Do Imaging Biomarkers Relate to Outcome in Patients Treated with VEGF Inhibitors?

James P.B. O’Connor1,3 and Gordon C. Jayson2,4

Abstract

The management of solid tumors has been transformed by the advent of VEGF pathway inhibitors. Early clinical evaluation of these drugs has used pharmacodynamic biomarkers derived from advanced imaging such as dynamic MRI, computed tomography (CT), and ultrasound to establish proof of principle. We have reviewed published studies that used these imaging techniques to determine whether the same biomarkers relate to survival in renal, hepatocellular, and brain tumors in patients treated with VEGF inhibitors. Data show that in renal cancer, pretreatment measurements of $K_{\text{trans}}$ and early pharmacodynamic reduction in tumor enhancement and density have prognostic significance in patients treated with VEGF inhibitors. A weaker, but significant, relationship is seen with subtle early size change (10% in one dimension) and survival. Data from high-grade glioma suggest that pretreatment fractional blood volume and $K_{\text{trans}}$ were prognostic of overall survival. However, lack of control data with other therapies prevents assessment of the predictive nature of these biomarkers, and such studies are urgently required.

Introduction

VEGF plays a pivotal role in angiogenesis by promoting endothelial cell proliferation, migration, and vascular permeability, which together support tumor growth and survival (1). This discovery has prompted considerable interest and resource investment in developing and testing efficacy of compounds that target VEGF or its receptors as potential anticancer therapeutics (2).

Randomized controlled phase II/III trials have shown survival benefits for bevacizumab (anti-VEGF monoclonal antibody) given as monotherapy in first-line metastatic renal cell cancer (mRCC; ref. 3) and in combination chemotherapy for first- and second-line metastatic colorectal cancer (mCRC; ref. 4), recurrent glioblastoma multiforme (5), and first-line non-small cell lung cancer (6). Similarly, survival benefit has been shown for the tyrosine kinase inhibitor sorafenib in mRCCs (7) and advanced hepatocellular cancer (HCC; ref. 8) and for sunitinib in mRCCs (9), all administered as monotherapy. Data from these and other studies have led to U.S. Food and Drug Administration (FDA) approval of bevacizumab, sorafenib, and sunitinib for use in the above cancer types (10).

Although widely prescribed, VEGF pathway inhibitors have failed to make the dramatic impact that was anticipated. In many tumor types, the survival benefit from addition of VEGF inhibitors to standard therapy has been incremental but marginal, with some phase III studies showing little clinical benefit (11, 12). This highlights the need for biomarkers of clinical outcome that identify those patients likely to gain significant clinical benefit from anti-VEGF therapies and to guide patient selection in future clinical trials of novel agents (12, 13).

Imaging-derived biomarkers (Table 1) have well-documented roles in assessing early pharmacodynamic effects induced by VEGF inhibitors in early-phase clinical trials (14). However, it is unclear whether the same imaging biomarkers have a role as prognostic or predictive indicators of clinical outcome in patients treated with VEGF inhibitors. Because this question has not been evaluated thoroughly before, we provide comprehensive evaluation of current studies of imaging biomarkers of outcome following VEGF inhibition. In addition, we discuss key issues in imaging biomarker validation and qualification and highlight the steps required before imaging biomarkers of outcome can be adopted for decision making in trials or clinical practice.

Current Evidence in Homogeneous Patient Populations

Multiple independent phase II trials and investigator-led studies in disease-specified (homogeneous) patient populations have shown significant relationships between particular imaging parameters and clinical outcome. The most widely studied group comprises patients with mRCCs, HCCs, and high-grade glioma (HGG) receiving a narrow...
range of dose levels (or a single dose level) of a specified VEGF inhibitor (Tables 2–4, Summary Box 1).

Most imaging data from clinical studies of angiogenesis inhibitors are derived from perfusion computed tomography (CT) or $T_1$-weighted dynamic contrast enhanced MRI (DCE-MRI). These imaging techniques are usually conducted by specialist research groups with dedicated acquisition and analysis protocols (14). In these techniques, a bolus of contrast agent is injected into a peripheral vein, and a series of dynamic images are acquired as the contrast agent enters and traverses the tumor microvasculature. The change in image contrast is measured within the tumor (based on density in CT and signal intensity in MRI), and from this measurement, estimates of the change in contrast agent concentration are obtained. Measuring (or estimating) a vascular input function from a feeding vessel then allows a model to be applied, from which 2 types of parameters are often derived: estimates of blood flow ($F$), which include the volume transfer constant ($K_{trans}$, a composite measure of blood flow, vessel permeability, and the endothelial surface area of tumor microvessels); and estimates of tumor blood or plasma volume (termed BV and $v_p$, respectively).

