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Clinical applications for dual energy CT versus dynamic contrast enhanced CT in oncology

Wolfgang M. Thaiss[a], Alexander W. Sauter[a,b], Malte Bongers[a], Marius Horger[a,*], Konstantin Nikolaou[a]

[a] Eberhard Karls University, Department of Radiology, Diagnostic and Interventional Radiology, Hoppe-Seyler-Str. 3, D-72076 Tübingen, Germany
[b] University Hospital Basel, Department of Radiology and Nuclear Medicine, Division of Nuclear Medicine, Petersgraben 4, CH-4031 Basel, Switzerland

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ABSTRACT

Both Dual Energy CT (DECT) and Volume Perfusion CT (VPCT) have gained interest in recent years with several studies providing evidence of benefits for both in a variety of oncological settings. These technologies open a new spectrum of diagnostic opportunities aiming at an improved detection and characterization of suspected tumor lesions, early evaluation of therapy response and generally more accurate treatment monitoring.

Here, we review and discuss current advances, beneficial aspects and potential shortcomings of both imaging modalities with regard to their clinical use in oncology.

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1. Introduction and available technologies

1.1. Why perfusion imaging?

There is a clear goal to develop procedures toward a higher degree of individualization of therapies and diagnostics, especially in the field of oncology. On this road to personalized medicine, imaging can provide important information of in vivo processes, using non-invasive biomarkers and technologies.

Tumors exhibit not only a heterogeneous pathology with respect to the cell type and the tissue origin, but also involve multiple pathways and cell processes, such as persistent growth signals, evasion of apoptosis, insensitivity to antigrowth signals, unlimited replicative potential, angiogenesis, invasion and metastasis [1]. Tumor angiogenesis and development of anti-angiogenic treatment regimens is a high priority area in cancer research. In case a tumor exceeds a diameter of 3 mm, an intrinsic blood supply is needed, as the diffusion range for oxygen and nutrition would become too large [2]. Thus, reproducible and standardized imaging biomarkers reflecting processes of tumor angiogenesis and/or treatment effects of anti-angiogenic tumor therapies are highly desirable.

1.2. Imaging techniques

To assess tumor angiogenesis, a number of targeted and functional imaging techniques are available. Dynamic contrast-enhanced ultrasound (DCE-US/CEUS) has been reported as a promising imaging tool for the depiction of tumor vasculature and perfusion in solid organs, such as in the liver [3]. However, DCE-US is not an ideal option for all organs, e.g., in the assessment of lung tumors, due to the restriction to acoustic windows. Also, the target area or target lesion using DCE-US is limited to a restricted field-of-view, as compared to other imaging techniques.

Dynamic contrast-enhanced MRI (DCE-MRI) is a state-of-the-art MRI technique for the elucidation of perfusion in tumor vessels and vascular permeability and has been validated in a larger number of animal models and patient studies. For example, Chang et al. found distinct changes of perfusion parameters in a patient study on lung cancer, indicating early treatment response of a combined chemotherapy regimen (bevacizumab, gemcitabine, cisplatin) [4]. DCE-MRI is performed during contrast media application, using fast T1-weighted three dimensional (3D) sequences [5]. Mostly, a pharmacokinetic model is used to determine semi-quantitative and quantitative perfusion parameters such as vascular permeability constants, trans-endothelial transport, reverse transport, plasma volume fraction and extracellular space fraction [6]. However, especially for DCE-MRI, several technical aspects have to be taken into account for correct perfusion quantification. Even tough the usually found (relatively low) concentrations of contrast agent in tissue show a direct correlation to the change in spin-lattice relaxation, several other factors also influence the relation of contrast concen-

* Corresponding author.
E-mail address: marius.horger@med.uni-tuebingen.de (M. Horger).

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tration and signal change in commonly used spoiled gradient echo sequences [7].

As with MRI, it is possible to obtain functional, molecular and dynamic information from positron-emission tomography (PET). [^{15}O]-labeled water or carbon monoxide have been used to analyze tissue perfusion [8], radio-labeled water being the gold standard method due to its unrestricted diffusibility. Owing to the short half-life of [^{15}O] of only a few seconds, on-site synthesis with a cyclotron and dedicated radiochemistry units is mandatory [9]. Beside functional information, e.g., on tumor perfusion, it is of interest to detect molecular markers that are highly expressed on the endothelium of tumor vasculature, such as VEGF and its receptors [10], integrins [11] and matrix metalloproteinases [12]. Here, modern PET tracers or innovative MR contrast agents play an important role. For example, the arginine-glycine-aspartic acid (RGD) peptide sequence binds to activated $\alpha_v\beta_3$ integrin, that is supposed to be a marker of activated vessels, and can be detected with labeled [^{18}F] [13] or with MRI with paramagnetic nanoparticles [14].

Currently, significant efforts are being made to analyze tumor tissue perfusion also using functional computed tomography (CT). These functional CT techniques are either based on time-resolved dynamic acquisitions (DCE-CT/Volume-perfusion-CT, VPCT) or based on spectral CT techniques, i.e., acquiring 2 CT energy spectra. These spectral CT techniques or Dual-Energy CT techniques (DECT) can be based on various scanner constructions, such as Dual-Source CT Scanners [15], multilayer spectral CT detectors [16], or rapid kV-switching of a single X-ray tube [17].

