prognosis than other MSCC patients and may live long enough to develop a local recurrence of MSCC. This study investigates prognostic factors and radiation schedules for functional outcome and local control of MSCC after radiotherapy (RT) in such patients.
Materials and methods: A total of 616 patients, 335 breast cancer and 281 prostate cancer patients, who were irradiated for MSCC between 1/1992 and 12/2003, were included in this retrospective multi-center study. Motor function was evaluated before RT and at 1 month, at 3 months and at 6 months after RT with a 5-point scale. Potential prognostic factors were investigated: age ($\leqslant$ 65 years versus > 65 years), performance status (ECOG 1–2 versus 3–4), number of involved vertebra (1–2 versus *3), pre-treatment ambulatory status (ambulatory versus non-ambulatory), time of developing motor deficits before RT (1–7 days versus 8–14 days and > 14 days), and radiation schedule (short-course RT, i.e. 1×8 Gy/1 day or 5×4 Gy/1 week, versus long-course RT, i.e. 10×3 Gy/2 weeks, 15×2.5 Gy/3 weeks or 20×2 Gy/4 weeks).
Results: Of the entire cohort, 197 patients (32%) showed improvement of motor function, 342 patients (55.5%) no change, and 77 patients (12.5%) deterioration. Of the 197 non-ambulatory patients prior to RT, 70 patients (36%) regained the ability to walk. Outcome was not associated with type of primary tumor, 105/335 (31%) breast cancer patients and 92/281 (33%) prostate cancer patients improved.
On multivariate analysis (ordered-logit model), functional outcome was significantly affected only by the time of developing motor deficits before RT (> 14 days better than 8–14 days and 1–7 days, $p < 0.001$). The radiation schedule did not have a significant impact ($p = 0.56$). Improvement of motor function was observed in 96/285 patients (34%) after short-course RT and 101/331 patients (31%) after long-course RT.
A recurrence of MSCC within the irradiated region of the spine (in-field recurrence) was observed in 61 patients (10%) of the entire series, 30 (9%) breast cancer patients and 31 (11%) prostate cancer patients. Median time to in-field recurrence was 9 months. According to Kaplan-Meier analysis, the 2-year-local control of MSCC was 77% after short-course RT and 92% after long-course RT ($p = 0.005$). Median survival was 19 months in the entire cohort. 167 patients (27%) died within 6 months after RT.
Conclusions: Functional outcome after RT was significantly influenced by the time of developing motor deficits before RT, but not by the radiation schedule (shourt-course RT as effcetive as long-course RT). Local control of MSCC was significantly better after long-course RT. Thus, patients with a poor expected survival could be treated with short-course RT, because a short treatment time means less discomfort for the patient. For patients with good survival prognosis, long-course RT should be applied to achieve better local control.

485 ORAL

Hypoxia-inducible Factor 1 (HIF-1) and Carbonic Anhydrase IX (CA 9) expressions in glioblastoma multiform to predict response to radiation therapy. Implication for combined treatment with carbogen and nicotinamide

J. Simon[1], K. Mokhtari[2], C. Genestie[3], A. Bissery[4], P. Jaillon[5], J. Mazeron[1].
[1]Pitie-Salpetriere Hospital, Department of Radiation Oncology, Paris, France; [2]Pitie-Salpetriere Hospital, Laboratoire de neuropathologie R Escourolle, Paris, France; [3]Pitie-Salpetriere Hospital, Service d'Anatomie pathologique, Paris, France; [4]Pitie-Salpetriere Hospital, Biostatistics and Medical Information Department, Paris, France; [5]Saint-Antoine University hospital, Department of Pharmacology, Paris, France

