Materials and Methods: Two LINACs prototypes are used: a 4.5 MeV (Institut Curie) and a 6 MeV (CHUV) to investigate the normal brain response and the antitumor effect of FLASH irradiation on GBM models in a preclinical study with an ultimate aim to apply this treatment to GBM bearing patients. For the studies on normal brain, C57B16/J mice were irradiated at the whole brain level at single doses ranging from 10 to 80 Gy FLASH (>50Gy/s), at 10 Gy CONV (0.04Gy/s) and sham irradiated (6 mice in each group). Two months post-irradiation, cognitive tests were performed on mice to evaluate the mid-term memory with a novel object recognition test (Acharya et al. 2009) and brains were sampled. Two hours before the sampling, mice were injected with BrdU, brains were collected and immunohistochemistry and NSCs quantification were performed on brain sections. To evaluate the FLASH antitumor effect, human GBM were engrafted to nude mice. The tumors were locally irradiated at 10 Gy CONV, from 10 to 30 Gy FLASH and sham irradiated. Tumor growth delay was measured.

Results: Our preliminary results show that 50Gy FLASH irradiation on the whole brain does not induce any macroscopic toxicity nor mice’s health alteration whereas a pan-encephalic irradiation of 10Gy CONV is the maximum tolerated dose for long term follow-up. The cognitive tests’ results show a drop in cognitive skills after 10Gy CONV irradiation whereas mid-term visual memorization is not significantly affected at 50Gy FLASH. In correlation, two months after irradiation, the quantification of NSCs shows their preservation in the SGZ at doses up to 20Gy FLASH whereas 10Gy CONV eradicates all the hippocampal NSCs at the same timepoint. Astrocytic toxicity has also been investigated and shows that 10Gy CONV irradiation induces a high level of gliosis and astrocytes’ remodeling whereas few gliosis and astrocytes’ modifications are observed after 50Gy FLASH. At the tumor level and at similar doses, the FLASH and CONV irradiations induce a similar growth retardation. Nevertheless, the FLASH irradiation’s innocuousness on normal tissue does allow a dose escalation and thus an enhancement of the tumor growth delay. We are currently escalating the dose to achieve the tumor control.

Conclusions: Altogether these results suggest that the FLASH radiotherapy allows the delivery of very high doses to the whole brain, sparing normal tissues and NSCs and eradicating tumor cells. In the follow up of these preliminary experiments we are developing orthotopic and spontaneous GBM models in mice (in collaboration with K. Schhors and D. Hanahan, EPFL) to define the molecular basis of the FLASH differential effect.
Results:
Volume change rates after RT have been calculated for each component as covariance structure (controlling for age). Intercepts and slopes for time across subjects and variance mixed models were computed with regional volumes as parametric mapping (SPM8). Longitudinal volumes have been performed on 77 MRI data sets using Matlab and statistical hippocampi, the lateral ventricles, and the whole brain was observer-independent, automated volumetry of the hippocampal avoidance (HA-WBRT).

Materials and Methods: 22 patients who had been assigned to HA-WBRT following clinical indication received MRI before and up to 19 months after treatment (Mean = 5 months). Observer-independent, automated volumetry of the hippocampi, the lateral ventricles, and the whole brain was performed on 77 MRI data sets using Matlab and statistical parametric mapping (SPM8). Longitudinal volumes have been tested for significant brain changes after HA-WBRT. Linear mixed models were computed with regional volumes as dependent variables and predictor variable time with random intercepts and slopes for time across subjects and variance components as covariance structure (controlling for age). Volume change rates after RT have been calculated for each region.

Results: At the group level, hippocampal [-0.02 ml (-0.19%) per month] and whole brain volumes [-2.03 ml (-0.19%) per month] showed decreases which did not reach significance. By contrast, the lateral ventricles significantly expanded [p < 0.0001; +1.2 ml (3.6%) per month (+43% per year)].

Conclusions: In this pilot study we observed no significant hippocampal atrophy after HA-WBRT. The lateral ventricles, however, expanded after treatment, indicating cerebral atrophy at a higher rate than reported in the literature on healthy subjects. While brain tissue degeneration seems to occur in this group of patients, hippocampal tissue is spared from this process.

