Values of the unenhanced stage of CT perfusion studies of liver: a multi-centre experience

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Aims and objectives

In the last few decades, the introduction in the clinical practice of anti-angiogenic therapies aiming at preventing tumour growth, spread, and capability of generating metastasis, has highly improved efficacy of cancer treatment [1]. Differently from chemo- and radio-therapies, the effects of anti-angiogenic therapies are visible early on lesion’s functional behaviour and only later on morphology [2]. Consequently, the interest around new approaches able to early estimate functional changes inside tissues has quickly grown up [3].

Computed Tomography perfusion (CTp) is a functional imaging techniques characterized by a high morphological and temporal resolution. Thanks to these characteristics, CTp has become one of the most promising techniques for the early assessment of the efficacy of anti-angiogenic therapies [4]. After drawing a region of interest (ROI) on the tissue to be analysed, it is possible to extract from each voxel of the ROI a time concentration curve (TCC). By applying specific methods and kinetic models to each TCC, it is possible to computer perfusion parameters related to tissue vascularization [5], that have shown to be effective both in tumour diagnosis [6] and prognosis [7].

One of the advantages of carrying out perfusion studies with CT is that the concentration of CA inside tissue is directly proportional to the attenuation of HU values. In the ideal conditions (i.e., without noise), tissue density values before CA arrival (i.e., the baseline attenuation value) should be constant in time. Therefore, after subtracting from each TCC its baseline value, what results is a signal in direct ratio with the CA concentration inside tissue, on which perfusion parameters are computed [8]. Accordingly, the correct selection of baseline values is crucial to achieve accurate perfusion values. In the literature, baseline values have been mainly computed accordingly to two methods. The first uses the same global baseline value for all the TCCs, computed as the average of liver density values inside the tissue ROI on the first image acquired [9]. The main drawback of this method is that it neglects local variations of tissue density values. On the contrary, the second method uses voxel-based baseline values that are selected for each TCC as the corresponding density value in the first CT image acquired [10]. However, the presence of noise and artefacts affecting the first CT image can alter baseline values and lead to incorrect perfusion values.

Mean density values reported in the literature for normal liver and measured through the use of unenhanced CT scans are around 50#65HU [11]. Other works, extend their range value to 30HU #70HU [12, 13] or even wider. Indeed, in a recent retrospective study involving 48 patients with normal liver who underwent two CT examinations carried out with two different CT scanners in less than one year [14], the mean liver density values measured ranged respectively from 9.6 to 63.2HU and from 20 to 77.2HU.

Despite CTp has proved to be a very useful tool in the oncologic field, the lack of reliability and reproducibility of perfusion results [15], and of CTp multi-centre studies proving the
effectiveness of this technique [16], is the main cause delaying its use in standard clinics. In the last few years, some steps forward have been taken to try solving these issues. Indeed, some works addressing the problem of assessing perfusion values reliability [17,18] and trying improving their computation [19] have been carried out. In addition, guidelines regarding the set-up of CTp studies have been drawn [15] with the aim of reducing variability factors affecting perfusion results and improving their reproducibility. However, despite the wide claim in the recent literature of multi-centre studies [20, 21], no data have been published so far in this regard, probably mainly due to the complexity of their set-up.

To the best of our knowledge, "Perfusion IndeX: Evaluation for Liver metastases (PIXEL)" is the first CTp multi-centre study on liver that has ever been carried out. The aim of this multi-centre study, involving 19 Centres and almost 400 patients, is the capability evaluation of perfusion parameters to predict the onset of hepatic metastases in patients with initially non-metastatic colorectal cancer, before the administration of anti-cancer therapies. In this work, we present a preliminary study that has been carried out on a subset of PIXEL data. In particular, we propose a new adaptive method permitting to compute accurate voxel-based baseline values and use it to evaluate whether baseline values of normal liver are reproducible in the different Centres.
Methods and materials

Patients

4 Centres that took part to PIXEL and that correctly followed the nominal acquisition protocol were chosen. 10 patients who did not develop metastases in the 3-year follow up were randomly selected from each of these Centres to be included in this preliminary study. 40 CTp examination pertaining to as many patients (age range 43-85 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 can be 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 identifier including two numbers, the former representing Centre ID and the latter corresponding to patient ID. For instance, the CTp examination of patient 28 belonging to Centre 16 is identified by ID C16N28.

Acquisition protocol

The acquisition protocol was defined during a first meeting between the responsible people of each hospital. A first unenhanced spiral 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 in order to include the portal vein trunk and the right hepatic parenchyma. The image acquisition started at the same time as the administration of 40ml of iodated
CA with a concentration of 350mg/l/ml, at 5ml/s. The CA bolus was followed by the injection of 20ml of physiologic solution. Patients were asked to breathe shallowly during all two minutes of the CTp acquisition phase. The CT tube current and voltage was kept fixed at 100mA and 80kV, respectively, with 1s rotation time and exposure of 100mAs. The tissue was acquired every 1s during the first 30s and every 3s for the remaining 90s, this yielding 60 scans, each composed of 8 sections of 5mm thickness.

