CT perfusion studies of lung cancer: automatic detection of misleading structures and artefacts

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Purpose

In the last few years, the increasing use of anti-angiogenic drugs aiming at reducing tumour's blood supply yielded the need of new measurement methods able to assess the efficacy of these new therapeutic approach [1]. Thanks to its capability of providing images at a high morphological resolution and functional information about the investigated tissues, CT perfusion (CTp) represents a promising imaging technique to be used in the oncological field [2]. Various studies report its potential capability of supplying necessary information for making diagnosis, discriminating benign from malignant lesions [3], tumour staging [4] and prognosis [5]. This widely available and non-invasive technique relies on the estimation of tissue's contrast agent delivery, and on the corresponding hemodynamic parameters, which can be derived from the analysis of the Time-Concentration Curves (TCCs) generated by the contrast agent reaching the tumor lesion, and as such it could be employed to detect changes in its vascular structure, hinting at possible anomalies in blood supply (i.e., tumour angiogenesis [6]).

However, the clinical use of CTp is still hampered by many problems mainly related to difficulties in measuring reproducibility and reliability of perfusion values [7]. Both these statistical properties also depend on TCCs’ fitting quality, starting from which perfusion values are computed. The presence of respiratory motion [8], and of various types of CTp acquisition and reconstruction artefacts such as beam-hardening and partial volume effect [9], heavily contribute to obtain flawed TCCs. Moreover, also the presence of vessels and bronchi inside lesion's tissue is responsible for misleading visual and quantitative analyses of perfusion colour maps. Indeed, if not excluded, these anatomical structures also alter the colour scale of perfusion maps, this having a bad influence even on local or global statistical indexes computed on lesion, exposing radiologists to the risk of formulating erroneous clinical considerations.

Some works started facing the problem of TCCs’ reliability, suggesting a method to detect voxels where the error in building a TCC could jeopardized the computed perfusion values [10] or even tried to improve the way a TCC is built, so as to reduce the number of possible flawed TCCs [11]. Some other studies deal with the presence of anatomical structures by manually removing them [12,13] or by simply discarding the highest perfusion or concentration values through using a threshold determined in advance [14].

To the best of our knowledge, this is the first work proposing a method to automatically detect physical structures responsible for unreliable perfusion values. In particular, we present a novel approach to automatically detect voxels characterized by high error values which are the main responsible for the unreliability of perfusion values. Preliminary plot of error values maps highlighted a spatial contiguity of high and low error values, just in correspondence of the physical structures such as vessels, bronchi, and artefacts. In order to find an adaptive approach to remove voxels affected by too high errors, we proposed an automatic thresholding based on statistical errors analysis. Physical
structures detected by radiologists and highlighted through manual annotation were compared with regions characterized by over-threshold errors present in the error maps. As a final remarks, it is worth noting that while vessels and bronchi are almost always correctly detected and contoured by radiologists, artefacts are harder to be identified and delimited. Indeed, we show some interesting cases where radiologists detected artefacts but were not able to delimit their border nor to correctly define their extent. We also discuss the possible consequences of these limits, also emphasizing the benefits brought by the introduction of our automatic error detection method.
Methods and materials

Perfusion CT protocol

16 patients with non-small cell lung cancer were enrolled for this study approved by the Institutional Review Board. First, a low-dose total-body axial CT scan was performed with a 256-slice CT system to detect and locate target lesions. Then, a 50mL short sharp bolus of iodinate contrast agent was intravenously injected at 5mL/s to allow a contrast-enhanced CT scan of the lesion's area. A total of 24 examinations were collected with patients in breath-hold supine feet first position. Each acquisition had a z-coverage of 55 mm (11 slices × 5-mm slice thickness), and was performed in 25 seconds, with a rotation time of 0.4 second, and at a tube voltage and current values of 80 kV and 250 mA, respectively. Image data were reconstructed to 220 cine images (512 × 512 pixel, 11 slices, 350 mm × 350 mm, 5-mm slice spacing, and a temporal resolution of 1.25 second). Accordingly, each acquisition provided 20 scans, corresponding to as many different sampling instant, of 11 levels each.

