Special Review

Beyond Correlations, Sensitivities, and Specificities: Case Examples of the Evaluation of Advanced Imaging in Oncology Clinical Trials and Cancer Treatment

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Although advanced imaging is an important component of oncology clinical trials, there has not been a lot of success in advancing its use from a research perspective. One likely reason is the lack of consensus on the methodology used to study advanced imaging in trials, which results in a disconcerted research effort and produces data that are difficult to collate for use in validating the imaging components being studied. Imaging is used in cancer clinical trials for various indications, and the study design needed to evaluate the imaging in a particular indication will vary. Through case examples, this paper will discuss how advanced imaging is currently being investigated in oncology clinical trials, categorized by the potential clinical indication for the imaging tool and offer suggestions on how development should proceed to further evaluate imaging in the given indication. Available National Cancer Institute resources that can assist in this process will also be discussed.

Key Words: Clinical trial; cancer imaging; study design.

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INTRODUCTION

In recent years, researchers have shown significant interest in using advanced imaging to improve the efficiency and success rates of clinical trials in oncology. In a clinical trial setting, imaging can be used to serve a number of clinical indications, which when described in chronological order relative to a patient's disease process, include diagnosis and staging, prognosis, as a predictive biomarker assay, as a pharmacokinetic (PK) or pharmacodynamic (PD) marker, early response assessment, and as the basis of a clinical trial end point. Definitions and examples of each of these indications are given in Table 1.

Currently, advanced imaging is most often studied as part of a secondary or correlative science objective within an oncology clinical trial investigating a therapeutic efficacy question. For example, in the trial Radiation Therapy Oncology Group (RTOG) 1106, an F18-fluoromisonidazole (FMISO) positron emission tomography (PET) scan is conducted at baseline to identify the presence of hypoxia and its role as a prognostic biomarker in nonsmall cell lung cancer (NSCLC) patients undergoing external beam radiation therapy. (ClinicalTrials.gov Identifier: NCT01507428). On the other hand, advanced imaging may sometimes be studied as the primary objective of a clinical trial without additional evaluation of an investigational therapeutic regimen. An example of this is American College of Radiology Imaging Network (ACRIN) 6678, a study which evaluated the role of F18-fluorodeoxyglucose (FDG) PET as an early response marker in NSCLC (NCT00424138).

However, despite the rich variety of functions imaging can serve in a clinical trial, most current oncology clinical trials use imaging in very limited roles, most commonly as the basis of a trial end point via validated response evaluation criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST), currently at version 1.1 (1). Part of the reason that imaging is not more heavily utilized for its other potential roles is the lack of validation of the imaging modality in those roles, which stems from reasons such as a lack of knowledge and consensus on appropriate validating methodology, as well as a general lack of data from prospective clinical trials that can be used to provide such validations. The lack of consensus

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TABLE 1. Clinical Indications for Which Imaging can be Performed in a Clinical Trial Setting

Role	Definition	Examples
Diagnosis and staging	To determine whether a lesion is positive or negative for malignancy	F18-FDG PET in lymphoma Nodal staging using F18-FDG PET in head and neck cancers (ACRIN 6685)
Prognostic marker	To determine the expected outcome under standard therapy for the patient's disease stage	Lesion size on anatomic imaging such as CT or MRI "High" versus "Low" SUV on F18-FDG PET in head and neck SCC, NSCLC, and gastroesophageal cancers
Predictive biomarker assay	To differentiate between patients expected to benefit clinically on one treatment relative to another from those not expected to experience such a benefit	I-123 scan predictive for I-131 therapy in thyroid cancer F18-FES PET predictive for hormonal therapy in breast cancer (EAI142)
Pharmacokinetics marker	To confirm that the drug has reached the intended target	F18-FLT PET "flare" in pancreatic cancer (EA2131)
Pharmacodynamic marker	To measure the effects of the drug on the body	Perfusion CT and DCE/DSC MRI in anti-angiogenesis targeted therapy
Early response indicator	To determine the expected ultimate outcome on a particular therapy regimen from changes in a tumor characteristic following a few cycles of treatment	F18-FDG PET response in gastric cancer after neoadjuvant chemotherapy (A021302) During-treatment F18-FDG PET evaluation of external beam radiation in NSCLC (RTOG 1106)
Basis of a Phase II trial end point	A pre- to posttreatment change measurement used to determine whether to proceed to the subsequent Phase III investigation	Complete metabolic response according to F18-FDG PET in cervical cancer
Basis of a Phase III trial end point	A pre- to posttreatment change that serves as a surrogate for a definitive clinical end point	PFS based on anatomic imaging

CT, computed tomography; DCE, dynamic contrast-enhanced; DSC, dynamic susceptibility contrast; FDG, fluorodeoxyglucose; FES, fluoroestradiol; FLT, fluorothymidine; MRI, magnetic resonance imaging; NSCLC, nonsmall cell lung cancer; PET, positron emission tomography; PFS, progression-free survival; SCC, squamous cell carcinoma; SUV, standardized uptake value.

contributes to the current status of imaging in clinical trials today, which is characterized by a fragmented research effort with investigations that try to establish the technical (eg, repeatability and reproducibility) and clinical (eg, correlations with clinical outcomes) validity of the imaging study but does not produce results that can be easily collated into a unified analysis to support further validation and development such as obtaining regulatory approval.

There are several issues that contribute to this fragmentation of effort. For instance, data on novel molecular imaging agents or functional methods for a particular tumor histology may not be generalizable to other tumor types. Furthermore, data used to support the use of an imaging test in one clinical scenario such as response evaluation may not be relevant when that same imaging test is being used in a different clinical role, for example, as a predictive biomarker assay. Similarly, the evaluation of an imaging biomarker to be used for disease characterization requires a different study design compared to an evaluation in a response assessment setting, and it is important for the imaging research community to recognize these differences. To make matters more complicated, in addition to a lack of standardization on technical issues such as acquisition protocols and postprocessing algorithms, there is a lack of consensus on basic issues such as imaging biomarker terminology. To combine results from different studies seeking to evaluate an imaging agent as an assay for a predictive biomarker, for instance, the definition of a "predictive biomarker" and how it is to be studied and validated should be standardized and understood by the community at large. In this paper, the authors will examine how advanced imaging has been evaluated in oncology clinical trials categorized by the imaging's clinical indication. Illustrative examples will be provided to demonstrate how the imaging has been studied and suggestions will be provided on potential future studies that can be performed to further clinical evaluation of the imaging tool for that clinical indication.

DIAGNOSIS AND STAGING

The process of differentiating benign from malignant disease can be broadly described as disease characterization and is a process central to clinical roles such as diagnosis (where disease characterization is being performed on the primary lesion) and staging (where distant lesions are being characterized). A variety of different imaging modalities can be used to characterize disease, whether it be an anatomic criterion such as lesion size, or a functional one such as uptake of the glucose derivative FDG on a PET scan. Although the decision to call a lesion benign versus malignant is often based on qualitative parameters in clinical practice, there is a growing trend in clinical trials to use more quantitative measures, especially if they can be repeated reliably. Different thresholds for positivity are as-