as tumour progression extending from the original tumour area.

Prognostic factors

Pre-radiotherapy variables recorded include age, duration of symptoms, neurological performance scale (NPS), corticosteroïd dependency, tumour diameter on pre-surgery and post-surgery CT-scan (RT-planning CT-scan), number of tumours, infiltration in midline structures, tumour localisation, histological subtypes (i.e. oligodendroglial, gemistocytic or sarcomateus components) and extend of surgery as stated in the operation report (table 2). The NPS was scored according to the MRC scale: 0 = no neurological deficit, 1 = some neurological deficit but function adequate for useful work, 2 = neurological deficits causing moderate functional impairment, 3 = neurological deficits causing major functional impairment and 4 = no useful function, inability to make conscious responses. NPS was

scored at start of radiotherapy and during each follow-up visit. Patients were classified according to the RTOG prognostic grouping described by Curran et al. (table 3) (2).

Radiotherapy

All patients had a simulation procedure including a planning CT-scan with i.v. contrast. Maximum tumour diameter as defined by the contrast-enhancing area was measured on the pre-operative and planning CT-scan. MRI data were not used for this analysis since MRI became only available in our institute since 1992 and comparison of tumour size between diagnostic MRI and planning CT-scan was not considered as adequate. To avoid movements of the head during treatment, patients were fixed to the treatment table with a transparent cast. A target volume was delineated on each slice of the planning CT-scan, covering the contrast-enhancing zone plus a margin of 1.5 cm. No whole brain or cone-down fields were used. A multiple field computer planning was made for each patient. Dose was defined at the isocenter. Individually cerrobend blocks were delineated for each field. The definitive blocks and position of isocenter were checked during a second simulation session. All patients were treated with a 6 MV linear accelerator. Corticosteroïds were not given on a prophylactic base but only when indicated.

From 1988 to 1989 all patients received a dose of 66 Gy/2 Gy in 6.6 weeks. Since the end of 1989 a prospective phase II study was started: A dose escalating hypofractionated scheme was given, starting with four fractions of 5 Gy and escalating to four fractions of 7,5 Gy in six steps. The dose rate of the linear accelerator was reduced to 15 cGy/min in this study. Radiation was given twice daily, with an interval of 8 hours and an overall time of 2 days (5). A scheme of 4 x 7.5 Gy in a dose rate of 15 cGy/min is considered biologically equivalent to 66 Gy in 6 weeks according to the LQ concept for an α/β of 2 Gy and a repair half time of 1.5 hr (6). The study was stopped after 28 patients because of time-consuming reasons on the accelerators. From 1992 to 1993 a hypofractionation scheme of 8 x 5 Gy, 3 times per week, was used for non-favourable patients and 66 Gy remained the dose for more favourable patients. The 8 x 5 Gy scheme is biologically equivalent to 70 Gy in 7 weeks. By most clinicians however this scheme was felt to be safer compared to the 4 x 7,5 Gy scheme in a reduced dose rate because of the much longer overall treatment time. Since the end of 1994 a hypofractionation scheme of 28 Gy in four fractions of 7 Gy in a normal dose rate (overall time of 8 -11 days) was the standard scheme for non-favourable patients and 66 Gy remained standard for favourable patients. Patients were classified as favourable when they fulfilled the following criteria: NPS 0-2, age less than 60 years, no mental disturbances, solitary tumour less than 6 cm in maximum diameter and no clinical deterioration in the period between surgery and start of radiotherapy. Since 1993 patients with a NPS $\leq$ 1 and a well circumscribed solitary tumour not exceeding 4.5 cm in maximum diameter and appropriate located, were treated with an interstitial Ir-192 boost of 40 Gy after an external beam dose of 60 Gy in 6 weeks. The boost was given with a median of 34 days after the external irradiation. Mean volume at the specified isodose was 47 cm3 and mean dose-rate was 61 cGy/hr.

The analysis included 198 patients. Twenty-two patients were treated with an interstitial boost (Ir-192 group). Sixty-six patients received the conventional external irradiation scheme of 66 Gy (66 Gy group). Forty-one patients were treated with the 8 x 5 Gy scheme, including 14 patients

from the phase II study with fraction doses of 5-6 Gy (40 Gy group). Forty-eight patients received the extreme hypofractionation scheme of 4 x 7 Gy, including 14 patients from the phase II study with fraction sizes of 6,5-7,5 Gy (28 Gy group). In twenty-one patients no irradiation was given (no-RT group).

Statistical methods

Survival was calculated from the date of surgery and survival curves were estimated by the Kaplan-Meier method. SPSS software was used for analysis of the data. The log-rank test was used to compare survival curves univariately. In the multivariate analyses (Cox-regression) the following prognostic factors were entered: Age, tumour size post-RT (continuously), deterioration pre-RT (yes or no), localisation (frontal or non-frontal), NPS (0-1, 2, 3-4), extend of resection (total or nearly total, partial, biopsy), number of tumours (solitary or multiple) and radiation group. Radiation schedule however was depending on pre-treatment factors, which should be considered when interpreting the results.

Results

Survival

Median survival for the Ir-192 group, 66 Gy group, 40 Gy group, 28 Gy group and no treatment group was respectively 16.2 months, 7.1 months, 5.6 months, 6.6 months and 1.8 months (Figure 1). Median survival for all patients receiving radiotherapy was 7.4 months (n=177) and 9.3 months for favourable patients treated with 60-66 Gy with or without Ir-192 (n=88). Distributions of prognostic factors per radiation group are shown in Table 1.

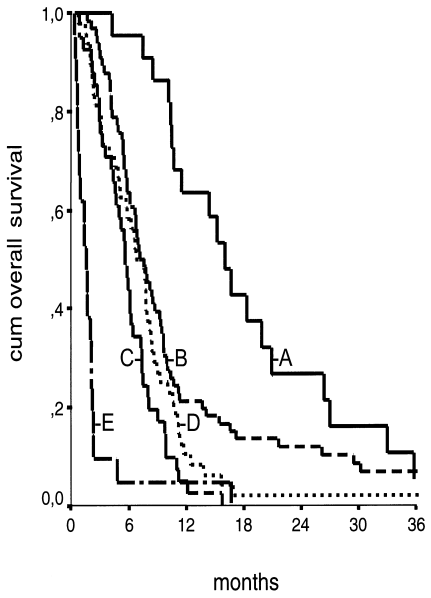

Figure 1. Actuarial survival by fractionation group. A= Ir-192 group, B= 66 Gy group, C= 40 Gy group, D= 28 Gy group, E= no RT group.

Table 1. Distribution of prognostic factors by fractionation group (NPS = neurological performance scale; RT = radiotherapy).

Fraction group	Mean age (yr)	Mean NPS	% tumours > 4 cm	% (nearly) total resec-tions	% deterioration before RT	Steroid dependency (≥ 5 mgr)
No RT	60	2.8	76%	5%	91%	100%
4 x 7 Gy	60	2.5	80%	4%	47%	77%
8 x 5 Gy	60	2.2	78%	12%	34%	73%
33 x 2 Gy	54	1.5	60%	23%	21%	36%
Ir-192 boost	55	0.8	38%	52%	0%	10%

Patients without treatment did significantly worse compared to all groups with treatment ($p<0.0001$). The Ir-192 boost group (n=22) survived significantly longer compared to the 66 Gy group ($p<0.0001$) at univariate analysis, but the p-value of this difference was reduced to 0.07 at multivariate analysis. Out of the 66 Gy group and hypofractionation groups, respectively 11 and 7 patients fulfilled the selection criteria for a boost, but were not treated with Ir-192, mainly because they entered the clinic in the period before the interstitial boost technique became available. They were used as a matched control group (Ir-192 control group). The median survival of the Ir-192 control group was 9.7 months which was not significantly different anymore compared to the Ir-192 group ($p=0.56$) with similar survival results at 2 year (fig 2). The Ir-192 control group had a borderline significant better survival ($p=0.038$) compared to the remaining patients from the 66 Gy group who were not eligible for an Ir-192 boost (n=55, Smed=7 months) (Figure 2).

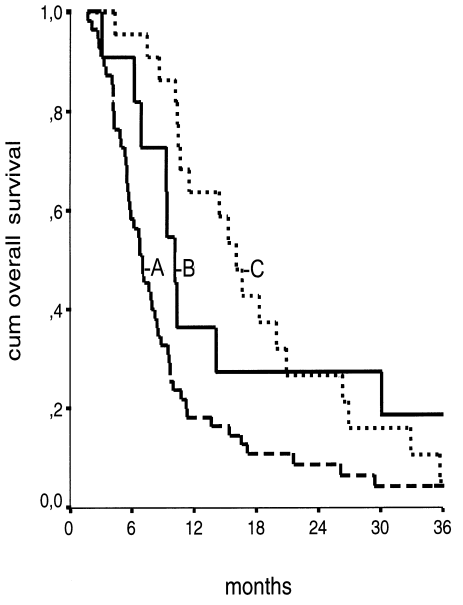

Figure 2. Actuarial survival of patients treated with (A) the conventional scheme not eligible for Ir-192 (n=55), (B) external irradiation only but eligible for an Ir-192 boost (n=18) and (C) patients treated with an Ir-192 boost (n=22).

The number of patients is too small however, to derive definite conclusions. The improved survival in the 66 Gy group compared to the hypofractionated groups at univariate analysis disappeared completely after correction for prognostic factors at multivariate analysis (Table 2). This was due to the overrepresentation of unfavourable prognostic factors in the hypofractionation groups. In three consecutive time periods between 1988 and 1998 there was no trend in survival results.

Table 2. Patients characteristics and univariate survival analysis (n=198) (NPS = neurological performance scale).

Variable	N	Median survival in months	log-rank test (p-value)
Fractionation			p<0.0001
No RT	21	1.6	
28 Gy	48	6.7	
40 Gy	41	5.6	
66 Gy	66	7.1	
Ir-192	22	16	
Age (years)			p=0.002
≤ 40	20	7.5	
41-50	31	7.1	
51-60	58	7.9	
61-70	64	5.9	
> 70	25	4.9	
Number of tumours			p=0.0031
Solitary	186	7.7	
≥ 2 tumours	12	3.7	
NPS			p<0.0001
0	22	9.4	
1	58	9.4	
2	47	5.6	
3	51	4.2	
4	20	2.2	
Corticosteroïds dependency			p<0.0001
0	49	10.3	
<5mg	33	9.4	
5-10mg	39	5.6	
>10mg	58	5.3	
Missing	19		
Extend of resection			p=0.0000
Total/nearly total	22	11.3	
Partial	62	6.2	
Biopsy	17	4.8	
Tumour size pre-surgery			p=0.0015
<4 cm	62	8.5	
4-5 cm	63	6.7	
5-6 cm	39	6.3	
6 cm	29	2.9	
Missing	5		

Deterioration between Surgery and RT			p<0.0001
No	125	8.2	
Yes	68	3.2	
Missing	5		
Tumour size postop.			p<0.0001
Increase	62	6.2	
Stable (± 0.5 cm)	78	5.6	
Decrease	41	9.8	
Missing	17		
Localisation			p=0.005
Pure frontal	50	8.2	
Other	148	5.9	

Recurrences

Follow-up CT was not performed in 26%, mostly because of a poor neurological condition. During follow-up of the remaining patients, 82% developed an in-field recurrence, 6% a recurrence at the margin of the RT fields and 3% a distant recurrence in the brain. Eight percent had no signs of a recurrence at time of death or last follow-up. Twenty-one of the twenty-two patients from the Ir-192 group developed a recurrence, all at the primary site.

Prognostic factors

Significant prognostic factors on univariate and multivariate analysis including hazard ratio's are shown in Table 2 and 3.

Table 3. Multivariate analysis of prognostic factors (Cox-regression for survival) (NPS = neurological performance scale; RT = radiotherapy).

Variable	Subgroups	Significance (p-value)	95% CI	Adjusted hazard ratio
Fractionation		<0.0001		
	0 Gy vs. Ir-192 group	<0.0001	8.2-56	21.5
	2 Gy vs. Ir-192 group	0.07	1-3	1.7
	5 Gy vs. Ir-192 group	0.03	1.1-4.1	2.1
	7 Gy vs. Ir-192 group	0.28	0.7-2.7	1.4
Resection		0.0001		
	Partial vs. (nearly) total	0.0007	1.4-3.2	2.1
	biopsy vs. (nearly) total	0.0000	1.9-5.7	3.3
NPS		0.0001		
	NPS 2 vs. NPS 0-1	0.24	0.5-1.2	0.8
	NPS 3-4 vs. NPS 0-1	0.007	1.2-2.9	1.8
Age	Continuously per year	<0.0001	1.02-1.05	1.03
Tumour size post-op	Continuously per cm	0.018	1.02-1.26	1.14
Deterioration before RT	yes or no	0.08	1-2	1.4

Fractionation, age, unifocality, NPS, corticosteroïd dependency, extend of resection, tumour size, deterioration before RT, postoperative decrease of tumour size and frontal localisation were prognostic factors at univariate analysis. Not of prognostic significance were midline infiltration (yes or no), ventrikel extension (yes or no), involved brain site (left or right), duration of symptoms (<1 months, 1-3 or >3 months), interval surgery-radiotherapy (less or more than 35 days) and histologic subtypes (pure gbm, gbm with gemistocytic, oligodendroglial or sarcoma components). At multivariate analysis age ($p<0.0001$), NPS ($p<0.0001$), use of corticosteroïds ($p=0.004$), extend of resection ($p=0.005$), Ir-192 boost ($p<0.0001$) and the post-operative size of contrast enhancing area ($p=0.02$) remained statistically significant factors. Clinical deterioration before start of RT and decrease of contrast enhancing area on the planning CT-scan were highly significant at univariate analysis but borderline significant at multivariate analysis. Deterioration, decrease of post-operative contrast enhancing and NPS however were strongly interrelated. Number of tumours and localisation (frontal or non-frontal) were not of prognostic value anymore.

Survival curves according to the prognostic grouping of the RTOG database are shown in Figure 3. Median survival for group III, IV, V and VI was respectively 10.7 months, 7.9 months, 7.7 months and 2.3 months (Table 4). This grouping was significantly predictive for outcome ($p<0.001$). Pairs of groups were compared using the log-rank test to detect differences. Group III and IV and group V and VI had significantly different prognosis from each other (resp. $p=0.0187$ and $p=0.0000$). Group IV and V were not significantly different ($p=0.22$).

During the interval between surgery and start of irradiation (mean 35 days), 37% of the patients expressed a clinical deterioration. There was no difference in median survival between patients with an interval $\leq$ 20 days, 21-30 days, 31-40 days and > 40 days (respectively 8.2, 6.6, 7.4 and 7.8 months). However, there were also no significant differences between interval group and both NPS, deterioration and change of tumour size (respectively $p=0.97$, $p=0.47$ and $p=0.45$, Chi-square test).

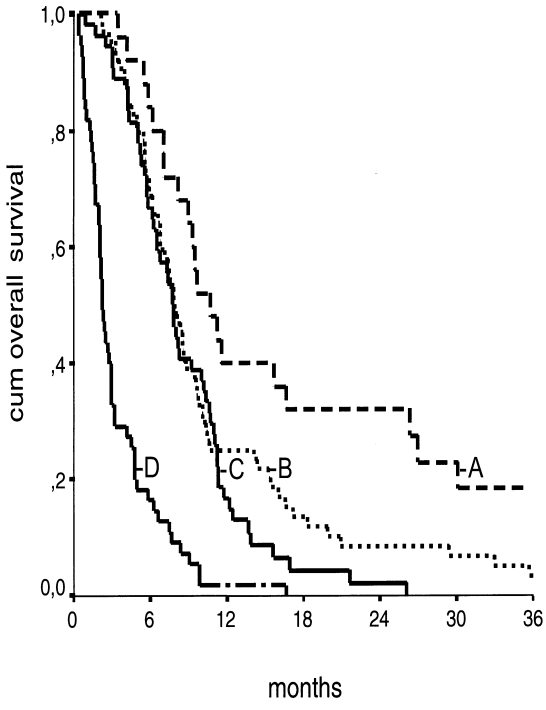

Figure 3. Actuarial survival according to RTOG-prognostic grouping. A = prognostic group III, B = group IV, C = group V and D = group VI.

The mean interval between surgery and RT-planning CT-scan was 28 days. No significant correlation was detected between extend of resection as stated by the neurosurgeon (biopsy excluded) and postoperative change of contrast enhancing area (p=0.143, Chi-square test).

Table 4. Literature review of median survival in months according to RTOG grouping* (KPS= karnofsky performance scale; RT = radiotherapy).

	III (% of pat.)	IV (% of pat.)	V (% of pat.)	VI (% of pat.)
Curran 1993, N=1290	18 (14%)	11.1 (35%)	8.9 (31%)	4.6 (20%)
Kleinberg 1997 N=102	22 (14%)	13 (32%)	8 (34%)	5 (20%)
Mohan 1998, N=201		9.2 (6%)	6.6 (69%)	3.1 (25%)
Present study N=198	10.7 (13%)	7.9 (32%)	7.7 (27%)	2.3 (28%)

*RTOG grouping for gbm (astrocytoma with anaplastic foci are not mentioned)

III: < 50 year, KPS 90-100
IV: < 50 year, KPS < 90
50 year, KPS 70-100, resection, able to work
V: ≥ 50 year, KPS 70-100, resected, can't work
≥ 50 year, KPS 70-100, biopsy, RT > 50.4 Gy
≥ 50 year, KPS < 70, normal mental status
VI: ≥ 50 year, KPS 70-100, biopsy, RT ≤ 50.4 Gy
≥ 50 year, KPS < 70, abnormal mental status

Palliative effect

The median period of neurological improvement or stabilisation after surgery was 3, 2 and 3 months for respectively the conventional group, the 8 x 5 Gy group and the 4 x 7 Gy group. For the Ir-192 group the median period of survival with a Karnofsky of ≥ 70 was 12 months.

Discussion

Survival of patients with a glioblastoma multiforme in the present study has not improved neither during the last decade nor compared to historical data from the literature, in spite of several technical developments. Survival was somewhat less in the more favourable prognostic groups compared to the literature but was comparable for patients in the poor prognostic groups (table 4). Distribution of patients over the prognostic groups was similar with others (table 4). The less intensive hypofractionated course in this study resulted in a similar survival with a similar palliative effect compared to the conventional fractionated scheme. Hypofractionated radiotherapy was tested in a few other phase II studies, using fraction doses of 3-5 Gy, mainly in a subgroup of poor prognosis patients (1;8;11;19;23).

They all concluded that survival results were comparable to those achieved after conventional radiotherapy without increasing toxicity. The conventional scheme of a 6 weeks irradiation period may be inappropriate for most of the glioblastoma patients, particularly for those with a short expected survival. Although there is a proven efficacy of radiotherapy for patients with malignant glioma (10;26), its role in poor prognosis patients is sometimes discussed (16). The irradiated poor prognosis patients in the present study had a significantly improved survival as compared to the non-irradiated group (6.6 vs. 1.8 months), although differences in prognostic factors were only minor. This suggests a comparable increase of survival by radiotherapy in poor prognosis patients compared the proven survival benefit for unselected malignant glioma patients. (10;26). In agreement with our results two recent retrospective studies in elderly patients showed a 4-6 months increased survival when treated with radiotherapy compared to sub-optimal or no irradiation (13;25). Furthermore, the addition of radiotherapy is entered as one of the determining factors in the poor prognostic classes of the RTOG prognostic grouping (2). The Scandinavian working group is currently investigating the benefit of hypofractionated treatment schedules in the Nordic glioma study in elderly patients.

Treatment with Ir-192 as a boost after external irradiation resulted in a significant better median survival compared to treatment with 60-66 Gy alone (16 versus 7 months). However the Ir-192 boost group was strongly interrelated with favourable prognostic factors as NPS, tumour size and absence of deterioration. When the Ir-192 group was compared to a selection out of the only external irradiated group eligible for Ir-192 (Ir-192 control group), the difference in survival was not significant anymore and survival rates at two years were similar. Thus, the improved survival of the Ir-192 group was at least part the result of patient selection, which was also found by others (3;12). Two randomised studies have been performed on the role of an Ir-192 boost, of which the only published study did not find a significant survival benefit after interstitial boost (12). Selker (abstract) reported an improvement in median survival, but this study has never been published (17). Even if there is an advantage of brachytherapy, advocated in several phase II studies (20;21;27), it is probably not more than a few months, without increasing the number of long term survivors. This should be weighted against the increased costs and toxicity. Dose escalation by focused stereotactic external radiation (radiosurgery) has become available and has the advantage of being an outpatient, non-invasive therapy, with the possibility of fractionation. Recent clinical comparisons between radiosurgery and brachytherapy in newly diagnosed or recurrent brain tumours resulted in similar survival for both treatment options (18;24). Currently, both the EORTC and the RTOG have conducted a randomised trial to investigate the therapeutic value of stereotactic radiosurgery as a boost in selected patients with malignant glioma.

The present study revealed age, NPS, addition of radiotherapy and extend of resection as prognostic factors at multivariate analysis, which is in agreement with other publications on prognostic factors (2;4;15;16;26). In this study a total or nearly total resection according to the statement of the neurosurgeon was of prognostic value. No difference was found between

partial resection and biopsy only. Despite the many studies on this issue there is no general consensus concerning the effect of cyto-reductive surgery on survival (14).
A negative prognostic influence of the waiting time for radiotherapy was expected given the rapid growth pattern of this disease, but was not found. The lack of such a correlation could be explained by the clinical tendency to advance start of treatment in clinically progressive, negative selected, patients.
Decrease of contrast enhancing area between the pre and post-operative scan was significant for prognosis at univariate analysis in our series, but not anymore at multivariate analysis. Wood et al. also found a relation between decrease in tumour size and survival, although not significant ($p=0.16$) (28). In a recent extensive study using pre- and postoperative quantitative radiological imaging, it was again concluded that decrease of tumour size by surgical resection may improve survival but its importance is less than other factors like age, performance status and adjunct of radiotherapy (9).
Karim et al introduced a T-classification for brain tumours, based on tumour size and midline infiltration, which is a common staging parameter in tumours outside the brain. Both parameters were indeed found to be of prognostic value in low-grade gliomas (7). In the present study on glioblastoma however, neither infiltration in midline structures nor penetration into the contralateral hemisphere was of significance for survival although midline penetration showed a tendency for decreased survival. This is in agreement with Stelzer et al. who found no significant influence of corpus callosum involvement at multivariate analysis. However, subgroup analysis revealed corpus callosum infiltration as an unfavourable prognostic factor among young, good performance status patients (22). Literature data on this tumour parameter are scarce.
Future directions: No definitive improvement in survival has been observed over the last 20 years in glioblastoma patients, despite several innovations in radiotherapy and chemotherapy. Considering the limited survival with standard treatments it is recommended to enter glioblastoma patients in trials investigating new alternative strategies, based on recent advances in our knowledge about the biology of malignant gliomas (15). At fundamental level we are currently investigating the cellular kinetics of malignant gliomas in relation to their genetic aberrations in glioma cell cultures and human glioblastoma multicellular spheroids, in order to individualise treatment in the future. At clinical level we consider the overall benefit of brachytherapy to be small and the current preference is to enter these patients in a phase I-II study combining external irradiation with interstitial hyperthermia. If not eligible for a trial, a hypofractionated course of radiotherapy is the recommended treatment schedule at our department for poor prognostic patients, with extension of this schedule to more favourable patients being under investigation.

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3. Brachytherapy; results of two different therapy strategies for patients with primary glioblastoma multiforme

RW Koot, M Maarouf, MCCM Hulshof, J Voges, H Treuer, C Koedooder, V Sturm , DA Bosch

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Summary

Background: We describe and compare two different strategies of brachytherapy for the treatment of patients with primary glioblastoma multiforme (GBM).

Methods*:* The study consisted of 84 patients. 45 patients were implanted with permanent or temporary low-activity ^{125}I seeds in Cologne and 21 patients were implanted with temporary ^{192}Ir wires in Amsterdam. Both groups received external beam radiation therapy (EBRT): the ^{125}I group received 10 - 30 Gy with the implant in situ and the ^{192}Ir group received 60 Gy before implantation. In Cologne, implantation was carried out after a diagnostic stereotactic biopsy whereas in Amsterdam implantation took place after cytoreductive diagnostic surgery. In addition, 18 patients in Amsterdam served as a control group. This group only received EBRT after cytoreductive surgery.

Results: In both groups mean age was between 50 and 55, 80 % of the patients were more than 45 years old. The mean implantation volume encompassed by the referenced isodose was 23 cm^3 for ^{125}I and 48 cm^3 for ^{192}Ir. Initial dose-rates were 2.5 - 2.9 cGy/hr for permanent ^{125}I, 4.6 cGy/hr for temporary ^{125}I and 44 -100 cGy/hr (mean 61 cGy) for ^{192}Ir. A total dose of 50 - 60, 60 - 80 and 40 Gy respectively was given at the outer margins of the tumor.

Median survival was approximately 16 months for both the ^{125}I group and the ^{192}Ir group. This was 6 months more than median survival in the control group. Re-operations were done in 4 (9%) patients of the ^{125}I group versus 7 (35%) patients of the ^{192}Ir group. No complications or late reactions were reported in the ^{125}I group, whereas 1 hemorrhage and 3 delayed strokes were observed in the ^{192}Ir group.

Conclusion The equal median survival times in these two brachytherapy groups with such different dose-rate radiation schedules support the hypothesis that dose-rate does not play a major role in the survival of primary GBM.

Introduction

Brachytherapy for malignant brain tumors has been practiced since the early 1980s. This therapy was developed as an additional internal boost of radiation in order to improve local tumor control in malignant astrocytoma. First, only patients with tumors that recurred after previous EBRT were treated with brachytherapy (2;3;6-8;11;15). Subsequently, brachytherapy applied as a boost to EBRT became part of the initial treatment of patients with malignant astrocytoma in some centers (3;9;10;15;19;24). The Cologne group started in 1982 with a treatment schedule combining brachytherapy at low dose-rates with EBRT (34). Non-randomized studies have reported improvement in survival, but it remained unclear whether this was an objective result, or whether it was due to a selection of patients with more favorable prognostic features (20;21;31;35;37). Thus far, two randomized studies on brachytherapy as a boost to EBRT in the initial treatment of patients with malignant astrocytoma have been published. In the first study, carried out by the Brain Tumor Cooperative Group, median survival increased significantly by 3.5 months (29). In the second study, carried out by the Toronto group, survival did not increase significantly (17). Moreover, this latter group stresses the fact that brachytherapy is an invasive procedure which can be associated with considerable morbidity. There were differences between these studies with respect to EBRT, stereotactic implantation technique, dose-rate and total dose.

To investigate the influence of different treatment strategies of brachytherapy on survival, we compared a German group of patients with a Dutch group of patients. Both groups received brachytherapy as a boost to EBRT in the treatment of primary glioblastoma multiforme (GBM), but very different treatment strategies were followed.

On the basis of these results we will try to outline the role of brachytherapy for malignant astrocytoma in the near future.

Patients and Methods

Patients

The study consisted of 84 patients with GBM according to Daumas-Duport(4), (astrocytoma grade 4 according to the WHO classification). Patients were consecutively enrolled and treated at the department of Stereotactic and Functional neurosurgery of the University of Cologne, Germany, or at the department of neurosurgery of the Academic Medical Center in Amsterdam, The Netherlands. Only patients with a supratentorial, well-demarcated tumor with a maximum diameter of 5 cm were eligible for brachytherapy. All patients signed an informed consent. In Amsterdam, patients were excluded when they were younger than 30 years (increased survival for young patients), when they had a Karnofsky Performance Score (KPS) of less than 70, or when the tumour was located in the midline. In Cologne, patients were excluded only if they had a KPS of less than 50. Patient and implant characteristics are summarized in Table 1.

In Cologne, 45 patients underwent brachytherapy with ^{125}I seeds between 1988 and 1995 and were analyzed retrospectively until 31-12-1997. The histopathological diagnosis was made by means of a stereotactic biopsy. During the same operation (tissue diagnosis by squash examination), or at the latest 14 days later, ^{125}I seeds were implanted. Between 1988 and 1990 all implants were permanent, in 1990 they were both permanent and temporary. From 1991 all

implants were temporary (90 days). All patients underwent EBRT with 10-30 Gy (mean 22 Gy) with the implant in situ.

