434 POSTER

Intraoperative radiotherapy (IORT) for high grade glioma of the brain – Treatment planning, dose verification, and results

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Introduction: Since May 1992, feasibility, perioperative morbidity, early and long term sequelae as well as survival times following intraoperative radiotherapy are being examined. From our experience, the determination of the correct beam angle and electron energy is difficult by clinical means alone. Therefore, we devised a method for exact pretreatment planning and post-treatment dose verification.

Materials and Methods: From May 1992 to October 1998, 50 patients with malignant gliomas of the brain were treated with IORT at our institution, 47 of which were evaluable at the time of analysis. 31 patients had a primary brain tumor, and 16 patients had recurrent tumors. The histological tumor types were distributed as fol-lows: glioma grade III (n = 22), and glioblastoma (n = 25).

Treatment was carried out as 20 or 25 Gy electron-beam IORT (14 or 18 MeV), followed by 60 Gy postoperative radiation in not previously irradiated patients. The craniotomy was measured in all three dimensions, and the optimal beam angle and the depth of the tumour bed were determined using a neuronavigation system. Afterwards, computerized quality control was carried out by reconstruction of the beam angle and the use of a standard treatment planning system (CadPlan).

Results: Perioperative complications were not increased (2 infections, 1 lethal haemorrhage and 1 malignant edema). 21/22 patients with increased brain pressure showed an improvement. Aphasia, hemiparesis, hemianopsia, psychosyndrom, gyrus angularis syndrom and convulsions were markedly reduced. 1-year survival for all patients was 54%, 2-year survival 14%. Median survival was 12.5 months (glioma III: 13.5 months, glioblastoma IV: 11 months). Median time to progression was 7 months. The only prognostic factor was tumour grade (p = 0.04). Extent of resection, tumour size, age, KPI, and treatment had no significant influence.

Conclusion: By using X-ray verification films, computerized quality control can be carried out after electron IORT. This way we could show that the neuronavigation method of pretreatment planning yields useful results. Side effects were not increased. Most tumour-associated symptoms could be alleviated. Compared to literature, median survival could be slightly improved.

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High-dose chemotherapy (HDCT) with G-CSF support before radiotherapy (RT) in malignant gliomas (MG): Phase II trial

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Purpose: To establish the activity of HDCT in large MG before RT.

Methods: 17 pts with MG less than 60 years and extensive measurable tumor were enrolled. Treatment consisted of carboplatin 200 mg/m^2 (or AUC × 8) plus cyclophosphamide 1000 mg/m^2 days 1–3 and G-CSF 5 mg/kg/day from day 2 (after CT) until hematologic recovery. Two cycles were given before standard RT if stabilization or response were observed after first cycle. Pts characteristics were: male/female 10/7; age 49 (23–59); KF 90% (70–100); GBM/AA, 14/3. Two pts were not assessable for response neither for survival (1 died before and another during the first cycle CT). All patients but one started RT and 11 completed treatment. Response was evaluated according to McDonald,s criteria.

Results: After first cycle of CT 7 pts progressed and 8 stabilized. Seven of them received a second cycle: 1 PR, 1 SD and 5 PD. MST was 7.4 m. Main toxicity was hematologic: in first cycle, neutropenia grade (G) 4 in 100%, thrombocytopenia G 4 in 73% and 3 in 27% and anemia G 3 in 7%. Median neutrophil and platelet recovery were reached on day 11 (8–17) and 13 (0–17), respectively and median number of days under 0.5 × 109/l was 6 (2–10). At second cycle neutropenia was G 4 in 100%, thrombocytopenia G 4 in 100% and anemia G 3 in 50%, and median number of days under 0.5 × 109/l was 7 (4–13). No toxic death was related with treatment.

Conclusions: This regimen showed limited activity in MG with large residual disease at expenses of significant toxicity.

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Treatment of glioblastoma multiforme (GBM) with teniposide (VM26) and lomustine (CCNU) followed by radiotherapy

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Purpose: GBM are frequent neoplasms of adult CNS and exhibit bad prognosis. Nitrosureas and podophylotoxines have some activity against GBM. Here we review our experience from 1996 to 1998.

Methods: Forty three patients (pts) with GBM were seen (23 males, 20 females). Projected treatment included chemotherapy (ChT) (VM26 120 mg/m^2 iv on day 1, and CCNU 120 mg/m^2 orally on day 2, every 28 days, if hematologic count recovery), three cycles in absence of progressive disease, and radiotherapy 60 Gy, after surgery or biopsy. PS <= 2. Thirteen pts did not received ChT (due to bad PS, rapid deterioration or family negative). Of them, four received radiotherapy up to 60 Gy.

