Materials & Methods: Between 1998 and 2002 53 patients with complex shaped meningiomas were treated at the dkfz. 34 female and 19 male patient were enrolled. In 34 patient radiotherapy was performed after surgery. In 19 cases radiotherapy was the primary therapy. The diagnosis was established in 18 patients according the imaging studies without a confirming by biopsy. In all cases dosage was performed to the median of the target volume (50% of the volume receive 100% of the dose). For inverse treatment planning the "KonRad® " or the "CORVUS® " system was used. Maximum dose of the brain stem and the spinal cord were constrained to 54 and 45 Gy, respectively. All patients were treated in a patient-specific Scotch-Cast mask. Each plan was verified before treatment by film dosimetry in a head and neck phantom. The "step and shoot" IMRT technique with a multileaf collimator integrated in a Primus (Siemens®) accelerator was used for treatment. Regular follow-up studies at our institution were performed.

Results: The median total dose was 57, 2 Gy (Range: 54 Gy 57,6 Gy). The mean tumor volume was 96,6 cc (Range: 74 - 16 cc). The volume which received less than 90% of dose ranged between 13 and 2% (mean: 6,7%). Treatment time ranged between 5 to 15 minutes. Additionally 5 minutes were needed for patient positioning. With a median follow-up of 25 months except for one patient with a marginal recurrence all patients are local controlled. The 4-year actuarial local control rate was 95%. As acute side effects only a RTOG/EORTC toxicity Grade I of the skin and slight dizziness were seen in 45% of the patients. Additionally a transient alopezia was found in all patient and 10 patients developed a conjunctivitis during therapy. A post-therapeutic cerebral edema in the follow-up MRI could be detected in 4 patients. In all cases the edema were clinically asymptomatic. Until now no late CNS toxicity was seen. The excising pretherapeutic neurological symptoms improved in 34% of the patients.

Conclusion: The use of a inverse planned and intensity modulated "step and shoot" approach is feasible in the clinical routine for complex shaped benign skull base meningiomas. No increased early or late toxicity could be evaluated compared to conventional treatment techniques. IMRT shows advantages in tumor dose and dose at the organs at risk. A longer follow-up is needed to control the success of the treatment.

309 POSTER

First line temozolomide (tmz) in recurrent or progressive oligodendroglioma. a phase II study (Gruppo Italiano Cooperativo Neuro-oncologia).

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Background: Oligodendroglial tumors respond to PCV chemotherapy in 60 to 75% of cases. However, toxicity is not negligible, and frequently imposes delays in re-cycling or early interruptions of treatment. TMZ has shown activity and optimal clinical tolerability as a second line regimen after PCV, but more data are required to establish whether it could replace PCV as standard first line chemotherapy.

Objectives: To evaluate in a phase II study Response Rate (RR), Time to Progression (TTP) and toxicity of TMZ in patients (pts) with oligodendroglioma.

Methods: Eligible were chemonaive pts with oligodendroglioma (OD) or oligo-astrocytoma (OA), progressive or recurrent after radiotherapy, with at least one measurable contrast enhancing lesion (* 1cm of diameter). Pathological diagnosis was centrally reviewed. Pts were treated with 150-200 mg/m^2 TMZ on days 1 to 5, every 28 days. Macdonald's criteria were applied when evaluating tumor response.

Results: Thirty-two pts were included in the study (median age 49 yrs, range 27-63 yrs; KPS 80, range 60-90; 21 OD). To date, twenty-eight pts are evaluable: 4 had Complete Response (CR) (14%), 9 had partial response (PR) (32%), while 9 pts (32%) remained stable for at least two months. Median TTP was 12 months, Progression Free Survival (PFS) at 6 and 12 months was 67% (CI 95%= 52-87%) and 45% (CI 95%= 29-70%), respectively. In responsive pts, PFS-6 and PFS-12 were 83% (CI 95%=64-100%) and 58% (CI 95%= 36-94%), respectively,. A total of 225 cycles of TMZ were administered (on average 7 per pt). Toxicity was mainly hematological, with grade 3-4 neutropenia and thrombocytopenia in 4 (12.5%) and 3 (9.3%) pts, respectively. No extra-hematological grade 3-4 side effects were reported, except for nausea and vomiting G3 in 3 (9.3%) pts. In 6 pts (18.7%) TMZ dosage was reduced to 150 mg/m^2 due to reversible hematological toxicity. Of the progressing 18 pts, 14 have started second line chemotherapy with PCV and 10 are evaluable for response: 1 CR and 2 PR (RR: 33%) plus 4 SD were obtained, with a PFS-6 and PFS-12 of 40 and 30%, respectively.

