T4 tumours and T1-4N2 tumours. Patients received 12 weeks of neoadjuvant capecitabine (2000mg/m2/day po for 14 days every 3 weeks) and oxaliplatin (130mg/m2 iv every 3 weeks). Starting on week 13, capecitabine was continued at 1650mg/m2/day continuously with concomitant radiotherapy 45Gy in 25 fractions followed by 5.4-9 Gy boost to primary tumour. TME was planned 6 weeks after chemoradiation. Post-operatively, patients received 12 weeks of capecitabine at 2500mg/m2/day for 14 days every 3 weeks. MRI was repeated after chemotherapy and CRT.

Results: Between November 01 and November 02, 22 patients were recruited. Median age was 62 (range=38-80). 21 patients had tumour threatening CRM. 19 patients were evaluable for radiological response and 18 patients have proceeded to TME. Following neoadjuvant capecitabine/oxaliplatin, all patients had objective responses (1 CR, 18 PRs). In addition, 80% of patients had symptomatic responses in a median of 22 days (i.e. after one cycle of chemotherapy) including reduced rectal bleeding (100%), improvement in diarrhoea/constipation (79%), diminished pelvic pain/tenesmus (64%) and weight gain/stabilisation (100%). Following CRT, tumour response was sustained in all patients. One patient was still inoperable, but all other patients had R0 resection with tumour regression away from the CRM. Pathological CR was found in 5 patients (28%) and in an additional 8 patients (44%), only microscopic tumour foci were found on surgical specimens. One patient died from myocardial infarction and 1 from pulmonary embolism. No grade 4 toxicity occurred during chemotherapy or CRT.

Conclusion: Capecitabine and oxaliplatin prior to synchronous CRT and TME produces almost universal tumour regression, rapid symptomatic response and may facilitate the achievement of R0 resection.

306 POSTER

Optimox study: Folfox7 compared to Folfox4 in metastatic colorectal cancer (CRC). Results of a randomized study.

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Background: FOLFOX4 has shown superiority over LV5FU2 in first-line therapy of metastatic CRC (de Gramont; J Clin Oncol 18:2938-2947, 2000). The limiting toxicity of the FOLFOX4 regimen is a cumulative sensory neurotoxicity which imposes to stop therapy in patients still responding. In the OPTIMOX study, a limited number of cycles (6 cycles of FOLFOX7) was administered to decrease the neurotoxicity and to later allow FOLFOX reintroduction.

Materials and methods: Patients (pts) were randomised between (arm A) FOLFOX4: oxaliplatin 85 mg/m^2 day (d)1, and folinic acid, 200 mg/m^2 d1 and d2, 5FU bolus 400 mg/m^2, followed by 5FU 22h continuous infusion 600 mg/m^2 d1 and d2 every two weeks and (arm B) FOLFOX7: oxaliplatin 130 mg/m^2 day (d)1, and folinic acid, 400 mg/m^2 d1 only, followed by 5FU 46h continuous infusion 2400 mg/m^2 every two weeks for 6 cycles followed by sLV5FU2: folinic acid, 400 mg/m^2 d1, 5FU bolus 400 mg/m^2, followed by 5FU 46h continuous infusion 2400-3000 mg/m^2 every two weeks for 12 cycles. FOLFOX7 was then reintroduced for 6 cycles or earlier in case of progression on sLV5FU2 in patients having a response or stable disease at the first FOLFOX administration. 623 pts have been enrolled. Arm A, 312 pts (%): M/F=59/41, PS 0/1/2=52/39/8, median age=63[29-80]; Arm B, 313 pts (%): M/F=61/39, PS 0/1/2=53/38/9, median age=64[32-80].

Results: Grade 3-4 toxicity (% of pts) was in arm A (FOLFOX4)/arm B (FOLFOX7): neutrophils 26/20, platelets 3/11, nausea 4/7, mucositis 2/4, diarrhea 9/9, hand-foot 0/2, alopecia 0/4, neurotoxicity 13/13, fatigue 1/1. Response rate (409 evaluated pts) was 58% in arm A (FOLFOX4) and 64% in arm B (FOLFOX7). Progression at first evaluation was 9% in arm A and 7% in arm B. The primary endpoint is the time to disease control (TDC) which is the progression-free survival of FOLFOX4 or FOLFOX7-sLV5FU2 plus the progression-free survival (PFS) of FOLFOX reintroduction in case of second response or stabilization. Median TDC was 10.3 months in arm A and 12.3 in arm B.

