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### Survival following treatment with RMP-7 and carboplatin in malignant glioma who grade III-IV: Comparison with matched controls

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**Purpose:** to assess survival following treatment with the bradykinin analogue RMP-7 (300 ng/kg) and carboplatin (AUC 7) in the treatment of recurrent chemotherapy naive high grade glioma.

**Methods:** Between Feb 95 and Oct 96, 45 patients median age 42. Karnofsky 80%. were treated q 28 days. Matched controls, untreated at relapse, were identified from a prospectively chosen database (MRC study BR02). Primary (1°) matching criteria were histology, age at diagnosis, history of fits. MRC neurological status at relapse, and planned radiotherapy dose. Seconding (2°) criteria were relapse-free time, extent of neurosurgery, and WHO performance status after surgery and before initial radiotherapy.

**Results:** 35 patients were matched to 87 BR02 patients using the 1° matching criteria, and 35 "best matches" were identified using in addition the 2° criteria. Using Cox's proportional hazards regression model, a series of multivariate analyses were performed, adjusting for the 1° matching criteria ± the 2°. Results for the comparison of the two groups were consistent across the analyses, with highly statistically significant hazard ratios of 1.93 to 2.20 in favour of the RMP-7 and carboplatin treated patients ( $0.022 < p < 0.003$ ).

**Conclusion:** The results from this non-randomised comparison suggest that patients receiving no chemotherapy on relapse have approximately twice the risk of death at any time compared to patients treated with RMP-7-carboplatin.

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### Permanent iodine-125 implants for recurrent malignant gliomas

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**Purpose:** To determine the efficiency and toxicity of permanent iodine-125 implants for recurrent malignant gliomas.

**Methods:** Between Jan 1989 and Apr 1996, 51 patients with histologically-confirmed recurrent malignant gliomas (19 non-glioblastoma malignant gliomas, 32 glioblastoma multiforme) received a permanent iodine-125 implant planned to deliver 0.05 Gy per hour (100 Gy in 1 year; 103.68 Gy at infinity) to the contrast-enhancing tumor periphery visualized on computerized tomography. The median age for the total group, non-glioblastoma (non-GBM) and glioblastoma (GBM) groups were 47.5, 56 and 39 years, respectively.

**Results:** The median survival for the total group, non-GBM and GBM was 1.5, 1.9, 1.2 years, respectively. Reoperations have been performed in 20 (43%) patients; 12 (60%) for tumor progression, 3 (15%) for radiation necrosis, 1 (5%) for brain abscess, 2 (10%) for catheter-related problems, and 2 (10%) for skull infection.

**Conclusion:** Permanent iodine-125 implants for recurrent malignant gliomas are associated with reasonable long-term survival and a low risk of radiation necrosis.

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### Intraoperative radiotherapy (IORT) of malignant brain tumors

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**Purpose:** Feasibility and morbidity of IORT for malignant tumours were examined.

**Methods and Materials:** Between May 1992 and October 1996 40 patients with primary malignant brain tumours were treated with IORT. The patient population included patients receiving primary treatment even as patients with relapses, who received second treatment. Therapy consisted of radical surgical resection and intraoperative electron beam therapy using total doses of 15 Gy to 25 Gy specified to the 90% isodose. Thereafter patients without prior treatment underwent percutaneous irradiation to a total dose of 60 Gy with respect to a small volume.

**Results:** No increase of perioperative morbidity as well as no increase of late sequelae with respect to the short follow-up were observed. The one year survival rate was 58.8% for grade III gliomas (WHO), and 45.5% for glioblastomas. Considering selection criteria according to Matsutani (initial therapy of a supratentorial, peripherally located astrocytoma grade III, or glioblastoma respectively, with less than 5 cm in diameter including a Karnofsky index of >60% and wide resection possible) there was a 1-year survival rate of 71.4%.

**Conclusions:** The feasibility of IORT is shown in this study. There is neither increasing of perioperative morbidity nor subacute sequelae.

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### The efficacy of radiosurgery (RS) alone or in combination with whole brain irradiation for brain metastases

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**Purpose:** Retrospective evaluation of treatment outcome after radiosurgery (RS) as a primary, single treatment modality, in combination with whole brain radiotherapy (WBRT), or as a salvage procedure after previous surgery or WBRT.

**Methods:** Between 1984 and 1996, 307 patients with a total of 460 brain metastases were treated radiosurgically. For 181 patients, RS was the only primary treatment modality, for 79 patients, RS was combined with WBRT. 49 patients were treated for recurrent CNS-disease after previous WBRT. The median prescribed dose was 20 Gy for primary treatment and 15 Gy combined with or after a course of WBRT.

**Results:** Median survival was 5.5 months. Local tumor control was 92%. Both results were not significantly different between the 3 patient groups. Neurological symptoms were stable or improved in 88% of patients with locally controlled brain metastases, thus preventing impaired quality of life secondary to progressive CNS-disease. Three patients had to be treated surgically for radiation necrosis. Few patients experienced temporary symptoms and could be effectively treated with steroids.

**Conclusion:** RS is an effective, non-invasive therapy in the interdisciplinary management of cerebral metastases. Treatment related morbidity is low, both after primary RS and after combined or salvage treatment. Considering excellent local control, short hospitalization and low treatment related morbidity, RS is an important modality for palliative treatment of CNS-metastases.

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### Three-dimensional treatment planning of brain gliomas: A dosimetric study of cerebral irradiation

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**Purpose:** The aim of the study is to analyze the advantages and the limits of the 3D conformal irradiation in the treatment of brain gliomas.

**Methods:** 60 patients with brain gliomas were irradiated according to a 3D conformal treatment planning. The patients with high grade gliomas received a total irradiation dose of 60 Gy (2 Gy/day). 51% of the patients had a glioblastoma, 31% an anaplastic astrocytoma, 13% an anaplastic oligodendroglioma and 4% a low grade oligodendroglioma. The risk of side effects of the therapy was quantified using the normal tissue complication probability - NTCP (parameter model by Kutcher and Lyman), calculated for the whole brain and for the chiasma opticum.

**Results:** The mean survival rate was 10 months in patients with glioblastoma and 18 months in patients with grade III gliomas. The most important prognostic factors were age and tumor histology. The NTCP for the whole brain ranged between 0.02% and 13%, the NTCP for the chiasma opticum ranged between 0.4e-10 and 0.2e-1. The NTCP for the whole brain was directly proportional with the tumor volume, while the NTCP for the chiasma opticum showed a dependence from the tumor location.

**Conclusion:** The 3D conformal irradiation with 60 Gy (2 Gy/day) offers no advantages concerning of tumor control, in comparison to the standard therapy. The precise definition of the tumor volume and the spare of the normal brain tissue offer good premise for a dose escalation. The clinical significance of NTCP must be better defined in future studies.