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Pattern of care and survival in a retrospective analysis of 1866 patients (pts) with glial tumours treated with radiotherapy (RT) in twelve Italian Centres from 1985 to 2003

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End-points: To analyse patterns of clinical presentation, staging and outcome in a multi-institutional series of radiotherapy treated malignant glioma pts and to evaluate actuarial overall survival (OS) in the different clinical and therapeutic subsets.
Materials and methods: Histology was reclassified using WHO system; performance status was defined according to the Karnofsky index and Order scale. Type of surgery, RT volumes, RT techniques and doses, supportive care, chemotherapy were analysed also according to the accrual period (1985–1990, 1991–1996, 1997–2003). Follow-up policies were very different in the different centers ranging from no follow-up to monthly clinical or strumental evaluation. The OS was calculated only for the pts with G3–4 astrocytoma and considering the centres with active follow-up (1145 pts), using the Kaplan-Meier method. Differences in actuarial overall survival (OS) were analysed with the log-rank test and the Cox-regression test.
Results: Statistically significant differences ($0.000 < p < 0.02$) in clinical, diagnostic and therapeutic features according to the accrual period are evident. In the last period were treated more pts aged plus than 60 years (27%, 42.3% and 50.7% respectively in the 3 groups), with worse Order score score (15%, 25%, 32% respectively), with lesions 3–5 cm large (35%, 45% and 50% respectively) with G4 disease (60%, 73%, 73% respectively). As for the diagnostic work up, the number of pts submitted to MRI or CT and MRI significantly increase in the more recent periods both in the pre-surgical and in the post surgical setting ($p = 0.000$). In the last period more pts were submitted to radical surgery ($p = 0.037$), and to conformal radiotherapy ($p = 0.000$), mainly on more limited volumes ($p = 0.000$). The majority of the pts were treated with RT doses >60 Gy (53.3%).
Median OS was 10 and 9 months respectively for the entire series and for G3-G4 patients. The univariate analysis showed a better survival for young pts ($p = 0.0000$), in those with better Order score ($p = 0.0000$), with G3 histology ($p = 0.0000$) and small disease ($p = 0.0027$). Among treatment variables, radical surgery ($p = 0.0001$), high RT dose ($p = 0.0000$), limited treatment volumes ($p = 0.0000$) and the use of chemotherapy ($p = 0.0000$) were related with a better survival. The multivariate analysis confirmed the importance of histology, tumour size, age, neurological performance status, radical surgery, dose of RT and volumes of treatment.
Conclusions: In Italy patterns of practice for malignant gliomas changed significantly during the last two decades. Staging procedures were increasingly accurate, surgery more aggressive and RT techniques more sophisticated. The relevance for OS of age, NPS and WHO histology, radical surgery, high dose radiotherapy on limited volumes is confirmed.

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Radiosurgery vs. hypofractionated stereotactic radiotherapy in patients with high grade gliomas

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Purpose: To compare results using two different approaches of stereotactic radiotherapy after conventional treatment in patients with high grade gliomas (HGG).
Patients and methods: a total of 47 patients with HGG are included. These patients received either boost or treatment in the relapse. In relation to previous well known prognostic factors of these patients, both groups were well balanced (see table).
All patients had KPS equal or superior to 70. Patients with radiosurgey (RS) received a median dose of 17.5 Gy at isocenter and patients with hypofractionated stereotactic radiotherapy (HFSRT) a median of 20 Gy at isocenter.
Results: MST from RS/HFSRT for all group was 18.4 months. The only prognostic factor observed was histology. For GBM group MST for RS and HFSRT were 14.9 and 15.5 months, respectively. And for AA group MST for RS and HFSRT was 24.2 months and not yet reached, respectively. No differences in overall survival (OS) were observed by type of treatment.
Toxicity: four groups of side effects were established; 1) seizures (15% for RS and 23% for SHFRT). 2) focal damage in radiotherapy field (8.8% for RS and 30% for SHFRT). 3) Neurocognitive damage (8.8% for RS and 0% for SHFRT). 4) Radiation necrosis (15% for RS and 0% for SHFRT).

