Do imaging biomarkers relate to outcome in patients treated with VEGF Inhibitors?

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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, CT and ultrasound to establish proof of principle. We have reviewed published studies using these imaging techniques to determine if the same biomarkers relate to survival in renal, hepatocellular and brain tumors in patients treated with VEGF inhibitors. Data show that in renal cancer, pre-treatment measurements of K^{trans} and early pharmacodynamic reduction in tumour 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 pre-treatment fractional blood volume and K^{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.

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INTRODUCTION

Vascular endothelial growth factor (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 anti-cancer therapeutics (2).

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

Though 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 demonstrating little clinical benefit (11, 12). This highlights the need for biomarkers of clinical outcome that identify those patients likely to gain significant

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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 if the same imaging biomarkers have a role as prognostic or predictive indicators of clinical outcome in patients treated with VEGF inhibitors. Since 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.

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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 are patients with mRCC, HCC 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 magnetic resonance imaging (DCE-MRI). These imaging techniques are usually performed 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 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, 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 two 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).

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

These biomarkers provide an assessment of the vascular characteristics of a tumor, prior to treatment and should serve as useful biomarkers of anti-VEGF therapy efficacy, since 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 pericyte 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).

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Metastatic renal cell carcinoma

Pre-treatment imaging biomarkers: Three independent prospective phase II studies of either sorafenib or sunitinib in patients with mRCC have reported that high MRI pre-treatment K^{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 RECIST) from non-responders, but did not relate to survival (21). In a separate retrospective study, tumors with greater 'enhancement', quantified by greater difference in HU between pre-contrast and arterial phase images, had longer PFS in patients treated with either sorafenib or sunitinib (22). Data are summarised in Table 2.

Acute pharmacodynamic change in imaging biomarkers: Retrospective CT image analyses have shown strong statistical relationships between early size and density changes to clinical outcome in mRCC treated with sorafenib or sunitinib (Table 2). Several studies in this clinical group have shown consistently that RECIST (where ≥ 30% reduction in tumor size in one dimension is required for response) measured at 4-16 weeks after initiation of therapy does not distinguish patients with shorter or longer PFS (23-26) or overall survival OS (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). Magnitude of tumor regression measured on MRI also relates significantly to PFS (19).

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Early reduction in vascular parameters also relates to survival in mRCC. Two studies have shown that the magnitude of HU reductions (ΔHU) at 4-16 weeks after the initiation of sorafenib or sunitinib were associated with greater tumor shrinkage and longer PFS intervals (25, 29). These data are supported by clinical trial data, where reduction in K^{trans} and equivalent ultrasound-derived measurements showed significant relationship with PFS (19) and OS (30) in patients treated with sorafenib. Consistent data are seen in mRCC treated with vatalanib (31). Together these studies support the hypothesis that early 'vascular response' relates to subsequent beneficial survival.

These data have prompted investigators to construct response criteria based on acute pharmacodynamic changes in size and density for mRCC 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, where patients with either reduction in HU (≥15%) or small size change (≥10% in one dimension) had 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, three independent studies have shown that variants of Choi criteria discriminate between mRCC patients with greater or lower PFS (24, 26, 33) and OS (24) following anti-VEGF therapy. In a fourth study, relationship between Choi criteria and OS were of borderline significance (p=0.0503), which may be explained by the inclusion of patients receiving multiple different therapies, (including both receptor tyrosine kinase inhibitors and bevacizumab) in the analysis (27).

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Key summary messages: Collectively, five 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 mRCC treated with VEGF pathway inhibitors, but may simply reflect that those with greater VEGF pathway activation are more responsive to VEGF 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^{trans}), measured between 4-16 weeks after treatment initiation, relate to improved PFS and OS. This suggests that reduction in tumor vessel flow and tumor permeability indicate response to therapy.