Table 1: Patients and implant characteristics.

	Cologne	Amsterdam BT	Amsterdam nBT
no. of patients	45	21	18
no. of matched patients	18	21	18
mean age (years)	51	54	53
patients > 45 years	84 %	80%	67%
m:f	1,6:1	1,9:1	1:1
KPS ≥ 70 (pt)	34 (76%)	21 (all)	18 (all)
tumour -midline (pt)	23	-	-
-non-midline (pt)	22	21	18
localisation-parietal (pt)	10	11	9
-frontal	8	5	5
-temporal	4	3	3
-occipital	0	2	1
diagnosis made by	biopsy	cytoreduction	cytoreduction
implantation after diagnosis	0-14 days	8-10 weeks	na
source	^{125}I	^{192}Ir	na
implants	perm (12) and temp (33)	temp only (21)	na
mean initial dose rate (cGy/hr)	2.7 (2.5 - 2.9) / 4.6 *	61 (44 - 100)	na
total dose (Gy)	50 - 60 / 60 - 80*	40	na
mean implant activity (mCi)	15.4 (4.6 - 40.1)	50.0 (25.2 - 90.0)	na
volume mean (cm3)	23	48	43 [x]
>15 cm3 (pt)	60%	95%	78% [x]
mean no of seeds	3 (1 - 7)	na	na
mean no of catheters	1 (1 - 3)	7 (4 - 9)	na
EBRT (Gy)	simultaneous, 10 - 30	before, 60	60

BT: brachytherapy; nBT: no brachytherapy; EBRT: external beam radiation therapy; KPS: Karnofsky Performance Score; Perm: permanent; Temp: temporary; Pt: patient; na: not applicable; Matched patients: age > 30 years, KPS ≥ 70, non mid-line tumour; mCi: millicuries; cGy: centigrays; *: permanent vs temporary; [x] :tumour volume after EBRT.

In Amsterdam, 21 patients underwent brachytherapy with ^{192}Ir wires between 1993 and 1997 and were analyzed prospectively until 31-12-97. The histopathological diagnosis was made by means of cytoreductive surgery. Subsequently, all patients underwent EBRT with 60 Gy in 6 weeks. ^{192}Ir wires were implanted after EBRT (about 10 weeks after surgery). All implants were temporary.

In Amsterdam, a control group of 18 GBM patients, only receiving EBRT after cytoreductive surgery, was also analysed retrospectively until 31-12-1997. This group consisted of patients

who fulfilled the brachytherapy criteria but who were treated before the study started (1993) or who refused brachytherapy.

Methods

In Cologne, low activity ^{125}I seeds (Amersham Buchler GmbH&CoKG) were used in both permanent and temporary implants. In permanent implants, 50 - 60 Gy was given at a mean initial dose-rate of 2.7 cGy/hr (2.5 - 2.9 cGy/hr, 0.6 - 0.7 Gy/day). In temporary implants, 60 - 80 Gy was given at a unique initial dose-rate of 4.6 cGy/hr (1.1 Gy/day). The biopsy and implantation were performed with the modified Riechert-Mundinger stereotactic frame (32). Leibinger software (STP release 2.0 and 3.1) was used for treatment planning (VAX 11/700 computer, Digital Equip. Corp., Maynard, Massachussets, USA / Workstation VS 3500, Digital Equip. Corp., Maynard, Massachussets, USA). Entry points and targets of the catheters were determined with regard to both individual dose distribution and safest path.

Surgical procedure in Cologne: under general anesthesia, the patient was mounted in the modified Riechert-Mundinger frame and transported to the CT scanner. The stereotactic CT-image data were downloaded on a terminal near the operating room and since 1991 they were fused with stored data of a recent MRI-scan. Stereotactic 3 dimensional (3-D) treatment planning was done in cooperation with a physicist. Calculations and optimization of the isodose curves, according to the 3-D contours of the tumor, and adjusting the activity and stereotactic position of the seeds took approximately 1.5 hours. The therapeutic isodose curve was prescribed to the edge of the contrast enhancing area. During the autoclavation of the selected seeds, the aiming bow was build up and the burr-holes were made. An outer catheter made of Teflon (OD: 2.0 mm, BEST-Industries, Inc. Springfield, Virginia, USA) was stereotactically placed and loaded with an inner catheter in which the ^{125}I seeds were placed. After verification by orthogonal X-ray, both catheters were glued in the burr-hole and cut off. The skin was stitched. Finally, the position of the catheters was checked with orthogonal X-ray tubes.

In Amsterdam, ^{192}Ir wires (0.12-0.23 mCi/mm, Amersham) were implanted temporarily. 40 Gy was given at a mean initial dose-rate of 61 cGy/hr (44-100 cGy/hr, 10.6 – 24 Gy/day). The Leksell stereotactic frame was used for implantation and treatment planning was done by combining the Nucletron (Plato) software data with the stereotactic coordinates. All catheters were implanted parallel to each other.

Surgical procedure in Amsterdam: under local anesthesia, the patient was mounted in a Leksell frame and transported to the MRI-scanner or CT-scanner. The stereotactic image data were downloaded on a terminal near the operating room. By means of 3-D visualization, the optimal angle and coordinates for parallel implantation in the tumor were calculated. According to the configuration of the tumor, a pre-planning was made to determine the number and stereotactic coordinates of the catheters. During these calculations, which took approximately one hour, the patient was brought under general anesthesia. Burr-holes (2 mm) were made with a high-speed twist-drill. Hollow catheters were introduced parallel to each other at the calculated depth and fixed to the skin. A CT-scan was made to check the position of the catheters and to determine the length of ^{192}Ir wires, followed by a definitive planning administering 40 Gy at 5 mm around the

contrast-enhancing zone. The catheters were removed as soon as the total dose of 40 Gy was reached.

Results

Survival

In Cologne, median survival was 13 months. Patients who were younger, who had smaller implanted volumes or who had a higher KPS survived longer. Patients with non-midline tumours also survived longer than those with midline tumors. (Survival data are summarized in Table 2).

Table 2 : Median survival in months (see also Figure 1).

	Cologne	Amsterdam BT	Amsterdam nBT
whole group	13	16	10
matched patients	17	16	10
≤ 45 years	48	26	30
>45 years	13	16	9
≤ 15 cm3	19	8[o]	11[x]
>15 cm3	10	17	9 [x]
KPS ≥ 70	15	16	10
KPS < 70	4	na	na
mid-line	11	na	na
non mid-line	17	16	10

BT: brachytherapy; nBT: no brachytherapy; EBRT: external beam radiation therapy; KPS: Karnofsky Performance score; na; not applicable; Matched patients: age > 30 years, KPS ≥ 70, non mid-line tumour; [o]: only 1 patient; [x]: tumour volume after EBRT.

Figure 1

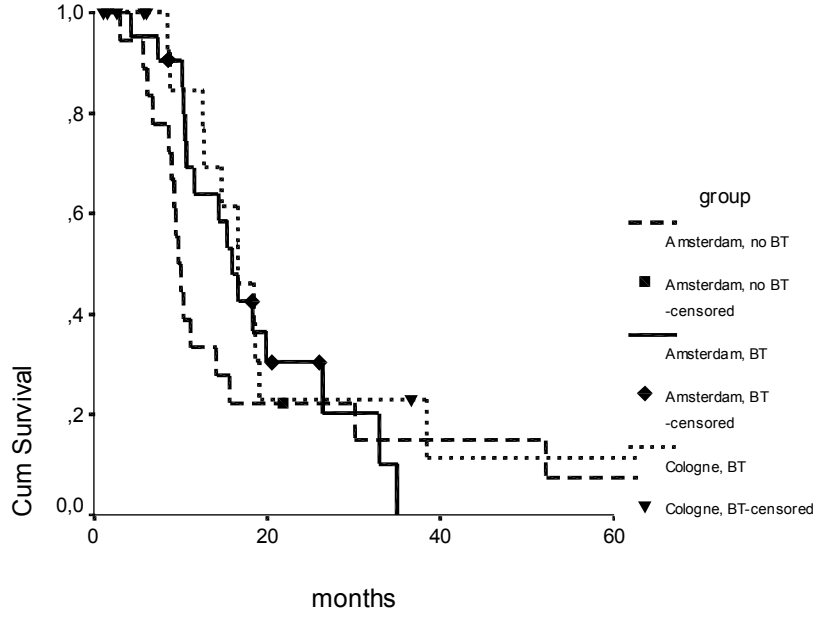

Figure 1: Kaplan Meyer survival curve of matched patients by group. BT: brachytherapy; no BT: no brachytherapy; censored: lost to follow-up.

Patients who were older than 30, who had a KPS of at least 70, and who had a non-midline tumour and who could therefore be compared with the Amsterdam brachytherapy group, had a median survival of 17 months (Figure 1).
In Amsterdam, median survival was 16 months in the brachytherapy group and 10 months in the non brachytherapy group (Figure 1). In both groups younger patients survived longer than older patients.

Adverse effects and re-operations.
In Cologne, no adverse effects were observed during or after brachytherapy. 23 patients (51%) developed recurrences outside the margins of the isodose distribution. Re-operations because of space-occupying lesions were done in 4 patients (9%). Of only 2 patients histological evaluation was done. One showed necrosis and the other showed malignant tumor cells. (Table 3).

Table 3: Adverse effects and re-operations.

	Cologne	Amsterdam BT
Adverse effects		
operation-related	0	1 (5%, arterial haemorrhage)
radiation-induced	0	3 (14%, palsy)
Re-operations	4 (9%)	7 (33 %)
necrosis	1	2
tumour	1	1
both tumour and necrosis	0	4
not evaluated	2	0

In Amsterdam, removal of the temporary implant caused an arterial hemorrhage in one patient (5%). Three patients (14%) developed sudden palsy 6-12 months after brachytherapy, resembling a vascular accident. Recurrences were seen in 20 patients (95%); all occurred at the original site. Re-operations because of space-occupying lesions were done in 7 patients (33%). Most histopathological specimens contained necrosis as well as malignant tumor cells. (Table 3).
In both brachytherapy groups, all implants were positioned accurately and according to the data of treatment planning.

Discussion
In this study, we found no significant differences in survival time between the two groups of patients with primary GBM, although they were treated with very different brachytherapy strategies at 2 institutes. Neither were there any significant differences when these groups were matched for criteria such as age, KPS and tumor localization.
However, some of the differences in brachytherapy strategies between the groups deserve extra attention. First, simultaneous EBRT and brachytherapy (Cologne) reduced overall treatment time. Although, from an oncological point of view, this reduction seems favorable for the treatment of primary GBM this is not shown by our study and is in accordance with reports in the

literature (16;28). Secondly, cytoreductive surgery (Amsterdam) did not increase survival more than did biopsy (Cologne). Although a controversy exists about the value of cytoreductive surgery compared to biopsy in high grade gliomas (13;14;23;25;26), there is general agreement that the impact of cytoreductive surgery on survival is very limited in patients over 65 (12). In our study, although only 10 % of the patients in the Amsterdam group were older than 65, the value of cytoreduction on survival could still not be demonstrated. One explanation for this is the much larger treated volume of the tumor in the cytoreductive group (48 vs 23 cm^3) at the time of implantation.

Furthermore, the isotopes, dose-rate, total dose, and the volume encompassed by the referenced isodose (outer margins of the tumor in Cologne, 0.5 cm beyond the outer margins of the tumor in Amsterdam respectively) differed. For low-grade brain-stem gliomas, ^{125}I is more suitable than ^{192}Ir. Possibly due to high-energy emission and less rapid dose fall-off, ^{192}Ir may cause side effects in the brain stem (22). Although most authors use ^{125}I for brachytherapy in supratentorial tumours, there are no reports indicating that radiation with ^{125}I leads to an increase or decrease in survival compared with ^{192}Ir in patients with high grade gliomas. The much higher dose-rate and the referenced isodose beyond the outer margins of the tumor in Amsterdam, may have contributed to the onset of a sudden palsy in some patients, resembling a vascular accident, 6-12 months after brachytherapy. This hypothesis was supported by histopathological investigation of brain tissue obtained by autopsy, showing abnormalities of the small vessels such as luminal occlusion, loss of endothelial structures and monocellular infiltrates outside the outer margins of the tumour. These vascular abnormalities were probably radiation-induced since they all occurred in the high dose area. On the other hand, these high dose-rates may be responsible for the equal survival times of the patients with large tumours (Amsterdam) and those with smaller tumors (Cologne).

Apart from the differences, there were also some similarities between the Cologne group and the Amsterdam group. First of all, survival in both groups for matched patients was the same (16-17 months) and was strongly influenced by age, KPS and tumor volume, as expected from all other reported data of patients with GBM. Survival in these 2 groups was roughly 6 months more than that in the control group without brachytherapy. Furthermore, selection bias was present in both groups. This was mainly because of the study design, which was not randomized, selecting patients according to various inclusion and exclusion criteria. Bias is always present when planning the treatment of patients with GBM in a non-prospective way. The latter means that the personal or collective experience of a group of neurosurgical oncologists is that a certain treatment is for the benefit of an individual patient, thus selecting patients with more favorable prognostic factors. Therefore, bias may, at least in part, explain the improved survival of brachytherapy patients in non-randomized studies like ours, as compared with the two randomized trials available (18;29), although the extent is difficult to assess (5). Another factor of bias which may have contributed to improved survival of brachytherapy patients is the high rate of re-operations. The number of re-operations in the group of Amsterdam (33%, ^{192}Ir) is similar to that in most previously reported studies, which used similar dose-rates and total dose of radiation, but used ^{125}I instead of ^{192}Ir (18;20;21;24;31;35;37). The number of re-operations in the group of Cologne (9%, ^{125}I) is very low. This may be explained by the relatively small

volumes irradiated (23 cm^3) and by the much lower dose-rate, causing less necrosis and less reactive edema urging re-operations. One may argue that treatment with brachytherapy by a referenced isodose which does not go beyond the outer margins of the tumor can not sufficiently prevent local recurrences, since it is known that these recurrences usually develop at or just outside the tumor margins (1;30). However, this is not shown in the current study.
Arterial hemorrhage occurred once in the group of Amsterdam after removal of the temporary implant, which is 5% of the patient group (21 patients), but which is only 0.7 % of all implanted catheters (142 catheters). This is less than the 1-2% risk of arterial hemorrhage during a stereotactic biopsy (33). The over-all complication rate in Amsterdam (19%) is similar to that in other series (21;27;36). No hemorrhage was seen in Cologne, most probably due to the more sophisticated 3-D planning system.

We have shown the results of two different strategies of brachytherapy for the treatment of patients with primary GBM. Despite these differences, survival of matched patients was equal with both strategies, which is approximately 6 months more than that of the control group. The weakness of our study is that both treated groups cannot be statistically compared because of the very diverse variables and methods. The strength of this study is that it shows that even large differences in brachytherapy strategies show no differences in survival. This makes it likely, that further progress in brachytherapy technology will not lead to further improvement in survival of patients with primary GBM in the near future, until more insight is available regarding favorable treatment factors. In the meantime we must try to minimise complications and late adverse effects.

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4. Quality of Life after Brachytherapy in Patients with Glioblastoma Multiforme

RW Koot, K de Heer, FJ Oort, MCCM Hulshof, DA Bosch, JCJM de Haes

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Summary

Background: As quality of life (QoL) is perhaps the most important outcome for patients treated for glioblastoma multiforme (GBM), we measured QoL in GBM patients after brachytherapy.
Methods: We measured QoL by questionnaires for both patients and partners pre-brachytherapy and at various time-points during follow-up in 21 GBM patients by an extension of the Rotterdam Symptom Checklist (e-RSCL), consisting of 4 subscales. The Karnofsky Performance Scale (KPS) was also measured. Analysis of variance was done to evaluate the direct effect of brachytherapy (visit 1-2, short-term) and during follow-up (visit 1-4, longer-term).
Results: Significant short-term effects were found for 2 subscales of the e-RSCL. Longer-term effects were found for all 4 subscales and for the KPS. A high correlation between partner and patient's QoL assessment was found.
Conclusion: QoL in GBM patients after brachytherapy can be carefully monitored with a subjective instrument such as the e-RSCL. Patients and partners experience QoL equally.

Introduction

As the median survival of GBM patients is less than one year, QoL of life is perhaps the most important outcome for patients and (palliative) treatment should therefore not interfere.
Brachytherapy or interstitial radiotherapy has been developed as an additional internal boost of radiation to improve local tumour control in patients with malignant astrocytoma. However, brachytherapy for malignant glioma has shown only moderate or no benefit at all in length of survival (13;14;24) . As brachytherapy is an invasive therapy, it may have large impact on the patient and its relatives. Treatment evaluation will finally become more balanced if social, mental and physical functioning as an outcome is incorporated into studies and if these items are combined with other items such as length of survival, morbidity and mortality.
The aim of the present study was to measure and follow prospectively the QoL in GBM patients treated with brachytherapy as adjunct to standard treatment. Secondary research questions concern the agreement between patients and their partners, and the relation between subjective QoL measurements such as the e-RSCL and more observer-rated measurements such as for example performance measured by the KPS.

Patients and methods

Patients and partners

This study included 22 patients with a primary GBM according to criteria of Daumas-Duport (astrocytoma grade 4 according to the World Health Organization) who underwent brachytherapy boost (40 Gy) after cytoreductive surgery and external beam radiotherapy (EBRT, 60 Gy in 6 weeks) between 1994 and 1999. Eligibility criteria for brachytherapy were 1) supratentorial, well demarcated GBM with a maximal diameter of 5 cm after EBRT; 2) Age > 30 years (increased survival for young patients); 3) KPS at least 70; 4) Non-midline tumour (3). Patients agreed to complete the QoL questionnaires during this study. The partners or relatives of all included patients were requested to participate in the study and to complete the partner QoL questionnaires. These questions concerned the patient's condition. The partner or relative who completed the questionnaire had to be the same person during the whole study. The partner was usually the husband, wife or child. Occasionally a very close relative completed the questionnaires.

Brachytherapy procedure

Brachytherapy usually took place 8-10 weeks after cytoreductive surgery and has been previously published (3). In summary, parallel-unloaded catheters were stereotactically placed under general anaesthesia. After verification of the position, the catheters were loaded with ^{192}Ir while the patient was kept in a shielded room for approximately 4 days until the end of the radiation. Catheters were thereafter simply removed at the neurosurgical ward. Total hospitalisation time was approximately 10 days. Corticosteroids were given up to 2 weeks after treatment to suppress acute effects of the brachytherapie. Patient and implant characteristics are summarized in Table 1.

Table 1. Patient and implant characteristics

No. of patients	22
Mean age (yrs)	55 (36-72)
Patients age > 45 yrs	86 %
M:F ratio	3,2 : 1
KPS ≥ 90	17 (81 %)
Localization	
frontal	7
parietal	9
temporal	3
occipital	2
Mean volume (cm3)	35 (13-63)
Mean no. of catheters	7 (4-11)
Mean Initial Dose rate (cGy/hr)	60 (42-100)
Median survival[X], whole group (months)	15(4-36)

[X]: from the time of the diagnosis (usually 8-10 weeks before the brachytherapy)

Measurements

RSCL questionnaire

The original Rotterdam Symptom Checklist (o-RSCL), a well-validated QoL instrument (5), was the core instrument to measure QoL in this study. This is a patient and partner 4-point Likert-type questionnaire covering 4 domains (subscales): physical symptom distress, psychological distress, activity level and overall evaluation of life quality. To evaluate more specifically the QoL for brain tumour patients, a brain tumour module consisting of 17 disease-related items, developed for our brachytherapy patients and their partners, was added. The generation and selection of disease-related items was based on extensive pilot interviews with GBM patients who underwent brachytherapy before this study started, administered by the senior author (HCJMH) who developed also the o-RSCL (5). These disease-related items were tested by internal consistency analysis, whether they could be added to the domain of the physical symptom distress or the psychological distress (see statistics and appendix). Items not belonging to whether the physical symptom distress or the psychological distress domain, were omitted. The new extended instrument (e-RSCL) was validated and used for this study. A lower (e)-RSCL-score corresponds to better function or less complaints.

Observer-assessed variables

The Karnofsky Performance Score (KPS, score 0-100) (11), Mini Mental State Exam (MMSE, score 0-30) (15) and Barthel-index for Activities of Daily Living (Barthel-ADL, score 0-20) (18) were recorded serving as observer-assessed variables to measure performance, cognition and activity. For the KPS, MMSE and Barthel-ADL a higher score corresponds to better function.

Study design

Patient and partner were asked to complete the e-RSCL, a few days before the brachytherapy (baseline, visit 1), at discharge usually 1 week after the brachytherapy (visit 2), every three months during the first year (visits 3-6) and every six months thereafter. Patients and their partners completed the forms (self-administration) separately at the neurosurgical ward (visit 1-2) and in the hospital during their outpatient visits, in the presence of a trial-nurse after the doctor's visit. The forms were thereafter blindly added to a database. If a focal deficit enabled the patient to complete the questionnaires, the trial-nurse assisted. Partners were under no circumstances allowed to help patients. In case a patient was not able to visit the outpatient clinic at the scheduled visit, the doctor and the trial-nurse visited him or her at home. Due to progression of the disease, most patients were unable to complete the questionnaire during the last period of their life. Under these circumstances, the partner was asked to continue completing the partner-module until the patient died. The first author (RWK) followed all patients at all visits.

Statistical analysis

Analysis of variance (ANOVA) was performed to test for significant changes over time in all variables. Due to the large dropout of patients we performed separate analysis for short-term (visit 1 and 2) and long-term effects visit (1-4). As the study was small, we chose the level of significance at 10% to keep sufficient power. In the ANOVA's of the e-RSCL, a factor "source of information" is added to test for significant differences between patients and partners. In case the sphericity assumption was not tenable (Mauchly's test), the Huynh-Feldt adjustment of df was applied.

To validate the e-RSCL, all variables were transformed to a 0-100 scale. The internal consistency of the o-RSCL and e-RSCL scale were assessed with Cronbach's α, using the data of the second visit. We considered 0.70 as the minimal alpha coefficient for a reliable scale (21).

Patients and partners QoL assessments were compared through Pearson's correlation coefficient. Pearson's correlation coefficients were also used to compare the observer-assessed variables to the e-RSCL at the second visit.

Results

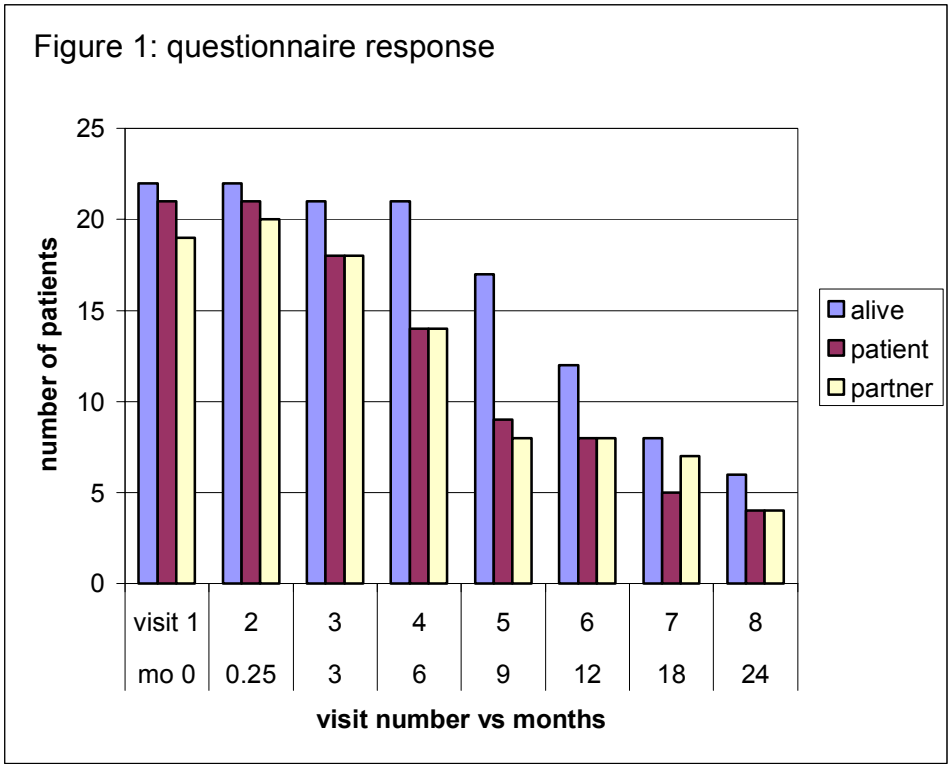
Questionnaire response

Twenty-one patients (95%) and 19 partners (86%) completed the QoL questionnaires at the first visit (Figure 1). The response rate for the questionnaires decreased during the follow-up. At visit four, 14 patients and partners completed the questionnaires (67%), at visit five only 9 patients (53%) and at visit 6 only 8 patients (67%) completed the questionnaires.

Questionnaire reliability and validity

All 17 additional items could be allocated to the physical symptom distress variables or the psychological distress variables of the o-RSCL, according to their content and their correlation with these variables, thus increasing reliability. Compared to the o-RSCL, Cronbach's α of all

scales increased in the e-RSCL. For patients, Cronbach's α of the psychological- and physical scale of the o-RSCL versus the psychological- and physical scale of the e-RSCL was 0.63, 0.60 versus 0.77 and 0.84 respectively at the first visit (N=21) and 0.85, 0.83 versus 0.86 and 0.91 at the second visit (N=20). For partners, Cronbach's α was 0.75, 0.68 versus 0.87 and 0.88 at the first visit and 0.81, 0.75 versus 0.86 and 0.89 at the second visit.



QoL before and immediately after the brachytherapy (short-term effects, visit 1-2)
Scores of 18 patients and partners who both completed the first two visits were available for the analysis of short-term effects. Analysis of variance (ANOVA) showed a main effect of the factor 'time' (first versus second visit) on activity level (F=8.38; df=1; p=0.010), and a main effect of the factor 'source of information' (patient versus partner) on the overall evaluation of life quality (F=5.27; df=1; p=0.035). Main effects on other variables were not significant, and there were no significant 'time x source of information' interaction effects on any of the outcome variables. The Barthel-ADL did not show any variance and had to be omitted from statistical analysis.

QoL during follow-up (longer term effects, visit 1-4)
Average scores of patients and partners who both completed the first four visits are presented in Table 2. Main effects of the factor 'time' (i.e. the first through fourth visit) were found on overall evaluation of life quality (F=2.31; df=3; p=0.078, N=11), activity level (Huynh-Feldt, F=3.46; df=1.455; p=0.069, N=12), psychological distress (F=2.42; df=3; p=0.084, N=12), physical symptom distress (Huynh-Feldt, F=4.65; df=2.139; p=0.018, N=12) and KPS (Huynh-Feldt, F=10.40, df=1.505, p=0.002, N=13). Time effect on MMSE (F=1.82; df=2.164; p=0.179, N=14) was not significant. From Table 2 it appears that the significant effects all indicated deterioration

of health (with KPS and MMSE scores generally decreasing, and scores of other variables generally increasing).
Main effects on the factor 'source of information' were significant only on the overall evaluation of life quality (F=11.23; df=1; p=0.007) and psychological distress (F=4.87; df=1; p=0.05), with partners indicating poorer life quality and more distress. There were no significant 'time x source of information' interaction effects. Baseline visits (visit 1) of patients who completed the first 4 visits did not differ from those of patients who completed fewer visits.

