Multicentre analysis of blood flow values of normal liver in CT perfusion examinations of patients with colorectal cancer

Poster No.: C-2932
Congress: ECR 2017
Type: Scientific Exhibit
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Keywords: Liver, Oncology, Computer applications, CT-Quantitative, CT, Computer Applications-General, Imaging sequences, Contrast agent-intravenous, Haemodynamics / Flow dynamics, Multidisciplinary cancer care, Tissue characterisation
DOI: 10.1594/ecr2017/C-2932

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Aims and objectives

The introduction in the clinical practice of anti-angiogenic therapies aiming at preventing tumour growth, spread, and capability of generating metastasis, has highly improved cancer treatment [1]. Since the main effects of these kinds of anti-tumour therapies are early visible on lesion’s functional behaviour and only later in time on cancer’s morphology [2], the interest for new approaches able to early estimate functional changes inside tissues has quickly grown up [3].

Thanks to its high morphological and temporal resolution, Computed Tomography perfusion (CTp) is one of the most promising functional imaging techniques for the earlier assessment of anti-angiogenetic therapies’ efficacy [4]. By analysing the CTp sequences achieved, it is possible to compute perfusion parameters containing useful information regarding tissue vascularization [5]. Indeed, these parameters have shown to be useful in tumour diagnosis [6] and prognosis [7].

Nonetheless, due to the lack of reliability and reproducibility of perfusion results, CTp is still not used in standard clinics [8]. Just recently, some steps forward have been taken to assess the reliability of the computed perfusion values [9,10] as well as to try improving their computation [11]. As regards results reproducibility, there are several factors, such as examination protocols and methodologies of data processing and analysis, which affect the CTp outcomes preventing the comparison of results achieved in different studies. Despite guidelines regarding the setup of CTp studies have been drawn in [5], it is still not clear whether, and to what extent, the use of different CT scanners could affect perfusion results achieved.

In order to introduce a new imaging technique in the standard clinical practice, the effectiveness of this technique has to be proved in a series of prospective multi-centre studies [12]. The need for perfusion multi-centre studies has been widely declared in the recent literature [13, 14], but the lack of specific guidelines and the complexity in setting up this kind of studies have prevented their implementation.

To the best of our knowledge, no results regarding wide CTp multi-centre studies of liver have been published so far. The widest European study on liver CTp is a French study named Perfusion IndeX: Evaluation for Liver metastases (PIXEL). The aim of this multi-centre study involving 19 Centres and almost 400 patients is the evaluation of perfusion parameters capability to predict the development of hepatic metastases in patients with initially non-metastatic colorectal cancer before the administration of anti-cancer therapies. In this work, preliminary results are analysed to evaluate whether the use of different CT scanners could affect the computation of perfusion values in normal liver.
Methods and materials

Patients

Three Centres that took part to PIXEL and that correctly followed the nominal acquisition protocol initially agreed were chosen. 10 patients were randomly selected from each of these Centres to be included in this preliminary study. 30 CTp examinations pertaining to as many patients (age range 46-85 years) were finally analysed. The inclusion criteria for patients in PIXEL were:

- age>18 y.o.
- absence of previous cancer pathologies
- having colorectal cancer
- free of liver metastases

Exclusion criteria are resumed as follows:

- presence of liver metastases at the time of cancer diagnosis
- having chronic liver diseases
- receiving chemotherapy before undergoing liver CTp
- undergoing cancer colorectal surgery before liver CTp
- being allergic to CA
- suffering from renal impairment
- being pregnant

The ID of each examination is described by two numbers, the former representing Centre ID and the latter corresponding to patient ID. For instance, the CTp examination of the 28\textsuperscript{th} patient of Centre 16 is described by the ID C16N28.

Acquisition protocol

A first unenhanced spiral CT scan was carried out on the liver to identify the correct region that had to be analysed. Right after, an axial CTp acquisition was performed so as to include the portal vein trunk and the right hepatic parenchyma. The image acquisition started contemporaneously with the administration at 5ml/s of 40ml of iodated CA, with a concentration of 350mgI/ml. The CA bolus was followed by the injection of 20ml of physiologic solution. Patients were asked to shallowly breath over the two minutes of the CTp acquisition phase. CT tube current and voltage were kept fixed at 100mA and 80kV, respectively, with a 1sec rotation time equals and exposure of 100mAs. The tissue was acquired every 1sec during the first 30sec and every 3sec for the remaining 90sec, yielding a total amount of 60 scans, each composed of 8 sections of 5mm thickness.
Perfusion Analysis

In each CTp examination, a central section was selected and two regions of interest (ROIs) were drawn, on the aorta and the liver, respectively. Whole tissue ROI had to lay within the liver borders in all the images of the CTp sequence and, possibly, should be placed quite far from liver margins to prevent partial volume effects. The ROI placement procedure must be carried out with a great care, excluding large vessels, such as portal vein or hepatic artery. An example of a typical ROI drawn on a liver section is represented in Fig. 1 on page 7.
**Fig. 1:** ROI of examination C8N7 drawn on normal liver, far from liver margins and excluding large vessels.

