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Local fluorouracil releasing microspheres (FU-M) with early radiotherapy (RT) in high grade gliomas (HGG): Preliminary safety assessment of a randomized phase II trial of early RT with or without FU-M in patients with complete surgical resection of HGG

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Rationale: HGG and especially glioblastoma multiforme have a poor prognosis. Median survival of patients (pts) treated with surgery and RT is 36 weeks (w), 40–50 w with the addition of chemotherapy. Biodegradable microspheres (M) are made of (d, l-lactic acid-co-glycolic acid) and are metabolized into CO_2 and H_2O. FU is a radiosensitizing and minimally neurotoxic drug, which is slowly released from M locally. Studies in rats with orthotopic tumoral implantation have shown FU-M and RT combination to be more effective than either treatment alone. Pilot clinical experience (Cancer 1999; 86: 325–30) motivated further development. Objectives of the ongoing multicentric randomized phase II trial (60 evaluable pts planned) are to assess efficacy (local progression free survival), safety and overall survival.

Methods: Pts with clinical and radiological suspicion of HGG with expected complete resection of tumor were randomized before surgery to local FU-M plus early RT (A) or early RT alone (B). Pts were treated after confirmation of the diagnosis by frozen biopsy during surgery. FU-M were injected around the walls of the resection cavity (A) and RT was begun within 7 days in both arms (59.4 Gy in 6.5 w). Pts in both arms received steroids during RT. Pts were assessed by MRI at baseline and every 3 months and by CT scan 24 hours and 6 w post surgery.

Results: 27 pts included from July 99 to December 00 in 8 centers are evaluable for safety, 13 A and 14 B. Glioblastoma/oligodendroglioma 10/3 in A and 13/1 in B, median age 53 years (35–69) in A and 54.5 (29–67) in B. Sex (m/f) 9/4 in A and 7/7 in B. Median dose FU-M received: 127 mg (106–132). Median volume FU-M received: 2.4 cm^3 (2–2.5). Median dose RT received: 59.4 Gy (59.4–60) A and 59.4 Gy (52.2–60) B. There was no definitive RT discontinuation due to toxicity. RT interruptions: 3 pts A (5 days, 7 days, 3 w) and 3 pts B (3 days, 7 days, 4 w). Alopecia 3 A, 5 B. No local healing complications were observed. Neurological adverse events occurred in: 9 pts A and 5 pts B, most of them reversible. 1 pt B died during treatment due to pulmonary embolism (after 52.2 Gy).

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Brain metastases treated by Leksell gamma knife – Results and prognostic factors for patients

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Purpose: To analyze treatment results, complications, prognostic factors and their significance in patients treated with Leksell gamma knife (LGK) for brain metastases (BM).

Methods: During 6 years 400 patients (pts) with brain metastases were treated by gamma knife with minimal follow up 10 months. There were 242 (61%) patients with solitary brain metastasis (SBM) and 158 (39%) with multiple (2–4) lesions (MBM). Median patients age was 58 years (ranged 33 to 76 years), the median treated volume was 7.5 ccm (ranged 0.4 to 35.5), the median of dose to margin was 21.5 (range 16 to 30 Gy) and median neurological functional class was 2.6 (range 1 to 3). The histological subtypes were as follows: 140 patients (35%) non-small lung cancer, 70 (17.5%) renal cell carcinoma, 52 (13%) breast carcinoma, 49 (12.3%) melanoma 39 (9.7%) colorectal carcinomas, other types in 13 (3.3%) and 37 (9.2%) with unknown primary location of malignant disease. Dependence of survival after irradiation of patients with BM on several chosen factors was analyzed by the acturial analyses. Three univariate analyses methods (Log rank, Breslow and Tarone-Ware tests) and one multivariate analysis method (Cox proportional hazards model) were employed. Variables with significant p-values ($p < 0.05$) at least in one of four actuarial analyses were considered possible risk factors for event.

