randomised into four groups with 7 animals in each group. One group was untreated. A second group received ZD6474 30 mg/kg daily as an oral gavage for 14 days, starting day 6 after tumour implantation. A third group received temozolomide 100 mg/kg for three days, day 9, 12 and 15 after tumour implantation. The fourth group was treated with both ZD6474 30 mg/kg and temozolomide as mentioned above. Animals were sacrificed on day 20 and tumour size was measured.
Results: ZD6474 30 mg/kg in combination with temozolomide significantly decreased median tumour area from 13 mm^2 (range 8–14) in untreated controls to 3 mm^2 (range 0–8) ($p = 0.003$) in the combination group.
Conclusions: The orally available VEGFR2/EGFR tyrosine kinase inhibitor ZD6474, reduced tumour growth in an intracerebral rat glioma model. Combination with temozolomide results in more than additive effects. These results reported justify further investigations on the combined effects of ZD6474 and temozolomide in malignant glioma.

488 ORAL

Different angiogenic phenotypes in primary and secondary glioblastomas

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Primary and secondary glioblastomas (pGBM, sGBM) are supposed to evolve through different genetic pathways including EGF receptor and PDGF and its receptor and thus genes that are involved in tumor-induced angiogenesis. However, whether other angiogenic cytokines are also differentially expressed in these glioblastoma subtypes is not known so far but this knowledge might be important to optimize an antiangiogenic therapy. Therefore we studied the expression of several angiogenic cytokines including VEGF, HGF, bFGF, PDGF-AB, PDGF-BB, G-CSF and GM-CSF in pGBMs and sGBMs as well as in gliomas WHO III the precursor lesions of sGBMs.
In tumor tissues expression of all cytokines was observed albeit with marked differences concerning intensity and distribution pattern. Quantification of the cytokines in the supernatant of 30 tissue-corresponding glioma cultures revealed a predominant expression of VEGF in pGBMs and significantly higher expression levels of PDGF-AB in sGBMs. HGF and bFGF were determined in nearly all tumor cultures but with no GBM subtype or malignancy-related differences. Interestingly, GM-CSF and especially G-CSF were produced less frequently by tumor cells. However, GM-CSF secretion occurred together with an increased number of simultaneously secreted cytokines and correlated with a worse patient prognosis and may thus represent a more aggressive angiogenic phenotype. Finally, we confirmed an independent contribution of each tumor-derived cytokine analyzed to tumor-induced vascularization.
Our data indicate that an optimal antiangiogenic therapy may require targeting of multiple angiogenic pathways that seem to differ markedly in pGBMs and sGBMs.

Poster presentations (Mon, 31 Oct)
Central nervous system

489 POSTER

Fractionated stereotactic radiotherapy for vestibular schwannoma: single institutional experience at the Princess Margaret Hospital, Canada

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Objectives: To assess the effectiveness of stereotactic fractionated radiation therapy (SFRT) in achieving local tumour control and hearing preservation in vetsibular schwannoma (VS). To document symptom presentation, and acute and long term treatment-related toxicities.
Methods: Retrospective review of 66 consecutive patients treated from October 1996 to February 2005. Five patients were excluded, two NF-2 associated, two discontinued at 28 and 30 Gy, and one received single fraction radiosurgery (15.5 Gy to the 90% isodose.)
Results: 61 patients were analyzed, 32 males and 29 females, age range 18–80 years (median 58). Median primary tumor volume was 4.9 cc (0.3–49). At presentation, imaging progression occurred in 28 (45.9%) and symptom progression in 8 (13.1%). Presenting symptoms included tinnitus (52.5%), gait instability (49.2%), CNV numbness (32.8%), facial nerve weakness (13.1%), and trigeminal neuralgia (4.9%). 95.1% had some degree of hearing loss and 24/61 (39.3%) had useful hearing at baseline. Formal baseline audiology was documented in 76%. Sixty patients received 50 Gy in 25 fractions, one received 52 Gy. Acute toxicities included grade I fatigue (43%), nausea (41%), grade I headache (20%), and occasional vomiting (5%). Grade II toxicities occurred in 5%. Most pre-existing cranial nerve V and VII dysfunction remained stable. No new cranial nerve palsies developed. One case of RT-induced Glioblastoma multiforme occurred 5.8 years post therapy. At a median follow up of 23.4 months, actuarial progression free survival was 98%. One patient experienced tumour progression at 2.3 months post-RT and underwent resection. Hearing function remained stable in 77% for all patients, in 82% and 67% with baseline useful and non-useful hearing. 6% noted improvement if initial hearing was useful.
Conclusion: FSRT for VS prescribed to 50 Gy in 25 fractions over five weeks is well tolerated. An excellent crude local control rate of 98.3% is achieved which is comparable to the published literature.