In distinction, most postlicensing investigator-led studies have used retrospective analyses of conventional CT or MRI data conducted on clinical workstations by operators with variable expertise in image analysis. Here, either tumor size change or density (measured in HU) or both are calculated (15). The principles behind deriving biomarkers from anatomical CT, perfusion CT, and DCE-MRI are shown in Fig. 1, and nomenclature for imaging biomarkers is detailed in Table 1.

These biomarkers provide an assessment of the vascular characteristics of a tumor before treatment and should serve as useful biomarkers of anti-VEGF therapy efficacy, as VEGF ligands binding to VEGF receptors are a key pathway mediating angiogenesis. The VEGF pathway acts through multiple related mechanisms, including augmented endothelial cell proliferation and survival; improved migration and invasion of endothelial cells; increased permeability of existing vessels; and enhanced chemotaxis and homing of bone marrow–derived endothelial cells and pericytes to angiogenic tissue sites (2). Anti-VEGF therapy acts to counteract these effects. In some models and clinical samples, there is evidence that VEGF inhibitors reduce vascular density, although it may be more important to restore normality to the vasculature by pruning disordered and chaotic vessels (16). Vascular permeability is reduced following administration of VEGF pathway inhibitors, and in some agents this has led to reduction in tumoral edema (17).

**Metastatic renal cell carcinoma**

**Pretreatment imaging biomarkers.** Three independent prospective phase II studies of either sorafenib or sunitinib in patients with mRCCs have reported that high MRI
pretreatment $K^{\text{trans}}$ (18–20) and high $v_p$ (18) were associated with longer progression-free survival (PFS). In a dynamic CT study in patients treated with either sorafenib or sunitinib, both $F$ and BV distinguished responders [defined by Response Evaluation Criteria In Solid Tumors (RECIST)] from nonresponders, but did not relate to survival (21). In a separate retrospective study, tumors with greater "enhancement," quantified by greater difference in HU between precontrast and arterial-phase images, corresponded to longer PFS in patients treated with either sorafenib or sunitinib (22). Data are summarized in Table 2.

