First in-human clinical translation of oxygen-enhanced MRI onto an MR-linac

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What was your motivation for initiating this study?

Hypoxia occurs in most solid tumours. This is important because the presence of hypoxia and its extent can reduce the effectiveness of radiotherapy, and lead to poor treatment outcomes. The radiobiology community knows that measurements of tumour hypoxia provide both prognostic and predictive biomarker information. However, there are no reliable, widely available, non-invasive tests that can evaluate tumour hypoxia; current methods are either invasive or require expensive and difficult-to-acquire components, such as positron emission tomography radiotracers.

We have developed a technique called oxygen-enhanced MRI (OE-MRI) over the last 15 years in Manchester (at the University of Manchester and The Christie Hospital) and London (at the Institute of Cancer Research and University College London). Briefly, the OE-MRI technique involves patients breathing 100% O2 gas during an MRI scan. This enables us to distinguish well-oxygenated tissues from those with low oxygen levels that are hypoxic. We have validated this technique previously and shown its use in the creation of response biomarkers in patients with lung cancer. However, the real game-changer would be the use of the technique to guide biologically adaptive radiotherapy, and so we have evaluated the potential of OE-MRI to do just this, in patients with head and neck (H&N) cancer, who were treated on an MR-linear accelerator (linac) system.

What is the most important finding of your study?

We worked hard to translate the OE-MRI technique onto the MR-linac system, which involved studies on phantoms and healthy volunteers. This work showed three key outputs in H&N patients. Firstly, we have shown that the technique is feasible – patients tolerate it well and we can detect similar signals to those seen on diagnostic machines. Secondly, we have shown that the signals can produce repeatable biomarkers – an important step for the development of useful biomarker tools. Thirdly, we have shown that OE-MRI biomarkers can detect changes in hypoxia that are induced by radiotherapy treatments delivered on the MR-linac system.

What are the implications of this research?

This first-in-human study shows the enormous potential of OE-MRI to make biologically adaptive radiotherapy a reality on an MR-linac system. Next, it will be important to replicate these findings elsewhere and then begin translation of the technique to different institutions and to those in different countries. It is early days, but if the next steps are successful, this imaging technique could begin to achieve the ultimate aim of any such scientific development, which is to make a difference to patients' lives.

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Real-world inverse planning for breast cancer: automatic versus manual plan in a large multi-centre Italian study

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What was your motivation for initiating this study?

The technological evolution in the last 20 years of machines that are dedicated to radiotherapy has led to growing demand from radiation oncologists for intensity-modulated treatments. Of all the patients that have benefited from this evolution, breast-cancer patients are probably the last, given the consolidated tradition of treatments with tangential fields with the manually planned field-in-field technique. However, also for this type of treatment, the demands in terms of sparing organs at risk as well as coverage and homogeneity within the target have made it challenging to design protocols that comply with the recommended clinical goals. Therefore, high-quality, intensity-modulated treatments are increasingly required. We hypothesised that automated planning, which could be achieved with the use of our autoplanning algorithm (guided planning solution, GPS), could be of great help in this context. To investigate this, GPS was used to generate automatically treatment plans for 240 patients in 24 Italian centres, and these plans were compared with clinically delivered, manually generated plans through the use of both dosimetric indices and blind clinician plan comparisons. The data of the patients who were included showed large variations in disease involvement (left and right side, lymph nodes or no lymph nodes, boost or not), delivery machine (linear accelerator or tomotherapy machine) and planning technique (volumetric modulated arc therapy or static, intensity-modulated radiotherapy).

What is the most important finding of your study?

The clinicians who were involved in the study preferred the fully automatic plans for 120 patients (50%) and the clinical plans for 96 patients (40%), scoring plan parity for 24 patients (10%). In the latter cases, the plans reached our initial goal of equivalence between manual and automatic plans even without any centre-specific GPS tuning. Based on dosimetric indices, the automatically generated plans were superior overall. Among centres, a large amount of heterogeneity was observed regarding the superiority of automated planning; in some centres, autoplanning was superior for the vast majority of patients, while in others, most of the manual plans were rated as superior. It is possible that the configuration of GPS was better suited to some centres than to others, and this indicates that there is room for improvement of autoplanning through the performance of centre-specific tuning of GPS.