490 POSTER

Phase II/III randomized study of edotecarin vs. temozolomide or nitrosourea in patients with recurrent glioblastoma (GBM): Phase II results

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Background: Recurrent GBM has a very poor prognosis. Despite the use of systemic chemotherapy, the median survival time after tumor recurrence is less than 6 months. Edotecarin (Edo), a novel inhibitor of topoisomerase I that showed activity in brain tumor models and a good safety profile in Phase I studies, was tested in this population in a large multinational Phase II/ III trial.
Methods: Eligible patients (pts) had histologically proven GBM at first relapse after initial surgical tumor debulking or biopsy, external beam radiotherapy and temozolomide (TMZ) – or nitrosurea-based adjuvant chemotherapy. Other eligibility criteria included Karnofsky performance status (KPS) $\geqslant 70$, age $\geqslant 18$, and measurable disease confirmed by Gd-MRI. Pts were randomized 2:1 to Edo (13 mg/m^2/q3w, IV) or control (TMZ, BCNU or CCNU at standard doses). Target sample size was 525 pts. Randomization was stratified by age, KPS, and prior chemotherapy. The primary objective was to demonstrate an overall survival (OS) advantage for Edo over the control arm. The trial was powered to detect a 33.3% improvement (from 6 to 8 month median). The trial design included an interim Phase II analysis, which was based on the first 50 response-evaluable (measurable disease and treated) pts randomized to Edo. The criterion for trial continuation was 3 confirmed objective responses by MRI using the MacDonald criteria as determined by independent central radiology review.
Results: From July 2003 to August 2004, 50 centers randomized a total of 118 pts, 79 to Edo and 39 to control. Pt characteristics were well balanced by treatment arm; 70% had prior TMZ, 43% had KPS $\geqslant 90$, 40% had age $\leqslant 50$. Although numerous eligibility issues were retrospectively identified, no confirmed responses were observed in the first 50 response-evaluable Edo patients or in any of the 118 pts. Estimated median OS is 6.5 for the 79 Edo pts and 6.6 months for the 39 controls. Toxicity profile was acceptable. The study was closed to enrollment due to the poor response rate.
Conclusions: This was the first randomized, multinational trial in pts with recurrent GBM after surgery and chemoradiation. Results demonstrated insufficient activity in the Edo arm to continue the trial.

491 POSTER

Radiotherapy for pituitary adenomas: a twenty-year cohort

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Background: Radiotherapy (RT) has proven effective in the management of pituitary adenomas. However, control rates decline and toxicity increases with prolonged follow-up. The aim of this retrospective study was to determine the long-term control rate and toxicity in a large series of patients from a single centre.

