Volumetric CT perfusion of focal and multifocal malignant liver lesions: Technique, clinical applications and correlation with conventional imaging

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Learning objectives

Review the technical aspects and clinical indications of volumetric CT perfusion (CT-p) for diagnosis and follow-up of focal and multifocal malignant liver lesions.

Background

CT#p represents one of the most interesting tools in the field of oncologic imaging to assess disease response or progression after therapy. The basis for its use is mainly related to the assumption that many drugs inhibit the proliferation of neoplastic cells by acting on the vascular network and this fact is probably going to become more evident with the development of therapy protocols based on the use of anti angiogenetic molecules, that play a negative feedback on blood vessel growth. Because all solid tumors require angiogenesis to grow and metastasize, an agent that successfully blocks angiogenesis has the potential to be a universally effective anticancer drug. So the progressive clinical diffusion of these new drugs and the increasing number of patients that are going to be treated and subsequently followed#up in time are likely going to require a technical and conceptual adaptation of conventional imaging modalities: in fact, this new kind of treatment may not change tumor size as a consequence of its action, deeply influencing at the same time the vascularisation of the lesion even before it becomes provable by conventional imaging.

The WHO recommends the use of RECIST criteria to evaluate the response to treatment, which could be:

-Complete Response (CR): Disappearance of all target lesions.

-Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

-Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

-Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

It's interesting to observe that the standard therapeutic response assessment (RECIST), based on tumor size changes, could show in any case discrepancies
with CT-p measurements. Within this clinical scenario the capability of evaluating
physiopathological modifications in neoplastic tissues rather than simply assessing rough
changes in size and shape may provide a more appropriate way of monitoring the effects
of treatment, eventually allowing tailored therapy.

**Imaging findings OR Procedure details**

**Patient Selection and Preparation**

Since the radiation load of any CT-p examination may exceed the accepted limits for
diagnostic procedures, adequate patient selection represent a major constraint in daily
clinical practice: i.e. patients with suspected benignant liver lesions should be referred for
other examination such as conventional CT or MRI and must not be scheduled for CT-p
since the risk of stochastic, and in some cases reported in literature, even deterministic
radiation damage is consistent. Patients that more likely will benefit from the clinical data
that can be extrapolated from a CT-p examination are those with multifocal malignant
lesions that cannot be treated with a radical approach: in fact, RECIST measurements
have been demonstrated not always adequate to monitor treatment outcome and
physiological changes occurring in cancer tissue after chemotherapy or radiation
therapy. Moreover, among these patients, the subjects that undergo antiangiogenetic
chemotherapy often present extensive tumoral necrosis with a substantial shrinking of
the lesions: in these cases a quantitative evaluation of antiangiogenetic induced necrosis
by CT-p can represent the most adequate approach to effectively monitor treatment
outcome. Recommendations for patients preparation are superimposable to those of a
standard CT examination; however the i.v. line must be of a sufficient gauge (18 G) to
allow contrast agent administration at a high-flow rate.

