Anti-VEGF Molecular Targeted Therapies in Common Solid Malignancies: Comprehensive Update for Radiologists[1]

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Angiogenesis is an essential component of the growth and dissemination of solid malignancies and is mediated by several proangiogenic factors. The most widely studied proangiogenic factor is vascular endothelial growth factor (VEGF). A major class of molecular targeted therapies (MTTs) inhibit the VEGF axis and are referred to as antiangiogenic MTTs. There are two main types of anti-VEGF MTTs: drugs targeting circulating VEGF and drugs interfering with the activity of the VEGF receptors. The cancers against which antiangiogenic MTTs have had the greatest effect are gliomas, non–small cell lung cancer, colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, and gastrointestinal stromal tumor. These cancers respond to antiangiogenic MTTs in a different way than they respond to conventional chemotherapy. Instead of the traditional Response Evaluation Criteria in Solid Tumors (RECIST), each of these cancers therefore requires its own individualized treatment response criteria (TRC). Examples of individualized TRC include the Response Assessment in Neuro-oncology (RANO) criteria for gliomas, modified RECIST for hepatocellular carcinoma, and Morphology, Attenuation, Size, and Structure (MASS) criteria for renal cell carcinoma. Furthermore, antiangiogenic MTTs have a unique spectrum of class-specific and drug-specific toxic effects, some of which can be detected at imaging. Increasing use of antiangiogenic MTTs in clinical practice necessitates that radiologists be aware of these drugs, their response patterns, and TRC as well as their toxic effect profiles.

Abbreviations: FDA = U.S. Food and Drug Administration; FLAIR = fluid-attenuated inversion-recovery; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; MTT = molecular targeted therapy; NSCLC = non–small cell lung cancer; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; TKI = tyrosine-kinase inhibitor; TRC = treatment response criteria; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; WHO = World Health Organization

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- List the anti-VEGF MTTs and the solid malignancies treated with them.
- Discuss the role of imaging in assessing treatment response, including the evolution of personalized TRC associated with these malignancies.
- Describe the role of imaging in detecting class-specific and drug-specific treatment-related complications associated with anti-VEGF MTTs.

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Introduction

The past decade has seen an explosion in the field of oncology, with the discovery of several new molecular mechanisms behind oncogenesis. The concurrent development of drugs targeting these molecular mechanisms with a high degree of specificity has enabled oncologists to deliver personalized cancer care. A major class of molecular targeted therapies (MTTs) act through inhibition of angiogenesis in cancer cells mediated by the vascular endothelial growth factor (VEGF) pathway and are aptly referred to as antiangiogenic MTTs (1).

From the time Dr Judah Folkman described antiangiogenic therapy as a potential anticancer treatment in 1971 (2), several antiangiogenic drugs have been developed and tried in clinical trials. Bevacizumab (Avastin) was the first anti-VEGF MTT that demonstrated prolonged survival in colorectal cancer and was approved by the U.S. Food and Drug Administration (FDA) in 2004 for metastatic colorectal cancer

TEACHING POINTS

- Bevacizumab was the first anti-VEGF MTT that demonstrated prolonged survival in colorectal cancer and was approved by the FDA in 2004 for metastatic colorectal cancer.
- The rationale behind these modifications is that bevacizumab restores the blood-brain barrier, resulting in decreased contrast material leak into the interstitium.
- Crabb et al, in their study of 51 patients with NSCLC treated with VEGF inhibitors and chemotherapy or chemotherapy alone, modified RECIST response assessment by subtracting the diameter of the cavity from the actual diameter of the tumor.
- In our experience, when pseudoprogression is suspected, the decision to change treatment should be deferred until after a follow-up study, which will show stabilization or improvement in the case of pseudoprogression.
- Bowel perforation has been reported in up to 2% of patients receiving bevacizumab, especially in patients with recent colonoscopy or bowel surgery, radiation treatment, primary tumor in situ, peritoneal carcinomatosis, or high antiangiogenic drug dose.

(3). The decade after the approval of bevacizumab for colorectal cancer has seen a dramatic increase in the number of antiangiogenic agents; the cancers in which benefit has been seen with these drugs include gliomas, non–small cell lung cancer (NSCLC), colorectal cancer, hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), and gastrointestinal stromal tumor (GIST).

Antiangiogenic MTTs differ from conventional chemotherapeutic drugs not only in their mechanism of action but also in the pattern of treatment response at imaging, necessitating the development of alternate treatment response criteria (TRC) (4). The frequent use of these drugs in clinical practice mandates that radiologists become familiar with these personalized TRC, so they can clearly and accurately discuss response with the oncology team. In addition, radiologists must be familiar with the unique spectrum of class-specific and drug-specific toxic effects of antiangiogenic MTTs, several of which can be diagnosed at imaging. Many of the MTTs are expensive and have potential complications; thus, accurate and timely determination of response to and toxic effects of these drugs is of paramount significance from both a clinical and economic standpoint.

Accordingly, the aim of this article is to provide a comprehensive review of the wide array of anti-VEGF MTTs used in solid malignancies and the alternate TRC and toxic effects associated with them.

Angiogenesis in Oncology

Angiogenesis, the mechanism of recruiting new blood vessels and a normal physiologic mechanism of tissue repair, is an essential component of the growth and dissemination of solid tumors (5). Angiogenesis is mediated by several proangiogenic factors, including VEGF, basic fibroblast growth factor, platelet-derived growth factor, and transforming growth factor (6). The most potent stimulus for production of these proangiogenic factors is hypoxia, which results from rapid tumor growth causing the tumor to outgrow its blood supply. Hypoxia causes activation of hypoxia-inducible factor–1α, which in turn upregulates proangiogenic factors (6).

Of all the proangiogenic factors, the most studied is VEGF (Fig 1). VEGF is an appealing antiangiogenic target because drugs targeting it do not have to depend on tumor penetration and also because, unlike cancer cells, endothelial cells are genetically stable and less likely to become treatment-resistant (7). VEGF binds to VEGF receptors (VEGFRs) 1, 2, and 3, of which VEGFR-2 mediates most of the actions of VEGF (8).

Inhibition of VEGF prevents new vessel formation, causes regression of newly formed microvessels (capillary dropout), decreases capillary leak (which decreases interstitial pressure in the tumor), and normalizes tumor vasculature (1). Vascular normalization and decrease in intratumoral pressure increase tumor blood flow, which can result in tumor growth transiently but eventually increases chemotherapy drug delivery to the tumor (1). Thus, these drugs are often used in combination with other oncologic therapies.

Antiangiogenic MTTs

Drugs blocking VEGF can bind to either VEGF in the circulation or VEGFR in the cell membranes (Table 1). Bevacizumab is a monoclonal antibody that binds to VEGF in the circulation and inhibits its binding to VEGFR by forming a protein complex (6). Aflibercept (Zaltrap) is a recombinant antibody containing human VEGFR-1 and -2 fused to the Fc portion of human IgG1, which interferes with the activation of VEGFR (9). Sunitinib (Sutent), sorafenib (Nexavar), cediranib (Recentin), pazopanib (Votrient), regorafenib (Stivarga), and axitinib (Inlyta) are small-molecule inhibitors of receptor tyrosine kinases (tyrosine-kinase inhibitors or TKIs). In addition to inhibiting VEGFR, these MTTs inhibit KIT, platelet-derived growth factor receptor (PDGFR), and several other kinases (10).

Evolution of Alternate TRC

Traditionally, radiologic assessment of tumor response has relied on size: product of the maximum diameters (World Health Organization [WHO] criteria) or sum of the long-axis diameters (Response Evaluation Criteria in Solid

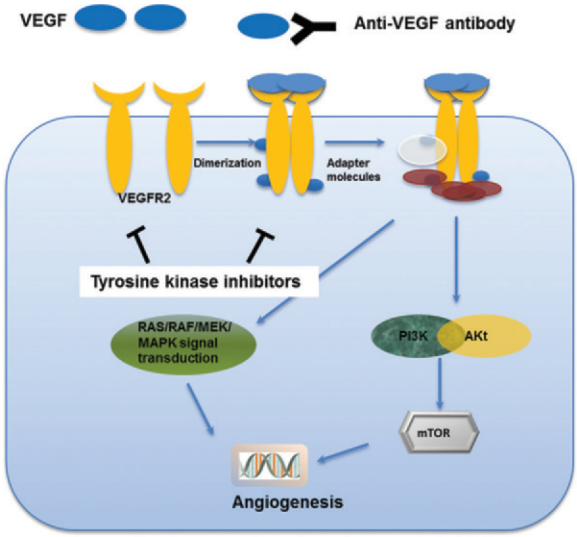


Figure 1. Diagram shows the VEGF axis and its inhibitors. *AKt* = protein kinase B, *MAPK* = mitogen-activated protein kinase, *MEK* = MAPK kinase, *mTOR* = mammalian target of rapamycin, *PI3K* = phosphoinositide 3-kinase, *RAF* = RAF serine/threonine protein kinase, *RAS* = guanosine-5′-triphosphate binding protein kinase, *VEGFR2* = VEGF receptor 2.

Table 1: Anti-VEGF MTTs

Drug	Molecular Targets	Cancers
Bevacizumab	Anti–VEGF A antibody	RCC, CRC, lung, brain
Aflibercept	Anti-VEGF antibody: Recombinant protein—human VEGFR-1 and -2 fused to Fc portion of human IgG1	CRC, brain
Sunitinib	VEGFR-1–3, PDGFR, KIT, Flt-3, CSF-1R, RET	RCC, GIST, HCC, NET
Sorafenib	BRAF/CRAF, VEGFR-2 and -3, Flt-3, KIT, PDGFR	HCC, RCC, CRC
Regorafenib	VEGFR-1–3, PDGFR-A and -B, KIT, RET, FGFR-1	GIST, CRC
Pazopanib	VEGFR-1–3, PDGFR-A and -B, KIT, cFms, FGFR-1and -3	RCC, non-GIST STS
Axitinib	VEGFR-1–3, PDGFR, KIT	RCC
Cediranib	VEGFR-1–3, PDGFR-A and -B, KIT	Brain

Note.—CRC = colorectal cancer, FGFR = fibroblast growth factor receptor, NET = neuroendocrine tumor, PDGFR = platelet-derived growth factor receptor, STS = soft-tissue sarcoma.

