

ASSESSMENT OF LUNG TUMOR RESPONSE BY PERFUSION CT*

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Perfusion CT permits evaluation of lung cancer angiogenesis and response to therapy by demonstrating alterations in lung tumor vascularity. It is advocated that perfusion CT performed shortly after initiating therapy may provide a better evaluation of physiological changes rather than the conventional size assessment obtained with RECIST. The radiation dose, the volume of contrast medium delivered to the patient and the reproducibility of blood flow parameters remain an issue for this type of investigation.

Key-words: Multidetector-row – Computed tomography, lung cancer, perfusion.

Several studies suggested that perfusion CT may be potentially useful in the assessment of patients undergoing chemotherapy, radiation therapy, and laser therapy (1-10). Perfusion CT is a tool which in theory can quantify the real perfusion of tissues by applying mathematical models and dedicated software to calculate the delivery of contrast agent and therefore blood to tissues (9). Perfusion CT is based on three different requirements. The first is the administration of contrast medium, in a small amount at high flow rate in order to get a short and sharp bolus. The second is based on the repetition of CT acquisition on the same volume of interest over time, before and after the intravenous administration of iodinated contrast medium to allow the study of the variation of density with time. The third requirement is the selection of the arterial input. The placement of a region of interest (ROI) on an artery permits to obtain a density-time curve of the selected vessel and is expressed in HU/sec. This graph is then compared to the density-time curve obtained in the tissue being analysed, also obtained by placing a ROI to make the distinction between the amount of contrast medium within vascular structures and the amount of contrast medium present in the interstitium. Therefore, it is now possible to quantify perfusion. Several kinetic models can be used to calculate the distribution of the contrast medium in the intravascular space and in the interstitial compartment. The calculation of perfusion parameters is performed using dedicated softwares. Qualitative analysis consists of the analysis of color maps (Fig. 1) that are automatically generated by soft-

ware for every perfusion parameter: Blood volume, blood flow, mean transit time, permeability-surface area product. The tumoral perfusion can be evaluated on a subjective manner, when the observer visually analyses the heterogeneity of the colors generated on the color map, or in an objective manner, with the graphical representation of the distribution in classes of perfusion values of each voxel in histograms.

Respiratory motions are potential factors hampering the reproducibility of perfusion parameters as well as the absolute values of CT-measured parameters. This aspect was evaluated in a study (5) with 11 lung tumor patients using two perfusion CT scanners obtained on a 16-MDCT scanner. The authors found that the absolute values and perfusion parameters in lung tumors were significantly influenced by motion and duration of data acquisition. However, this study included only a small number of patients and did not utilize new-generation CT scanners. The use of a 64- or 320-MDCT scanner can improve misregistration through more extensive coverage (16 cm in a single rotation), while reducing respiratory artefacts. The use of a respiration-gated perfusion CT is another potential solution to misregistration artefacts. Moreover, new perfusion software is currently available in daily practice, thus facilitating the evaluation of perfusion data sets. A crucial issue related to perfusion CT concerns the dose of radiation delivered to the patient and the contrast material, which is potentially toxic for the kidneys. Fraioli et al. (10) measured the radiation dose during perfusion CT at $21,7 \text{ mSv} \pm 1,6$ using a 64-detector row dual-source scan-

ner with a tube voltage at 100 kV and tube current at 120 mAs with an automatic tube current modulation. We have to be aware that the radiation dose delivered during this perfusion CT study is much smaller than those given during radiotherapy for lung cancer.

Some experiments were conducted to evaluate (11, 12) the relationship between CT perfusion parameters and differentiation characteristics in lung tumors. Using first-pass perfusion imaging with 64-detector row CT in 45 peripheral lung carcinomas, no significant differences in perfusion parameters were found among different histological subtypes. Xiong et al. (12) found that CT perfusion characteristics, mainly blood flow values, were useful in assessing lung cancer differentiation. In this study, the authors found a decrease in CT perfusion parameters coincided with a decrease in the differentiation grade of lung cancer. Blood flow, blood volume, and peak enhancement intensity values were thus found to be lower in poorly differentiated lung cancer. The authors concluded that CT perfusion imaging may be a potential tool for the evaluation and early identification of tumor angiogenesis in addition to being able to assess tumor grade *in vivo*.

Concerning monitoring therapy, several case studies revealed changes in tumor perfusion parameters in patients with NSCLC who were treated with "non-vascular targeting" agents. Wang et al. (1) found a significant decrease in blood flow and volume in a patient following two cycles of chemo-radiotherapy, while Kiessling et al. (4) described a reduction in tumor perfusion in a patient after two cycles of chemotherapy. The effects of chemotherapy and antiangiogenic agents have also been investigated (7, 10). The effects of angiogenesis and EGFR inhibitors were evaluated in a study including 23 patients with a dual-source CT at baseline and 3 and 6 weeks after

