Routine body perfusion CT approaches clinical reality

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The most crucial process to assess in a tumor for efficient management is neo-angiogenesis. Currently, no reliable biomarker is available to measure angiogenesis, and direct microvessel density assay requires frequent biopsies for serial tumor monitoring. Technological innovations in imaging, however, have enabled the capture of physiological information in addition to anatomic details. One promising imaging technique for acquiring physiological information about angiogenesis is perfusion CT, which provides anatomic information as well.

PERFUSION CT FOR ONCOLOGY

Clinical management in oncology shifted after the concept of tumor neo-angiogenesis was introduced. This process of new blood vessel growth is critical for tumor growth and metastasis. Newer generations of oncologic treatment regimens target neo-angiogenesis, delivering less systemic toxicity than did conventional cytotoxic agents. Anti-angiogenic drugs are targeted specifically to the growth factors that stimulate neo-angiogenesis.

In tumor tissue, the release of several abnormal mediators such as vascular endothelial growth factor (VEGF) leads to development of a new network of capillaries. Angiogenic vasculature differs in several aspects from that in normal mature tissue. Blood vessels in tumors are typically dilated and tortuous, with abnormal branching patterns and dead ends, and they lack organized structure into arterioles, capillaries, and venules. These tumor blood vessels have increased permeability over normal tissue.

Angiogenic factors increase microvessel density, which is defined as the mean number of endothelial cells or endothelial cell clusters in a given number of microscopic fields that are clearly separate from adjacent tumor cells and connective tissue elements. Microvessels are highlighted by staining the endothelial cells with anti-CD34 antibodies.

Microvessel density has been established as a prognostic indicator for many cancers, and the most direct strategy to monitor anti-angiogenic therapy would therefore be periodic biopsy. This approach is invasive, however, and likely unacceptable to patients. Moreover, estimates of microvessel density may not reflect the overall tumor biology if a single-site biopsy is used, due to the heterogeneity of perfusion within the tumor.

Noninvasive imaging, on the other hand, can be repeated in patients with larger volume coverage than biopsies. Imaging studies allow assessment of physiological parameters-such as blood volume, blood flow, permeability, and mean transit times-that reflect tumor biology. Imaging may therefore be superior to microvessel density measurement for assessing angiogenesis. Perfusion CT involves dynamic scanning after administration of iodinated contrast material followed by mathematic modeling to study contrast material kinetics in the tissue. Estimates of tumor perfusion parameters such as blood flow, blood volume, mean transit time, and permeability-surface area product can be derived by applying kinetic models to the CT perfusion data set (see table). Among the various mathematic models that have evolved for performing perfusion studies, the
deconvolution method is currently the most validated and widely used approach. Perfusion CT involves acquisition of unenhanced images followed by a series of postcontrast dynamic images in axial cine mode with static table position. The unenhanced images are obtained to select the region of interest for dynamic imaging of tumor perfusion. Because current CT techniques (four- to 64-slice CT) allow scanning of only 2 to 4 cm of tumor tissue, careful selection of region of interest is key. Breath-hold is crucial for perfusion CT study of upper abdominal viscera where breathing artifacts are more likely. Duration of scanning ranges from 30 seconds to two minutes from arrival of contrast, depending on clinical need, organ of interest, and analytical method. Time of arrival of contrast may vary depending on the location of the tumor. Contrast would arrive earlier in a lung mass, for example, than a mass in the foot. Earlier reports recommended scanning for at least two minutes when permeability measurement was required, but current recommendations advocate shorter durations. A recent study reported that a 65-second scan is adequate for measurement of permeability of colorectal carcinoma. Radiation dose, breath-hold demands, and patient motion invariably limit the maximum duration of scanning. There is always a trade-off between radiation dose and temporal resolution.

ONCOLOGIC APPLICATIONS

Clinical imaging tools for evaluation of angiogenesis should help the oncologist select optimum treatment by tailoring the dose of anti-angiogenic drugs, detecting early anti-angiogenic response, and analyzing impact of treatment on tumor progression. Data on body tumor imaging with perfusion CT are emerging in studies of various applications. One drawback is the wide variability of scanning techniques and mathematical modeling used in these studies. Furthermore, most of the studies use a small sample. Readers should be aware of these limitations before drawing conclusions from these studies and implementing these applications in routine practice.

