Functional Imaging of Tumors Using Dynamic Multislice Computed Tomography (MSCT)

Studying the perfusion characteristics of tumors with dynamic CT is an exciting new area of research. Functional imaging might allow in vivo assessment of tumor microvascularity.

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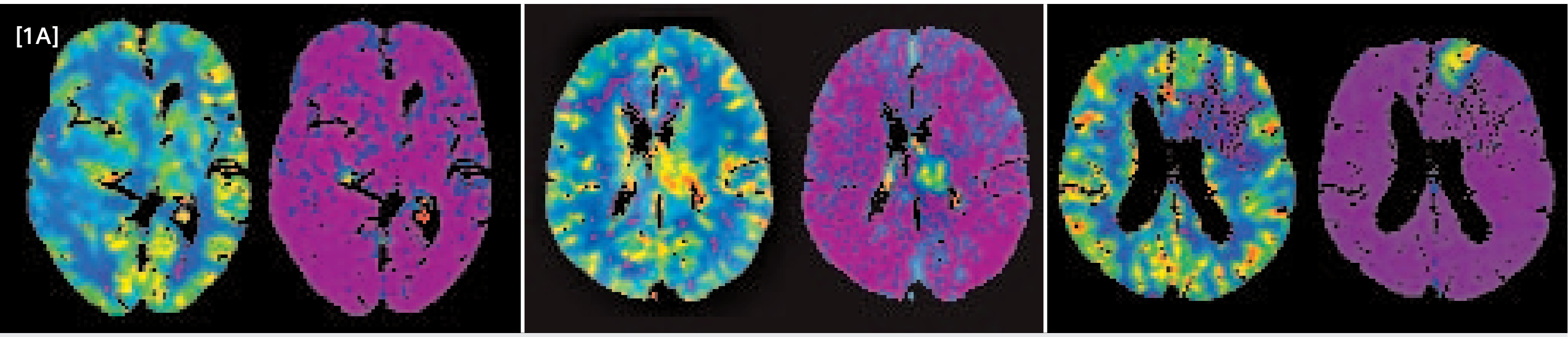
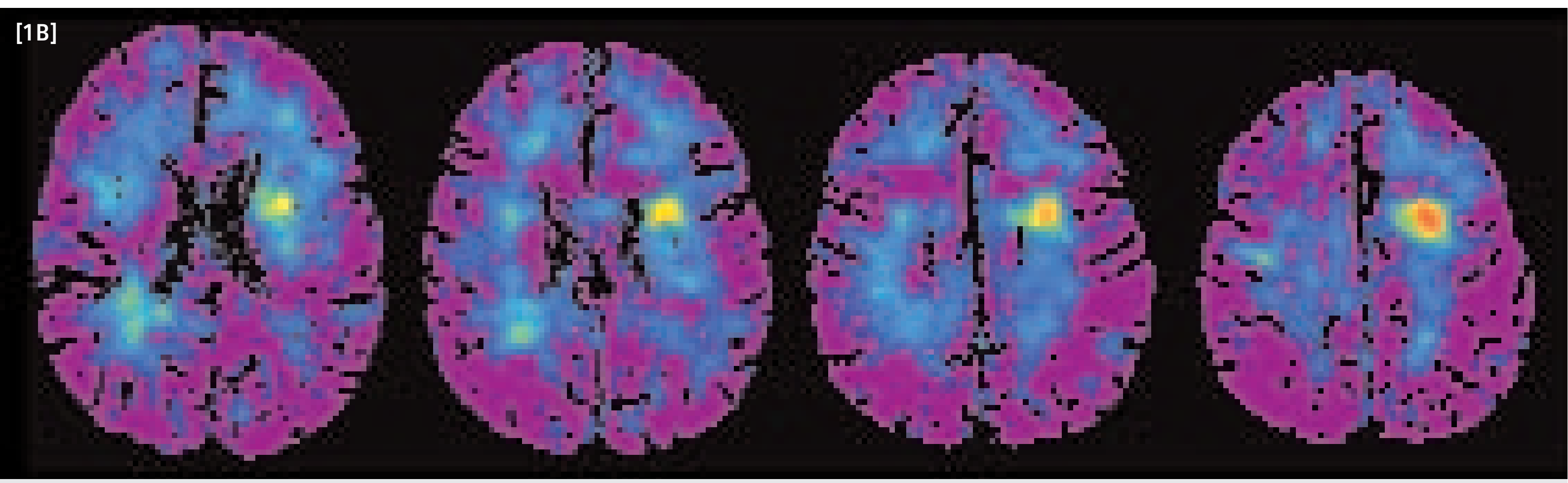
Dynamic Computed Tomography (CT) scanning after IV injection of iodine contrast was proposed in the very early days of CT. In fact, dynamic evaluation was actually one the first "CT-applications." The SOMATOM® 2 and DR (1978, 1982) featured extensive ROI-based tools, allowing the analysis of time attenuation curves (TAC). The goal was tissue characterization by extracting information from the temporal course of enhancement. Already in the early 1980s, modeling algorithms were described in the literature for the quantitative calculation of cerebral blood flow and for hepatic perfusion. However, cerebral applications suffered from the insufficient temporal resolution available at that time. Although the introduction of continuously rotating scanners, pioneered by Siemens with the SOMATOM Plus (1988), removed this limitation, the central nervous system (CNS) was already seen primarily as an MRI domain. The introduction of spiral CT for the first time allowed scanning the whole liver twice during the course of enhancement. This type of multiphase (arterial and portal venous) liver imaging, a dynamic scan at low temporal resolution, very quickly turned into a standard CT procedure. The renaissance of dynamic CT came in the middle of the 1990s, with the introduction of thrombolytic therapy in acute stroke. With CT being the primary imaging modality, getting additional hemodynamic information from the same device without having to move the patient appeared attractive. Advances in computing power meant that quantitative dynamic analysis was possible on a pixel basis. Since their market introduction in Siemens Perfusion CT software in 1998, color perfusion parameter images have become a standard evaluation tool for acute stroke.

