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Overview

Functional Imaging Biomarkers: Potential to Guide an Individualised Approach to Radiotherapy

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Abstract

The identification of robust prognostic and predictive biomarkers would transform the ability to implement an individualised approach to radiotherapy. In this regard, there has been a surge of interest in the use of functional imaging to assess key underlying biological processes within tumours and their response to therapy. Importantly, functional imaging biomarkers hold the potential to evaluate tumour heterogeneity/biology both spatially and temporally. An ever-increasing range of functional imaging techniques is now available primarily involving positron emission tomography and magnetic resonance imaging. Small-scale studies across multiple tumour types have consistently been able to correlate changes in functional imaging parameters during radiotherapy with disease outcomes. Considerable challenges remain before the implementation of functional imaging biomarkers into routine clinical practice, including the inherent temporal variability of biological processes within tumours, reproducibility of imaging, determination of optimal imaging technique/combinations, timing during treatment and design of appropriate validation studies.

Key words: Biomarker; cancer; functional imaging; magnetic resonance imaging; positron emission tomography; radiotherapy

Statement of Search Strategies Used and Sources of Information

Literature including PubMed, Medline and the Cochrane library were searched for articles published in the English language. Search terms included: radiotherapy, PET, MRI, CT, functional imaging, biomarker, adaptive, hypoxia, proliferation, radio-resistance.

Introduction

In current practice, radiotherapy is used at a uniform dose to a particular type of tumour, irrespective of features of the underlying tumour biology and taking no account of tumour changes occurring during the course of treatment. Multiple clinical features, such as the TNM staging system, provide a degree of prognostic information regarding tumour outcomes, but are not predictive of outcomes with specific treatments. A predictive biomarker would provide information on the effect of a specific therapy on outcome. The identification of robust prognostic and predictive biomarkers would transform the ability to determine the optimal treatment modality and to individualise the intensity of treatment, leading to improvements in the therapeutic ratio.

In the search for such biomarkers, there has been a surge of interest in the use of imaging, particularly metabolic and molecular imaging techniques, to reflect underlying tumour biology [1,2]. These indicators of tumour biology could provide prognostic and predictive information beyond conventional clinical factors [3,4]. Importantly, imaging biomarkers hold the potential to evaluate tumour heterogeneity/biology, both spatially and temporally. Significant recent advances have been made in the application of functional imaging to the radiotherapy process, with an ever-increasing range of imaging techniques available based

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mainly on positron emission tomography (PET) or magnetic resonance imaging (MRI) [3,5]. A number of clinical trials, proposed or underway, are intended to use imaging as a biomarker to allow the modification of therapy [6–8]. Imaging at baseline may provide additional prognostic and potentially predictive data [9]. Spatial information may be used in target volume selection [10,11] and in addition has led to the concept of a 'biological target volume' [1,11] (the use of functional imaging in tumour targeting and dose painting strategies is beyond the scope of this review and is covered elsewhere in this special issue [12]). In addition, it is recognised that tumours respond variably during a course of fractionated radiotherapy [13]. The concept of adaptive radiotherapy takes into account patient and/or tumoral changes occurring during treatment [14]. Imaging biomarkers offer the opportunity to assess this response during treatment and allow a timely therapeutic alteration.

The potential for functional imaging to provide robust prognostic and predictive biomarkers to guide treatment strategy relies upon an ability to acquire quantitative data reflecting tumour biology [15]. Key factors identified that modify the outcome of radiotherapy [16,17] are (i) hypoxia [18], (ii) proliferation of tumour clonogens or cancer stem cells before or during treatment [19] and (iii) intrinsic radioresistance. Therefore, it is of particular interest to image factors or processes such as hypoxia and proliferation, in addition to inter-related processes of metabolic activity and perfusion, which influence the outcome of radiotherapy.

Key Biological Processes in Tumour Tissues

Several complex biologically inter-related processes distinguish neoplastic from normal tissues. Some of these hallmarks of malignancy that enable tumour growth, invasion and dissemination include: autonomous replication, ability to resist cell death, induction of angiogenesis and increase in proliferative signalling [20]. Quantification of these processes using imaging techniques before treatment or monitoring changes during radiation therapy forms the basis of imaging biomarkers (Figure 1).

