progenitor proliferation, and REST/NRSF, a transcriptional repressor of neuronal differentiation genes. Previous studies have shown that neither c-Myc nor REST/NRSF alone could cause tumor formation. To determine whether c-Myc and REST/NRSF act together to cause medulloblastomas, we used a previously established cell line derived from external granule layer stem cells transduced with activated c-myc (NSC-M). These immortalized NSCs were able to differentiate into neurons in vitro. In contrast, when the cells were engineered to express a doxycycline-regulated REST/NRSF transgene (NSC-M-R), they no longer underwent terminal neuronal differentiation in vitro. When injected into intracranial locations in mice, the NSC-M cells did not form tumors either in the cerebellum or in the cerebral cortex. In contrast, the NSC-M-R cells did produce tumors in the cerebellum, the site of human medulloblastoma formation, but not when injected into the cerebral cortex. Furthermore, the NSC-M-R tumors were blocked from terminal neuronal differentiation. In addition, countering REST/NRSF function blocked the tumorigenic potential of NSC-M-R cells.
Conclusion: Our findings indicate that abnormal expression of REST/NRSF and Myc in NSCs causes cerebellum-specific tumors by blocking neuronal differentiation and thus maintaining the "stemness" of these cells. Furthermore, these results suggest that such a mechanism plays a role in the formation of human medulloblastoma. Furhtermore, to our knowledge, this is the first study in which abnormal expression of a sequence-specific DNA-binding transcriptional repressor has been shown to contribute directly to brain tumor formation.

Poster presentations (Wed, 26 Sep, 09:00−12:00)
Central Nervous System

2506 POSTER

Investigation of histological correlate of ^{11}C-methionine (MET) PET uptake of brain gliomas by image fusion for navigated surgery

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Background: The objective of the study was to investigate the histological correlate of ^{11}C-methionine (MET) PET uptake of brain gliomas by image fusion for navigated surgery.
Methods: Twenty-seven patients (18 male, 9 female; mean age 42 years; range 11−77 years; 8 low-grade and 11 high-grade astrocytomas or mixed gliomas, 8 oligodendrogliomas) underwent MET PET studies preoperatively.
Results: MET PET tumor uptake was detected in 26 of 27 patients (96.3%). The quantitative MET tumor standardized uptake value (SUV) ratio was significantly higher in malignant gliomas and oligodendrogliomas than in low-grade gliomas (2.76 / 2.62 vs. 1.67, $p = 0.03$). Generally, qualitative visual grading of MET uptake revealed 2 main patterns: focal MET uptake in 12 and uniform global MET uptake in 11 patients. Focal uptake corresponded to malignant glioma histology in 66.7%, and uniform global uptake to oligodendroglial histology in 72.7%. In oligodendrogliomas, global MET uptake constituted 81.5% (range 53.8% and 135%) of the MRI T1 tumor volume on average and was limited to the MRI FLAIR tumor volume in 86% (7/8) of patients. Tissue samples of focal MET uptake areas correlated with histological anaplasia in 66.6% (8/12 glioma patients), although 62.5% (5/8 patients) lacked MRI contrast enhancement.
Conclusion: MET PET image fusion may facilitate targeting of anaplastic foci in homogeneous MRI-non-enhancing gliomas for biopsy, may identify oligodendroglial histology preoperatively as well as characterize biologically active tumor volumes within MRI T1/FLAIR tumor areas of patients candidates for resection.

2507 POSTER

Temozolomide (TMZ) concomitant to radiotherapy (RT) plus 12 cycles of maintenance chemotherapy in newly diagnosed GBM: is more better?

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Background: TMZ concomitant to radiotherapy followed by 6 cycles of maintenance chemotherapy improves median survival in newly diagnosed GBM. In the same group of patients, MGMT promoter methylation status has been correlated to improved survival and PFS. The aim of the present study was to assess the activity of TMZ concomitant to RT followed by 12 cycles of maintenance chemotherapy or up to a contrast enhanced MRS shows the presence of tumor. We also asses the correlation with MGMT promoter methylation status.
Materials: Adult patients with newly diagnosed histologically confirmed GBM were were treated with TMZ (75 mg/m^2/day) concomitant to radiotherapy (60 Gy/30F) followed by TMZ (150–200 mg/m^2 days 1−5, q28). We tested the relationship between MGMT promoter methylation status and clinical outcome of patients enrolled in the trial. MGMT promoter methylation was analyzed by methylation specific PCR (MSP).
Results: 104 consecutive patients (67 males), median age 53 (range 20−73), median KPS 90 were enrolled with a median follow up of 16 months (range 4−62). Of these 98.1% had a debulking surgery. Six patients (5.5%) discontinued chemotherapy for toxicity, and 64 (58.2%) for disease progression. The entire population obtained a median TTP of 11 months (95% CI: 8.5−13.5), and a median survival of 23 months (95% CI: 15.6−30.3). Median TTP and median survival were 29 months (CI 95% 20.0−38.0) and 38 months (95% CI: 20−56) respectively in methylated patients (32.7%) compared to 9 months (CI 95% 8.3−9.7) and 17 months (95% CI: 13−17) in unmethylated patients (67.3%) ($p < 0.0001$ both for TTP and MST).
Conclusions: A marked correlation between MGMT methylation status and clinical outcome has been showed in GBM patients treated with TMZ concomitant to RT followed by TMZ maintenance chemotherapy. The continuation of maintenance chemotherapy up to a lesion was present in MRS results in positive outcome in terms of survival. Further large studies would be required for more definitive conclusions on how long the maintenance chemotherapy should be delivered.

2508 POSTER

^{11}C-methionine-PET based substrate for target definition in stereotactic radiosurgery of brain metastases

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Purpose/Objective: Recently, target delineation in brain tumors, based traditionally on CT and MRI, has improved by using biologic imaging: ^{11}C-methionine positron emission tomography (MET-PET). However, no studies have so far quantified the tumor extension in MET-PET concerning the definition of targets in the stereotactic radiosurgery (SRS) of brain metastases. The purpose of this work is to investigate the recognition of a margin in the SRS of brain metastases by comparing these two imaging modalities using image fusion.
Materials and Methods: CT, gadolinium enhanced T1-weighted MRI and MET-PET were separately performed within 2 weeks in twenty patients with a total of 97 brain metastases for SRS treatment planning. The MET-PET and MRI studies were analyzed by two independent observers. These image sets (CT/MRI and CT/MET-PET) were then fused utilizing the Pinnacle System. The CT/MRI clinical target volume (CTV) (CTV-MRI) was defined as the contrast-enhanced area on CT/T1 gadolinium-MRI fusion images. CT/MET-PET CTV (CTV-MPET) was defined as the area of an accumulation of CT/MET-PET, which was apparently higher than that of normal tissue on CT/MET-PET fusion images. A threshold value for the tumor/normal tissue index of 1.7 was considered for the tumor in all lesions. In addition, CTV-MRI-1 mm, CTV-MRI-2 mm, CTV-MRI-3 mm and