Table: patients characteristics before radiotherapy (RS and SHFRT)

Variables	Radiosurgery	Stereotactic HF RT	P value
Age (median)	50	44	0.81
Sex: male/female	25/9	7/6	0.34
Tumour size (mm)	30	27	0.93
Surgery: Resect/Bx	33/1	10/2	0.32
Histology: GBM/AA	21/13	4/9	0.11
Chemo: yes/no	24/10	10/3	0.94

Conclusions: In spite of limited number of patients, we can conclude that the two modalities of high precision radiotherapy for HGG do not show differences in OS. Histology remains the most important factor. However, side effects could be more important in terms of radiation necrosis and neurocognitive damage in patients treated by single dose.

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Craniospinal radiotherapy in adult medulloblastoma

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Purpose: To evaluate the outcome and prognostic factors of adult patients with medulloblastoma.
Materials and methods: We evaluated 26 adult ($\geqslant$17 years old) medulloblastoma patients with a median age of 27 (range, 17–42 years) treated between April 1994 and September 2003 at Hacettepe University, Radiation Oncology Department. All patients' pathology slides were centrally reviewed. The Radiation Therapy Oncology Group (RTOG) "Late radiation morbidity scoring schema" was used in our review to grade severe complications. The standard-risk stratification for analysis was defined as a reported gross total resection (<1.5 cm^2 residual) and no evidence of metastatic tumor outside the posterior fossa on both CSF analysis and complete spine imaging. Staging was retrospectively verified according to the Chang Classification system. All patients were treated with craniospinal fractionated external beam radiotherapy (EBRT). A dose of 30.6 Gy with 1.8 Gy/fraction/day was prescribed for M0 patients; while 36 Gy was adjusted for patients with positive CSF findings. Posterior fossa was boosted to a total dose of 54 Gy. Spinal seeding metastasis was also boosted to a total dose of 50 Gy. While 20 (77%) patients were treated with EBRT alone, only 6 (23%) patients received sequential adjuvant chemotherapy. Survival time was calculated from the date of completion of radiotherapy.
Results: Male/female ratio was 1.2 (14/12). Preradiotherapy Karnofsky Performance Scale (KPS) was recorded as median 100 (range 70–100). Patients were staged as: T1 = 1; T2 = 15; T3 = 5; T4 = 1; T-unknown = 4; M0 = 23; M+ = 3 (M1 = 1, M2 = 2). Thirteen patients (50%) were classified as poor risk (10, STE; 3, M+). The median follow-up time was 46.5 months (range, 5–126 months). Majority of the patients had gross total excision (GTE) of the primary tumor (GTE: 16 patients, Subtotal excision-STE: 10 patients). Patients were referred to radiation oncology after a median duration of 1 month (range 1–3 months). Median radiotherapy treatment duration was 42 days (range 36–51 days). The 5-year actuarial recurrence free survival rates for recurrence free, distant metastasis free, disease free and overall survival were 82.5%, 90.8%, 73.5% and 89.7% respectively. Univariate analysis of variables including patient characteristics (age, gender, Karnofsky performance status-KPS), treatment modalities and factors (surgical extension: gross total versus subtotal – residual disease >1.5 cm^2; radiotherapy alone versus sequential chemotherapy; overall radiation treatment time; time to radiotherapy), and tumor characteristics (standard versus poor risk; Chang classification: T-stage, M-stage) failed to show an association with recurrence free, distant metastasis free and overall survival. The 5-year actuarial recurrence free survival rates for recurrence free, distant metastasis free, disease free and overall survival were 82.5%, 90.8%, 73.5% and 89.7% respectively. None of our patients experienced grade 3 or 4 late morbidities in their follow up period.

Conclusions: Yet, the current standard of care seems to remain craniospinal irradiation after maximal surgical resection of the primary neoplasm without clear indications for adjuvant chemotherapy.

