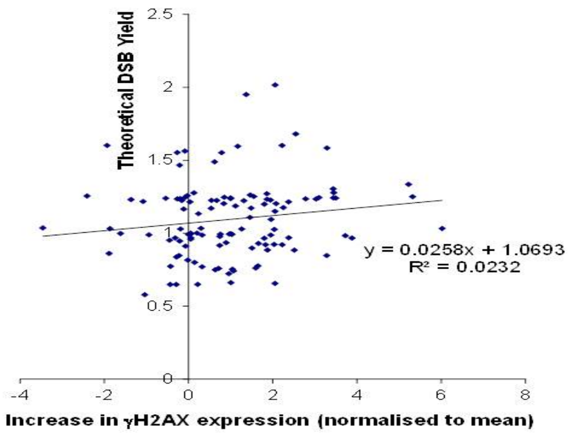
Purpose/Objective: Comparison of theoretical estimation of lethal DNA damage of normal mammalian cells during exposure to low-kV X-rays with an ex vivo assessment of double-strand strand breaks (DSBs) in tissue irradiated in vivo.

Materials and Methods: 130 patients were treated with Intrabeam intraoperative radiotherapy of the tumour bed following breast cancer resection. Tissue samples were taken from the resection wall before and after irradiation with 50 kV X-rays. Doses of 5 to 6 Gy were delivered at 1 cm from the edge of a treatment applicator. Time for dose delivery varied between 10 and 40 minutes. Tissue samples were sectioned and stained for phosphorylated γH2Ax, representative of DNA repair, to assess damage before and after irradiation. The proportion of stain was recorded on multiple slides spanning samples from 130 patients. Monte Carlo radiation transport calculations were used to determine the spectra of secondary electrons at the samples in situ. These spectra were used as input to a damage simulation code producing expected levels of damage. In combination with expected repair rates and irradiation times, theoretical estimates of DSBs remaining at the end of irradiation were made based on the linear-quadratic model of radiation damage with repair.

Results: Considerable variability was found in change in γH2Ax expression between pre and post-irradiation sections, though there is a trend for decreased accumulation with longer irradiation time, consistent with increased proportional repair. The theoretical results suggest a reduction in damage with increasing applicator size due to both increased beam hardening and longer irradiation times. There is however little similarity between theoretical and experimental determination of induced DSBs, with poor correlation as shown in the figure.



Conclusions: Assessment of DNA damage occurring in humans is difficult and rare. We found poor correlation between theoretical DSB estimates and those made using ex vivo assessment of tissue samples. It is likely that insufficient time was available post irradiation for accumulation and equilibrium of γH2Ax. With potentially slow repair and a diversity of cell types present in sections, larger numbers of patients may allow differences in in vivo normal tissue repair with dose-rate to be distinguished above levels of noise and uncertainty in both the measurements and the model.

PO-1078

Ionizing radiations sustain Glioblastoma cell dedifferentiation to a stem phenotype through Survivin

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Purpose/Objective: Glioblastomas (GBM) are some highly lethal brain tumors despite a conventional treatment associating surgical resection and subsequent radio-chemotherapy. Amongst these heterogeneous tumors, a subpopulation of chemo- and radioresistant GBM stem-like cells appears to be involved in the systematic GBM recurrence. Moreover, recent studies showed that differentiated tumor cells may have the ability to dedifferentiate and acquire a stem-like phenotype, a phenomenon also called plasticity, in response to microenvironment stresses such as hypoxia. We hypothesized that GBM cells could be subjected to a similar dedifferentiation process after ionizing radiations (IR), then supporting the GBM rapid recurrence after radiotherapy.

Materials and Methods: In the present study we established several differentiated GBM cell lines isolated from patient resections and subjected them to a clinically relevant IR dose (3 Gy). We then characterized, after long term culture, the phenotypic and functional alterations displayed by these GBM cells using *in vitro* techniques (qPCR, western blot, flow cytometry, limiting dilution clonogenic assays) and *in vivo* experiments (orthotopically-xenografted nude mice).

Results: We demonstrated that the exposure of differentiated GBM cells to a subtoxic IR dose potentiated the long-term reacquisition of stem-associated properties such as the ability to generate primary and secondary neurospheres, the expression of stemness markers and an increased tumorigenicity. We also identified during this process an up-regulation of the anti-apoptotic protein survivin and we showed that its down-regulation by YM-155, a selective survivin inhibitor used in anti-cancer clinical trials, led to the blockade of the IR-induced plasticity.

Conclusions: Altogether, these results demonstrated that irradiation could regulate GBM cell dedifferentiation via a survivin-dependent pathway. Targeting the mechanisms associated with IR-induced plasticity will likely contribute to develop some innovating pharmacological strategies for an improved radiosensitization of these aggressive brain cancers.

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Single W18O49 nanowire: a multifunctional nanoplatform for image-guided dose-enhancement radiation therapy

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