What are the implications of this research?

Globally, the study showed that automatic planning for breast-cancer treatment can be used to reduce treatment planning workload vastly while keeping the quality of the treatment plans high.

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Is Monte Carlo uncertainty a good predictor of the need for manual adjustments of deep-learning contours?

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What was your motivation for initiating this study?

Deep learning (DL) has been proven to be highly efficient in many computer vision tasks, including the delineation of contours of organs at risk (OARs) in radiotherapy. OAR contouring takes time in a clinical setting and DL technology has been shown to reduce that time. However, clinical edits are still required to correct some of the DL predictions prior to the calculation of a dose plan for the patient.

Moreover, generally, models do not provide information regarding regions that are difficult to contour and regarding which the model might be uncertain. Previous studies suggest that regions with high model uncertainty might require increased attention and more manual editing than regions where models are certain.

In this study, we aimed to assess whether the amount of manual editing of automatically contoured OARs in routine clinical practice could be predicted by the uncertainty of the auto-contouring system computed using Monte Carlo dropout.

What is the most important finding of your study?

We found that the uncertainty of our DL models and the amount of contour edits were weakly correlated. There were important differences between the correlation scores for the different structures we analysed, namely the heart and the oesophagus.

What are the implications of this research?

Monte Carlo dropout has been used in previous studies to estimate contour uncertainty and as a predictor of contour errors for some structures. However, we found weak correlations between contour edits and model uncertainty, which suggested that the Monte Carlo uncertainty computed for our model was not a strong predictor of manual adjustments of contours for the two structures we analysed.

We showed that in some cases this method might not be a suitable approach to highlight contour regions that might need a clinician's attention. However, this finding may depend on the loss function that was used to train the model; therefore, the finding that this is not a way forward is not conclusive.

Our research is a step toward understanding how model uncertainty and contour quality are related, and how to build better-calibrated models, and it highlights the need for further research.

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TCP predictions of an automated dose painting strategy based on FDG and FMISO PET imaging

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What was your motivation for initiating this study?

Solid malignant tumours, such as those that occur in head and neck (H&N) cancer, may contain oxygen-deprived sub-regions due to an impaired blood supply and impaired oxygen consumption in the cells. Tumour hypoxia is considered one of the main determinants of cell radio-resistance and among the leading causes of radio(chemo)therapy failure in H&N cancer. Indeed, in half the patients who have locally advanced H&N cancer, recurrences occur within two years of treatment, many of which develop within the high-dose tumour bed of radiotherapy. Spatial-dose modulation through dose escalation in the radiation-resistant sub-regions appears to be a promising solution to this problem, and we wanted to explore this possibility with the aim of improving patients' poor prognoses.

Functional imaging with positron emission tomography (PET) could offer a way to characterise quantitatively the microenvironment. This information could be used to determine the dose-escalation level that is required to counteract cell radio-resistance. However, researchers debate how this dose-escalation level can best be determined based on the imaging information.

Our group has previously proposed a method that involves passage through all the steps that lead to the determination of the required dose escalation level with a dose painting-by-contours approach. This approach is based on 18F-fluoromisonidazole (FMISO) PET imaging. In this study, we aimed to develop this method further. We envisaged a way to combine synergistically the information extracted from combined PET images that are acquired with different radiotracers (i.e. 18F-fluorodeoxyglucose (FDG) PET and FMISO PET) to create a personalised treatment that was tailored to the biological and functional characteristics of each patient. Furthermore, we wanted to understand whether the theorised, biologically-guided dose painting prescription would be clinically feasible in terms of fulfilling the clinical goals of target coverage and sparing the organs at risk (OARs). Finally, we wanted to evaluate whether the treatment plans would be acceptable from a radiobiological standpoint through the assessment of the resulting tumour control probability (TCP) of the planned dose distribution and through consideration of the underlying radiosensitivity, which was extracted from the PET images.

As the steps in the process were numerous and the number of patients that were considered was relatively large, to standardise the whole process and make it user-independent we were interested in the development of an automated pipeline. This automated system would have, as sole input, the FDG and FMISO PET images, the planning computed tomography and the contoured structures, and it could be designed to perform all the steps from the dose-prescription determination to the final TCP assessment.