Perfusion maps

Two Regions Of Interest (ROIs) delineating aorta and lesion's contours were manually drawn by two 25-year experienced radiologists in agreement on a reference slice. The best sequence of 20 slices (one for each scan) whose ROI best matched with that of the reference slice was then selected and lesion's ROIs were manually translated and shifted on it to better follow lesion's movement. TCCs were built for each pixel within the lesion's ROI by fitting voxel's HU values with a sigmoidal model based on Hill's equation [11]. BF values, expressed in mL/min/100 g, were computed by applying the maximum-slope method to TCCs and were finally represented through colorimetric maps. Perfusion values lower than 1 mL/min/100 g were considered as being unlikely compliant with physiological values and hence ascribable to numerical errors. For this reason, in colorimetric maps they were represented with the pink colour.

Automatic error detection

A goodness-of-fit index was introduced to quantify fitting errors that could bring to statistically unreliable perfusion values. In particular, the mean value $\mu_#$ of the absolute value of residuals $\#$, evaluated as the distance in each time instant between TCC's and original HU's values (the original HU image is shown in Fig. 1 on page 8(c)), was calculated for each voxel. Also, $\mu_#$ values can be represented through colorimetric maps (Fig. 1 on page 8(a)). $\mu_#$ values were gathered into an histogram to allow statistical
selection of a threshold value \( T \) that can be used to select those voxels that should be excluded from perfusion analysis. A valid threshold value can be obtained by applying the 2-# rule to the histogram, this allowing to highlight voxels characterized by error values higher than \( T=E[\mu_#]+2\# \). Fig. 1 on page 8(b) is an example of \( \mu_# \) histogram thresholded with \( T \) (the red vertical line), where values lower or greater than \( T \) are respectively depicted in the cyan and the blue colours. The corresponding thresholded error map (TEM) is shown in Fig. 1 on page 8(d), where voxels characterized by values of \( \mu_#>T \) are always showed in the blue colour while the others in cyan. As a final consideration, we expect that voxels characterized by lower errors correspond to more reliable perfusion values.
Fig. 1: (a) colorimetric map of $\mu e$ and its histogram (b) thresholded using the $2\sigma$ rule. The red vertical line separates error values lower (in the cyan colour) and higher (in the blue colour) than threshold $T$. (c) ROIs of a bronchus (in the yellow colour) and of a beam-hardening artefact (in the green colour) and its corresponding TEM (d).

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**Manual segmentation**

Two observers (hereafter, reader A and reader B) analysed for each examination the whole sequence of CT images to detect the presence of vessels, bronchi, and artefacts inside the target lesion. Then they manually drew ROIs on the reference slice to contour borders of those structures that were visible on the best sequence. Fig. 2 on page 8(a) illustrates examples of three vessels (in the red colour) and two bronchi (in the blue colour) identified by readers. Fig. 2 on page 8(b) and (c) represent two examples of as many kinds of artefacts that have been contoured by radiologists (green ROIs).

Anyway, while vessels and bronchi’s borders were generally well visible and easily traceable, contouring artefacts and determining their extension was often harder insomuch as, in some cases, readers were only able to detect their presence.

Fig. 2: (a) 3 vessels (red ROIs) and 2 bronchi (yellow ROIs) were detected by reader B. In (b) there is an example of artefact caused by partial volume effect and contoured by reader A. In (c), reader B segmented beam-hardening effects produced by high concentration of contrast agent inside cava vein.

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**Comparison between manual annotation and automatic detection**
Difficulties found in establishing the artefacts extent guided the choice of the method used to compare results obtained with the automatic and manual detection methods described above. Accordingly, we decided to conduct a statistical analysis by considering the number of vessels and bronchi that were found (or missed) and the presence of artefacts in a given region. Different kinds of artefacts inside the same lesion were considered separately.