Together, significant relationships between imaging biomarker and outcome were reported in 15 studies of mRCC treated with VEGF inhibitors found in literature search. Only one other study, with nine patients, failed to demonstrate a positive relationship between imaging biomarkers and survival (34). Three further conclusions can be drawn. Firstly, greater significance was seen in studies with larger patient numbers. Studies with greater than 45 patients had consistent significant associations with survival (PFS or OS) of $p < 0.025$. Secondly, 13 of the 16 studies had significant relationships to PFS or OS, rather than radiological response alone. Thirdly, early pharmacodynamic reduction in vascular parameter generally showed stronger statistical relationship to survival than pre-treatment measurements of vascular parameters and greater patient numbers were

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needed to achieve the same significance when size change was used as an early pharmacodynamic measure 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) (35). Data from one study of 28 patients with mRCC treated with interferon therapy did not show a significant relationship of pre-treatment or early pharmacodynamic change in K^{trans} or BV to PFS (36), implying that advanced vascular imaging may be predictive of benefit in mRCC treated with VEGF inhibitors. However, one ultrasound study in small patient numbers showed similar early pharmacodynamic change in patients treated with sorafenib and placebo (34).

The studies discussed above were all performed in pre-treated 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 pre-treatment and early change K^{trans} as a predictive biomarker of PFS and OS in mRCC, comparing 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^{trans} and HU are predictive.

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Locally advanced HCC and other solid tumors

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

While these data provide some indication that pre-treatment and early pharmacodynamic changes in imaging biomarkers for HCC following anti-VEGF therapy have similar direction of relationship to clinical outcome, relationships are weaker than in mRCC. 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

Pre-treatment imaging biomarkers: Three studies of patients with pre-treated 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 monotherapy (44), or in combination with various cytotoxic chemotherapy agents (45, 46) (Table 4). A fourth study in 31 patients with recurrent anaplastic astrocytoma showed a trend towards statistical significance (47). Notably, these four studies included a substantial number of subjects (mean 45 patients).

Acute pharmacodynamic changes in imaging biomarkers: Four studies of recurrent HGG 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 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 overall survival (49). Intriguingly, the same research group has shown that early increase in tumor perfusion related to overall survival in both primary (50) and recurrent GBM (51), possibly reflecting normalization of tumour vasculature following therapy, leading to improved blood flow but reduced vessel permeability and oedema.

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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, post-progression therapy and image analysis, patients with low pre-treatment BV and K^{trans} had beneficial OS in glioma. This apparent paradox may be understood by considering three further studies of patients with HGG receiving combinations of corticosteroids, cytotoxic chemotherapy and radiotherapy but without anti-VEGF therapy, where low BV and low K^{trans} identified less aggressive tumors by grade (52-54). Thus BV and K^{trans} appear prognostic rather than predictive in HGG treated with VEGF pathway inhibitors, perhaps contrary to data from 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, randomised prospective studies where 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, when in evaluating clinical outcome (55).

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One approach has been to define sub-regions within tumors based on functional imaging (for example, 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 strong association with time to progression (48) and OS (47) in pre-treated patients on single agent VEGF inhibition. This parameter has also distinguished progressors from non-progressors in patients receiving bevacizumab and cytotoxic therapy (56). Similarly, studies report that the amount of tumor with high BV (48) or low/skewed ADC values (57-59) shows 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 sub-region 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 imaging might be used to interrogate the relationship to outcome. For example, in four studies of primary rectal cancer and mCRC treated with bevacizumab and cytotoxic therapy, pre-treatment 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 ten patients (66) and to OS in 50 patients (67), suggesting that imaging measurements of the functional and structural

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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.

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CURRENT EVIDENCE IN MIXED (PHASE I) PATIENT POPULATIONS

Numerous early phase clinical trials of VEGF pathway inhibitors have examined the relationship between 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 sub-groups 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 'non-progression' 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}) (69-72). Similar approaches were implemented in phase I/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. While multiple studies of vatalanib in mCRC demonstrated greater reduction in K^{trans} in patients without progressive disease (69, 73), no survival advantage was seen 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

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imaging biomarkers to weak endpoints with no proven relationship to PFS or OS, such

as non-progression.

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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 centre, followed by multi-centre reproducibility testing (78). Co-efficient 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). This suggests that K^{trans}, *BV* and size have sufficient precision for clinical use.

