Improving radiotherapy via novel drug-radiation interactions.

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The prognosis of patients with pancreatic cancer is very poor, with an approximate 5-year survival rate of 4-5%. There is, therefore, an urgent need to develop new therapeutic strategies. Early stage invasive breast cancer patients are commonly treated using breast conserving surgery (BCS) and radiotherapy (R/T). Although treatment is often effective, and prognosis significantly better than with pancreatic cancer, a significant proportion of individuals will develop local recurrence (LR), indicating a failure of primary therapy. A variety of clinico-pathological parameters are associated with risk of LR such as age, nodal status, tumour size, grade and vascular invasion. The rate of LR is particularly high in women under the age of 40 and although LR rates can be decreased by use of additional R/T, the associated LR rate is still, unfortunately, high. The reason why young women have such a worse prognosis remains unclear. Risk factors are used to assist patient stratification into low and high risk to determine initial treatment decisions but currently there is no method of identifying those patients at high risk of developing LR after therapy. There is, therefore, a need for biomarkers of response to allow more effective treatment, particularly as survival after relapse is poor, especially if diagnosed within 2 years after BCS.

The cytotoxicity of conventional R/T, is primarily mediated via the production of reactive oxygen species (ROS) and free radicals, that leads to increased oxidative stress, lipid and protein peroxidation, DNA damage and cell death. Redox buffering systems, signalling pathways and DNA repair systems are often deregulated in cancer cells and can interfere with the effectiveness of R/T. A number of studies have shown, in vitro, that the regulation of R/T response is complex with a number of pathways being interlinked. This project will examine expression of specific proteins in cancer, concentrating on breast and pancreatic cancer, via histopathology based techniques and correlate response to R/T. It will also, using a variety of in vitro systems (2D and novel 3D), use agents to modify important, clinically relevant, targets to improve therapeutic response. As hypoxia is a major contributor to radioresistance drug efficacy will be examined under both normoxic and hypoxic conditions (single agent and combined with radiation).

Please **email a CV with a covering letter** to Dr Stewart Martin (stewart.martin@nottingham.ac.uk), who can also supply more information to interested parties.