Table 2: Quality-of-life scores of patients and partners who both completed all questionnaires during the first 4 visits.

		patients			partners		
	visit	mean	sd	n	mean	sd	n
Overall evaluation of life quality	1	22,73	17,12	11	28,79	16,82	11
Activity level		12,55	20,55	12	10,76	18,16	12
Psychological distress		21,99	8,82	12	23,34	15,13	12
Physical symptom distress		15,90	9,83	12	16,54	10,33	12
MMSE		28,71	3,00	14			
Barthel ADL		20,00	0,00	14			
KPS		91,92	5,60	13			
Overall evaluation of life quality	2	27,27	17,12	11	40,91	17,26	11
Activity level		19,91	22,59	12	21,76	24,70	12
Psychological distress		23,94	11,32	12	30,79	14,72	12
Physical symptom distress		16,34	10,90	12	17,55	10,85	12
MMSE		28,57	3,03	14			
Barthel ADL		20,00	0,00	14			
KPS		91,15	6,18	13			
Overall evaluation of life quality	3	37,88	19,85	11	39,39	20,10	11
Activity level		14,93	18,16	12	10,42	17,36	12
Psychological distress		30,09	15,75	12	30,74	14,04	12
Physical symptom distress		20,77	10,79	12	20,97	12,46	12
MMSE		26,21	6,45	14			
Barthel ADL		20,00	1,57	14			
KPS		87,69	10,92	13			
Overall evaluation of life quality	4	37,88	13,10	11	40,91	25,13	11
Activity level		25,97	26,38	12	29,17	29,57	12
Psychological distress		26,66	16,48	12	34,49	19,48	12
Physical symptom distress		23,18	12,36	12	23,03	13,07	12
MMSE		26,43	8,06	14			
Barthel ADL		19,57	1,16	14			
KPS		80,77	14,27	13			

Overall evaluation of life quality, activity level, psychological distress and physical symptom distress belong to the Extended Rotterdam Symptom Checklist. MMSE, Barthel-ADL and KPS belong to the observer-assessed variables.

Comparison of patient and partner

The correlation coefficients of the self-reported tests (e-RSCL) between patient and partner in equal subscales for visit 2 were highly significant in all cases. For overall evaluation of life

quality, physical symptom distress, psychological distress and activity level, correlation coefficients were 0.72, 0.81, 0.63 and 0.83 respectively.

Comparison of self-reported tests (e-RSCL) with observer-assessed variables
Physical symptom distress was the only subscale of the e-RSCL that correlated significantly with the KPS (CC=0.49; p=0.030, N=21). Activity level was the only subscale of the e-RSCL that correlated significantly with the MMSE (CC=0.48; p=0.033, N = 21). There were no other significant correlations between self-reported tests and observer-assessed variables. During the study the observer-assessed variables remained longer stable than the self-reported tests.

Discussion
We investigated prospectively and longitudinally the QoL as assessed by patients and partners of GBM patients who underwent brachytherapy. There are several brain tumour studies in which QoL is not only expressed as performance, measured by the physician-related KPS, but also by a self-report multidimensional QoL instrument (2;4;7;10;12;16;20;22;23;26-29). However, most of these studies use one single time assessment in the follow-up for their analysis. For brain tumour patients treated with brachytherapy the study of Bampoe (3)is the only longitudinal and multidimensional study in a prospective randomised trial as far as we know. The only other study using more follow-up time points concerns low-grade glioma (12). Our study not only considers QoL prospectively in GBM patients treated with brachytherapy but also takes into account the partner's view and may thus provide useful extra information, especially when the validity of patient's judgement is in question, as may be seen in patients with brain tumours.

Questionnaire response
With a small sample size (n=22) and a compliance of only 53% at 9 months (visit 5), we consider this as a major weakness of our study, although the response rate of Bampoe (66%) (3) was not much higher and that of Choucair (40%) (4) was even worse. The e-RSCL is easy to complete within 10 minutes for healthy patients, but may take considerably more time for patients who are mentally and/or physically ill. After the doctor's visit, patients were asked to fill in the questionnaires in the presence of the trial-nurse. Some patients who were in a moderate condition refused to stay any longer to fill in the questionnaires. This may explain the low compliance in particular at visit 5, (9 patients died between visit 4 and 6). Sending the questionnaires to the patient's address would have troubled the results, as the separate completion of the forms was not guaranteed. Therefore we decided to accept a higher dropout at these visits. Filling in the forms before or during the doctor's visit or visiting at home by the trial nurse could have increased compliance.
One of the objectives of this study was to follow the QoL of the patients in the last phase of their life by their partners who still completed the questionnaires. This objective was however not realized, as most partners did not return the forms, even after repeated calls. Apparently, partners gave low priority to complete questionnaires in the last phase of their partners' life.
For short-term follow-up we analysed the first 2 visits, for longer-term follow-up we chose to analyse only the first 4 visits because of the still acceptable number of patients and the

reasonable follow-up period. Although 14 patients and partners answered the questionnaires at the fourth visit (Fig 1), there were only 11 to 14 couples that completed all questionnaires during the first 4 visits (Table 2).
As the brachytherapy study was not randomised and consisted of highly selected patients (81% of the patients with a KPS of 90-100), a control group of GBM patients with evenly matched base-line performance could not be recruited. This is another weak point in this study.

Questionnaire reliability and validity
As the internal consistency of all subscales of the o-RSCL improved, the e-RSCL seems to be a reliable and well-validated instrument. Although no earlier reliability and validity data were available as the e-RSCL was specially developed for this study, we believe that the e-RSCL, with its addition of a brain tumour module, should therefore preferentially be used for QoL measurements in patients with brain tumours instead of the o-RSCL.

Short-term effects on QoL
Between visit 1 and 2, significant changes were found for activity level. Although the brachytherapy procedure was well tolerated, the deterioration in activity level means that the patients felt more dependent. The significant factor source of information on the overall evaluation of life quality means that the partner experiences the impact of the brachytherapy on the QoL more serious than the patient.

Longer-term effects on QoL
Between visit 1 and 4, significant changes were found for overall evaluation of life quality, activity level, psychological distress, physical symptom distress and KPS. This means that within 6 months after the brachytherapy both the QoL and performance are seriously impaired. Although the partners had a more pessimistic or more critical view about the QoL in general, the differences between patients and partners were only significant for the overall evaluation of life quality and psychological distress. Interesting is the fact that the patients experienced a serious deterioration after the brachytherapy (between visit 2 and 3) whereas the partners experienced this deterioration around the brachytherapy itself (visit 1 and 2).
The timing of the QoL assessment (1 week after and then not for 3 months) does not tease out acute effects of the brachytherapy followed by recovery by the time of 3 months, since the questionnaire covers only the last week before the visit. Although the patients did not complete forms, they were seen 6 weeks after the brachytherapy in the out patient clinic. None of the patients who completed the first 4 visits showed acute effects.

Comparison of patients and partners
Differences in QoL experience between patients and partners were also found in other studies with diseases not affecting cognition as well in studies with brain tumours patients (26). Patients in general rate QoL higher than partners. In our study the differences between patient and partner did not increase during the first four visits and in fact the correlation between patient and partner is highly significant. Reasons for this discrepancy with other studies may be the selection of

patients with an initially very high performance and the fact that assumed cognitive impairment only slightly interferes with an adequate interpretation of his or her situation. Another reason may be the fact that brain tumour patients suffer less than patients with other malignancies and partners therefore filling in the forms less biased, leading to higher scores. The significant correlation between patient and partner means that during the progression of the disease, when the patient finally may not be able to complete the forms anymore, the partner can give a reliable impression of the patient's QoL. Moderate to high patient-proxy agreement was also reported in a recently published review of health-related quality of life studies (25).

Comparison of self-report questionnaires (e-RSCL) and observer assessed variables

Several studies stress the fact that KPS and Barthel-ADL are insufficient measurements for the assessment of health-related quality of life (23). Such measurements fall short of the criteria required by the World Health Organization's definition of health: '… a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.'

During the follow-up the discrepancy between the observer- assessed variables and the self-reported questionnaires increased, which is to our opinion not surprisingly in patients with brain tumours. This is due to a ceiling effect of observer-assessed variables, in particular the KPS (8), which has been noted by other investigators who use a multidimensional instrument (17). It means that performance is longer preserved than QoL, which is in general the rule unless the tumour is directly affecting motor activities by its location.

The effect of treatment

Different reports about the role of radiotherapy on cognition and quality of life in general are known. Some reports stress the damage of radiotherapy on cognitive function in patients with (low grade) tumours (7;9;19). Other studies found no or limited effect of radiotherapy on cognitive function in (low grade) tumours (10;12;27). In a study of long term survivors of high-grade glioma after treatment with chemotherapy and radiotherapy, most long-term survivors had severe cognition impairment. However, since this impairment was measured at least 5 years after the diagnosis was made, it was impossible to determine whether this cognitive impairment could be attributed to 'progression of the disease' or to late side-effects of either the radiotherapy or the chemotherapy (6). In our study, the survival is in fact too short to reach a conclusion concerning cognitive function.

In the study of Bampoe (3) there were no significant differences in QoL between the implant and non-implant groups. Compared to samples from a normal population and to samples from studies with tumours at different locations but not in the brain (5), the psychological distress in our study was relatively high. This is in agreement with the literature reporting in general high levels of psychological distress in brain tumour patients (1;7;26). Whether this is a tendency in general in brain tumour patients or in brachytherapy patients in particular, cannot be answered by the current study as a control group was not investigated. We believe however that the psychological impact of brachytherapy, a therapy with no proven benefit in high-grade glioma patients, is considerable as indicated by the patients' partners. It should therefore be used only cautiously.

Appendix: Extended Rotterdam Symptom Checklist (e-RSCL) for patients, used in this study.

Appendix Extended Rotterdam Symptom Checklist

Date:

During the last week, did you suffer from:	not at all	a little	pretty	very much	domain (not in hand-out)
lack of appetite	not at all	a little	pretty	very much	phys
irritability	not at all	a little	pretty	very much	psych
tiredness	not at all	a little	pretty	very much	phys
worrying	not at all	a little	pretty	very much	psych
sore muscles	not at all	a little	pretty	very much	phys
depressed mood	not at all	a little	pretty	very much	psych
lack of energy	not at all	a little	pretty	very much	phys
low back pain	not at all	a little	pretty	very much	phys
nervousness	not at all	a little	pretty	very much	psych
nausea	not at all	a little	pretty	very much	phys
despairing about the future	not at all	a little	pretty	very much	psych
difficulty sleeping	not at all	a little	pretty	very much	phys
headaches	not at all	a little	pretty	very much	phys
vomiting	not at all	a little	pretty	very much	phys
dizziness	not at all	a little	pretty	very much	phys
sore mouth/pain when swallowing	not at all	a little	pretty	very much	phys
anxiety	not at all	a little	pretty	very much	psych
decreased sexual interest	not at all	a little	pretty	very much	phys
heartburn/belching (acid indigestion)	not at all	a little	pretty	very much	phys
shivering	not at all	a little	pretty	very much	phys
tingling hands or feet	not at all	a little	pretty	very much	phys
abdominal aches	not at all	a little	pretty	very much	phys
tension	not at all	a little	pretty	very much	psych
loss of hair	not at all	a little	pretty	very much	phys
burning/sore eyes	not at all	a little	pretty	very much	phys
difficulty concentrating	not at all	a little	pretty	very much	phys
shortness of breath	not at all	a little	pretty	very much	phys
dry mouth	not at all	a little	pretty	very much	phys
diarrhoea	not at all	a little	pretty	very much	phys
constipation	not at all	a little	pretty	very much	phys
palpitations	not at all	a little	pretty	very much	phys
a tired feeling in the head	not at all	a little	pretty	very much	phys
sound intolerance	not at all	a little	pretty	very much	phys
light intolerance	not at all	a little	pretty	very much	phys
crying fits	not at all	a little	pretty	very much	psych
worries whether things will turn out OK	not at all	a little	pretty	very much	psych
sore skin	not at all	a little	pretty	very much	phys
the feeling that it is too much	not at all	a little	pretty	very much	psych
difficulty expressing yourself	not at all	a little	pretty	very much	phys
an unreal feeling	not at all	a little	pretty	very much	psych
an unsafe feeling	not at all	a little	pretty	very much	psych
difficulty writing	not at all	a little	pretty	very much	phys
difficulty reading	not at all	a little	pretty	very much	phys
not being able to keep your attention	not at all	a little	pretty	very much	phys
forgetfulness	not at all	a little	pretty	very much	phys
slowness	not at all	a little	pretty	very much	phys
incontinence	not at all	a little	pretty	very much	phys
difficulty seeing	not at all	a little	pretty	very much	phys

Please mark the situation that is most appropriate to you during the last week.

	not able	not able without help	able with difficulties	able without difficulties	
care for myself (wash etc.)	0	0	0	0	act level
walk about the house	0	0	0	0	act level
light housework/household jobs	0	0	0	0	act level
climb stairs	0	0	0	0	act level
heavy housework/household jobs	0	0	0	0	act level
walk out of doors	0	0	0	0	act level
go shopping	0	0	0	0	act level
go to work	0	0	0	0	act level

How did you generally feel during the last week:	0	very good	overall eval
	0	good	
	0	pretty good	
	0	not good, not bad	
	0	pretty bad	
	0	bad	
	0	very bad	

First part (not bold): original Rotterdam Symptom Checklist (o-RSCL); second part (bold): 17 additional disease-related items resulting in the e-RSCL. Partners received an identical questionnaire. Last column: domain attributed to; phys: physical symptom distress; psych: psychological distress; act level: activity level; overall eval: overall evaluation of life quality.

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5. What is the value of emission tomography studies in patients with a primary glioblastoma multiforme treated by ^{192}Ir brachytherapy

RW Koot, JBA Habraken, MCCM Hulshof, AMJ Paans, DA Bosch, J Pruim

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Summary

Background: We studied the use of ^{201}Thallium SPECT and L-[1-^{11}C]-tyrosine PET with a primary glioblastoma multiforme who had been treated with ^{192}Ir brachytherapy after surgery and external beam radiation therapy. We hypothesised that the patients most likely to benefit from further surgery after deterioration would be those with radiation necrosis and would be recognised by a negative emission tomography scan.
Methods: 21 patients underwent ^{201}Thallium SPECT performed before brachytherapy, and this was repeated in 19 patients when recurrence was suspected. Nine patients also underwent a PET scan at the same time. Nine patients underwent a second operation.
Results: SPECT and PET were highly concordant concerning the prediction of radionecrosis and/or tumour recurrence. Repeat surgery did not lead to a significant increase in survival. There was not a significant association between the duration of survival and tumour-to-background ratio but the number studie was small. Both SPECT and PET showed highly active lesions, which were proved to be recurrent tumour by clinical and histological follow-up.
Conclusion: Although PET and SPECT are both highly sensitive in detecting active tumour tissue, emission tomography was not clinically valuable in patients with a primary glioblastoma treated with brachytherapy.

Introduction

We have reported experience of the use of brachytherapy, as an additional boost after surgery and external beam radiation therapy, in a well-defined group of patients with a primary glioblastoma multiforme (10). This approach had been previously reported to potentially improve survival, complicated sometimes by focal radiation necrosis, which required a second debulking operation (6;16).

Differentiation between necrosis and tumour recurrence is not achieved clearly by either CT or MRI but such evidence can be obtained by functional imaging such as ^{201}Tl-SPECT (1;9;12;21) or ^{11}C-amino acid PET (3;4;15;18). We now report our experience of emission tomography in differentiating between these two states. Data from the emission tomography studies were analysed to assess the sensitivity of SPECT and PET in detecting vital tumour tissue. Furthermore, because with a tracer such as ^{201}Thallium, an index of tumour-to-background ratio can be interpreted for tumour activity (8;11;13;19), we compared median survival with tumour-to-background ratios observed in individual patients.

Patients and methods

Twenty-one patients with a newly diagnosed glioblastoma multiforme were recruited over a period of 5 years. All underwent brachytherapy after cytoreductive surgery and external beam radiation therapy, as described in detail elsewhere (10). A baseline ^{201}Thallium-SPECT scan was performed in each patient just before the implantation of ^{192}Iridium sources. Thallium is an analogue of K+ and Na+, although much larger. Cell influx is dependent on the metabolic rate (ATP-ase dependent) of the cell, but limited due to an intact blood-brain-barrier (BBB) in normal circumstances. In tumour areas and certainly after surgery, with a disturbed BBB, thallium can reach tumour cells more easily and thus more influx may be seen. Some authors found a significant correlation between the amount of thallium uptake, grade of malignancy and survival in patients with high-grade glioma. (8;11;13;19). Thallium SPECT studies were acquired in all subjects with a brain dedicated SPECT system (Strichman Medical Equipment 810X), one hour after the injection of approximately 185MBq ^{201}Thallium. Data processing was comparable with PET data processing except for the isodensity contour, which was 40% for SPECT. Tumour-to background ratios were compared with the individuals' survival periods.

Tyrosine PET studies were performed statically from 20 minutes onwards after injection of 200 MBq L-[1-^{11}C]-tyrosine. Subjects had fasted and scan time was 20 minutes. The use of and the characteristics of this radiopharmaceutical as well as detailed technical information about the PET scanner (Siemens/CTI ECAT 951) have been described elsewhere (15). The images were displayed on a computer screen and regions of interest (ROIs) were placed over the tumour in the relevant planes using a 70% isodensity contour. In addition a large background ROI was defined in the contra lateral hemisphere. The data of the different planes were summed and a tumour-to-background ratio was calculated from the 2 sets of summed data.

Apart from the computer calculations, all scans were blindly analyzed by a nuclear medicine consultant, who decided whether tumour recurrence/progression was likely or not. Analysis was based on routine data recording. During follow-up, each patient eventually showed clinical deterioration. They were then investigated with MRI and if a new recurrent mass lesion was

seen a second SPECT was carried out. A PET scan was also performed if the patient was clinically fit to transport to the PET-facility in Groningen (9/21). We used L-[1-^{11}C]-tyrosine as radio-isotope because of the advantage of quantification of the protein synthesis rate (15;20). The resolutions of PET and SPECT scanners are 4-6 and 7-10 mm respectively. Table 1 summarises the characteristics of Tl-SPECT and TYR-PET.

Table 1: Differences between SPECT and PET used in this study

SPECT	PET
^{201}Thallium	L-[1-^{11}C]-tyrosine
7-10 mm resolution	4-6 mm resolution
1+, large atom	amino-acid
Na/K ATP-ase dependent	protein synthesis rate
brain uptake if BBB is disrupted	no disturbance with inflammation (in contrast with FDG)
less suitable at skull base	no uptake in radiation necrosis
cheap	expensive
generally available	requiring extensive laboratory facilities (cyclotron)

Results

Nineteen (19/21) patients were considered possible candidates for further surgical debulking on the basis of MRI images. Two patients who had widely infiltrating disease did not undergo further emission studies.

Sixteen of the 19 follow-up SPECT studies and eight of the 9 PET studies were considered to show tumour recurrence/progression. The one patient whose PET was negative also had a negative SPECT scan so that both techniques raised the suspicion of necrosis (patient 8 in Table 2). Two patients had negative SPECT: one was diagnosed to have necrosis at re-operation but active tumour was found at autopsy, in the other no abnormalities were found at autopsy (patients no 14 and 17 in Table 2). All nine PET scans had results that were concordant with the follow-up SPECT scans.

The tumour-to-background ratios of the 21 baseline Tl-SPECT scans in Table 2, ranged from 1 to 10.75. Only 6 patients had a ratio of 1, indicating that in all the other patients some active tumour was still present at the time of brachytherapy treatment. The tumour -to-background ratios in the 19 follow-up Tl-SPECT studies ranged from 1.33-5.12. Although there was not a significant difference between the pre- and post –brachytherapy ratios (p=0,48, 95% CI, paired t-test), the baseline studies showed a lower tumour-to-background ratios with the exception of patients 8 and 12. (Table 2); this indicated a very active tumour at time of brachytherapy and good response at follow-up.

Pathological Findings

Nine patients wished to undergo re-operation. This was performed even though 8 of them had a scan that suggested tumour recurrence (4 patients had only Tl-SPECT, 5 both Tl-SPECT and TYR-PET). The tissue obtained at surgery showed tumour recurrence in 8 patients with, in some cases, also large fields of necrosis. The tissue removed was in general greyish pale with extensive fibrous bands. The vessels were thin, looked very fragile with a bamboo-spine yellow

aspect. Some calcifications were found. Relaxation of the surrounding brain after resection was very limited due to the fibrous architecture of the (peri)irradiated field. In one patient only necrosis was found in the specimen. This specimen may have been non-representative tissue (sampling error), because at autopsy, 10 months later, a very large recurrent glioblastoma was found.
One patient, whose Tl-SPECT scan suggested radionecrosis, one patient whose Tl-SPECT scan did not show an abnormality and one patient whose Tl-SPECT and TYR-PET both suggested necrosis, did not undergo a second operation.

Table 2: Scan characteristics.

Patient no	Age	Scan report SPECT post	Scan report PET	Result of reoperation	Result of autopsy	Survival (months)	T/B ratio SPECT pre	T/B ratio SPECT post	T/B ratio PET (post)
1	61	+	+	+	na	33	1.65	1,97	1,28
2	55	+	na	na	na	15	2,62	3,58	na
3	62	+	+	+	+	37	1,54	1,95	1,28
4	51	+	+	+	na	18	3,2	5,12	1,36
5	42	+	+	+	na	13	2	3,41	1,32
6	51	+	+	na	na	32	1	1,84	1,75
7	58	+	+	na	na	15	1,81	2,5	1,56
8	51	-	-	na	na	30	5,5	1,35	1,13
9	57	+	+	na	na	9	1	3,31	1,83
10	60	+	na	na	na	10	1,84	3,64	na
11	57	+	+	+	na	35	1,47	3,2	1,57
12	48	+	na	+	na	12	10,75	3,95	na
13	62	na	na	na	na	10	7,38	X	na
14	61	-	na	-	+	20	2,13	2,17	na
15	34	na	na	na	na	8	6,44	X	na
16	32	+	na	+	na	27	1	1,6	na
17	63	-	na	na	-	21	1,37	1,44	na
18	73	+	na	na	na	35	1	3,41	na
19	71	+	na	na	na	15	1	1,33	na
20	36	+	na	+	na	17	1,53	2,69	na
21	54	+	na	na	na	17	1	1,94	na

T/B ratio: tumor-to-background ratio; SPECT: ^{201}Thallium SPECT; PET: L-[1-^{11}C]-tyrosine PET; Pre: pre-brachytherapy; Post: post-brachytherapy; + = tumour positive; - = tumour negative; survival: after initial diagnosis.

Survival

All 21 patients died, although some of them survived for almost 3 years after initial diagnosis (Table 2). Twenty patients died as a result of local recurrence of tumour. One patient died as a result of a pulmonary embolus and was found to be free of tumour at autopsy. The median

survival of the 9 patients who underwent reoperation was 20 months as compared to 15 months in the 12 who did not undergo reoperation (not a significant difference).

Tumour-to-background radioactivity ratio and duration of survival.

The tumour-to-background radioactivity ratio's are summarised in Table 2. There were not clear associations between survival and baseline pre-brachytherapy Tl-SPECT, post-brachytherapy Tl-SPECT, or post-brachytherapy TYR-PET (0.369 (p=0.099, n=21), 0.370 (p=0.119 n=19 and 0.328 (p=0.389 n=9), respectively (Pearson, 2 tailed test)). Patients who lived longer than 30 months after initial diagnosis showed in general a lower tumour-to-background ratio at the post-brachytherapy SPECT scan than patients who survived shorter (Figure 1).

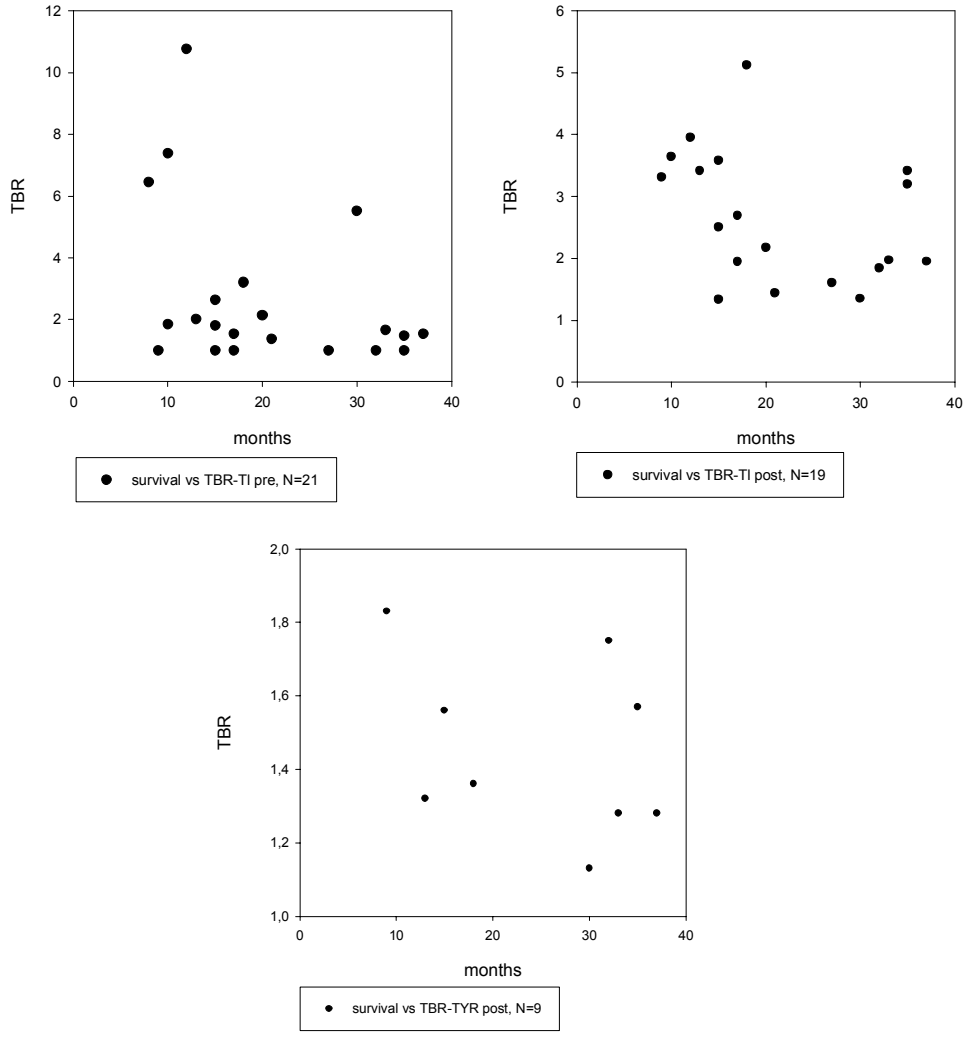

Figure1. Comparison between Tumour to background ratio for ^{201}Thallium SPECT a) pre-brachytherapy and b) post-brachytherapy and c) L-[1-^{11}C]-tyrosine PET post brachytherapy and the duration of a patient's survival.

Discussion

Our findings demonstrated the use of emission tomography in a group of patients with a highly malignant glioblastoma multiforme, who despite receiving adjuvant brachytherapy, all died within 3 years of diagnosis.

In all patients but one, death was a result of tumour recurrence, however, preceding clinical deterioration could also involve radio necrosis. SPECT and PET were equally sensitive in detecting tumour recurrence in the patients studied: eight with a tumour and one with only necrosis. The tumour-to-background ratio radioactivity was not significantly associated with the duration of survival.

Although the value of our results is limited due to small numbers, it is clear that in this particular group of the patients activity of the tumour was only temporarily decreased after treatment and survival was not significantly longer. This appears to have been reflected in only 6 patients with a ratio of 1 at the time of brachytherapy, in all the other cases showing evidence of persisting active tumour at the time of brachytherapy. The main potential value of emission studies is to identify when deterioration is due purely to radiation induced necrosis. This seems to be very rare in patients with an aggressive tumour. The one patient who died from a pulmonary embolus 21 months after diagnosis might have shown recurrent tumour if he had lived for longer.

Taking these findings together with other studies (3-5;17), indicates that differentiation between recurrent glioma and necrosis after extensive irradiation (EBRT plus brachytherapy) might be useful more in patients with a lower graded malignant glioma or a secondary glioblastoma multiforme.

