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The role of cellular damage repair for the biological effect of intraoperative radiotherapy (IORT) with low-dose rate 50 kV X-rays

Autor: Xiaolei Liu
Institut / Klinik: Klinik für Strahlentherapie und Radioonkologie
Doktorvater: Prof. Dr. F. Wenz

Beam hardening and sublethal damage (SLD) repair may reduce the experimental relative biologic effectiveness (RBE) of 50kV Photon Radiosurgery System (PRS, INTRABEAM) used for intraoperative radiotherapy. In order to address the relative role of beam hardening on RBE of 50kV X-rays, the RBE values from the PRS were determined for irradiation of MCF7 breast cancer cells, when irradiated with PRS bare probe, and a 4cm spherical applicator in air or in tumor bed. As irradiated by the PRS bare probe, or with applicator in air at 16.2Gy/h and 17.5Gy/h, the mean RBE values were 1.61 and 1.31, while being 1.47 and 1.37 by 14.3Gy/h and 13.8Gy/h (0.9mm difference of solid water material in beam path) ($p>0.05$). When irradiated at 11.0Gy/h and 8.5Gy/h, the mean RBE values were 0.99 for the irradiation with applicator in air and 1.16 in tumor bed (3.8mm difference of solid water material in beam path) ($p>0.05$). As irradiated in tumor bed, the mean RBE values were 1.31 and 1.37 by 17.5Gy/h and 13.8Gy/h (1.7mm difference of solid water material in beam path). This suggests that the beam hardening caused by 0.9mm, 1.7mm and 3.8mm thickness solid water material in beam path may not affect RBE of 50kV PRS X-rays ($p>0.05$). When irradiated at 8.5Gy/h in tumor bed, 11.0Gy/h with applicator, and 11.9Gy/h only with the PRS bare probe, the PRS bare probe irradiation showed an increased RBE values compared with the other two conditions ($p<0.05$), which indicates that beam hardening by the applicator material may affect RBE.
To explore the role of p53 on SLD repair, the lymphoblastoid TK6 WT (p53 wild type), TK6 E6 (p53 suppressed), and WTK1 (p53 mutant), were tested. WTK1 cells exhibited a shouldered survival curve, indicating the involvement of SLD repair. In contrast with a previous report [Little et al., J.Biol.Chem. 270:11033-6, 1995], a radiation-induced, p53-dependent G1/S checkpoint was demonstrated in TK6 WT, which was absent in TK6 E6 and WTK1 cells. TK6 E6 showed a slower accumulation in and release from G2 arrest following irradiation compared with TK6 WT. Compared with p53-deficient TK6 E6, p53 mutant WTK1 showed fewer apoptotic cells (2.3% at 24h) ($p<0.05$), fewer DSB foci (3-4 residual DSB at 24h) ($p<0.05$), quicker and stronger G2/M checkpoint recovery (release completely at 24h) and no permanently arrested cells following irradiation. This suggests that radioresistance of WTK1 is probably due to error-prone repair, intact G2/M checkpoint and selective removal of damaged cells by apoptosis. The absence of functional p53 is not the only determinant factor for radioresistance of WTK1.