Table 2: Alternate TRC

Malignancy	Alternate TRC
Gliomas	RANO criteria (14)
NSCLC	Incorporation of tumor cavitation (Crabb et al) (15)
Colorectal cancer	Morphologic criteria (Chun et al) (16)
HCC	mRECIST (17,18), RECICL (19)
RCC	SACT criteria (20), MASS criteria (21)
GIST	Choi criteria (22)

Note.—MASS = Morphology, Attenuation, Size, and Structure; mRECIST = modified RECIST; RANO = Response Assessment in Neuro-oncology; RECICL = Response Evaluation Criteria in Cancer of the Liver; SACT = Size and Attenuation CT.

Tumors [RECIST]) of target lesions (11–13). Several studies have shown that antiangiogenic MTTs in solid tumors cause morphologic changes, such as a decrease in vascularity, which manifest as decreased attenuation and enhancement at imaging with or without concurrent changes in size. As such, the size-based WHO and RECIST criteria can underestimate treatment response in these tumors. Incorporation of a subjective component to response assessment was proposed by these studies, leading to the evolution of several alternate TRC (4) (Table 2).

Gliomas

Antiangiogenic MTTs

Glioblastoma is the most common and most aggressive brain tumor, with a very poor 5-year survival rate of less than 10%. Despite aggressive treatment with surgery, adjuvant radiation therapy, and systemic chemotherapy with PCV (lomustine, procarbazine, vincristine) and temozolomide, glioblastoma tends to recur in most patients, usually in less than 10 months (9). The commonly used chemotherapeutic drugs in recurrent glioblastoma include temozolomide, irinotecan, PCV, and platinum-based compounds.

In 2009, the FDA approved bevacizumab for recurrent glioblastoma either alone or with irinotecan after a phase II trial of 167 patients showed objective response rates of 28% and 38%, respectively, and median progression-free survival of 9.2 months and 8.7 months, respectively (23). Owing to the possible radiosensitizing effect, bevacizumab has also been evaluated in combination with radiation therapy and temozolomide (9). Other antiangiogenic drugs under evaluation in glioblastoma are aflibercept, cediranib, XL-184, and cilengitide (9). In addition to their inhibition and normalization of angiogenesis, antiangiogenic agents—especially bevacizumab and cediranib—have a steroid-sparing effect in glioblastoma, as they decrease the vasogenic edema (9). They have also been used to manage radiation necrosis (24).

Alternate TRC

Magnetic resonance (MR) imaging is the most commonly used imaging modality for assessment of treatment response in glioblastoma. In 1990, Macdonald et al (25) proposed new criteria to assess treatment response in gliomas, taking into account the WHO criteria (product of the longest diameter and its longest perpendicular diameter at contrast-enhanced computed tomography [CT]), steroid use, and clinical and neurologic assessments. However, these criteria do not take into account factors that influence enhancement, including radiation therapy and chemotherapy, the nonenhancing component of the tumor, the timing of the acquisition, and multifocal tumors. Pseudoprogression (ie, a transient increase in enhancement after radiation therapy with concurrent temozolomide chemotherapy) has been reported to occur in up to 30% of patients with glioblastoma (26).

Several clinical trials, including the BRAIN study and AVAglio study, evaluated bevacizumab in relapsed glioblastoma using adaptations of the Macdonald criteria (23,27). The rationale behind these modifications is that bevacizumab restores the blood-brain barrier, resulting in decreased contrast material leak into the interstitium. This can result in overestimation of treatment response (pseudoresponse) and underestimation of the nonenhancing tumor (26) (Fig 2). Similarly, the use of bevacizumab in radiation necrosis can also be a confounding factor in assessment of true treatment response (26).

The RANO working group proposed the RANO criteria to overcome the limitations of the Macdonald criteria (14). To address pseudoprogression, the RANO criteria suggest disease progression only if a predominant component of the new enhancement is outside the radiation field during the first 12 weeks of treatment or when the progression is confirmed at pathologic analysis (26). The RANO criteria proposed the assessment of treatment response with FLAIR or T2-weighted images in addition to gadolinium-enhanced images to determine the nonenhancing tumor component (Fig 2). The minimum sequences required to assess response according to the RANO criteria are nonenhanced T1-weighted imaging, T2-weighted or FLAIR imaging, and contrast-enhanced T1-weighted imaging in two orthogonal planes.

Measurable lesions are enhancing lesions with two perpendicular diameters greater than or equal to 10 mm, not including cystic or necrotic areas. Nonmeasurable lesions are those that are too small, seen only on T2-weighted or FLAIR images, or ill-defined. A maximum of five measurable lesions are recommended as targets, and the sum of the product of the orthogonal diameters of the target lesions is used for response assessment. Nontarget lesions that are enhancing or seen only on T2-weighted or FLAIR images should be assessed subjectively for changes in size and enhancement, with use of advanced MR imaging techniques when necessary.

Although the RANO criteria recommend subjective assessment of the nonenhancing tumor component on FLAIR or T2-weighted images, it is often difficult to differentiate the high signal intensity due to tumor progression from high signal intensity due to other causes, like radiation, ischemia, or infection. New techniques like perfusion MR imaging, MR spectroscopy, diffusion-weighted imaging, and use of novel positron emission tomography (PET) tracers are being evaluated as biomarkers to identify both enhancing and nonenhancing tumors, which can enable further evolution and refinement of the RANO criteria (28).

Non–Small Cell Lung Cancer

Antiangiogenic MTTs

Most lung cancers (85%) are of the non–small cell type (NSCLC) and include the squamous and nonsquamous subtypes (adenocarcinoma, large cell carcinoma, and others) (29). Stage IV

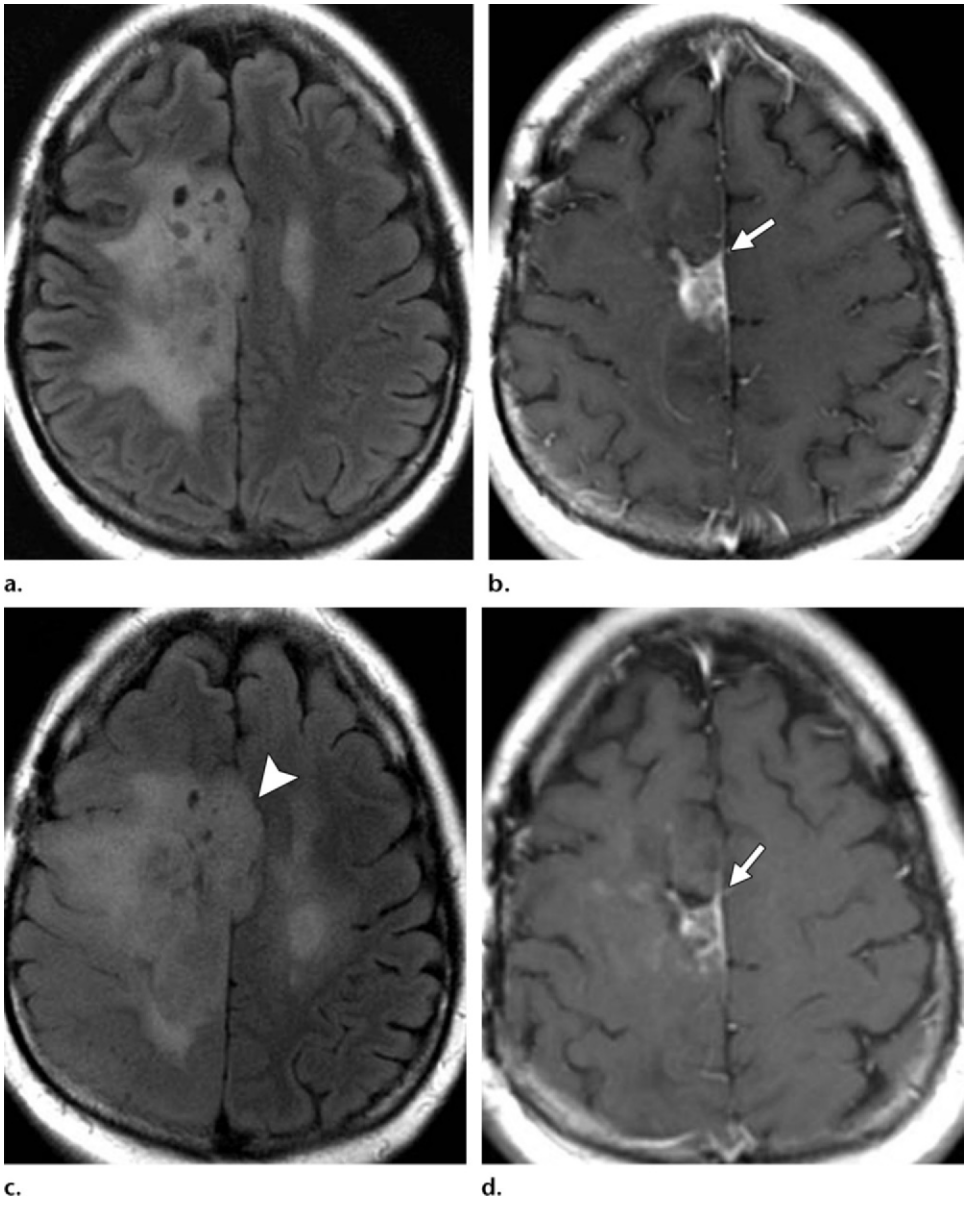


Figure 2. Recurrent glioblastoma in a 38-year-old man treated with bevacizumab and irinotecan. **(a, b)** Axial fluid-attenuated inversion-recovery (FLAIR) **(a)** and gadolinium-enhanced T1-weighted **(b)** MR images of the brain at baseline show a tumor that is hyperintense on the FLAIR image, with mild enhancement (arrow in **b**) in the superior component of the tumor. Note that the FLAIR image demonstrates greater extent of the tumor. **(c, d)** Corresponding MR images after two cycles of treatment show a decrease (20%) in enhancement of the tumor (arrow in **d**), consistent with stable disease according to the Macdonald criteria. Although there is a decrease in enhancement of the tumor at follow-up, the FLAIR image shows worsening edema and tumor extending beyond the midline (arrowhead in **c**), consistent with disease progression according to the Response Assessment in Neuro-oncology (RANO) criteria. The patient demonstrated clinical deterioration and underwent surgery, which confirmed disease progression.