Perfusion Imaging of Tumors

In recent years, interest has extended to perfusion imaging of tumors. This is mainly motivated by the prospect of visual-



[1A] **IMAGES OF BLOOD VOLUME** (left) and Permeability (right). Left: Astrocytoma (WHO grade II), middle: Anaplastic Glioma (WHO grade III), right: Lymphoma. (Data courtesy of Peter Schramm, M.D., Heidelberg, Germany)

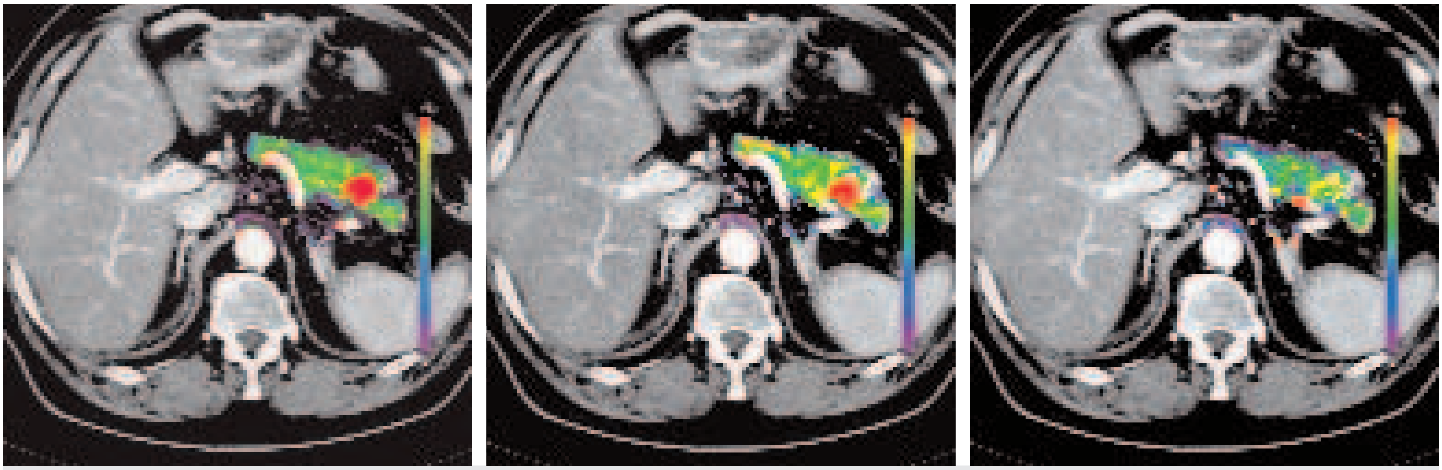


[1B] **PERMEABILITY IMAGES** in four 5-mm slices of a patient with lymphomatosis. The blood-brain-barrier disturbance in the whole white matter compartment is clearly delineated with excellent spatial resolution. (Data courtesy of Peter Schramm, M.D., Heidelberg, Germany)

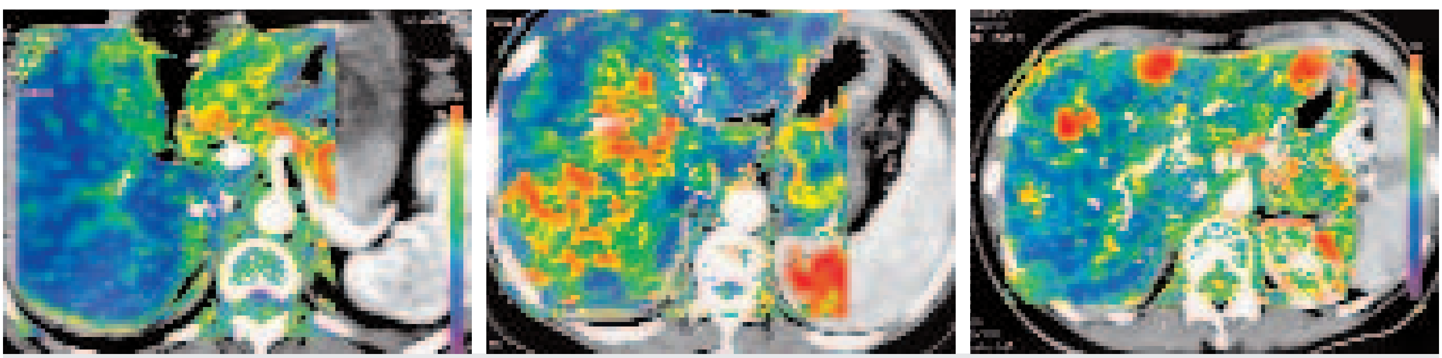
izing angiogenesis (or its modification by therapy) before changes become morphologically evident. Most tumors have higher vessel density, resulting in an increased blood volume (BV). As tumor vessels also differ in their microvascular characteristics, they often exhibit increased permeability (P); i. e., increased extravascular leakage of blood into interstitial spaces. These changes are, of course, the very reason why staging CT after IV contrast is one of the most common indications for modern MSCT: Tumors enhance more and stay enhanced longer than normal tissue. The capability to quantify these changes of vascularity and permeability would be highly valuable to differentiate between different tumor types. It might also allow monitoring early changes occurring as a consequence of therapy. We combined a technique first used in the ’80s in nuclear medicine, the so-called Patlak approach, with a local TAC correlation analysis. The advantage of this approach over other techniques, such as deconvolution, is that it allows the extraction of information about blood volume and permeability during the first pass of the contrast medium, resulting in shorter effective scan times. It also requires fewer data points, an important benefit for volume perfusion with reduced temporal resolution.

Brain Tumors

In terms of method, brain tumors are the easiest to analyze. Motion can be restricted by simple means. Normal brain tissue has a narrowly regulated blood flow and the blood brain barrier (BBB) causes its permeability to be close to zero. Changes of BV and P can therefore be more easily detected as they occur against a constant background. In a study of 35 patients conducted at the University of Heidelberg using *syngo* Neuro Perfusion CT, it was shown that brain tumors of different histopathology and malignancy could be reliably differentiated and classified by quantitatively comparing



[2A] PATIENT WITH small insulinoma at the tail of the pancreas. 3-mm section. Left: Blood flow (BF), middle: Blood Volume (BV), right: Permeability (P). In accordance with the benign nature of this lesion BF and BV are significantly increased, while P does not differ from normal pancreatic tissue.