What is the most important finding of your study?

It was shown that the proposed solution, based on functional imaging, to boost doses that would target hypoxic regions and simultaneously would take into account the heterogeneous density of clonogenic cells in the tumour was clinically feasible, in terms of target coverage and OAR dose constraints. Dose escalation levels were in the range of other empirical dose sculpting studies that have been published. The radiobiological evaluation of the treatment plans with consideration of the underlying radiosensitivity extracted from PET images has predicted high tumour control probability levels for all the considered targets.

What are the implications of this research?

There are several potential clinical implications and applications. First, the proposed method can provide initial information on two key features of tumours that are related to the treatment outcome, namely the density of clonogenic cells and their radiosensitivity. This information enables the determination of the dose levels that would be necessary for personalised treatment that was tailored to the biological and functional characteristics of each patient.

The method could be further applied to subsequent examinations that are performed early during the treatment and it could be used to determine the need for treatment adaptation, taking into account the delivered dose distributions.

Furthermore, automated planning will make it possible to handle a large number of patients as time and resources in the clinic will be saved. It will also facilitate inter-centre comparisons.

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Novel optimisation functions designed for re-irradiation treatment planning

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What was your motivation for initiating this study?

Re-irradiation for locoregional recurrence or second cancers after previous radiotherapy is a promising treatment technique for use at a large variety of treatment sites. Treatment planning of re-irradiation cases is often more complex than standard planning, as the exact irradiation sites of organs at risk and the amount of radiation they received during previous treatment must be considered. Despite this, there have been very few technical developments to support treatment-plan optimisation in the re-irradiation setting; instead, it is often assumed that the procedure involves optimisation of a normal treatment plan, with a few extra considerations during evaluation of the final plan. This study aimed to construct well-posed optimisation functions that were designed for re-irradiation planning in a research version of RayStation v11A, with the properties listed here:

- The functions use the total equivalent dose in 2Gy fractions (EQD2) with organ-specific α/β, where the previously delivered EQD2 is mapped voxelwise to the re-irradiation CT using deformable registrations.
- The functions' EQD2 level for penalisation during optimisation is dependent voxelwise on the previously delivered EQD2.
- The functions enable the delivery of a user-specified minimum EQD2 that is unpenalised in the re-irradiation treatment. This property is only active for voxels in which the normal tissue threshold EQD2 level was already exceeded in previous treatments.
- The functions account for tissue recovery per radiotherapy course using user-specified recovery coefficients in the interval [0, 1].
- The functions enable the delivery of a user-specified EQD2 to an organ if the voxelwise EQD2 mapping from previous treatments is deemed to be too uncertain for use in optimisation due to large anatomical changes.
- The functions provide the user with visual feedback of the delivered and total EQD2 during optimisation.

What is the most important finding of your study?

This proof-of-concept study showed that the optimisation functions adjusted according to the list above could be implemented and used in a research version of a commercial treatment planning system. The quality of the re-irradiation plan was improved through the introduction of these novel functions, especially with respect to the target homogeneity and conformity when the re-irradiation target overlapped with regions of high delivered EQD2, as indicated in Figure 1. The first use of the functions for retrospective re-irradiation planning indicated advantages in terms of speed, flexibility, and general confidence in the optimisation; for instance, no trawling through the optimisation functions was required to identify whether a high function value was genuinely optimisation-dependent or because the dose had already been exceeded in previous treatments. The functions are undergoing further extensive evaluation in the support tool for re-irradiation decisions guided by radiobiology (STRIDeR) project. Results from re-planning that had used these novel functions in a cohort of patients treated for pelvic re-irradiation were presented at ESTRO 2022 by Dr Louise Murray (abstract OC-0126) and have recently been submitted for publication. We are currently extending this work to brain and lung cancers.