NSCLC is associated with a dismal 5-year survival and is managed with systemic chemotherapy, with surgery and radiation therapy reserved for special situations (30). Combination chemotherapy with platinum compounds, taxanes, and pemetrexed is the mainstay of therapy for nonsquamous NSCLC (30).

In 2006, bevacizumab was approved for use with carboplatin and paclitaxel as first-line treatment of patients with advanced nonsquamous NSCLC on the basis of a randomized trial that showed a statistically significant survival benefit for patients receiving bevacizumab with chemotherapy compared with patients receiving chemotherapy alone (31). Bevacizumab is recommended with chemotherapy for NSCLC of nonsquamous histologic type (adenocarcinoma, large cell carcinoma, NSCLC not otherwise specified); NSCLC whose epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK)

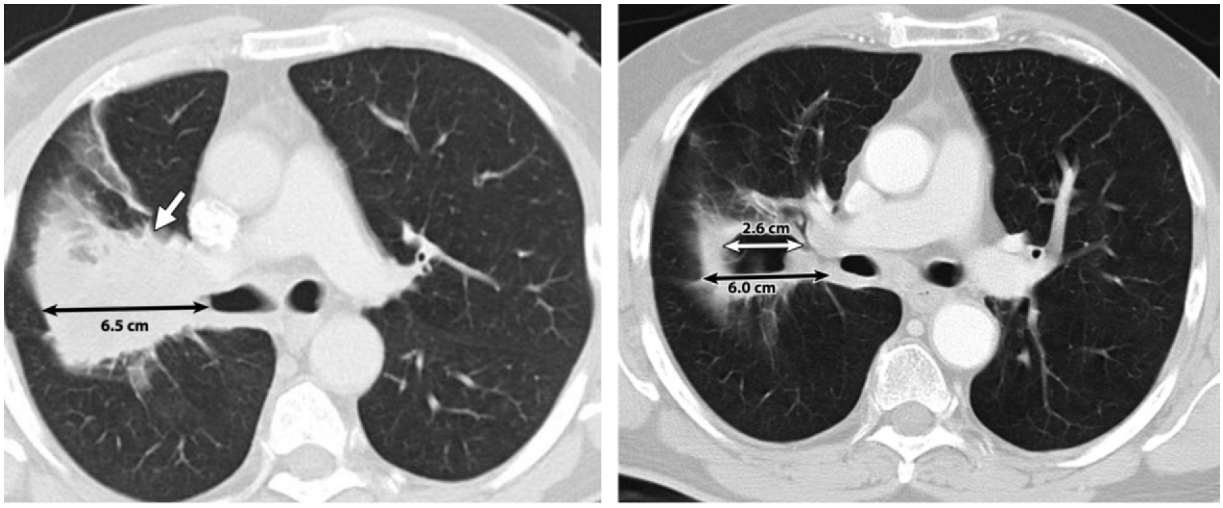


Figure 3. Stage III NSCLC (adenocarcinoma) in a 55-year-old man treated with paclitaxel, carboplatin, and bevacizumab. **(a)** Axial CT image of the chest at baseline shows a large right perihilar mass (arrow) measuring 6.5 cm in longest diameter. **(b)** Follow-up CT image after three cycles of treatment shows marked central cavitation in the tumor. Measurement of the tumor according to RECIST 1.1 criteria (6.0 cm) demonstrates no significant change in size, which qualifies as stable disease. However, the alternate method of subtracting the cavity (2.6 cm) from the tumor demonstrates a greater than or equal to 50% decrease in the longest dimension, consistent with a partial response according to RECIST 1.1 criteria.

gene rearrangement status is either negative or unknown; and NSCLC patients without a recent history of hemoptysis (Fig 3). Bevacizumab can be used as monotherapy for maintenance if used with chemotherapy initially. Bevacizumab is not used with NSCLC of squamous histologic type due to reports of life-threatening pulmonary hemorrhage, especially with central and cavitating tumors.

Alternate TRC

Bevacizumab causes central tumor necrosis in response to antiangiogenesis, with tumor cavitation indicating response to treatment. Tumor cavitation occurs in 14%–24% of lung cancer patients treated with antiangiogenic drugs (15,32). In a study of 72 patients with NSCLC treated with chemotherapy and bevacizumab, tumor cavitation was noted in 19% of cases (33) (Fig 3). Three distinct patterns of tumor cavitation were observed: cavitation in a dominant nodule, cavitation in a nondominant nodule, and cavitation in a nondominant nodule with surrounding interstitial abnormalities. Recurrence was seen as filling-in of the cavity in 79% of patients (33).

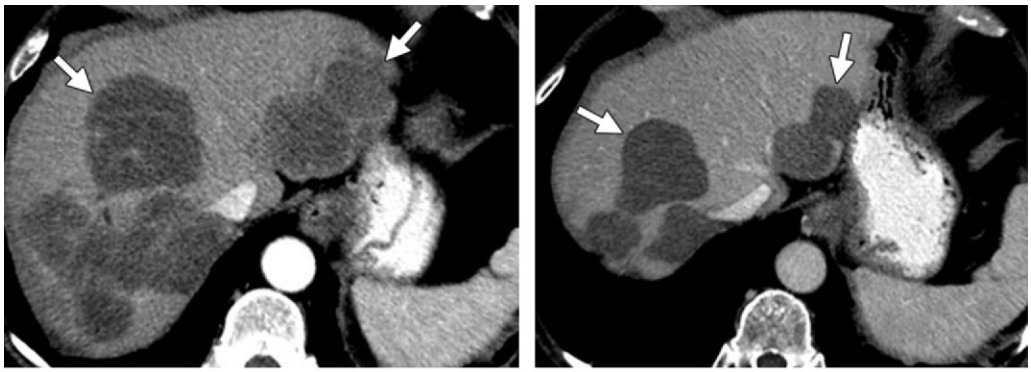
Interpreting treatment response in the setting of tumor cavitation is challenging. RECIST-based criteria, which use the sum of the longest diameters of target lesions to determine treatment response, do not take into account the loss of tumor volume that occurs due to cavitation. Crabb et al (15), in their study of 51 patients with NSCLC treated with VEGF inhibitors and chemotherapy or chemotherapy alone, modified RECIST response assessment by subtracting the diameter of the cavity from the actual diameter of the tumor (Fig 3). They found that this assessment also allowed classification of disease progression, which occurs by filling-in of the cavitary portion of the tumor with unchanged size. Cavitation was noted in 24% of patients receiving VEGF inhibitors and/or chemotherapy; the authors concluded that the modified response assessment may alter outcomes in clinical trials, although a difference was noted in only a minority of patients in their study (15).

The new response criteria for NSCLC proposed by Lee et al (34) for evaluating response to EGFR TKIs is based on a similar domain and was found to have statistically significant correlation with survival. Of the 75 patients in their study, 16 nonresponders according to RECIST criteria achieved a partial response according to the new response criteria (34).

Colorectal Cancer

Antiangiogenic MTTs

The prognosis of colorectal cancer depends on the stage of disease at the time of diagnosis. Stage IV colorectal cancer was conventionally associated with a grim prognosis, with survival of less than 6 months after diagnosis. The outcome has significantly improved in the past decade due to improved surgical techniques, chemotherapeutic regimens, and new MTTs. Currently, the most widely used first-line regimens for metastatic colorectal cancer are FOLFOX (combination of 5-fluorouracil and leucovorin [5-FU/LV] and oxaliplatin) and FOLFIRI (combination of 5-FU/LV and irinotecan).



a. b.

Figure 4. Stage IVB KRAS-mutant colorectal cancer in a 75-year-old man treated with FOLFOX and bevacizumab. **(a)** Axial contrast-enhanced CT image of the liver shows multiple heterogeneously hypoattenuating lesions (arrows) consistent with metastases. **(b)** Follow-up CT image after five cycles of chemotherapy shows decreased size and enhancement of the liver lesions (arrows). The lesions demonstrate decreased attenuation (from 56 HU to 32 HU) and appear homogeneous with a sharp tumor-liver interface, consistent with a favorable treatment response.

Bevacizumab was approved by the FDA for first-line treatment in metastatic colorectal cancer in 2004 in combination with FOLFOX and FOLFIRI (3). Bevacizumab can be combined with second-line regimens if it has not been used with the first-line regimen (35,36). Regorafenib has been shown in recent trials to have activity in metastatic colorectal cancer refractory to chemotherapeutic drugs and was approved by the FDA in 2012 (37,38). Aflibercept is being evaluated with second-line FOLFIRI following progression with first-line non–irinotecan-containing regimens.

Alternate TRC

Both bevacizumab and conventional chemotherapeutic regimens alter the morphologic characteristics of tumors, affecting overall heterogeneity, enhancement, and distinctness of margins, in addition to size (16,39,40) (Fig 4). These morphologic changes correlate with replacement of tumor tissue by fibroconnective tissue (16). In a study of 50 patients with liver metastases from colorectal cancer treated with bevacizumab and conventional chemotherapy, Chun et al (16) found that tumors responding to treatment showed a change in morphology from heterogeneous lesions with ill-defined margins to homogeneous lesions with a sharp tumor-liver interface (Fig 4). They further found that the morphologic response correlated well with pathologic complete response. Histologic tumor regression determined by the percentage of residual viable tumor cells has been shown to correlate with clinical outcome (16).