Baseline computation

In each CTp examination, a central section was selected and a ROI was drawn on the liver. 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 so as to avoid partial volume effects. In general, the ROI placement procedure must be carried out with a great care so as to exclude big 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 8.
Fig. 1: ROI of examination C8N7 drawn on normal liver, quite far from liver margins and excluding large vessels.

References: Electrical, Electronic and Information Engineering "Guglielmo Marconi", University of Bologna - Bologna/IT

The baseline value of each TCC was automatically determined by employing an adaptive 3D filtering algorithm. First of all, the time instant corresponding to the contrast agent arrival inside tissue was found for each voxel. This time point corresponds to the time instant separating the baseline portion of the TCC from its enhanced part. An example of where this time instant is found is reported in Fig. 2 on page 8.
The original TCC is reported in the blue colour. The red vertical line corresponds to the time instant selected by the algorithm as arrival instant of contrast agent inside tissue.

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Thereafter, the baseline value was computed for each voxel as the average of the TCC density values referred to the baseline portion. For each examination, the baseline values were represented through the use of colorimetric maps and mean, standard deviation (std), and range were computed.

**Statistical analysis**

One-way analysis of variance (ANOVA) (p-value $\leq 0.05$) was applied to check for differences of mean baseline values among Centres. 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, quite far from liver margins and excluding large vessels.

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Fig. 2: The original TCC is reported in the blue colour. The red vertical line corresponds to the time instant selected by the algorithm as arrival instant of contrast agent inside tissue.

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Results

ROIs area mean and std values in Centres 1, 8, 16, and 17, were of $20.1\pm6.0\text{cm}^2$, $25.9\pm7.6\text{cm}^2$, $22.3\pm7.0\text{cm}^2$, $21.7\pm8.7\text{cm}^2$, respectively.

Baseline colorimetric maps obtained in each Centre are shown in Fig. 3 on page 13.

![Baseline colorimetric maps](image)

**Fig. 3:** Baseline colorimetric maps of Centres 1 (a), 8 (b), 16 (c), 17 (d).

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As one can see, all the colorimetric maps show local homogeneities. The presence of a local spatial correlation is also demonstrated by the gradual passage of baseline values from lower to higher baseline values that in colorimetric maps results in progressive colour gradients. This spatial correlation reflects the local spatial coherence of tissue features. Moreover, since the baseline values obtained with our algorithm are computed in each voxel by using only data pertaining to one TCC, independently from the signal of the neighbouring voxels, the baseline local spatial homogeneity can be considered as a qualitative indicator of the algorithm goodness.

Baseline mean, std, and range values computed for each Centre are resumed in Table 1 on page 13.
Table 1: Baseline mean, std, and range values of 40 examinations acquired in 4 different Centres.

<table>
<thead>
<tr>
<th>Centre</th>
<th>Mean (HU)</th>
<th>Std (HU)</th>
<th>Range (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57.4</td>
<td>13.3</td>
<td>34.4 – 75.8</td>
</tr>
<tr>
<td>8</td>
<td>60.5</td>
<td>16.3</td>
<td>28.0 – 79.0</td>
</tr>
<tr>
<td>16</td>
<td>57.7</td>
<td>11.1</td>
<td>42.0 – 78.6</td>
</tr>
<tr>
<td>17</td>
<td>62.3</td>
<td>3.8</td>
<td>57.6 – 68.2</td>
</tr>
</tbody>
</table>

As the first consideration, all the histograms are multimodal meaning that the baseline values can be arranged into groups. As one can see, Centre 8 is the one presenting the widest range of baseline values. By comparing on the histograms ranges of the various Centres, it is possible to note that in Centre 8 there are some baseline values that are very low with respect to those of the other Centres. By deepening the analysis, we realized that these values mostly pertained to one patient affected by quite a severe liver steatosis (with a mean liver value of 8.9HU, 10HU lower than 21.6HU, the mean spleen value [22]). While histograms of Centres 1 and 16 show distributions with similar range, Centre 17 is characterized by a very narrow distribution, also confirmed by a low std value, that is almost one third with respect to the other Centres.
 Nonetheless, all the four Centres present very similar mean baseline values, as it is confirmed by results of one-way ANOVA, stating that the differences between the mean values in the four Centres are not statistically significant.
Fig. 3: Baseline colorimetric maps of Centres 1 (a), 8 (b), 16 (c), 17 (d).

Table 1: Baseline mean, std, and range values of 40 examinations acquired in 4 different Centres

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Fig. 4: Histograms of baseline values referring to all the examinations of Centres 1 (a), 8 (b), 16 (c), 17 (d). The red vertical lines points out the mean value.
Conclusion

The unenhanced baseline value is a parameter that highly affects the accuracy of the perfusion parameters computed. The adaptive algorithm proposed in this work to achieve correct baseline values has been created to try improving the two methods that are mainly used in the literature and has shown to provide good results without using prior information regarding the length of baseline. In addition, baseline values of normal liver of patients with colorectal cancer found in this study are compliant with values of normal liver in healthy subjects reported in the literature.

The preliminary results of this multicentre study points out a higher homogeneity of values in Centre 17, although there is no evidence that Centres introduce variability on baseline values. Consequently, at present there is not any proof that the baseline values vary across Centres.
References