Contrast-enhanced DCE-CT or VPCT is in principal based on the exchange of iodinated contrast agents between the intravascular space and the extravascular interstitial space. The main advantages of this approach is that the CT-based techniques can be easily integrated in a clinical routine setting, due to short-duration scans and the independence of a cyclotron [18]. In addition, a linear relationship of iodine contrast-concentrations and the CT absorption numbers (Hounsfield Units, HU), reduced cardiac motion artifacts and short breath-hold examinations are further advantages. To further increase the perfusion coverage, either large CT-detectors have been introduced [19,20], or the anatomical coverage for perfusion imaging has been increased without enlarging the CT detector width, i.e., by combining repeated spiral scanning and continuous table movements, e.g., in so-called shuttle-modes [21]. The parameters derived from CT perfusion imaging correlate well with tumor angiogenesis reflected by histological markers such as microvessel density (MVD) and VEGF expression [22]. Previous studies have also documented that higher MVD is associated with higher blood flow and blood volume values [23]. Regarding the assessment of therapy response, Tacelli et al. determined whether CT perfusion can depict early perfusion changes in lung cancer treated with anti-angiogenic drugs [24]. The authors could disclose that patients treated with conventional chemotherapy with bevacizumab had a significant perfusion reduction, as compared to patients without anti-angiogenic treatment [24]. Finally, using VPCT-derived perfusion values as predictive and prognostic imaging biomarkers, non-small cell lung cancer with high perfusion values seems to be more sensitive to chemoradiotherapy and CT perfusion parameters are a significant predictor of early tumor response and overall survival [25].

2. Using technological advances for clinical robustness, reproducibility and reliability

2.1. VPCT

Volume Perfusion CT (VPCT), or dynamic contrast-enhanced CT [DCE-CT]) represents a relatively novel technique, which makes use of additional temporal information that is not provided by conventional two- or three-phase contrast-enhanced CT (CECT) examinations, enabling perfusion measurements in large volumes (e.g., tumors or organs). The aim is to provide a more accurate perfusion-based tumor characterization by excluding sampling errors caused by limited scanning in the *z*-axis, as with previous CT-perfusion protocols comprising only of few slices or a typical detector-width of 2–4 cm. Conventional CECT protocols use specific time points (e.g., arterial and venous phase) after the application of an iodine-based intravenous contrast agent, in order to detect and characterize parenchymal lesions. Although CT protocols are by no means perfectly standardized with regard to timing and number of scans, an early arterial phase (around 15–20 s post injection [p.i.]), a hepatic or portal venous phase (around 60–80 s p.i.) proceeded or not by a non-enhanced CT scan is widely used for abdominal imaging. Supplementary scans (e.g., equilibrium phase) might be added, depending on the clinical question.

These multi-phase CECT studies are useful in order to characterize hypervascularized lesions, e.g., hepatocellular carcinoma (HCC) or to better detect tumors of specific patterns of vascularization and/or perfusion (e.g., neuroendocrine tumors). However, these examinations miss valuable information, which can be provided by a acquisition of the passage of contrast agent with a higher temporal resolution, by better characterizing lesions in terms of hemodynamics, including quantitative values on blood flow, blood volume and vessel wall permeability. Also, a significant number of parenchymal lesions may be missed due to improperly chosen delay time and acquisition phases, or due to unusual enhancement patterns of the lesion itself. A typical example would be a hypovascularized HCC lesion, that does not show characteristic wash-in/wash-out contrast kinetics, but that can still be identified in a VPCT-scan as highly or exclusively arterialized hepatic lesion, in contrary to HCC precursor lesions, i.e., regenerative nodules or low-grade dysplastic liver nodules. Similarly, identification of primarily hypovascularized liver lesions (e.g., metastases from colorectal or pancreatic carcinoma) is much more accurate using VPCT by using dedicated software options for data post-processing, to separately display the dual hepatic blood supply delivered by the hepatic artery and the portal vein, as metastases are usually entirely supplied by arterial blood flow. Furthermore, the impact of different patterns of tumor vascularization on the detection and characterization of a given parenchymal lesion has been demonstrated for a variety of cancer entities, such as GIST, metastases or colorectal cancer [26–28]. Correspondingly, detection of smaller liver metastases can be improved by displaying VPCT-derived color maps of liver lesions exclusively supplied by arterial blood flow.

To overcome the shortcomings of conventional CECT and to provide significant additional information as discussed above, VPCT measures dynamic changes in tissue-contrast density over time, utilizing repetitive CT scans over a volume of interest after intravenous application of a contrast agent bolus. While the contrast agent passes through the intra- and extravascular space of the tissue under investigation, the measured attenuation changes can provide additional information that is otherwise not captured. With additional data such as an image-derived arterial input function and the time density curves from spleen and portal vein, several tissue-specific parameters can be calculated using kinetic modeling techniques, and results are displayed as parametric color maps. Thus, pathologic regions that differ from surrounding healthy tissue or adjacent organs can be accurately identified.

For the calculation of semi-quantitative and quantitative perfusion parameters as derived from VPCT-datasets, a number of mathematical models can be used. For example, a simple one-compartment model can be used to estimate blood flow (BF) and time to peak (TTP) covering the time from the initial contrast arrival and arterial enhancement to peak density in the

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