major complications were recorded: a bilateral blindness 2 years following the administration of 55 Gy (2 Gy per fraction) in a 14 year-old girl; a bitemporal glioblastoma 9 years following the administration of 50 Gy in a 1 year-old girl. All patients required GH and thyroid hormone replacements and the endocrinological condition deteriorated in 12. Severe psychological disturbances recorded in 11. RT administered to a dose of 45–55 Gy provide an excellent and durable local control when administered early in the course of disease.

258 ORAL

A PHASE III MULTI-INSTITUTIONAL RANDOMISED TRIAL OF LONIDAMINE (L) AND POST-OPERATIVE RADIOTHERAPY (RT) IN SUPRATENTORIAL MALIGNANT GLIOMA

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Lonidamine, an indazole carboxylic acid derivative, was reported in Phase II/III trials to have efficacy as radiopotentiator in malignant glioma.

Between October 1990 and August 1994, 191 pts. with supratentorial malignant glioma were randomly allocated to treatment with RT or RT + L, following surgical resection. Prior to randomisation patients were stratified according to age. One patient was ineligible and excluded from the study (not malignant glioma).

Patients (pts) in arm A (98 pts) received RT alone (50 Gy whole brain plus 14 Gy coned-down boost to the tumour volume, 2 Gy/day for 5 days a week), those in arm B (92 pts) received RT + L (150 mg 3 times daily for 1 year starting from 3 days before irradiation). The groups were comparable in median age, performance status, TNM classes, sex, residual tumour size after surgery and histologic grade. Median follow up was 49 weeks. Intention to treat analysis failed to demonstrate significance difference in the survival rates and shapes of the survival curves between the two treatment arms.

Cumulative survival at 12 and 24 months calculated by the Kaplan-Meier method were 50% ± 5% and 13.4% ± 4% for arm A, 49% ± 5% and 13.4% ± 4% for arm B. ($P > 0.4$). The Cox proportional hazards model confirmed the prognostic variables of age ($P < 0.002$), Karnofsky performance status ($P < 0.02$) and histologic grade ($P < 0.03$). No subgroup examined demonstrated a survival or response advantage for the combination arm. Both acute and late radiation reactions were similar in the two groups. This trial fails to substantiate therapeutic synergy of RT + Lonidamine with this dosage and schedule in the postoperative radiotherapy of malignant glioma.

259 ORAL

RADIOTHERAPY FOR GRADE II GLIOMAS

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From 1980–1991, 164 patients with a WHO-grade II astrocytoma received radiotherapy following surgery at UCSF. All patients had CT or MRI for diagnosis and/or treatment planning. Radiation doses were above 50 Gy in most patients, usually 54 Gy or 59.4 Gy. The 5- and 10-year overall survival rates were 79% and 67%, respectively; the median survival was 12.9 years. In the multivariate analysis, KPS, histology and duration of symptoms were significant. Age, location, surgical extent, or radiation dose were not significant. The 5-year survival rates for patients with KPS $\leq$ 70 and KPS > 70 were 60% and 87%, respectively. The 5-year survival rates for the different histologies were 95% for (mixed) oligodendroglial, 78% for ordinary, and 57% for gemistocytic astrocytomas. The 5-year survival rates for patients with a duration of symptoms $\leq$2 months versus >2 months were 65% and 83%. Progression free survival rates at 2-, 5- and 10-years were 77%, 68% and 50% respectively. In predicting progression free survival, only KPS was significant. Histology was important in predicting the survival following progression, with a 5-year survival of 83% in recurrent (mixed) oligodendroglial versus 33% in recurrent ordinary astrocytoma.

260 ORAL

HIGH-DOSE CHEMOTHERAPY (HDC) FOLLOWED BY AUTOLOGOUS BONE MARROW TRANSPLANTATION (ABMT) IN PLACE OF CRANIOSPINAL IRRADIATION (RXT) IN YOUNG CHILDREN TREATED FOR MEDULLOBLASTOMA (MB)?

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Cranio-spinal RxT is the standard prophylaxy in MB but, because of its late effects, children under 3 years of age are currently treated with conventional chemotherapy in order to delete or even avoid RxT. Among these patients treated without RxT in the SFOP study, 20 relapsed under conventional chemotherapy and entered a study of HDC followed by ABMT. Their median age at diagnosis was 23 m (R5-71) and the relapse occurred at a median time of 6.3 m (±5 m) after initiation of chemotherapy. A complete surgery of local relapse was performed in 4/20 and these patients were not evaluable for response. Sixteen out of twenty had measurable disease at primary site (9 pts) at metastatic sites (3 pts) or both (4 pts). Conditioning regimen consisted of combination Busulfan 600 mg/m^2 over 4 days and Thiotepa 900 mg/m^2 over 3 days. After recovery of aplasia, pts with local relapse received local RxT limited to posterior fossa. Among the 16 pts with measurable disease, following HDC, 6 CR, 6 PR, 3 NR, 1 NE were observed (Response rate 75%). For the 20 pts, EFS is 60% with a median follow up of 9 m post BMT (R3-65). Nine pts with localized relapse are alive NED without craniospinal RxT. Toxicity was high but manageable. One complication related death occurred 1 m post BMT. In conclusion: with a 75% response rate, this HDC proved to be very efficient in relapsed MB. A longer follow up is necessary to demonstrate whether, after local relapse, HDC could replace craniospinal RxT as prophylaxis of CNS metastases.