[2B] HEPATIC PERFUSION INDEX (HPI). Left: Normal patient, HPI about 20%. Middle: HCC: large lesion with HPI 40 to more than 50%. Right: Liver metastasis, focal lesions with HPI > 50% (Data courtesy of Xue Huadan, M.D., PUMC, Bejing, China)

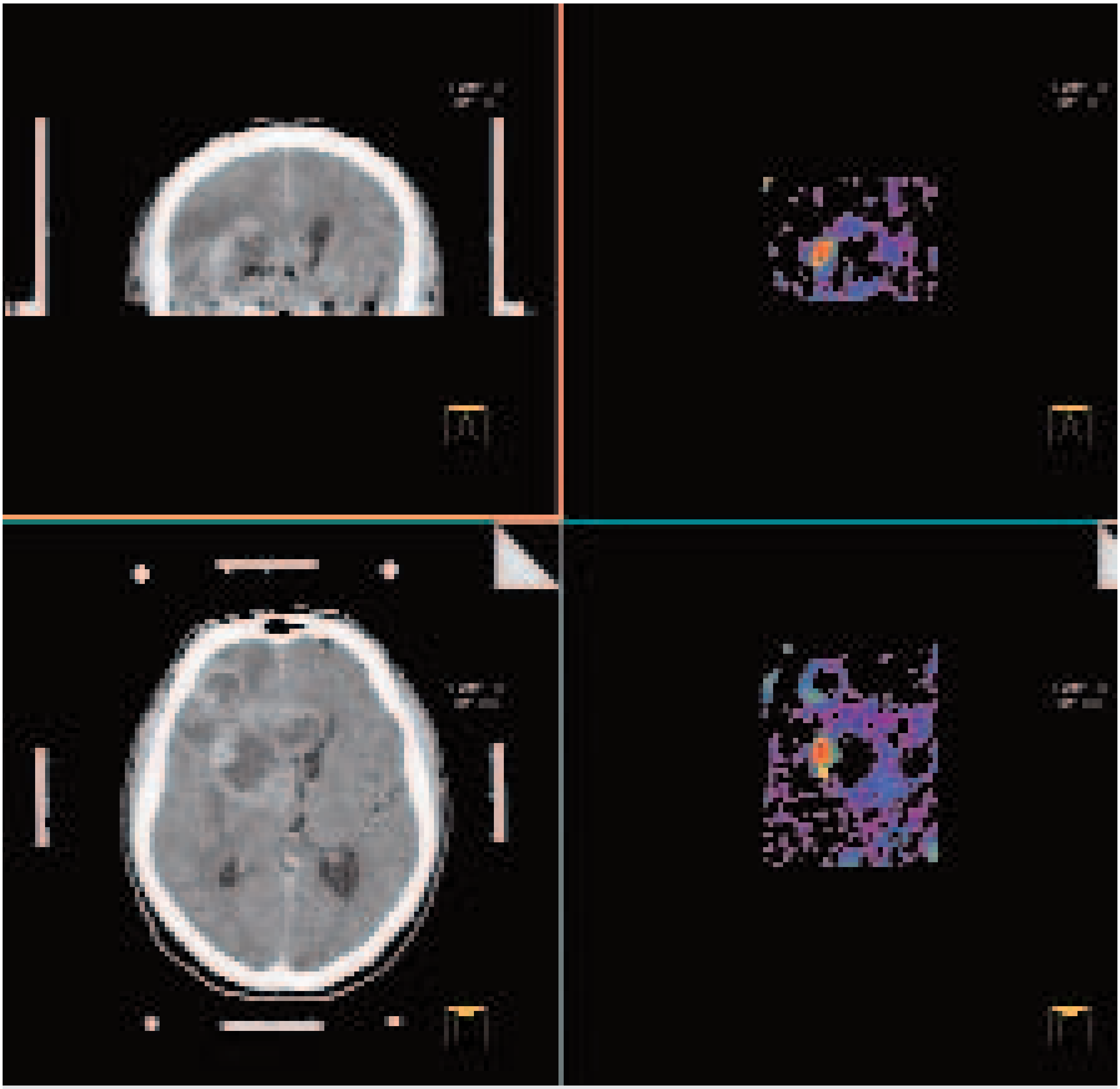
their values of BV and P (Figure 1A). The analysis was based on two 10-mm sections and a 40-s dynamic scan. Image quality and contrast-to-noise ratio can be further increased by using higher density contrast media and dedicated multiphase injection protocols. Figure 1b shows an example of a patient with lymphomatosis. In addition to a larger focal lesion, the BBB disturbance affecting the whole white matter is clearly delineated. Analysis was done in 5-mm slices; it is noteworthy that the diffuse white matter permeability is less than 10 percent of normal white matter blood flow. This indicates the high sensitivity of the technique.

