Theragnostic imaging for radiation oncology: dose-painting by numbers

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Theragnostic imaging for radiation oncology is the use of molecular and functional imaging to prescribe the distribution of radiation in four dimensions—the three dimensions of space plus time—of radiotherapy alone or combined with other treatment modalities in an individual patient. Several new imaging targets for positron-emission tomography, single-photon-emission CT, and magnetic resonance spectroscopy allow variations in microenvironmental or cellular phenotypes that modulate the effect of radiation to be mapped in three dimensions. Dose-painting by numbers is a strategy by which the dose distribution delivered by inverse planned intensity-modulated radiotherapy is prescribed in four dimensions. This approach will revolutionise the way that radiotherapy is prescribed and planned and, at least in theory, will improve the therapeutic outcome in terms of local tumour control and side-effects to unaffected tissue.

Diagnostic imaging, from radiographs to CT, has been used throughout the history of radiotherapy to define the site to which the radiation should be delivered for patients with cancer. Theragnostic imaging is a method by which the radiation dose can be delivered in the four dimensions of space and time to achieve the optimum outcome after radiotherapy.

What does theragnostic imaging mean? From the Greek words therapeia (to treat medically) and gnosis (knowledge) theragnostic imaging refers to the use of information from medical images to determine how to treat individual patients. Rapid technological and scientific progress in molecular and functional imaging, in radiotherapy planning and delivery, and in clinical radiation biology is making radiotherapy guided by theragnostic imaging a realistic goal.

Molecular imaging is providing new research opportunities in the preclinical and clinical development of new therapies and in the study of small-animal models of human disease.1,2 To take full advantage of the curative potential of modern, high-precision radiotherapy, high-quality imaging is needed for identification of target volumes. Conversely, optimum use of the spatial information provided by molecular imaging requires radiotherapy; radiation is a therapeutic agent that can be modulated in the four dimensions of space and time, and the dose can be precisely defined to produce a specified local effect of a given magnitude. This review explores the latter perspective.

Intensity-modulated radiotherapy (IMRT)

One of the key features underpinning this research is the theoretical and technological development of IMRT and inverse treatment planning (figure 1).1 IMRT is the administration of non-uniform intensities of radiation (or photon fluence profiles) to patients as a way to create a specified, non-uniform absorbed dose distribution. This approach has become feasible as a result of the increased computer control of linear accelerators used for radiotherapy during the past few decades, in combination with the introduction and refinement of the multileaf collimator—a computer-controlled device, typically consisting of 20 or more thin collimator plates. The multileaf collimator is used to create irregularly shaped fields that conform to the target volume and modulate the radiation-beam intensity.

Traditionally, radiotherapy dose plans have been forward planned—ie, a small number of radiation-beam portals are selected on the basis of the location of the target volume and any healthy structures that need to be avoided. Each beam is assigned a weight that determines
its relative contribution to the total absorbed dose. A computer program, commonly operating on a set of CT images covering the anatomical region irradiated, is then used to calculate the dose distribution, and the irradiated dose from each beam is then normalised to achieve the prescribed dose in the target volume. Inverse treatment planning, by contrast, takes a prescribed dose distribution as the starting point and uses a mathematical optimisation algorithm to identify a set of beam intensities that approximates the prescribed dose distribution as closely as possible. Typically, the dose distribution is specified as a desired homogeneous dose in the clinical target volume plus several dose-volume constraints for the dose delivered to crucial healthy structures or organs at risk in the surrounding volume of healthy tissue.

IMRT and inverse treatment planning have provided new methods to deliver non-uniform or shaped dose distributions that are almost impossible to deliver with conventional static radiation beams. Exploration of the therapeutic potential of non-uniform dose distributions is a challenge for preclinical and clinical radiation research.

Theragnostic imaging for radiation oncology
Theragnostic imaging for radiation oncology aims to map in three dimensions the distribution of a tumour, tissue, or functional feature, and to provide information about the clinical response of tumours or healthy tissues to radiotherapy. In solid tumours, the aim is to provide images of phenotypic or microenvironmental characteristics known to affect the clinical response. Most research has been based on imaging techniques that use radionuclide-labelled compounds: single-photon-emission CT (SPECT) or positron-emission tomography (PET). However, dynamic contrast-enhanced magnetic resonance (MR) imaging and spectroscopy also have much potential. Research has also focused on radiobiological mechanisms that affect—or are suspected to affect—the outcome after radiotherapy and for which an appropriate imaging surrogate exists.