Conclusions: The activity of temozolomide as a first line chemotherapy appears to be superimposable to that of PCV, with better clinical tolerability and, seemingly, no cross-resistance. Randomized trials are warranted.

310 POSTER

Stereotactic radiosurgery for cerebral melanoma metastases

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Background: To identify prognostic factors for patients with melanoma brain metastases treated with stereotactic radiosurgery (SRS).

Material and Methods: One hundred three patients with 153 intracranial melanoma metastases underwent Linac-based SRS alone or with whole brain irradiation (WBI; n=51) between Nov 1991 and Oct 2001. Median age was 51 years (18-93 years). KPS was > 70 in 78.6% (n=81). Single brain metastasis presentation comprised 58% (n=60). Treatment sequence was SRS alone (n = 78), SRS+WBI (n = 19), WBI+ salvage SRS (n = 29), and SRS + salvage WBI (n = 27). Median tumor volume was 1.9 cm^3 (0.06 76 cm^3). Median SRS minimum peripheral dose was 18 Gy (range, 10-24 Gy). Median patient follow-up was 6 months for all patients and 16 months (range, 2-46 months) for patients alive at time of analysis. Median imaging follow up was 3.2 months for all patients and 10 months (range, 0-37 months) for patients alive. Kaplan-Meier method, log rank test, and Classification and Regression Tree models (CART) were used. Patients were classified according to the Stereotactic Score Index (SIR).

Results: *SRS alone* vs. combined treatment (SRS + WBI, SRS + salvage WBI, WBI + salvage SRS) achieved 63% LC in 1 year vs. 27% respectively (p= 0.009). "SRS first" had higher 1-year LC than "WBI first" (51% vs. 26%; $p < 0.05$). Tumors ≤ 2 cm^3 had better 1-year LC than > 2cm^3 (52% vs. 38% respectively; $p < 0.05$). This is especially true for *SRS alone* treated lesions where smaller tumor volume (≤ 2 cm^3 vs. > 2 cm^3) demonstrated superior 1-year LC (84% vs. 43% respectively; $p < 0.05$). Actuarial median survival for all patients was 7 months and one year OS was 27.8% from time of SRS. Patients with absence of systemic disease demonstrated significantly better survival than those with active systemic disease (8 vs. 5 months respectively; $p < 0.05$). SIR ≥ 6 at presentation predicted significantly longer survival with 29% of patients alive at 1 year compared to 5% for those patients with SIR < 6 ($p < 0.05$).

Conclusions: *SRS alone* is an effective treatment modality for cerebral melanoma metastases achieving 84% 1-year LC for properly selected patients who have small melanoma brain metastasis (≤ 2 cm^3) and should be considered in patients with SIR ≥ 6. Selection bias towards treating patients with more biologically aggressive disease with combined SRS and WBI may have played a role in the inferior LC observed for the combined treatment group (SRS + WBI).

311 POSTER

Temozolomide (TMZ) combined with radiotherapy (RT) versus radiotherapy (RT) alone in newly diagnosed glioblastoma multiforme (GBM): A randomized phase III study

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Background: Despite aggressive treatment glioblastoma multiforme is associated with high rate of recurrence and poor survival. Temozolomide, a new oral alkylating agent, has shown effectiveness in the treatment of malignant gliomas. A multicentric randomized phase III study was conducted

to compare the efficacy and safety of TMZ administered concomitantly and sequentially to RT versus RT alone in patients with newly diagnosed GBM.