Results: A complete and partial regression was observed in 294 (73.5%) patients, cessation of growth activity in 77 (19.25%) and local progression in 29 (7.25%). Out of 400 patients, 376 (86.5%) patients died and 54 (13.5%) patients are still alive with minimal follow up period of 10 months. Acute toxicity appeared in 24 (10%) patients (score 3, 4) and late in 11 (4.6%) patients. Median survival for patients with SBM was 9 months and for patients with MBM 6 months. The statistically significant prognostic factors in this series of patients with SBM were: age, status of primary tumor, pretreatment neurological symptoms (NFC), histology (better results for renal cell carcinoma and breast carcinoma), the interval longer then 25 months between diagnosis of primary tumor and SBM and the dose to the tumor periphery (20 Gy and higher). The statistically significant prognostic factors for patients with MBM were: sex, performance status (KF), status of primary tumor, other dissemination outside brain.

Conclusions: Treatment of BM by LGK provided sufficient local control in 93% of patients and the improvement of severity neurological symptoms in 69% pts with SBM and in 54%pts with MBM. The most favorable subgroup with a relatively long life expectancy (for SBM and MBM) was defined as a group with no evident active disease outside brain and without progression of primary tumor.

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Radiochemotherapy with paclitaxel in malignant glioma: results of a phase II study

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Purpose: In a phase II study, the feasability and outcome of a combined radiochemotherapy appraoch was evaluated in patiets with malignant glioma.

Methods: Radiotherapy was given with 60 Gy in conventional fractionation. Paclitaxel was applied on days 0-3, 14-17, 28-31 of radiotherapy. Paclitaxel was started with 20 mg/m*/d and escalated in 10 mg steps until inacceptable toxicity occurred. Subsequent patients were treated with the previous dose level.

Results: From 1996 to 2001, 46 patients were treated in the protocol. 21 patients had grade III and 25 patients grade IV gliomas. 19 patients had a macroscopically complete resection, 27 patients had an incomplete resection or biopsy only. The treatment was well tolerated with very few subjective side effects. Dose limiting toxicity was leucopenia with grade IV leucopenia occurring at 60 mg/m*/d. Mild allergic reactions occurred in 4 instances. 2 patients developed a thrombosis, one patient a lung embolism. 1 patients developed a fatal pneumonia with a normal white blood count. Median survival for grade III glioma was 17 months, for grade IV glioma 10 months.

Conclusion: Radiochemotherapy with paclitaxel was a well tolerated regimen. There was no convincing improvement in median survival.

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Fractionated stereotactic radiotherapy without whole-brain irradiation in the management of brain metastases

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Purpose: Fractionated stereotactic radiotherapy (FSRT) combines the accurate focal dose delivery of stereotactic radiosurgery with radiobiological advantages of fractionation. Retrospective series showed local control and survival benefits in patients with brain metastases even when only few fractions are employed. The aim of this study was to analyze tolerance and efficacy of FSRT as single modality treatment.

Materials and Methods: 29 patients (20 men and 9 women, mean age 64 years) with 31 metastases were treated with FSRT at our Institution between July 1998 and February 2001. Eligibility criteria were: histological evidence of extracranial primary cancers, 3 or fewer lesions on MRI examination, maximal diameter 3 cm, performance status less or equal to 2. Histologies were: non small-cell lung cancer (18), colon cancer (5), renal cell cancer (3), breast cancer (2) and melanoma (1). Median volume of metastases was 5.5 cm3 (range 0.8-18.8). Patients were immobilised in a Howmedica Leibinger Gmbh relocatable frame (Freiburg, Germany) using cast material made of self-hardening bandages. The planning target volume provided an additional margin of 2 mm in all directions to account for frame inaccuracies; the target volume was encompassed by and prescribed to the 80% isodose.Twenty-one patients were treated with 2 fractions of 12 Gy and 8 with 3 fractions of 8 Gy, delivered on a 6 MV linear accelerator in routine clinical use with 6 non-coplanar arcs.