The biological basis underpinning significant relationships between imaging biomarkers and clinical outcome require greater understanding. For example, data presented here suggest that pre-treatment K^{trans} and BV may be beneficial when high in mRCC and low in HGG. This apparent paradox is likely to reflect that 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, performed, monitored, recorded, reported and archived to 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 biomarkers 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 to an analyte (85). Nonetheless, these issues must be addressed to qualify imaging parameters as biomarkers of clinical outcome.

CONCLUSIONS

Emerging evidence suggests that pre-treatment and early pharmacodynamic imaging biomarkers have consistent relationship to outcome following VEGF inhibition in some homogeneous cancer patient groups, particularly in mRCC. The majority of data cited here are 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 demonstrate that these preliminary findings are robust, accurate and reproducible and to determine if the relationship with outcome is predictive rather than prognostic in any combination of disease type and drug. There may also be a role 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 where imaging biomarkers define randomisation into treatment groups. These steps will determine if functional imaging biomarkers have future clinical role as prognostic or predictive indicators.

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Summary Box 1: Imaging biomarkers of outcome in anti-VEGF therapies

No phase I (mixed population) study has shown significant association between imaging biomarkers and TTP, PFS or OS

Non-progression has an association with some imaging biomarkers but is a weak clinical endpoint

Pre-treatment (K^{trans}) and acute change biomarkers (size, HU, K^{trans}) show promise as predictive and/or prognostic indicators but utility may be specific to each tumor-drug combination

Biomarkers sensitive to tumor spatial heterogeneity provide additional prognostic information compared with average parameter values

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Summary Box 2: Unmet Needs for Imaging Biomarkers

Determine the range, standard deviation 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 multi-centre studies

Determine if 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/III clinical trials

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TABLES

Table 1: Imaging biomarkers of clinical outcome: definitions and units.

Parameter	Definition	Unit	Notes
1D size	One dimensional measurement	mm	Usually longest axis dimension; short axis dimension for lymph node lesions
2D size	Bi-dimensional measurement	mm^2	Multiply longest axis dimension by the perpendicular measurement
3D size	Three dimensions measured	mm^3	Approximates the tumor as a cube
WTV	Whole tumour volume	mm^3	Measures the 'true' tumor margins
ETV	Enhancing tumour volume	mm^3	Measurement depends on the precise definition of tumor enhancement
HU	Hounsfield unit of density	-	-
F	Blood flow	$ml/g\ min^{-1}$	-
K^{trans}	Volume transfer constant between plasma and the extracellular extravascular space	min^{-1}	Composite parameter affected by blood flow, capillary permeability and capillary surface area
v_p	Fractional blood plasma volume	%	-
BV	Fractional whole blood volume	%	-

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Table 2: Relationship of imaging biomarker to clinical outcome in metastatic RCC