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Imatinib plus hydroxyurea: safety and efficacy in pre-treated, progressive glioblastoma multiforme (GBM) patients (pts) – an update on the initial 30 pts

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Background: GBM is one of the most aggressive malignancies with a median survival of about 1 year. In newly diagnosed GBM combined treatment including surgery and chemo-/radiotherapy leads to 2 years progression free survival (PFS) of 11% and 2 years overall survival of 26%. The prognosis is even worse in pts with recurrent GBM. Many malignancies of the brain including GBM express platelet derived growth factor receptors (PDGF-R). Imatinib, a tyrosine kinase inhibitor of Bcr-Abl, PDGF-Rs and the Kit receptor, showed remarkable clinical efficacy in chronic myeloid leukaemia and gastrointestinal stromal tumours. In GBM, however, single agent efficacy was probably limited due to the blood brain barrier (BBB). Therefore Hydroxyurea (HU) which freely penetrates and potentially modulates the BBB was combined with imatinib to study if efficacy could be improved.
Methods: From June 2001 to September 2003 30 GBM pts refractory to radiation therapy and chemotherapy containing ACNU and temozolomide were treated with imatinib 400 mg/day and HU 1000 mg/day as continuous daily, oral dosing, followed by clinical examination and magnetic resonance imaging every 6 weeks.
Results: All 30 pts are evaluable for safety and efficacy. Initial ECOG-performance status was 1–2, the median age was 44 yrs (16–71). Results after a median treatment period of 19 weeks (4–145) were one complete response (CR) lasting 12 months, 4 partial responses (PR) lasting a median of 3 months (3–29), 11 stable diseases (SD) for a median of 6 months (3–33) and 13 progressive disease (PD). There were no grade 3 or 4 toxicities. 27 deaths occurred: 2 pts died of pulmonary embolism and 25 pts of disease progression, 2 pts after a period of SD of 25 and 34 months. 3 pts remain alive, 2 pts without progression for 32 and 28 months respectively, 1 pt had a disease progression after 26 months of SD and is in another period of SD since 4 months with the combination chemotherapy temozolomide plus pegylated liposomal doxorubicin. Six months PFS was 32%, 2 years PFS was 16%.
Conclusions: Combination therapy of imatinib and HU was well tolerated and effective in this group of recurrent, refractory GBM pts, with a response rate of 20% (CR+PR) and a clinical benefit rate of 57% (including SD), 2 years PFS was 13%. Based on these results, additional studies have been initiated to further explore this regimen.

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Imatinib plus Hydroxyurea in Pretreated Non-Progressive Glioblastoma (GBM) – a Single Center Phase II Study

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Introduction: GBM is a platelet derived growth factor receptor (PDGF-R) positive malignant brain tumor with a median survival of less than 15 months. While single agent Imatinib (I) did not show significant activity the combination of I plus Hydroxyurea (HU) could demonstrate efficacy in a group of 30 progressive pretreated GBM patients with progression free survival at 6 months and 24 months of and 16% respectively. 37% of the patients eperienced a stable disease (SD) as best response with longterm stabilisation for more than 2 years being possible. GBM although one of the most aggressive solid tumors usually shows a short period of disease stabilisation after primary treatment or effective treatment of the first relapse. Therefore the efficacy of I plus HU was analysed in a Phase II study in GBM pts before progression was confirmed. As the role of enzyme-inducing anticonvulsive drugs in this setting is not clear only non-enzyme-inducing anticonvulsive drugs were allowed in this study.
Methods: From 2003, December up to 2005, June 30 non-progressive GBM pts were included, all of them in a phase of stable disease for more than 6 weeks following effective primary or secondary treatment after the first relapse including surgery, radiotherapie and at least one chemotherapeutic regimen. No enzyme-inducing anticonvulsive drugs were allowed. 600 mg of I and 1000 mg of HU were given as a continuous daily dosage, all pts were followed up by blood cell count weekly and magnetic resonance imaging every 6 weeks.
Results: In 2005, October all pts will be eligible for toxicity and 27 pts for 6 months progression free survival, 25 pts are male, 5 pts female, the median age is 44 years (32 to 71). All 30 pts had prior radiotherapy, 21 pts had temozolomide containing chemotherapy and 9 pts not temozolomide containing regimens only. The median observation time now is 10 months. 6 months PFS is 14 out of 18 pts so fare. Hematotoxicity grade 3 and 4 occurred in 13 out of 27 pts (leucocytopenia grade 3: 9 pts; leucocytopenia grade 4: 2 pts; thrombocytopenia grade 3: 6 pts) and required dose reduction of HU in 12 cases, dosereduction of I in 2 cases and G-CSF subcutaniously in 5 cases. There was no febrile neutropenia, no interruption of the study due to toxicity and no treatment related death.
Conclusion: In the examined regimen the combination of I (600 mg/day) and HU (1000 mg/day) was feasible but showed a significant higher rate of hematotoxicity compared to the combination with I 400 mg daily. The 6 months PFS data are promising, observation time, however, is short. Efficacy and toxicity data of the entire group of pts will be updated for the ECCO 2005 meeting.