In low-grade gliomas, radiolabeled amino-acid tracers (tyrosine, methionine) (and their derivates (3-[(123)I]iodo-alpha-methyl-L-tyrosine (IMT) or [18F]-fluoro-ethyl-tyrosine (FET)) are reliable tools to discriminate between recurrence and necrosis. Henze *et al.* reported that for 3-[(123)I]iodo-alpha-methyl-L-tyrosine (IMT) SPECT was more sensitive than FDG PET in discriminating between necrosis and recurrence (7). On the other hand PET shows improved discrimination for small lesions compared to SPECT (14), and radiolabeled amino-acid PET is theoretically the most suitable investigation in a patient with a low grade glioma. One disadvantage in the use of ^{11}C-labeled amino acids is the requirement for an on-site cyclotron. For high-grade tumours however, Bader *et al*. found that amino-acid tracers (imaged with SPECT) were not better than tracers like FDG (imaged with PET) in identifying tumour and in discriminating between tumour recurrence and radio necrosis (2).

The median survival in our group was 16 months, compares with that of only nine months generally reported patients with a glioblastoma treated by surgery and external radiation. However, in our previous study (10) a similar group to the present, who did not receive ^{192}Ir brachytherapy had a median survival of 10 months, this was not significantly shorter than this series, patient selection reflecting the importance of survival.

Emission tomography studies are highly sensitive in detecting vital tumour tissue, and in identifying when deterioration may be due to necrosis. However, in our view, this is not useful in patients undergoing investigation for deterioration after treatment of a primary glioblastoma multiforme because of the extremely high likelihood that tumour recurrence will be the cause.

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6. Long term effects of radiation on human brain

- 6.1 Temporal lobe destruction after irradiation for a rhinopharyngeal carcinoma

RW Koot, D Troost , KP Dingemans, MA van den Bergh Weerman , DA Bosch

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Summary

We describe a patient who revealed severe temporal lobe radiation injury 5 years after irradiation for a rhinopharyngeal carcinoma. Extensive involvement of the microcirculation, consisting of a perivascular inflammatory reaction and structural changes of the vessel wall were found after autopsy. The observed dissections of the endothelium have not been earlier described in detail.

Introduction

Histopathological alterations in neuronal tissue exposed to radiation are predominantly seen in the white matter (6) and are probably due to small vessel injuries (1;2;4;10-12;14;16). Vascular endothelial cells have the most rapid turn over among the components of the central nervous system and are directly injured by the ionising radiation starting with ultrastructural changes in the capillary basement membrane. The following histopathological alterations develop slowly and as a matter of fact there is little brain tissue available for examination of patients who have been irradiated years before. We present the clinical and neuropathological findings of a patient who was irradiated 5 years earlier for a rhinopharyngeal carcinoma.

Case history

A 55-year-old man was admitted with signs of loss of hearing, smell and taste. A carcinoma of the dorsal wall of the rhinopharynx was found. On CT scan the skull base, clivus and ventral part of the foramen magnum were infiltrated with tumour. No intracranial spread was seen. The tumour was irradiated by lateral ports with 40 Gy in 32 fractions with a surdosage of 70 Gy at the tumour. The irradiation field (40 Gy) extended from the skull base up to C-3. It was estimated that the temporal lobes received 50 Gy. Six months later the patient developed orthostatic hypotension. During the following 5 years, his character and intelligence changed. He became aggressive, depressed, developed memory deficits, and was admitted several times at the psychiatric ward. A CT scan of the brain and skull base showed that the white matter in the temporal lobes became hypodense. The rhinopharyngeal carcinoma was in complete remission with no signs of metastasis. After an attempted suicide, the patient developed a pneumonia, from which he died at the age of 60.

Autopsy revealed a severe pneumonia. The remainder of the systemic examination showed no significant abnormalities. Remnants of the carcinoma diagnosed earlier were not found.

The formalin-fixed brain weighed 1325 g; the temporal lobes were soft. Coronal slides through the brain revealed completely destroyed white matter in the temporal lobes with a relative sparing of the overlying cerebral cortex (Figure 1a). These slides show some gradation of changes from areas closest to the field of radiation (medial) to farthest away (lateral).

Histology: *Cortex:* The temporal cortex, normal at macroscopy, showed mild focal damage. Loss of neurons was obvious, but many were still intact. GFAP and Vimentin staining showed a strong diffuse astrocytosis. An extensive and diffuse microglial MHC class II proliferation was observed in the irradiated parts of the cortex and in the brainstem. Some microglial proliferation was also present in areas of the cortex where the adjacent white matter was conserved.

White matter: Apart from the near complete white matter destruction, the preserved myelinated areas in the field of irradiation showed extensive gliotic changes. Neurofilament and silver stains showed loss of axons but the remaining axons appeared intact. Rounded macrophages, Tal1B5 and CD 68 positive, were sparse in the grey matter but abundant in the remaining white matter.

(Peri) vascular zone: Arterioles in the white matter showed thickened fibrotic vessel walls (Figure 1b). Endothelial cells were frequently swollen. Larger branching arteries of the circle of Willis appeared undamaged except for some atherosclerotic changes. Blood-brain barrier (BBB) damage, visualised with fibrinogen antibody staining, showed an enhanced reaction in the white

but not in the grey matter. Leakage of fibrin into the surrounding tissue was focally present in the grey matter and slightly more extensive in the white matter.
In both white and grey matter mild lymphocytic infiltration was observed, in most cases around small vessels but occasionally focally in the parenchyma. The perivascular cells were CD45, CD3, and CD8 positive, CD20, CD79a and CD4 negative and therefore belonged to the cytotoxic/suppressor T-cell subset. The conventional Leder stain and immunohistochemistry (IHC) for elastase did not reveal granulocytes except an incidental intravascular cell. Tryptase positive mast cells were not identified.
In the border zone between white and grey matter, a proliferation of small and medium-sized vessels was observed at several locations. These telangiectatic foci were thin-walled and enlarged and some of them showed fibrinoid necrosis in their walls (Figure 1c). The condensations stained blue with Martius Scarlett Blue (MSB), were collagen IV positive and weakly stained by tenascin. Several vessels showed a discontinuity in their endothelial lining as observed with endothelial markers Ulex Europeus, Factor VIII and CD 31. Staining for alpha Smooth Muscle Antigen (αSMA) revealed discontinuity of the muscular layer of the vessel wall as well. Most of the enlarged vessels even appeared fully devoid of αSMA staining. Perivascular haemorrhages were not observed, although the structure of these vessels appeared extremely fragile. Detachment of the endothelium was frequently observed in small vessels (Figure 1 d,e) and confirmed with EM (Figure 1 f). Some of the endothelial cells, which contained unexpectedly large numbers of Weibel-Palade bodies, extended deep into the lumen of some vessels. Thrombosis was observed only incidentally. Platelets were rarely observed both with IHC (CD 61) and EM.

Discussion

This patient belongs to the very scarce cases in which the human brain was irradiated deliberately for the treatment of an adjacent tumour with a long follow-up and in which brain tissue was available for IHC and EM. The findings suggest that the slowly progressive destruction, mainly of the white matter, is caused by radiation-induced endothelial damage. This damage leads to a dissection of the vessel wall, followed by thrombosis and occlusion. The slowly progressive character of the destruction points at the fact that the vessel wall is irreversible damaged. These findings support the theory that small vessel injuries precede to, or constitute the primary cause of the final damage to the white and grey matter or to parenchymal alterations in other organs after irradiation.
Radiation effects of vessels have extensively been described, but only after conventional staining and not in such a detail. Early radiation effects (weeks) have been found to constitute of swelling of the endothelial cells, cytoplasm vacuolisation, detachment from the underlying matrix, infiltration of mononuclear cells into the perivascular matrix and exsudation of fibrin from the vessels into the white matter (BBB damage) (2;4). At later stages, thickening of the vessel wall with progressive endothelial cell loss, perivascular fibrous tissue formation, focal calcifications, vascular obliteration with or without thrombotic changes, large irregular fragile capillary telangiectasia and sometimes even spontaneous haemorrhage were seen (3;7-9;15). From our

study, it is obvious that vessel wall dissections play a major role in the observed structural changes in small vessels after irradiation. These changes in the microcirculation are both time- and dose-related and have their origin in direct injury by ionising radiation of the endothelium, which is one of the most vulnerable components of the CNS (13). The observed changes are not pathognomonic for irradiation but are also found in atherosclerosis (2). However, they comprise a picture, especially in combination with predominant white matter degeneration, which is very characteristic of radiation-induced myelopathy or encephalopathy (5;13).

If we consider the impaired microcirculation as a major first step in the development of radiation injury, the differences in susceptibility between the white and grey matter can at least partly be explained in terms of vascularisation. The white matter, in particular in the peri-ventricular area, contains very few tiny vessels. This is indeed the area where the first radiographic abnormalities in the development of radiation injury after whole brain irradiation are seen. The number and structure of these vessels may determine the vulnerability for irradiation of the perivascular matrix, leading to the more vulnerable status of the white matter. On the other hand, we observed that after a longer period of follow-up (5 yr), the grey matter is also involved, although to a lesser extent.

As demonstrated clearly by immunohistochemistry and EM, vessels of equal size and structure are more severely affected when they are located in the white matter than in the grey matter. Why are these vessels more vulnerable? An answer is yet unclear.

The enlarged and teleangiectatic vessels showed some immunohistochemical features that have not been described earlier. The lining endothelium of the vessels was frequently disrupted and detached from the underlying basement membrane, often forming conspicuous vessel wall dissections with fibrin and thrombin formation without platelet involvement. This dissection will finally lead to occlusion of the vessel and may be a major cause of the slow progression of the myelin destruction.

In summary, we have shown a case of severe radiation injury of the brain due to irradiation of a rhinopharyngeal carcinoma. Involvement of the microcirculation is impressive and apparently contributes to the development of radiation injury. Although this is an extreme example of radiation injury, we believe that, to a lesser extent, impairment of the microcirculation is common in irradiated patients with a longer follow up. This is currently under investigation. It stresses the fact that for tumours located in the close vicinity of brain, the susceptibility of the brain vasculature must be taken into account.

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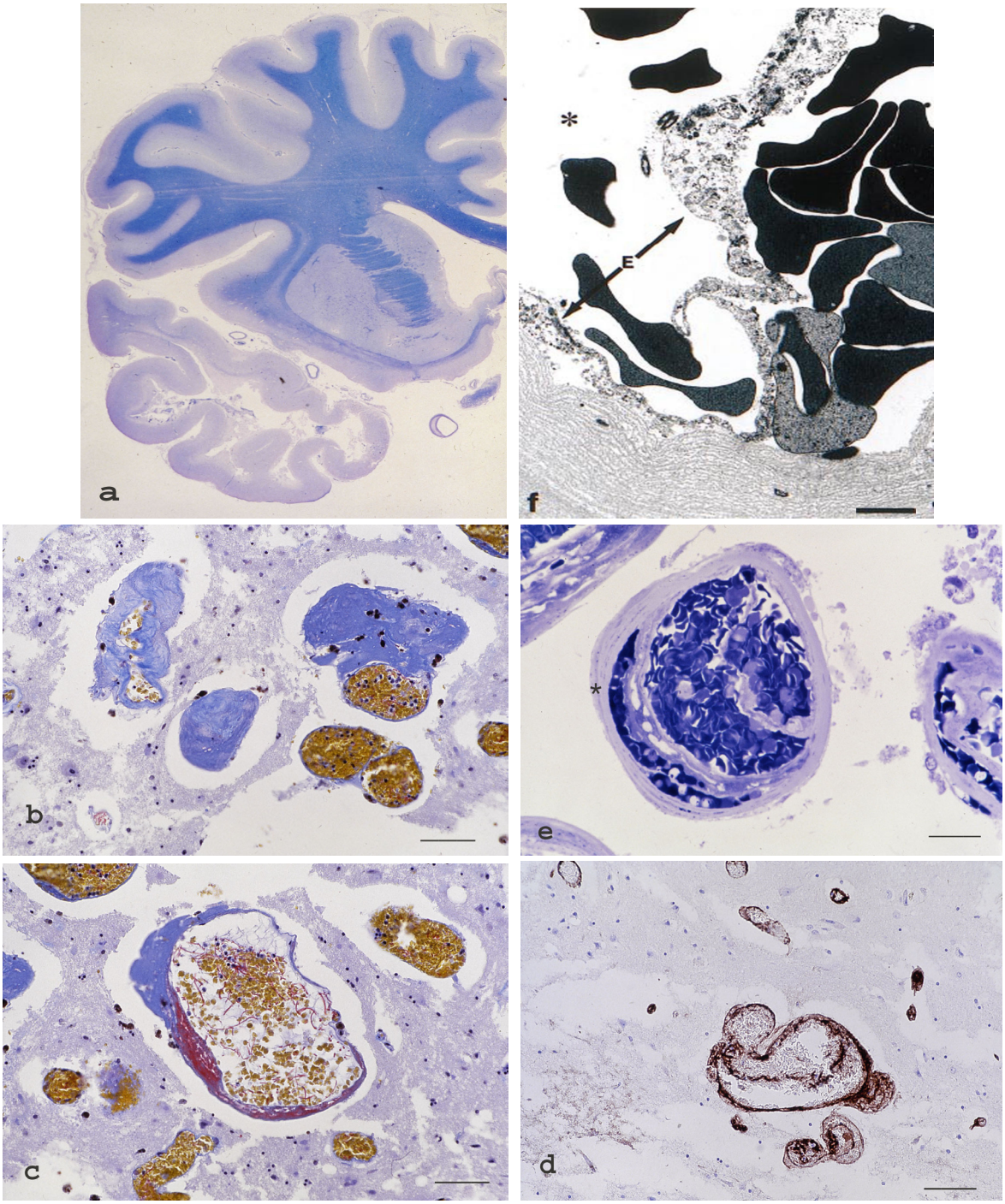

Figure 1. Extensive radiation injury of the temporal lobe. **a**, Coronal slice through part of the left frontal and temporal lobe. The white matter of the temporal lobe has almost completely disappeared, Klüver Barrera stain. **b,** White matter of the temporal lobe. Extensive vessel wall fibrosis, MSB stain. Bar = 70 µm. **c,** White matter of the temporal lobe. Fibrinoid necrosis (red), MSB stain. Bar = 70 µm. **d,** White matter of the temporal lobe. Dissection in small vessel. Factor VIII stain. Bar = 70 µm. **e**, Vessel wall dissection. White matter of the temporal lobe. Detachment of the endothelium from the underlying basement membrane (*). Semi-thin section. Toluidin blue. Bar = 25 µm. **f,** Electron microscopic section of a small vessel with endothelial detachment and vessel wall dissection. Note the multiplication of the basal laminae (bottom). * = Capillary lumen. E = Endothelium. Bar = 2 µm. Full colour : section A

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6. Long term effects of radiation on human brain

- 6.2 Cerebral necrosis after 25 Gy radiotherapy in childhood followed 28 years later by 54 Gy radiotherapy

RW Koot, LJA Stalpers, E Aronica, DA Bosch

Clincal Neurology and Neurosurgery 2007;109:607-612

Summary

The development of brain necrosis is life-long risk of repeat radiation therapy, even after a long time interval and a moderate radiation dose.

We report on a 34-year-old patient who had prophylactic cranial irradiation with 25 Gy and adjuvant chemotherapy in childhood for leukaemia and in adulthood, 28 years later, therapeutic radiotherapy with 54 Gy for an atypical (WHO grade II) meningioma. About two years later he developed a contrast-enhancing lesion on MRI-scan that was indicative of a tumor according to a thallium-201 (^{201}Tl) SPECT scan. Histopathology of the operated contrast-enhancing lesion showed extensive radionecrosis.

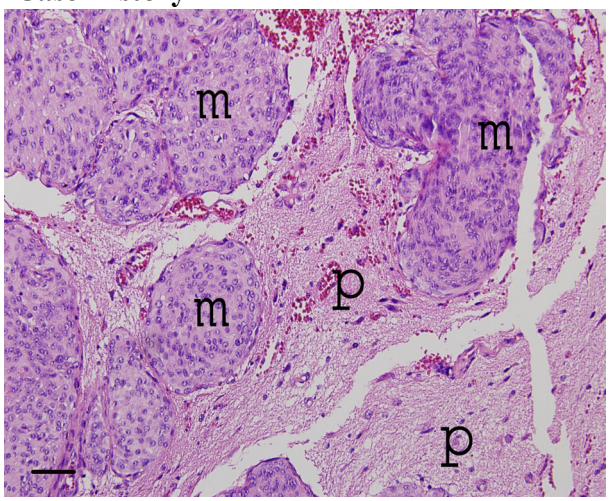
Radiation necrosis is a small but serious risk after repeat radiation therapy, even after a very long-term interval, the delivery of small fractions and an average cumulative total dose. Patients undergoing repeat radiotherapy therefore need to be followed life-long for potential late radiation toxicity.

Introduction

Cranial external beam radiation therapy is an essential element in the treatment of primary brain tumors, metastasis and the involvement of the central nervous system by leukaemia or lymphoma. Radiotherapy has also been applied after subtotal resection of meningiomas in eloquent areas, or after (sub)total resection of atypical or anaplastic meningiomas (WHO grade II or III) to delay progression. Apart from this, prophylactic cranial radiotherapy has been given in the 1970's to children suffering from leukaemia as part of the total treatment. Nowadays, prophylactic cranial radiotherapy is given as part of several study protocols for example in lymfoblastic Non-Hodgkin Lymfoma, Burkitt's lymphoma and for small cell lung cancer (limited disease or complete remission). Radiation injury consisting of debilitating cognitive decline after total doses of 30-60 Gy, occurring months to years after cranial radiation exposure in both children and adults may be seen (6;26), with a strong additive effect of chemotherapy on the development of radiation necrosis (12;22). Exposure to even higher total cranial radiation doses, for example with additional brachytherapy, or with a second irradiation after a substantial period of time in-between, may cause radiation necrosis, also called liquefaction or coagulation necrosis. Due to the vulnerability of the endothelial cells (19) to radiation and putative interactions between these endothelial cells and the migrating inflammatory cells as a result of the radiation-induced inflammatory response, the blood-brain barrier becomes disrupted. In consequence, contrast-enhanced CT or MRI is not able to discriminate between radiation necrosis and tumor and therefore PET or SPECT is advised (14;24), although new MRI techniques such as Diffusion Tensor Imaging have been successfully reported for differentiation (10) .

We present the clinical, neuroradiological and neuropathological findings of a patient with a contrast-enhancing lesion after prophylactic irradiation in childhood for leukaemia and therapeutical irradiation in adulthood for an atypical meningioma to bring under attention that the development of radiation necrosis is a substantial risk even after a long time interval between these two irradiation treatments.

Case History



A 5-year-old patient was successfully treated in 1976 for Acute Lymphatic Leukaemia (ALL) with corticosteroids, mercaptopurine, methotrexate and vincristine. As was usual in those days, he received also prophylactic whole brain radiotherapy, 25 Gy in 13 fractions (1x1 Gy "accustom fraction" plus 12x2 Gy). Complete remission was achieved. In the years thereafter he developed learning difficulties for which he attended special education.

Figure 1: Meningioma (m) infiltrating the cerebral parenchyma (p) (resection 2004). Staining HE. Bar = 150 µm.

In 2003, at the age of 32 years, a growth hormone deficiency was diagnosed without other hormonal deficits for which he received growth hormone substitution treatment. He started complaining of headaches some months later, followed by visual disturbances at the end of 2003. The ophthalmologist found papillary oedema and an MRI scan showed a large left sided frontal lesion, suspect for a meningioma. Complete resection (Simpson grade I) was achieved in January 2004. The tumor consisted of conglomerations of tumor cells in a whirl-like or sheet-like pattern. Cells and nuclei were clearly polymorphic. Tumor fragments were infiltrating the parenchyma (Figure 1). Ki67, a marker for proliferation activity was highly elevated (20%) as well as Histon H3, a marker for mitosis. The meningioma was classified as an atypical (WHO grade II), possibly radiation-induced, and the patient was treated with external beam radiation therapy consisting of 54 Gy in fractions of 1.8 Gy.

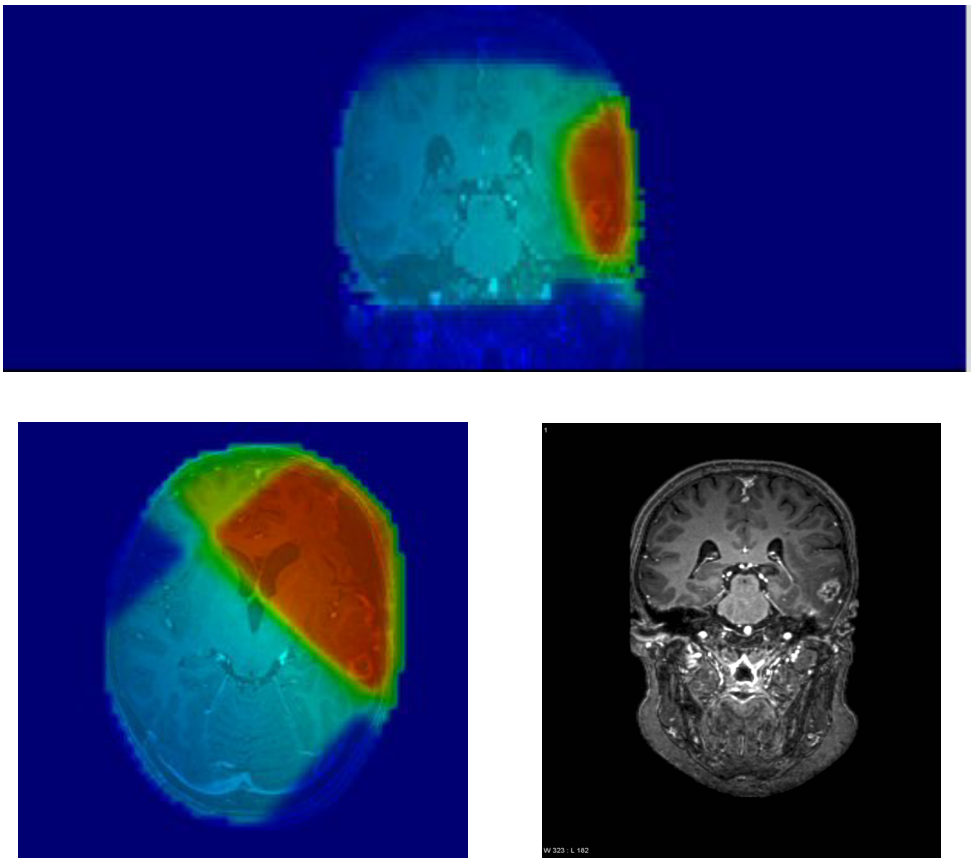


Figure 2: Post-irradiation, pre-operative T1-contrast MRI (December 2005; right), and overlay of radiation dose distribution delivered in 2004 (up and left). The temporal necrosis in the left temporal region developed just within the high radiation dose region (red). Full colour: section B

After this second course of radiotherapy, he mentioned a further decline in neurocognition. Subsequent MRI's in 2004 and 2005 showed no abnormalities. In October 2005, 18 months after the radiotherapy, a 14 mm large new contrast-enhancing lesion was seen on MRI located on the left temporal side, more caudally and posteriorly located than the atypical meningioma (Figure 2). This tumor was located in the parenchyma of the brain, without any obvious dural relations, so that a primary brain tumor (GBM) was also considered in the differential diagnosis. To discriminate between tumor and radiation necrosis, a ^{201}Thallium SPECT scan was made, which

was reported as being suggestive for recurrent tumor (Figure 3). In November 2005, the size of the lesion was moderately increased to 15 mm. Stereotactic radiotherapy treatment (LINAC) was considered, but not without new histophatological confirmation.
Resection without neurological deficit took place in January 2006 and was verified by a MRI within 48 hours post-operatively. The histology showed fragments of pre-existent parenchyma with extensive areas of necrosis and reactive gliosis (Figure 4). Thickened eosinophylic vessel walls and luminal narrowing were frequently seen. Many of these vessels show perivascular infiltration of T-lymphocytes and macrophages. No tumor cells were found, although an extensive gliosis was present. The overall picture was consistent with cerebral necrosis.

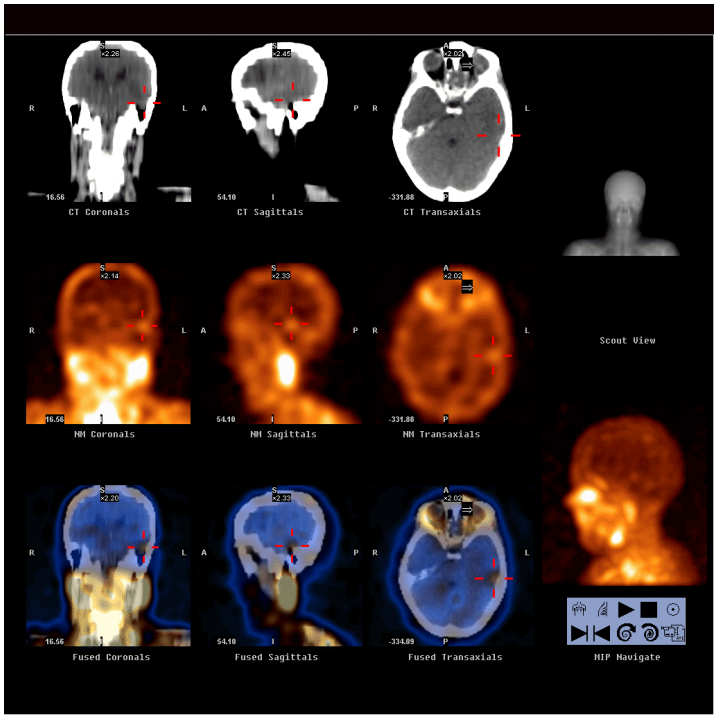


Figure 3 (left): ^{201}Tl SPECT scan and fusion with non-enhanced CT-scan. Accumulation of ^{201}Tl in the region of contrast-enhancement on the T1-MRI

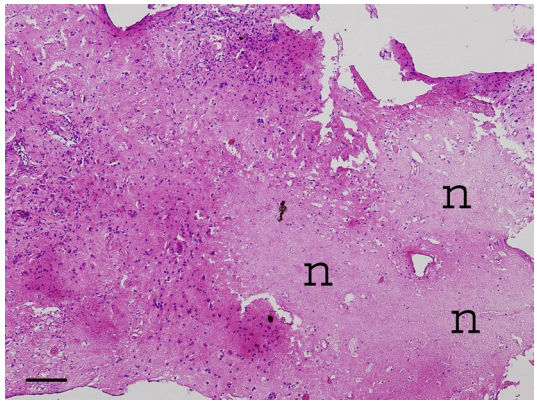


Figure 4 (up): Fragments of pre-existent parenchyma with extensive areas of necrosis (n) and reactive gliosis (resection 2006). Staining HE. Bar = 200 µm

Discussion

Kinetics of late normal tissue complications after radiotherapy, also called radiation injury, are extensively described by Jung *et al*. Patients free from complications plotted against years after radiotherapy are generally described by exponential regression. The kinetics of radiation injury of the brain however are different as the risk of temporal necrosis after radiation for nasopharyngeal carcinoma increases continuously with time after radiotherapy treatment (9). Radiation injury of the brain is seen months to years after cranial radiation and is clinically characterised as deficits in short memory, spatial relations, visual motor processing, quantitative skills and attention (17;25). Hippocampal dysfunction is a prominent feature of these neuropsychological sequelae if the temporal lobe is within the radiation field. In fact, the severity of the cognitive deterioration appears to depend upon the radiation dosage delivered to the medial temporal lobes (1). How exactly the cellular processes may lead to radiation injury, is unknown. Classically, two hypotheses of radiation injury have been proposed. According to the vascular hypothesis damage to the endothelium by ionising radiation may lead to a

microangiopathy, resulting in vascular insufficiency and infarction followed by white matter necrosis (8). According to the glial hypothesis radiation-induced ablation of glial precursors may result in demyelinative necrosis (3). However, neither hypothesis adequately accounts for the fact that many patients with significant cognitive deterioration show no (radiological) signs of overt vasculopathy or demyelination (25). Neuropsychological sequelae following radiation may therefore be caused by interference of the neurogenesis of the hippocampus. The hippocampal dentate gyrus is a remarkable dynamic structure involved in neocortical processing and a major site of postnatal and adult neurogenesis. Irradiation (low dose) has only minor effects on the generation of astrocytes and oligodendrocytes, but the production of neurons is almost entirely ablated (15), leading to a decline in cognitive functioning.
The radiological CT or MRI image of radiation injury is diverse including a dilated ventricular system, white matter changes and in the most severe case a contrast- enhancing lesion compatible with a radiation-induced tumour or radionecrosis.

