CT perfusion of lung tumour: do morphological and functional heterogeneity correlate?

Poster No.: B-0087
Congress: ECR 2015
Type: Scientific Paper
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Keywords: Lung, Oncology, Computer applications, CT, CT-Quantitative, Imaging sequences, Computer Applications-General, Computer Applications-Detection, diagnosis, Multidisciplinary cancer care, Tissue characterisation, Cancer
DOI: 10.1594/ecr2015/B-0087

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Purpose

Currently, diagnosis and monitoring of lung cancer mainly rely on a visual based morphological analysis [1], primarily performed with computed tomography (CT).

Assessment of treatment effects of conventional chemotherapeuticals are visually performed after about 1 or 2 months, by considering the change in tumour size according to RECIST [2] to make further decisions. However, when employing with molecularly targeted therapeutic agents, it is possible to assess their effect much before that changes in volume become visible [3].

Just recently, several imaging studies have focused on the characterisation of tumour heterogeneity [4]. Although inter-tumour heterogeneity across various malignancies and lesions has been relatively well described, the intra-tumour heterogeneity (i.e., different biological characteristics within the subtypes of cancer cells), though acknowledged, has little been investigated. Nevertheless, it is worth noting that intra-tumour heterogeneity will probably have enormous implications in the middle term for the personalized treatment of patients with cancer [5], and will be increasingly utilized in clinical routine [6]. But, new imaging criteria are needed to better characterize treatment response in oncology.

Several oncological studies have been published on the use of functional imaging techniques such as MR, US, PET and, in the last years, CT perfusion (CTp). This functional technique is based on scanning the same volume over time before, during, and after intravenous administration of contrast agents to detect temporal changes in the vascular structure of the tissue volume of interest. In particular, CTp has shown to be a promising technique for diagnosing primary or metastatic tumours [7], assessing the efficacy of the therapies, monitoring the tumour response [8], and hopefully, early predicting the likelihood of response to anti-angiogenic therapies [9].

CTp has paved the way for the evaluation of the lesion functional heterogeneity, based on the analysis of the colour maps representing perfusion parameters, which may provide additional information regarding the functionality of tumour vasculature [6], for instance in terms of blood flow (BF) [4], with respect to the most widely used morphological analysis.

The aim of this study was to compare morphological and functional heterogeneity of primary non-small cell lung cancer (NSCLC), with the purpose of finding out possible correlations. To this aim, we devised two different local-heterogeneity indices, computed for each voxel to measure the morphological heterogeneity on the reference section and the functional heterogeneity on the BF perfusion map. The two heterogeneity maps finally achieved were considered for possible correlations.
Methods and materials

Perfusion CT protocol

14 patients (for a total of 22 examinations) underwent axial CTp, performed on a 256-slice CT system, feet first in the supine position.

An initial low-dose unenhanced full-body CT scan was performed to identify the target lesions at baseline conditions. A 50 mL intravenous bolus of contrast agent was then injected at 5 mL/s for axial cine contrast enhanced CT.

A single acquisition of duration 25 seconds, with patient instructed for breath-hold, giving 20 scans with 55 mm of z-coverage (11 slices × 5-mm slice thickness, 0.4-second rotation time, at 80 kV, 250 mA) was performed for each patient. Image data are reconstructed to 220 cine images (512 × 512 pixel, 11 slices, 350 mm × 350 mm, 5-mm slice spacing, 1.25-second temporal resolution).

Accordingly, the generic protocol yields M scans, each corresponding to different sampling instants, of K levels each (i.e., M=20, K=11).

Perfusion Maps

The target lesions and the arterial input (aorta) were selected in agreement by two radiologists on a reference slice. For each lesion, the radiologists manually drawn on the reference slice the region of interest, ROI.

BF functional maps of the reference slice (Fig. 1 on page 9) were obtained by fitting the values of the temporal sequence relative to each voxel, using a sigmoid-shape model arising from the Hill Equation, and computing the Maximum-Slope method [10] during the first-pass phase. BF is expressed in mL/min/100 g.
**Fig. 1**: Example of cine sequence related to the aligned reference slice.

**References**: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT

BF values strictly lower than 1 mL/min/100 g are considered as being unlikely compliant with physiological values and rather ascribable to numerical errors (since the computing method forces BF to have positive values only), hence marked as unreliable and pointed out in the color map with the "pink" color [11].

**Lung tumour heterogeneity: a taxonomy**

At present, there is no ground-truth reported in the literature and the evaluation of the degree of heterogeneity of a tissue is left to the visual analysis by radiologists, and possibly undergoing in a certain level of subjectivity. It is therefore necessary to identify this heterogeneity assigning it a more objective measure, that however shall be finally submitted to radiologists’ opinion.
Hence, as a first attempt of validation, a three-class categorization of the various heterogeneities present in lung lesions was performed, to constitute a taxonomy. Then, the morphological heterogeneity was visually assessed by two radiologists using a 3-point scale, corresponding to the three different types of heterogeneities (Fig. 2 on page 9). First, a structure is homogeneous if the lesion tissue does not present any heterogeneous regions, micro-inhomogeneous if it is characterized by different density point sources distributed over the entire lesion, and macro-inhomogeneous if it is characterized by the presence of one, or more, regions with coarse tissue density markedly different from the background.