### Table 2. Relationship of imaging biomarker to clinical outcome in metastatic renal cell cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Modality</th>
<th>Beneficial parameter</th>
<th>Time interval</th>
<th>Outcome measure</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td>Baseline image parameter</td>
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<tr>
<td>Hahn (18)</td>
<td>48</td>
<td>Sorafenib</td>
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<td>High $K^{\text{trans}}$</td>
<td>—</td>
<td>PFS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High $v_p$</td>
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<td>PFS</td>
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<td>Sorafenib</td>
<td>DCE-MRI</td>
<td>High $K^{\text{trans}}$</td>
<td>—</td>
<td>PFS</td>
<td>0.02</td>
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<td>Bjarnason (20)</td>
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<td>Sunitinib</td>
<td>DCE-MRI</td>
<td>High $K^{\text{trans}}$</td>
<td>—</td>
<td>PFS</td>
<td>0.043</td>
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<tr>
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<td>32</td>
<td>Sorafenib or sunitinib</td>
<td>DCE-CT</td>
<td>High $F$</td>
<td>—</td>
<td>PFS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High BV</td>
<td></td>
<td>R vs. NR</td>
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<td></td>
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<td></td>
<td></td>
<td>PFS</td>
<td>NS</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>R vs. NR</td>
<td>0.02</td>
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<tr>
<td>Han (22)</td>
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<td>Sorafenib or sunitinib</td>
<td>CT</td>
<td>Large enhancement</td>
<td>—</td>
<td>PFS</td>
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<td>Early change in image parameter</td>
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<td>Flaherty (19)</td>
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<td>Sorafenib</td>
<td>DCE-MRI</td>
<td>$K^{\text{trans}}$</td>
<td>3–12 wk</td>
<td>PFS</td>
<td>0.01</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1D size</td>
<td></td>
<td>PFS</td>
<td>0.05</td>
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<tr>
<td>Thiam (23)</td>
<td>39</td>
<td>Sunitinib</td>
<td>CT</td>
<td>$&gt;10%$ 1D size</td>
<td>6 wk</td>
<td>PFS, NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RECIST</td>
<td></td>
<td>PFS, NS</td>
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</tr>
<tr>
<td>van der Veldt (24)</td>
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<td>Sunitinib</td>
<td>CT</td>
<td>Modified Choi</td>
<td>5–14 wk</td>
<td>OS, NS</td>
<td>&lt;0.001</td>
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<td>Abel (28)</td>
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<td>Sunitinib</td>
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<td>$&gt;10%$ 1D size</td>
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<td>OS</td>
<td>0.031</td>
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<tr>
<td>Smith (25)</td>
<td>53</td>
<td>Sorafenib or sunitinib</td>
<td>CT</td>
<td>$&gt;10%$ 1D size</td>
<td>4–16 wk</td>
<td>PFS, NS</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$&gt;15%$ mean HU</td>
<td></td>
<td>PFS</td>
<td>0.011</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td>$&gt;40%$ HU in one lesion</td>
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<td>PFS</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RECIST</td>
<td></td>
<td>PFS</td>
<td>NS</td>
</tr>
<tr>
<td>Nathan (26)</td>
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<td>Sunitinib or cediranib</td>
<td>CT</td>
<td>Modified Choi</td>
<td>12 wk</td>
<td>TTP, NS</td>
<td>0.002</td>
</tr>
<tr>
<td>Krajewski (27)</td>
<td>70</td>
<td>Sorafenib or sunitinib</td>
<td>CT</td>
<td>Modified Choi</td>
<td>4–17 wk</td>
<td>OS</td>
<td>0.0503</td>
</tr>
<tr>
<td>Cowey (29)</td>
<td>30</td>
<td>Sorafenib or sunitinib</td>
<td>CT</td>
<td>$&gt;10%$ 1D size</td>
<td>4–8 wk</td>
<td>Tumor shrinkage</td>
<td>0.0053</td>
</tr>
<tr>
<td>Smith (33)</td>
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<td>Sorafenib or sunitinib</td>
<td>CT</td>
<td>$&gt;40%$ HU in one lesion</td>
<td>4–17 wk</td>
<td>PFS, TTP, NS</td>
<td>&lt;0.0001</td>
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<tr>
<td>Lamuraglia (34)</td>
<td>9</td>
<td>Sorafenib</td>
<td>DCE-US</td>
<td>$%$ CA uptake</td>
<td>2 wk</td>
<td>PFS</td>
<td>NS</td>
</tr>
<tr>
<td>Lassau (30)</td>
<td>38</td>
<td>Sunitinib</td>
<td>DCE-US</td>
<td>time to peak intensity</td>
<td>2 wk</td>
<td>OS, DFS</td>
<td>0.007</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>wash in slope</td>
<td></td>
<td>DFS</td>
<td>0.0002</td>
</tr>
<tr>
<td>de Bazelaire (31)</td>
<td>10</td>
<td>Vatalanib</td>
<td>ASL</td>
<td>1D size</td>
<td>4 wk</td>
<td>TTP, NS</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$F$</td>
<td></td>
<td>TTP</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ASL, arterial spin labeling; DFS, disease-free survival; NR, nonresponder; NS, not statistically significant; PFS, progression-free survival; R, responder; RECIST, Response Evaluation Criteria In Solid Tumors; US, ultrasound.
Consistent data are seen in mRCCs treated with vatalanib (19) and OS (30) in patients treated with sorafenib. Early reduction in vascular parameters also relates to subsequent beneficial outcome in mRCCs treated with VEGF pathway inhibitors and to compare these criteria with RECIST. This approach follows the Choi criteria evaluation of metastatic gastrointestinal stromal tumors treated with imatinib, in which patients with either reduction in HU (≥15%) or small size change (≥10% in one dimension) had a stronger association with beneficial PFS than that seen with RECIST (32). Despite some variation in image acquisition, lesion selection criteria, analysis of density changes, and measurement timing, 3 independent studies have shown that variants of Choi criteria discriminate between patients with mRCCs with greater or lower PFS (23, 25, 27) and OS (27). The magnitude of tumor regression measured on MRI also relates significantly to PFS (19).