Study	N	Drug	Modality	Beneficial parameter	Time interval	Outcome measure	P value
Baseline image parameter							
Hahn (18)	48	Sorafenib	DCE-MRI	High K^{trans} High v_p	-	PFS PFS	0.0269 0.0138
Flaherty (19)	17	Sorafenib	DCE-MRI	High K^{trans}	-	PFS	0.02
Bjarnason (20)	17	Sunitinib	DCE-MRI	High K^{trans}	-	PFS	0.043
Fournier (21)	32	Sorafenib or Sunitinib	DCE-CT	High F High BV	-	PFS R v NR PFS R v NR	NS 0.04 NS 0.02
Han (22)	46	Sorafenib or Sunitinib	CT	Large enhancement	-	PFS	0.008
Early change in image parameter							
Flaherty (19)	17	Sorafenib	DCE-MRI	↓ K^{trans} ↓ 1D size	3-12w	PFS PFS	0.01 0.05
Thiam (23)	39	Sunitinib	CT	↓ >10% 1D size RECIST	6w	PFS PFS	<0.05 NS
Van de Veldt (24)	54	Sunitinib	CT	Modified Choi RECIST	5-14w	OS PFS OS PFS	<0.001 <0.001 NS NS
Abel (28)	75	Sunitinib	CT	↓ >10% 1D size	9w	OS	0.031
Smith (25)	53	Sorafenib or Sunitinib	CT	↓ HU ↓ >15% mean HU >40% ↓ HU in one lesion RECIST ↓ >10% 1D size	4-16w	PFS PFS PFS PFS PFS	<0.0001 0.011 0.002 NS 0.019
Nathan (26)	20	Sunitinib or Cediranib	CT	Modified Choi RECIST	12w	TTP TTP	0.002 NS
Krajewski (27)	70	Sorafenib or Sunitinib or Bevacizumab	CT	Modified Choi RECIST ↓ >10% 1D size	4-17w	OS OS OS	0.0503 NS 0.002
Cowey (29)	30	Sorafenib or Sunitinib	CT	↓ HU	4-8w	tumor shrinkage PFS	0.0053 NS
Smith (33)	31	Sorafenib or Sunitinib	CT	>40% ↓ HU in one lesion *and* ↓ >20% 1D size	4-17w	TTP	<0.0001
Lamuraglia (34)	9	Sorafenib	DCE-US	↓ % CA uptake	2w	PFS	NS
Lassau (30)	38	Sunitinib	DCE-US	↓ time to peak intensity ↓ wash in slope	2w	OS DFS DFS	0.007 0.0002 0.02
De Bazelaire (31)	10	Vatalanib	ASL	↓ 1D size ↓ F	4w	TTP TTP	NS 0.008

Table 3: Relationship of imaging biomarker to clinical outcome in locally advanced HCC

Study	N	Drug	Modality	Beneficial parameter	Time interval	Outcome measure	P value
Baseline image parameter							
Jiang (37)	23	Bevacizumab, gemcitabine and oxaliplatin	DCE-CT	*BF*, *BV* High K^{trans} (n=14)	-	PFS R v NR	NS 0.016
Hsu (38)	31	Sunitinib, TG and 5FU	DCE-MRI	High K^{trans}	-	NP v P	0.008
Early change in image parameter							
Jiang (37)	23	Bevacizumab, gemcitabine and oxaliplatin	DCE-CT	↓ BF, BV, K^{trans} ↓ HU ↓ 1D size	10w	PFS PFS PFS	NS NS 0.005
Yopp (39)	17	FUDR and Bevacizumab	DCE-MRI	↓ parameter similar to K^{trans}	2w	TTP	0.002
Lassau (40)	42	Bevacizumab	DCE-US	↓ parameter similar to K^{trans} ↓ wash in slope	3d	OS R v NR	0.0002 0.03
Hsu (38)	31	Sunitinib, TG and 5FU	DCE-MRI	↓ K^{trans}	2w	OS PFS	0.007 0.006
Zhu (41)	25	Sunitinib	DCE-MRI	↓ K^{trans}	2w	PFS	<0.05
Faivre (42)	26	Sunitinib	CT	Modified Choi	4w	OS TTP	NS 0.0182

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Table 4: Relationship of imaging biomarker to clinical outcome in high grade glioma

Study	N	Drug	Modality	Beneficial parameter	Time interval	Outcome measure	P value
Baseline image parameter							
Zhang (44)	45	Bevacizumab	DCE-MRI	Low K^{trans} Small ETV	-	OS OS	0.0298 0.0026
Verhoeff (45)	21	BV and Irinotecan	DCE-MRI DSC-MRI	Low K^{trans} Low rBV	-	OS OS	<0.03 <0.03
Kreisl (47)	31	Bevacizumab	DCE-MRI	Small ETV	-	OS	NS (0.0793)
Pope (57)	59	Bevacizumab	DWI	ADC histogram metric	-	OS PFS	0.055 0.008
Ellingson (46), Pope (58)	84	BV +/- various cytotoxic agents	T_1w-MRI + DWI (n=44)	Small ETV Higher ADC ADC histogram metric	-	PFS PFS PFS	0.0309 0.02 0.001
Early change in image parameter							
Zhang (44)	45	Bevacizumab	DCE-MRI	↓ K^{trans}	4d	OS	NS
Kreisl (47)	31	Bevacizumab	DCE-MRI	↓ ETV ↓ K^{trans}	4d	OS OS	0.0008 NS
Sawlani (48)	16	Bevacizumab	DCE-MRI DSC-MRI	↓ K^{trans} ↓ volume of tumor with high BV values	6w	TTP TTP	NS 0.002
Verhoeff (45)	21	Bevacizumab and Irinotecan	DCE-MRI DSC-MRI	↓ K^{trans} ↓ rBV	3w	OS OS	NS NS
Jain (56)	20	Bevacizumab and cytotoxics	T_1w-MRI	↓ ETV	Variable	NP v P	0.001
Ellingson (46), Ellingson (59)	84	Bevacizumab and cytotoxics	T_1w-MRI DWI	↓ ETV More tumor with ↓ ADC	4-6w	OS OS	NS 0.0013
Sorensen (49)	28	Cediranib	DCE-MRI	↓ K^{trans} ↓ rBV	24hr	OS PFS OS	0.0039 0.0015 0.0056

