Clinical Imaging 50 (2018) 5–12

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Characteristics of computed tomography perfusion parameters in non-small-cell-lung-cancer and its relationship to histology, size, stage an treatment response

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ARTICLE INFO

Keywords:
Lung
Lung cancer
Perfusion imaging
Computed tomography
Imaging biomarker

ABSTRACT

Objectives: To analyze computed tomography perfusion (CTP) parameters in NSCLC.
Materials and methods: Prospective study, 152 patients with NSCLC. CTP parameters were correlated with histology, stage, size and response to conventional chemotherapy/radiotherapy.
Results: Neuroendocrine tumours presented higher BV (p 0.002). Negative correlation of PMB (p 0.003) and positive of MTT (p 0.046) with T stage was found. BF showed negative correlation with size. No differences were found with the RECIST levels of response to chemotherapy/radiotherapy.
Conclusions: CTP parameters were highly variable. Neuroendocrine tumours presented higher BV and PMB values. Perfusion parameters do not differ depending on the stage and do not predict response to treatment.

1. Introduction

Lung cancer is a major public health problem because it accounts for 13–20% of all cancer diagnoses and still represents the leading cause of death due to cancer, with a five-year survival rate of 15–20% [1,2].

Platinum derived therapies have been introduced as a tool for non-resectable lung cancer, and as a result of which, important advances have taken place in survival rates [3,4]. However, despite improvements in therapeutic management, toxicity remains an ongoing concern, which could probably be alleviated with a more precise and effective prediction of response. Therefore, an appropriate selection of patients and monitoring of response to treatment by CTP could be helpful to use a more cost-effective and tailored therapy.

The biological mechanisms that determine the sensitivity to chemotherapy are complex and not well-known, and may be related to tumour hypoxia or to the expression of certain genes and proteins involved in the synthesis and repair of DNA [5,6] by tumour. The adaptive response to a hypoxic microenvironment leads to a neoangiogenesis, which increase the ability to metastasize and the multi-resistance to drugs [5,6]. Therefore, it is important to know the vascularity pattern of the tumour at the time of the diagnosis, as this information can provide relevant biological data and can potentially be used to identify patients with different response rates to treatment.

Some studies have shown a direct correlation between CTP parameters and histological biomarkers of angiogenesis, such as MVD and VEGF, in different tumours [7,8] and particularly, in lung cancer [9–11].

CTP has received much attention from the radiologic community because of its oncologic applications. Over the last few years, important advances have been made in CTP studies, with the introduction of faster scanners and whole tumour evaluation. Furthermore, new software allows for correcting both noise and motion, thus reducing artifacts. As

Abbreviations: CTP, computed tomography perfusion; NSCLC, non-small-cell-lung cancer; CTx, chemotherapy; RTx, radiotherapy; BF, blood flow; BV, blood volume; PMB, permeability; MTT, mean transit time; MVD, microvessel density; VEGF, vascular endothelial growth factor; ROI, region of interest; RECIST, Response Evaluation Criteria in Solid Tumours

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https://doi.org/10.1016/j.clinimag.2017.12.001
Received 3 May 2017; Received in revised form 27 October 2017; Accepted 1 December 2017

a result, data evaluation can now be achieved in a simpler way [12–14].

CTP perfusion parameters could be used to determine the nature and behaviour of the tumour. In the non-small cell lung cáncer, CTP shows promising results for patients treated with antiangiogenic therapy, however, for those treated with conventional chemotherapy or radiotherapy the results are controversial [15–18]. Whereas CTP in NSCLC has been evaluated by investigators on small series of patients and on restricted areas of interest rather than the whole tumour, they have not yet been included in the clinical practice as more studies are needed with large series of patients to test the new scanner softwares.

Therefore, our study aims to prospectively assess, in a large series of patients with lung cancer, the characteristics of quantitative whole tumour CTP parameters; to check if such characteristics can provide biological information at the time of the diagnosis; and find out whether or not they can predict response to treatment with cytotoxic chemotherapy and radiotherapy.

2. Material and methods

The authors declare that there are no conflicts of interest. The authors had full control of all the data and information presented in this manuscript. Written informed consent was obtained from all the patients involved in the study, and the entire study protocol was approved by the Ethics Committee.

2.1. Patients

Between January 2010 and December 2015, 183 patients with biopsy-proven NSCLC were prospectively enrolled in this study. CTP was performed on all patients before receiving any treatment. Fig. 1 illustrates the flow chart of the patients included in this study.