261 ORAL

DOSIMETRIC CONSIDERATIONS IN THE OUTCOME OF MEDULLOBLASTOMA

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Seventy-three patients aged 2 to 48 years were treated for medulloblastoma (MB). Chang staging was: 7% T1, 42% T2, 16% T3a, 27% T3b, 8% T4. Thirty-three percent of patients had spinal axis (SAX) staging. Median radiation doses were posterior fossa (PF) 52 Gy, whole brain (WB) 40 Gy, and SAX 35 Gy. Fraction sizes ranged 0.5–3 Gy (median 1.7 Gy WB, 1.7 Gy SAX, 1.8 Gy PF).

The 5-year overall and disease-free survival are 67% and 59%, respectively. PF control was better for patients receiving >50 Gy to the PF (86% vs 42%, $P = 0.0007$). PF dose >50 Gy gave improved actuarial and disease-free survival. PF control was improved when patients were treated with fraction $\geq$1.7 Gy/day to the brain and spine (84% vs 51%, $P = 0.0006$). When PF was controlled, neuroaxis control was better if >30 Gy to the SAX (97% vs 71%, $P = 0.05$). WB dose did not have an impact on neuroaxis control, but few patients received $\leq$30 Gy WB. Incidence of extra-CNS metastases is 13% and 20% at 5 and 10 years, respectively. Patients with continuous PF and neuroaxis control have an extra-CNS relapse rate of 10%.

Our data confirm a dose response >50 Gy for PF control in MB. SAX dose of >30 Gy is necessary for neuroaxis control. Fraction size >1.7 Gy appears to improve local control. Ten percent of patients develop extra-CNS metastases despite CNS control.

262 ORAL

LOW EXPRESSION OF PLASMINOGEN ACTIVATOR INHIBITOR (PAI) TYPE I (PAI1) AND HIGH LEVEL OF PAI TYPE 2 (PAI2) ARE ASSOCIATED TO A BETTER OUTCOME IN GLIOMAS

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Urokinase-type plasminogen activator (uPA) and PAI1, are involved in invasive phenotype of several tumors, and have been recently described in malignant gliomas. Expression and tissular localization of PAI2, as well as the clinical relevance of these proteases, need however to be investigated. In the present study, 42 patients with glioma were analyzed for expression of uPA, PAI1, and PAI2 (oligodendrocytoma (n = 2), glioma

grade I–II (n = 6), grade III (n = 6). and grade IV (n = 28)). (1) Median cytosolic levels of *uPA and PAI1* as determined by ELISA, were respectively 0.03 ng/mg protein (range 0.003–0.16) and 11.9 ng/mg protein (range 0.25–161.8). The highest levels of PAI1 were found in grade IV tumors as compared to grades I–III ($P < 0.001$). Expression of uPA and PAI1 was confirmed by Northern blot and *in situ* hybridization which localized PAI1 predominantly around neoangiogenic foci, both in tumor and endothelial cells. (2) *Expression of PAI2* antigen was heterogeneously distributed among tumors (median = 0.18 ng/mg protein, range 0.02–6.8) but was undetectable in control tissues. This data was confirmed by *in situ* hybridization. (3) *Univariate analysis* demonstrated that high levels of PAI1 are associated with a shorter disease-free survival both for the overall population ($P = 0.02$), and the grades IV ($P = 0.06$). In grade IV gliomas, high levels of PAI2 are, in contrast, highly correlated to a better overall survival rate at 18 months (48% vs 0%, $P = 0.015$). Our preliminary results suggest that, in malignant gliomas, PAI1 and PAI2 may be useful in the analysis of therapeutic protocols. Further studies should precise their biological role, in order to evaluate them as potential therapeutic target.

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INTRALESIONAL RADIOIMMUNOTHERAPY OF MALIGNANT GLIOMAS AS ADJUVANT SETTING IN NEWLY DIAGNOSED TUMOUR OR AS RESCUE TREATMENT IN RECURRENT LESIONS

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Two I-131 labelled murine Monocolonal Antibodies (MAbs) BC-2 and BC-4 raised against tenascin (TN), were intralesionally infused in 48 patients bearing a malignant glioma: 28 with recurrent disease (Rec) and 20 cases with newly diagnosed tumour (New). All patients were previously treated with surgery and radio-chemotherapy. Twenty-four Rec cases underwent further surgery which obtained a total or subtotal removal of tumour mass in 10 of these. In total 25 patients had intralesional RIT when the disease was minimal. The radiopharmaceutical was given at a dose of 4 mg of MAbs and 2405 MBq of ^{131}I. The infusions were repeated up to six. The local treatments were always well tolerated. The radiation dose to the tumour was on average >300 Gy per cycle. The median survival was, in total, 18 months. Intralesional RIT produced 12 complete remissions (6 in Rec and 6 in New), 6 partial remissions (4 in Rec and 2 in New). In 19 cases (15 Rec and 5 New) the progression of disease was recorded. The overall response rate was 37.5% (35.7% in Rec and 40% in New). These data demonstrate the capability of this new therapeutic technique to achieve, in a significant number of cases, a long lasting control of malignant gliomas and suggest the opportunity to apply this treatment when the disease is reduced owing to previous traditional cares. (Work supported by National Research Council program (Italy): Clinical Applications of Oncology Research, subproject n.8.)