According to the learning difficulties during primary and secondary school, this patient could have been suffered from radiation injury, most probably caused by the prophylactic whole brain radiation during childhood. Neurocognitive decline progressed substantially after the second course of radiation in adulthood for an atypical meningioma in which the left medial temporal lobe was also irradiated for the second time. Subsequently this patient developed a contrast-enhancing lesion, situated away from the original meningioma; the lesion was however located in the radiation field which was exposed to a total cumulative dose of 79 Gy. Although highly suspected for radionecrosis, this lesion showed some progression on MRI and a moderate uptake of ^{201}Tl, indicative of tumor instead of necrosis according to most of the literature concerning ^{201}Tl-SPECT (14;20). ^{201}Tl has been used to both localise and characterise the viability and malignancy of gliomas (4;28). In radiation necrosis, however, only rarely some accumulation of ^{201}Tl is observed (11). Other authors reported however, that various stages of radionecrosis may show high uptake of ^{201}Tl (5;27). The reason for this high uptake has yet to be understood. As (late) radionecrosis is thought to be caused by endothelial damage, a higher uptake in the surrounding cells may result from leakage of radiopharmaceuticals through the blood brain barrier (18).

This case is an uncommon presentation of radionecrosis as it is usually seen within the parenchyma immediately surrounding a tumor. Peritumoral parenchyma seems to be more vulnerable to radiation and chemotherapy as was suggested by the observation that the latency period for the development of (peritumoral) radionecrosis in glioma patients appears to be approximately five times shorter than in other patients receiving an equivalent radiation dose (most often radiated for nasopharyngeal carcinoma) (13;23).
The management of radiation necrosis is predominantly surgical in the face of raised intracranial pressure or progression on conservative treatment. However, there is ample evidence that surgery is not always necessary, and resolution may be obtained after corticosteroid therapy alone in some cases (21;29). No survival benefit was noted for maximal resection versus conservative management (17).

The 5 years risk of 5% severe complications has been estimated to occur after a total dose of 50 Gy to 2/3 of total brain volume and after 60 Gy to 1/3 of total brain volume using standard fractionation (7). This expected incidence may be underestimated because many patients die early without confirmation of cerebral radiation necrosis. Necrosis is a serious risk (up to 17%) after high dose brain radiotherapy for an accumulative dose of 78-94 Gy in 2 Gy daily fractions (2) and is seen up to five fold as frequent after subsequent chemotherapy (17). Other authors, however, stress the capability of the brain, even in re-irradiation, to recover from clinically occult radiation damage (8;16). In our patient, assuming 50% recovery from radiotherapy in childhood (50% of 25Gy), we estimated that 12.5Gy + 54 Gy = 66.5Gy would lead to a re-irradiation risk for necrosis between 5-10% within 5 years. As previously mentioned, the continuous increasing risk with time to develop brain radiation injury after radiotherapy makes life-long follow-up mandatory (9).
In this patient, who received prophylactic whole brain radiotherapy plus systemic chemotherapy in childhood and a full course of postoperative radiotherapy 28 years later (assuming at least 50% recovery of occult damage), the risk of development of radiation necrosis had to be accepted (17).

In summary: We described a case of extensive radionecrosis after 25 Gy radiotherapy and chemotherapy in childhood followed 28 years later by 54 Gy radiotherapy. Radiation necrosis is a small but serious risk after repeat radiation therapy, even after a very long-term interval, the delivery of small fractions and an average cumulative total dose. Patients therefore need to be followed life-long after repeat radiotherapy for the potential late radiation toxicity, in particular those who were treated for benign disease.

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6. Long term effects of radiation on human brain

- 6.3 Does radiation influence the severity of peritumoural tissue changes in the human brain; an immunohistochemical analysis

RW Koot, R Brand, E Aronica, DA Bosch, D Troost

Submitted

Summary

Background: Radionecrosis and peritumoural white matter radiation injury are common in long-term surviving patients treated with brachytherapy. The purpose of this study was to classify by immunohistochemistry in more detail the peritumoral white matter changes and to investigate a possible relationship between radiation (intensity) and these white matter injuries.

Methods: Three groups of 10 Glioblastoma Multiforme (GBM) patients were studied after surgery only, surgery and External Beam Radiation Therapy (EBRT, 60 Gy) and surgery, EBRT plus brachytherapy (BT, 60 +40 Gy). Specimens were stained with markers for inflammation, matrix qualities and small vessel wall properties. A linear mixed model was used for statistical analysis.

Results: The peritumoural white matter frequently showed infiltration of T-lymphocytes, macrophages and discontinuity of the endothelial lining and dissections of the wall of small vessels. Interaction between marker positivity and the type of marker was virtually absent (p=0.83) hence a model was used with only 2 main effects. The overall effect of marker positivity was significant (p=0.04). Post-hoc contrasts showed that the difference for marker positivity of markers between the EBRT (60 Gy) group and the EBRT plus BT (100 Gy) group (on the average 0.03) was not significant (p=0,92). The non-irradiated group differed significantly from both the EBRT and the EBRT plus BT group, the differences being 0.46 and 0.43 respectively with both p-values below 0.001.

Conclusion: Radiation does influence the severity of peritumoural tissue changes in GBM patients. Statistical analysis showed that after 60 Gy irradiation, the marker expression was significantly reduced compared with no irradiation. Expression did not significantly alter after augmentation of the radiation dose from 60 to 100 Gy. It seems likely that this decrease of marker expression is caused by the irradiation(s), although also the difference in interval between the GBM manifestation and the tissue harvesting might play a role.

Introduction

Classically, two hypotheses have been proposed with regard to the histopathological alterations seen in normal neuronal tissue exposed to radiation, so called radiation injury. According to the glial hypothesis radiation-induced ablation of glial precursors may result in demyelinative necrosis (2). According to the vascular hypothesis damage of the endothelium by ionising radiation may lead to a microangiopathy (6) in and around small vessels lying in the white matter (9). Whatever the mechanism of origin may be, a prominent migroglial inflammatory response is often detected in the brain tissue of patients irradiated for malignant glioma, particularly in the white matter and around small vessels (13). Since 30-40 % of heavily irradiated patients (for example after brachytherapy) need a re-operation, and supported by the findings of our brachytherapy patients (10) who very often showed radiation necrosis but also severe radiation injury in the peritumoral parenchyma (dilatation of ventricles/atrophia cerebri, white matter changes), it is attractive to hypothesize about a relationship between radiation intensity and the severity of radiation injury. In particular the involvement of the inflammatory response deserves further investigation.

The purpose of this study was therefore to classify by immunohistochemistry in more detail this peritumoural white matter inflammatory response and to investigate a possible relationship between radiation intensity and these white matter reactive changes.

Material and methods

Three groups were formed, containing the specimens of 10 patients with GBM each (4). The first group of 10 specimens came from 10 patients who were not irradiated at all. The specimens were taken during first operations or at autopsy. The second group of 10 specimens was collected from 10 patients who underwent cytoreductive surgery followed by 60 Gy external beam radiation therapy (EBRT, 30 fractions of 2 Gy). The specimens were taken during re-operation after the EBRT or at autopsy. The third group of 10 specimens consisted of 10 patients who had previously undergone cytoreductive surgery followed by 60 Gy EBRT and 40 Gy additionally brachytherapy (BT, total cumulative dose 100 Gy). The specimens were taken during re-operation after the brachytherapy or at autopsy. The procedure of stereotactic brachytherapy is described elsewhere (10). Patient characteristics are outlined in Table 1, in which also the interval between presentation of first symptoms and tissue harvesting are given.

The neural tissue obtained by autopsy was processed according to routine histopathological procedures as soon as possible with the shortest delay possible. After fixation in 4% neutral formaldehyde for 2-3 weeks, the brain was cut. Tissue blocks for paraffin embedding were processed and paraffin embedded. Tissue obtained by operation was immediately processed according to routine histopathological procedures. Conventional staining of paraffin sections consisted of Hematoxylin and Eosin (HE), Gomori, Leder, Elastica van Gieson (EvG), Klüver-Barrera, Martius Scarlett Blue (MSB) and periodic acid-Schiff (PAS). For the immunohistochemical demonstration of cellular antigens, 5-µm paraffin slides were treated with a battery of 15 mono- and polyclonal antibodies directed to involved processes i.e. inflammatory reactions (CD3, CD 8, LCA, CD 20, CD 79a, CD 68, HLA-DR), matrix qualities (elastase, tryptase, fibrinogen) and small vessel wall properties (factor VIII, CD 34, Ulex Europaeus

Agglutinin type 1 (UEA-1), α-smooth muscle actin type 1 (α-SMA-1), CD 31). Three slices of each immunohistochemical staining were thoroughly examined light microscopically by two authors simultaneously (RWK, DT); a total of 450 specimen (30 patients x 15 immunomarkers) was studied. Staining was noted as 0=no staining, 1+= some staining, 2+= moderate staining, 3+= (very) strong staining. To exclude tumour interactions, only peritumoural white matter was used for this study. Peritumoural white matter was defined as tissue adjacent to the lesion that did not include the visible microscopical infiltration zone or significant reactive gliosis.

Table 1: Patient characteristics.

Group	No radiotherapy	60 Gy EBRT	100 Gy EBRT + BT
Mean age in years (range)	50 (32-79)	30 (4-54)	52 (37-62)
Diagnosis (n)	GBM (10)	GBM (10)	GBM (10)
F/M	3:7	3:7	4:6
Median time between start of symptoms and histology in months (range)	1 (0.5-4)	na	na
Median time between EBRT and histology in months (range)	na	30 (1-55)	na
Median time between BT and histology in months (range)	na	na	12.5 (8-32)
Histology obtained by operation vs autopsy	8:2	7:3	10:0
Median survival after diagnosis in months (range)	15 (1.25-35)	32 (3-65)	19 (12-35)

EBRT: external beam radiation therapy, BT: brachytherapy, GBM: glioblastoma multiforme, na: not applicable

Statistical Analysis

A linear mixed model was used to calculate the effect of the *grouping* variable ("No radiotherapy", "60Gy EBRT" and "60Gy EBRT + 40 Gy BT") and the effect of the *type of markers* (1-15) on *marker positivity*. The patient was entered as the random effect while the other two variables were treated as fixed covariates. First the interaction between *group* and *type of marker* was tested. When this turned out to be highly insignificant, the interaction was removed from the model and the main effects of *group* and *type of marker* were estimated. As covariance structure between the measurements we used the default type of "Variance Components".

As an additional analysis the markers were a priori classified by the staining substrate (for example all inflammatory or endothelial markers classified as one marker group (*type of marker Recoded*), thus allowing evaluation of the same effects using less degrees of freedom and improving interpretation of the model coefficients.

Results

The peritumoural white matter frequently showed lymphocytic infiltration around small vessels in the peritumoural tissue and occasionally focally at more distance in the parenchyma. These infiltrative lymphocytic cells stained positive for CD3, CD8, CD45 and negative for CD20 and

CD79a, thus belonging to the cytotoxic/suppressor T-cell subset. Macrophages, HLA-DR and CD 68 positive were also frequently found but not in the specimen of every patient. Almost no neutrophils, except an incidental intravascular cell, nor tryptase positive mast cells were detected. Discontinuity of the endothelial lining and dissections of the wall of small vessels were sometimes observed and stained with markers for the endothelium such as Factor VIII, CD 31, CD34 and UEA-1, and markers for the muscular layer of the vessel wall of small arterioles such as α-SMA-1. Fibrogen was found abundantly in the immediate peritumoural zone.
In a linear mixed model interaction between *marker positivity* and the *type of marker* was virtually absent (p=0.83) hence a model was used with only 2 main effects. The interpretation is that there is no evidence that differences between the groups depend on the type of marker (or vice versa, no evidence that differences between the markers depend on the radiation type). The overall effect of *marker positivity* was significant (p=0.04). Post-hoc contrasts showed that the difference for *marker positivity* of markers between the EBRT (60 Gy) group and the EBRT plus BT (100 Gy) group (on the average 0.03) was not significant (p= 0,92). The non-irradiated group differed significantly from both the EBRT and the EBRT plus BT group, the differences being 0.46 and 0.43 respectively with both p-values below 0.001.

Table 2. *Observed* mean positivity per immuno-marker.

Group	No radiotherapy	60 Gy EBRT	100 Gy EBRT + BT
1. *T-lymfocytes*, CD3	1.4	1.4	2.0
2. *T-cytotoxic-suppressor cells*, CD8	0.9	0.8	1.1
3. *Lymfoid cells*, CD 45	1.6	1.2	1.7
4. *B-lymfocytes*, CD 20	0	0	0.2
5. *Plasma-cells*, CD 79a	0.7	0.4	1.2
6. *Macrophages/ monocytes*, CD 68	2.0	1.6	1.9
7. *Macrophages/ microglia*, HLA-DR	1.9	1.7	2.1
8. *Myeloids/ neutrophils*, elastase	0.4	0.5	0.8
9. *Mastcells*, tryptase	0.2	0.2	0.6
10. *Endothelium*, factor VIII*	1.8	1.7	1.6
11. *Endothelium*, CD 34*	1.6	1.7	1.6
12. *Endothelium*, UEA-1*	1.4	1.3	1.0
13. *Smooth Muscle Antigen*, α-SMA-1**	1.1	1.5	1.8
14. *Endothelium (thrombocytes),* CD 31	1.6	1.5	1.7
15. *Fibrinogen/fibrin*, fibrinogen	2.2	1.6	2.3

Italic: reactivity, arabic: antibody/CD code. Mean positivity: 0: no positive cells (-), 0.5: incidentally a positive cell (+/-), 1: several perivascular located positive cells (+), 2: several perivascular cuffs of positive cells (++), 3: extensive perivascular cuffs of postive cells and parenchymal infiltration (+++), * dissections and endothelial discontinuity, ** discontinuity of muscular layer. EBRT: external beam radiation therapy, BT: brachytherapy, UEA: Ulex Europeus Agglutinin.

From a descriptive point of view, the *observed* mean positivities per group and marker are outlined in Table 2. The reader should bear in mind that the within-correlation of the individual values underlying table 2 is of course ignored and therefore the table merely describes the measurements but cannot be used for inference on the differences between the subgroups.
In Table 3 we describe the *estimated* marginal mean marker positivity for each situation as a consequence of the linear mixed model. Note that the differences between the groups are the same among all markers and vice versa by virtue of the model!
Subsequent analysis for *type of marker Recoded* (sub-classifications of markers with the same staining substrate to increase power) did not influence significantly the results (data not shown).

Table 3: *Estimated* mean positivity for each marker and each subgroup, based on a linear mixed model without interaction and patient as random effect.

Group	No radiotherapy	60 Gy EBRT	100 Gy EBRT+BT
Relative mean staining over all markers	0.46**	-0.03*	(0) (=reference category)
1. *T-lymfocytes*, CD3	1.86	1.37	1.40
2. *T-cytotoxic-suppressor cells*, CD8	1.19	0.70	0.73
3. *Lymfoid cells*, CD 45	1.76	1.27	1.30
4. *B-lymfocytes*, CD 20	0.33	0	0
5. *Plasma-cells*, CD 79a	2.13	1.64	1.67
6. *Macrophages/ monocytes*, CD 68	1.03	0.54	0.57
7. *Macrophages/ microglia*, HLA-DR	2.19	1.70	1.73
8. *Myeloids/ neutrophils*, elastase	0.83	0.34	0.37
9. *Mastcells*, tryptase	0.59	0.10	0.13
10. *Endothelium*, factor VIII	1.96	1.47	1.50
11. *Endothelium*, CD 34	1.90	1.41	1.44
12. *Endothelium*, UEA-1	1.49	1.00	1.03
13. *Smooth Muscle Antigen*, α-SMA-1	1.86	1.37	1.40
14. *Endothelium (thrombocytes),* CD 31	1.73	1.24	1.27
15. *Fibrinogen/fibrin*, fibrinogen	2.26	1.77	1.80

**: $p<0.01$ * $p=0.92$

Discussion

This study was done to investigate a possible relationship between radiation (intensity) and the occurrence of radiation injury and/or inflammatory response in the peritumoural white matter of GBM patients and to characterise the response in more detail. Unexpectedly, we did not find a positive-, but a significantly negative correlation with a decrease for all markers tested in the irradiated patients. As there was no difference between the 60 EBRT and the 100 Gy EBRT plus BT, a dose-response relationship could not be established for amounts of more than 60 Gy. The highest response observed was present in the non-irradiated cases and consisted of inflammatory cells like macrophages (CD68, HLA-DR) and lymfocytic cells (CD3, CD8, CD45), belonging to

the cytotoxic/suppressor T-cell unit, and endothelial markers (factor VIII, CD34, Ulex Europeus Agglutinin, CD31) as well as fibrinogen.

In contrast with the available literature, we focused on the peritumoural white matter for two reasons. First of all, GBM is a very heterogeneous tumour as compared to the surrounding tissue, which may lead to all kind of reactive tissue patterns. It is known that these tumours frequently show factor VIII, CD31, CD34, fibrinogen, CD68 and CD3 positivity (1;3;5;7;17) in very different amounts. Some of these markers are seriously influenced by post-surgical chemoradiation (chemotherapy combined with radiotherapy) or Y-knife radiosurgery, and some of them are even used to evaluate response to therapy (5;17-19). We therefore feel that the effects of radiotherapy are better studied in the peritumoural tissue. Secondly, after heavy irradiation (EBRT plus BT), clear changes in the peritumoural tissue are seen during re-operation indicating that the irradiation leads to serious peritumoural damage. These pathological changes are obviously responsible for the post-radiation architecture of the brain, characterized by ventricular dilatation, atrophia cerebri and decreased plasticity of the brain found during operation (16).

Peritumoural tissue for examination is scarce; there are only a very few studies published in which peritumoural tissue is available for examination. Operation techniques, sometimes in very eloquent areas, improve constantly, taking out the maximum of tumour and the minimum of surrounding brain tissue. Re-operations for GBM after radiation in which peritumoural tissue becomes available for examination are even scarcer as most (elderly) patients don't undergo re-operations for GBM. We therefore collected five of our specimens from autopsies where peritumoural tissue is amply available.

Unfortunately, there are to our knowledge no publications in the literature that studied the staining pattern of immunohistochemical markers in relation to radiotherapy in the peritumoural tissue of the human brain. Almost all published studies describe the effect in the tumour itself rather than in the peritumoural tissue. It must be emphasized, however, that tumour cells can be cultured from histologically normal brain acquired from a distance greater than 4 cm from the gross tumour. In this respect the peritumoural tissue response may show some overlap with tumoural tissue (15).

Macrophages are capable of killing tumour cells and display phagocytized antigenic epitopes to NK and T lymphocytes and are together with microglial cells key determinators of the immune system in neoplasia of the brain (8;12;14). Deininger *et al* found a depletion of CD68 positive cells in GBM tissue after radiochemotherapy and an increase of CD 68 activity in tumours without post surgical treatment (5). These findings are different from the work of Kureshi *et al* who found an increase of infiltrating macrophages and cytokine expression in areas of radiation necrosis after EBRT or interstitial brachytherapy for malignant glioma (11). Szeifert *et al* showed a decrease of CD34 and FVIII activity of endothelial cells in tumour tissue compared to peritumoural non-irradiated tissue by 3-12 months but this was found after Y knife surgery without EBRT (17). In another study this author found an intense lymphocytic infiltration in the peritumoural parenchyma (predominance CD-3 positive t-cells) of well-controlled tumours more than 6 months after Y knife treatment (18). This lymphocytic infiltration was absent in the poorly controlled tumours of 2 patients surgically treated less than 6 months after Y-knife treatment.

In summary, we found a significant decrease for the intensity of staining after irradiation with 60 Gy for the markers tested. The intensity did not significantly alter after augmentation of the radiation dose from 60 to 100 Gy. It seems likely that this decrease of inflammatory reaction is caused by the irradiation(s), although also the difference in interval between the GBM manifestation and the tissue harvesting may have played a role.

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7. Typical radiological and pathological presentations in brachytherapy patients

7.1. A 59 year old man operated for a de novo GBM treated with External Beam Radiation Therapy (EBRT) and brachytherapy (BT) afterwards. Reoperated five months later for progression of the intracerebral lesion on CT scan (fig7.1a), suggestive for tumour progression on ^{201}Thallium SPECT scan (fig 7.1b).

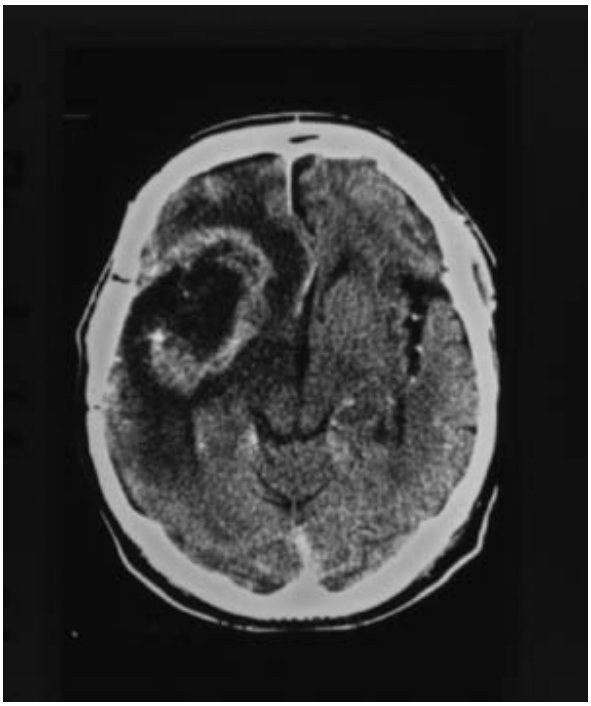

Fig 7.1a: CT-scan contrast enhanced showing large right frontal mass 5 months after brachytherapy. Full colour: section C

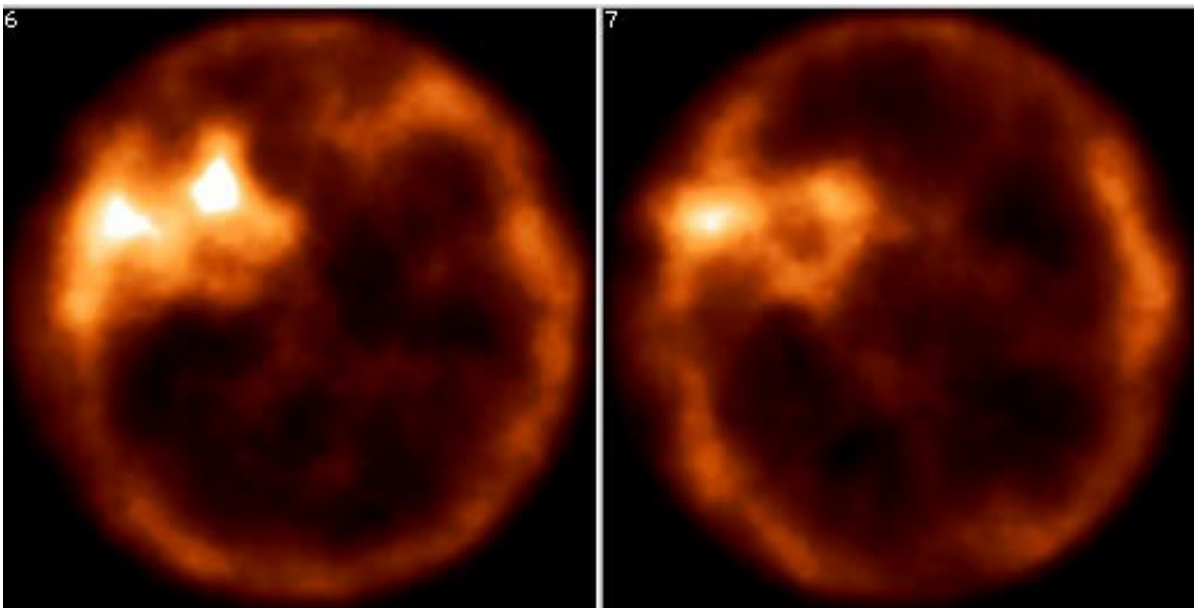

Fig 7.1b: ^{201}Thallium SPECT scan 5 months after brachytherapy suggestive for tumour recurrence cq progression.

The removed tissue of the irradiated field was pale, yellow with extensive fibrous bands and an elastic configuration. The vessels were thin and looked fragile. The findings per-operatively were mainly compatible with radionecrosis. Histopathological examination showed extensive radionecrosis, calcifications and some areas of vital brain tissue; viable tumour cells could not be found (fig 7.1c). Four months after the reoperation, he suddenly became hemiplegic. CT-scan showed a very small hypodense area adjacent to the implantation volume in the intern capsule. The patient was treated with warfarin for 6 months without any improvement. He died 10 months after the reoperation (15 months after the brachytherapy).

At autopsy a very large GBM was found in the right hemisphere, in tight connection with the dura mater with small focal hemorrhagic lesions and necrosis (fig7.1d). The mitotic rate was remarkably high. The internal capsule adjacent to the tumour showed an ischemic infarction. The vessel walls in this area were also hypertrophic with occluded lumina (fig 7.1e).

Conclusion: Tissue taken for pathology was not representative/non-conclusive; vital tumour was not examined.

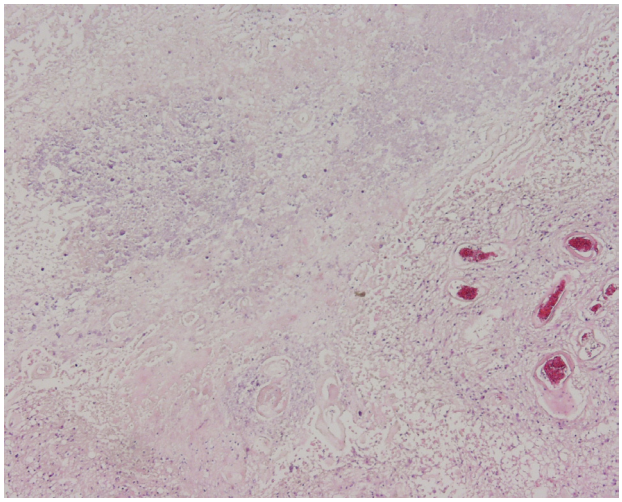

Fig 7.1c: Tissue obtained during reoperation: necrosis and calcifications. Full colour: section C

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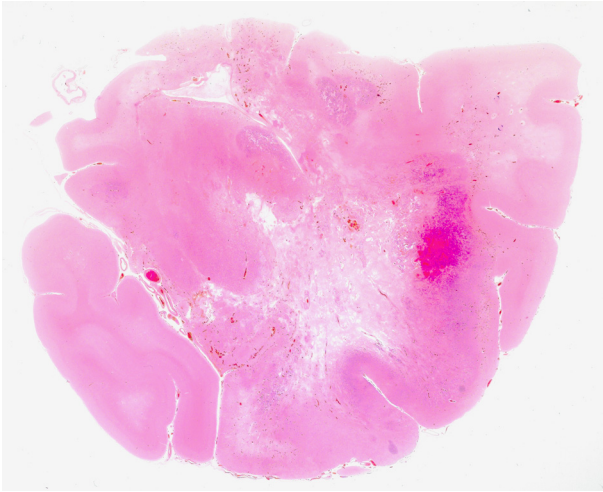
Fig 7.1d: Tissue obtained at autopsy: large mainly necrotic GBM with hemorrhages and calcifications.