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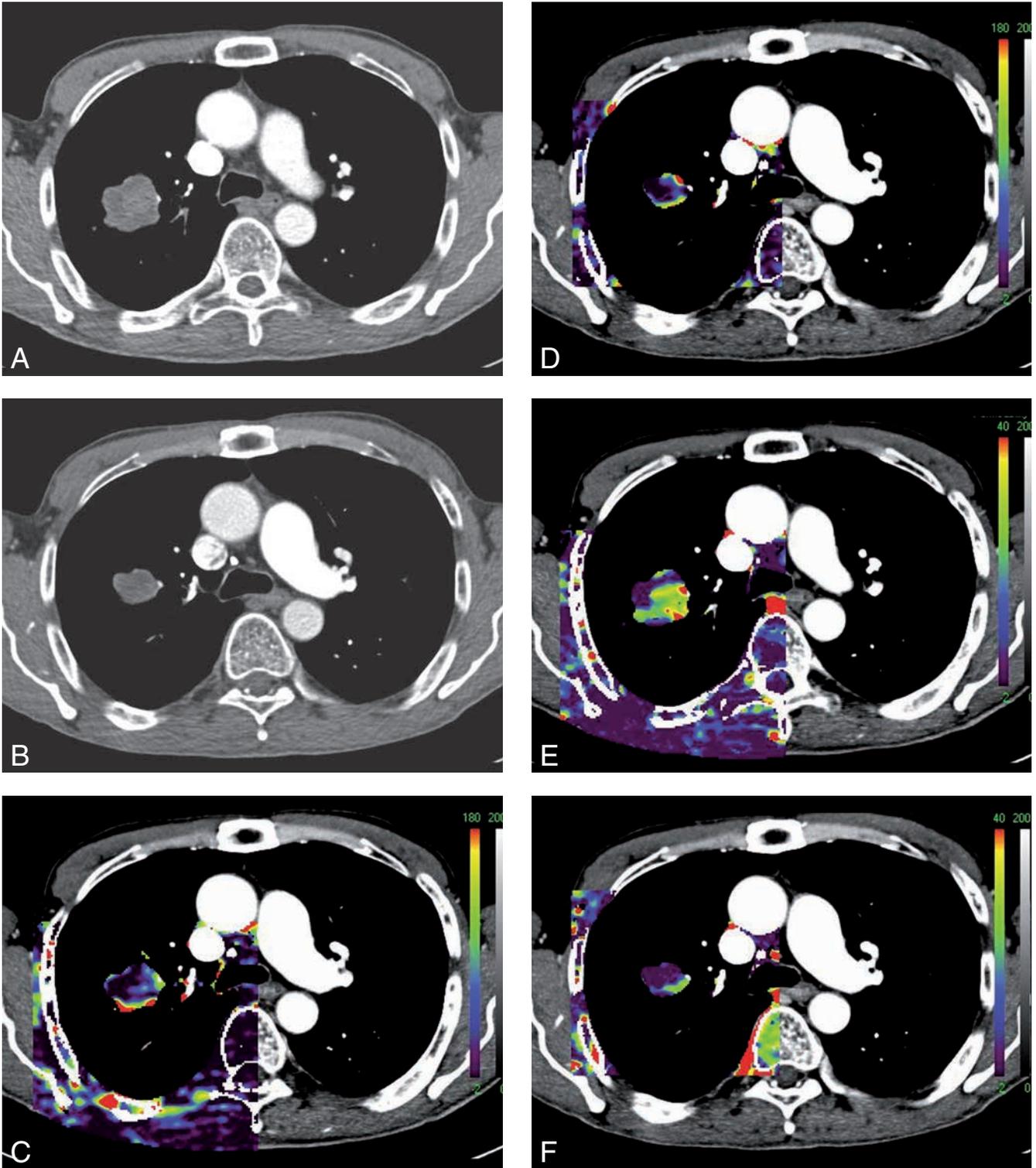


Fig. 1 (A-F). — Patient addressed for adenocarcinoma of the right upper lobe (RUL).

Transverse CT images obtained after injection of contrast medium at the level of the left pulmonary artery at baseline (A) and after 1 cycle of antiangiogenic therapy (B) showed decrease of the tumor size in the RUL.

Functional CT maps of mean blood volume at baseline (C) and after 1 cycle of antiangiogenic therapy (D) were measured and decreased from 5.4 ± 6.5 mL/100 mL to 4.4 ± 6.1 mL/100 mL respectively.

Functional CT maps of mean capillary permeability at baseline (E) and after 1 cycle of antiangiogenic therapy (F) were measured and decreased from 5.9 ± 6.0 mL/100 mL/min to 3.3 ± 5.02 mL/100 mL/min respectively.

Courtesy of Nunzia Tacelli, M.D. and Martine Rémy-Jardin, M.D., Ph.D., C.H.R.U. Lille, Hôpital Calmette, Boulevard du prof. J. Leclercq, 59037 Lille Cedex, France.

treatment. Mean tumor perfusion decreased significantly from 39.2 mL/100 g/min at baseline to 15.1 mL/100 g/min at week 3 and 9.4 mL/100 g/min at week 6. Tumor perfusion was lower in RECIST responders versus non-responders at week 3 and week 6 respectively.

Another experimental investigation performed by Fraioli et al. (10) assessed 45 patients with an unresectable NSCLC > 20 mm. Subjects underwent perfusion CT (64-detector row dual-source CT) at baseline and 40 days after treatment with chemotherapy and angiogenic inhibitors. Some patients also benefited from a follow-up perfusion CT 90 days after therapy. The authors showed that treatment-induced changes in perfusion may be identified using perfusion CT. They found that blood flow, blood volume, and permeability values were lower in responding patients compared with other patients. Discrepancies between perfusion measurements and RECIST evaluation were also observed. In approximately one-third of patients, the size of the lesion was considered stable at the first CT follow-up using RECIST criteria, although vascularisation parameters increased. In contrast, in the patients classified as stable disease based on RECIST, a proportion of subjects showed various changes in perfusion parameters, suggesting a tumor response to therapy. The authors emphasized the fact that

macroscopic changes in tumor size (RECIST) did not reflect the biological changes induced by therapy. It is thus possible that perfusion CT performed shortly after initiating therapy may be more useful for clinical planning, as it provides a better evaluation of physiological changes rather than the conventional size assessment obtained with RECIST.

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