Since we are interested only in detecting those structures that could hamper perfusion values, we choose TEM as the ground truth and the ROIs visually recognized by radiologists as the test condition. Hence, for each examination, a true positive (TP) value was attributed for each vessel, bronchus, or artefact detected by both TEM and radiologists. Instead, a true negative (TN) value was assigned in the case of no structure detected by both TEM and radiologists in the whole lesion. A false positive (FP) value was then assigned for each structure identified by radiologists but not highlighted by TEM. It is important recalling that the presence of FP values does not necessarily mean a reader’s mistake, but can also represent the effective presence of a structure that does not alter the reliability of the corresponding perfusion values. Finally, regions highlighted by TEM, but not manually detected by readers, were considered as being false negative (FN) values after that, during a second stage analysis, radiologists declared in agreement that the regions effectively corresponded to either a bronchus, or a vessel, or an artefact. The four different outcomes for this approach have been collected in three different contingency tables: one for vessels, one for bronchi, and the last one for artefacts. FP rate (FPR) and FN rate (FNR) were then calculated for each contingency table as follow:

\[
FPR = \frac{FP}{FP + TN}
\]

\[
FNR = \frac{FN}{TP + FN}
\]
Fig. 1: (a) colorimetric map of $\mu^*$ and its histogram (b) thresholded using the 2-$\mu^*$ rule. The red vertical line separates error values lower (in the cyan colour) and higher (in the blue colour) than threshold $T$. (c) ROIs of a bronchus (in the yellow colour) and of a beam-hardening artefact (in the green colour) and its corresponding TEM (d).

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Results

The threshold method was applied to the error histograms referring to the 24 examinations, and relative TEMs were built accordingly. It is worth noting that all voxels corresponding to error values beyond threshold are arranged into connected structures, together with pink pixels, suggesting that similar errors are associated to connected voxels, hence to structured regions.

Table 1 on page 15 contains results of visual matching between manual annotation and automatic segmentations of vessels, bronchi, and artefacts for the two radiologists. In the 24 analysed examinations, a total amount of 53 structures that could hamper perfusion values have been revealed. Specifically, 34 artefacts, 12 vessels (with mean area of about 19 mm$^2$), and 7 bronchi (with mean area around 22 mm$^2$) were detected.

Table 1: A summary of the three contingency tables for each reader, besides false positive rate (FPR), and false negative rate (FNR), relative to vessels, bronchi, and artefacts.

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As one can see, readers showed very good performance in detecting both vessels as bronchi as shown, by the very low values of FPR and FNR. In particular, FPR of both reader for bronchi and of reader A for vessels, was even 0%. Fig. 3 on page 15(a) shows an example of ROIs drawn by reader A around two vessels (pointed out in the red colour) and an artefact due to partial volume effect (contoured in the green colour). All these three areas find a correspondence with the regions highlighted in the blue colour within TEM (Fig. 3 on page 15(b)). In Fig. 1 on page 15(c) there is an example of ROIs drawn by reader B, showing contours of a bronchus (in the yellow colour) and of a beam-hardening artefact (in the green colour), corresponding to the regions highlighted in blue in TEM (Fig. 1 on page 15(d)).
Fig. 3: In (a) reader A contoured borders of two vessels (the red ROIs) and outlined the region corresponding to the partial volume effect artefact (green ROI). In (b) its corresponding TEM is represented.

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Anyway, scenario changes for artefacts, that worsen performance of both readers. Indeed, although many of these structures can be correctly detected, as it happens in the two cases just presented, there are not few examinations where the correct identification of artefacts becomes a very challenge task. For instance, Fig. 4 on page 16(a) shows a lesion affected by both motion artefact (pointed out by the green arrow), and beam-hardening effect (contoured by the green ROI) due to the proximity of the aorta. In particular, the motion artefact is caused by pulsation of this big vessel that moves the nearest part of the lesion, while beam-hardening effect is caused by the presence of a calcification inside the aorta. Some of the streaks that characterize the beam-hardening effect were contoured by reader B with a few green ROIs, by way of example, but both radiologists detected the presence of beam-hardening artefacts, scattered on the whole lesion. This observation could lead observers to discard this perfusion map, worried about the high probability of possible misleading content. Anyway, the corresponding TEM illustrated in Fig. 4 on page 16(b) clearly shows those areas of the lesion that are effectively affected by very high error values, hence limiting the extent of the region to be discarded and allowing to regain information from perfusion map, accordingly.
Fig. 4: (a) shows an example of lesion affected by motion artefacts (pointed out by a green arrow) and beam-hardening effect (highlighted by reader B with some exemplificative ROIs on the streak), and its corresponding TEM (b).

