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Original paper

Early tumor response prediction for lung cancer patients using novel longitudinal pattern features from sequential PET/CT image scans

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Purpose: A new set of quantitative features that capture intensity changes in PET/CT images over time and space is proposed for assessing the tumor response early during chemoradiotherapy. The hypothesis whether the new features, combined with machine learning, improve outcome prediction is tested.
Methods: The proposed method is based on dividing the tumor volume into successive zones depending on the distance to the tumor border. Mean intensity changes are computed within each zone, for CT and PET scans separately, and used as image features for tumor response assessment. Doing so, tumors are described by accounting for temporal and spatial changes at the same time. Using linear support vector machines, the new features were tested on 30 non-small cell lung cancer patients who underwent sequential or concurrent chemoradiotherapy. Prediction of 2-years overall survival was based on two PET-CT scans, acquired before the start and during the first 3 weeks of treatment. The predictive power of the newly proposed longitudinal pattern features was compared to that of previously proposed radiomics features and radiobiological parameters.
Results: The highest areas under the receiver operating characteristic curves were 0.98 and 0.93 for patients treated with sequential and concurrent chemoradiotherapy, respectively. Results showed an overall comparable performance with respect to radiomics features and radiobiological parameters.
Conclusions: A novel set of quantitative image features, based on underlying tumor physiology, was computed from PET/CT scans and successfully employed to distinguish between early responders and non-responders to chemoradiotherapy.

1. Introduction

Lung cancer is one of the most frequent cancers and at the same time one of the deadliest worldwide [1]. Eighty-five percent of lung cancer cases belong to non-small cell lung cancer (NSCLC), which is usually diagnosed at advanced stages and is thus more challenging to treat. Thus, early assessment of tumor response to treatment from medical images has lately acquired great interest in the oncology field [2], given the possibility to adapt the treatment and improve patients' clinical outcomes.

Response to treatment can be assessed through invasive biopsies and/or non-invasive imaging examinations. Unlike biopsies, the latter approach provides both spatial and temporal sampling of the malignant lesion [3]. In particular, hybrid Positron Emission Tomography/Computed Tomography (PET/CT), which provides both functional and anatomical information of the tumor, is one of the most powerful tools to assess tumor response [4]. Response Evaluation Criteria in Solid Tumors (RECIST [5]) guidelines recommended to measure changes in the size of the lesion as surrogates for tumor response. However, these changes usually occurs at a late stage, after the end of therapy, whereas modifications in the metabolic activity of tissue are suitable for an early assessment of the response. Positron Emission Response Criteria in Solid Tumors (PERCIST [6]) guidelines suggested that, among others, metrics based on standard uptake values (SUV) could improve anatomical-based prediction, given the higher functional predictive power of PET. However, the widely used single measurement of mean or maximum SUV within a region of interest (ROI) has been criticized for its sensitivity to confounding factors [7] and limited prediction accuracy with

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respect to tumor response to treatment [8].

Given the wide availability of radiological images in the clinical routine, procedures from the field of image analysis have been borrowed, attempting to extract quantitative, reliable, meaningful and discriminative information from medical images. In particular, recently, the development of radiomics has provided clinical researchers with a novel powerful tool to predict tumor response. In this field, radiological images are automatically converted into quantitative parameters, the so-called radiomics features, which describe different properties of the image in a localized region [9]. These features are then typically fed in machine learning algorithms that provide an estimation of the predictive power of such features with respect to the selected outcome [10]. In previous lung cancer studies the prediction power of image and radiomics features from CT and PET scans has been investigated and found to outperform current guidelines in predicting tumour response to treatment. A study by Ganeshan et al. [11] has reported that the Area Under the Curve (AUC) resulting from the Receiving Operator Characteristic (ROC) curve of a single-CT heterogeneity feature, computed for a training set, was 0.60. Additionally, in a more recent work by Aerts et al. [12], selected single-CT features reached a performance of 0.65 for a validation dataset of lung cancer patients who underwent radiotherapy or concurrent chemoradiotherapy. In both cases, features were tested in the context of survival analysis. Selected PET features from the radiomics literature, namely contrast and coarseness, led to AUC values of 0.82 and 0.80 respectively, when analyzing training data [13]. Other studies [14,15] evaluated histogram-based parameters from PET images to predict response to treatment on restricted datasets. Few studies evaluated the predictive performance of providing both CT-based and PET-based features, which were suggested to improve classification with respect to single-modality features [16]. Furthermore, features taken from repeated examinations were found to improve predictions based on clinical, geometrical and SUV features from a single time-point [17], increasing AUC from 0.68 to 0.86 computed on validation data. Finally, a recent study by Toma-Dasu et al. [18] based on customized features for describing the tumor response to radiotherapy based on repeated PET/CT images, accounting also for the delivered dose of radiation by the time of the second exam, reported a significant AUC of 0.89 when applying leave-one-out cross-validation.