Material and methods: Between January 2000 and December 2002, 110 patients with pathologically confirmed newly diagnosed GBM were randomized to receive either TMZ 75mg/m^2/daily orally, concomitantly with RT (60 Gy in 30 fractions, Group A: n=57), followed by 6 cycles of TMZ (150mg/m^2, days 1-5 and 15-19 every 28 days) or RT alone (60 Gy in 30 fractions, Group B: n=53). The patients characteristics are comparable for both treatment groups.

Results: Median time to progression (TTP) was significantly higher in Group A (13.3 months) compared to Group B (7.6 months) (p=0.015). Progression free survival (PFS) at 1 year: Group A: 58%, Group B: 17%. Overall survival (OS) was also significantly better in the combined modality group: 1year OS: 55% vs 16%; 2years OS: 15% vs 0% (p=0.0001). Toxicity was mainly haematological; in the TMZ+RT Group Grade 3 leukopenia in 2 pts and Grade 3 thrombocytopenia in 3 pts was observed. One patient experienced Grade 4 neutropenia, thrombocytopenia and sepsis leading to death. 2 patients discontinued therapy because of myelosuppression. The other side effects were mild: rash (3 pts), constipation (1 pt), arthralgies (1 pt). In the RT alone Group was observed Grade 3 thrombocytopenia in 1 patient.

Conclusions: TMZ combined with RT (concomitantly and sequentially) appears to be more effective than RT alone in patients with newly diagnosed GBM. The combined modality treatment was well tolerated in our patients.

312 POSTER

Combined treatment with Radiotherapy and Temozolomide in recursive partitioning analysis (RPA) class V-VI glioblastoma patients. Preliminary results of a multicenter prospective study.

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Background: To determine feasibility, toxicity, and efficacy of a new combined curative treatment with Temozolomide (TMZ) and Radiotherapy (RT) in patients with poor prognosis, pathologically proved, glioblastoma multiforme.

Patients and Methods: Patients with histological diagnosis of glioblastoma multiforme, submitted to biopsy only or partial resection, age > 49 years, Karnofsky Performance Status > 50, (RPA class V-VI) were prospectively treated with curative RT (60Gy in 30 fractions of 2Gy for 5 days a week) and full dose of TMZ (200mg/m^2 for 5 days) administered during RT (the first day of the forth week of irradiation, at the time of the 16th dose of RT), followed by TMZ (200mg/m^2 for 5 days) every 28 days for six courses. Toxicity was recorded using the Common toxicity criteria version 2.0 and the overall survival was calculated from the time of surgical procedure (biopsy or resection with macroscopic residual disease).

Results: From March 2002 to January 2003 were enrolled 20 patients (3 female and 17 male) with a median age of 61.5 years (range 51-72). A total of 82 courses of TMZ were administered (median 4, range 1-7) and all patients completed the planned RT at 60Gy. The most common toxicity was hair loss in the treatment area (20/20 patients); a grade 2 neutropenia was observed in 3/20, grade 2 thrombocytopenia in 2/20, grade 2 vomiting in 1/17, and grade 1-2 nausea in 4/20. At the last follow-up (15/03/2002), 14 patients are alive with survival ranging from 2 to 12.5 months. Six patients died respectively at 2, 2, 2.5, 5, 6, and 7 months.

Conclusions: these very preliminary data seem to demonstrate that a combined curative treatment with RT and TMZ is feasible with low-moderate toxicity in poor prognosis glioblastoma patients. The study is ongoing.

313 POSTER

Incidence and severity of anaemia in patients with primary lymphoma of the central nervous system treated with high-dose methotrexate

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Background: Only little data is available on anaemia in patients (pts) with non-Hodgkin's lymphoma (NHL). In pts with extracerebral NHL treated with polychemotherapy, anaemia grade 1 (haemoglobin [Hb] 9.5-10.9 g/dL) or 2 (Hb 8.0-9.4 g/dL) according to the World Health Organization (WHO) classification was observed in about 28% and WHO grade 3 (Hb 6.5-7.9 g/dL) in about 10% of pts. We evaluated the incidence and severity of anaemia in pts with primary central nervous system lymphoma (PCNSL) before and during treatment.