- **Liver tumors.** The liver is a unique organ for perfusion CT imaging because it has two arterial inputs: the hepatic artery and the portal vein. Malignant liver lesions such as hepatocellular carcinoma have predominantly a hepatic arterial supply and thus demonstrate increased arterial tumor perfusion values in CT scans. Studies have established that micrometastases alter liver perfusion despite the absence of gross disease. Hence, it is conceivable that this technique might help detection of micrometastases in selected patients by mapping areas of altered liver perfusion.

It has been shown that in healthy individuals, CT-derived hepatic arterial and portal venous perfusion values are inversely correlated, whereas in a setting of liver metastases, there is a direct positive correlation between these values. Miles et al reported that increased peritumoral arterial perfusion and increased global liver perfusion indicate a more favorable outcome following chemotherapy. Tsushima et al reported that HCC has nine times greater hepatic arterial perfusion than background liver parenchyma, whereas colorectal carcinoma metastases demonstrate only four times greater arterial perfusion. A few patients with HCC showed a decrease in hepatic perfusion values following transarterial chemoembolization.

- **Pancreatic carcinoma.** Successful surgical management of pancreatic adenocarcinoma is often fraught with difficulties due to late clinical presentation and the limited ability of cross-sectional imaging modalities to detect small lesions. Sensitivity in detecting a pancreatic mass 2 cm or smaller is 58% to 77%, even with the use of MSCT. Pancreatic adenocarcinomas are usually hypovascular, however, and detection of change in this perfusion pattern could aid in early detection, when these masses are still resectable. Other tumors and disease processes in the pancreas may also alter pancreatic perfusion. Miles et al reported a decrease in pancreatic perfusion in patients with type 1 diabetes mellitus and failing pancreatic transplant, whereas pancreatic perfusion increased in insulinoma and Wilson's disease compared with healthy individuals. Another study reported increased blood flow and blood volume in insulinoma compared with background pancreatic parenchyma. Time to peak enhancement and tumor permeability were comparable to normal pancreas, however. Even in the absence of disease in the pancreas, it has been reported that pancreatic perfusion decreases with advancing age. Abe et al validated pancreatic perfusion CT by showing excellent agreement of pancreatic tumor blood flow measurement between perfusion CT and xenon CT.
• **Colorectal carcinoma.** CT perfusion is evolving as a promising tool for evaluation of rectal carcinoma and treatment monitoring. Goh et al investigated the optimum scanning duration and z-axis coverage for perfusion CT of colorectal cancer. They reported that a 65-second scanning duration is required for reliable permeability measurements, and increasing the z-axis coverage did not improve the reproducibility of perfusion measurements. In our institution, we have investigated the role of perfusion CT before and after treatment in patients with rectal carcinoma to monitor treatment response. We found that rectal carcinoma showed substantially higher blood flow (Figure 1) and shorter mean transit time when compared with normal rectal wall. Following chemoradiation treatment, rectal carcinoma showed considerable reduction in blood flow and increase in mean transit time. Early anti-angiogenic treatment effects can also be monitored with this technique. Willet et al reported a drop in tumor perfusion in patients with rectal carcinoma two weeks after initiation of bevacizumab therapy, further supporting the role of perfusion CT in tumor angiogenesis assessment.

• **Prostatic carcinoma.** Tumor size and the location of the prostate gland often make detection of prostatic carcinoma by imaging challenging. Although tumor visualization is improved using transrectal ultrasound and MRI, perfusion CT enables direct visualization of tumor physiology and aids treatment planning (Figure 2). Prior studies reporting that cancer-containing regions of the prostate gland showed increased blood flow, blood volume, and permeability cautioned readers that blood volume and permeability could be measured precisely only in regions of increased tumor blood flow. Harvey et al observed that acute hyperemic response following radiotherapy resulted in an increased global prostatic perfusion at one to two weeks that was maintained in six to 12-week scans.