Background: Tumour hypoxia is known to be associated with resistance to radiotherapy. Hypoxia induces the expression of HIF-1 and downstream genes such as CA 9.
Materials and methods: We examined the expression of HIF-1 and CA 9 by immunohistochemistry in GBM biopsies, and investigated their relationship with response to radiation therapy (RT). The response to RT was assessed by comparing contrast-enhanced MRI obtained before and six weeks after the completion of radiotherapy. Assessment of odds ratio were based on the logistic regression model with stepwise adjustment. The multivariate model included HIF-1 and CA 9 coded on a semi quantitative scale according to the positive tumour cell percentage (0 = no expression; + < 10%; ++ = 11%-50%; +++ = >50%), and age.
Results: Fifty six consecutive patients with inoperable glioblastoma treated with RT (59.4 Gy in 1.8 Gy/fraction), were included in this study (median age: 56 years, range, 30 to 67 years). Nineteen of those patients received carbogen and nicotinamide (C/N) during RT. HIF-1 was expressed in 33 of 56 (59%), and CA 9 in 38 of 52 (73%) of tumours. Tumour HIF-1 expression correlated significantly with that of CA 9 (Kappa = 0.23, $p = 0.003$). The response rate to RT for the entire population was 29%. HIF-1 and CA 9 expressions were correlated inversely with the rate of response to RT (univariate analysis: HIF-1 +: odds ratio 0.21, 95%CI: 0.06–0.71; CA 9 +: odds ratio 0.15, 95%CI: 0.04–0.59). Multivariate analysis showed that HIF-1 + (OR = 0.13, 95%CI: 0.03–0.65), CA 9 +++ (OR = 0.21, 95%CI: 0.04–0.98) and age (OR = 0.91, 95%CI: 0.82–0.99) were independent predictors of response to RT. Response rates to RT without C/N were 60% for tumours HIF-1–/CA 9–, versus 8% for those HIF-1+/CA 9+ ($p = 0.001$). In the group of patients irradiated with C/N, response rates were 50% and 38% for HIF-1–/CA 9– and HIF-1+/CA 9+, respectively. Median progression free survival was 26 weeks for patients HIF-1–/CA 9–, 16 weeks for patients HIF-1+/CA 9+ without C/N, and 26 weeks for patients HIF-1+/CA 9+ with C/N ($p = 0.007$).
Conclusions: Glioblastomas with expression of HIF-1 and/or CA 9 were associated with a significantly worse response to RT, independently of known prognostic factors. Carbogen and nicotinamide could reverse hypoxic profile of GBM.
Grant from Regional PHRC: AOR 03059, Assistance Publique – Hopitaux de Paris.

486 ORAL

Phase II study of erlotinib single agent therapy in recurrent glioblastoma multiforme

M. Vogelbaum, D. Peereboom, G. Stevens, G. Barnett, C. Brewer.
Cleveland Clinic Foundation, Brain Tumor Institute, Cleveland, Ohio, USA

Background: We have evaluated the activity of erlotinib (Tarceva, OSI-774) monotherapy for the treatment of recurrent glioblastoma multiforme (GBM) in a single center Phase II trial.
Methods: Patients with documented recurrent or progressive GBM who have received previous radiation therapy and cytotoxic chemotherapy were eligible for enrollment. No enzyme-inducing anti-epileptic agents were allowed. Patients were treated with 150 mg of erlotinib per day until tumor progression or study withdrawal. Tumor response was determined by MRI. Analysis for EGFR amplification and/or mutation was performed.
Results: A total of 31 patients were enrolled and treated in this trial. We have observed no complete responses (CR) and 8 partial responses (PR) for an objective response rate of 25.8%. An additional 5 patients have had disease stabilization for greater than 3 months (SD) for a tumor control rate of 41.9% (13/31). Fifteen patients have had MRI-confirmed tumor progression (PD) within 3 months of starting erlotinib and an additional 3 patients were taken off study due to neurological deterioration but without MRI evidence of tumor progression. Although most responders subsequently developed disease progression, the median time to progression was longer for responders (355 days) than that for patients with SD (199 days) or those with PD (84 days). Three patients (9.7%), all with PR, remain progression-free on erlotinib for more than 1 year with one approaching 2 years of treatment. Five patients (16.1%) have survived for more than 1 year following the start of therapy. 6-month progression free survival was observed in 25.8% (8/31) which compares favorably to historical controls. There has been no correlation with the presence or absence of EGFR amplification, rash or diarrhea. The EGFR gene activation domain was screened for mutations in all responders; only one case of a confirmed mutation was identified.
Conclusions: Erlotinib appears to show activity against recurrent GBM in this small, single center Phase II study. The lack of correlation with biomarkers which have been established for anti-EGFR therapy of other cancers raises questions as to the mechanisms underlying the clinical benefit observed in this trial.

