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The effect of particle therapy on tumour angiogenesis

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, which remains the leading cause of cancer-related mortality worldwide. Anti-angiogenic drugs, such as recombinant endostatin (RE), have been intensely studied to inhibit tumour angiogenesis in NSCLC, leading to mixed and often disappointing results in (pre)clinical trials. Despite the fact that previous studies revealed distinct differences in angiogenic effects between proton and photon irradiation, combination treatments with RE and proton therapy remain underexplored.

Therefore, this in vitro study investigates the up- and down-regulation of angiogenic processes in three cells lines that are relevant to the NSCLC tumour microenvironment (human lung fibroblasts (HLF), Human Umbilical vein endothelial cells (HUVEC) and lung adenocarcinoma (A549) cells) after low and high doses of 230 MeV proton (Trento Proton Therapy Centre) and photon irradiation (NRF iThemba LABS), combined with RE. In addition, the impact of the combination treatment is evaluated on cell migration, tubulogenesis, invasion and cell proliferation. Thus far data analysis from these experiments has revealed that cell migration appears to be slowed down in a radiation dose dependent manner. Protons slowed the migration of A549 cells down by approximately 40% compared to X-rays at high doses. The analyses on the HUVEC migration data are currently being finalized. No significant differences ($p<0.05$) were seen in the invasion of HUVECs after proton and photon exposure. Similarly, minimal apoptotic differences were seen in all three cell types exposed to protons and photons ($p>0.05$). In these instances, RE yielded no greater cell killing or inhibitory benefit on cell invasion. Proliferation assays (MTT) showed a dose dependent decrease in cell proliferation after proton and photon exposure. No significant effect of RE could be observed in all three cell lines. Tubulogenesis data from photon experiments are being finalized, but the tubulogenesis proton data showed a significant effect of RE on HUVEC tube formation ($p=0.00025$). Additionally, protons alone also significantly inhibited tube formation ($p<0.05$) however, this effect is not dose dependent. Protein expression analysis is currently under way and will be presented at the 2nd Workshop "Trento Proton Beam Line Facility".

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