In view of these morphologic changes, RECIST-based criteria are suboptimal for interpretation of treatment response in liver metastases from colorectal cancer and do not reflect histologic tumor regression. Chun et al (16) found that RECIST criteria did not correlate with survival, in contrast to morphologic criteria. In another study by Chung et al (39), evaluating treatment response by using tumor size and attenuation changes at CT (≥10% decrease in size or ≥15% decrease in attenuation) was a better predictor of time to tumor progression than changes in tumor size alone. This study evaluated 59 patients treated with bevacizumab-containing chemotherapy (n = 30) or chemotherapy alone (n = 29) and found more favorable responses with modified CT criteria than with RECIST 1.1.

Hepatocellular Carcinoma

Antiangiogenic MTTs

HCC is the most common primary liver tumor and the third most common cause of cancer mortality in the world. The management of HCC is determined by the extent of disease at diagnosis and the status of the background liver as determined by the Child-Pugh classification. There are several treatment options for patients with unresectable HCC who do not meet the criteria for liver transplantation, including radiofrequency ablation, transarterial chemoembolization, transarterial radioembolization, stereotactic body radiation therapy, and systemic chemotherapy. Cytotoxic chemotherapy has poor response rates in HCC.

Sorafenib was approved for advanced HCC in 2007 on the basis of a phase III trial (Sorafenib HCC Assessment Randomized Protocol [SHARP] trial), which showed significant survival benefit for patients receiving sorafenib (41). Currently, sorafenib is indicated for unresectable and extensive HCC that is not suitable for liver transplantation, for localized HCC that is inoperable due to comorbidities, and for metastatic HCC (Fig 5).

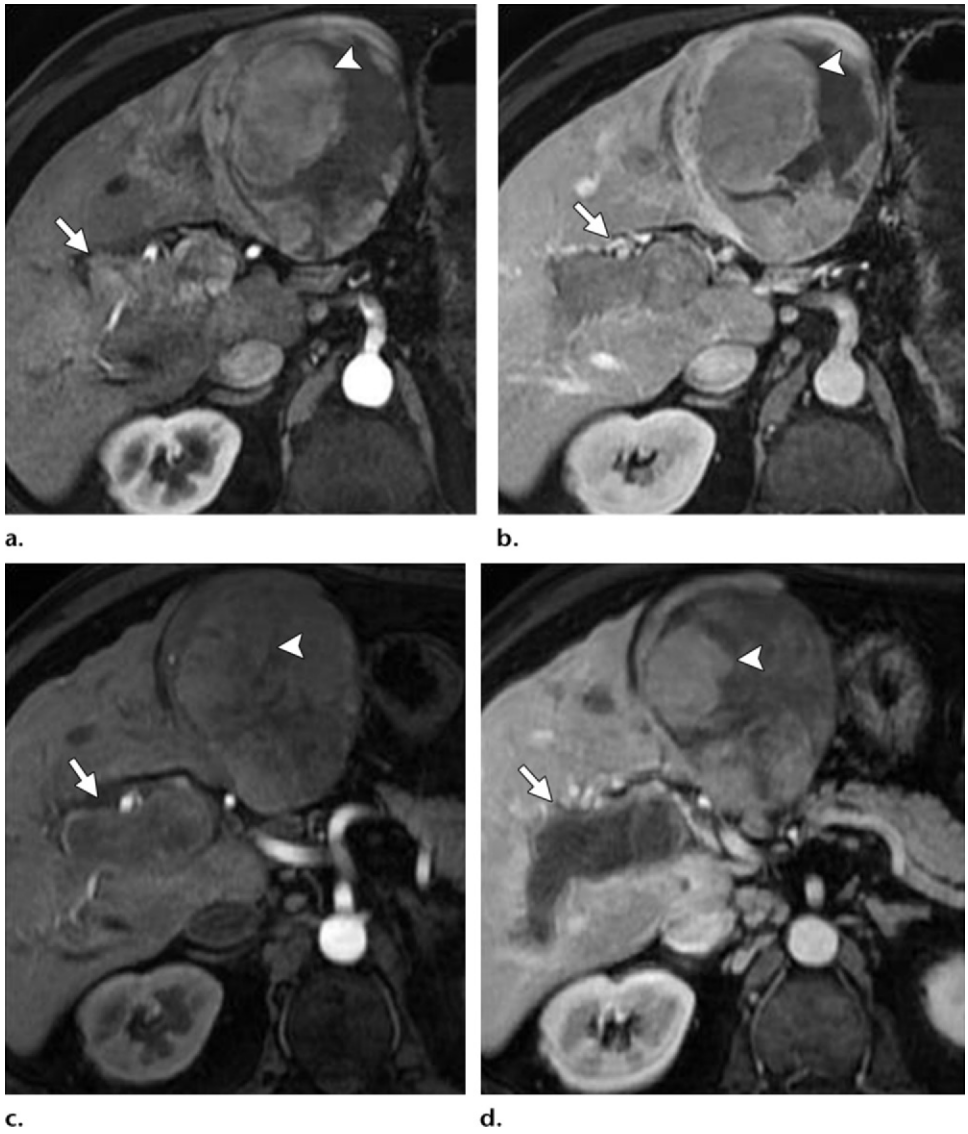


Figure 5. HCC in a 46-year-old man treated with sorafenib. **(a, b)** Arterial phase **(a)** and venous phase **(b)** axial gadolinium-enhanced fat-suppressed T1-weighted MR images show a large, exophytic, predominantly necrotic mass in the left lobe with a dominant hypervascular component anteriorly (arrowhead). The portal vein is dilated with an enhancing tumor thrombus (arrow). **(c, d)** Corresponding MR images after 4 months of treatment show a decrease in the arterial enhancement of the dominant hypervascular component of the mass (arrowhead in **c**) and the tumor thrombus (arrow in **c**). There is more necrosis in the tumor **(d)** with a decrease in the size of the dominant enhancing component (arrowhead in **d**). The tumor thrombus is completely devascularized (arrow in **d**).

The response to sorafenib is determined by the Child-Pugh status, with better outcome for patients with Child-Pugh A disease than Child-Pugh B disease.

Alternate TRC

HCC is a hypervascular tumor that shows marked enhancement in viable areas of the tumor during the arterial phase of imaging (Fig 5). The action of MTTs like sorafenib in HCC is seen as a decrease in the arterial enhancing component of the tumor and an increase in tumor necrosis. Studies have shown that RECIST criteria correlate poorly with clinical benefit in HCC treated with antiangiogenic MTTs, as these criteria do not take into account the concept of viable tumor tissue (41,42).

In 2008, the American Association for the Study of Liver Diseases (AASLD) and the Journal of the National Cancer Institute (JNCI) together proposed new guidelines, referred to as modified RECIST (mRECIST), for assessing treatment response in clinical trials for HCC (17,18). mRECIST differs from RECIST in that only the enhancing portion of the target lesions during the arterial phase of dynamic imaging is measured in response assessment (17,18,43) (Fig 5). In a retrospective study of 53 patients with

HCC treated with sorafenib, Edeline et al (43) found that patients classified as having stable disease according to RECIST had a different overall survival according to mRECIST.

The Response Evaluation Criteria in Cancer of the Liver (RECICL) were proposed to overcome the limitations of mRECIST in evaluating irregular tumors (19). RECICL differs from mRECIST in that it incorporates two-directional measurement (product of the diameters of the major axis and the axis perpendicular to it) and evaluation of all phases of enhancement for detecting new lesions. In their study of 156 patients with HCC treated with sorafenib, Arizumi et al (19) concluded that only RECICL correlated with overall survival.

Renal Cell Carcinoma

Antiangiogenic MTTs

The 5-year survival for RCC decreases from 80%–90% for localized disease to 7%–12% for advanced disease (44). Up to 30% patients with RCC have metastatic disease at presentation. The management of metastatic RCC is difficult, as RCC is refractory to conventional chemotherapy.

Better understanding of the genetics of RCC, especially the upregulation of the proangiogenic von Hippel–Lindau gene, led to the development of MTTs with antiangiogenic activity. Sunitinib was the first MTT to be approved by the FDA in 2006 for advanced RCC following demonstration of a statistically significant progression-free survival (45). Subsequently, four other TKIs with antiangiogenic action have been approved for advanced RCC: sorafenib, pazopanib, axitinib, and bevacizumab with interferon. The National Comprehensive Cancer Network (NCCN) guidelines recommend all the anti-VEGF MTTs for RCC of clear cell histologic type and sunitinib and sorafenib for RCC of non–clear cell histologic type.

Alternate TRC

As with other solid tumors, TKIs cause little tumor shrinkage in metastatic RCC, with treatment response seen as a decrease in enhancement at contrast-enhanced CT (Figs 6, 7). Therefore, RECIST is suboptimal in evaluating the therapeutic efficacy of TKIs. Smith et al (20) proposed the Size and Attenuation CT (SACT) criteria based on long-axis measurements and volumetric mean tumor attenuation changes at contrast-enhanced CT.

These criteria were further refined to account for structural and morphologic changes by proposing the MASS criteria (21). In addition to size and attenuation, the MASS criteria use morphologic or structural changes, including marked central necrosis (defined as a change of >50% between the enhancing area and area of fluid attenuation on posttherapy images) and marked central fill-in (defined as subjective change of central necrosis to solid enhancement), to identify patients with favorable, indeterminate, and unfavorable responses (Fig 7).

In their study of 84 patients, Smith et al (21) found that a favorable response according to MASS criteria had sensitivity of 86% compared with 17% for a partial response according to RECIST for identifying patients with a good clinical outcome of progression-free survival of more than 250 days. In a multi-institutional study of 70 patients with metastatic RCC treated with anti-VEGF MTTs, a decrease in the sum of the long-axis diameters of the target lesion by 10% at the first posttreatment CT examination was a better early predictor of outcome than RECIST 1.0, Choi criteria, or greater than 15% or greater than 20% attenuation changes (46). A subsequent validation study confirmed that the criterion of 10% shrinkage was a reproducible radiologic indicator (47).