Results: Thirty pts received ChT (17 males, 13 females). Mean age 58 y old (36–77). Disease completelly resected: 11, partially resected: 11 and just biopsed: 8. Eleven pts received one cycle of ChT; 9 pts, 2 cycles; 10 pts, 3 cycles. Only 8 pts (27%) completed our projected treatment. No pts without resection completed treatment. Toxicity: Two neutropenia grade 3, one thrombocytopenia grade 3 and three grade 4. One hyperbilirubinemia grade 4. Progressive disease to ChT 15/30 (50%). Survival: Pts treated with ChT ± RT: median survival 6 months (1–19). Alive 10/30 (33%) (mean 8.1 months, range 1–16) (2 biopsed, 8 resected) Dead 20/30 (67%) (mean 4.9 months, range 1–19) (6 biopsed, 14 resected). Pts not treated with ChT: median survival 3 months (1–12). Alive 3/13 (23%), all three resected, one also irradiated (mean 5.6 months, range 2–12).

Conclusions: Although randomized studies have shown benefit with combined therapy, GBM survival is short. Patients not able to end the treatment fared worse. Non resected tumors also fared worse. Although this treatment was well tolerated it seems to bear low activity. New drugs, new strategies and new techniques are needed.

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Radiotherapy in primary spinal cord astrocytoma

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Purpose: Primary spinal cord astrocytoma are rare tumors and the role of radiotherapy remains controversial. This study is a retrospective analysis of patients treated at our department with this diagnosis.

Material and Method: Between May 1975 and December 1997, 24 patients with histologically proven spinal cord astrocytomas were treated with external radiotherapy by either Co-60 or 6 MV photon beam. Median age was 19 years (2–41 years). 11 of them were male and 13 were female. 14 of astroctoma were grade I, 6 of them grade II and 4 grade III. 10 patients had subtotal excision and 14 had only biopsy. Patients were treated with 100–200 cGy daily fractions and given to a median 4950 cGy (3500–6000 cGy) external radiotherapy to primary tumor region with a safety margin at both ends. Chemotherapy was given to 8 patients.

Results: Median follow-up time was 38.6 months ranging between 2–149 months. 17 patients died of their disease. 2 patients have progression and 5 patients are followed with stable disease. Grade, sex, age, duration of symptoms, extent of the surgery were not found as statistically significant prognostic factors. 5 year overall survival was 44.6% and progression free survival was 40.3%.

Conclusion: Our results are in consistent with other retrospective series in the literature and radiotherapy seems to improve the survival as an adjuvant treatment modality especially in subtotally resected tumors.

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Stereotactic radiotherapy for solitary brain metastases as alternative to surgery

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Objectives: To assess efficacy, toxicity and cost-effectiveness of stereotactic radiotherapy (SRT) for solitary brain metastases.

Patients and Methods: Fifty-seven patients with solitary brain metastases (1 to 3 lesions) were treated with SRT with or without whole-brain

irradiation (WBRT). The SRT dose was prescribed to the 90% isodose and the target volume encompassed the enhancing tumour including a 2 mm safety margin.

Results: Median local progression free survival was 19 months and the median survival was 10 months. The majority of patients had a functional improvement as measured prospectively by the activities of daily living. Neurological deterioration was noted in 2 patients within 1 month of SRT. There was no survival benefit in patients receiving WBRT in combination with SRT.

Conclusions: The results of SRT in patients with solitary brain metastases appear equivalent to neurosurgical excision in terms of local control and survival. SRT is a useful palliative treatment – it is well tolerated, non-invasive and out-patient based and is particularly of value in situations where survival is determined by the systemic course of disease. The role of WBRT in combination with SRT remains to be defined.

439 PUBLICATION

Biological evaluation on short course conformal radiotherapy of malignant gliomas

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Purpose: The 3D conformal radiotherapy gives the possibility for different dose escalation forms. It has been tried to establish a biological dose distribution model to evaluate the advantages of 3D treatment planning and to examine different therapeutic dose regimens.

Methods: Biological equivalence equations based on LQ model were utilized to transform the physical dose calculation of Voxelplan-Virtuose 3D treatment planning system. In this way theoretical biological dose distributions could be generated. Conventional opposed fields and 3D conformal treatment plans of patients with suprasellar glioma were investigated, biological equivalent dose /BED/ formula and 2.0 for alfa/beta ratio of CNS normal tissues were assigned. Physical and biological dose distributions and histograms were compared to each other. The main staindpoint was the dose of the midline structures.

Results: The superiority of the 3D conformal teletherapy proved unambiguous evaluating the biological dose distribution model. The protection of the vital regions remained significantly better under a "hypofractionated" regimen of 2.5 Gy daily single doses and with adopted conformal shrinking fields technique, than with conventional 2 Gy fractionated opposed fields treatment.

Conclusion: This experiment suggests that a shorter-course conformal radiotherapy regimen with definitive dose may be the therapeutical choice for suprasellar-lobar high grade gliomas with poor prognosis. Evolution of different biological dose distribution models probably will help us choose better therapeutic regimens in different sites as well.