PO-0802
Outcomes of fSRT compared to SRS for brain metastases by using volumetric surrogates for fractionation
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Purpose/Objective: Hippocampal-avoiding whole brain radiotherapy (HA-WBRT) for multiple brain metastases may prevent treatment-related cognitive decline, compared to standard WBRT. Reduction in hippocampal volume over time has been shown to be significantly related to decline in memory and learning. This study aims at exploring brain volume changes after whole brain radiotherapy with hippocampal avoidance (HA-WBRT).

Materials and Methods: 22 patients who had been assigned to HA-WBRT following clinical indication received MRI before and up to 19 months after treatment (Mean = 5 months). Observer-independent, automated volumetry of the hippocampi, the lateral ventricles, and the whole brain was performed on 77 MRI data sets using Matlab and statistical parametric mapping (SPM8). Longitudinal volumes have been tested for significant brain changes after HA-WBRT. Linear mixed models were computed with regional volumes as dependent variables and predictor variable time with random intercepts and slopes for time across subjects and variance components as covariance structure (controlling for age). Volume change rates after RT have been calculated for each region.

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Purpose/Objective: Local control (LC) rate is inversely related to the volume and size of the brain metastases treated with SRS. We aimed to demonstrate the potential role of fSRT with increasing volumes in order to improve LC.

Materials and Methods: Between 2001-2004, 180 patients with brain metastases were treated with stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (fSRT). Sixty-five percent were treated for newly diagnosed, whereas 35% for progressive brain metastases after previous whole brain radiotherapy. Median number of metastases was 2 and distributed as single 43%, 2-3 mets 33%, 4-10 mets 16% and >10 mets 8%. Median age was 59 years (29-87 years); 38% was female, 62% male. Primary tumor site was lung in 65%, breast in 16%, gastrointestinal 7%, kidney 5%, melanoma 2% and others 5%. Patients were grouped according to the diameter of the largest metastasis as ≤10mm in 15%, 11-20mm in 36%, 21-30 mm in 31% and >30 mm in 18%. Patient fixation was made with thermoplastic masks. CT and MR simulation with contrast was made on-site at the same day. GTV was equal to PTV. All treatments were performed on TrueBeam STx with Novalis (Varian, Palo Alto, USA and BrainLAB AG, Feldkirchen, Germany) using flattening filter free beams and non-coplanar multiple partial arcs. Decision for fractionation was made according to the size of the largest metastasis, cumulative volume and location of the metastases. Percentage of fSRT in diameters of ≤10mm, 11-20mm, 21-30 mm and >30 mm were 15%, 57%, 91% and 100%. Median peripheral doses were 18 Gy for single fraction (14-20 Gy), 24 Gy for 3 fractions (18-27 Gy) and 30 Gy for 5 fractions (22.5-40 Gy) treatments.

Results: At a median follow-up of 6 months (1-38 months) median overall survival (OS) was 12 months for the whole group (newly diagnosed group 13 months, progressive group 8 months, p=0.004). OS curves separated significantly in patients with ≤20mm, 21-30 mm and >30mm diameters with median OS as 17, 12 and 7 months, respectively (p=0.01). LC at 1 year for the newly diagnosed patients was 79%, and for the progressive patients 69% (p=0.01). One-year LC rate for ≤10mm, 11-20mm, 21-30 mm and >30 mm diameter was 100%, 74%, 70% and 69%, respectively (p=0.02, for ≤10mm vs others). Specifically in the group with large metastases (>30 mm, n=33) all of whom were treated with fSRT, one-year LC rate was 100% for the newly diagnosed patients, and 47% for progressive patients. Salvage treatment was performed as SRS in 25 patients (14%), WBRT in 7 patients (4%) and surgery in 2 patients. Repeat SRS to the same target was done in one patient. Radionecrosis was observed in 10 patients (5.6%), and all were treated with steroids or bevacizumab without surgery.

Conclusions: Single fraction SRS can achieve high local control for small brain metastases. For larger metastases fSRT can successfully replace SRS with improved LC and lower toxicity.

PO-0803
Optimization of GTV definition and treatment planning in lung-sparing VMAT for pleural mesothelioma
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