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Review

Mechanism and non-mechanism based imaging biomarkers for assessing biological response to treatment in non-small cell lung cancer

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Abstract Therapeutic options in locally advanced non-small cell lung cancer (NSCLC) have expanded in the past decade to include a palate of targeted interventions such as high dose targeted thermal ablations, radiotherapy and growing platform of antibody and small molecule therapies and immunotherapies. Although these therapies have varied mechanisms of action, they often induce changes in tumour architecture and microenvironment such that response is not always accompanied by early reduction in tumour mass, and evaluation by criteria other than size is needed to report more effectively on response. Functional imaging techniques, which probe the tumour and its microenvironment through novel positron emission tomography and magnetic resonance imaging techniques, offer more detailed insights into and quantitation of tumour response than is available on anatomical imaging alone. Use of these biomarkers, or other rational combinations as readouts of pathological response in NSCLC have potential to provide more accurate predictors of treatment outcomes. In this article, the robustness of the more commonly available positron emission tomography and magnetic resonance imaging biomarker indices is examined and the evidence for their application in NSCLC is reviewed.

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1. Introduction

Lung cancer is the leading cause of cancer related mortality worldwide, with 1.8 million new cases causing 1.6 million deaths in 2012 [1,2]. Non-small cell lung cancer (NSCLC) accounts for 80–90% of lung cancers, with a greater prevalence of adenocarcinoma (43% of cases) over squamous cell (SCLC; 23%) and other subtypes (34%) [3]. Prior to radical treatment, anatomic evaluation with contrast-enhanced CT and evaluation of metabolic activity with [^{18}F] fluorodeoxyglucose positron emission tomography (^{18}FDG-PET CT) is standard of clinical care, along with pathology for cancer subtype, and molecular profiling in advanced disease. Response evaluation in the majority of clinical trials is provided by CT-based size criteria (response evaluation criteria in solid tumours, RECIST). However, size based response evaluation is generally insensitive to early biological changes and often fails to identify responses in patients who experience either cytostasis or pseudoprogression [4–6]. These scenarios are more often encountered with molecularly targeted agents, where inter-tumoural heterogeneity and intra-tumoural heterogeneity lead to more varied treatment responses than is seen for cytotoxic agents [7,8]. Biological changes that occur for up to 12 weeks following treatment initiation are dominated by apoptosis, necrosis, cystic degeneration, intra-lesional haemorrhage, oedema and/or immune cell infiltration. They potentially herald survival benefit but may not be identified with anatomical imaging, thus compromising clinical decision making both within trials and out-with [9].

A range of novel, non-invasive imaging probes have been developed in solid tumours, including NSCLC, with the potential to interrogate a combination of both anatomic (size-based) and functional tumour characteristics of the tumour and its microenvironment [5,10,11]. Features evaluable with PET, CT and magnetic resonance imaging (MRI) include metabolism, tissue water diffusion, perfusion, chemical composition and hypoxia. The most widely used of these techniques in the clinical trials setting is ^{18}FDG-PET CT. MRI remains underexploited despite its ability to provide both anatomical and functional (physiological and pathophysiological) information in a single examination [12]. Our centre is currently contributing to coordinated multicentre trials evaluating MRI and PET functional imaging in a range of malignancies, including NSCLC and liver metastases (EORTC QuIC-ConCept Innovative Medicines Initiative). This review considers the requirements of a viable response biomarker for use in clinical trials and provides an overview of the evidence for using mechanism and non-mechanism biomarkers in NSCLC treated with a range of existing and novel treatment options.

2. Quantitative imaging biomarkers in NSCLC

For an oncologic biomarker to be viable it must be: (1) accurate and reproducible over time and across institutions; (2) closely coupled to presence of disease (sensitivity and specificity of the biomarker) and; (3) changes in activity should act as a surrogate for the endpoint sought from therapy (survival) [13,14]. Within clinical trials, imaging biomarker based response criteria aim to inform early 'go/no-go' decisions, increasing efficiency, reducing the cost of early phase studies and minimising exposure of patients to futile therapies [10]. From a practical perspective, cost, patient tolerability and availability are important, and rigorous quality control is required for use in multicentre trials.

To date, CT-size based evaluation remains the most commonly used technique in NSCLC drug trials [10], often supplemented by metabolic information from ^{18}FDG-PET CT. Where size and metabolic evaluation yield misleading results, added specificity and sensitivity are potentially afforded by an increasing range of PET and MRI techniques [15] (Fig. 1). With MRI, standard T1W, T2W or proton density sequences provide anatomic information, while functional techniques allow water diffusion (diffusion weighted [DW] MRI), tumour perfusion (on DCE MRI), hypoxia (on blood oxygen level dependent [BOLD] MRI), ventilation (using a range of techniques including O_2 enhanced MRI), and tissue composition (magnetic resonance [MR] spectroscopy and UTE MRI) to be interrogated [16–19]. Several of these techniques remain investigational at specialist centres only.

2.1. Biomarker mechanism, measurement methodology and repeatability

2.1.1. Size

Size-based treatment response was systematised for cross sectional imaging in 1981, and forms the basis of the RECIST criteria (1.0 in 2000, updated to 1.1 in 2009) [14,20,21]. RECIST 1.1 are validated against prospectively documented outcome data from more than 6500 patients with more than 18000 solid tumour deposits, and provide a balance between ease of application and ability to predict response linked to progression free survival [14]. Following immunotherapy and targeted agents, these criteria can wrongly identify cytostasis or slow growth as stable or progressive disease [22–24] (Fig. 2). Size based response evaluation is also delayed by up to 12 weeks following therapy. Repeatability of RECIST criteria in NSCLC indicate there is overlap between inter-observer measurement variability and the size change required for progressive disease so that RECIST progression is often misclassified [25], an error that occurs less frequently for partial response, due to the requirement of a larger change in size [25,26]. Although tumour volumetry produces measurements