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Preliminary results of a phase II study: Irinotecan (CPT 11) in chemotherapy naive patients with glioblastoma

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CPT 11 shows activity in mice bearing human central nervous system tumor xenografts. The aim of the study is to evaluate the efficacy of CPT 11 in 2 groups of chemotherapy naive patients (pts) with glioblastoma (Gb): A, pts with unresectable tumor or uncomplete resection, 3 cycles (c) before radiotherapy, and B, pts with recurrent tumor. CPT 11 is administered every 3 weeks, at 350 mg/m^2. Brain CT scan or MRI evaluate the response every 3 c. As of today, 45 pts are included (A = 25, B = 20), 36 are evaluable for safety. Median age is 51 years [26–73], M/F = 20/16, and PS 0 (10 pts), 1 (16 pts) and 2 (10 pts). On 126 c (median 3 [1–9], A = 3 [1–7], B = 4[1–9]) worst grade (gr) toxicity, per c and per pt, in group A and B (A/B) is:

Toxicity	Neutropenia	FN	Diarrhea	As	Al	CS		
Grade	3	4		3	4	3	3	3
Per c (52/74)	3/6	3/1	1/1	2/3	–	3/4	–	2/6
Per pt (19/17)	1/1	2/1	1/1	2/2	–	3/3	-/3	1/2

FN: febrile neutropenia, As: asthenia, Al: alopecia, CS: cholinergic syndrom

On ten patients reviewed by the external radiological committee in each group: in group A, 1 PR not confirmed, 4 SD and 2 MR; in group B, 2 PR, 3 SD and 1 MR. Recruitment is still on going in group B. CPT 11 is active in pt with Gb with mild toxicity profile.

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Combined therapy of PNET/medulloblastoma in children and young adults – Single institution expirience

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Purpose: This study was aimed to 1) evaluate treatment results of combined therapy (surgery, postoperative craniospinal radiotherapy with or without chemotherapy) and to 2) assess factors affecting prognosis.

Patients and Methods: During the period 1986–1996 we treated 78 pts with combined modality therapy. Entry criteria were histolgically proven diagnosis, age under 22 yrs. and previously no history of malignant disease. M:F = 48:24, aged from 1 yr. up to 22 years (Me = 8.6 yrs.). Postoperatively all pts. had CT examination, myelography or mieloscan. Also liquor was tested on malignant cells. According all these data we used Chang classification and Jencinns classification for prognostic factors. Survival rates were calculated using Caplan-Meier method and differences between curves with log-rank test.

Results: During the follow-up period with Me = 3 yrs, 2-year and 5-years overall survival and DFS were 66% and 51% respectively, and 53% and 47%. We diagnosed 32 relapses. Among investigated prognostic factors significantly better prognosis was in pts with total or subtotal tumor removal, without involvement of brain stem or spinal cord and without postoperative meningitis. Younger children had significantly poorer survival when compared with young adults. Pts. who started radiotherapy within 2 months, after surgery had better survival but without statistical significance. Finding of malignant cells in CSF seemed not to be significant risk factor.

Conclusion: Based on these factors standard and high risk group could be defined. Combined chemotherapy should to be investigate particularly for high risk subgroup.

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Continuous hyperfractionated accelerated radiation therapy (chart) with fotemustine for malignant gliomas

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Purpose: To evaluate the toxicity and efficacy of CHART concomittant with intravenous fotemustine for patients (pts) with malignant gliomas.

Methods: In October 1996 we initiated a prospective study in patients with newly diagnosed anaplastic astrocytoma and glioblastoma. Seventeen pts; 12 males and 5 females, were eligible for the study. Eligibility criteria included: Histopathological confirmation, age between 16 and 70 years, a Karnofsky performance status of 70% or over, and normal liver function and normal blood counts. Radiochemotherapy was initiated 2–4 weeks after surgery. The portals were designed as opposed laterals covering the entire tumor volume + edema + 2 cm margin in the first phase (12 days) and tumor + edema in the second phase (4 days). Irradiation was continued all 7 days of the week, twice a day with at least 8 hours interval, with 1.6 Gy/fr. Hence a total of 5140 cGy was delivered in a total of 16 days. Fotemustine was given simultaneously with RT; 100 mg/m^2 IV on days 1st, 8th and 15th of treatment. Treatment evaluation follow up was performed with cranial CT/MRI 6 weeks after the completion of treatment and every 3 months in first year.

Results: All of the patients completed the treatment per protocol and only one greater than grade 2 toxicitiy (grade 3 trombocitopenia) was observed through all the treatments and the following 4 weeks. Six pts had died and 11 pts still alive and median survival is 14 months.

Conclusion: This treatment schedule is well tolerated without any serious side effects and median survival is highly comparable with the best reported results.