Results: Median follow-up period was 11 months (range 2-27 months). Local tumor control (LC) was defined as no increase in the tumor's maximal

diameter on axial plane images. Crude LC rate was 81% (25/31). Six patients failed locally, 2-3 months after FSRT(median 9). Actuarial 1-year LC rate was 74%. Median survival time was 351 days, with actuarial overall survival rate at 12 and 18 months of 48% and 14% respectively. Thirty-eight percent of patients (11/29) developed new metastases outside the treatment volume after 2-24 months (median 11)and 4 received whole-brain irradiation as salvage treatment. In the majority of patients (10/29) the cause of death was systemic tumor progression. All treatments were well tolerated and no acute complications were seen, with the exception of transient headache and limited nausea.

Conclusion: This retrospective study suggests that FSRT with few fractions and a short treatment period is a tolerable and effective form of intensive local treatment of brain metastases.

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Three different fractionation schemes in glioblastoma multiforme: a single center experience with 430 patients

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Purpose: To evaluate the role of fractionation in the management of newly diagnosed glioblastoma multiforme (GBM).

Patients and methods: From January 1980 to June 2000, 430 consecutive patients with histologically confirmed GBM were treated at our institution. Median age was 59 years (19-81), Karnofsky Performance Status >/= 70 in 290 patients. 86 patients had a biopsy, 344 underwent resection. Primary radiotherapy was given in conventional fractionation - 5 x 2.0 Gy, total dose 60.0 Gy (n = 97). Postoperative radiotherapy was given hypofractionated - 5 x 3.5 Gy, total dose 42.0 Gy - (January 1980 - July 1983; n = 104) or hyperfractionated - 5 x 3 x 1.5 Gy, total dose 54.0 Gy (August 1983 - June 2000; n = 229). Survival probabilities were computed using the method of Kaplan-Meier.

Results: Median actuarial survival probabilities were as follows: All patients 8.6 months; biopsy 5.9 months vs. resection 9.0 months (p = 0.03); hypofractionation 8.2 months vs. hyperfractionation 9.05 months vs. conventional fractionation 8.5 months (p = 0.56). In a proportional hazards model, independent variables indicating a better prognosis were younger age (< 59 years vs. >/= 59 years: RR 0.84, 95%-CI 0.76-0.93), good performance status (KPS >/= 70 vs. KPS < 70: RR 0.83, 95%-CI 0.75-0.92), normal LDH level (LDH < 240 vs. LDH >/= 240: RR 0.77, 95%-CI 0.67-0.89) and total dose (RR 0.98/extra Gy, 95%-CI 0.97-0.99).

Conclusions: In this pure GBM series fractionation did not affect survival. Shortening treatment time by modifying fractionation does not compromise life expectancy. Besides the validation of known prognostic factors like age, KPS and total dose we found elevated LDH levels to have a strong negative influence on survival.

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Temozolamide in previously treated high-grade gliomas patients

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Objectives: To assess the efficacy and toxicity of temozolamide in high grade glioma patients previously treated.

Patients and Methods: Histologically proven high grade glioma patients (pts) with measurable disease were included. Temozolamide was administered at a dose of 150 mg/sqm five consecutive days every four weeks. If no grade III or IV toxicity appeared dose could be increases up to 200 mg/sqm. Response was assessed every 3 courses according to McDonald's criteria and therapy maintained until progression or unacceptable toxicity.

Results: 49 patients have been included, 33 (67%) males, median age 48 (22-69), ECOG performance status 0/1/2 in 5/23/21 pts. Median tumour area was 13.5 cm2 (1-63) Previous chemotherapy lines 0/1/2/3 in 4/36/5/3 pts, with a median of 4 chemotherapy courses per patient (0-8). All except 1 had received radiotherapy. Histology was glioblastoma 30, anaplastic astrocytoma 14, oligodendroglioma 2, and oligoastrocytoma 3.