503 POSTER

Cyberknife radiosurgery for spinal metastases

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Purpose/Objective: To determine the effectiveness and safety of Cyberknife radiosurgery in the treatment of spinal metastases.
Materials/Methods: From 1996 to 2003, 31 patients with 33 spinal metastases were treated using Cyberknife image-guided radiosurgery (Accuray, Inc., Sunnyvale, CA) at Stanford on an institutional review board-approved protocol. The goal of treatment was to deliver 16–25 Gy in 1–3 fractions, doses estimated to be effective based on prior experience in treating brain metastases of similar histologies. Patients were followed clinically and radiographically for at least 3 months or until death.
Results: After a mean follow-up of 10 months (range 0–22 months), 19 patients were alive and 12 were dead at last follow-up. No death was treatment-related. Fifty-four percent (14/26) of symptomatic patients experienced improvement of symptoms after treatment. Three patients developed clinical and radiographic signs of treatment-related spinal cord injury following treatment.
Conclusions: Cyberknife radiosurgery is effective and generally safe in the management of spinal metastases. The tolerance of the spinal cord to hypofractionated radiation within the range of doses administered in this study is not yet well understood. Prior chemotherapy or radiation may be additional confounding factors. At present, the ease of radiosurgical treatment and the effectiveness in alleviating pain must be weighed against the potential for spinal cord injury, especially for lesions of the thoracic spine.

504 POSTER

Tumor volume reduction from 3 Gy-fractions measured in brain metastases and implications for clinical trials of response modifiers

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Purpose: To calculate the dose necessary to control brain metastases with fractionated external beam radiotherapy (RT). Such data can guide the choice of doses in prospective clinical trials of RT alone or RT plus sensitising agents.
Methods: We determined the volume of 238 brain metastases in 81 patients treated with 10x3 Gy of whole-brain RT (WBRT) from serial pre- and post-treatment contrast-enhanced computed tomography (CT) scans. Imaging was performed within 14 days in 154 lesions, between 15 and 28 days in 72 lesions, and after > 28 days in all others. Furthermore, repeated CT scans after more than 1 month were available in 90 lesions.
Results: The median number of brain metastases per patient was 3 (range 1–5). Forty-two percent of the metastases showed solid contrast-enhancement, whereas 31% had ring-shaped contrast enhancement, i.e. central necrosis, of <50% and 27% had more central necrosis. The median pre-treatment volume was 2.6 ccm (range 0.03–85.5 ccm). A complete remission (CR) occurred in 24% of the lesions, whereas 3% showed further enlargement at first CT. The other lesions were either stable or smaller with a median volume reduction of 51%. Progression-free survival at 6 months was 100% in the CR group and 63% in the PR/NC group ($p < 0.05$). Regarding all 238 lesions, the median maximum volume reduction was 0.9 ccm. The best result was evident on scans obtained between 66 and 120 days after WBRT (median 1.5 ccm vs., for example, 0.6 ccm if the scans