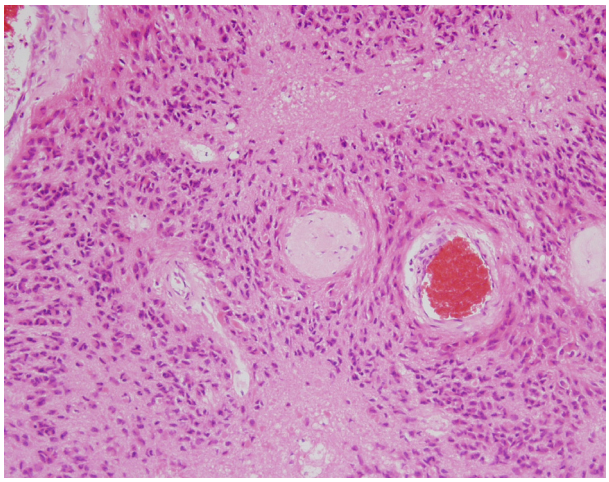


Fig 7.1e: Tissue obtained at autopsy: hypertrophic vessel wall and occluded lumina of small vessels.

7.2. A 59 year old lady was operated in 1995 for a right frontal glioblastoma multiforme and treated with EBRT and additional brachytherapy afterwards. She was reoperated 29 months after the BT because of a progressive decline in performance and bradyphrenia. On CT a contrast enhancing lesion was found (fig 7.2a), which was with SPECT and PET strongly suggestive for tumourrecurrence.

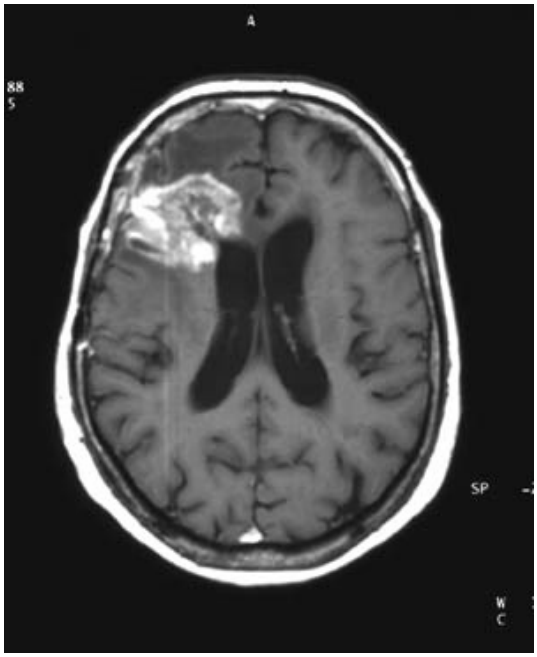


Fig 7.2a: MRI contrast enhanced T1, 29 months after the brachytherapy before reoperation. Full colour: section D

During operation, a soft pearlgrey and yellowish lesion was found superficially, suggestive for necrosis. The deeper parts of the lesion showed more tumorous tissue with some yellow, partially calcified bamboo-spine-like fibrous bands (fig 7.2b), being microscopically the remnants of small arteries with endovascular hypertrophy and luminal narrowing (fig 7.2c). The surrounding tissue showed necrosis as well as vital GBM. After a short recovery, she deteriorated clinically and died at the age of 62, 37 months after the first operation. Autopsy showed a very adhesive dura and a very large partly necrotic GBM. Microscopically numerous necrotic fields and vital tumour tissue was seen (fig 7.2d). More in the periphery of the tumour proliferation of thin walled vessels was seen, sometimes with cavernous lumina (fig 7.2e). In other regions of the tumour, hypertrophic and thrombosed small vessels were frequently found (fig 7.2f).

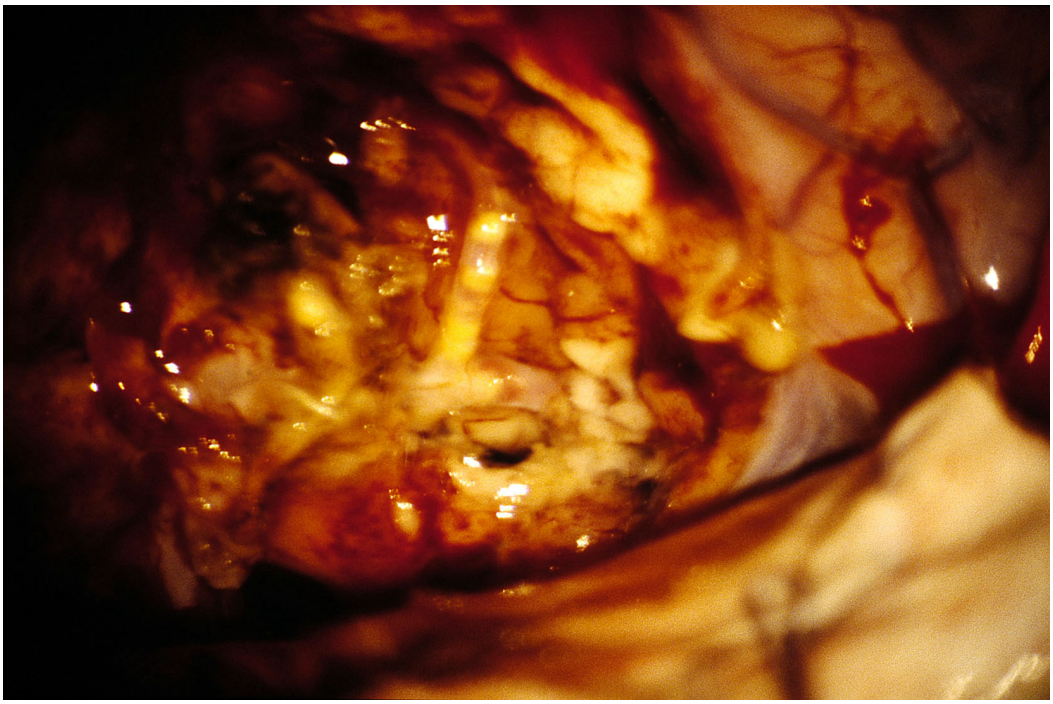


Fig 7.2b: Reoperation after brachytherapy, note the yellow longitudinal structures, which are calcified small vessels.

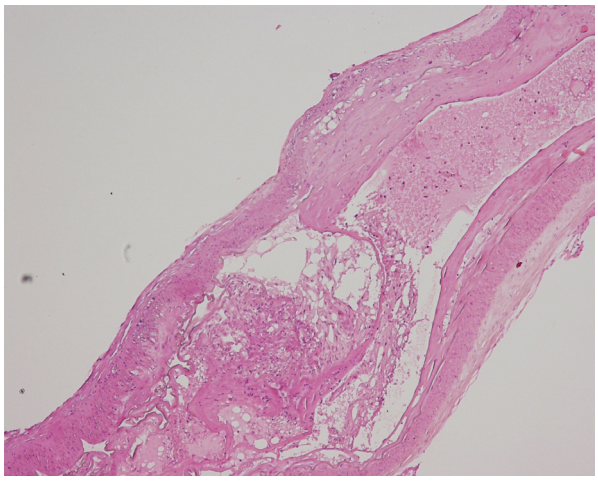
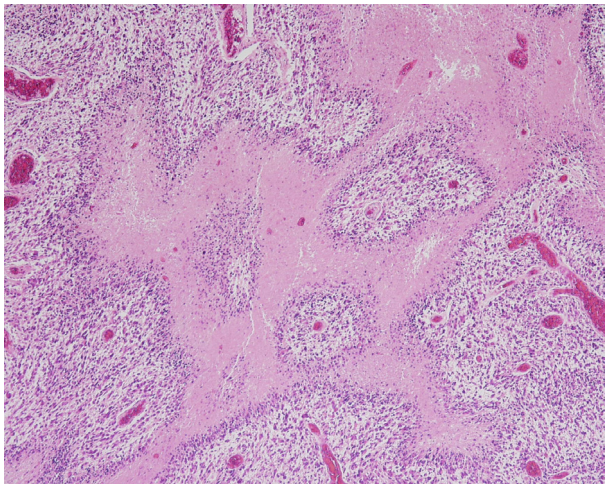


Fig 7.2c: Tissue obtained during reoperation: histology (HE) of the vessels shown in figure 7.2b.

Fig 7.2d: Tissue obtained at autopsy: fields with vital tumour and necrosis. Full colour: section D



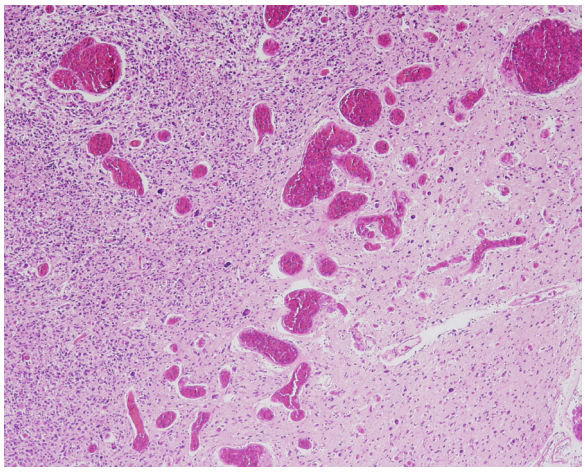


Fig 7.2e: Tissue obtained at autopsy: cavernous vessels in the periphery of the tumour.

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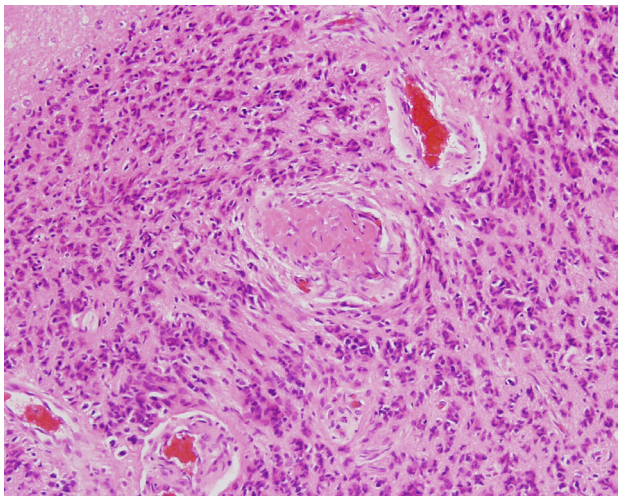

Fig 7.2f: Tissue obtained at autopsy: hypertrophic and thrombosed small vessels

Conclusion: Longest survivor of our study. Second surgery did not add any quality of life due to the post-radiation architecture of the brain.

7.3. A 63 year old man was operated for a left frontoparietal GBM and received EBRT and BT. He developed 15 months after the brachytherapy a progressive aphasia and mild neurological deficit at the right side. MRI showed a stable residual contrast-enhancing lesion without edema (fig7.3a). ^{201}Thallium scan showed no suspicion for tumour recurrence (fig7.3b), HMPAO SPECT showed a decreased perfusion in the frontoparietal region (fig7.3c) suggestive for radiation-induced vasculopathy.

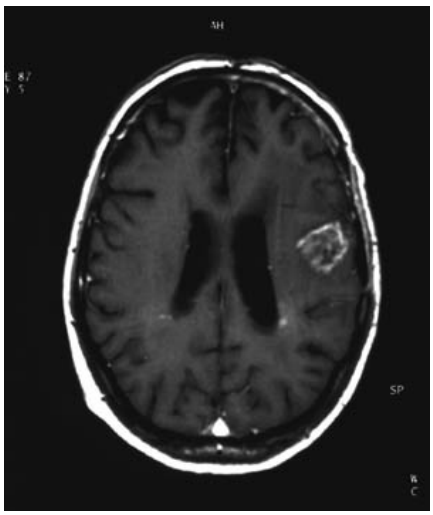

Fig 7.3a: MRI contrast enhanced T1 showing residual lesion without any mass effect near the Broca area 15 months after brachytherapy.

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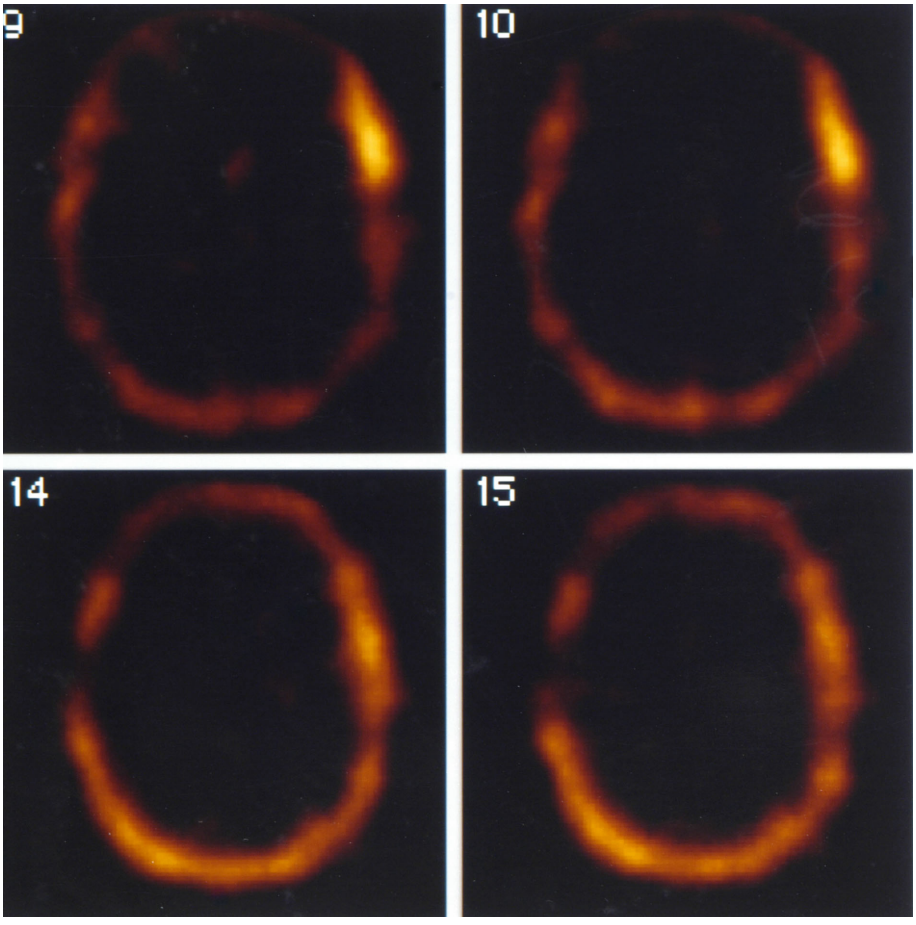


Fig 7.3b: Thallium SPECT scan 15 months after brachytherapy not suggestive for tumour recurrence/progression nor for radionecrosis. Full colour: section E

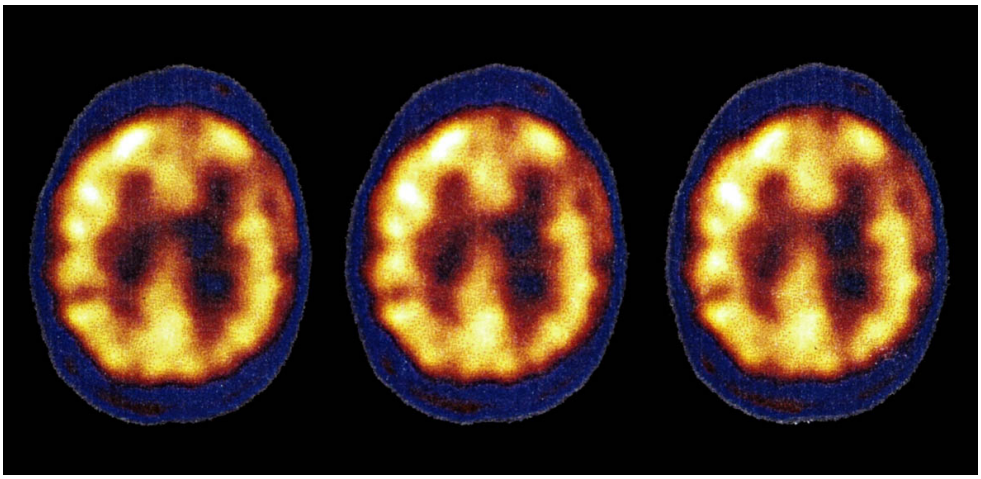


Fig 7.3c: HMPAO SPECT suggestive for decreased vascularistion near the Broca area 15 months after brachytherapy

He developed pulmonary pathology and died 21 months after the surgery for GBM. At autopsy, apart from a metastatic carcinoma of the lung that was the reason for his death, no viable tumour was found in the operated and irradiated region. The brain showed extensive gliosis at the localization of the initial cerebral tumour, with necrotic parts, hypertrophic vessels and calcifications (fig 7.3d). Infiltrations of mononuclear cells were frequently seen (fig 7.3e). Almost all vessels were more or less damaged with frequent thrombosis (fig 7.3f), compatible with the HMPAO result. **Conclusion**: Peritumoural tissue changes after brachytherapy.

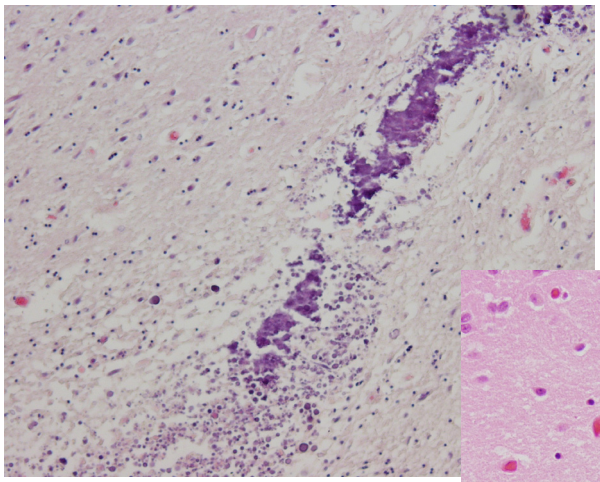
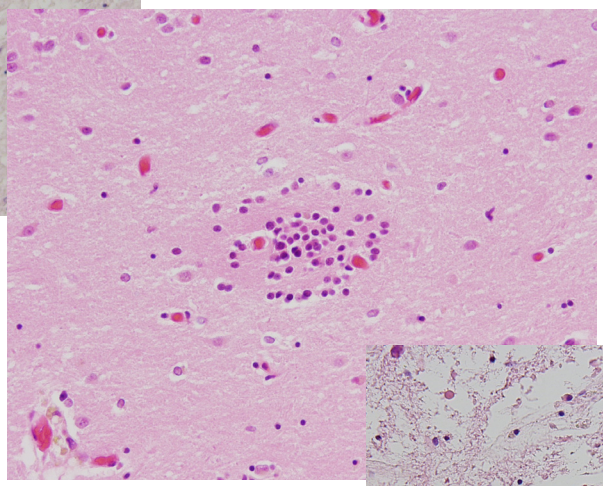


Fig 7.3d: Tissue obtained at autopsy: gliosis and calcified parts.

Fig 7.3e: Tissue obtained at autopsy: infiltration of (perivascular) mononuclear cells**.**



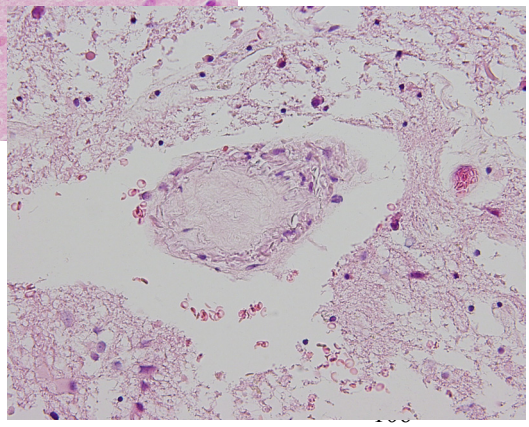


Fig 7.3f: Tissue obtained at autopsy: damaged vessel with thrombosis in necrotic gliotic tissue.

7.4. A 51 year old patient operated for a GBM in the right parietal region and treated with EBRT and brachytherapy afterwards, underwent MRI scanning 6 months later because of nausea and vomiting (fig7.4a).

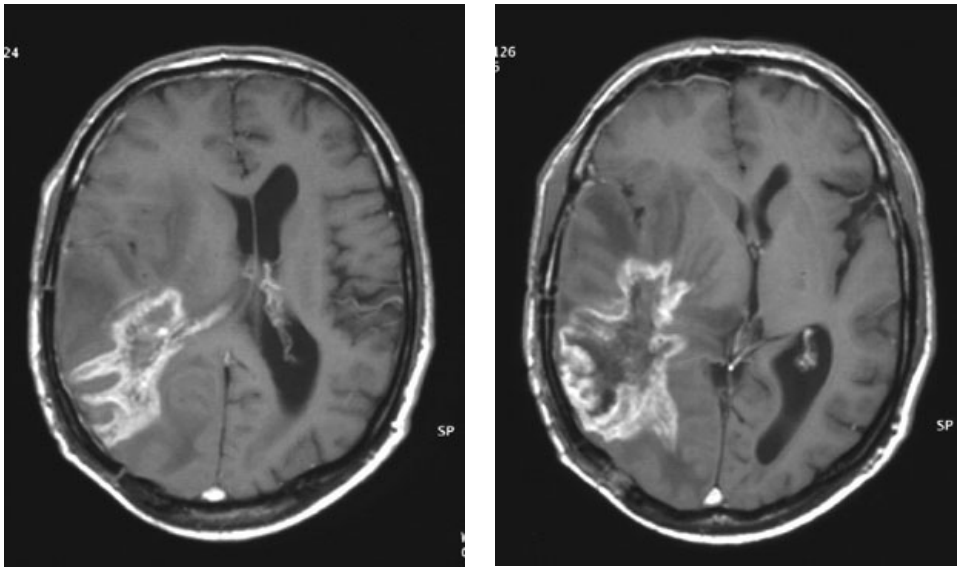


Fig 7.4a: T1-MRI scan contrast enhanced 6 months after brachytherapy

This scan indicated mass effect with midline shift to the left, very suggestive for tumourrecurrence. With ^{201} Tl-SPECT this was confirmed, but with ^{11}C-tyrosine PET was negative (fig7.4b+c). Because no further surgery was done and no autopsy was permitted after his death 3 years later, no definitive conclusion can be drawn from these radiological studies. Probably the MRI images mainly showed radiation induced enhancement and edema because the patient suvived for another 2 years. In retrospect, the thalium SPECT images might indicate only elevated blood perfusion in the lesional area. **Conclusion**: Only patient with pure radionecrosis.

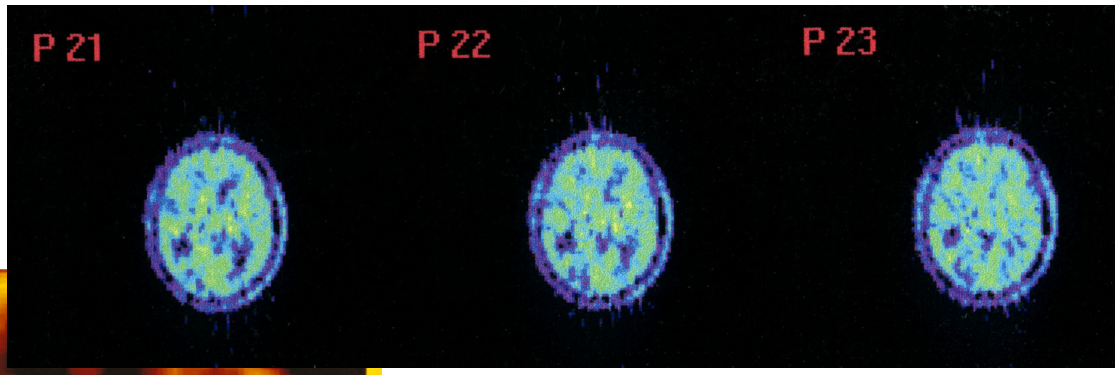


Fig 7.4c: 11C-tyrosine PET unsuspected for tumour recurrence. Full colour: section F

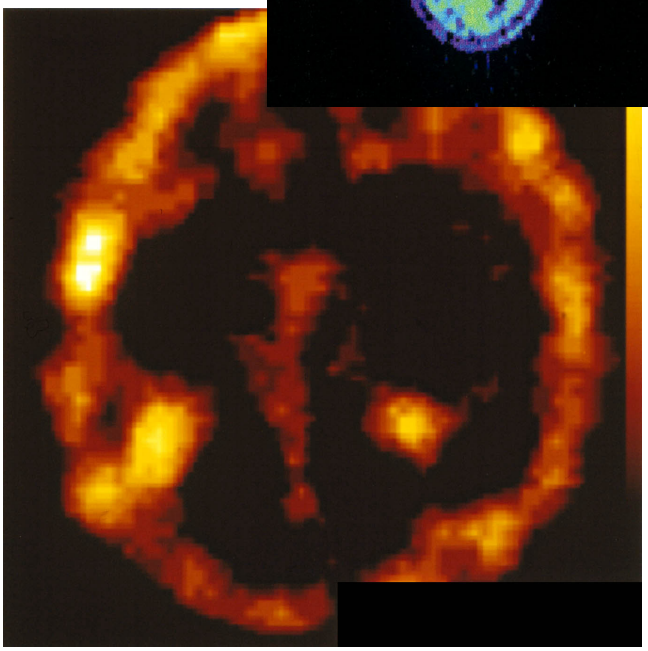


Fig 7.4b: ^{201}Thallium SPECT scan supected for tumour progression.

8. Summary and Conclusion

Summary

Chapter 1. This thesis encompasses the upfront treatment of glioblastoma multiforme with additional high dose radiation boost after resection and external beam radiation therapy (EBRT). The first chapter consists of an overview of the literature regarding the diagnosis of malignant glioma and the treatment options focusing on radiation. As the desired radiation dose to achieve tumour control is far above the maximum tolerated dose of the brain, interstitial radiotherapy (brachytherapy) seemed promising in the upfront treatment for a highly selected group of glioblastoma multiforme patients fulfilling certain criteria. This is described in the second part of the first chapter were the outline of the study, incorporating patients with primary glioblastoma multiforme with a maximal diameter of 5 cm in one hemisphere and with a Karnofsky Performance Score of at least 70, is presented.

Chapter 2. Glioblastoma Multiforme is one of the most devastating primary tumours in oncology. Median survival of all patients after surgery and radiotherapy is less than one year, with only a few patients surviving more than 2 years.
In the last decennium new techniques in diagnostics as well as in treatment have been developed for neuro-oncology patients. The use of MRI, CT-simulation, conformal radiation techniques, and hypofractionation became standard and have a small not significant effect on the treatment results in the AMC. Apart from this, younger patients have a slightly better survival with gross total tumour removal than elderly people, in whom biopsy and resection give no difference in outcome.
In general, the younger the patient, the longer the survival after treatment. In our hospital with standard surgical and external beam radiation therapy, the median survival is 7 months. In the highly selected group for brachytherapy after an additional interstitial boost the median survival was 16 months.

Chapter 3. Two different strategies of interstitial boost (brachytherapy), as were carried out in the University Hospital in Cologne and in the AMC Amsterdam showed no different outcomes with regard to survival. In both patient groups median survival was 16 months, indicating that the effect of brachytherapy is essentially no more than the slowing down of the process of tumour growth. Differences in dose-rate and tracer (Iodine-125 vs Iridium192) do not influence the final results.
In a matched historical group that did not receive brachytherapy, however, the median survival was 10 months, being not significantly different. This indicates, that well-circumscribed more peripheral tumours and the age of the patient are the important factors for survival.
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Chapter 4. Quality of life after brachytherapy in patients with glioblastoma multiforme was studied with Qol questionnaires for both patients and partners with an extension of the Rotterdam

Symptom Checklist (e-RSCL) consisting of the 4 subscales Overall evaluation of life quality, Activity level, Psychological distress and Physical Symptom distress. Significant short-term effects were found for 2 subscales and longer-term effects were found for all subscales. A high correlation between partner and patient's Qol assessment was found. The psychological impact of brachytherapy, a therapy with no proven benefit in high-grade glioma patients, is considerable. An interstitial boost (brachytherapy) after External Beam Radiation treatment should therefore be used only in highly selected patients.

Chapter 5. Emission tomography studies can be used to discriminate between tumour recurrence and radionecrosis after treatment with brachytherapy for glioblastoma multiforme and may be useful to select patients with radiation necrosis for second surgery after brachytherapy. Thallium SPECT and Tyrosine PET were highly concordant concerning the prediction of radionecrosis and/or tumour recurrence but in almost all cases active tumour was predicted. This means, that with primary GBM clinical deterioration is almost always due to tumour recurrence.Pathological proof confirmed the presence of active tumour in all cases which underwent second surgery.Pure radiation necrosis probably does not exist without concomitant active tumour in brachytherapy patients treated for GBM and no added value of emission tomography could be found.