**Local-Heterogeneity Maps**
In order to assess the morphological and functional heterogeneity we measured the local heterogeneity of the reference image section and that of the BF map. To this purpose, we used two different local-based indices, calculated on small square regions centred on each voxel, namely, the local standard deviation (lSD) and the local coefficient of variation (lCV) (Fig. 3 on page 10) [12], respectively. While SD is the well-known statistical tool measuring the dispersion around a mean of values, the coefficient of variation (CV) represents a "normalized" SD, essentially a common SD "weighted" by the mean value [8]. Finally, this computation repeated for each voxel within the ROI yields two corresponding ISD and ICV maps.

![Fig. 3](image)

**Fig. 3**: Blood flow (BF) map of ID2 (a) and a 9×9 region R (b) showing the perfusion values considered for the computation of the local coefficient of variation (lCV) stored in the corresponding pixel of the lCV map (c).

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Therefore, higher lSD values correspond to wide spatial variations of HU values, that is to a higher contrast and, ultimately, a higher heterogeneity. Similarly, regions with higher values of lCV hint at a correspondingly wide spatial variation of BF values, suggestive for a higher functional heterogeneity.

**Data Analysis**

The Pearson correlation (PC) index was employed to study the correlation between the two local-heterogeneity maps. The PC index provides values ranging from -1 and
+1, these representing a perfect negative and positive linear dependence between two variables, here represented by the two heterogeneity indices, whereas 0 points out the absence of linear correlation.

As a matter of fact, a local PC (IPC) index is computed on small square regions centred on each voxel, and the resulting IPC values are stored in a newly created IPC (colorimetric) map, in practice using the same procedure previously employed for the generation of the local heterogeneity maps.

For the sake of completeness, the brown colour points out voxels where IPC values are not significant.
Fig. 1: Example of cine sequence related to the aligned reference slice.

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Fig. 2: Early taxonomy of heterogeneities.

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**Fig. 3:** Blood flow (BF) map of ID2 (a) and a 9×9 region R (b) showing the perfusion values considered for the computation of the local coefficient of variation (ICV) stored in the corresponding pixel of the ICV map (c).

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Results

As expected, most cases showed a meaningful correlation between morphological and functional information. In addition, morphological local-heterogeneity maps recall the taxonomy previously defined by the two radiologists.

The correlation maps also provide a graphical representation of the correlation between the two local-heterogeneity maps, hence the assessment was carried out by visual interpretation. In general, the local correlation between the morphological and functional local-heterogeneity maps is positive in the presence of local heterogeneities (or local homogeneities) on both maps. Conversely, the local correlation results to be negative in the presence of a morphological heterogeneity and a functional homogeneity, or vice versa. As for possible threshold values, the analysis of results suggests that a strong positive (or negative) correlation can be assigned when values are greater than 0.6 (or less than -0.6).

Here, we reported three significant cases, (hereafter ID1, ID2 and ID3) showing the different information that can be extracted through observing the correlation maps.
Fig. 4: Hounsfield unit (HU) image of ID1.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 5: Colorimetric map of ID1 for blood flow (BF). The pink colour points out unreliable BF values.

**References:** Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 6: Local standard deviation (ISD) colorimetric map of ID1. The brown colour points out unreliable ISD values.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 7: Local coefficient of variation (ICV) colorimetric map of ID1. The brown colour points out unreliable ICV values. Red arrows point out the discontinuity present in the BF perfusion map.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
**Fig. 8**: Local Pearson correlation (lPC) colorimetric map of ID1. The brown colour points out unreliable lPC values. The orange arrow points out a negative correlation due to a morphological homogeneity coupled with a heterogeneous functional behaviour.

**References**: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT

In the first examination, the low ISD (Fig. 6 on page 29) values which almost characterize the whole morphological heterogeneity map hint at a lesion that, in the static conditions, is substantially homogeneous, as one can see from the HU image (Fig. 4 on page 28). In contrast, the high ICV (Fig. 7 on page 30) values of the functional heterogeneity map suggests a discontinuity in the functional parameters of the lesion (Fig. 5 on page 28) (highlighted by the red arrows in Fig. 7 on page 30).

The IPC colorimetric map (Fig. 8 on page 31) offers a panoramic representation of the correlation between these two local-heterogeneity maps. The small regions highlighted
by the red colours suggest the presence of a tissue with same degree of homogeneity, or heterogeneity, in its morphology and functional behaviour. Instead, nothing can be inferred by the green regions due to a lacking in the linear correlation between the two local-heterogeneity maps. The lower blue part of the lesion is characterized by a heterogeneous morphology that, however, has a homogeneous functional behaviour, as the negative values suggest. Nonetheless, the negative correlation in the central part of this lesion (highlighted by the orange arrow in Fig. 8 on page 31) here stems from a morphological homogeneity coupled with a heterogeneous functional behaviour.

