Has Quantitative Multimodal Imaging of Treatment Response Arrived?

□□*Commentary on O'Connor et al., p. 6674*

Thomas E. Yankeelov[1,2,3,4,5,7] and John C. Gore[1,2,3,4,6,7]

Although there have been dramatic increases in the range and quality of information available from noninvasive imaging methods, their application in clinical trials has been limited. One promising approach is to apply imaging techniques in preclinical studies designed to mimic a corresponding clinical trial in order to inform that trial. (Clin Cancer Res 2009;15(21):6473–5)

In this issue of *Clinical Cancer Research*, O'Connor and colleagues (1) contribute a valuable article on the application of multimodal imaging to quantify the antivascular effects of an anti-vascular endothelial growth factor (VEGF) therapy in colorectal cancer. Their report is of particular interest because they performed their studies in both preclinical and clinical settings. In the preclinical studies, the authors employed the HM-7 colorectal xenograft model and used *in vivo* microbubble contrast-enhanced sonography (MCES, ref. 2) to assess various hemodynamic parameters before and after treatment and then followed these with *ex vivo* studies using microcomputed tomography (μCT, ref. 3) to generate vascular casts of the tumors post excision. The μCT experiments showed that the tumors displayed a reduction in perfused vessels, whereas the MCES studies showed a decrease in tumor blood volume 24 to 48 hours after treatment. In the clinical study, the authors employed dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI, ref. 4), and those data showed changes in blood volume and enhancement that were consistent with the preclinical data. This article is of interest not only because of the particular results it reports on the primary and secondary aims (to assess the temporal evolution of the antivascular effects of G6-31 and to use cross-species imaging to provide insight into drug mechanism, respectively), but also for the more general implications for translational imaging upon which we now focus.

Current methods for assessing treatment response are limited. For example, although serial biopsies can be obtained to monitor tumor status, these are invasive and therefore may be clinically impractical or available only infrequently. They also provide poor spatial sampling and may prove to be misleading. The current standard-of-care radiological assessment of treatment response is based on the response evaluation criteria in solid tumors (RECIST), which offers an overly simple method for evaluating tumor growth on cross-sectional CT or magnetic resonance images (5). The sum of the longest diameter for all measurable lesions is computed and a post-treatment percent change in the baseline sum is then used to classify the degree of response into one of four categories: complete response, partial response, stable disease, and progressive disease. Although RECIST is a practical tool, it is recognized that it often is inadequate because its assessment of clinical response is based on only uni-dimensional changes. However, intervention-induced changes in tumor viability and eventually its volume are manifestations of earlier and complex treatment-induced molecular and cellular effects. Thus, improved methods are needed to characterize those early molecular and cellular changes that may predict treatment outcome and dictate the course of therapy. These early changes demand more quantitative, sensitive, and specific indices of response.

In recent years there have been dramatic increases in the range and quality of information available from noninvasive imaging methods, therefore, several imaging techniques are now potentially available to assess tumor status and predict treatment response quantitatively. These have often been used in preclinical studies of animal models, but with mixed results that have been confounded by lack of standardization of imaging protocols, inadequate understanding of the underlying mechanisms, and/or absence of appropriate validation to assist their interpretation. Consequently, there are legitimate obstacles that inhibit moving these methods from the laboratory to the clinic. However, there remains a compelling need for validated imaging biomarkers so that these methods can positively influence patient care. To this end, the cancer imaging community has begun to systematically evaluate clinically viable imaging methods to establish which method (or combination of methods) is most appropriate for predicting response to specific treatments (see, e.g., ref. 6). By testing the ability of emerging imaging techniques to characterize the effects of particular treatments, it may be possible to accelerate their application, acceptance, and incorporation into clinical trials and, ultimately, have a direct impact on personalized medicine.

Authors' Affiliations: [1]Institute of Imaging Science and Departments of [2]Radiology and Radiological Sciences, [3]Biomedical Engineering, [4]Physics and Astronomy, [5]Cancer Biology, and [6]Molecular Physiology and Biophysics, Vanderbilt University; and [7]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee

Received 8/31/09; accepted 8/31/09; published OnlineFirst 10/27/09.
Grant support: T.E. Yankeelov is supported, in part, by a Career Development Award from the National Institutes of Health (NIBIB 1K25 EB005936).