Tumour burden and clonogen density
At the most fundamental level, molecular imaging has the potential to define the real target volume—the volume consisting of malignant cells that need irradiation to a therapeutic dose to control the disease.\(^7\) One example is the use of proton MR spectroscopy to discriminate between benign prostate hyperplasia and malignant tissue,\(^7\) and the application of this information in the planning of conformal transperineal implantation of therapeutic iodine-125 seeds in the prostate.\(^7\)

PET scanning with 18-fluorodeoxyglucose is commonly used as a proxy for tumour burden and has been intensively investigated for staging of various solid cancers. However, \(^{18}F\)FDG is a hexokinase substrate indicative of glucose metabolism and is an indirect probe that reflects the activity of target enzymes rather than their concentration.\(^2\) Bos and colleagues\(^7\) investigated the correlation between \(^{18}F\)FDG activity (assessed visually on an arbitrary four-point scale by three observers) and various histopathological and immunohistochemical markers in breast tumours.\(^7\) They concluded that \(^{18}F\)FDG uptake is a function of: the microvasculature for delivery of nutrients; SLC2A1 (GLUT1) for transport of \(^{18}F\)FDG into cells; hexokinase for entry of \(^{18}F\)FDG into glycolysis; and the number of tumour cells in the volume, the proliferation rate, number of lymphocytes, and hypoxia-inducible factor 1α (HIF1α) for upregulation of SLC2A1.

Tumour hypoxia
Low partial oxygen pressure in human tumours as measured with polarographic microelectrodes is associated with poor outcome in patients receiving radiotherapy.\(^4\) Although tumour hypoxia is associated with malignant progression and a poor prognosis after other treatment modalities as well as after radiotherapy,\(^8\) the idea that hypoxic regions in solid tumours constitute a resistance problem for radiotherapy seems reasonable. One strategy to resolve this problem is to boost the radiation dose to hypoxic regions of the tumour, provided that these regions can be imaged in three dimensions. Several radionuclide-labelled compounds have shown preferential uptake or long-lasting retention in hypoxic tumour regions in clinical and preclinical studies. One class of these agents is compounds that contain a 2-nitroimidazole group (eg, fluoride-18-misonidazole, iodide-123-iodoazomycin arabinoside, and βD-111-Iodoazomycin galactopyranoside. Another class of compounds includes copper-62-labelled diacetyl-bis(N(4)-methylthiosemicarbazone) and technetium-99m-labelled 4,9-diaza-3,3,10,10-tetramethyldecane-2,11-dione dioxime. The mechanism of action of these agents is not completely understood, but they seem to be bioreducible compounds retained in regions with hypoxic cells with intact mitochondria. One difficulty with all of these agents is that the signal-to-background ratio is poor. The search for better markers continues.\(^9\)

Dynamic contrast-enhanced MR imaging visualises differences between tissues in the behaviour of a gadolinium-based contrast medium.\(^11\) One example of this technique is BOLD (blood-oxygen-level dependent) imaging, which is being investigated as an indirect method for mapping of hypoxic regions in tumours.\(^11\) Work in progress has shown a significant correlation between pimonidazole immunostaining of coregistered histological sections and the value of R2*, a relaxation rate that is sensitive to deoxyhaemoglobin concentration, derived from BOLD.

Hypoxia causes activation of several cellular response pathways,\(^1\) and one of the most important of these is regulated by HIF1α. Collaborative work by Harris’s group at Oxford University and our group at the Gray
Cancer Institute, suggests that the outcome after definitive radiotherapy in patients with squamous-cell carcinoma of the head and neck depends on the exact hypoxic pathways activated in a tumour. If this finding is correct, hypoxic radioresistance is much more than just the absence of oxygen. Again, the requirements for molecular imaging would be changed. Serganova and colleagues’ study on imaging of HIF1α transcriptional activity in tumours in mice has also shown that it is feasible to map the activation of a specific pathway by use of PET.

**Tumour proliferation**

Several randomised controlled trials have provided evidence on the importance of overall treatment time, especially in squamous-cell carcinoma of the head and neck, with evidence from other tumour sites being less strong. This feature has been linked to rapid tumour-cell proliferation during radiotherapy as a resistance mechanism in fractionated radiotherapy. Thus, there is a rationale for theragnostic imaging of tumour-cell proliferation, and research on this topic has focused on radionuclide-labelled nucleosides or aminoacids as possible imaging agents. Several studies have looked at radionuclide-labelled deoxyuridines, but the signal-to-noise ratio is poor, owing to the rapid degradation of these compounds in vivo. This problem was largely solved by the development and clinical testing of [18F]-3′-deoxy-3′-fluorothymidine (FLT). Two clinical studies found encouraging correlations between local FLT-specific uptake values and the Ki-67 labelling index detected in biopsy samples by immunohistochemistry. Ki-67 is a protein expressed in all phases of the cell cycle but not in resting cells; it is therefore used widely to measure cell proliferation. Despite these encouraging results, a study in animals showed limited incorporation of [18F]-FLT into DNA relative to background and further validation studies seem warranted.