The radiation-induced changes of brain tissue are described in more detail in *chapter 6* on the basis of pathological case studies focusing on changes in the microvasculature.

Chapter 6.1. Radiation treatment for nasopharyngeal carcinoma may cause radiation injury of the brain in the field of radiation. Liquefaction necrosis with radiation injury of the microvasculature of one or both temporal lobes may be a manifestation of successful treatment.

Chapter 6.2. Cerebral necrosis after irradiation can be found after brachytherapy, but also after high cumulative dose of conventional external radiation. Even after an interval of 28 years with a cumulative dose of 79 Gy (25 Gy in childhood, 54 Gy in adulthood) there is a substantial risk in developing radionecrosis.

Chapter 6.3. Peritumoural alterations of the parenchymal architecture in GBM consist of endothelial abnormalities and infiltrations of mainly T-cell lymphocytes and macrophages. Quantification of these abnormalities between GBM patients without radiotherapy and patients with external beam radiotherapy showed that in the not-irradiated patients these parameters are expressed more than in the irradiated cases. Additional brachytherapy did not further influence this observation.

Chapter 7. The follow-up of brachytherapy patients is characterized by very different and unpredictable patterns not only clinically but also radiologically. Clinical symptoms and radiological images do sometimes not correlate at all. Illustrative cases are presented in this chapter.

Conclusion

A decade ago, stereotactic brachytherapy for GBM seemed to be an effective therapeutic strategy in patients with a well-circumscribed tumour, when given as an addition to surgery and EBRT. At that time, radiotherapy was the only proven effective additional treatment for malignant glioma (21).

Many procedures and years later, randomized trials failed to show a benefit on survival with brachytherapy in the up-front treatment for primary GBM (10;15).

Moreover, the timing of brachytherapy (prior to-, concomitant with-, or after EBRT), the choice of temporary or permanent implants delivering low dose rate brachytherapy, the source (I^{125} or Ir^{192}) or even the use of the most sophisticated planning techniques have not shown significant differences in median survival form earlier work on similar patients (5-7;11;12;14;19;23).

Despite all efforts, in up to 50-80% GBM patients still show local recurrences within 2 cm of the treatment volume. (1;3;14;17;22).

This lack of benefit in terms of survival was in concordance with the experiences we gained during the treatment of our brachytherapy patients: Apart from a new admittance and extra operation with isolation during irradiation (Ir^{192}), a small risk of haemorrhage during the catheter implantation, a small risk of infection, and a small risk of cerebro-spinal fluid leakage and poor wound healing around the intervention, we observed some early delayed complications requiring high doses of steroids for longer periods but more often delayed complications consisting of neurological decline (4;9;13) based on radiation injury. At follow-up, all GBM's recurred without a significantly improved survival. This intense treatment had a considerable impact on the quality of life for both (2;8) the patient and his or her family.

It can be concluded that additional radiotherapy given stereotactically by LINAC, Y-knife or brachytherapy, after delivering the standard total dose of 60 Gy external beam radiation for malignant glioma, even applied in highly selected cases, is not able to achieve local control and is only in a small subset giving longer palliation. (10;16;18). The value of brachytherapy is that it offers focal treatment, but the GBM shows to be both a locally recurrent and infiltrating disease.

After extensively reviewing the literature on brachytherapy, Vitaz et al (20) recommended no longer the use of additional high dose boost by brachytherapy in the formal treatment of malignant glioma.

Evaluating our series, we came to the same conclusion that after all it is difficult to argue in favour of the routine use of additional brachytherapy for primary glioblastoma multiforme. Local control will almost never be achieved due to the spreading of the disease as well as the limited brain tolerance for radiation.

Stereotactic brachytherapy should therefore not be a part of malignant glioma protocols. Advances in surgical techniques based upon nowadays available techniques such as neuronavigation, functional MRI, brain mapping and cortical stimulation in awake craniotomies may increase surgical indications for many tumors previously considered inoperable.

However, brachytherapy for low-grade gliomas, metastases or recurrent meningiomas may be effective and deserves to be more extensively studied.

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Samenvatting en conclusie

Samenvatting

Hoofdstuk 1. Dit proefschrift gaat over de behandeling van het Glioblastoma Multiforme (GBM) door middel van een extra toegevoegde lokale vorm van bestraling (brachytherapie) aan de standaard behandeling bestaande uit chirurgie en uitwendige radiotherapie. GBM is de meest voorkomende en kwaadaardigste hersentumor bij volwassenen die uitgaat van de steuncellen van de hersenen, de zogenaamde astrocyten. Het eerste hoofdstuk gaat over de gegevens uit de literatuur en de behandelingsmogelijkheden toegespitst op bestraling. Uitwendige bestraling is aan een maximum dosis gelimiteerd ten einde schade aan het omliggende gezonde hersenweefsel te voorkomen. Voor tumorbehandeling is echter een hogere dosis gewenst. Deze extra dosis kan gegeven worden door radioactieve bronnen met een zeer geringe stralingsreikwijdte in de tumor te plaatsen, zogenaamde brachytherapie. Voor een patiëntengroep die aan bepaalde criteria voldeed leek dit een veelbelovende toegevoegde behandeling. De selectie criteria en de opzet van de studie worden in het tweede deel van hoofdstuk 2 besproken. Inclusiecriteria zijn onder andere een diagnose GBM, een maximale tumor diameter van 5 cm en een Karnofsky score van minimaal 70 (onafhankelijkheid van anderen in de dagelijkse verzorging).

Hoofdstuk 2. De mediane overleving van het GBM na operatie en uitwendige bestraling is minder dan 1 jaar; bijna alle patiënten zijn binnen 2 jaar na het stellen van de diagnose overleden. In het afgelopen decennium zijn nieuwe diagnostische technieken en behandelingsmogelijkheden ontwikkeld voor neuro-oncologie patiënten. Het gebruik van MRI, CT-simulatie in de bestralingsplanning, meervelden technieken en hypofractionering worden veelvuldig toegepast maar hebben een beperkt niet significant effect op de behandelingsresultaten in het AMC. Jongere patiënten hebben een betere overleving bij een zo radicaal mogelijk uitgevoerde operatie, terwijl er bij ouderen geen verschil in overleving wordt aangetoond tussen patiënten die alleen maar een biopt voor het stellen van de diagnose ondergingen vergeleken met patiënten die een grote resectie ondergingen. In het algemeen is het zo dat hoe jonger de patiënt is, des te beter de overleving. De mediane overleving van GBM patiënten ligt in het AMC rond 7 maanden. In een sterk geselecteerde patiëntengroep die additionele brachytherapie ondergingen was de overleving 16 maanden.

Hoofdstuk 3 beschrijft twee zeer verschillende protocollen van de (stereotactische) brachytherapie. Vergeleken wordt het protocol uit Keulen, Duitsland met dat uit het AMC, Nederland. Dit protocol verschilt op bijna alle punten; de radioactieve bron verschilt, het tijdstip na de operatie en de uitwendige radiotherapie, het aantal geplaatste bronnen, de bestralingsduur, de totale dosis bestraling en de snelheid van toedienen (dose-rate). In beide groepen is de overleving ongeveer 16 maanden. Dit verschilt niet significant van een vergelijkbare groep van patiënten met een GBM die geen brachytherapie ondergingen. Dit houdt in dat vorm van het GBM (scherp omschreven) en ligging (perifeer) naast leeftijd van de patiënt belangrijke overlevingsindicatoren zijn.

In *hoofdstuk 4* wordt de kwaliteit van leven onderzocht bij patiënten met een GBM die brachytherapie ondergingen met een voor dit doel speciaal ontworpen uitbreiding van de Rotterdamse Symptom Check List voor zowel patiënten als partners bestaande uit 4 subschalen. Significante korte termijn effecten werden in 2 subschalen aangetoond, terwijl op de langere termijn alle subschalen significant verschilden. Er bestond een hoge correlatie tussen patiënten en partners. Ofschoon brachytherapie goed verdragen wordt, is met name de psychische belasting voor zowel patiënt als partner aanzienlijk en is terughoudendheid ten aanzien van het indiceren van stereotactische brachytherapie op zijn plaats.

Hoofdstuk 5 gaat over de toegevoegde waarde van specifieke onderzoeken (PET en SPECT) die onderscheid zouden kunnen maken tussen het terugkeren van de tumor (recidief) en het optreden van klachten ontstaan door radionecrose (doodbestraald weefsel). Thallium SPECT en Tyrosine PET zijn even gevoelig in het voorspellen van radionecrose of tumorrecidief. In bijna alle gevallen werd tumorrecidief voorspeld. Dit houdt in dat klinische achteruitgang na brachytherapie bij GBM patiënten in bijna alle gevallen werd veroorzaakt door tumorrecidief, zoals ook bleek bij reoperatie. Pure radionecrose zonder actieve tumor komt waarschijnlijk niet voor bij GBM patiënten die behandeld zijn met brachytherapie en in dat kader is aanvullend onderzoek met PET en/of SPECT niet zinvol.

Hoofdstuk 6. Aan de hand van case-reports wordt bestudeerd welke eventuele veranderingen na hoge dosis radiotherapie op korte en/of lange termijn in de hersenen kunnen optreden.

6.1. Aan de hand van een bestraalde patiënt met een nasopharynx carcinoom (keel kanker), is gekeken naar de afwijkingen in de temporaalkwabben die ter hoogte van de schedelbasis liggen. Deze afwijkingen zijn indrukwekkend en spelen zich voornamelijk af op het niveau van de microcirculatie.

6.2. Het optreden van radionecrose is bekend na brachytherapie maar kan ook optreden na een hoge cumulatieve dosis externe radiotherapie, zelfs als deze met een groot tussentijds interval wordt gegeven. Zelfs na een interval van 28 jaar bestaat tussen 25 Gy op de kinderleeftijd en 54 Gy op volwassen leeftijd is er een risico op radionecrose.

6.3. Peritumorale veranderingen in de hersenen bij GBM patiënten bestaan voornamelijk uit ontstekingsverschijnselen (T-cellen en macrophagen) en vaatwand (endotheel) veranderingen. Kwantificatie laat zien dat patiënten zonder radiotherapie meer van deze reacties vertonen dan bestraalde (al dan niet met brachytherapie) patiënten.

Hoofdstuk 7. Tijdens het vervolgen van GBM patiënten behandeld met brachytherapie deden zich soms zeer onvoorspelbare gevolgen voor, zowel klinisch als radiologisch, welke lang niet in alle gevallen met elkaar correleerden. Enkele illustratieve patiënt-geschiedenissen worden in dit hoofdstuk belicht.

Conclusie

Brachytherapie leek 10-15 jaar geleden een effectieve toegevoegde behandeling na operatie en uitwendige bestraling bij GBM patiënten met een scherp omschreven tumor. Tot dan toe was alleen radiotherapie effectief gebleken.
Jaren later bleek uit gerandomiseerde studies dat de overleving door toevoeging van brachytherapie bij het de novo GBM na chirurgie en uitwendige radiotherapie niet significant langer werd.
Het tijdstip waarop de brachytherapie werd toegediend (voor, tegelijk of na de uitwendige radiotherapie), alsmede de keuze tussen tijdelijke of blijvende implantaten, de bronsoort (^{125}I of ^{192}Ir) en zelfs de meest geavanceerde planningstechnieken hebben niet geleid tot significante verschuivingen in de mediane overleving. Ondanks alle inspanningen recidiveren 50-80% van de GBM patiënten met een tumor binnen 2 cm van het met brachytherapie behandelde volume.
Dit uitblijven van succes in toename van overleving in de literatuur strookt met de ervaringen die wij opgedaan hebben tijdens de behandeling van in totaal 27 patiënten met een primair GBM. Afgezien van een tweede ziekenhuis opname en extra operatie met isolatie, een klein risico op een tijdens de ingreep optredende (ernstige) bloeding, infectie, liquorlekkage of slechte wond genezing constateerden we zowel korte termijn als lange termijn neveneffecten van intensieve radiotherapeutische behandeling. Alle GBM's recidiveerden zonder winst in overleving en de brachytherapie had soms een grote negatieve invloed op de kwaliteit van leven van zowel de patiënt als van de partner.

Samenvattend kan gesteld worden dat het toevoegen van stereotactische radiotherapie door LINAC, Y-knife of brachytherapie aan de standaard behandeling van het GBM (chirurgie en 60 Gy uitwendige radiotherapie) niet leidt tot lokale tumorcontrole. Brachytherapie wordt gegeven met het oog op lokale tumorcontrole, maar het GBM recidiveert onder brachytherapie zowel lokaal als met diffuse infiltratie in het omliggende hersenweefsel.
In een overzichtsartikel waarin de meest relevante literatuur over brachytherapie bij het GBM op een rijtje wordt gezet, concludeert Vitaz dat er in het behandel traject van een de novo GBM eigenlijk geen indicatie bestaat voor brachytherapie.
Dit standpunt wordt door de uitkomsten van onze patiëntenstudie gesteund; lokale tumorcontrole wordt eigenlijk nooit bereikt als gevolg van de diffuse uitgroei van het proces alsmede de beperkte tolerantie van hersenweefsel voor bestraling.
Stereotactische brachytherapie hoort daarom niet thuis in behandelingsprotocollen van het maligne glioom. Progressie in chirurgische mogelijkheden, mede gebaseerd op de heden ten dage beeldvormende technieken waaronder neuronavigatie, functionele MRI, brain mapping en corticale stimulaties peroperatief bij patiënten die niet onder algehele anesthesie zijn leidt tot een toename van chirurgische indicaties van laesies die vroeger als inoperabel werden beschouwd. Het verdient aanbeveling verdere studie te doen naar de effectiviteit van brachytherapie voor laag-gradige gliomen, metastases of recidiverende meningeomen.

Authors and affiliations

Dr. E. Aronica, Department of Neuropathology, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

M.A. van den Bergh Weerman, Department of Neuropathology, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Prof. dr. D.A. Bosch, Department of Neurosurgery, Academic Medical Centre, University of Amsterdam PO Box 22660, 1100 DD Amsterdam, The Netherlands

Dr. R. Brand, Department of Medical Statistics, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands

Dr. F.W. Dekker, Department of Epidemiology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands

Dr. K.P. Dingemans, Department of Pathology, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Ir. J.B.A. Habraken, Department of Nuclear Medicine, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Prof. dr. J.C.J.M. de Haes, Department of Medical Psychology, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Drs. K. de Heer, Department of Internal Medicine, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Dr. M.C.C.M. Hulshof, Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Dr. C. Koedooder, Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Dr. Med. M. Maarouf, Department of Stereotactic and Functional Neurosurgery, University of Cologne, Kerpenerstrasse 62, 50931 Cologne, Germany

Dr. F J. Oort, Department of Medical Psychology, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Prof. dr. A.M.J. Paans, Department of Nuclear Medicine and Molecular Imaging, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands

Dr. J. Pruim, Department of nuclear medicine and molecular imaging, University Medical Centre Groningen, PO Box 30001, 9700 RB Groningen, The Netherlands

Drs. E.C. Schimmel, Arnhem Radiotherapy Institute, PO Box 60160, 6800 JD Arnhem, The Netherlands

Dr. L.J.A. Stalpers, Department of Radiotherapy, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Prof. Dr. Med. V. Sturm, Department of Stereotactic and Functional Neurosurgery, University of Cologne, Kerpenerstrasse 62, 50931 Cologne, Germany

Dr. H. Treuer, Department of Stereotactic and Functional Neurosurgery, University of Cologne, Kerpenerstrasse 62, 50931 Cologne, Germany

Prof. dr. D. Troost , Department of Neuropathology, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands

Prof. dr. Med. J. Voges, Department of Stereotactic and Functional Neurosurgery, University of Cologne, Kerpenerstrasse 62, 50931 Cologne, Germany

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Hanneke De Haes. Dat brachytherapie een intensieve behandeling was bleek vanaf het begin. Dankzij jouw vindingrijkheid konden specifieke aan stereotactische brachytherapie gerelateerde quality of life aspecten ook daadwerkelijk gemeten worden. Hiervoor ontwikkelde je aan de hand van interviews met brachytherapie patienten een prachtige gevalideerde aanvulling op de Rotterdam Symptom Checklist.

Dirk Troost. Uren hebben we coupes beoordeeld, ondertussen de dagelijkse beslommeringen doornemend. Een patholoog op de OK is uiterst waardevol, en maar op zeer beperkte schaal elders beschikbaar. Het gebeurde maar zelden dat je er naast zat!

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Curriculum vitae

Na het eindexamen gymnasium β in 1982, werden twee uitlotingsjaren gevuld met een studie biologie, vervulling van de militaire dienstplicht en voorbereidend jaar klassiek gitaar aan het Utrechts Conservatorium. In 1991 behaalde ik het arts-examen aan de Rijks Universiteit van Utrecht. Tijdens de geneeskunde studie bezocht ik Zimbabwe voor het co-schap gynaecologie (D. Verkuyl, Bulawayo, Zimbabwe) en Schotland voor een huisartsenstage (B. Bichan, Fraserbourgh, Schotland). In de periode 1991-1993 was ik arts-assistent chirurgie in het St. Elizabeth ziekenhuis Tilburg (dr. Chr. vd Werken), arts-assistent neurologie in het Slotervaart ziekenhuis Amsterdam (dr. J.J. vd Sande) en toegevoegd onderzoeker in het Research Laboratorium Neurologie aan de universiteit van Utrecht (dr. P.R. Bar). Vanaf 1993 was ik eerst als AGNIO, later als AGIO, werkzaam op de afdeling neurochirurgie van het Academisch Medisch Centrum in Amsterdam (prof. dr. D.A. Bosch). In deze periode heb ik mij verdiept in de stereotactische interstitiële radiotherapie in samenwerking met de afdeling radiotherapie van het AMC (prof. dr. D. González-González†, prof. dr. C.C.E. Koning), wat geleid heeft tot dit proefschrift. In dit kader bezocht ik 6 weken de afdeling functionele en stereotactische neurochirurgie van professor V. Sturm aan de universiteit van Keulen. Inschrijving in het specialisten register in november 2001. Vanaf november 2002 tot november 2003 was ik als neurochirurg verbonden aan hôpital Lariboisière in Parijs (prof. B. George), gevolgd door een 3 maanden durende stage aan de kinderneurochirurgische afdeling van hôpital Necker in Parijs (prof. A. Pierre-Kahn). Daarna werkte ik als stafarts in het AMC (prof. dr. D.A. Bosch, prof. dr. W.P. Vandertop) met als specifiek aandachtsgebied de kinderneurochirurgie. Per 1 mei 2006 ben ik werkzaam in het Leids Universitair Medisch Centrum (prof. dr. R.T.W.M. Thomeer).

Section A

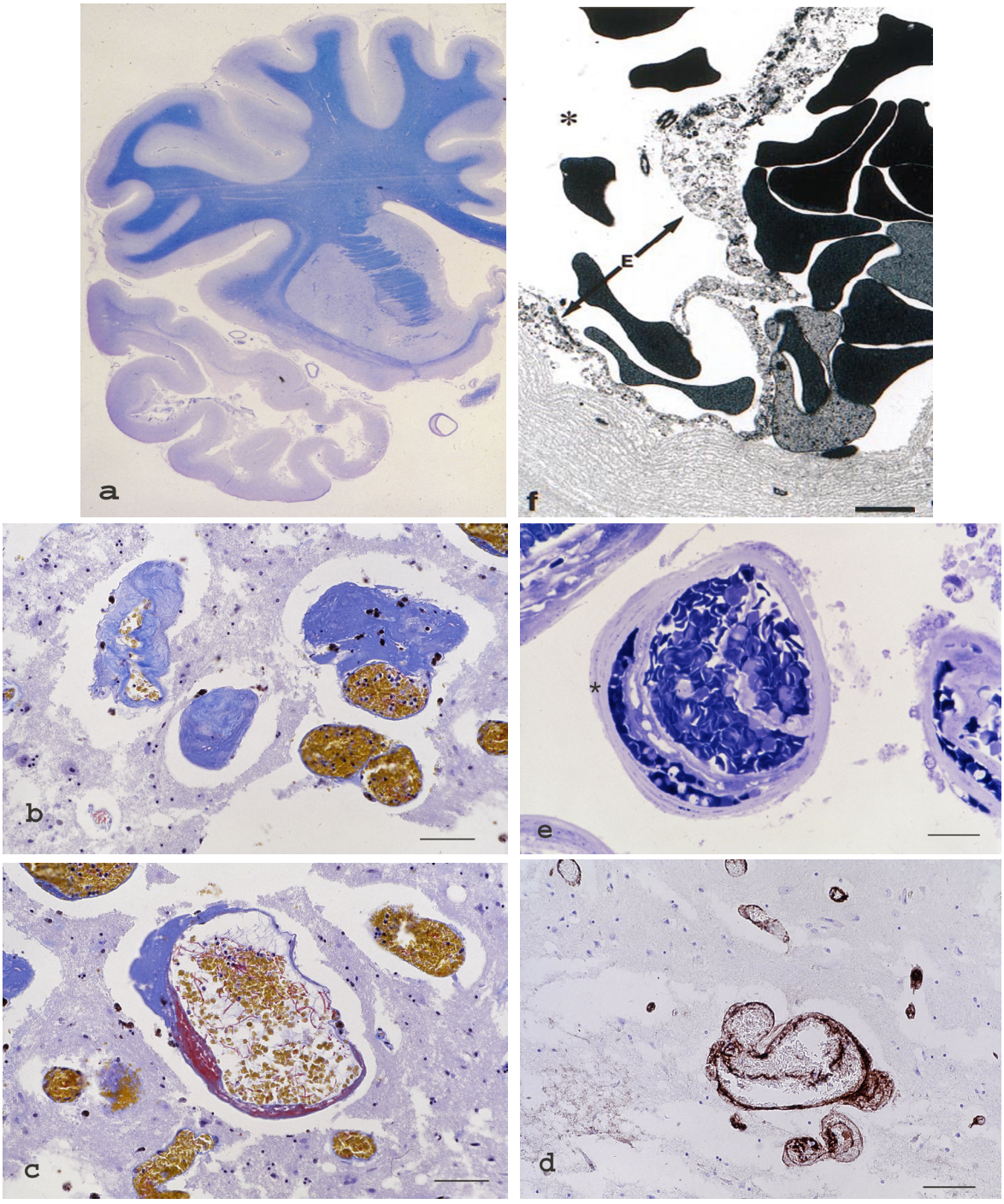


Figure 6.1.1. Extensive radiation injury of the temporal lobe. **a**, Coronal slice through part of the left frontal and temporal lobe. The white matter of the temporal lobe has almost completely disappeared, Klüver Barrera stain. **b,** White matter of the temporal lobe. Extensive vessel wall fibrosis, MSB stain. Bar = 70 µm. **c,** White matter of the temporal lobe. Fibrinoid necrosis (red), MSB stain. Bar = 70 µm. **d,** White matter of the temporal lobe. Dissection in small vessel. Factor VIII stain. Bar = 70 µm. **e**, Vessel wall dissection. White matter of the temporal lobe. Detachment of the endothelium from the underlying basement membrane (*). Semi-thin section. Toluidin blue. Bar = 25 µm. **f,** Electron microscopic section of a small vessel with endothelial detachment and vessel wall dissection. Note the multiplication of the basal laminae (bottom). * = Capillary lumen. E = Endothelium. Bar = 2 µm.

Section B

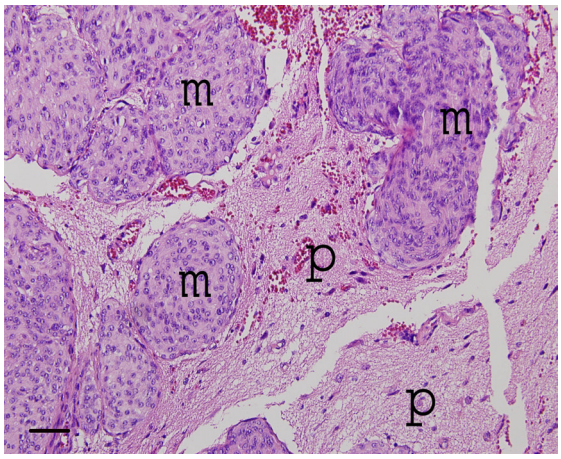
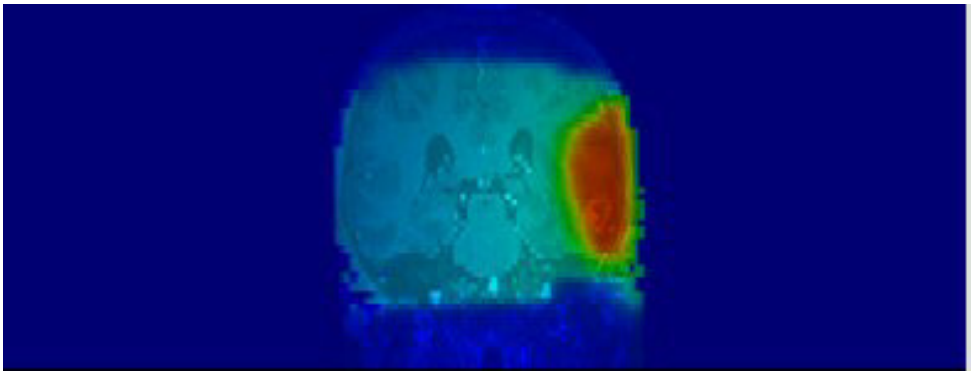
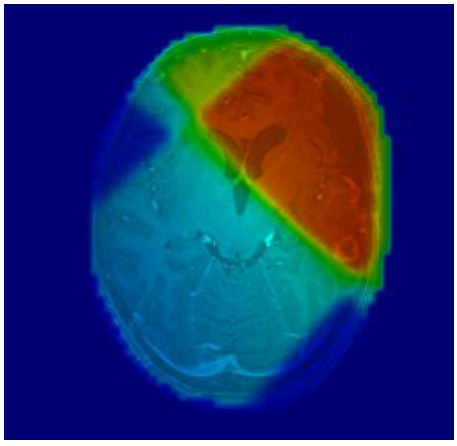


Figure 6.2.1: Meningioma (m) infiltrating the cerebral parenchyma (p) (resection 2004). Staining HE. Bar = 150 µm.





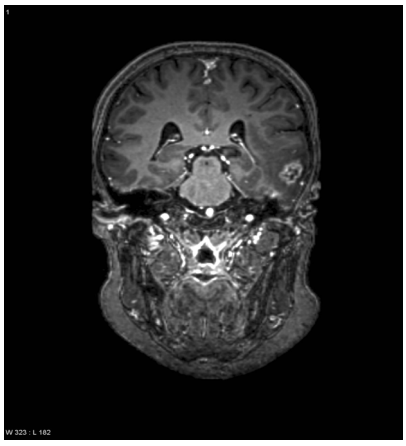


Figure 6.2.2: Post-irradiation, pre-operative T1-contrast MRI (December 2005; right), and overlay of radiation dose distribution delivered in 2004 (up and left). The temporal necrosis in the left temporal region developed just within the high radiation dose region (red).