Requests for reprints: Thomas E. Yankeelov, 1161 21st Avenue South, Vanderbilt University Medical Center, Nashville, TN 37212-2310. Phone: 615-322-8354; Fax: 615-322-0734; E-mail: thomas.yankeelov@vanderbilt.edu.

doi:10.1158/1078-0432.CCR-09-2257

One area in which cancer imaging provides unique insights is in vascular imaging (7). It is well known that a tumor cannot grow beyond a few cubic millimeters without recruiting a new vasculature. This process of tumor-driven angiogenesis leads to tumor blood vessels that are fragile, leaky, tortuous, nonhierarchical, and therefore quite different from their normal physiological counterparts (8). As nearly all malignancies are thought to be dependent upon these pathologic vessels, a number of techniques have been developed as candidate imaging biomarkers for imaging tumor associated-blood vessels; examples include DCE-MRI (4), contrast-enhanced CT (3), ^{15}O labeled H_2O for PET studies (9), and MCES (2). Unfortunately, and as the authors correctly observe, given a particular antivascular or anti-angiogenic drug, the time course of its effect on vascular status (i.e., blood volume, blood flow, vessel permeability, etc.) is usually not well characterized, which translates into a lack of knowledge of when to apply the appropriate imaging technique(s) to assess response. Preclinical animal data can, therefore, help to design clinical trials by identifying the appropriate time points for doing correlative imaging studies. This is the approach used by O'Connor and colleagues; they report multimodality, multiparametric *in vivo* and *ex vivo* studies of the response of colorectal cancer tumors to anti-angiogenic therapy in both preclinical and clinical settings. Multimodality data can provide insight into drug mechanism by reporting on complementary aspects of drug action. They reported multiple MRI [a mixed measure of vessel perfusion and permeability (K^{trans}), plasma volume (v_p), extravascular extracellular volume fraction (v_e), and tumor volume], ultrasound [relative blood flow (rBF), relative blood volume (rBV), mean transit time (MTT)], and CT (vascular volume) measurements (see Fig. 1). An interesting and important finding was that μCT and MCES revealed a significant reduction in perfused vessels and rBV, respectively, in mice following treatment with G6-31 at the

