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Biological effects of low-energy x-rays (50 kV) used for Intraoperative Radiotherapy (IORT)

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Intraoperative radiotherapy (IORT) is being tested in a clinical trial for highly selected early-stage breast cancer patients. A miniaturised x-ray machine ("Intrabeam®", Carl Zeiss Surgical GmbH) delivers a highly localised, isotropic field of 50 kV x rays to the tumour bed during surgery. Several aspects of this new treatment modality are different from conventional fractionated radiotherapy: low photon energy, a highly localised radiation field with steep dose gradient, a single large fraction applied during surgery, and protracted irradiation allowing continuous induction and repair of sublethal damage (SLD). The aim was to address the biological effects of these properties involved in IORT. A solid-water phantom for simulating for tumour-bed irradiation with applicators was constructed. Human cell models relevant to breast cancer treatment were tested as well as V79 hamster cells for comparison with published data. 6 MV x rays were were included for comparison. Results of the three major aspects may be summarized as follows:

1) RBE values for 50 kV x rays from Intrabeam at surviving fractions (SF) 0.02-0.5 were 1.22-1.52 for human cells in the solid-water phantom at the highest dose rate 15.1 Gy/h (8.1 mm from applicator surface). For V79 hamster cells, RBE was in the range 1.18-1.40 at SF 0.02-0.5 for Intrabeam irradiation 15.1 Gy/h, whereas the RBE in the similar range 1.41-1.30 at SF 0.5-0.05 was validated for a surface therapy machine Dermopan. Thus an increased relative RBE of 50 kV x rays was determined for diverse cell types and two different radiation modalities. Lower RBE values which were not significantly different from 1 at the distant depth (22.9 mm at a low dose rate 4.1 Gy/h) suggested remote normal tissue may be spared by the decreasing physical dose. For fixed time irradiation at different distances from the applicator surface, the RBE for human cells decreased with decreasing dose rates in contrast with expectations from the linear-quadratic (LQ) formalism.

2) Efficient SLD repair was observed for the V79 and MCF7 cell lines but not for normal fibroblasts (time intervals 45 min-6h). This was related to the shape of the survival curve showing a typical shoulder for V79 and MCF7 which was absent in GS4. SLD repair after irradiation with 50 kV x rays from Dermopan was validated using V79 cells. The kinetics of SLD repair suggested an initial repair halftime $T_{1/2}$ of 15 min for V79 with a slowing down of the repair rate after 10-15 min. For MCF7, $T_{1/2}$ was constant at 39 min for time intervals up to 40 min, which is relevant for the time required to deliver IORT with 50 kV x rays. The influence of different $T_{1/2}$ on modeling calculations of tumour control probability (TCP) was assessed showing that a longer $T_{1/2}$ of 40 min instead of 15 min resulted in slightly higher TCP.

3) The kinetics of induction and decay of DNA repair foci detected by γH2AX after acute irradiation was similar in different cell types with maximum mean number of foci at 30 min after irradiation. Approximately 80% - 90% of the maximum number of repair foci had formed 8 min post irradiation. The majority of foci disappeared (65%-90%) in 6-8 h post irradiation, with few residual foci detected at 24 h. The decay halftimes for the fast repair component were from 50 min to 3 h. The maximum number of foci in V79 produced by 4.7 Gy of 50 kV x rays from Intrabeam was found to decrease with decreasing dose rates, indicating some repair during protracted irradiation. Furthermore, the decay rate of 53BP1 foci in GS4 was relatively constant in the low-dose region (0-2 Gy), and nearly all induced foci could be removed in 24 h post irradiation. However, the cellular repair system appeared to be saturated in the high-dose region (8-16 Gy) with fewer foci induced by increasing dose and more residual foci present after 24 h. Although normal skin fibroblasts showed no split-dose recovery, the induction and decay dynamics in DSB repair foci are similar to the other cell types. This suggested that SLD is not identical to the lesions detected by γH2AX or 53BP1. The knowledge of RBE and of the biological effects in repair and recovery involved in IORT gained in this project will be important for optimizing IORT with low energy photons as a treatment option for highly selected patients with low-risk breast cancer.