Soft-Tissue Sarcoma

Antiangiogenic MTTs

More than 50 histologic subtypes of soft-tissue sarcoma are known, of which GIST is the most common subtype. The mainstay of GIST therapy is surgical resection. GISTs less than 2 cm in size with a low mitotic rate (<5 per 50 high-power fields) are regarded as benign. However, all other GISTs larger than 2 cm have the risk of developing metastasis and local recurrence. Imatinib is the first-line drug used in treatment of patients with advanced or metastatic GIST and was approved by the FDA in 2002. Subsequently, imatinib was also found to have a role in the adjuvant and neoadjuvant setting in GIST.

For patients with primary or secondary resistance to imatinib, sunitinib was approved by the FDA in 2006 as a second-line drug. Studies have shown that sunitinib has better activity in GISTs with KIT exon 9 mutations and GISTs that do not harbor mutations in KIT or wild-type GISTs than in GISTs with KIT exon 11 mutations. Sunitinib is therefore being evaluated as first-line therapy for certain wild-type GISTs, including GISTs occurring in pediatric patients, succinate dehydrogenase (SDH)–deficient GISTs, and GISTs associated with syndromes like neurofibromatosis (48). Regorafenib was approved in 2013 for imatinib- and sunitinib-resistant GIST as a third-line agent.

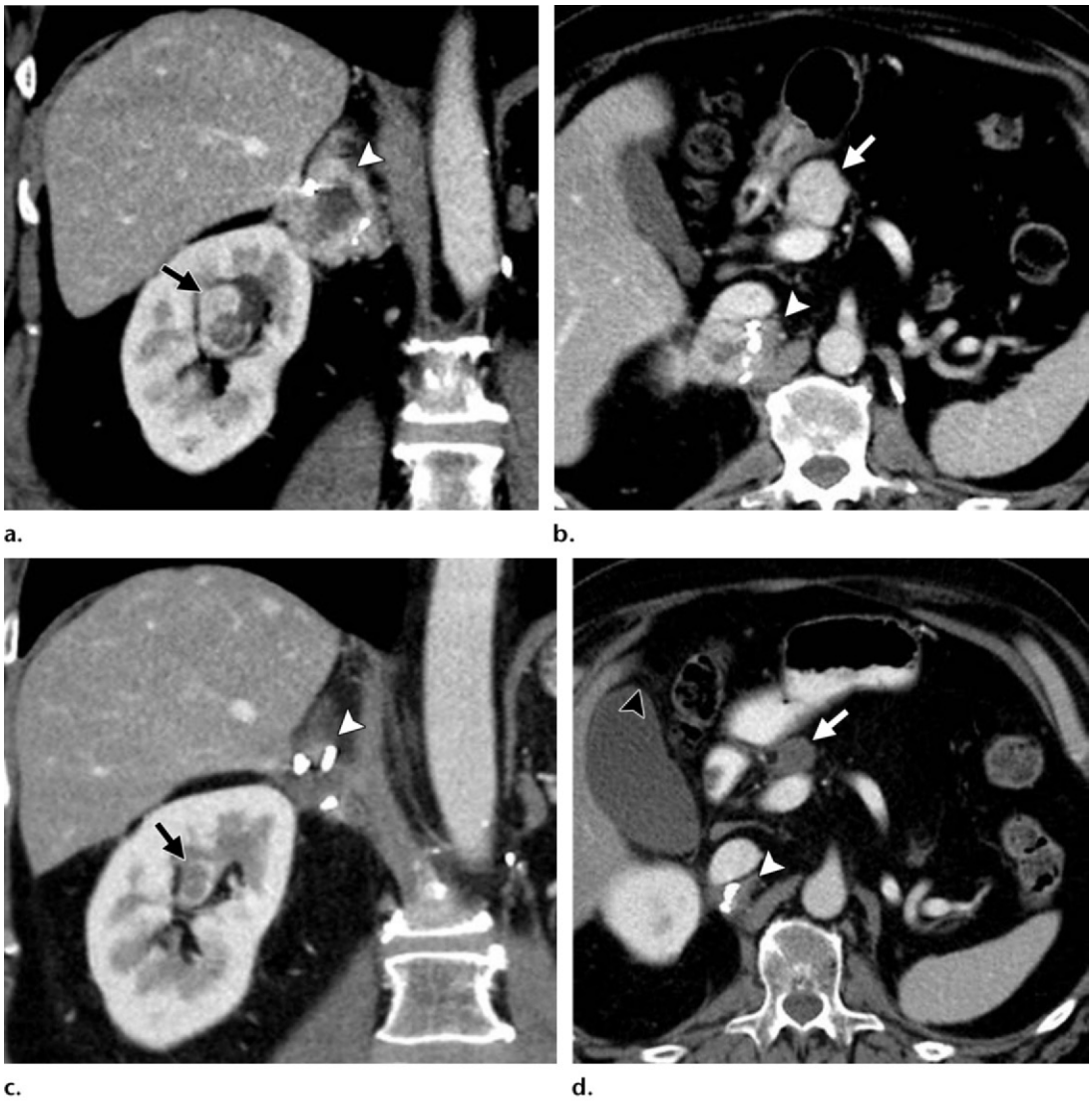
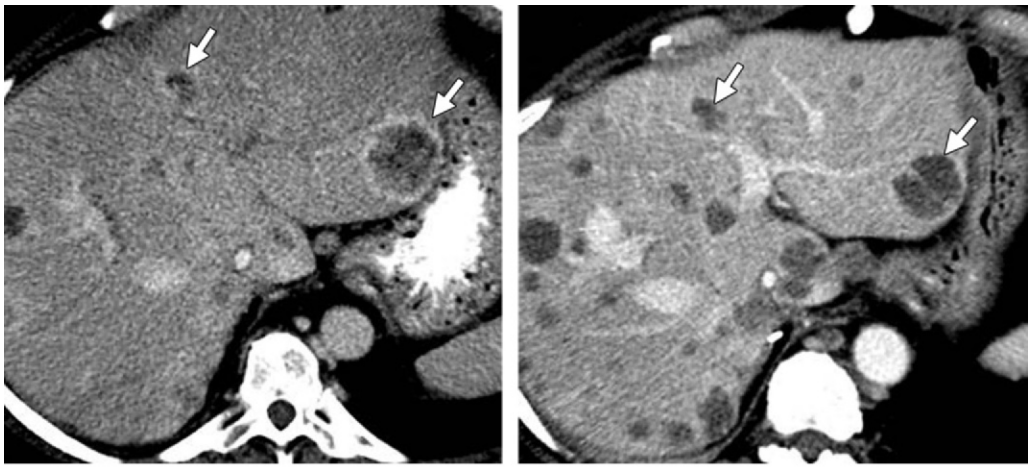


Figure 6. Metastatic RCC in a 62-year-old man. Contrast-enhanced CT images of the abdomen before **(a, b)** and 2 months after **(c–e)** treatment with sunitinib show a decrease in the size and enhancement of metastatic deposits in the right kidney (black arrow), pancreas (white arrow), and right adrenal gland (white arrowhead in **a–d**). However, there is new gallbladder distention with minimal pericholecystic stranding (black arrowhead in **d**, arrowheads in **e**), which resolved with temporary discontinuation of sunitinib. The patient had right upper quadrant discomfort and mildly elevated results of liver function tests.

As with GIST, non-GIST soft-tissue sarcoma frequently metastasizes and is difficult to treat due to resistance to conventional chemotherapy. Several TKIs that inhibit the VEGF axis are under research in non-GIST soft-tissue sarcoma; pazopanib was the first to be approved for advanced soft-tissue sarcoma (excluding adipocytic soft-tissue sarcoma and GIST) in 2012 (49) (Fig 8).

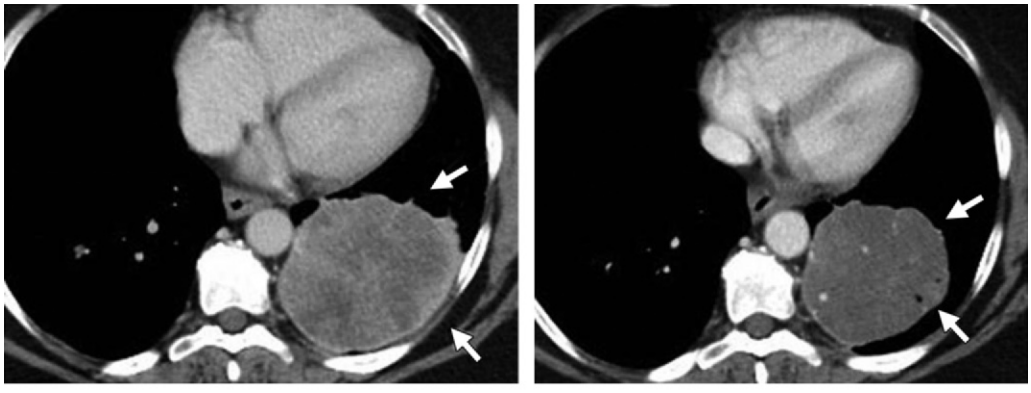
Alternate TRC

Imatinib causes a uniform decrease in tumor attenuation with little change in tumor size in metastatic GIST (Fig 9). Interpreting treatment response of metastatic GIST to imatinib by using RECIST underestimates the response (50). On the basis of this observation, the Choi criteria were proposed, which incorporate attenuation changes in target lesions: a 10% decrease in one-dimensional size or 15% decrease in attenuation



a. b.

Figure 7. Metastatic RCC in a 58-year-old man treated with sorafenib. Axial contrast-enhanced CT images of the abdomen at baseline **(a)** and 1 month after treatment **(b)** show complete resolution of the peripheral enhancing rim of the index lesions (arrows). In comparison with the baseline, there is a more than 40 HU decrease in the attenuation of all lesions, consistent with a favorable response according to the Morphology, Attenuation, Size, and Structure (MASS) criteria. The increase in the number of lesions on the posttreatment image can be confused with disease progression (pseudoprogression).



a. b.