Body Tumors

The same technique can also be applied to body tumors. However, there are additional acquisitional and methodological difficulties. This is mainly due to motion during acquisition (breath-hold failure, bowel motion) and to a much higher variability of the perfusion characteristics of normal tissues. Careful adaptation to the location is required. Figure 2A shows a small (1.3 cm) pancreatic insulinoma. Analysis with *syngo* Body Perfusion CT with just 35-s scan time shows that, while the tumor has significantly increased blood flow and blood volume, its permeability is not different from normal pancreatic tissue. This agrees with the benign nature of this lesion. Supporting the small lesion size, scanning was done in 3-mm sections. Figure 2B shows three examples of the hepatic perfusion index (HPI) calculated as the fraction of arterial to total hepatic perfusion. Research using *syngo* Body Perfusion CT for therapy monitoring and follow-up of tumors has just begun.

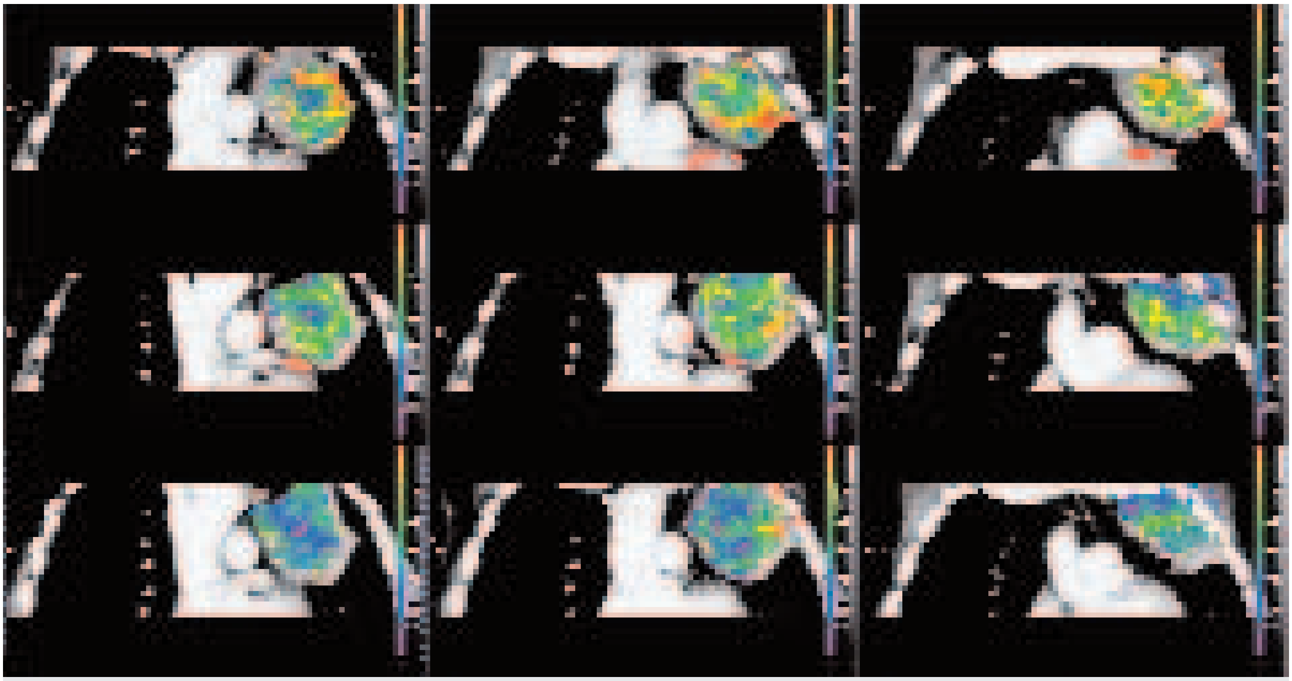
Volume Perfusion Imaging

Currently, restricted volume coverage in combination with motion is the biggest limitation of tumor perfusion imaging.



[3] PATIENT WITH GLIOBLASTOMA before a stereotactic biopsy. Left: Standard contrast planning CT. Right: 3D permeability data displaying a small focal lesion against a background of less pronounced BBB disruption over the whole tumor. (Data courtesy of Peter Schramm, M.D., Heidelberg, Germany)

Area detectors might one day completely overcome this restriction. If the approach is not modified, however, they will entail a considerable increase in exposure. It is therefore worthwhile to also consider alternatives. Unlike in ischemic applications, enhancement changes in tumors occur more slowly. As the robustness of the Patlak method allows a quantitative analysis even for a few data points, we currently investigate whole-tumor perfusion imaging based on fast repetitive spiral scanning. After performing a baseline spiral over the tumor, contrast is injected with a multiphase injection protocol. The initial part of the arterial input function is measured with a single level dynamic scan, immediately followed by repeated spirals over the tumor for 50 to 60 s. Preliminary results are very promising. Figure 3 shows a patient with glioblastoma scanned in the course of a stereotactic planning procedure. The standard contrast CT shows a



[4] **VOLUME PERFUSION IMAGING** from multiple spirals. Coronal reformats of permeability data of a patient with bronchial carcinoma. First row: Before therapy. Second row: After one week of radiotherapy. Third row: After two weeks of radiotherapy and application of a vascular targeting drug. (Data courtesy of Vicky Goh, M.D., Paul Strickland Scanner Centre, Northwood, UK)