Material and methods: 121 pts (62 male, 59 female, median age 62 years [range 22-83 years]) with newly diagnosed PCNSL received a total of 437 cycles high-dose methotrexate (HD MTX, 4 g/m^2 body surface area per cycle, repeated every 2 weeks up to a maximum of 6 cycles).

Results: Only 4 of 45 evaluable pts (8.9%) had mild (WHO grade 1) anaemia before chemotherapy. During HD MTX, anaemia (Hb d 10.9 g/dL) was seen in 61 pts (50.4%). Anaemia WHO grade 1 and 2 was observed in 24 pts (19.8%) each. The highest grade seen when considering all HD MTX-treated pts was anaemia WHO grade 3. It was observed in 13 pts (10.7%). Regarding the HD MTX cycles received, anaemia WHO grade 1 and 2 occurred in 137 cycles (31.4%), and anaemia WHO grade 3 was observed in 14 (3.2%) cycles. 286 cycles (65.4%) of HD MTX were not associated with anaemia.

Conclusions: We conclude that in contrast to pts with extracerebral NHL, PCNSL pts are rarely anaemic at the time of diagnosis, and significant anaemia often only develops during HD MTX therapy. The incidence of anaemia WHO grade 1 and 2 in PCNSL pts treated with HD MTX seems to be higher, and severe anaemia (WHO grade 3) at least equally frequent compared to pts with extracerebral NHL treated with polychemotherapy. Anaemia may mimic neurological symptoms related to PCNSL and may therefore even influence therapeutic intervention and outcome. Moreover, a positive correlation between Hb levels and quality of life in pts with haematological malignancies has been reported. Additionally, anaemia was found to be an independent prognostic factor in NHL patients. Therefore, like pts with extracerebral NHL, PCNSL pts treated with HD MTX should be carefully watched for signs and symptoms of anaemia, and, if indicated, be given blood transfusions and/or erythropoietin according to international guidelines. First data of our pts treated with erythropoietin shows an adequate Hb response. Updated results will be presented.

314 POSTER

Partial brain irradiation (PBI) or whole brain irradiation (WBI), the justified solution

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Background: Postoperative conventional radiotherapy (RT) improved survival for glioblastoma multiforme (GBM) and astrocytoma anaplasticum (AA), but local recurrences were stile a reason of pore outcome. The main purpose of this study was to compare response in patients (pts) with malignant astrocytoma treated by PBI and WBI. Also, an evaluation was made to the acute radiation toxicity.

Materials and methods: Between 1998-2000, 70 pts with supratentorial malignanat astrocytomas treated at the Institute of Radiotherapy and Oncology in Skopje were enrolled in study. Pts were randomized in two groups according the used treatment volume. The treatment volume in the group with PBI covered the contrast-enhancing lesion with 2 sm added margins. They also underwent additional CT scan in the treatment position. In bout groups we applied postoperative conventional RT with 2 Gy daily fractions, to a total dose of 60 Gy. 73% of pts belonged to the group <= 60 years of age, with median age of 40.08 and the rest 27% have a median age of 66.89. Histology consisted of GBM in 77% pts (ratio 3.4:1). Amount of the initial Karnofsky performance status >=80% was 67%.

Results: Objective response (according to WHO criteria) was achieved at 33 (97%) pts with WBI and at 31 (88%) pts with PBI. The overall survival was 12.84 mounts (m), 13.51 m at those with WBI and 12.17 m with PBI. One and two year survival rates at all pts were 31%, 16% respectively. The median disease free survival was 11.8 m, regarding the pts with WBI; it was 11.8 m compared to 10.54 m at the pts with PBI. Median survival at pts with GBM was 8.11 m and at the AA 28.81 m. Favorable prognostic factors on survival according Long-Rank test, were: KPS, histology, age, preoperative duration of symptoms, cortico-therapy during irradiation, the time from the surgery to RT, operation and tumor size. Acute radiation toxicity to brain, ear and skin, evaluated according to RTOG/EORTC score system were more expressed at the pts with WBI.

Conclusions: Although the limitation of the treatment volume does not prolong the duration of survival, its application is justified. Due to rescuing the normal brain tissue PBI leads to a possibility for apply high radiation dozes that could improve the local tumor control.