Hypoxia

Tumour hypoxia is a well-recognised cause of radioresistance [17,21]. Acute hypoxia is due to temporal changes in perfusion of the vasculature [22]; these changes can occur within a timescale of minutes [23]. Chronic hypoxia is caused by the short distance oxygen can diffuse from the disordered tumour vasculature into tumour tissue;

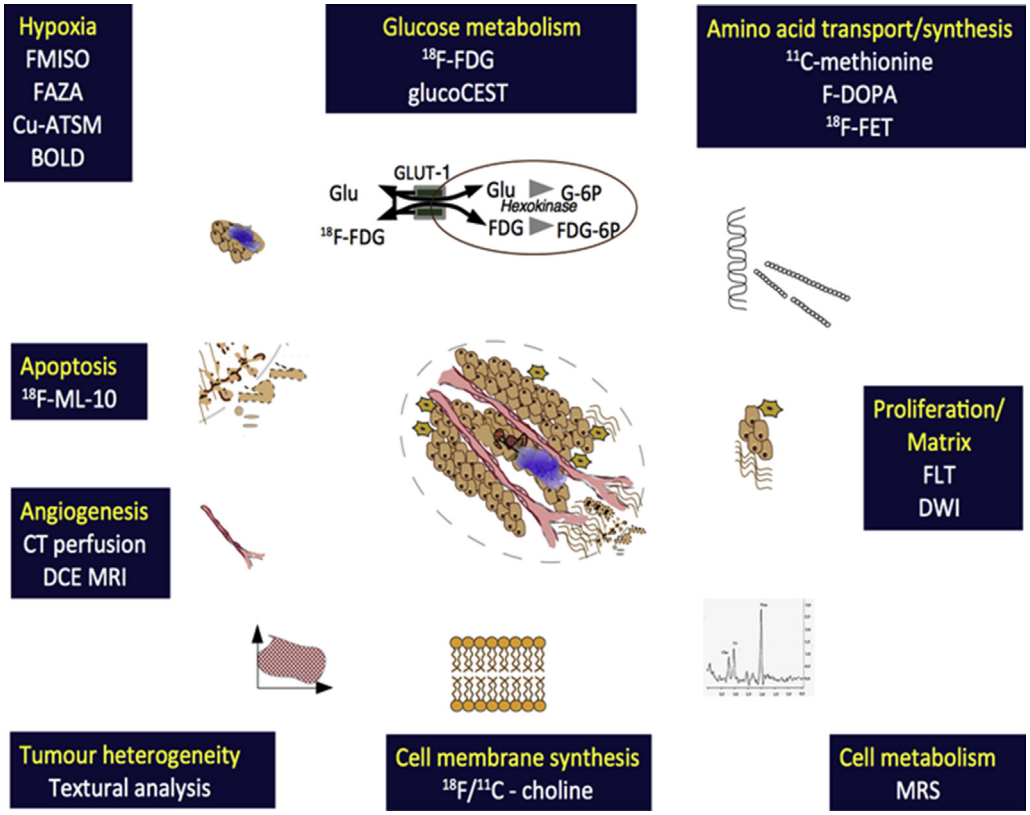

Fig 1. Functional imaging and the tumour micro-environment: the variety of current and developing imaging biomarkers as a function of diverse aspects of the neoplastic milieu. ^{18}F-FDG, ^{18}fluorine fluoro-2-deoxy-D-glucose; glucoCEST, glucose chemical exchange saturation transfer magnetic resoance imaging; F-DOPA, 3,4-dihydroxy-6-fluoro-L-phenylalanine; FET, fluoroethyltyrosine; FLT, fluorothymidine; DWI, diffusion-weighted imaging; MRS, magnetic resonance spectroscopy; DCE, dynamic contrast-enhanced; CT, computed tomography; ML-10, 2-(5-fluoropentyl)-2-methyl malonic acid; FAZA, fluoroazomycin arabinoside; FMISO, fluoromisonidazole; CuATSM, copper(II)-diacetyl-bis(N^4-methylthiosemicarbazone); BOLD, blood oxygen level-dependent.

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