**References:** Advanced Research Center on Electronic Systems

Time concentration curves (TCCs) of each voxel of the tissue ROI were fitted by using a sigmoidal-shaped curve \( f(t) \) based on the Hill equation, employed to model the pharmacokinetic of the contrast agent [9, 15], and described as:

\[
    f(t) = E_0 + (E_{MAX} - E_0) \frac{t^\alpha}{(EC_{50})^\alpha + t^\alpha}
\]

**Fig. 2:** Hill's equation

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where \( E_0 \) and \( E_{MAX} \) represent the baseline and the saturation values expressed in Hounsfield Units (HU), respectively, \( EC_{50} \) is the time instant of half-maximum response concentration and \( \# \) is the non-linear parameter mostly affecting the slope of the curve.

BF values were computed according to the single-input method, following a voxel-based approach, by applying the Maximum Slope method [16] to each TCC of the ROI within the first-pass phase. In particular, BF values represent the ratio between the maximum slope of the fitted TCC \( f(t) \) and the peak density reached by the TCC of the arterial input \( f_a(t) \):

\[
    BF = \left. \frac{df(t)}{dt} \right|_{max} \frac{max}{f_a(t)|_{max}}
\]

**Fig. 3:** Maximum slope equation

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BF values (expressed in ml/min/100g) are visualised by means of functional colorimetric maps. Finally, mean and standard deviation values of BF were computed for each examination.
Statistical analysis

One-way ANOVA (p-value#0.05) was applied to data of BF values distributions of the three Centres to verify whether the use of different CT scanners introduced variability on computation of the averaged perfusion values. Tukey test (p-value#0.05) was used to verify whether these Centres introduced variability, independently from inter-patients variability. Statistical analysis was performed using R software (version 3.0.1, The R Foundation for Statistical Computing).
Fig. 1: ROI of examination C8N7 drawn on normal liver, far from liver margins and excluding large vessels.

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Results

ROIs mean±standard deviation area in Centre 1, 8, and 16, were 20.0±6.0cm², 23.6±7.0cm², 22.2±7.0cm², respectively. BF mean, standard deviation (std), and range values (in mL/min/100g) are shown in Table 1 on page 10.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Mean (mL/min/100g)</th>
<th>Std (mL/min/100g)</th>
<th>Range (mL/min/100g)</th>
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<tbody>
<tr>
<td>1</td>
<td>34.4</td>
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<td>22.8 – 47.4</td>
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<tr>
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Table 1: BF mean, std, and range values of 30 examinations acquired in 3 different Centres.

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An example of BF colorimetric maps achieved in the three Centres can be found in Fig. 4 on page 10.

![BF colorimetric maps](image)

Fig. 4: Examples of BF colorimetric maps achieved in the normal liver in Centres 1 (a), 8 (b), and 16 (c) using the single input method.

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Results of one-way ANOVA highlights that differences between mean BF values obtained in the three Centres are statistically significant (p<0.01). This statistical test states that there is at least one couple of Centres whose mean perfusion values are significantly different, independently from within-patients variability. To know which the Centres involved are, it is necessary referring to results of the Tuckey test. While no significant differences were found between mean BF values of Centre 1 and Centre 8 or 16, mean BF values of Centres 8 and 16 resulted to be significantly different and this difference has been proved not to be attributable to within-patients variability.
Images for this section:

Table 1: BF mean, std, and range values of 30 examinations acquired in 3 different Centres.

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![Fig. 4](image1.png)  ![Fig. 4](image2.png)  ![Fig. 4](image3.png)

Fig. 4: Examples of BF colorimetric maps achieved in the normal liver in Centres 1 (a), 8 (b), and 16 (c) using the single input method.

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Conclusion

The use of different examination protocols and methodologies of data processing and analysis affecting perfusion results is one of the main causes preventing CTp application in the standard clinical practice. Before adopting this imaging technique in clinical practice, the achievement of results confirming its effectiveness in prospective multi-centre studies is needed.

To the best of our knowledge, PIXEL is the first CTp multi-centre study that has been carried out on liver. In this work, a preliminary analysis of BF values achieved in a subset of 30 patients pertaining to three different Centres of the PIXEL cohort has been carried out. All the CTp examinations considered were acquired by using the same protocol and processed with the same perfusion software.

The preliminary results achieved in this study highlight that, despite employing same acquisition protocol and same software, data acquired in different Centres can lead to significantly different perfusion results that cannot be ascribed to within-patients variability. Accordingly, before comparing perfusion results referring to CTp examinations acquired in different Centres, some kind of normalization has to be performed.


