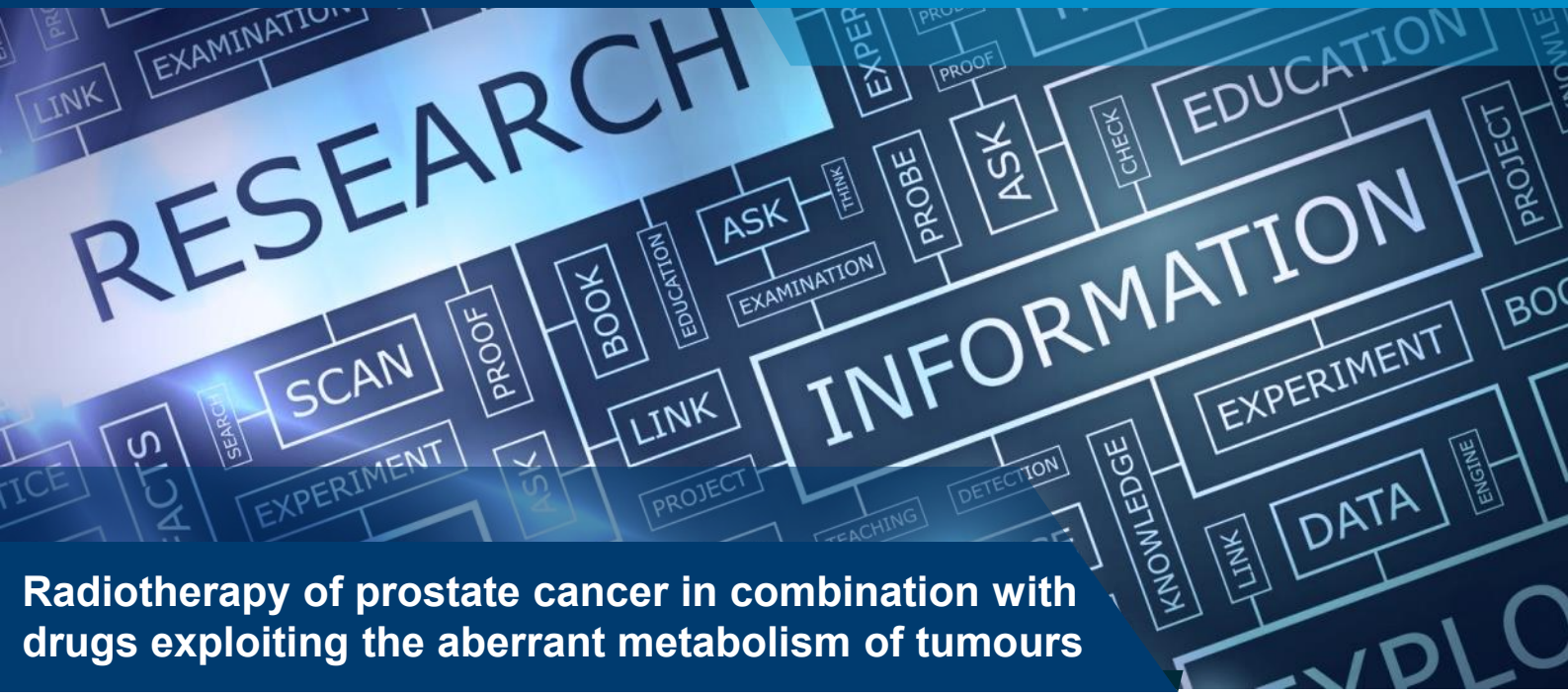
CHIEF SCIENTIST OFFICE

CODE: TCS/16/38

RESEARCH PROJECT BRIEFING



Radiotherapy of prostate cancer in combination with drugs exploiting the aberrant metabolism of tumours

AIMS

Prostate cancer affects 1 in 8 men in Scotland and around one third receive treatment with radiation (radiotherapy). It is believed that the effectiveness of radiotherapy will be increased by combining it with agents which sensitise cancer cells, but not normal cells, to radiation. One way to sensitise these cells is through the use of drugs affecting the abnormal metabolism of tumours, which contributes to their aggressiveness and resistance to therapy.

The aim of this project was use drugs to target the abnormal metabolic properties of cancer cells and demonstrate how these drugs interact with radiation in order to enhance the selective killing of cancer cells by radiotherapy.

KEY FINDINGS

- Glucose is an important source of energy in all cells, and glucose uptake and utilisation is increased in cancer cells where it provides energy for growth, survival and spreading. We showed that preventing prostate cancer cells from utilising glucose makes these cells more sensitive to radiation-induced killing.
- The metabolism of tumours is regulated by many cell signalling pathways. We demonstrated that a drug which activates one signalling pathway which regulates metabolism, called AMPK, has the potential to target metabolically active cancers in combination with radiotherapy.
- Synthesis of fatty acids is increased in cancer cells, and they are used for signalling and incorporation into cell membranes during proliferation. We have previously shown that inhibiting production of fatty acids sensitised cancer cells to radiation. It has recently become apparent that cancer cells also take up increased levels of fatty acids from their surrounding environment and we have now found that blocking fatty acid uptake increased the cancer-killing effectiveness and radiosensitising activity of these drugs.