Figure 8. Metastatic synovial sarcoma in a 39-year-old man treated with pazopanib. Axial contrast-enhanced CT images of the chest at baseline **(a)** and 1 month after treatment **(b)** show a decrease in enhancement and internal heterogeneity of a lung metastasis (arrows) with a mild decrease in size.

is deemed a partial response; an increase in size of 10%, new intratumoral nodules (nodule within a cyst), or an increase in intratumoral nodules is deemed progressive disease (22) (Fig 9).

In a study of 40 patients, Choi et al (22) found that these criteria correlated well with PET responses and had greater sensitivity than RECIST for identifying PET responders. Subsequent studies showed that Choi criteria also correlated with progression-free survival and disease-specific survival (51). Response of imatinib-resistant GISTs to sunitinib has radiologic features identical with those of imatinib response; therefore, Choi criteria are applicable to sunitinib responses as well (52).

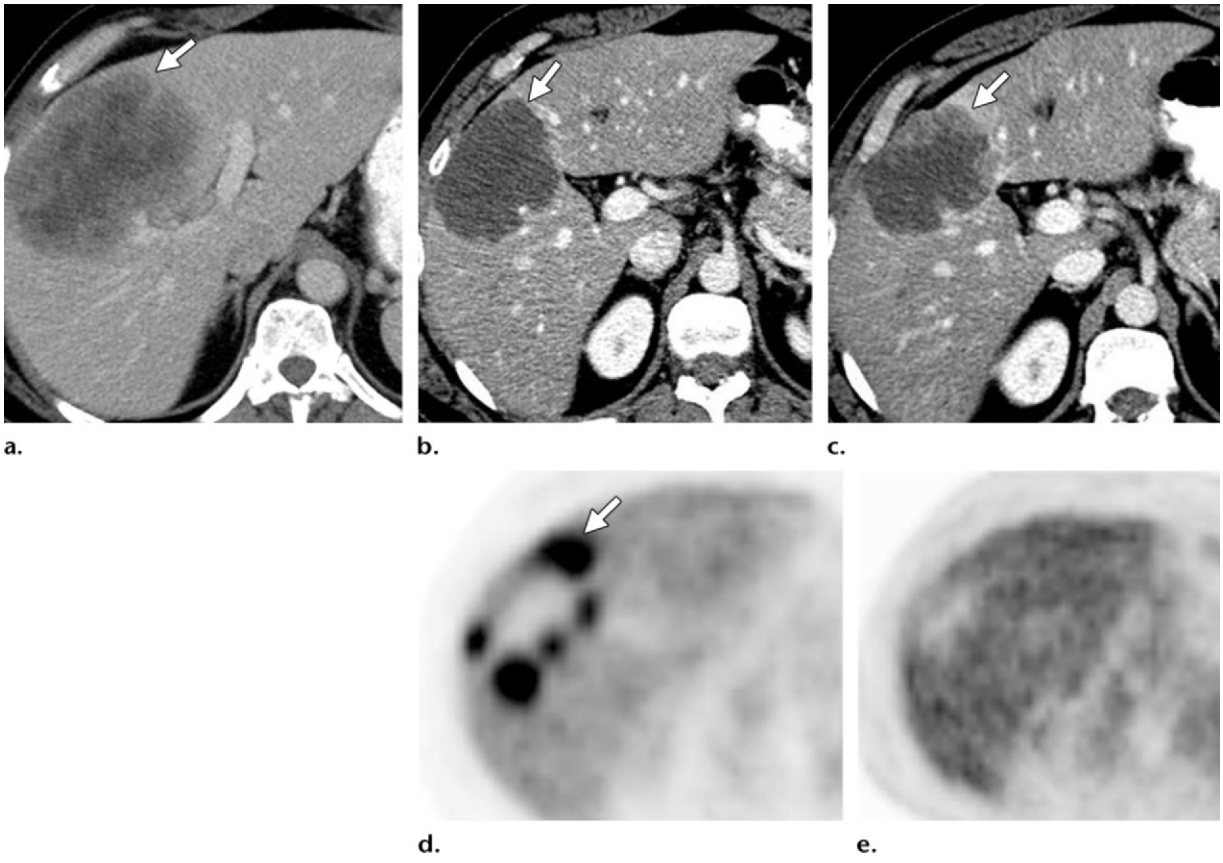
Recurrent GISTs with intratumoural nodules or masses show a decrease in attenuation, producing a "cyst-within-nodule-within-cyst" appearance that correlates with resolution of radiotracer uptake at PET/CT (52) (Fig 9). With respect to non-GIST soft-tissue sarcoma, Stacchiotti et al (53) showed that Choi criteria had greater sensitivity for assessing treatment response compared with RECIST.

Contrary to earlier observations favoring Choi criteria over RECIST for assessing treatment response in GIST, a recent phase II trial of 20 patients treated with third-line regorafenib found that RECIST 1.1 and WHO criteria performed better than Choi criteria in assessing treatment response (54). This observation needs to be validated in larger prospective studies.

Unusual Patterns of Treatment Response: Beyond the Alternate TRC

Antiangiogenic MTTs are associated with unusual patterns of treatment response not addressed by

Figure 9. Metastatic GIST in a 43-year-old man initially treated with imatinib. **(a, b)** Axial contrast-enhanced CT images of the chest at baseline **(a)** and 6 months after treatment **(b)** show a marked decrease in the attenuation of a liver metastasis (arrow) with a concurrent decrease in size. **(c)** Follow-up CT image 12 months after the start of treatment shows no change in the size of the metastasis, but there is a nodule-within-mass recurrence (arrow). **(d)** Fluorine 18 fluorodeoxyglucose PET/CT image shows the recurrence as intense metabolic activity in the nodular areas (arrow). Sunitinib treatment was started. **(e)** Follow-up PET/CT image 3 months later shows resolution of the metabolic activity.



the alternate TRC. These patterns are being increasingly recognized and are a potential source of confusion and challenge for the radiologist (40). Treatment with antiangiogenic MTTs can unmask previously isoattenuating liver lesions that become apparent after treatment due to the decrease in attenuation (Fig 7). Such lesions can be interpreted as new liver lesions and are definable with RECIST as progression. This phenomenon of pseudoprogression is commonly encountered with liver metastases from colorectal cancer or RCC (Fig 7).

Response to MTTs can sometimes be associated with an increase in size despite the decrease in attenuation. This increase in size can be due to intratumoral edema or to the appearance of the masked isoattenuating component of the lesion. In such cases, follow-up images usually show subsequent size decrease. Antiangiogenic MTTs like sunitinib can occasionally induce intratumoral hemorrhage due to disruption of intratumoral blood vessels. Hemorrhage can result in an increase in tumor attenuation, mimicking intratumoral nodules. MR imaging and PET/CT can be useful in such cases to demonstrate the hemorrhage and exclude metabolic activity, respectively.

In our experience, when pseudoprogression is suspected, the decision to change treatment should be deferred until after a follow-up study, which will show stabilization or improvement in the case of pseudoprogression. Discussion with the treating oncologist and correlation with the clinical status of the patient and tumor markers, together with follow-up imaging, can help differentiate pseudoprogression from true progression (40). Commonly used tumor markers include carcinoembryonic antigen (CEA) in colorectal cancer, α-fetoprotein (AFP) in HCC, serum prostate-specific antigen (PSA) in prostate cancer, chromogranin A in neuroendocrine tumors, cancer antigen (CA) 19-9 in pancreatic cancer, CA-125 in ovarian cancer, and CA 27-29 in breast cancer. Although there can be a temporal difference between change in tumor marker level and radiologic changes, correlation with tumor marker status is often helpful in the setting of unusual treatment responses.

An additional step that can help in interpreting atypical responses at imaging is to know the performance status of the patient by discussing it with the clinician. Commonly used scales for scoring the performance status of patients based on ability to perform daily activities include the Karnofsky score (scale of 100–0, where 100 indicates perfect health and 0 indicates death) and the Eastern Cooperative Oncology Group (ECOG)/WHO/Zubrod score (scale of 0–5, where 0 is perfect health and 5 is death). A good score on the performance scale and declining tumor markers can help in giving the benefit of the doubt to the patient when an unusual treatment response is encountered at imaging.

Novel Imaging Techniques: Future Directions in Tumor Response Assessment

Objective response to MTTs at imaging often lags behind response at a molecular level. Newer imaging techniques are being explored to detect and predict early responses by using functional imaging techniques.

Changes in tumor neovascular channels in response to antiangiogenic MTTs can be monitored by using perfusion MR imaging techniques, including dynamic susceptibility contrast-enhanced (DSC) imaging and dynamic contrast-enhanced (DCE) imaging (55). DSC MR imaging (T2- and T2*-weighted imaging) allows estimation of perfusion parameters like relative blood volume (rBV), relative blood flow (rBF), and mean transit time (MTT). Studies have shown that rBV correlates with tumor vascularity and grade, especially in gliomas (56), and that changes in relative cerebral blood volume and flow correlate with radiologic response to antiangiogenic drugs (28). DCE MR imaging (T1-weighted imaging) allows estimation of capillary permeability and calculation of the volume transfer constant (K^{trans}) and rate constant (k^{ep}) in highly vascular tumors like RCC and gliomas (57,58). High values of K^{trans} indicate high blood flow and high permeability, and changes in it after treatment represent a true pharmacodynamic effect of the drug (57,58).

MR imaging techniques that rely on intrinsic contrast—like arterial spin labeling (ASL) MR imaging, where inflowing arterial blood is magnetically inverted or saturated, and blood oxygen level–dependent (BOLD) MR imaging, where vascular function is analyzed by using deoxyhemoglobin—are under research as tools for antiangiogenic therapy response assessment (59,60). Decrease in tumor blood flow at ASL MR imaging has been shown to predict a favorable outcome in metastatic RCC treated with antiangiogenic therapy (59). MR spectroscopy, which helps in analyzing the chemical makeup of tumors, has been shown to be useful in differentiating true progression from pseudoprogression (28). Novel PET tracers like ^{18}F-fluorothymidine, which is an indicator of cellular proliferation, have been shown to demonstrate recurrent tumor better than ^{18}F-fluorodeoxyglucose and correlate with outcome (28).