Early reduction in vascular parameters also relates to survival in mRCCs. Two studies have shown that the magnitude of HU reductions (ΔHU) 4 to 16 weeks after the initiation of sorafenib or sunitinib was associated with greater tumor shrinkage and longer PFS (23, 25, 27) and OS (27). The magnitude of tumor regression measured on MRI also relates significantly to PFS (19).

These data have prompted investigators to construct response criteria based on acute pharmacodynamic changes in size and density for mRCCs treated with VEGF pathway inhibitors. The magnitude of HU reductions (ΔHU) 4 to 16 weeks after the initiation of sorafenib or sunitinib was associated with greater tumor shrinkage and longer PFS (23, 25, 27) and OS (27). The magnitude of tumor regression measured on MRI also relates significantly to PFS (19).

**Key summary messages.** Collectively, 5 studies have reported that patients with more highly vascular renal tumors have beneficial outcome when treated with VEGF pathway inhibitors. To our knowledge, no published data contradict these findings. Investigators have suggested that this finding indicates that greater drug delivery (18) is a key determinant of outcome in mRCCs treated with VEGF pathway inhibitors but these data may simply reflect that those tumors with greater VEGF pathway activation are more responsive to VEGF.

### Table 3. Relationship of imaging biomarker to clinical outcome in locally advanced hepatocellular cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Modality</th>
<th>Beneficial parameter</th>
<th>Time interval</th>
<th>Outcome measure</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang (37)</td>
<td>23</td>
<td>Bevacizumab, gemcitabine, and oxaliplatin</td>
<td>DCE-CT</td>
<td>BF, BV, Ktrans</td>
<td>10 wk</td>
<td>PFS</td>
<td>NS</td>
</tr>
<tr>
<td>Hsu (38)</td>
<td>31</td>
<td>Sunitinib, TG, and 5-FU</td>
<td>DCE-MRI</td>
<td>High Ktrans (n = 14)</td>
<td>—</td>
<td>R vs. NR</td>
<td>0.016</td>
</tr>
<tr>
<td>Yopp (39)</td>
<td>17</td>
<td>FUDR and bevacizumab</td>
<td>DCE-MRI</td>
<td>Parameter similar to Ktrans</td>
<td>2 wk</td>
<td>PFS</td>
<td>NS</td>
</tr>
<tr>
<td>Lassau (40)</td>
<td>42</td>
<td>Bevacizumab</td>
<td>DCE-US</td>
<td>Parameter similar to Ktrans</td>
<td>3 d</td>
<td>OS</td>
<td>0.002</td>
</tr>
<tr>
<td>Hsu (38)</td>
<td>31</td>
<td>Sunitinib, TG, and 5-FU</td>
<td>DCE-MRI</td>
<td>Wash in slope</td>
<td>2 wk</td>
<td>R vs. NR</td>
<td>0.03</td>
</tr>
<tr>
<td>Zhu (41)</td>
<td>25</td>
<td>Sunitinib</td>
<td>DCE-MRI</td>
<td>Ktrans</td>
<td>2 wk</td>
<td>PFS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Faivre (42)</td>
<td>26</td>
<td>Sunitinib</td>
<td>CT</td>
<td>Modified Choi</td>
<td>4 wk</td>
<td>OS</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Acute pharmacodynamic change in imaging biomarkers.
Retrospective CT image analyses have shown strong statistical relationships between early size and density changes and clinical outcome in mRCCs treated with sorafenib or sunitinib (Table 2). Several studies in this clinical group have shown consistently that RECIST (in which ≥30% reduction in tumor size in one dimension is required for response) measured at 4 to 16 weeks after initiation of therapy does not distinguish patients with shorter or longer PFS (23–26) or overall survival (OS; refs. 24, 27, 28). However, multiple studies have shown that when the threshold for response is reduced from 30% size change to 10%, early tumor shrinkage successfully discriminates between patients with shorter or longer PFS (23, 25, 27) and OS (27). The magnitude of tumor regression measured on MRI also relates significantly to PFS (19).