**New imaging targets**

Many of the new imaging targets under investigation are of immediate interest for theragnostic imaging for radiation oncology. Examples are cyclin D (which is overexpressed in many cases of squamous-cell carcinoma of the head and neck, for example, for assessment of tumour-cell proliferation), and mitogen-activated protein kinase for measurement of activation of the RAS-signalling pathway. Epidermal growth factor receptor (EGFR) is expressed in many tumours of epithelial origin and is implicated in several processes associated with the malignant phenotype. Clinical studies have shown a relation between EGFR expression and the outcome of definitive radiotherapy in cancer of the head and neck. Our work has suggested that EGFR expression is directly linked to the time factor in radiotherapy, making this an interesting target for theragnostic imaging. Regions with high EGFR expression have a large capacity for accelerated repopulation, and these regions would probably benefit from accelerated radiotherapy (ie, delivered in a shorter overall time).

With the current advances in molecular risk profiling and the search for fingerprints of malignant phenotypes that are sensitive to a specific type of modified radiotherapy, many new theragnostic imaging targets are likely to be identified in the coming years.

**Functional imaging of crucial healthy tissues**

Optimisation of the therapeutic ratio of IMRT must take into account the dose distribution in healthy tissue as well as tumours. The dose distribution to healthy tissues can be determined through placement of simple constraints on the clinically acceptable maximum dose to an organ at risk or by specification of a single variable of the dose-volume histogram, such as the fraction of the total organ volume receiving a dose that exceeds a threshold value. However, just as with tumours, the full four-dimensional dose distribution should ideally be constrained. One interesting idea is to lower the risk of side-effects by reducing the dose absorbed in regions of an organ that have special functional importance. These regions could be identified by use of functional imaging. Seppenwoolde and colleagues incorporated lung-perfusion information from SPECT directly into the radiotherapy-plan optimisation for patients with medically inoperable non-small-cell lung cancer. The researchers showed that this procedure increased the relative weights of radiation beams passing through hypoperfused lung regions and reduced the predicted risk of side-effects to healthy tissue compared with conventionally optimised treatment plans.

**From dose-painting to dose-painting by numbers**

Dose-painting was the term coined by Ling and colleagues in their review of image-guided radiotherapy. The idea was to visualise tumour subvolumes with a potential resistance problem and to paint some additional dose onto that volume. This notion was applied in a study by Chao and co-workers, who identified regions with pronounced retention of [62Cu(II)-diacetyl-bis(N(4)-methylthiosemicarbazone)] on a PET scan of a patient with a squamous-cell carcinoma of the head and neck. In a planning study, they showed that 80 Gy could be delivered in 35 fractions to the hypoxic target volume, with 70 Gy in 35 fractions delivered to the rest of the clinical target volume. By use of standard bioeffect modelling to adjust for the slightly higher dose per fraction in the hypoxic target volume, the biological equivalent dose to this volume is about 82 Gy in 2 Gy per fraction. The researchers used dose-volume histograms to show that this dose distribution could be planned and delivered by means of inverse-planned IMRT.
Although much research is needed before dose-painting can be introduced into clinical practice, the issue is whether this step is far enough. The problem with discrete volumes is that they are binary: voxels are either inside or outside the volume. However, the clinical and biological reality is that there are gradients of oxygen tension or three-dimensional distributions of the density of radioresistant cellular phenotypes. This discrepancy led me to propose a more radical change in the way theragnostic imaging can be used in prescribing four-dimensional dose distributions—dose-painting by numbers. Named after the painting-by-numbers activities in children’s activity books, the principle is illustrated in figure 2 in a patient with localised prostate cancer, a tumour type characterised by regions with substantial hypoxia. The clinical target volume, typically defined on a CT or MR scan, is transferred to the BOLD MR scan, and an intensity histogram is calculated for the marker of hypoxia. These intensities will correspond to voxel oxygenation status covering the full range from normal to anoxic. The non-linear scale indicates the prescribed dose as a function of marker intensity. A lower boundary of 70 Gy ensures that no part of the tumour will have a prescribed dose lower than the standard prescription. An upper boundary of 85 Gy is defined to limit the dose to any structure in the patient, and this value is repeated in figure 2 to indicate that it is a ceiling on the prescribed dose. Then, all of the prescribed doses on a pixel-by-pixel basis are used to specify the desired dose distribution in inverse-treatment-planning software. The technical feasibility of this procedure was shown by Alber and colleagues, who modified their inverse-planning software to implement dose-painting by numbers on the basis of 18F-misonidazole imaging data.

Dosimetric features of IMRT delivery

Although a review of the advantages and drawbacks of IMRT compared with conventional radiotherapy is beyond the scope of this report, a brief summary of some of these from the viewpoint of dose-painting by numbers is relevant. Three-dimensional conformal radiotherapy (3D-CRT) is a broad class of radiotherapy techniques that aim to improve the match between the clinical target volume and the volume irradiated to a high radiation dose. This aim is achieved without intensity modulation by use of a limited number of static beams. 3D-CRT plans typically reduce the volume of healthy tissue that receives a high dose, while increasing the dose to the clinical target volume.