Conclusions: FOLFOX7 followed by sLV5FU2 has similar toxicity and efficacy than FOLFOX4 and is a more convenient regimen. Updated data for the whole population should be available for the meeting concerning Response Rate, PFS, TDC, % of surgery of metastasis and FOLFOX7 reintroduction.

Central nervous system tumours

307 POSTER

Upregulation of HC gp-39 gene in astrocytic gliomas

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Background: Astrocytic gliomas are highly malignant, lethal and the most common glial tumors of the central nervous system. Present knowledge recognizes only a fraction of the biological mechanisms presumably to initiate and promote astrocytic glioma formation. Changes in gene expression are important determinants of normal cellular physiology and, if disturbed, directly contribute to abnormal cellular physiology, including cancer. In this context, the identification, cloning and characterization of differentially expressed genes can be expected to provide relevant and important insights into the molecular determinants of tumor initiation and progression.

Materials and Methods: Serial Analysis of Gene Expression (SAGE) has been used for the comparison of gene expression profiles between normal brain and glioblastoma multiforme (GBM). Expression levels of about 47000 genes represented by approximately 284000 of 10 bp "tags" in normal brain and GBM SAGE libraries were compared by accessing SAGEmap database of NCBI. Northern blot hybridization was used for verification of SAGE results.

Results: SAGE showed that human cartilage glycoprotein-39 gene (HC gp-39) had the greatest change in tumour cells. The abundance of HC gp-39 tags was 82 fold higher in GBM library. Northern analysis of brain tumour and normal brain tissue panels confirmed the results of SAGE and showed very high expression levels of HC gp-39 gene found exclusively in astrocytomas of higher grades, anaplastic astrocytoma and GBM. Overexpression of this gene was detected in 14 of 16 GBMs and 6 of 16 anaplastic astrocytomas analyzed. Two GBM samples revealed lower content of HC gp-39 mRNA as compared to other 14 GBM samples but still higher than in normal brain. Low level of HC gp-39 mRNA was detected in samples of normal brain adjacent to anaplastic astrocytomas and GBMs, this mRNA was not detectable at all in WHO grade II astrocytomas and in adjacent normal brain samples. It was not also detected in other brain tumour types. In addition to 1.7 kb mRNA present in all positive cases and found in human chondrocytes and synoviocytes, Northern blot hybridization revealed the larger-sized transcript of HC gp-39. This larger-sized transcript was associated mostly with astrocytomas of higher grades and could arise from alternative processing that may alter the translation product or regulate mRNA stability.

Conclusion: The overexpression of HC gp-39 gene and the appearance of larger-sized transcript may be an important feature of higher grades astrocytomas and can be used as an additional factor for distinguishing between astrocytomas and anaplastic astrocytoma or between GBM and other types of human brain tumours in the cases of ambiguous histological diagnosis.

308 POSTER

Inverse planned stereotactic intensity modulated radiation therapy (IMRT) in the treatment of complex shaped benign meningiomas of the skull base: Acute-, late toxicity and preliminary results.

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Purpose/Objective: The efficiency of radiotherapy for the primary treatment of benign meningiomas and as adjuvant treatment for subtotally resected or recurrent meningiomas has been demonstrated by large modern series. But by using conventional radiotherapy and even stereotactic radiotherapy it is difficult to achieve doses of more than 54 Gy which allows excellent long time control rates, without exceeding the tolerance doses of the surrounding critical normal structures. The aim of this clinical phase I study is to establish inverse treatment planning and IMRT for complex shaped meningiomas of the skull base in the daily clinical routine. Further objectives of this study were to assess the safety, the efficiency and the side effects of inverse planned stereotactic IMRT in the treatment of benign meningiomas of the base of skull.

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).

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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