FIGURE

Figure 1: Schematic representation of image biomarkers derivation and meaning. Top panel: Conventional CT images are used routinely to measure tumor size, typically in one dimension, and tumor density. These biomarkers are measured routinely on clinical workstations. Bottom panel: Functional images are shown for DCE-MRI, but similar principles apply to perfusion CT. Measurement of tumor size (both whole volume and enhancing tumor volume; ETV) require region of interest delineation and then segmentation based on an enhancement threshold. Tracer kinetic modelling (or the central volume theorem; CVT) is applied to the data, from which parameters such as flow, permeability and blood volume are derived.

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Figure 1:

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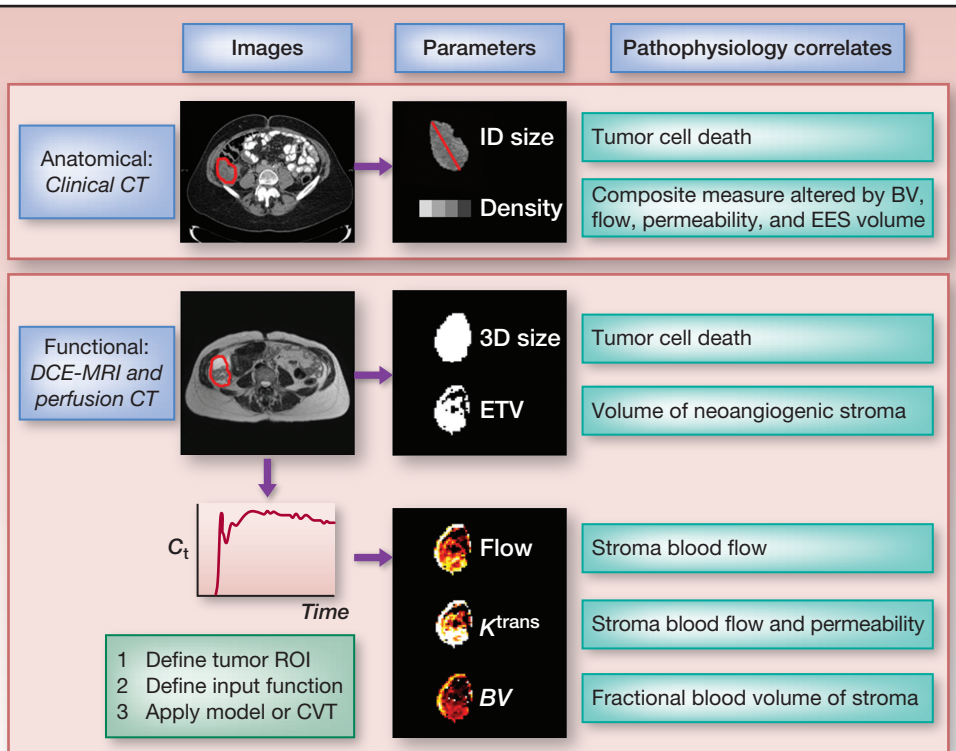
Clinical Cancer Research

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

James P B O'Connor and Gordon C Jayson

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