Early reduction in vascular parameters also relates to survival in mRCCs. Two studies have shown that the magnitude of HU reductions (ΔHU) 4 to 16 weeks after the initiation of sorafenib or sunitinib was associated with greater tumor shrinkage and longer PFS (23–26) or overall survival (OS; refs. 24, 27, 28). These data are supported by clinical trial data, in which reduction in Ktrans and equivalent ultrasound-derived measurements showed a significant relationship with PFS (19) and OS (30) in patients treated with sorafenib. Consistent data are seen in mRCCs treated with vatalanib (31). Together, these studies support the hypothesis that early “vascular response” relates to subsequent beneficial survival.
pathway inhibition. Further studies are required to test these hypotheses. Furthermore, 11 studies provide strong evidence that pharmacodynamic changes in imaging biomarkers (size, HU, modified Choi criteria, or $K^{\text{trans}}$), measured between 4 and 16 weeks after treatment initiation, relate to improved PFS and OS. This suggests that reduction in tumor vessel flow and tumor permeability indicates response to therapy.

Together, significant relationships between imaging biomarker and outcome were reported in 15 studies of mRCCs treated with VEGF inhibitors found through a literature search. Only one other study, with 9 patients, failed to show a positive relationship between imaging biomarkers and survival (34). Three further conclusions can be drawn. First, greater significance was seen in studies with larger patient numbers. Studies with more than 45 patients had consistently significant associations with survival (PFS or OS) of $P < 0.025$. Second, 13 of the 16 studies showed significant relationships to PFS or OS, rather than radiologic response alone. Third, early pharmacodynamic reduction in vascular parameter generally showed a stronger statistical relationship to survival than pretreatment measurements of vascular parameters, and greater patient numbers were needed to achieve the same significance when size change was used as an early pharmacodynamic measurement of survival.

These findings alone do not distinguish between imaging biomarkers being predictive (associated with response to a specific drug) or merely being prognostic indicators (associated with disease outcome, irrespective of treatment; ref. 35). Data from one study of 28 patients with mRCCs treated with IFN therapy did not show a significant relationship of pretreatment or early pharmacodynamic change in $K^{\text{trans}}$ or BV to PFS (36), implying that advanced vascular imaging may be predictive of benefit in mRCCs treated with VEGF inhibitors. However, one ultrasound study with a small number of patients showed similar early pharmacodynamic change in patients treated with sorafenib and placebo (34).

### Table 4. Relationship of imaging biomarker to clinical outcome in high-grade glioma

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Drug</th>
<th>Modality</th>
<th>Beneficial parameter</th>
<th>Time interval</th>
<th>Outcome measure</th>
<th>$P$</th>
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<tr>
<td>Baseline image parameter</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang (44)</td>
<td>45</td>
<td>Bevacizumab</td>
<td>DCE-MRI</td>
<td>Low $K^{\text{trans}}$</td>
<td>—</td>
<td>OS</td>
<td>0.0298</td>
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<td>Verhoeff (45)</td>
<td>21</td>
<td>Bevacizumab and irinotecan</td>
<td>DCE-MRI</td>
<td>Small ETV</td>
<td>—</td>
<td>OS</td>
<td>0.0026</td>
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<tr>
<td>Kreisl (47)</td>
<td>31</td>
<td>Bevacizumab</td>
<td>DCE-MRI</td>
<td>Low $K^{\text{trans}}$</td>
<td>—</td>
<td>OS</td>
<td>&lt;0.03</td>
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<td>Pope (57)</td>
<td>59</td>
<td>Bevacizumab</td>
<td>DWI</td>
<td>Small ETV</td>
<td>—</td>
<td>OS</td>
<td>NS (0.0793)</td>
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<tr>
<td>Ellingson (46), Pope (58)</td>
<td>84</td>
<td>Bevacizumab ± various cytotoxic agents</td>
<td>T$_1$w-MRI + DWI ($n=44$)</td>
<td>Small ETV</td>
<td>—</td>
<td>PFS</td>
<td>0.0309</td>
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<tr>
<td>Zhang (44)</td>
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<td>Bevacizumab</td>
<td>DCE-MRI</td>
<td>$K^{\text{trans}}$</td>
<td>4 d</td>
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<td>NS</td>
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<td>Kreisl (47)</td>
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<td>6 wk</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>DSC-MRI</td>
<td>volume of tumor with high BV values</td>
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<td>$K^{\text{trans}}$</td>
<td>3 wk</td>
<td>OS</td>
<td>NS</td>
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<td>Jain (56)</td>
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<td>Bevacizumab and cytotoxics</td>
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<td>Ellingson (46), Ellingson (59)</td>
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<td>Bevacizumab and cytotoxics</td>
<td>T$_1$w-MRI</td>
<td>ETV</td>
<td>4–6 wk</td>
<td>OS</td>
<td>NS</td>
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<td>Sorensen (49)</td>
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<td></td>
<td>BV</td>
<td></td>
<td>PFS</td>
<td>0.0015</td>
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<td></td>
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<td></td>
<td>OS</td>
<td>0.0056</td>
</tr>
</tbody>
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Abbreviations: ADC, apparent diffusion coefficient; DWI, diffusion-weighted images; DSC, dynamic susceptibility contrast; NP, nonprogressors; P, progressors.
The studies discussed above were all conducted in pretreated patients who had received varying chemotherapy, immunotherapy, and clinical trial therapies previously. Patients also had varying dose levels of VEGF inhibitors both within individual studies and between studies and had metastases in a range of organ sites. Despite these factors, these data provide a strong rationale for prospective validation of pretreatment and early change in $K_{\text{trans}}$ as a predictive biomarker of PFS and OS in mRCCs in comparisons among multiple VEGF inhibitors with control data from patients receiving therapies that do not target VEGF. The data also support testing the hypothesis that early pharmacodynamic reductions in $K_{\text{trans}}$ and HU are predictive of survival.