264 POSTER

EMBOLIZATION AND RADIATION THERAPY OF CHEMODECTOMA OF THE TEMPORAL BONE

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Between September 1986 and January 1993, a total of 12 patients with primary (8) or recurrent (4) chemodectomas of temporal bone were treated. Diagnosis was assessed by clinical examination and radiographic studies (7) or by histological confirmations (5). All patients presented with group III disease and four presented with brain involvement. All patients were treated with embolization either within one week before initiation of radiation therapy (10), or 3 and 4 years before, respectively. All patients were irradiated with a wedged field technique using 60 Co gamma rays or 12 MV photons. The total tumour doses were 45 Gy/25 fx (4) or 50.4 Gy/28 fx (8). Ten evaluable patients have been followed for 13 to 84 months (median 32). Nine evaluable patients had local tumour control defined as having no evidence of progression of disease clinically or radiographically to the date of analysis, whereas in one patient tumour progressed. Cranial nerve paresis improved in 6 patients after a latency of 22 to 72 months (median 44). This study demonstrates that radiation therapy with preceeding embolization therapy is an effective treatment for advanced chemodectomas

265 POSTER

RADIATION THERAPY IN OPTIC GLIOMAS OF CHILDHOOD: PROGNOSIS AND LONG TERM SEQUELA

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Thirty-three children with the diagnosis of optic glioma were admitted to Department of Radiation Oncology in Ankara University Faculty of Medicine between 1973 and 1994. Twenty-two patients were female and 11 were male, with a female:male ratio of 2:1. Their ages ranged between 1 to 18 (mean:8.4, median:7). Six patients (18.2%) presented with neurofibromatosis. Twenty-nine patients (87.9%) had histopathological diagnosis of astrocytoma. Tumors were confined to the optic nerve in 5 patients (15.1%), confined to the chiasma in 6 patients (18.2%) and involved both the optic nerve and chiasma in 22 patients (66.7%). Subtotal resection of the tumor was performed in 20 patients (60.6%). Thirteen patients received irradiation as sole therapy. Two patients were irradiated for recurrent tumors. Mean follow-up was 158 months. Actuarial survival for 5 and 10 years were 91.9% and 77.9% respectively. Age, sex and subtotal resection did not appear to correlate with survival. Presence of neurofibromatosis reminded bad prognosis. One patient developed precocious puberty, two others developed panhypopituitarism and one posterior hypopituitarism. One patient was diagnosed as organic brain syndrome at the age of 30 and two patients had anxiety disorder. Radiotherapy proved to be an effective for tumors involving chiasma where surgery is not feasible. Long term follow-up would disclose either treatment or tumor induced sequela.

266 POSTER

PET-FDG UPTAKE AS A PROGNOSTIC INDICATOR IN GLIOMAS

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Positron Emission Tomography (PET) with 18-Fluorodeoxyglucose (FDG) provides quantitative and qualitative data on cerebral glucose consumption and is used in the evaluation of intracranial neoplasms. We have examined the value of PET-FDG uptake on glial tumor prognosis.

Material and Methods: PET scans of 31 patients with Grade 2–4 gliomas were evaluated prospectively on a semiquantitative scale from 0–4 according to avidity of 18-FDG uptake. Mean age of the patient group was 40.4 years, mean follow-up period was 42 months. Actuarial progression free survival was calculated as correlative endpoint.

Results: High FDG-uptake scores correlated with a worse prognosis (42% vs. 22% actuarial 5 year progression free survival, $P < 0.05$, high vs. low scores,). Age and Grade however were stronger indicators ($P < 0.001$). PET-FDG scores appeared more germane in the case of high grade tumors, indicating a better ability to discriminate the tumors with the poorest prognosis.

Conclusion: Avidity of FDG uptake in our patient group provided additional and complementary information to conventional factors such as age and grade with regard to prognosis.

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CHEMOTHERAPY FOR LOW GRADE GLIOMAS

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Complete surgical resection is the standard treatment for low grade gliomas (LGG) but it is sometimes impossible to perform. Radiation therapy has been extensively used as a complementary treatment or as the only treatment in inoperable tumors. Anyway, because of its deleterious long term effects, recent attempts have been made in order to investigate the efficacy of chemotherapy (CT) in young children and/or huge inoperable tumors. Since 1990, 35 low grade glioma patients (pts) have been treated with the SFOP BB CT protocol which includes: 7 cycles of carboplatin, procarbazine, etoposide, cisplatin, vincristin, cyclophosphamide, for 16 to 18 months. They were 16 males and 19 females aged 6 m to 104 m (median 25 m). The tumor was located in the optic pathway/hypothalamus in 22 pts, cerebral hemispheres in 3, basal