Material and methods: Using our institutional database all patients receiving radiotherapy for a pituitary adenoma between 1974 and 2003 were identified and data on presentation, treatment, local control and toxicity recorded.
Results: 389 patients were identified. 199 (51.2%) were male, median age 54 (range 14–82), medium follow-up 8.9 years (range 0.1–30.4). Detailed information on presentation was available on 373 patients., Of these 188 (50.1%) were non-secreting and 101 secreted growth hormone, 53 prolactin, 22 ACTH and 9 other. 260 showed extra-sellar extension. 277 underwent surgery followed by adjuvant radiotherapy, the remainder radiotherapy alone. Before 1988, RT was delivered by lateral opposed fields to a dose of 35–37.5 Gy in 15 fractions (174 patients), after 1988 it was delivered by a 3-field approach to a dose of 45 Gy in 25 fractions (215 patients). Only 12 tumours progressed, giving 10 and 20-year actuarial control rates of 96.2% (2 patients relapsed after > 20 years). 10 of the 12 were macro-adenoma with extra-sellar extension. Hypopituitarism was the most common toxicity seen. 267 (68.6%) of patients had deficiency of one or more pituitary hormone, 126 prior to radiotherapy and 141 after. The actuarial deficiency attributable to RT at 10 years was 18.5% for ACTH, 22.4% TSH and 17.4% testosterone (men only). The actuarial rate of CVA at 10 years was 10.4%. Three patients developed visual deterioration potentially attributable to radiation-induced optic neuropathy. Three intra-cranial tumours occurred subsequent to irradiation: one < 1 year, second at 6.2 and third at 29.2 years following RT.
Conclusion: Radiotherapy, delivered alone or adjuvant to surgery, achieves a high rate of durable local control. The rate of hypopituitarism is high and attributable to disease, surgery and RT. The risks of radiation-induced visual loss and secondary intra-cranial tumours are low and ought not to dissuade from irradiation when clinically indicated.

492 POSTER

Development of fractionated stereotactic radiotherapy for meningioma

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From the initiation of the stereotactic radiotherapy program at our instituition in 1997, radiation planning techniques have evolved. This has allowed for improvement in dose conformity and increased sparing of critical structures in the treatment of frequently complex shaped meningiomas. The stereotactic program utilizes a Radionics™ treatment system with three planning programs; XKnife™, XPlan™, and S-IMRT™, The XKnife™ and S-IMRT™ systems utilize multiple non-coplanar fields with beams shaped by mini-multileaf collimators (MMLC). Since 2001, 50% of cases have been treated with stereotactic intensity modulated radiotherapy (S-IMRT).
Patients treated within the fractionated stereotactic program from February 1997 until December 2004 were reviewed. Meningiomas were predominantly benign or diagnosed on imaging alone (74.7%) and were mostly skull based (61%). Median size of primary lesion was 26cc (range 0.4–243.2 cc) and median dose prescribed was 50 Gy in 25 fractions over 35 days. In patients with a minimum of 6 months follow up and no prior irradiation (n = 75), median follow up was 22 months. Two-year progression free survival was 91.5% (95%CI: 83.6–100%). Acute toxicity was mild (Grade 1 or 2) and involved nausea, headache, alopecia and fatigue. Late toxicity was seen in less than 5% of cases but longer follow-up is required. Analysis of predictors for progression-free survival using hazard ratios (HR) were; benign/ radiologically diagnosed tumours (HR = 0.31), primary tumour volume >26 cc (HR = 4.88, p = 0.054), number of prior surgical interventions (HR = 2.86 for 2 or more operations) and location of meningioma (HR = 3.22 for parafalcine/convexity meningiomas). However, only primary tumour volume approached statistical significance.
Fractionated stereotactic radiotherapy can be delivered with minimal acute and late toxicity and excellent local control. Further long-term evaluation is required

493 POSTER

A clinical study of intensity modulated radiotherapy (IMRT) using the simultaneous integrated boost method for malignant gliomas