**Choice of Scan Protocol**

Unfortunately there is no literature consensus for liver CT-p scan protocols: since
most studies were performed with CT scanners capable only of short z-axis perfusion
examination and wide-volume scanners were introduced only recently on the market, the
choice of optimal acquisition parameters is still a matter of debate. From a personal point
of view CT-p examination should cover the whole surface of the tumor in order to provide
clinically useful information: i.e. if the available z-axis for CT-p is limited to 4 to 5 cm as
in 64-MDCT scanners, one can miss therapy induced changes or disease progression
outside this longitudinal field of view. At this regard the introduction of dual-source
and wide panel (128-detector rows and beyond) may represent a relevant technical
improvement. In our institution CT-p is performed with a 2 x 64-detector row dual-
source scanner (Siemens Definition, Siemens Medical Solutions, Forchheim Germany).
A preliminary non contrast acquisition of the upper abdomen (100 kV, CAREdose with quality reference set at 120 mAs, detector configuration: 24 x 1.2 mm, rotation time: 0.3 s, slice thickness: 3.0 mm, reconstruction interval: 3 mm, reconstruction kernel: B30) is performed to adjust CT-p acquisition on the longitudinal extent of the liver. Scanning length may be varied between 130 mm and 200 mm, depending on liver dimensions and disease localization. A total of 60 mL of high concentration (400 mg of iodine/mL) nonionic iodinated contrast medium (Iomeron 400; Bracco Imaging SpA, Milan, Italy) is injected using a fractioned injection protocol (30 mL at 4 mL/s, 10 mL at 2 mL/s, 20 mL at 1 mL/s followed by a 20 mL saline flush at 1 mL/s) using a dual-head power injector (Medrad Stellant Dual; Medrad, Palo Alto PA, USA). CT-p starts immediately after the injection with a free breathing dynamic acquisition (100 kV, CAREdose with quality reference set at 120 mAs, detector configuration: 64 x 1.2, rotation time: 0.3 s, slice thickness: 3.0 mm, reconstruction increment: 3 mm, total scan time: 60 s, 4D range = 130-200 mm / 5 s per scan, reconstruction kernel: B30). All patients are instructed to perform the respiration in a constant manner, to avoid excessive liver motion that may hamper post-processing and prolong image evaluation. Since the Siemens CT-p software is based on a hybrid Patlak model to extrapolate perfusion parameters from attenuation variations in liver vessels and parenchyma, the contrast administration protocol is adapted to best fit the physiological calculations:

**Patlak model**

"Patlak" two compartment model: after the injection in the intravascular compartment, contrast agent will pass to interstitial space with a constant rate of efflux ($k_1$).

Contrast agent will also pass from the interstitial space to the intravascular space with a constant rate ($k_2$).

Patlak’s analysis:

\[
\frac{C(t)}{C_b(t)} = rbv + Pm \frac{\int C_b(t)dt}{C_b(t)}
\]

- $C(t)$ : c.a. concentration at time $t$
- $C_b(t)$ : blood concentration at time $t$
- $rbv$ : relative blood volume
- $Pm$ : permeability
the Patlak model assumes that after the injection the contrast agent will pass from the intravascular compartment to the interstitial compartment and from the interstitial compartment to the intravascular compartment with constant rates so that the backflow can be assumed as null and the two compartments remain at the equilibrium state. The administration of contrast agent in a fractioned fashion helps to achieve a steady state of iodine concentration in both vessels and parenchyma that is optimal for Patlak model.

Fig.: Contrast Administration Protocol for Patlak Model.

References: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY

On the other hand, software from other vendors (i.e. GE) are based on different models such as the Distributed model:
Vascular bed is represented as a cylinder of length $L$ with a blood volume $V_b$. The interstitial tissue is represented as another cylinder around the first one with a blood volume $V_e$. Contrast medium enters the capillary at a flow rate $F$ and starts to diffuse in the extra-vascular compartment, so the blood concentration of contrast medium $C_b(x,t)$ is a function of axial position and time ($t$). The interstitial tissue concentration instead depends only on time.

**Fig.**: Details of Distributed Model.

**References**: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY

in this case the concentration of iodine in the intravascular and interstitial compartments are not assumed to be constant and the achievement of a steady state is not relevant for physiological calculations and contrast agent can be administered in a single, sharp bolus.
Post Processing Techniques

Ideally, dynamic CT images required for perfusion imaging consist of a series of subsequent CT images from exactly the same anatomical position. A mismatch between the CT images would severely impede the calculation of the perfusion parameters and cause motion artifacts. But for typical scan times in perfusion imaging, motion through breathing is usually unavoidable. Therefore, motion correction is needed to exactly realign the acquired CT images. The Siemens Syngo Volume Perfusion CT Body's advanced motion correction features a unique algorithm that allows an elastic alignment. Elastic means that not only linear corrections in x, y and z direction are performed but that parts of the anatomy image can be stretched or compressed in order to match the dynamic CT images. Once the correction algorithm has been applied the corrected dataset is available for post-processing, including the following steps: application of
a predefined evaluation template for liver, input of target volumes of interest (VOI) and volumetric segmentation of organ and tumor, color coded displaying of perfusion parameters, creation of composite images allowing a merged display of an anatomical image with a color parameter display in the target volume, application of VOI and ROI (region of interest) measurement tools for a detailed analysis of perfusion characteristics.