487 ORAL

The VEGF-R tyrosine kinase inhibitor ZD6474 enhanced the anti-tumoural effects of temozolomide in the intracerebral BT4C rat glioma model

M. Sandström[1], M. Johansson[1], A. Bergenheim[2], R. Henriksson[1,3].
[1]Dept of Radiation Sciences, Oncology, Umeå, Sweden; [2]Department of Pharmacology and Clinical Neuroscience, Neurosurgery, Umeå, Sweden; [3]AstraZeneca AB, Sweden

Background: Malignant glioma is characterized by extensive pathological neovascularisation. Vascular endothelial growth factor (VEGF) is commonly believed to be the key positive regulator of glioma angiogenesis. ZD6474 is a potent, orally active, low molecular weight inhibitor of VEGF receptor tyrosine kinase activity with additional inhibitory effects on the epidermal growth factor (EGF) receptor tyrosine kinase. Temozolomide is an alkylating agent that recently has become standard treatment of glioblastoma in a concomitant schedule with radiotherapy followed by adjuvant temozolomide. We have previously shown that ZD6474 significantly inhibit tumour growth in an orthotopic intracerebral glioma model. In the present study we have investigated if ZD6474 in combination with temozolomide have any synergistic effects on the tumour growth in an intracerebral rat glioma model.
Material and methods: The effects of ZD6474 and temozolomide were investigated in the intracerebral BT4C rat glioma model. Animals were

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

C. Herold-Mende[1], S. Karcher[1], H. Steiner[1], R. Ahmadi[1], G. Vasvari[2], A. Unterberg[1]. [1]*University of Heidelberg, Neurosurgery, Heidelberg, Germany;* [2]*University of Heidelberg, ENT-Department, Heidelberg, Germany*

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

E. Koh, B.-A. Millar, C. Menard, H. Michaels, M. Heydarian, S. Ladak, S. Mckinnon, N. Laperriere. *University of Toronto, Dept. of Radiation Oncology, Toronto, Canada*

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

M. Gilbert[1], M. Campone[2], A.A. Brandes[3], S. Gertler[4], S. Green[5], C. Fowst[6], J. Caulkins[5], A. Ingrosso[6], M. Foley[5]. [1]*MD Anderson Cancer Centre, Neuro-Oncology, Huston, USA;* [2]*Centre Renè Gauducheau, Oncologie Médicale, Nantes Saint Herblain cedex, France;* [3]*Azienda Ospedaliera di Padova, Medical Oncology, Padova, Italy;* [4]*Ottawa Hospital The Ottawa Hospital – General Campus, Regional Cancer Centre, Ottawa, Canada;* [5]*Pfizer Inc., Clinical Research Oncology, New London, USA;* [6]*Pfizer Inc., Clinical Research Oncology, Milan, Italy*

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

D.S. Conkey[2], A. Gregor[2], G.R. Kerr[2], P. Statham[3], M. Strachan[4], S. Erridge[1,2]. [1]*University of Edinburgh, Western General Hospital, Edinburgh, United Kingdom;* [2]*Edinburgh Cancer Centre, Western General Hospital, Edinburgh, United Kingdom;* [3]*Department of Neurosurgery, Western General Hospital, Edinburgh, United Kingdom;* [4]*Department of Endocrinology, Western General Hospital, Edinburgh, United Kingdom*

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.