Overall response rate was 22:4%, with complete response (CR) in 4 patients (8.2%, 2 patients with oligoastrocytoma and 2 with anaplastic astrocytoma), and partial response (PR) in 14.3% (7 pts). stable disease (SD) was achieved in 22.4%. Response according to histology was glioblastoma 10% PR (3), 33% SD (10), overall response 10% anaplastic astrocytoma 14.3% CR (2), 21.4% PR (3), 64.3% progressive disease (PD) (9), overall response 60% and oligodendroglioma or oligoastrocytoma 40% CR (2), 20% PR (1), 20% SD and 20% PD, overall response (60%). Actuarial median survival of all patients was 36 weeks (CI95% 27-44). glioblastoma 29 weeks (CI95% 12-45), anaplastic astrocytoma 46 weeks (CI95% 3.5-88), median survival is not reached for oligodendroglial tumours with a median follow up of 88 weeks (21-197).

No grade III or IV toxicity has been reported, and main toxicity were mild thrombocytopenia and moderate nausea easily controlled with 5-HT3 antagonists.

Conclusions: Temozolamide is active in high-grade glioma patients, even if previously chemotherapy treated. Anaplastic astrocytoma and oligodendroglial tumours appear to have better response and survival. This treatment is well tolerated with minimal toxicity

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Expression of PDGF-R, DCC, MDM2 and P16 in human gliomas

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Gliomas constitute a group of very aggressive and almost incurable primary brain tumors. Changes in the expression of the oncogenes PDGF-R and MDM2 and that of the suppressors DCC and p16, have been associated to tumor progression. In this work we studied, by immunohistochemistry, the expression of the aforementioned molecules in 41 gliomas of different histological grade of malignancy [low grade (LGA), anaplastic astrocytoma (AA) and glioblastoma multiform (GBM)]. A high expression of PDGF-R (>50% of positive cells) was found associated with the histological grade (40% of GBM vs. 15% LGA and AA tumors, NS). Only a few cases presented overexpression of the oncogene MDM2, with no differences among the three groups of gliomas, and the expression of DCC was lost in only 11% of the GBM. On the other hand, found a significant association between the loss of expression of the suppressor p16 and the histological grade (LGA: 0%, AA: 12% and GB 26%, p<0.05). This correlation was not modified when variables such as sex, age and Karnofsky status were introduced in the analysis. Among all the molecules analyzed, only p16 staining showed a significant correlation with overall survival. While 78% of the patients with the longest survival (>1 year) expressed p16, only 22% of those who were alive for less than one year after diagnosis did (p<0.05). In conclusion, the association between the loss of the cell cycle inhibitor p16 expresssion in human gliomas and the histological grade was independent of the other prognostic variables studied. Moreover, this lack of expression showed a correlation with a shorter overall survival.

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Temozolomide as a second line regimen after BCNU and procarbazine in recurrent glioblastoma multiforme: A phase II study

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Purpose: To investigate the efficacy of temozolomide (TMZ) in relation to response rate, toxicity, and progression free survival at six months (PFS-6), a phase II study was conducted in patients with recurrent glioblastoma multiforme (GBM) following surgery plus radiotherapy and a first-line regimen based on nitrosourea, procarbazine and vincristine.

Patients and Methods: 42 patients with GBM, of which 8 (19%) were previously low grade astrocytoma or oligodendroglioma, were administered TMZ at the dose of 150 mg/m^2/daily for five days every 4 weeks.

Results: The response was assessed in all 42 patients: we observed 2 complete responses (CR) (4.7%), 6 partial responses (PR) (14.3%), and 9 stable disease (SD) (21.4%), with CR + PR = 19% (95% Confidence Interval [CI] = 7–31%). The median TTP for all 42 patients was 11.7 weeks, (CI = 9–22%) while progression free survival at 6 months (PFS-6) and at 12 months (PFS-12) was 24% (CI = 14–42%) and 8% (CI = 2–27), respectively.