**Fig.**: Normal Liver: enhancement trend of the normal liver during CT-p.

**References**: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY

**Measurements of Haemodynamic Parameters**
References: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY
- BF: The blood flow is a measure of the blood that passes a tissue in a certain time frame. It is usually correlated with the metabolism of that specific tissue. It is measured in ml / 100 ml x minute. Increased BF in solid tumors is a quantitative marker of the presence of intratumoral shunts.

- BV: The blood volume is the fraction of blood within a tissue. It is often expressed as percentage. It is measured in ml / 100 ml. Increased BV in solid tumors is a quantitative marker of the presence of neoformed vessels.

- MTT: Mean Transit Time is the mean time used by blood to go from arteries to veins. It is measured in sec. Decreased MTT in solid tumors is a quantitative marker of the presence of low resistance vessels.

- PS: The permeability is determined as the transfer constant for the diffusion of plasma into the interstitial space. It is measured in ml / 100 ml x minute. Tumors tend to build
leaky vessels with an elevated permeability. This effect has especially been shown in certain brain tumors where an elevated permeability indicates the damage of the blood-brain barrier.

- ALP: The arterial liver perfusion image shows the blood flow that has its origin in the hepatic artery.

- PLP: The portal venous liver perfusion shows the blood flow that has its origin in the portal vein.

- HPI: The hepatic perfusion index is the relation of arterial perfusion to total liver perfusion given in %.

**Imaging Findings**

Even if CT-p should not be used with the intent of characterizing a focal liver lesions, the reporting radiologists must be aware of the differences of perfusion parameters between the most common histological subtypes of liver cancers and the most common alterations induced by therapy in order to properly evaluate CT-p examinations. Also a familiarity with the most common TAC (time-attenuation-curves) profiles is required since they can be useful in differentiating the vascularization trend and the blood-dynamics of a lesion. Image interpretation criteria are reported below.

- Hepatocellular carcinoma:
Fig.: Multifocal HCC: baseline CT-p and conventional MRI in a patient candidate to antiangiogenetic treatment.

References: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY
**Fig.** HCC necrosis after RF: the treated area is no longer vital with a complete hypoperfusion as compared to normal surrounding parenchyma and focal recurrence. **References:** M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY
Fig.: HCC recurrence after RF: focal recurrence adjacent to the treated area shows vital perfusion; however the tissue seems to be less vascularized than the primary cancer. A comparison with conventional and DWI MR sequences is also reported.

References: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY
Prevalent arterial perfusion, high BF and BV, short MTT, permeability may be variable depending on grading, high ALP and HPI.

- Cholangiocellular carcinoma:
Fig.: CCC: recurrence after surgery visualized at baseline CT-p in a patient candidate to antiangiogenic treatment.

**References:** M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY

Mixed arterial-portal perfusion, low BF and BV, short MTT, permeability may be variable depending on grading, low ALP and HPI.

- Metastases:
**Fig.**: Metastases from colon cancer: CT-p before and after chemotherapy demonstrate lesion shrinkage and hypoperfusion.

**References:** M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY

Perfusion depending on histology (metastases from RCC, Melanoma, NET show prevalent arterial perfusion, metastases from lung, colon and other cancers show prevalent portal perfusion), low BF and BV, short MTT, permeability is usually increased as compared to surrounding liver parenchyma, low ALP and HPI.

- Lesions follow-up after treatment:
Fig.: Metastases from colon cancer: CT-p before and after chemotherapy demonstrate dimensional stability of the lesion but a substantial hypoperfusion due to central necrosis.

References: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY
Fig.: Metastases from colon cancer: CT-p before and after chemotherapy demonstrate dimensional stability of the lesion but a substantial hypoperfusion due to central necrosis. Quantitative analysis clearly shows a decrease of BF, BV and permeability.