• **Cervical carcinoma.** Tumor oxygenation is an important prognostic factor for cervical carcinoma being treated with radiotherapy. Well-oxygenated tumor is radiosensitive, whereas hypoxia results in tumor radioresistance. Perfusion parameters were found to correlate with tumor oxygenation. Haider et al reported a moderate positive correlation of blood flow with tumor oxygenation in 32 patients with cervical cancer. A relationship between CT perfusion parameters and tumor and nodal staging was also observed. These findings indicate that perfusion CT has a potential role in risk stratification for cervical cancer.

• **Lymphoma.** CT plays a key role in diagnosis and treatment monitoring of lymphoma. Morphologic CT criteria such as nodal size and appearance, however, show poor correlation with lymphoma grade and activity. As angiogenesis is not a predominant feature of lymphomas, perfusion imaging has not drawn the attention of researchers for tumor angiogenesis assessment. Dugdale et al evaluated 39 patients with lymphoma and found that median perfusion values of lymph nodes were higher in active disease and intermediate/high-grade lymphoma when compared with inactive disease and low-grade lymphoma, respectively. Blood flow substantially decreased when nodal disease became inactive, but there was no correlation of permeability with disease activity or grades of lymphoma.

It is important to emphasize that none of the perfusion CT acquisition or analytical techniques are standardized for implementation in routine clinical practice for oncologic body imaging, and all of the perfusion parameters calculated by commercial software are only estimates and not absolute values. One of the principal limitations of CT perfusion is the limited scanning volume. Current four- to 16-slice CT scanners allow 2-cm tissue coverage for dynamic CT acquisition. Even with a 64-slice scanner, the maximum coverage is only 4 cm. Hence, only a portion of the tumor or organ can be sampled for perfusion measurements. Scan volume selection is thus a crucial aspect of scanning technique.

Another issue is patient motion, which may be corrected by registration within the image plane. Patient motion out of image plane, however, causes data loss and errors in perfusion values. Respiratory gating may improve motion problems at the expense of temporal resolution. Adequate patient instruction for breath-hold, with immobilization straps over the abdomen, may help. Beam-hardening artifacts from metallic stents, prostheses, and surgical implants can also result in variation in the perfusion values, and careful selection of region of interest for scanning is important here as well. Likewise, adequate distention of hollow viscus such as colorectum or stomach with saline or any neutral contrast is crucial for optimum perfusion measurements. In our institution, we use 250 to 300 mL of saline to distend the rectum before conducting perfusion CT studies. Radiation dose is an important concern in implementing perfusion CT in routine clinical practice.
Currently, the radiation dose is two to four times greater for perfusion CT than routine contrast-enhanced CT of the same region using the same scanning parameters, depending on the scanner.

FUTURE DIRECTIONS
Efforts to improvise further perfusion CT applications are ongoing. Respiratory gating, for example, would reduce misregistration breathing artifacts. Measurement of peak tissue enhancement can provide more physiological data by normalizing them for the patient's body weight and dose of contrast medium administered. Such an approach could determine the standardized perfusion value (SPV), defined as the ratio of tumor perfusion to mean whole-body perfusion. Mean whole-body perfusion is cardiac output divided by patient weight. Miles et al reported that SPV measurements correlated with standardized uptake value measured on FDG-PET for lung nodules. The threshold of SPV to distinguish between benign and malignant lesions would be 1.5. The increasing availability of PET/CT raises the possibility of combining CT perfusion imaging with PET as well. This combined PET/CT/perfusion "triple" imaging could obtain anatomic, metabolic, and angiogenic information about tumor with a single scan.

Some vendors have recently introduced a table toggle technique to increase scan coverage and address current limitations in scanning volume in perfusion CT. In this technique, the scanner couch toggles between two locations for dynamic acquisition. This application is only possible, however, at the expense of temporal resolution, which would be five seconds instead of one second in static table technique.

Currently available iodinated intravenous contrast materials are limited by their short intravascular life. Further research should develop new agents with a longer intravascular life that could overcome these difficulties. Using automatic exposure control and low tube potential could optimize radiation dose during serial dynamic scanning.

Perfusion CT offers new opportunities for detection, risk stratification, and therapeutic monitoring of tumors. Although extensively researched in current literature, the clinical role of perfusion CT in the body is still evolving. Further research and improvements in acquisition and analytic techniques would open doors for perfusion CT to become a routine protocol for oncologic imaging and expand its clinical applications.

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