Fig. 9: Hounsfield unit (HU) image of ID2.
Fig. 10: Colorimetric map of ID2 for blood flow (BF). The pink colour points out unreliable BF values.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 11: Local standard deviation (ISD) colorimetric map of ID2. The brown colour points out unreliable ISD values.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 12: Local coefficient of variation (ICV) colorimetric map of ID2. The brown colour points out unreliable ICV values.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
**Fig. 13**: Local Pearson correlation (IPC) colorimetric map of ID2. The brown colour points out unreliable IPC values. The white arrow points out the positive correlation of a morphologically heterogeneous region characterized by a functional heterogeneity, while the pink arrow indicates the positive correlation of a region arising from morphological and functional homogeneities.

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In the second examination, the ISD map (**Fig. 11** on page 34) shows a substantial homogeneity, reflecting what can be seen in the HU image (**Fig. 9** on page 32). The perfusion BF map (**Fig. 10** on page 33) essentially highlights two different regions characterized by lower (the blue one) and higher (the remaining colours) perfusion. It is interesting to note that the region in blue, characterized by a lower perfusion, reveals a high functional heterogeneity in the ICV map (**Fig. 12** on page 35), whereas the region characterized by a higher perfusion hints at a functional homogeneity.
In this case, the correlation map (Fig. 13 on page 36) does not show well-defined correlation regions. The morphologically heterogeneous region indicated by the white arrow is also characterized by functional heterogeneity, while the positive correlation in the region pointed out by the pink arrow arises from morphological and functional homogeneities.

As regards the blue and the green regions, what stated for the previous examination still holds.

**Fig. 14**: Hounsfield unit (HU) image of ID3.

**References**: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 15: Colorimetric map of ID3 for blood flow (BF). The pink colour points out unreliable BF values.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 16: Local standard deviation (ISD) colorimetric map of ID3. The brown colour points out unreliable ISD values.

References: Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 17: Local coefficient of variation (ICV) colorimetric map of ID3. The brown colour points out unreliable ICV values.

**References:** Radiology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS - Meldola/IT
Fig. 18: Local Pearson correlation (IPC) colorimetric map of ID3. The brown colour points out unreliable IPC values.

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In the third patient, the lesion is homogeneous both morphologically (Fig. 16 on page 39) and functionally (Fig. 17 on page 40), as shown by the two local-heterogeneity maps, which reflect the substantial homogeneities appreciable in the HU image (Fig. 14 on page 37) and in the BF perfusion map (Fig. 15 on page 38). It is worth noting that in this examination the lowest IPC (Fig. 18 on page 41) values are not below -0.6, this preventing strong negative correlations. This lesion manifests an almost coherent behaviour, from both morphological and functional points of view, showing a strong positive correlation in a wide region, just in correspondence of the homogeneities in the two local-heterogeneity maps.
**Fig. 4:** Hounsfield unit (HU) image of ID1.

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Fig. 9: Hounsfield unit (HU) image of ID2.

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Fig. 10: Colorimetric map of ID2 for blood flow (BF). The pink colour points out unreliable BF values.

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**Fig. 11:** Local standard deviation (ISD) colorimetric map of ID2. The brown colour points out unreliable ISD values.

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Fig. 12: Local coefficient of variation (ICV) colorimetric map of ID2. The brown colour points out unreliable ICV values.

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Conclusion

Often, most of times information regarding lung tumour heterogeneity can be successfully derived from morphological analysis of a CT sequence. This study aims at showing that morphological analysis only can be so inadequate as to even mislead clinical consideration.

The IPC maps resulted very useful to highlight concordant as well as discordant degrees of homogeneities (or heterogeneities) and, together with the worthy support of the local-heterogeneity maps, makes the reader aware of the type of the mostly expected agreement (either homogeneous or heterogeneous). Most important, in the absence of correlation the local-heterogeneity maps are needed to discriminate between the sources of heterogeneity, whether it is morphological or functional.

As a matter of fact, the most expected result probably is that morphological homogeneous regions would also show a homogeneous functionality, as those shown in the third examination. Or else, that coherence regards the heterogeneous feature as well, when a heterogeneous functional behaviour can be ascribed to a morphologically heterogeneous regions, as in the second case discussed.

Nevertheless, the most important source of information arises from severe mismatches between morphological and functional heterogeneities, as one could see in the first examination. This lesion, considered by radiologists as being structurally homogeneous, results quite surprisingly characterized by a necrotic core and a distinct high perfusion region. Therefore, although the tissue is apparently homogeneous, at a coarse grain, it hides a heterogeneous functionality in terms of perfusion, at a underlying, not visible, layer. In conclusion, the strategy presented as well as the colorimetric maps achieved represent a valid support to radiologists for clinical considerations and, in the last analysis, for the making decision stage. Detecting the tissue capability of expressing a different functionality, though preserving the same appearance, could be of fundamental utility in clinical routine, and it also represents a step forward to translation of the CTp in standard clinics.
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