Abstract

The emerging field of targeted therapy is ushering in a new era of targeted/functional imaging, which compliments and sometimes improves upon traditional anatomic imaging for diagnosis, early assessment of treatment response, and estimation of durability of therapeutic success. Targeted/functional imaging has already had an impact on clinical management. With such methods, one may either measure the target directly or assess downstream effects. The former may provide greater specificity, whereas, the latter may have broader applicability. The clinical question will guide selection between the two. The primary modalities currently used clinically include nuclear medicine techniques, such as planar or single photon emission computed tomography or positron emission tomography, and MR based techniques, such as dynamic contrast enhanced MR imaging. An understanding of the physics and clinical applications of targeted/functional imaging and their requisite molecular imaging agents aides image interpretation. Combining such imaging with anatomic imaging is often advantageous. For the future, clinical trials of targeted/functional imaging are needed in addition to and in parallel with clinical trials of targeted therapeutics given the obvious synergy between the two.
1. INTRODUCTION

The emerging field of targeted therapy is ushering in a new era of targeted/functional imaging. Although powerful in most circumstances, meta-analyses of some tumor types found that an anatomic reduction in tumor size alone had no or only a weak correlation with patient survival (1,2). Two recent Phase III trials of therapies targeting the epidermal growth factor receptor demonstrated similar small reductions in tumor size; however, one drug improved the median overall survival rate by more than 50% compared to placebo, whereas the other did not (3,4). When present, anatomic changes in tumors take time to occur. Instead of waiting weeks to months to see an anatomic change in tumor size, a goal of targeted/functional imaging is to evaluate the response to a drug in a matter of days to a few weeks, before anatomic change occurs. This can be especially important for patients with short life spans such as those with advanced lung cancer who may have only months to live. In this case, selecting the appropriate therapy and gauging its efficacy in an individual patient in a timely fashion is paramount. Furthermore, some tumors, such as pancreatic cancer, can undergo a desmoplastic response, which is difficult to distinguish from residual tumor after treatment by anatomic imaging.

In such situations and if the therapy is tumoristatic instead of tumoricidal, functional imaging may prove useful. Functional imaging may also prove useful for selecting patients who are most likely to respond to a given drug. This is an important goal given the known heterogeneity of response to treatment in populations of patients thought to have the same tumor phenotype. Furthermore, within a patient, different metastases may respond variably to a given therapy, and identifying the nonresponding metastases may guide treatment alterations, including whether to institute local therapy. Thus, there are a number of situations where functional imaging may be useful for guiding patient care.

2. CLINICAL USE OF FUNCTIONAL IMAGING

Functional imaging has already had an impact on patient care. There is a great deal of experience with some imaging agents in oncology such as $^{111}$In-octreotide for imaging neuroendocrine tumors that express somatostatin receptors and metaiodobenzylguanidine (MIBG), which mimics norepinephrine and accumulates in neurosecretory granules such as those of pheochromocytomas. Newer nuclear medicine imaging agents for single photon emission computed tomography (SPECT) imaging and for positron emission tomography (PET) imaging as well as functional imaging with magnetic resonance (MR) techniques are adding to the armamentarium of targeted/functional imaging methods.

Targeted therapy and targeted/functional imaging have already found synergy in the clinical setting. In addition to diagnosis and staging, imaging can be used for patient selection, for example, to select patients that have a positive or negative response to a functional imaging agent at baseline. This can then be used for comparison after a targeted therapy is delivered. For example, patients with suspected gastrointestinal stromal tumors (GISTs) may be screened for tumors positive for $^{18}$F-fluoro-2-deoxyglucose ($^{18}$F-FDG) uptake on PET imaging prior to initiation of imatinib therapy.

Imaging can also be used for monitoring the effect of imatinib treatment. For example, dramatically decreased $^{18}$F-FDG uptake by GISTs signifies that imatinib is effective (Fig. 1)