

Imaging techniques used for the real-time assessment of angiogenesis in digestive cancers

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Abstract

Angiogenesis has a critical role in primary tumor growth and the development of metastases. Several angiogenesis inhibitors were recently developed, being a very attractive target for digestive tumor therapy. However, individualized therapy should not only be based on the pre-treatment imaging evaluation, but also on sensitive monitoring of microvascular changes during treatment. State-of-the-art imaging techniques have the potential to visualize and characterize angiogenesis, although the technology and methodologies employed are recent and need further validation. The aim of this series of reviews was to analyze and enhance current knowledge and future perspectives about the real-time assessment of angiogenesis in digestive cancers, used for the longitudinal monitoring of the effects of chemo-radiotherapy (including anti-angiogenic therapies), as well as for the precise targeting of drugs through molecular-based drug-delivery systems.

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FROM THE EDITOR

Angiogenesis plays a critical role in tumor growth and metastasis. Most of the digestive cancers depend strictly on the development of an adequate blood supply in the form of neovascularization, which has a pivotal role in primary tumor growth and the development of metastasis. Thus, new blood vessels formed inside the tumor are usually highly permeable and provide a route for cancer cells to enter blood circulation^[1]. Tumor vascularization has been attracting a lot of attention in recent years due to possible implications in semi-quantitative diagnosis, as well as in prognosis stratification and targeted treatment^[2]. There are several ways traditionally proposed for investigation of tumor vascularization, but all these methods have several methodological flaws, including artifacts induced by air or fat [contrast-enhanced transabdominal ultrasound (US)], reduced resolution [contrast-enhanced computer tomography (CT)] or invasiveness (angiography or surgery)^[3].

Categorizing the patients through mini-invasive procedures, before chemotherapy or surgery, is of crucial importance. This has implications for the appropriate design of clinical trials, but also for the improvement of the decision making process, by selecting the tumors that are most likely to respond to treatment. Recently developed angiogenesis inhibitors represent a highly attractive target for tumor therapy, since they theoretically offer the hope of long-term control of tumor progression^[4]. Several anti-angiogenic inhibitors were recently developed

and have already been proven to be effective in clinical trials: bevacizumab (recombinant humanized anti-VEGF monoclonal antibody), cetuximab (anti-EGFR monoclonal antibody), erlotinib (tyrosine-kinase inhibitor), *etc*^[5]. Even though anti-angiogenic treatments are an established anti-cancer therapy, several mechanisms of tumor evasion and refractoriness have been described after inhibition of a single pro-angiogenic pathway, due to compensatory upregulation of different angiogenic pathways^[6]. Tailoring the anti-angiogenesis therapy as a function of the pre-operative imaging evaluation would be the next step, with a consequent decrease of toxicity, as well as an increase of median progression-free survival. Furthermore, these procedures would possibly allow a sensitive monitoring of microvascular changes caused by chemoradiotherapy or other ablative treatments. The ultimate goal would be to achieve an early diagnosis where the “angiogenic switch” could be delayed and tumor evasion mechanisms could be prevented, in order to induce a dormant state, while transforming cancer into a chronic disease^[7].

The main objectives of our series of reviews include the discussion of several advanced imaging techniques, complementary used for the real-time assessment of angiogenesis in digestive cancers. The advanced imaging techniques discussed will include several “red-flag” endoscopic techniques used for the depiction of minute changes in the vessel pattern of preneoplastic and neoplastic lesions (tri-modal imaging including autofluorescence imaging, zoom endoscopy and narrow band imaging)^[8]. Utility of Doppler-optical coherence tomography (D-OCT) for the depiction and quantification of low-velocity, low-volume blood flow will also be reviewed^[9]. These techniques will be supplemented by the presentation of confocal laser endomicroscopy and the potential applications of this breakthrough technique for the in-vivo assessment of vascularization based on the use of specific vascular contrast agents^[10]. Targeted contrast-enhanced ultrasound and its role in the depiction of angiogenesis, as well as ultrasound-directed drug delivery and the physics behind sonoporation will also be discussed^[11]. A comprehensive discussion will focus also on the use of contrast-enhanced endoscopic ultrasound (including specific harmonic imaging)^[12]. Current and future hybrid imaging techniques like real-time virtual sonography (a combination of US/EUS with CT/magnetic resonance imaging) will also be briefly described^[13]. Lastly, molecular imaging perspectives and new developments of targeted

contrast agents will be critically analyzed^[14].

The aim of this series of reviews will be to analyze and enhance the current knowledge and future perspectives of the *in-vivo*, real-time assessment of angiogenesis in digestive cancers, used for the longitudinal monitoring of the effects of chemo-radiotherapy (including anti-angiogenic therapies), as well as for the precise targeting of drugs through molecular based drug-delivery systems.

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