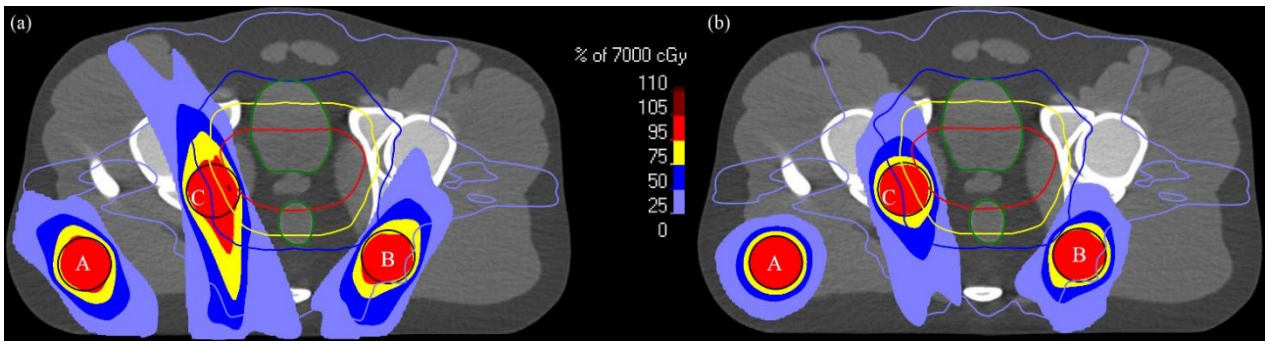

Figure 1. Superimposed EQD2 distributions (α/β=3Gy for all voxels) of three re-irradiation plans for scenarios A, B and C, respectively. The re-irradiation EQD2 is shown as colour wash (>1750cGy) together with the iso-EQD2 lines of the previously delivered EQD2. Panel (a) shows EQD2 distributions using the standard optimisation functions and panel (b) using the novel functions. The contours of the three planning target volumes for fictional re-irradiations are marked in black and the contours of the bladder and rectum in green.

What are the implications of this research?

Re-irradiation planning is often complex as well as time- and resource-intensive, and planners would benefit from dedicated technical development of this task. Functionality, such as the novel optimisation functions proposed here, is a first step towards thorough consideration of previous radiotherapy treatments and has the potential to be instrumental in the future of re-irradiation planning by improving plan quality and reducing the overall clinical burden of re-irradiation planning.

Beyond re-irradiation, some design features of the proposed optimisation functions could be relevant in other radiotherapy settings in which multiple courses or treatment modalities with different fractionation schedules must be considered together. This includes co-optimisation of brachytherapy and external radiotherapy, other multimodality treatments such as proton-photon therapy, and sequential boost treatments.

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Enhanced RBE for late compared to early normal tissue damage in vivo

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What was your motivation for initiating this study?

My dedication to proton radiobiological research can be divided into many categories. Firstly, it is an absolute privilege to work with state-of-the-art technology that has so much potential to affect the quality of the lives of cancer patients positively. Secondly, I think it is of utmost importance that in-vivo research is quantitatively optimised to improve all aspects and the potential of proton radiotherapy. Thirdly, it is magnificent how two groups of professionals, physicists and biologists, can come together to work towards the same goal; one in which millimetres of precision and laws are fundamental and in which variations in physiology are inevitable. Finally (but not least), it is important to use the information we have and act on it. Relative biological effectiveness (RBE) is a hot topic of discussion, and we know that RBE is not constant for all tissues, doses/fractions, endpoints, linear energy transfer and so on. Now we must use this knowledge to research each fundamental step in a way that can be translated into clinical relevance.

What is the most important finding of your study?

We irradiated a lot of mice legs in the centre of a 3cm spread-out Bragg peak with a panel of single doses of either pencil-beam scanning protons or 6MV photons. Afterwards, we analysed the development of acute skin damage and fibrosis in the mice for up to a year after treatment. We found that the ED50 (the dose at which 50% of the mice were affected) for fibrosis was lower for protons compared with photons. In this study, we calculated an RBE of 1.05 for acute damage and 1.28 for fibrosis. These results suggested that the RBE for fibrosis was higher than that for acute skin damage.

Another important finding was our discovery of the complexity of performing in-vivo radiobiological research. At the moment, we are still establishing whether joint fibrosis is a good RBE model for late effects. This is why we are repeating these experiments with single doses and with a fractionated dose scheme.

What are the implications of this research?

The results from this study suggest that there may be a higher RBE for late effects compared with that for early effects in vivo. This has been indicated by a variety of in vitro studies. Of course, more in vivo studies that investigate the factors that affect the RBE are required, but considerations regarding how to take account of the varying RBE in the clinic are emerging.

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