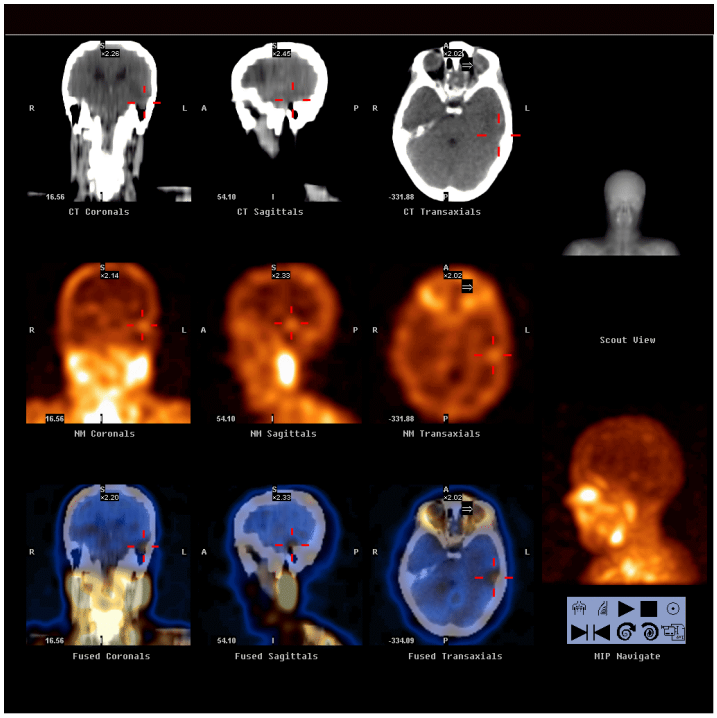


Figure 6.2.3 (left): ^{201}Tl SPECT scan and fusion with non-enhanced CT-scan. Accumulation of ^{201}Tl in the region of contrast- enhancement on the T1-MRI

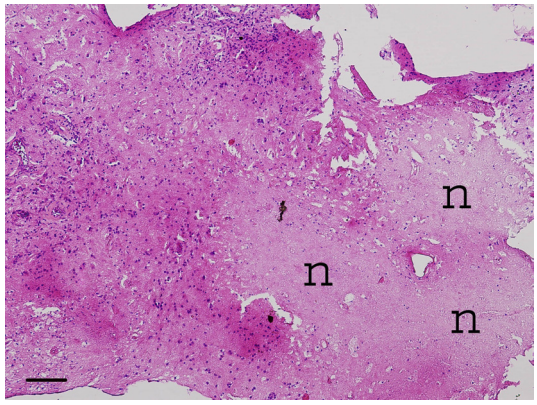


Figure 6.2.4 (up): Fragments of pre-existent parenchyma with extensive areas of necrosis (n) and reactive gliosis (resection 2006). Staining HE. Bar = 200 µm

Section C

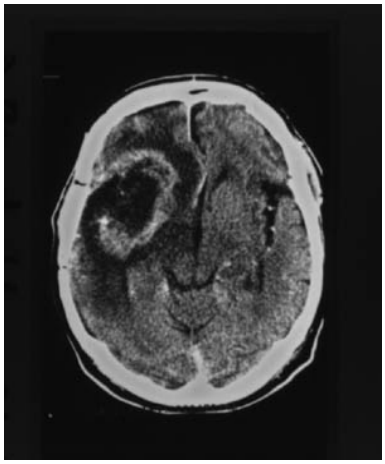


Fig 7.1a: CT-scan contrast enhanced showing large right frontal mass 5 months after brachytherapy.

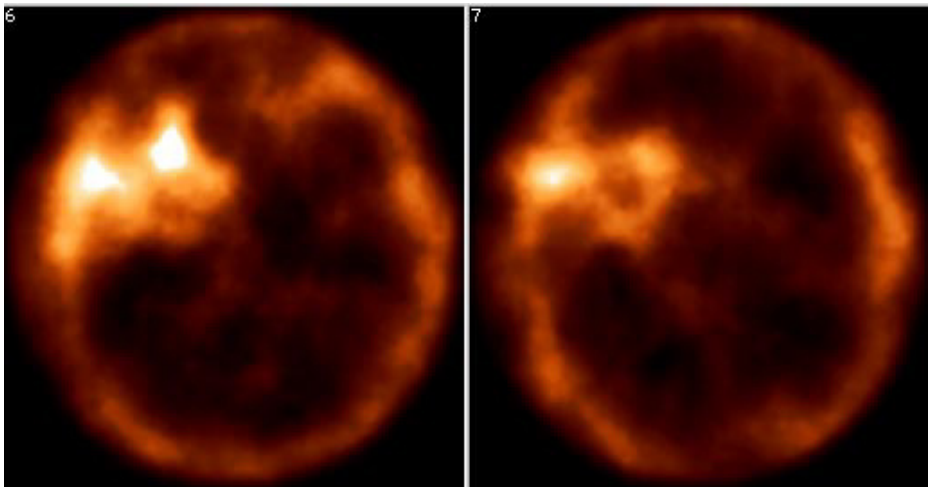


Fig 7.1b: ^{201}Thallium SPECT scan 5 months after brachytherapy suggestive for tumour recurrence cq progression.

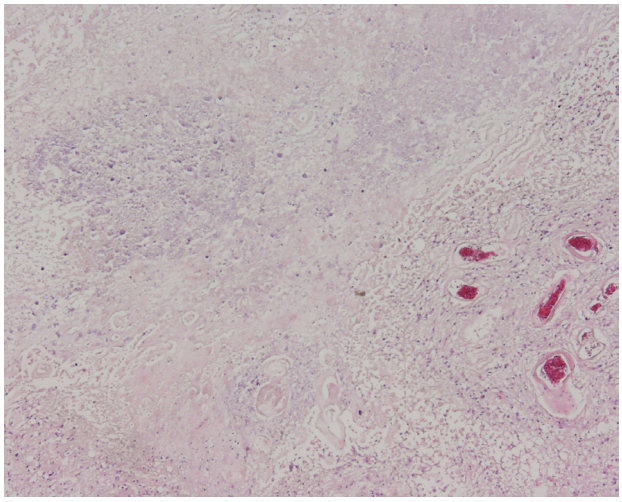


Fig 7.1c: Tissue obtained during reoperation: necrosis and calcifications. Full colour: section C

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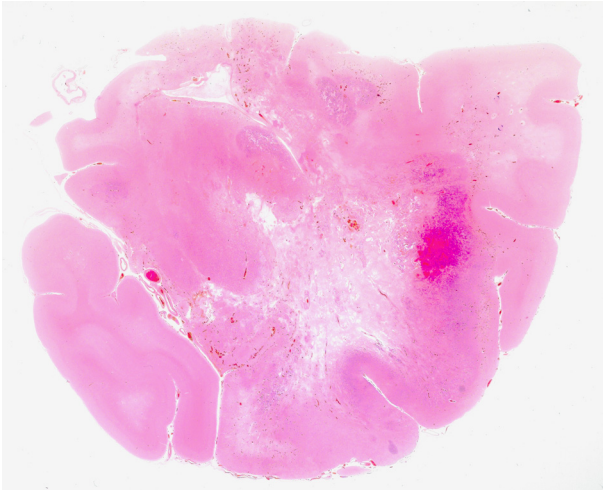
Fig 7.1d: Tissue obtained at autopsy: large mainly necrotic GBM with hemorrhages and calcifications.



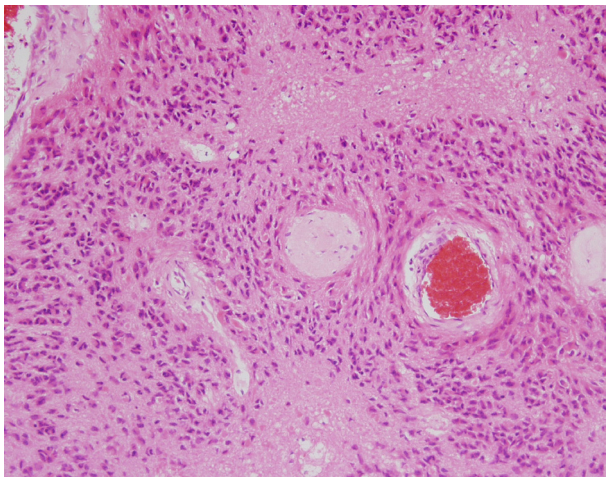


Fig 7.1e: Tissue obtained at autopsy: hypertrophic vessel wall and occluded lumina of small vessels.

Section D

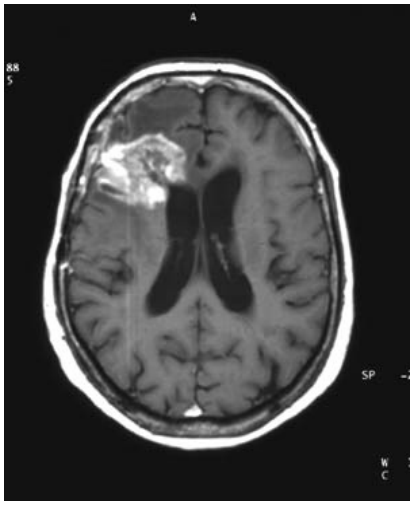
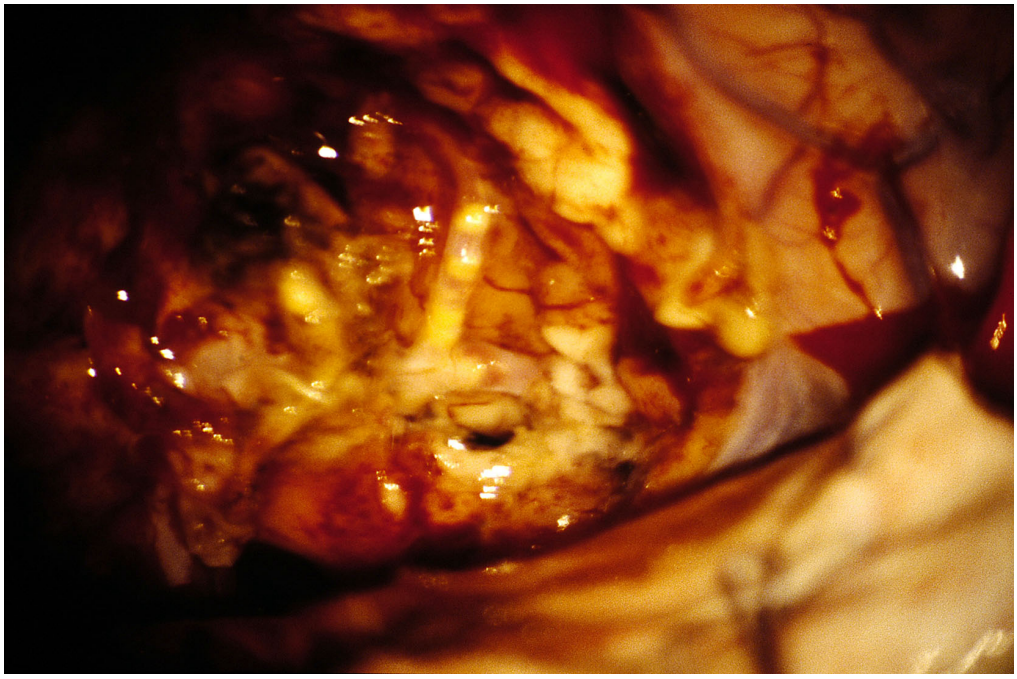


Fig 7.2a: MRI contrast enhanced T1, 29 months after the brachytherapy before reoperation.

Fig 7.2b: Reoperation after brachytherapy, note the yellow longitudinal structures, which are calcified small vessels.



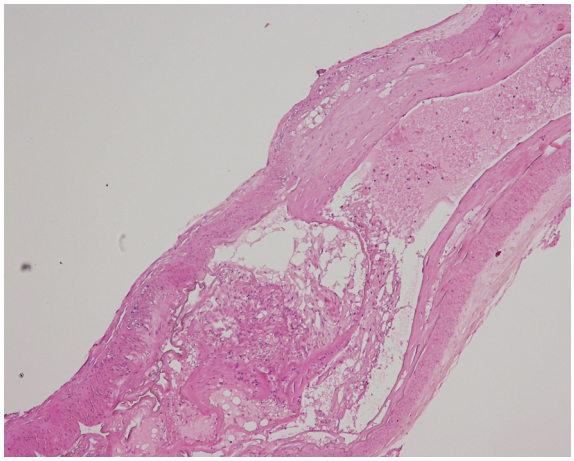
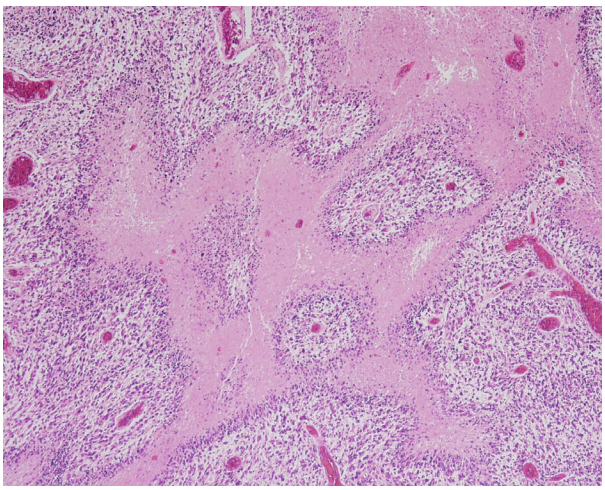


Fig 7.2c: Tissue obtained during reoperation: histology (HE) of the vessels shown in figure 7.2b.

Fig 7.2d: Tissue obtained at autopsy: fields with vital tumour and necrosis.



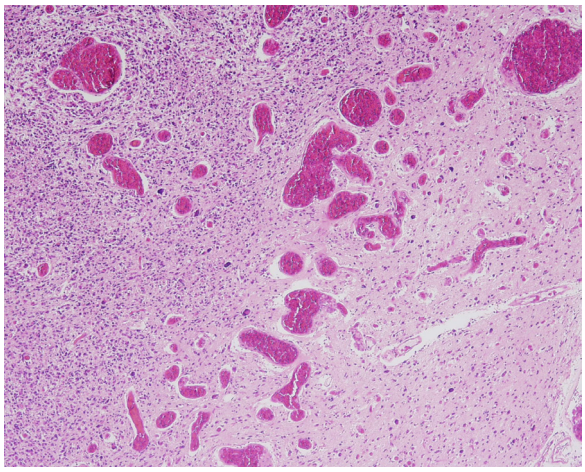


Fig 7.2e: Tissue obtained at autopsy: cavernous vessels in the periphery of the tumour.

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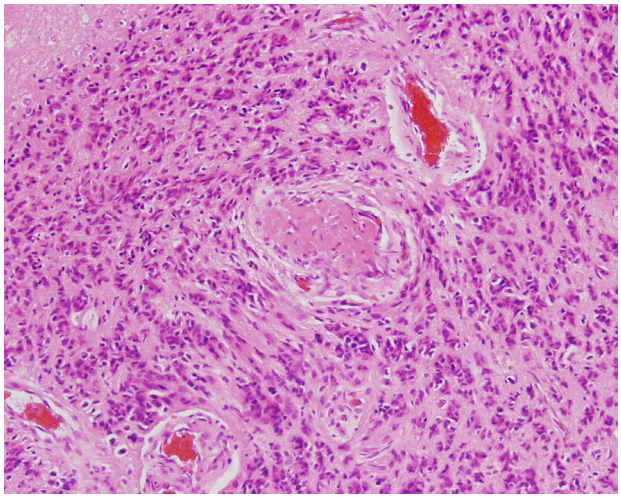

Fig 7.2f: Tissue obtained at autopsy: hypertrophic and thrombosed small vessels

Section E.

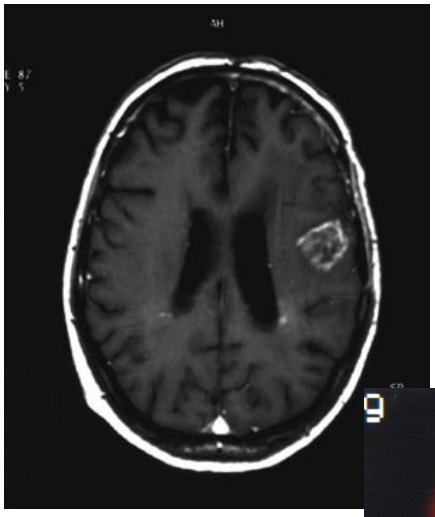

Fig 7.3a: MRI contrast enhanced T1 showing residual lesion without any mass effect near the Broca area 15 months after brachytherapy.

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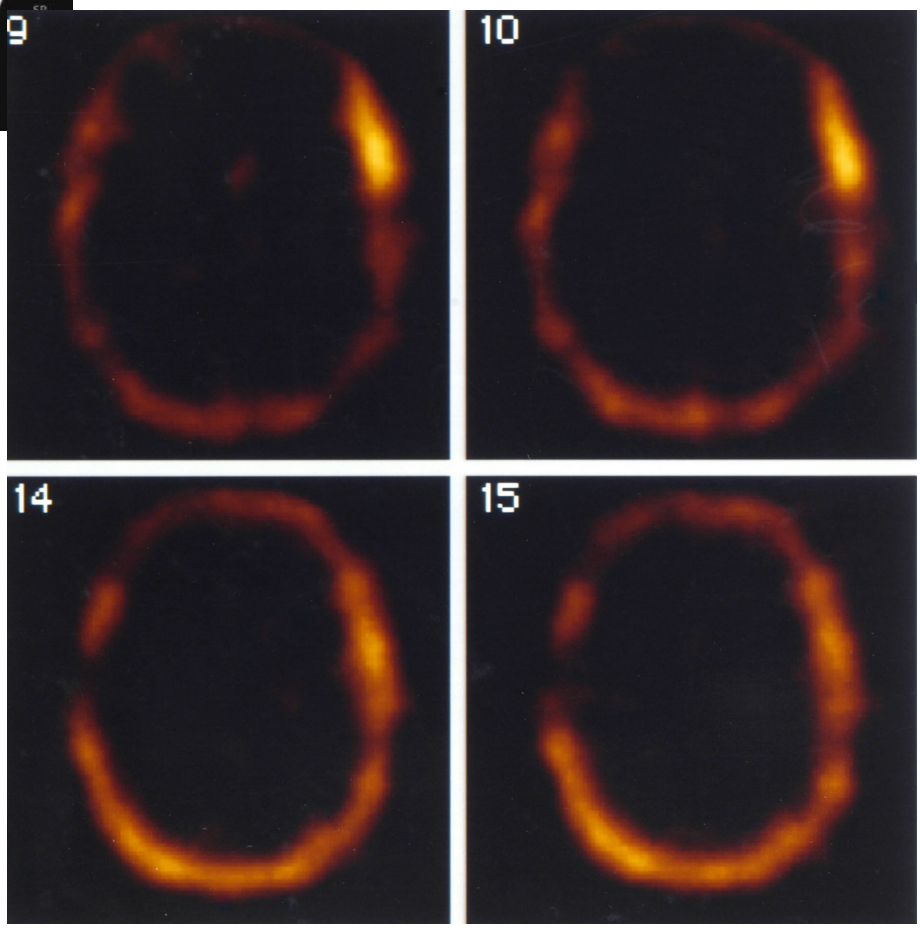

Fig 7.3b: Thallium SPECT scan 15 months after brachytherapy not suggestive for tumour recurrence/progression nor for radionecrosis.

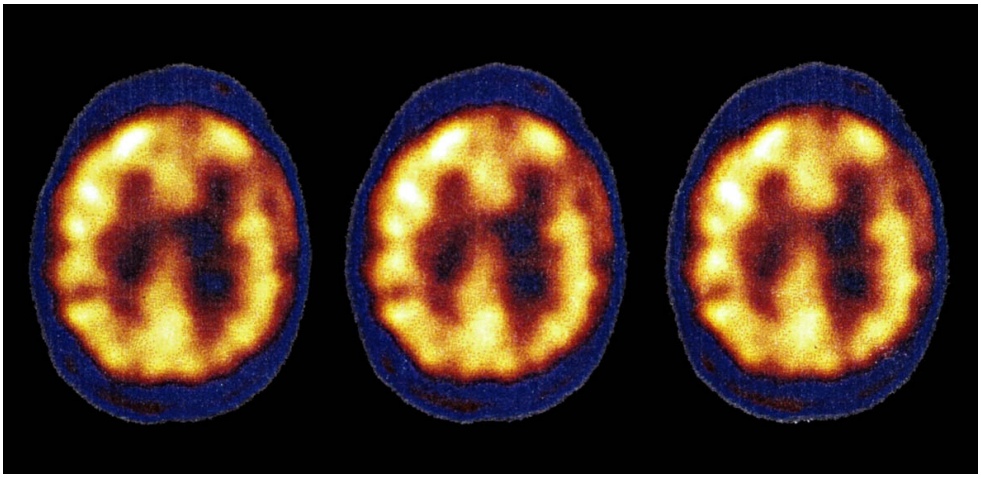

Fig 7.3c: HMPAO SPECT suggestive for decreased vascularistion near the Broca area 15 months after brachytherapy

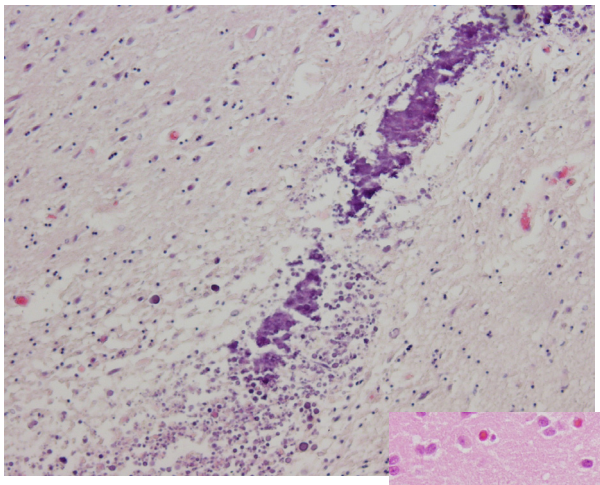

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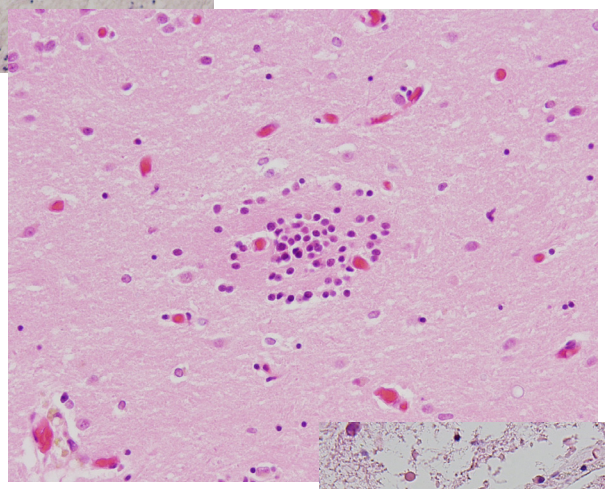
Fig 7.3d: Tissue obtained at autopsy: gliosis and calcified parts.

Fig 7.3e: Tissue obtained at autopsy: infiltration of (perivascular) mononuclear cells.



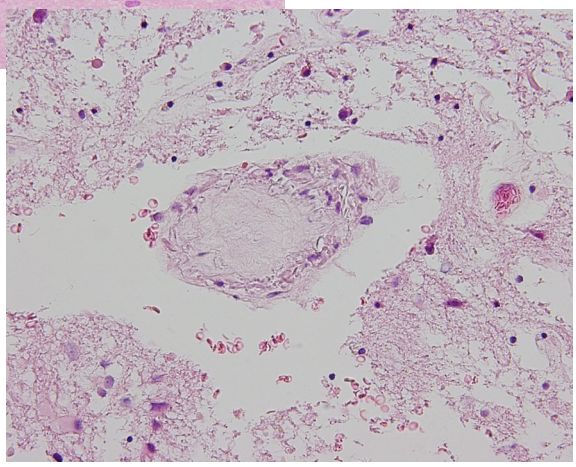


Fig 7.3f: Tissue obtained at autopsy: damaged vessel with thrombosis in necrotic gliotic tissue.

Section F

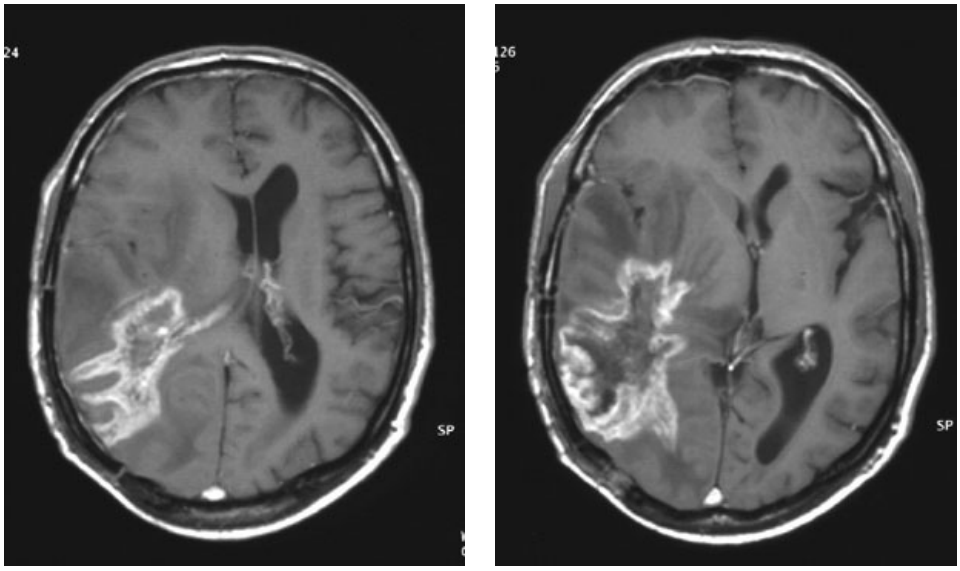


Fig 7.4a: T1-MRI scan contrast enhanced 6 months after brachytherapy

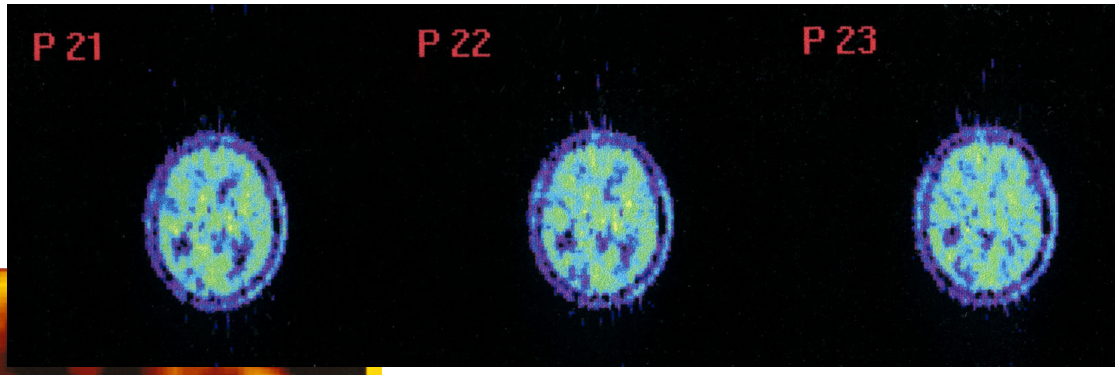


Fig 7.4c: 11C-tyrosine PET unsuspected for tumour recurrence.

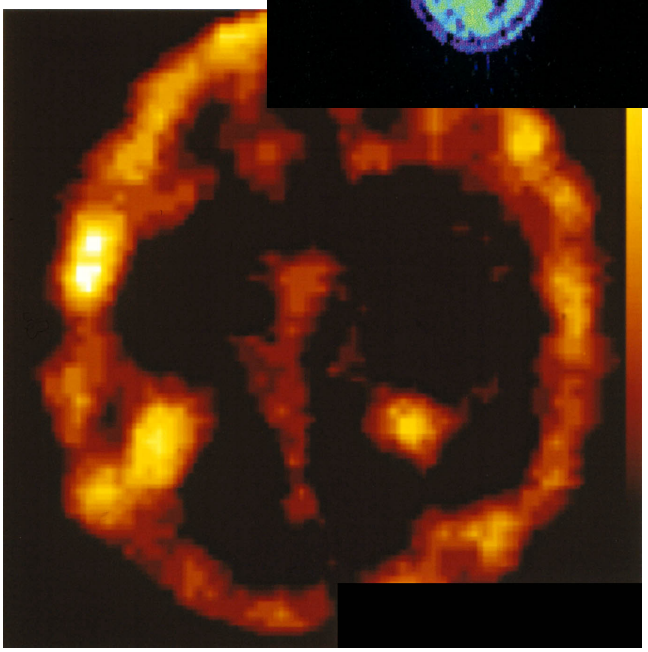


Fig 7.4b: ^{201}Thallium SPECT scan supected for tumour progression.