References: M. Anzidei; Radiological Sciences, "Sapienza" University of Rome, Rome, ITALY

In case of good response to treatment all lesions usually show a decrease of global perfusion, decreased BF and BV, increased MTT and decreased permeability.

Images for this section:
Vascular bed is represented as a cylinder of length $L$ with a blood volume $V_b$. The interstitial tissue is represented as another cylinder around the first one with a blood volume $V_e$. Contrast medium enters the capillary at a flow rate $F$ and starts to diffuse in the extra-vascular compartment, so the blood concentration of contrast medium $C_b(x,t)$ is a function of axial position and time ($t$). The interstitial tissue concentration instead depends only on time.

**Fig. 1**: Details of Distributed Model.
Fig. 2: Contrast Administration Protocol for Distributed Model.

- **Contrast Agent:**
  50-60 mL @ 6-8 mL/s,
- **Saline flush:**
  20 mL @ 5 mL/s
“Patlak” two compartment model: after the injection in the intravascular compartment, contrast agent will pass to interstitial space with a constant rate of efflux ($k_1$). Contrast agent will also pass from the interstitial space to the intravascular space with a constant rate ($k_2$).

**Patlak’s analysis:**

\[
\frac{C(t)}{C_b(t)} = rbv + Pm \int_0^t \frac{C_b(t)}{C_b(t)} dt
\]

- $C(t)$: c.a. concentration at time $t$
- $C_b(t)$: blood concentration at time $t$
- $rbv$: relative blood volume
- $Pm$: permeability

**Fig. 3:** Details of Patlak Model.
Fig. 4: Contrast Administration Protocol for Patlak Model.

- **Contrast Agent:**
  - 32 mL @ 4 mL/s,
  - 16 mL @ 2 mL/s,
  - 60 mL @ 1 mL/s

- **Saline flush:**
  - 20 mL @ 1 mL/s
**Perfusion Parameters**

- **BP**: Blood Flow is the flow rate of blood in the vascular space of a tissue region.
- **BV**: Blood Volume is the volume of blood inside the vascular space of a tissue region.
- **MTT**: Mean Transit Time is the mean time used by blood to go from arteries to veins.
- **PS**: Permeability Surface is the total product of permeability and total surface area of endothelium in a unit mass of tissue.

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**Fig. 5**: Perfusion Parameters and Phatological Alteration in Hepatic Carcinogenesis.
**Fig. 6:** Multifocal HCC: baseline CT-p and conventional MRI in a patient candidate to antiangiogenetic treatment.
Fig. 7: CCC: recurrence after surgery visualized at baseline CT-p in a patient candidate to antiangiogenetic treatment.
**Fig. 8:** Metastases from colon cancer: CT-p before and after chemotherapy demonstrate lesion shrinkage and hypoperfusion.
Fig. 9: Metastases from colon cancer: CT-p before and after chemotherapy demonstrate dimensional stability of the lesion but a substantial hypoperfusion due to central necrosis.
Fig. 10: Metastases from colon cancer: CT-p before and after chemotherapy demonstrate dimensional stability of the lesion but a substantial hypoperfusion due to central necrosis. Quantitative analysis clearly shows a decrease of BF, BV and permeability.
Fig. 11: HCC necrosis after RF: the treated area is no longer vital with a complete hypoperfusion as compared to normal surrounding parenchyma and focal recurrence.
**Fig. 12:** HCC recurrence after RF: focal recurrence adjacent to the treated area shows vital perfusion; however the tissue seems to be less vascularized than the primary cancer. A comparison with conventional and DWI MR sequences is also reported.
Fig. 13: Normal Liver: enhancement trend of the normal liver during CT-p.
Conclusion

The progress in CT field has led to the possibility to use CT-p on the whole liver volume. Demands of CT-p for therapeutic effect evaluation and prognosis analysis in oncology patients are rapidly increasing, relying on the higher confidence from the radiologists in diagnosing response or failure of treatment, thus redirecting therapy. Adequate knowledge of technical details and a next-generation radiologic semeiotics and language are required to properly perform and interpret CT-p examinations.

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