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Fig. 5 on page 17(a) reports one more example of lesion affected by artefacts that were not correctly identified by radiologists. The lesion illustrated includes a bronchus in its anterior part, correctly identified by both readers (with the ROI in the yellow colour) and by TEM (shown in Fig. 5 on page 17(b)), and an additional beam-hardening artefact that is very difficult to be detected to the naked eye. Indeed, reader A described this lesion as free from artefacts while reader B detected the presence of a very light beam-hardening artefact scattered on the lesion, finally classified as being negligible. On the contrary, TEM clearly points out that the apparently harmless artefact, so light insomuch as to be difficult to be revealed to naked eye, heavily influences the overall reliability of perfusion values. Furthermore, it is worth noting that the high percentage of unreliable voxels (almost 20%), together with their displacement (they are scattered on the whole lesion surface), should recommend radiologists caution in using the content of perfusion map, or worse suggest to directly discard it.
**Fig. 5:** (a) reported an example of lesion where the presence of artefacts is difficult to detectable to the naked eye but clearly visible with TEM (b). Also, the green ROI in (a), drawn by reader B, contours a bronchus that was identified by both readers.

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The uncertainty of readers about the extension of artefacts also covers a very important role in assessment of which perfusion values considering. For instance, Fig. 6 on page 18(a) represents a case where both radiologists detected a bronchus in the posterior part of the lesion (ROI in the yellow colour) and a beam-hardening artefact due to a very high concentration of contrast agent inside the near right pulmonary artery (ROI in the green colour). In reality, as one can see from TEM (Fig. 6 on page 18(b)), the extent of artefact is not limited only to the small medial portion of the lesion identified by readers, but regards a wider area also extending to the anterior-medial and middle part of the tumour (the blue and the pink voxels). Since to the naked eye it is impossible to establish the real extent of these regions characterized by high error values, there is a very high probability of considering as being reliable perfusion values that are not and, in that case, of coming to misleading clinical considerations.
Fig. 6: (a) lesion containing a bronchus (contoured by the yellow ROI) affected by beam-hardening effect (delimited by the green ROI) whose extension is difficult to be assessed to the naked eye. (b) the corresponding TEM.

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### Table 1

<table>
<thead>
<tr>
<th>Reader</th>
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<th>Vessels</th>
<th>Bronchi</th>
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<td>FP</td>
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Table 1: A summary of the three contingency tables for each reader, besides false positive rate (FPR), and false negative rate (FNR), relative to vessels, bronchi, and artefacts.

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Fig. 3: In (a) reader A contoured borders of two vessels (the red ROIs) and outlined the region corresponding to the partial volume effect artefact (green ROI). In (b) its corresponding TEM is represented.

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Fig. 1: (a) colorimetric map of $\mu_0$ and its histogram (b) thresholded using the 2-$\#$ rule. The red vertical line separates error values lower (in the cyan colour) and higher (in the blue colour) than threshold $T$. (c) ROIs of a bronchus (in the yellow colour) and of a beam-hardening artefact (in the green colour) and its corresponding TEM (d).

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Fig. 4: (a) shows an example of lesion affected by motion artefacts (pointed out by a green arrow) and beam-hardening effect (highlighted by reader B with some exemplificative ROIs on the streak), and its corresponding TEM (b).

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**Fig. 5:** (a) reported an example of lesion where the presence of artefacts is difficultly detectable to the naked eye but clearly visible with TEM (b). Also, the green ROI in (a), drawn by reader B, contours a bronchus that was identified by both readers.

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![Fig. 5](image1)

**Fig. 6:** (a) lesion containing a bronchus (contoured by the yellow ROI) affected by beam-hardening effect (delimited by the green ROI) whose extension is difficult to be assessed to the naked eye. (b) the corresponding TEM.

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![Fig. 6](image2)
Conclusion

In the last few years, many step forward clinical utilization of CTp have been done, starting from adoption of new CT technologies up to the usage of new strategies of data processing. Anyway, the assessment of the reliability of perfusion values still represents an open issue. The problem brought by the presence of vessels and bronchi, which jeopardize distribution of perfusion values and alter local and global measurements, is often faced through manual segmentation and exclusion of these anatomical structures. Anyway, the greatest part of acquisition and reconstruction artefacts is not so easy to be detected to the naked eye, and they inevitably affect the quality of perfusion values, accordingly.