Locally advanced HCC and other solid tumors

Relationships observed between imaging biomarkers and outcome in mRCCs may hold true in other solid tumors. In one study of locally advanced HCCs receiving bevacizumab and cytotoxic therapy, high pretreatment $K_{\text{trans}}$ indicated which patients had a RECIST response (37). In another study, high pretreatment $K_{\text{trans}}$ indicated those patients with HCCs who did not develop progressive disease on sunitinib and cytotoxic therapy (38). However, pretreatment $K_{\text{trans}}$ did not relate to PFS or OS in either study. Four studies have shown that, similar to mRCCs, acute pharmacodynamic changes in $K_{\text{trans}}$ or similar parameters relate to delayed clinical progression in HCCs (38–41). Another has shown that the modified Choi criteria discriminated between shorter or longer PFS intervals, but unlike mRCC data, no relationship was seen with OS (42). Data are summarized in Table 3.

Although these data provide some indication that pretreatment and early pharmacodynamic changes in imaging biomarkers for HCC following anti-VEGF therapy have a similar direction of relationship to clinical outcome, the relationships are weaker than in mRCCs. This may reflect smaller patient numbers (mean of 27 patients in 6 studies) and having concomitant administration of various cytotoxic regimens in several studies. Similarly, early pharmacodynamic changes reported in other homogenous populations, such as thyroid cancer, have not related to survival (43), but this may reflect small patient numbers.

High-grade glioma

Pretreatment imaging biomarkers. Three studies of patients with pretreated recurrent glioblastoma multiforme receiving bevacizumab reported that less vascular tumors...
were associated with better PFS and OS. Low $K_{trans}$, low BV, and small enhancing tumor volume (ETV) at baseline were all positive prognostic factors in patients treated with bevacizumab as monotherapy (44) or in combination with various cytotoxic chemotherapy agents (refs. 45, 46; Table 4). A fourth study in 31 patients with recurrent anaplastic astrocytoma showed a trend toward statistical significance (47). Notably, these 4 studies included a substantial number of subjects (mean of 45 patients).

**Acute pharmacodynamic changes in imaging biomarkers.**

Four studies of recurrent HGGs have reported early pharmacodynamic reductions in $K_{trans}$ following bevacizumab with or without cytotoxic therapy between 4 days and 6 weeks after initiation of therapy, akin to mRCC and HCC data. However, unlike the results from mRCC and HCC studies, reductions in $K_{trans}$ did not show significant relationships with PFS or OS in HGG (44, 45, 47, 48). These data differ from a similar sized study of 28 glioblastoma multiforme patients with recurrence treated with cediranib, where early reduction in $K_{trans}$ was significantly related to OS (49). Intriguingly, the same research group has shown that early increase in tumor perfusion related to OS in both primary (50) and recurrent glioblastoma multiforme (51), possibly reflecting normalization of tumor vasculature following therapy, leading to improved blood flow but reduced vessel permeability and edema.