DCE CT is less complex than perfusion MR imaging and provides comparable perfusion parameters. Limited data on the utility and reproducibility of DCE CT in response assessment after antiangiogenic therapy have shown strong correlation between contrast enhancement characteristics and tumor microvessel density (61). Perfusion CT has been shown to differentiate early responders from nonresponders in lung cancer (62), HCC (63), and GIST (64) treated with MTTs. In metastatic GIST, volume perfusion CT has been shown to differentiate pseudoprogression from true progression by demonstrating lack of perfusion in treated metastases that enlarge in size due to myxoid degeneration or hemorrhage (64). Limitations of DCE CT include limited coverage, which can be overcome by improvement in technical hardware, and errors in estimation of parameters due to artifacts of motion and beam-hardening (61).

Complications Associated with Antiangiogenic MTTs

VEGF mediates several normal physiologic mechanisms, ranging from maintaining endothelial integrity to normal wound healing. Interference with these physiologic mechanisms by antiangiogenic MTTs can be counterproductive and result in several class-specific toxic effects (65,66). In addition, some of the MTTs have unique drug-specific toxic effects (Table 3).

Neurologic Complications

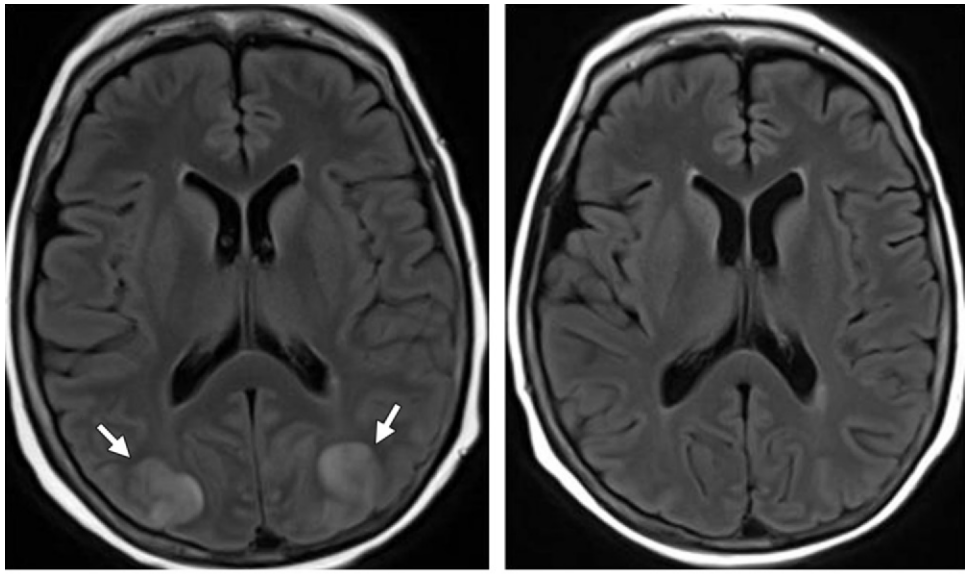
Bevacizumab and TKIs like sunitinib and sorafenib have rarely been associated with posterior reversible encephalopathy syndrome (PRES), a condition earlier reported to be associated with severe hypertension, pre-eclampsia or eclampsia, renal disease, organ transplantation, and immunosuppressive and cytotoxic chemotherapy drugs. PRES manifests clinically as headache, nausea, seizures, and visual loss (67). CT and MR imaging findings in PRES include cortical and subcortical white matter abnormalities in the occipital, posterior temporal, and parietal lobes (65) (Fig 10).

The pathophysiology of PRES associated with antiangiogenic MTT is hypothesized to be related to cerebral vascular endothelial cell damage, which impairs cerebrovascular autoregulation, causing cerebral edema. Seet and Rabinstein (67)

Table 3: Complications Associated with Antiangiogenic MTTs

Organ System	Complication	MTTs Implicated
Neurologic	PRES	Bevacizumab, sorafenib, sunitinib
Pulmonary	Tumor cavitation and hemoptysis	Bevacizumab
	Pneumothorax	Bevacizumab
Gastrointestinal	Pneumatosis intestinalis	Bevacizumab, TKIs
	Bowel perforation	Bevacizumab, TKIs
	TBF	Bevacizumab, TKIs
	Enterocolitis	TKIs
Hepatobiliary	Hepatic steatosis	Bevacizumab, TKIs
	Cholecystitis	TKIs
Pancreatic	Pancreatitis	TKIs
Vascular	Thromboembolism (arterial, venous)	Bevacizumab, TKIs
Miscellaneous	Thyroid dysfunction	TKIs
	Proteinuria	Sunitinib
	Hypertension	Bevacizumab, sunitinib
	Hand-foot syndrome	Sunitinib

Note.—PRES = posterior reversible encephalopathy syndrome, TBF = tumor-bowel fistula.



a. b.

Figure 10. Metastatic colorectal cancer treated with bevacizumab and FOLFOX in a 59-year-old woman who presented with headache and one episode of seizures. **(a)** Axial FLAIR image shows patchy hyperintense signal within the bilateral occipitoparietal regions (arrows), consistent with PRES. **(b)** Corresponding image after discontinuation of bevacizumab shows resolution of the hyperintense signal.

concluded that markedly elevated blood pressure seen with bevacizumab can cause endothelial damage and PRES. PRES responds promptly to withdrawal of bevacizumab with resolution of imaging findings.

Pulmonary Complications

Antiangiogenic MTTs cause cavitation in lung cancer and other types of pulmonary metastases. The postulated mechanism for tumor cavitation is central necrosis of lesions due to inhibition of angiogenesis. Although studies have shown that tumor cavitation does not increase the risk of hemoptysis, bevacizumab is contraindicated in patients with a recent history of hemoptysis due to the risk of hemorrhage (32,33). Similarly, cavitation in subpleural tumors due to antiangiogenic MTT can cause spontaneous pneumothorax (65), although this is not widely reported.

Gastrointestinal Complications

Pneumatosis intestinalis has been reported in association with bevacizumab and TKIs like sunitinib secondary to mucosal damage result-

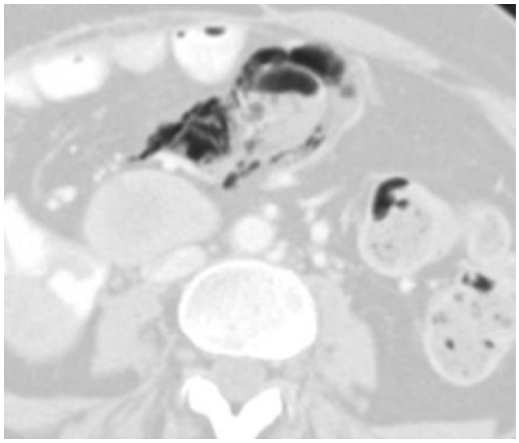
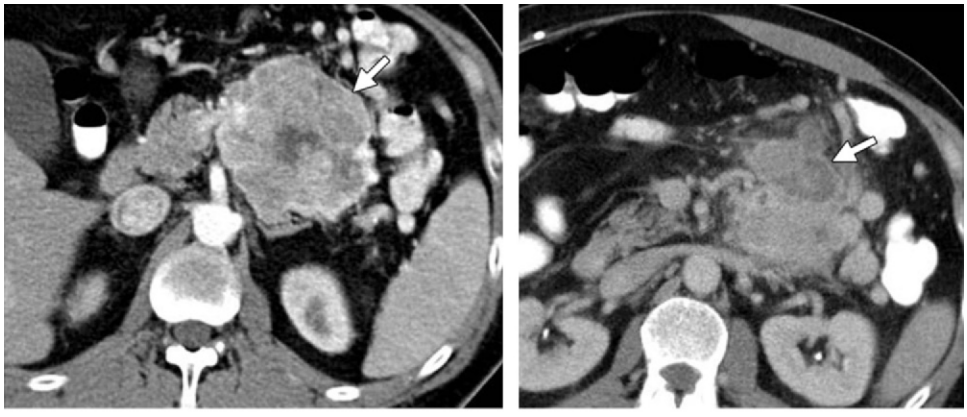


Figure 11. Colorectal cancer in a 63-year-old woman treated with adjuvant irinotecan and bevacizumab. Axial CT image of the abdomen shows intramural air in the colonic wall, consistent with pneumatosis intestinalis. This was managed conservatively with withdrawal of bevacizumab.



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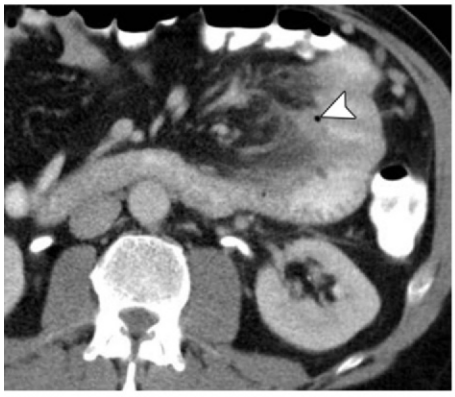


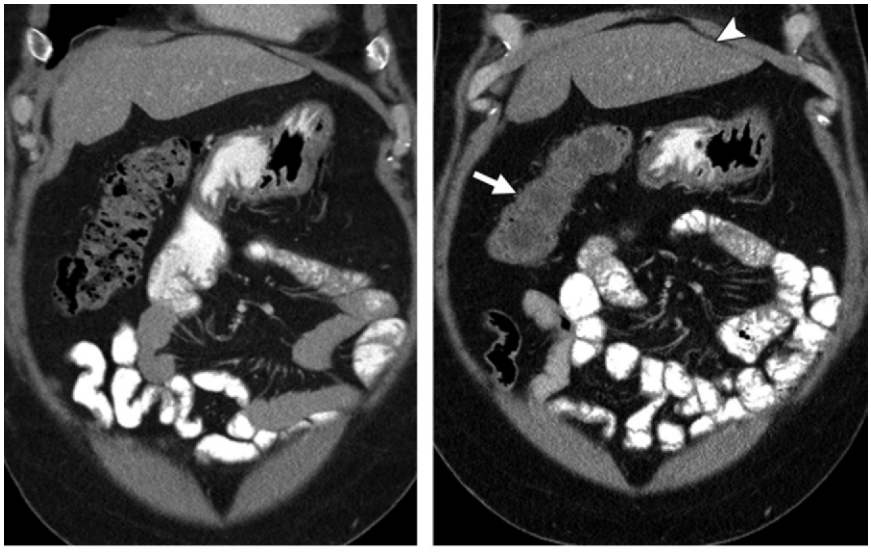
c.