Although the aforementioned features have demonstrated strong discriminative power, they often focus either on spatial patterns or on temporal changes of the lesion. At the best of our knowledge, none of them describes longitudinal changes in spatial patterns and, more precisely, none of them correlates the distance from the border of the tumor with local PET/CT changes, which might relate to the physiology of the tumor tissue. These observations have therefore motivated us to design a set of features (longitudinal pattern features, LoP) that spatially describe intensity changes in the cancerous masses as a function of the distance from the tumor border. The proposed method is based on dividing the tumor volume into a number of zones based on the distance to the tumor border and computing mean intensity changes within each zone, for CT and PET scans separately. Based on these changes, a support vector machine (SVM) was trained to classify NSCLC patients' response to treatment using LoP.

2. Materials and methods

2.1. Clinical data

Two ^{18}F-FDG-PET/CT scans (Fig. 1) acquired before and during radiotherapy, respectively, were available for 30 NSCLC patients who underwent two types of treatment: (i) 15 patient underwent concurrent chemoradiotherapy, which entailed one cycle of cisplatin and vinorelbine before radiation and two cycles during radiotherapy; (ii) 15 patients underwent sequential chemoradiotherapy, which consisted of three cycles of the chemotherapy agents described above before radiation. As different chemotherapy schedules were expected to influence PET images differently, these two groups (concurrent and sequential) were kept separated in the analysis.

PET/CT scans (Biograph40; Siemens Medical Solutions) were acquired using the same machine and setup before and during treatment. A 4D respiration-correlated CT was acquired for planning purposes, but a primary 3D CT was available for this study. PET images were corrected for scatter and decay, rebinned and reconstructed using an ordered-subset expectation maximization 2D algorithm with 4 iterations and 8 subsets. Acquisition parameters were homogeneous across patients and the amount of injected radiotracer was based on the patient's weight. Clinical information, such as the TNM classification and stage, treatment information, such as time intervals and dose prescriptions, and overall survival at 2 years were also available (Table 1). The first PET/CT scan was acquired before the radiation treatment, whereas the second scan was obtained at around the second treatment week. In Table 1, Δt_{ex} refers to the time interval between the two exams (range: 10–21 days) and Δt_{RT} to the time interval between the beginning of the radiation treatment and the acquisition of the second PET/CT scan (range: 6–13 days). More detailed information about image acquisition and treatment protocols is given in [18,19].

Mean volumes from the first exam were 49.70 ml (range: 3.21–119.33 ml) and 88.80 ml (range: 3.29–236.11) in patients receiving sequential and concurrent chemoradiotherapy, respectively, and 49.92 ml (range: 1.79–105.20 ml) and 75.98 ml (range: 2.64–214.79 ml) from the second scan. These measures refer to primary gross tumor volumes, segmented in a semi-automatic way, as described in Section 2.2.

2.2. Image processing

Before feature extraction, four pre-processing steps were performed (Fig. 2): intensity normalization, resampling, segmentation of the tumor and registration of the two PET/CT scans.

Intensity normalization. CT and PET images were normalized in order to bring to a common scale intensity values from different patients and different exams. PET images were transformed into SUV units. Regarding CT images, they were expressed in Hounsfield units (HU) and subsequently linearly rescaled. For each image, two ROIs were manually drawn to obtain mean intensities of air (I_{AIR}) and cardiac blood pool (I_{HEART}). By imposing air to be −1000 HU and blood to be 50 HU, the slope (m) and the offset (q) of linear transformations were estimated (Eq. 1) and then applied to linearly rescale the intensity value of each voxel.

$$\begin{cases} -1000 = m \cdot I_{AIR} + q \\ 50 = m \cdot I_{HEART} + q \end{cases} \quad (1)$$

Resampling. In order to avoid artifacts in subsequent processing steps, both PET and CT images were isotropically resampled to 0.98 mm, the smallest spatial resolution.

Image segmentation. A semi-automatic segmentation method based on a 3D level-set algorithm (using MiaLite [20]) was used to delineate the tumor boundaries on CT and PET images separately. The process was applied to both scans acquired before and during the treatment. The key parameters, such as intensity thresholds, blocking regions and smoothing factors, for the segmentation process were empirically defined to achieve the best visual result. Segmentations were performed by a trained medical engineer and revised by a research radiologist with 2-year clinical experience working in a cancer hospital.

Image registration. PET/CT images from the second exam were aligned to images from the first exam by first registering CT scans and then applying the same transformation to PET images. CT-CT registration was performed in two steps: first manually (using MeVisLab [21]) and then automatically (using ITK [22]). In the latter step, registration was performed only on the region defined by the tumor masks from the