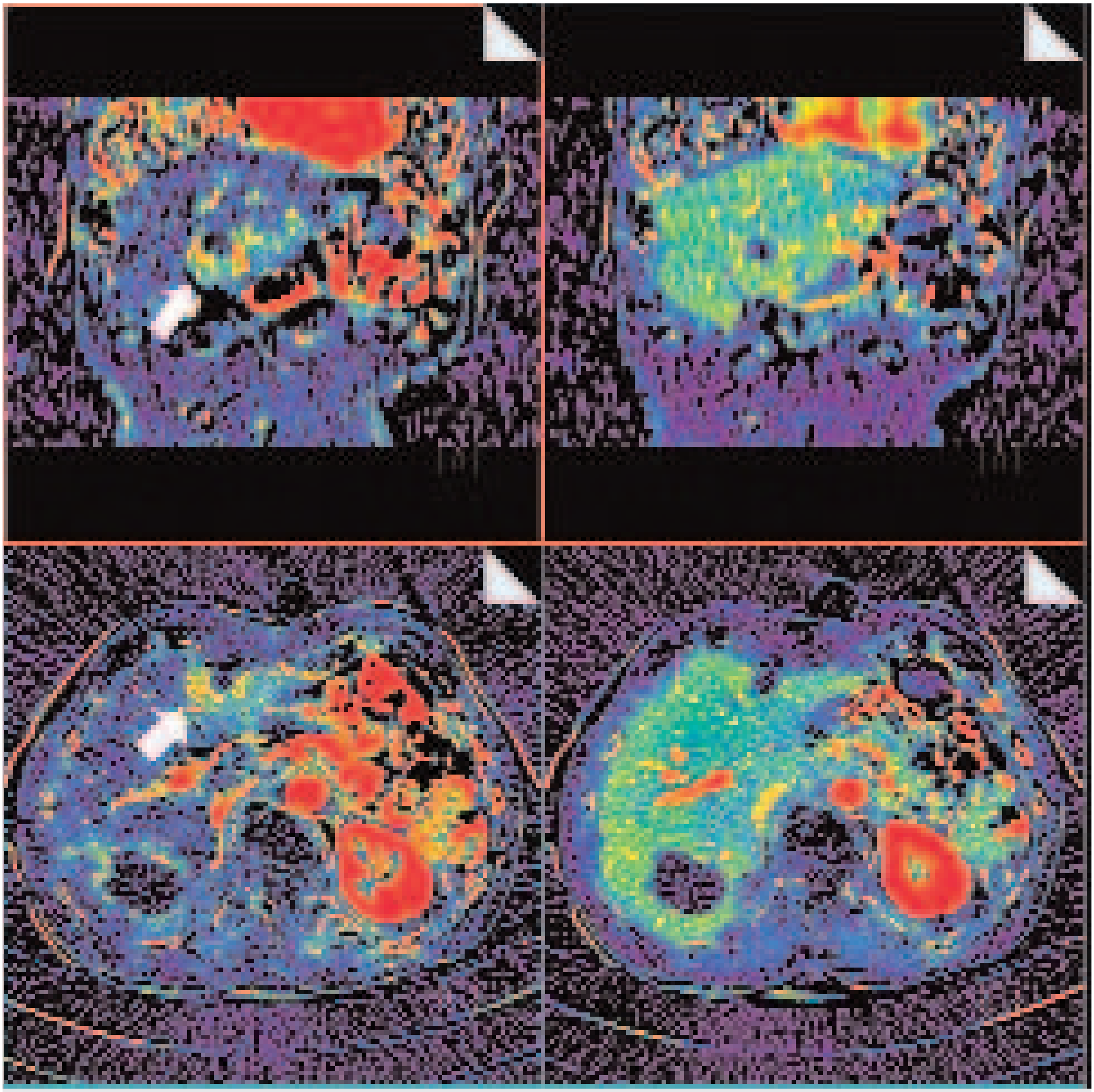
large enhancing lesion; 3D permeability imaging shows BBB disruption in the whole tumor with a prominent focal lesion. An ongoing study will test whether or not these lesions are the most promising targeting points. The multispiral technique can also be applied to the thorax, the most challenging body region for dynamic scanning. Figure 4 is from a therapy study conducted at the Paul Strickland Scanner Center in the UK using a vascular targeting agent in combination with radiation therapy. Volume perfusion imaging was used to see if therapy effects can be detected before tumor size changes. Eight spirals were performed every 10 s, allowing the patient one breathing cycle between each scan. Experimental techniques such as these are very valuable for understanding the effects of new forms of therapy. They are certainly still challenging to perform and will require further development before they are ready for routine use.

Normalized Liver Enhancement

As the historic example of liver imaging shows, sometimes "seemingly less" might be fully sufficient for clinical routine. Reading follow-up scans of patients at risk of developing new liver lesions or recurrences is a major part of the radiologist's workload in some hospitals. It has been shown that an increased ratio of arterial liver enhancement to peak enhancement is a sensitive indicator of occult metastases and might also point to neoangiogenesis after therapy. We are currently investigating whether a normalized display of the arterial enhancement fraction can serve as a practical surrogate for HPI and be used as an indicator for angiogenetic activity. Standardized plain, arterial, and venous volume scans of the liver are matched by non-rigid registration, plain CT is subtracted, and the difference color-coded. This provides a sensitive display of increased arterial enhancement. Figure 5 shows a patient seven months after RF ablation of several liver metastases. While the thin rim enhancement around the large lesion is probably not significant, the larger increase around the small lesion warrants further follow-up.

Conclusion

Dynamic MSCT of tumors is an exciting new area of research. Studying its capabilities has just begun. Further work will show how it can be optimally applied to routine differential diagnosis, therapy, and monitoring of tumors.



[5] PATIENT WITH LIVER METASTASIS 7 months after RF ablation. Left column: Arterial enhancement. Right column: Portal venous enhancement. Increased arterial enhancement around small lesion (arrow) might be a sign of neoangiogenetic activity. (Data courtesy of Andreas Mahnken, M.D., Aachen, Germany)