Figure 12. Neuroendocrine tumor of the pancreas treated with 5-fluorouracil, leucovorin, and bevacizumab in a 49-year-old man who presented to the emergency department with acute abdominal pain. **(a)** Baseline contrast-enhanced CT image shows a large, hypervascular, exophytic pancreatic mass (arrow). **(b, c)** Axial contrast-enhanced CT images at the time of acute presentation show a decrease in tumor size (arrow in **b**) with new peritumoral stranding due to jejunal perforation (arrowhead in **c**).

ing from microvessel thrombosis and ischemia (68) (Fig 11). Pneumatosis can occur in asymptomatic patients and can occur early after starting MTT (69). One study showed that 71% of 24 patients with pneumatosis after MTT were asymptomatic (69). Timely detection of pneumatosis is imperative for optimal management, as most patients can be managed conservatively with prompt discontinuation of the MTT (69). Pneumatosis can be complicated by bowel perforation and tumor-bowel fistula (TBF).

Bowel perforation has been reported in up to 2% of patients receiving bevacizumab, especially in patients with recent colonoscopy or bowel surgery, radiation treatment, primary tumor in situ, peritoneal carcinomatosis, or high antiangiogenic drug dose (70) (Fig 12). It is usually recommended to discontinue bevacizumab at least 6 weeks before elective surgery, as it interferes with healing and increases the risk of anastomotic dehiscence (71). TBF represents contained perforation of bowel into tumor. In our experience with 51 patients, TBF was commonly seen with sarcomas, especially GISTs; was often asymptomatic; and was seen with both treatment response and progression (72). TBF is usually managed conservatively by discontinuing treatment but often persists at CT follow-up.

TKIs have been reported to cause enterocolitis, which manifests clinically as diarrhea and abdominal pain and radiologically as fluid-filled



a. b.

Figure 13. GIST in a 50-year-old man treated with sunitinib. Coronal reformatted CT images at baseline **(a)** and after 6 months of treatment **(b)** show diffuse thickening of the colon (arrow in **b**) with hyperemia, consistent with colitis. The patient had diarrhea. There is also a decrease in the attenuation of the liver (arrowhead in **b**), consistent with steatosis.

bowel loops and diffuse bowel wall thickening with or without ascites (70) (Fig 13). Rarely, TKIs can cause ischemic colitis (73).

Hepatobiliary and Pancreatic Complications

Antiangiogenic TKIs like sunitinib and pazopanib have been shown to cause asymptomatic elevation of serum aminotransferases and bilirubin (45,74). Hepatic steatosis has been reported with sunitinib, pazopanib, and bevacizumab, especially in combination with chemotherapy (66) (Fig 13). Gallbladder complications associated with antiangiogenic MTT can range from asymptomatic gallbladder distention and edema to acute acalculous cholecystitis (75) (Fig 6). The underlying mechanism is vascular endothelial damage and reduction in gallbladder blood flow (75). Management of these complications requires temporary or permanent drug withdrawal. Re-challenge should always be monitored with imaging due to the risk of recurrence of complications (75).

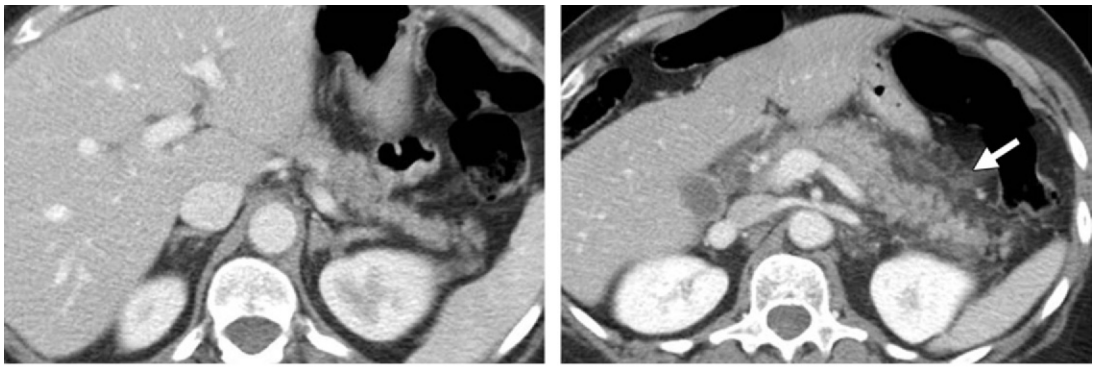
Asymptomatic elevation of serum lipase has been observed in more than 50% of patients taking antiangiogenic TKIs (76). However, acute pancreatitis is rare, occurring in up to 5% of cases (77) (Fig 14). The mechanism of pancreatic enzyme elevation and pancreatitis is thought to be secondary to pancreatic ischemia (78). In a study of 15 patients with MTT-associated pancreatitis detected at imaging, pazopanib and sunitinib were the most common offending MTTs and pancreatitis was more often focal, was usually uncomplicated, and resolved with conservative measures but recurred with re-challenge (78).

Vascular Complications

Anti-VEGF MTTs alter the hemostatic balance by interfering with the integrity of endothelial cells and increase the risk of bleeding. In a meta-analysis comparing chemotherapy with and without bevacizumab in metastatic colorectal cancer, the risk of bleeding requiring transfusion or life-threatening bleeding was 5% and 2%, respectively (79). Rare cases of hemorrhagic episodes including pulmonary hemorrhage have been reported with bevacizumab and sunitinib (80,81).

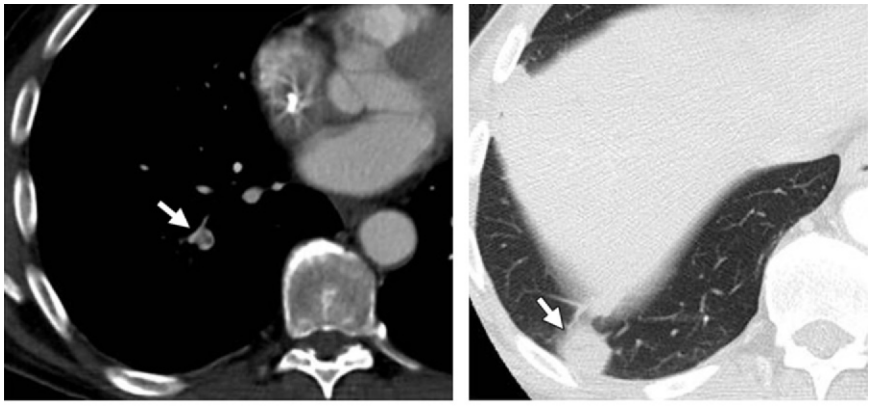
The literature on the risk of arterial thromboembolism (ATE) and venous thromboembolism (VTE) associated with anti-VEGF MTTs is controversial. While a pooled meta-analysis of 15 randomized trials to study the risk of bevacizumab-associated VTE showed increased risk, two other studies concluded there was no such risk of VTE with bevacizumab, though there was increased risk of ATE (82,83). Anti-VEGF TKIs have been found to increase the risk of ATE in a pooled analysis of phase II and III trials (84), while in another study they were not associated with VTE (85) (Fig 15). ATE associated with MTTs manifests as arterial thrombosis, resulting in cardiac and cerebrovascular events; VTE manifests as deep venous thrombosis and pulmonary embolism.

Management of thromboembolism associated with MTTs is challenging. Patients who develop thromboembolic complications often continue



a. b.

Figure 14. NSCLC in a 63-year-old woman treated with carboplatin and bevacizumab. Axial contrast-enhanced CT images before **(a)** and after **(b)** two cycles of treatment show an enlarged pancreas with peripancreatic stranding (arrow in **b**), consistent with acute pancreatitis. This was managed conservatively with discontinuation of bevacizumab.



a. b.

Figure 15. Metastatic colorectal cancer treated with FOLFOX and aflibercept in a 65-year-old man who presented for routine restaging. Axial CT images of the chest after four cycles of chemotherapy show a filling defect in the right lower lobe pulmonary arterial branch (arrow in **a**) with a peripheral pulmonary opacity (arrow in **b**), consistent with pulmonary embolism with a pulmonary infarct. This was attributed to a vascular toxic effect associated with aflibercept. The patient was clinically asymptomatic and therefore continued the treatment with anticoagulation.

the offending drug and undergo anticoagulation, as the risk of bleeding is less than the benefit of anticoagulation (86). There are no established recommendations for prophylaxis against thromboembolic and hemorrhagic complications associated with MTT (87).

Miscellaneous Complications

Thyroid dysfunction, especially hypothyroidism, has been reported to occur with sunitinib, sorafenib, pazopanib, and axitinib (88). The incidence was as high as 90% in some studies (88). Drug-specific toxic effects associated with sunitinib include hand-foot syndrome, rash, and proteinuria.

Conclusion

Anti-VEGF MTTs have helped define personalized cancer medicine for more than a decade. Awareness of the novel response appearances with antiangiogenic MTTs has led to the development of personalized TRC. Unanticipated sites of toxic effects have also been described with these drugs. Given the anticipated increase in their use in clinical practice, radiologists will benefit tremendously from understanding the various treatment response patterns and toxic effect profiles of anti-VEGF MTTs.

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