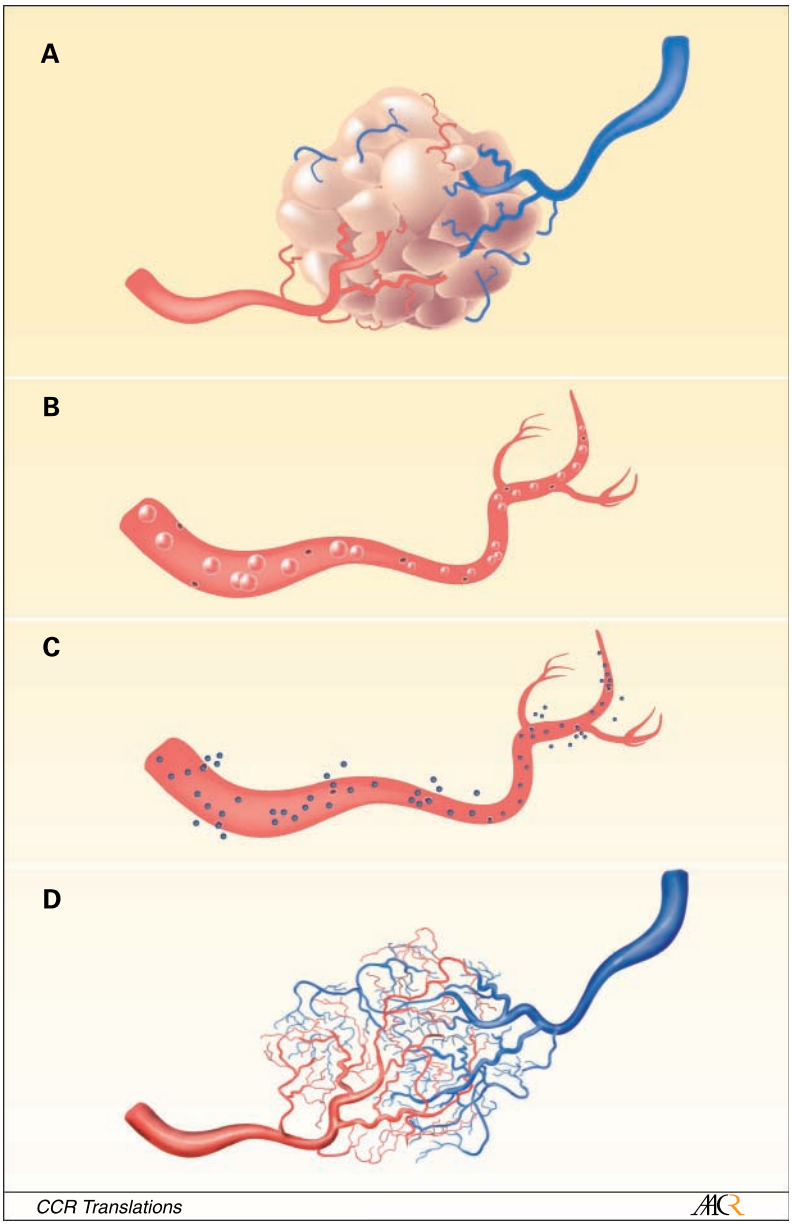

Fig. 1. The figure depicts the methods used to characterize the distinctively fragile and leaky blood vessels (*A*). In the study by O'Connor and colleagues, the authors made use of *in vivo* DCE-MRI and MCES, as well as *ex vivo* μCT. The contrast agents they selected for their study allowed them to probe different aspects of the tumor vasculature. For example, *B,* because the contrast agent used in MCES is intravascular, it can report on rBF, rBV, and MTT; *C,* whereas the DCE-MRI contrast agent is an extravascular agent and therefore reports on v_p, v_e, and K^{trans}. *D,* the μCT study used an intravascular contrast agent, which, when combined with the high-resolution *ex vivo* imaging, can display the vessels in 3D and determine vascular volume. As these methods report on different, but related, aspects of tumor vessels, it is reasonable to hypothesize that more can be learned about, for example, a drug's mechanism of action by studying all three. The article by O'Connor and colleagues investigates the changes these techniques report during a longitudinal study of treatment response.

48-hour time point. Similarly, reductions in the fractional v_p and the enhancing fraction were also seen at the 48-hour time point in human DCE-MRI data. These findings provide an exciting example of clinical data mirroring its preclinical counterpart.

These results point to a number of possible future studies, in which the results could be built upon and expanded. For example, in order to more fully elucidate the temporal and spatial relationships between the parameters, it will be necessary to do serial, *in vivo*, multimodality measurements that can be coregistered to a common imaging space (10). Indeed, the data presented in O'Connor and colleagues show that there is a complex temporal evolution to the imaging parameters, and it is not unreasonable to hypothesize that the spatial evolution is also complex and informative. Such data will be well suited to address the order in which various anticancer drugs work. It is important to note that access to this temporal and spatial evolution is only available through imaging because only imaging techniques can provide such physiologically meaningful data noninvasively, in 3D, and *in vivo*-and do so repeatedly in the same animal or human (11).

Although there have been dramatic developments in quantitative imaging of cancer in the last several years, there is still much work to be done in validating the emerging techniques and determining when to use these tools. The investigation by O'Connor and colleagues points the way to one possible direction to address these important issues and brings us one step closer to the acceptance of quantitative, multimodality imaging in clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. O'Connor JPB, Carano RAD, Clamp AR, et al. Quantifying antivascular effects of monoclonal antibodies to vascular endothelial growth factor: insights from imaging. Clin Cancer Res 2009;15:6674–82.
2. Qin S, Caskey CF, Ferrara KW. Ultrasound contrast microbubbles in imaging and therapy: physical principles and engineering. Phys Med Biol 2009;54:R27–57.
3. Paulus MJ, Gleason SS, Kennel SJ, et al. High resolution X-ray computed tomography: an emerging tool for small animal cancer research. Neoplasia 2000;2:62–70.
4. Yankeelov TE, Gore JC. Dynamic contrast enhanced magnetic resonance imaging in oncology: theory, data acquisition, analysis, and examples. Curr Med Imaging Rev 2007;3:91–107.
5. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
6. Manning HC, Merchant NB, Foutch AC, et al. Molecular imaging of therapeutic response to epidermal growth factor receptor blockade in colorectal cancer. Clin Cancer Res 2008;14:7413–22.
7. Cai W, Chen X. Multimodality molecular imaging of tumor angiogenesis. J Nucl Med 2008;49[Suppl 2]:113S–28S.
8. Fukumura D, Jain RK. Imaging angiogenesis and the microenvironment. APMIS 2008;116:695–715.
9. de Langen AJ, van den Boogaart VE, Marcus JT, et al. Use of H2(15)O-PET and DCE-MRI to measure tumor blood flow. Oncologist 2008;13:631–44.
10. Slomka PJ, Baum RP. Multimodality image registration with software: state-of-the-art. Eur J Nucl Med Mol Imaging 2009;36 [Suppl 1]:S44–55.
11. Giesel FL, Mehndiratta A, Locklin J, et al. Image fusion using CT, MRI and PET for treatment planning, navigation and follow up in percutaneous RFA. Exp Oncol 2009;31:106–14.