The two most frequently aired arguments against IMRT are that this method of planning and delivery makes quality assurance very difficult and that there might be an increased risk of radiation-induced secondary cancers. Certainly, quality assurance is much more demanding with IMRT techniques than with 3D-CRT or with conventional radiotherapy. However, more and more reports have been published from clinical departments reporting their experience with the introduction of clinical and dosimetric quality-assurance programmes for IMRT. The quality assurance needed does not differ substantially between a dose plan prescribed on the basis of theragnostic imaging and that prescribed on the basis of a limited number of specified point dose constraints. The possible increase in radiation-induced second cancer in long-term survivors after IMRT remains controversial. In a review, Hall and Wu pointed out that the change from conventional radiotherapy techniques to 3D-CRT is expected to reduce the incidence of radiation-induced cancers as a result of the relative decrease in the healthy-tissue volume receiving high doses of radiation. However, a change from 3D-CRT to IMRT typically involves an increase in the number of fields used. Furthermore, because a large proportion of the radiation field is shielded by the collimator during irradiation, the time for which the accelerator beam is switched on will increase by a factor of two or three. This feature will increase the total body

![Figure 2: BOLD MR image of a patient with prostate cancer](image)
exposure owing to leakage radiation. Hall and Wu estimate that IMRT will increase the frequency of second cancers in patients surviving for 10 years to 1.75% compared with 1.00% after conventional radiotherapy. 10-year survival in most solid cancers is below 50%, so this higher rate corresponds to an increase of less than 0.5% in all cases treated. Clearly, this effect will be outweighed by any clinically relevant gain in control of the primary tumour resulting from IMRT. Hall and Wu underscored the uncertainties in these estimates, but they must be regarded as current best values. The issue of radiation-induced second cancers will be most important in children and other patients with long life expectancy. Again, there is no major difference between standard IMRT and IMRT prescribed by dose-painting by numbers.

Are we ready for dose-painting by numbers?

Validation of the imaging target is the first objective in building the case for a new theragnostic imaging procedure. This aim generally involves two steps. The first is to show that the imaging variable correlates with a local biological property, such as a local micro-electrode measurement of oxygen tension for hypoxic imaging or a mitotic index or a Ki-67 labelling index for imaging of cell proliferation. The second step is to show the clinical importance of the validation marker for the radiobiological characteristic in question; for example, that the Ki-67 labelling index actually selects for a benefit from accelerated radiotherapy. This step might at first seem superfluous, but it is needed to justify the prescription of a specific temporal modulation of radiotherapy based on the imaging information.

Even with a validated imaging target, temporal stability is a concern. The usefulness of theragnostic imaging in prescribing four-dimensional dose distributions obviously depends on the short-term and long-term stability of the three-dimensional map of density of specific cellular phenotypes or microenvironmental variables. Oxygenation is one example: intermittent closing and opening of vessels can cause microscopic changes in oxygenation, so-called acute hypoxia, on a typical time-scale of minutes. The extent to which this process affects hypoxia as estimated with radionuclide-labelled compounds is not clear. In addition, there is reoxygenation of hypoxic regions after the radiation cell killing a few hours after each dose fraction and throughout the full 6–7 weeks of fractionated radiotherapy. Even if reoxygenation does occur, boosting of the radiation dose to the region that was hypoxic at the start of therapy can still be worthwhile. Studies of the temporal stability of hypoxia maps are in progress in several centres.

Spatial resolution is poorer with PET, SPECT, and MR spectroscopy than with MR imaging and CT and there can be difficulties with partial volume artefacts. At present, commercial high-resolution clinical PET scanners have a full width at half-maximum resolution of 3.5–5.0 mm in both the axial and transverse planes. The development of CT-PET and MR-PET scanners might help in reducing the partial volume artefacts and could improve the accuracy of image coregistration. By contrast, the achievable resolution with current PET scanners should be seen on the scale of achievable spatial precision in delivering 33 dose fractions in the clinic. This requirement defines an effective limit on the steepness of gradients that are deliverable in the clinic, which, with current radiotherapy technology, is probably not much better than the above 3–4 mm. Clearly, dose-painting by numbers will need optimum precision of the planning dosimetry and the multileaf-collimator technology as well as immobilisation of the patient and reproducibility. Physiological organ movement is another possible limitation that is being addressed by several research groups.

In conclusion, theragnostic imaging for radiation oncology will revolutionise the whole process of radiotherapy prescription and planning. At the present rate of progress, a realistic prophecy is that this therapeutic principle will be in early clinical testing within the next 5 years.

Conflict of interest

I declare no conflicts of interest.

References