**Key messages.** Data in recurrent HGG initially appear to contradict the relationships described in mRCC and HCC. Despite some variation in on-study treatment regimen, postprogression therapy, and image analysis, patients with low pretreatment BV and $K_{trans}$ had beneficial OS in glioma. This apparent paradox may be understood by considering 3 further studies of patients with HGG receiving combinations of corticosteroids, cytotoxic chemotherapy, and radiotherapy but without anti-VEGF therapy, in whom low BV and low $K_{trans}$ identified less aggressive tumors by grade (52–54). Thus, BV and $K_{trans}$ appear to be prognostic rather than predictive in HGG patients treated with VEGF pathway inhibitors, perhaps contrary to the data from patients with mRCC.

These data also raise the possibility that early pharmacodynamic imaging biomarkers may relate to outcome for some anti-VEGF therapies (cediranib), but not for others. Such hypotheses require formal investigation in adequately powered, randomized prospective studies in which both treatment arms undergo equivalent image acquisition and analysis.

**Role of measuring tumor heterogeneity**

The majority of cited studies express imaging data in relatively simple terms, such as size (measured in one dimension) or averaged functional parameter (mean or median values of HU, $K_{trans}$, or BV). There is evidence of added value in applying advanced image analysis methods to quantify the spatial heterogeneity within a tumor, in the evaluation of clinical outcome (55).

One approach has been to define subregions within tumors based on functional imaging (e.g., enhancement or necrosis) and then to compare how such biomarkers relate to response, progression, or survival. For example, in HGG, the volume of enhancing tumor tissue (ETV), rather than the whole tumor volume, has shown a strong association with time to progression (TTP; 48) and OS (47) in pretreated patients on single-agent VEGF inhibition. This parameter has also distinguished progressors from nonprogressors in patients receiving bevacizumab and cytotoxic therapy (56). Similarly, studies report that the amount of tumor with high BV (48) or low/skewed apparent diffusion coefficient (ADC) values (57–59) show a relationship to tumor PFS and OS that is obscured when average values of BV and ADC are used. However, these approaches rely on **a priori** assumptions to define the subregion of interest, and further work is required to define objective, data-driven tumor regions (60, 61) that relate to response, relapse, and clinical outcome.

Heterogeneity-based data challenge the way in which imaging might be used to interrogate the relationship to outcome. For example, in 4 studies of primary rectal cancer and mCRC treated with bevacizumab and cytotoxic therapy, pretreatment and early acute pharmacodynamic changes in tumor $F$, $K_{trans}$, and BV did not relate to extent of tumor regression or RECIST response (62–65). This finding could be interpreted as proof that imaging biomarkers do not relate to outcome in this setting. However, separate studies that quantified spatial arrangements of vascular heterogeneity and tumor margins reported relationships to tumor response in just 10 patients (66) and to OS in 50 patients (67), suggesting that imaging measurements of the functional and structural characteristics of the tumor vasculature may relate to prognosis and response in anti-VEGF therapies but that specialist analyses may be required to detect these relationships.

**Current Evidence in Mixed (Phase I) Patient Populations**

Numerous early-phase clinical trials of VEGF pathway inhibitors have examined the relationship among dose level, imaging biomarker, and outcome data. These studies typically recruit patients who have received extensive previous treatment and have a wide range of tumor types. In these studies, imaging (most commonly DCE-MRI) has been a secondary endpoint and often restricted to small subgroups of patients (14).

No study has shown a convincing relationship between PFs or OS and imaging parameters following VEGF inhibition in a mixed patient population (68). Studies that have defined “nonprogression” as an endpoint have shown that $K_{trans}$ reduction discriminated between patients with progressive disease (no significant or minimal early pharmacodynamic change in $K_{trans}$) and those without progressive disease (significant pharmacodynamic change in $K_{trans}$, refs. 69–72). Similar approaches were implemented in phase I and II trials of more homogeneous patient groups including vatalanib in mCRC (73) and bevacizumab in inflammatory breast cancer (74). However, the value of such an endpoint is highly questionable. Although multiple studies of vatalanib in mCRC showed greater reduction in $K_{trans}$ in patients without progressive disease (69, 73), no survival advantage was seen.
Imaging Biomarkers and Outcome Following VEGF Inhibition

Summary Box 2. Unmet needs for imaging biomarkers

- Determine the range, SD, and reproducibility of imaging biomarkers in each patient group to power prospective studies.
- Better understand the tumor biology measured by clinical imaging biomarkers and their accuracy.
- Prospective evaluation of imaging biomarkers using rigorous and robust acquisition and analysis in multicenter studies.
- Determine whether imaging biomarkers have a predictive or only prognostic relationship to anti-VEGF therapies in appropriately powered studies.
- The above needs must be addressed before imaging can guide patient selection in biomarker-driven phase II and III clinical trials.

