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Delivering Functional Imaging on the MRI-Linac: Current Challenges and Potential Solutions

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Abstract

Magnetic resonance imaging (MRI) is a highly versatile imaging modality that can be used to measure features of the tumour microenvironment including cell death, proliferation, metabolism, angiogenesis, and hypoxia. Mapping and quantifying these pathophysiological features has the potential to alter the use of adaptive radiotherapy planning. Although these methods are available for use on diagnostic machines, several challenges exist for implementing these functional MRI methods on the MRI-linear accelerators (linacs). This review considers these challenges and potential solutions.

Keywords: Biomarkers; Functional imaging; MRI; Radiotherapy

Introduction

The magnetic resonance imaging (MRI)–linear accelerator (linac) combination is a new advance in delivering radiotherapy to patients as it enables real-time adaptation of treatment. Although the essential element of radiotherapy planning in the MRI environment is anatomical imaging, there is also the possibility to perform functional imaging during the therapy planning window, with the ultimate aim of augmenting the available tumour and organ information to inform clinical decision-making. In this review, we consider which functional imaging methods may have added value for use with the MRI-linac and consider the challenges to implementing these methods and potential solutions to overcome them.

Which Functional MRI Biomarkers Should be Measured on the MRI-Linac?

Tumours are complex biological structures that contain neoplastic cells surrounded by a stroma consisting of endothelial cells, immune cells, fibroblasts, pericytes, and the extracellular matrix [1,2]. Tumours recruit these ostensibly normal cells and the interaction between the tumour and stroma contributes to the development of abnormal traits termed the 'hallmarks of cancer'. These hallmarks are sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, reprogramming of energy metabolism, evading immune destruction, and activating invasion and metastasis, in what is termed the 'tumour microenvironment' [3].

Clinical imaging methods can provide serial non-invasive assays of all features of the microenvironment [4]. More specifically, MRI can probe several hallmarks of cancer using clinically available methods such as T_1-weighted imaging, T_2^*-weighted imaging or diffusion-weighted imaging (DWI). These sequences are usually used to create qualitative images

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with a focus on tumour and organ morphology, but can be adapted to enable derivation of quantitative parameters that indirectly measure features of the microenvironment [5]. In addition, MRI can measure signals that quantify glucose metabolism and the reprogramming of energy metabolism (through glucose-chemical exchange saturation transfer (CEST) imaging) [6], and can interrogate the aberrant biochemistry seen in tumours through CEST imaging, magnetic resonance spectroscopy (MRS; of protons and other nuclei, such as phosphorus) and ^{13}C-MRI [7], although the latter methods require non-proton radiofrequency (RF) channels and specialist coils.

The above MRI techniques can all be analysed to derive quantitative parameters. When these parameters are a 'defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions' [8,9] then they can properly be termed 'imaging biomarkers'. Both imaging and bio-specimen biomarkers are used widely in oncology to diagnose, predict, and stratify patients into different treatment groups, and also to monitor response to therapy [10]. Perhaps the two most likely candidate techniques for application on the MRI-linac are DWI [11] and dynamic contrast-enhanced (DCE)-MRI [12] derived through T_1-weighted imaging (Figure 1). Both of these techniques are already used widely in healthcare in their qualitative formats and can be readily adapted for quantitative imaging biomarkers.

Some potential MRI biomarkers for use on the MRI-linac system are detailed in Table 1, including DWI, DCE-MRI (both relatively mature methods) and oxygen-enhanced (OE)-MRI (an emerging method) as examples to illustrate the potential issues for implementation of functional MRI in the MRI-linac environment. Each biomarker measures a different aspect of the tumour microenvironment with different associated risks, as the measurement precision, accuracy, biological validation, clinical validation, and clinical utility are known to variable extents [13]. As with any biomarker, measurement timings are critical to detecting responses and can reflect different underlying biology at different times [14]. Given the different sensitivities of the biomarkers to underlying tumour pathophysiology, the choice of biomarker is critical; for example, in a PET-CT based study investigators showed that the abnormal sub-regions in a tumour varied in their relative spatial positions when the biomarker chosen measured hypoxia (HX-4 tracer), perfusion (dynamic contrast-enhanced CT), or abnormal energetics (2-[^{18}F]-fluoro-2-deoxy-D-glucose [FDG] tracer) [15]. Therefore, studies that employ functional imaging biomarkers must use a biomarker that has sufficient validation, measures the desired relevant underlying biology, and is employed at an appropriate time interval during therapy.

DWI

DWI is an MRI technique that is sensitive to measuring the random Brownian motion of water molecules within tissues. In simplified terms, highly cellular tissues or those with cellular swelling exhibit lower apparent diffusion coefficients (ADCs), due to the restriction and hindrance of movement for free water molecules caused by cell membranes and other microscopic tissue features; thus malignant tumours tend to have lower ADC values due to a combination of higher cellularity, increased tissue disorganisation, and increased extracellular space tortuosity. At present, DWI is used clinically to improve differentiation of benign from malignant lesions, to monitor treatment response after chemotherapy or radiation, to differentiate post-therapy changes from residual active tumour, and to detect recurrent tumour [11].

Quantitative ADC has been investigated widely as a biomarker of cell death, proliferation, and aberrant cell replication. In the radiotherapy setting, ADC values have been reported to increase during the initial few weeks of therapy in studies of cervical [16], rectal [17], prostate [18], and other tumours. Several such studies report that the increase in ADC may indicate beneficial clinical outcome, although large definitive studies are lacking. One clear advantage of using ADC as an imaging biomarker is its sensitivity, but this needs to be weighed against the fact that changes in ADC are very non-specific and can be influenced by formation of necrosis, apoptosis, altered vasculature, altered cell membrane permeability, and other factors [19,20].

DCE-MRI

DCE-MRI is generally performed outside of the brain using T_1-weighted imaging. Here, a bolus of gadolinium-based contrast agent is injected into the vasculature and multiple T_1-weighted images are acquired rapidly to track the passage of the bolus through tissues. Typically, images are acquired every 1–20 seconds, depending on the spatial resolution requirements and the analysis strategy to be employed. Data can be quantified either as changes in signal intensity due to the arrival, accumulation, and washout of contrast agent or can be converted into an estimate of change in contrast agent concentration. This latter approach — recommended for quantitative DCE-MRI in cancer [21] — requires preparatory sequences to enable estimation of the tissue native T_1 values. The most common analysis approaches are to either perform a heuristic analysis to measure the initial area under the curve up to a given time point, t after contrast agent arrival in the tissue ($IAUC_{(t)}$), or to apply a pharmacokinetic model to estimate parameters, such as the endothelial transfer coefficient (K^{trans}) or volume of the extravascular extracellular space (v_e) [12].

In oncology, DCE-MRI biomarkers have been mainly used to investigate angiogenesis. In the radiotherapy setting, DCE-MRI biomarkers at baseline and during treatment have been shown to have variable relationships to improved outcome [22], with biomarkers related to K^{trans} or v_e having a predictive role in some studies but not in others. These mixed data are likely to reflect variation in measurement implementation and measurement timing as well as likely true pathophysiological differences, but do highlight that, at least in some circumstances, DCE-MRI has potential to assist clinical decision-making for patients undergoing radiation-based therapeutic regimens.

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