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Background: Although many methods have been tried in the treatment for malignant gliomas, the prognosis of malignant gliomas remains dismal. Median survival times (MST) for patients with malignant glioma after surgery and radiotherapy (RT) are reported between 6 and 9 months. A clinical study of intensity modulated radiotherapy (IMRT) using the simultaneous integrated boost (SIB) method was done for malignant gliomas. The strategy is that hypofractionated radiotherapy with a large fraction size may be effective for malignant gliomas, because the survival curves for malignant glioma cell lines in vitro show a large shoulder indicating a low ratio.
Methods: Between 2001 and 2003, 12 patients with histologically proven malignant gliomas (7 glioblastomas, 4 anaplastic astrocytomas, and 1 anaplastic oligodendroglioma) were enrolled in this study. The gross tumor volume (GTV) was defined as the contrast enhanced lesion on the pre-operative MRI T1 weighted images. IMRT delivered 70 Gy/28 fractions (fr)/daily 2.5 Gy to GTV and 56 Gy/28 fr/daily 2.0 Gy to the surrounding edema defined as the clinical target volume annulus (CTV-a). The time to local recurrence and death was calculated from the first day of IMRT, and the failure patterns were evaluated.
Results: No delay of IMRT due to acute radiation toxicity was observed, and no late neurotoxicity was noted in any patients. Although the MST for the 12 patients was 19 month with the 2-year survival rate of 43%, all patients showed loco-regional recurrence within 27 month. Local recurrences were noted in the center of GTV for eight patients and in the CTV-a for two patients. The remaining two patients showed intracranial recurrences outside of the radiation field.
Conclusions: Modest increase in the fraction size and total RT dose (70 Gy/28 fr/5.6 weeks) to the GTV did not improve the local control of malignant gliomas, although this fractionation was feasible and safe clinically. Marked increase in fraction size (>5 Gy) without increasing the total RT dose is our next strategy.

494 POSTER

Detection of heat shock protein 90 (hsp90) in brain tumors with a new monoclonal antibody, mab 4c5

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Background: The purpose of this study was to determine the possibility of using a new monoclonal antibody (mAb) against heat shock protein 90 (HSP90), mAb 4C5, previously characterized in our laboratory, as a potential prognostic marker in diagnosed cancer of the central nervous system.
Methods and Materials: A total of 13 high-grade (III and IV according to WHO) cases of brain tumors were selected from the archive of 417 Veterans Administration Hospital, in order to perform a tissue micro array (T.M.A) study. Paraffin blocks of formalin fixed tumor tissues were used to prepare a hematoxylin-eosin stained slide, from which regions without necrosis and inflammation were chosen for further processing. A tissue array was created from the selected regions, using a 0.6 mm diameter punch. Sections of 5 μm from the new multitumor paraffin block were transferred to slides, in order to examine immunohistochemically the prognostic value of mAb 4C5 and its potential correlation with other known markers. For all the markers immunohistochemistry was performed according to specific protocols. Section were stained with 3.3diaminobenzidine (DAB) and counterstained with Mayer's hematoxylin.
Results: In this T.M.A study immunostaining of mAb 4C5 was performed on highly invasive tumors of the central nervous system and compaired to staining obtained with 10 commercially available markers, including HSP90-α, HSP90-β, MMP2, MMP9, TIMP1, TIMP2, NM23, CD44, and S-100. Intense 4C5 immunoreactivity was obtained in 11 out of 13 cases examined. Interestingly immunostaining with the two commercially available anti HSP90 antibodies was always weaker and in some cases negative either for the α or for the β-isoform of HSP90. MAb4C5 gave negative staining in two cases of metastatic adenocarcinomas localized in the brain and in the cerebellum respectively, both of which had origin from a primary tumor in the gastrointestinal system. When mAb4C5 immunoreactivity was compared to that obtained with the other markers tested, a strong correlation in the expression profile between NM23 and mAb4C5 was observed in all 6 cases of high grade glioblastomas examined.
Conclusion: Our current results show that a) mAb 4C5 crossreacts with both the α- and the β-isoform of HSP90 b) there is a potential correlation between expression of mAb4C5 and NM23 in high grade glioblastomas and c) mAb4C5 may be usable as a prognostic marker to identify highly invasive brain tumors.