in phase III clinical evaluation of the agent in mCRC (75). Likewise, the clinical benefit of bevacizumab in metastatic breast cancer has been questioned (11). These data emphasize that phase I trials should restrict functional imaging to the detection and quantification of early pharmacodynamic changes as evidence of proof of principle. Investigators must be wary of reporting the relationship of imaging biomarkers to weak endpoints with no proven relationship to PFS or OS, such as nonprogression.

Future Directions

The studies reviewed have considerable variation in data acquisition, analysis, and interpretation. Each imaging modality has its strengths and weaknesses that are important to consider when interpreting image biomarker studies. These issues are reviewed in detail elsewhere (14, 76, 77) but must be addressed before imaging parameters become validated and qualified biomarkers of progression and survival for clinical use (Summary Box 2).

Determining measurement precision and accuracy

Imaging biomarkers require rigorous and robust evaluation in one center, followed by multicenter reproducibility testing (78). The coefficient of variation for $K^{trans}$ and BV has been less than 15% in abdominal and pelvic tumors (62, 79) and approximately 7% in the brain (80), indicating good measurement precision. Similar data have been reported in CT and MRI measurements of size (62, 81). These findings suggest that $K^{trans}$, BV, and size have sufficient precision for clinical use.

The biologic basis underpinning significant relationships between imaging biomarkers and clinical outcome requires greater understanding. For example, data presented here suggest that pretreatment $K^{trans}$ and BV may be beneficial when high in mRCC and low in HGG. This apparent paradox is likely to reflect the relationship of low $K^{trans}$ and low BV to lower grade glioma (52), whereas in mRCC, it is postulated that vascular tumors have more target (VEGF) or superior drug delivery (18).

Validating and qualifying imaging biomarkers

Imaging biomarkers reviewed here are neither validated nor well qualified. Few imaging studies described here were planned, conducted, monitored, recorded, reported, and archived in accordance with good clinical laboratory practice standards, with defined quality control and standard operating procedures. Recognizing these problems, the FDA and NIH have outlined standards for image acquisition and analysis in biomarker development (78, 82), drawing lessons from established roadmaps that guide the development of prognostic and predictive biofluid assays (83).

Applying these ideas to imaging biomarkers is far from trivial. Biofluid specimens allow measurement of an analyte using an in vitro diagnostic device in a process that is quite separate from collection of the sample from the patient (13, 84). In distinction, imaging biomarkers are biophysical signals measured on clinical scanners in an “off-label” manner, for which they do not have regulatory approval. Image signals cannot be isolated in a manner comparable with an analyte (85). Nonetheless, these issues must be addressed to qualify imaging parameters as biomarkers of clinical outcome.

Conclusions

Emerging evidence suggests that pretreatment and early pharmacodynamic imaging biomarkers have a consistent relationship to outcome following VEGF inhibition in some homogeneous cancer patient groups, particularly in mRCC. The majority of data cited here are from single-arm phase II trials or similar patient populations that have used PFS or TTP as surrogate endpoints for OS.

Well-designed large prospective studies are required to show that these preliminary findings are robust, accurate, and reproducible and to determine whether the relationship with outcome is predictive rather than prognostic in any combination of disease type and drug. A role may also exist for evaluating retrospective CT data on tumor size and density from large randomized controlled trials with control/placebo and treatment arms (35). If such studies confirm prognostic relationships, then further studies are required in which imaging biomarkers define randomization into treatment groups. These steps will determine whether functional imaging biomarkers have a future clinical role as prognostic or predictive indicators.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.P.B. O’Connor, G.C. Jayson

Development of methodology: J.P.B. O’Connor, G.C. Jayson

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.P.B. O’Connor, G.C. Jayson

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.P.B. O’Connor, G.C. Jayson

Writing, review, and/or revision of the manuscript: J.P.B. O’Connor, G.C. Jayson

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.P.B. O’Connor, G.C. Jayson

Study supervision: J.P.B. O’Connor, G.C. Jayson

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Do Imaging Biomarkers Relate to Outcome in Patients Treated with VEGF Inhibitors?

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