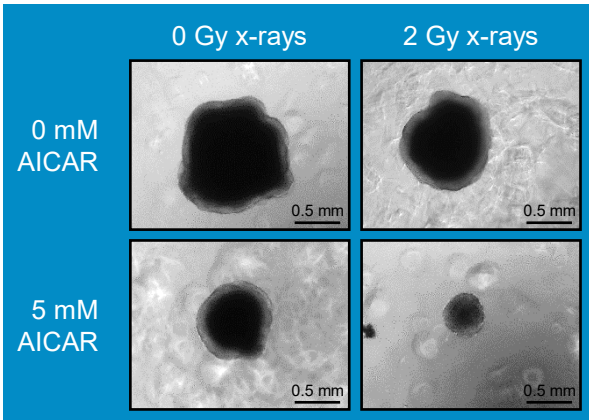
WHAT DID THE STUDY INVOLVE?

This study involved determining which features of cancer cell metabolism were most likely to be involved in their response to radiation. Drugs affecting these features were then tested as single agents to determine how they affect the growth, survival, metabolism, and signalling of cells derived from prostate cancers. The drugs were then investigated in combination with x-rays to assess their ability to sensitise the cells to radiation. Combinations which were effective were further assessed in order to determine the mechanisms of interaction and sensitisation, including their effects on cell cycle and expression of proteins involved in cell death and uptake of fatty acids. A three-dimensional tumour model was also used to better represent small tumour metastases which were the target of the therapies being evaluated in this study.

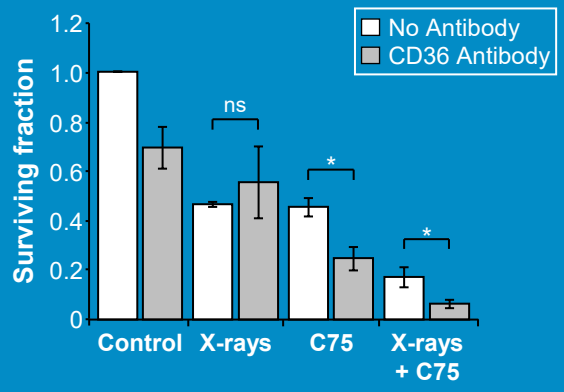
WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Results generated in this study demonstrate that drugs affecting the abnormal metabolic properties of prostate cancer cells have potential to enhance the effectiveness of radiotherapy. We have shown that combining radiation with drugs which prevent glucose utilisation, regulate metabolic signalling, block fatty acid synthesis and uptake are effective means of increasing the radiation-induced cell kill and tumour growth delay. As metabolic re-programming is a common feature of many tumour types, it is likely that this method of radiosensitising will be applicable to other cancer types.

In the next step, these drugs should be tested in animal models in order to determine the most effective means of administration of therapies and whether non-tumour cells are affected. The drugs should also be evaluated in combination with targeted radiotherapy for prostate cancer. This should include radiopharmaceuticals which seek and bind to prostate-specific membrane antigen (PSMA), which is expressed in advanced disease, thus delivering radiation directly to the tumour site.



Images of a three-dimensional prostate tumour model 21 days after treatment with x-rays, AICAR (a drug which activates the energy regulating AMPK pathway) or a combination of both. Combination treatment of AICAR with x-rays had the greatest effect on tumour growth delay.



Survival of prostate cancer cells after treatment with x-rays or drug (C75, which inhibits fatty acid production) in the absence or presence of an antibody (anti-CD36, which blocks uptake of fatty acid). The antibody enhanced the cancer killing effect of radiation and drug. * = significant difference, ns = no significant difference.

WHAT IMPACT COULD THE FINDINGS HAVE?

- Our findings highlight the ability of drugs targeting the abnormal properties of cancer cells to enhance the effectiveness of commonly applied radiotherapy of prostate cancer.
- Drugs used in this study enhanced the cancer killing properties of radiation, thus increasing the likelihood of successful treatment of patients suffering from prostate and perhaps other forms of cancer.
- By describing the mechanisms by which radiation and radiosensitising drugs interact, this is likely to lead to development of improved formulations of drugs and combination therapies with more selective activities, thus reducing unwanted side-effects in patients.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Data from this project was presented at the Scottish Radiotherapy Research Forum, November 2017, and the National Cancer Research Institute (NCRI) Cancer Conference, November 2018.

The following manuscripts were published in peer-reviewed open access journals:

Nile DL, Rae C, Nixon C, Gaze MN, Mairs RJ. The suppression of DNA repair induced by PARP-1 inhibitors rucaparib and olaparib in combination with the radiopharmaceutical ^{131}I-MIBG in noradrenaline transporter expressing xenograft tumours. Cancer Therapy & Oncol Int J. 2018:10;555787.

Rae C, Sey CHC, Mairs RJ. Radiosensitization of prostate cancer cells by 2-deoxyglucose. Madridge J Oncogen. 2018;2:30-34.

Rae C, Mairs RJ. AMPK activation by AICAR sensitizes prostate cancer cells to radiotherapy. Oncotarget 2019:10;749-759.

Rae C, Fragkoulis GI, Chalmers AJ. The cytotoxicity and radiosensitizing activity of fatty acid synthase inhibitor C75 is enhanced by blocking fatty acid uptake in prostate cancer cells. Submitted for publication.

CONCLUSION

Using drugs which target the abnormal metabolic properties of cancer cells has the potential to increase the effectiveness of radiotherapy. These drugs and combinations are likely to prevent the growth, spread and survival of tumours while non-tumour cells remain unaffected.

RESEARCH TEAM & CONTACT

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This project into radiotherapy of prostate cancer received £295,710 in funding from the CSO and ran from 1st April 2017 until 31st December 2019.