images, the understanding of the significance of the imaged physiological properties with respect to treatment outcome and the reproducibility of the imaging prior to and during treatment.
Treatment adaptation to the heterogeneous response of the tumour to therapy can be based on pre-treatment imaging and, potentially more reliably, to consecutive scans during therapy. Although response monitoring appears appealing, first the challenges of providing reproducible quantitative images and image registration for possibly shrinking tumours have to be met. Again, increased dose to the most slowly responding volumes of the tumour or selection of patients for alternative yet more toxic therapies are an option.
Concluding, biological imaging can be used for radiotherapy treatment planning both in a qualitative manner, e.g. for target delineation, and a quantitative manner, e.g. for directed dose escalation or response monitoring. The demands on the quality of the imaging equipment and image analysis software are huge and reliable methods are still being developed. Nevertheless, biological imaging bears great potential both for the optimization and individualization of radiotherapy.

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Clinical status of bio-imaging for radiotherapy

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Bio-imaging leads to the characterization and quantification of cellular and sub-cellular metabolic pathways and allows to better understand the complexity of tumour biology. It includes nuclear medicine techniques as well as magnetic resonance imaging using dynamic contrasted enhancement or spectroscopic analysis or molecular contrast agents.
These new imaging techniques had been widely employed in many fields of oncology giving additional information compared to anatomical imaging, traditionally based on computed tomography (CT) and magnetic resonance imaging (MRI). In radiation oncology growing interest towards molecular imaging has developed in the last few years.
Positron emission tomography (PET) with the tracer 18F-fluorodeoxy-glucose (FDG) has shown to have a clinical impact on diagnosis and staging of several cancer types being also recommended by international cancer practice guidelines. Using FDG-PET in pre-treatment evaluation, radiotherapy with curative intent may be precluded in patients with previously undetected metastases and changes in gross target volumes (GTV) and planning target volumes (PTV) as well as in dosage and schedules can be recorded since a better delineation of loco-regional disease is offered by these imaging modalities. This leads to the new concept of biologic target volume (BTV).
Therefore, bio-imaging may help to visualize sub-volumes characterised by functional parameters involved in radio-resistance such as hypoxia, proliferation and cancer metabolism and to discover the biologic behaviour of the tumour, monitoring the response to therapy and the molecular changes in tumour biology during treatment. These intriguing opportunities may support dose escalating strategies and multimodal approaches.
PET tracers such as 18F-fluoromisonidazole (FMISO), 18F-fluoroazomycin-arabinoside (FAZA) and 60CU (II)-diacetyl-bis (NA-methylthiosemi-carbazone) and dynamic contrast enhanced (DCEMRI) have been evaluated as hypoxia tracers.
Still several uncertainties remain regarding the most appropriate tracer to use, the method of quantification, how to manage setup variation and target movements, the image processing and particularly the different image registration methods (rigid and not rigid algorithms), the various approaches for definition of volumes of interest (VOI) in GTV contouring and finally the best way to apply this imaging to radiotherapy tumour response.
In conclusion clinical data support the role of molecular imaging in staging and planning for radiotherapy but for individualized treatment in the form of biologic image-guided radiotherapy results from preliminary clinical trials have to be awaited and further analysis are required.

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Functional imaging methods for oncology

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The primary goal of what is now termed "Molecular Imaging" is the visualisation pathological processes at the cellular level, often long before disease symptoms become clinically apparent. The ability to do this confers two major benefits: earlier diagnosis of disease and targeting of individual therapy. Both PET and SPECT have been used in this way for many years, but with limited spatial resolution. In very recent years the idea of molecular MRI has evolved, with the advantage of considerably greater spatial resolution than either PET or SPECT. Typically, diagnostic MRI has relied on the effects of pathology on the water molecules in the tissue, and as a consequence has provided indirect and, frequently, rather non-specific information on the underlying processes. With the advent of molecular MRI we now have the ability to gain information on the expression, upregulation or downregulation, of specific molecules associated with pathology.
In principle, any ligand (intracellular, extracellular or vascular) could be targeted, but there are significant challenges to crossing cellular barriers with the majority of MRI contrast species currently in use. Thus, endovascular targets represent the most accessible and, hence, most widely studied targets to date. The vascular endothelium plays an essential role in normal vascular physiology, and its functional phenotype is dynamically responsive to pathological stimuli. Many of the vascular endothelium's functions are mediated by surface adhesion molecules that can be rapidly upregulated, and this is a common feature of acute neurological disease. These molecules provide an accessible tag with which we can identify the presence of disease within the brain using our new MRI contrast agents. We have discovered that we can detect adhesion molecules using ligand-targeted MRI contrast agents early in the progression of experimental brain disease [1–5]. Moreover, we are able to do this at a time when the presence of pathology is undetectable by either existing imaging methods or clinical scoring.
There is now evidence to suggest that tumour cells use inducible endothelial adhesion molecules to promote their adhesion to the vascular endothelium. Both VCAM-1 and E-selectin have been found to be upregulated in a number of tissues containing metastases, and we have recently demonstrated VCAM-1 upregulation in human brain tissue containing breast cancer metastases. However, the role of such adhesion molecules in metastasis development remains unclear. In this talk I will discuss the various novel targeted contrast agents that we have been developing in Oxford and our recent studies in models of brain metastasis, which indicate the potential of molecular MRI for acute tumour detection and monitoring of therapy.

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Validation of bio-imaging methods for radiotherapy

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Pre-clinical evaluation of biological imaging is important to validate markers such as hypoxic markers in the context of curative radiotherapy. Outcome after fractionated irradiation is determined by several factors: the number and intrinsic radiation sensitivity of tumour stem cells, repopulation, reoxy-genation, recovery from sublethal damage, and redistribution. Over the last years we studied different biomarkers for proliferation (BrdU), vasculature (CD31), perfusion (Hoechst33348), and hypoxia (pimonidazole) in a panel of 10 different head and neck squamous cell carcinomas in nude mice. The data were correlated with local tumour control probability after clinically relevant irradiation with 30 fractions within 6 weeks. In parallel, single dose irradiations were performed. In the studied panel of tumour models analysis Pimonidazole binding correlated with local tumour control after fractionated irradiation but not with radiobiological hypoxia. CD31 and perfusion were not correlated with local tumour control or radiobiological hypoxia. Radiation sensitivity to single dose under clamped hypoxia correlated strongly with sensitivity to fractionated irradiation and with Pimonidazole binding. Our data indicate that evaluation of biological imaging using clinically relevant fractionation schedules and endpoints allows preclinical validation of biomarkers in the context of curative radiotherapy. Pimonidazole binding predicts local tumour control after fractionated irradiation. The data suggest that Pimonidazole doesn't reflect radiobiological hypoxia but rather the number and/or radiation sensitivity of tumour stem cells.
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