Patients were included in the present study based on the following inclusion criteria: older than 18 years, histologic diagnosis of NSCLC, no prior specific treatment and tumour diameter greater than 2 cm. The exclusion criteria included: studies of poor technical quality due to motion, beam hardening artifacts, excessive noise or improper staining; tumours that were difficult to separate from other lesions, such as atelectasis, pneumonitis or lymphangitis; and patients who did not continue follow-up in our hospital.

The following information was collected from patients' clinical files: gender, age, tumour histology, radiological stage (using the Seventh edition of the TNM, AJCC/IASLC classification of lung cancer), volume and the longest axial diameter for the assessment of RECIST and treatment.

27 patients did not receive specific cancer treatment because they have advanced disease with limited baseline clinical situation, they voluntarily refused treatment, or, they died prior to therapy initiation.

The 95 patients who received radiotherapy or conventional chemotherapy with platinum derivatives, associated or not to RTx, as first-line therapy, were classified in the first follow-up CT as: complete response, partial response, stable disease or progressive disease; based on revised RECIST1.1 [10] criteria applied solely to the lesion on which CTP studies were performed. Studies were assessed by two senior chest radiologists independently and by consensus and when there was disagreement.

2.2. CT perfusion technique

CTP imaging studies were performed with a Dual-source CT with 128 rows of detectors (*Flash Definition®*, *Siemens*; *Forcheim*, *Germany*). An expert chest radiologist fixed the length of the study on the topogram in order to include the longitudinal extent of the lesion. When necessary, CT acquisition without a contrast agent was performed to localize the lesion.

All patients were instructed to avoid lung motion during the study, by using breath hold at tidal expiratory volume, whenever possible.

Following the requirements of the deconvolution model; the injection protocol consisted in the administration of 50 ml of iodinated contrast material at 5 ml/s *Iopromida 300*, (*Ultravist® Bayer Schering Pharma*; *Berlin*, *Germany*) for 10s, followed by a saline flush (50 ml of saline at 5 ml/s).

Two seconds after the start of the injection, a scan acquisition was

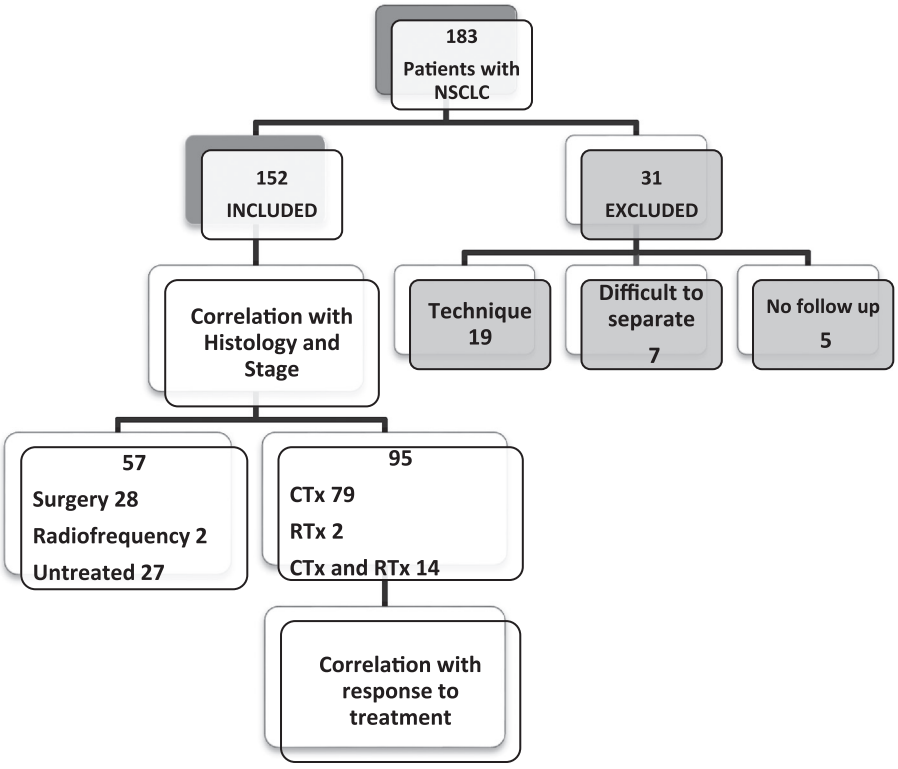

Fig. 1. Flow chart of patients included in the study. NSCLC: non-small-cell-lung cancer; CTx: chemotherapy; RTx: radiotherapy.