In this study, an automatic method to reveal voxels affected by high fitting error and, hence, most probably characterized by less reliable perfusion values, has been proposed and compared with manual segmentation carried out by radiologists. As the first consideration, results confirmed that voxels characterized by higher error values and structured into connected regions correspond to artefacts or anatomical structures, such as vessels and bronchi. The outcome confirms the goodness of our temporal error index that shows a marked spatial coherence although being calculated for each voxel, without exploiting any information relative to its neighbours. Indeed, as one can see by observing the colorimetric map of $\mu_#$ in Fig. 1 on page 21(a), values of error index reach their peaks within the regions where vessels, bronchi, or artefacts were detected. Accordingly, we can state that the presence of these structures inside lesions worsen quality of fitting, this hampering computation of reliable perfusion values.

Performance of both readers were very good when detecting anatomical structures, with FPR always reaching 0%, except for reader B who detected two very small vessels on the border of a lesion that were not highlighted by the map, neither by the other observer. Their FNR was also very low, with a total amount of one bronchus and one vessel missed by reader A and one bronchus and two vessels not detected by reader B. Things change for artefacts, the structures that are more often present inside the lesions (64.15%, against 22.64% for vessels and 13.21% for bronchi). While anatomical structures are generally well defined and detectable in all slices, artefacts may also affect one slice only and very lightly, thus becoming in some cases practically impossible to be detected by human eye. The variety of their nature and of the way they manifest themselves are therefore the main causes of the difficulties that also very expert radiologists can meet when evaluating CTp images. The first challenge regards the definition of the extension of artefacts. Indeed, in 11 cases, radiologists correctly identified the presence of artefacts but were not able to circumscribe the region affected by their presence. This uncertainty could lead readers not to rely on perfusion information referring to the area outlined as being affected by artefacts, which sometimes could even cover the whole lesion. The use of TEM could instead allow identifying lesion’s areas characterized by more reliable content, which could be the only ones exploited to make clinical considerations.
Moreover, there were some cases where radiologists were able to manually draw ROIs delimiting areas affected by artefacts but, once compared with the regions highlighted inside TEM, it resulted to be too wider (16.67% of the overall cases) or too smaller (12.50%). Once again, the first case can lead radiologists to discard a priori perfusion maps even if the area effectively affected by artefacts is not extended as much as they guessed. On the contrary, the second case is even worse, since it can lead readers to consider as being reliable perfusion values that indeed, are seriously affected by high error values and, hence, could contain misleading information. The same consideration can be extended to the 14 FN artefacts that have not been detected by none of the readers, but were correctly detected by TEM.

The automatic statistical method we propose proved to manage in well identifying structures affecting fitting quality, and hence reliability of perfusion values. In addition, it was possible to highlight the presence of artefacts hardly detectable to the naked eye and defining their extent. Through TEM's analysis it is possible to easily see which part of the content of a perfusion map is more reliable, whether it is necessary to discard an examination or it is possible to use it, even though very extended artefacts seem to affect the lesion. Presence of vessels, bronchi, and artefacts inside lesion tends to jeopardize results, altering the right perception of perfusion patterns and the reliability of statistical analysis or of any other quantitative computation. By excluding high error regions highlighted within TEM, it is possible to prevent radiologists from misinterpreting perfusion maps and to obtain more reliable quantitative results.

Even though further studies on thresholding methods could improve automatic method for detection of unreliable perfusion values, the proposed approach just covers a fundamental role in both qualitative and quantitative analysis of perfusion maps. For this reason, we strongly suggest to use it, trusting that it could represent a step forward to clinical utilization of CTp.
Fig. 1: (a) colorimetric map of $\mu#$ and its histogram (b) thresholded using the 2-$\#$ rule. The red vertical line separates error values lower (in the cyan colour) and higher (in the blue colour) than threshold $T$. (c) ROIs of a bronchus (in the yellow colour) and of a beam-hardening artefact (in the green colour) and its corresponding TEM (d).

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