PET/CT Radiomics in Lung Cancer

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Quantitative extraction of imaging features from medical scans ('radiomics') has become a major research topic in recent years. Numerous studies have emphasized the potential use of radiomics for computer-assisted diagnosis, as well as for predicting survival and response to treatment in patients with lung cancer. Furthermore, radiomics is appealing in that it enables full-field analysis of the lesion, provides nearly real-time results, and is non-invasive.

Keywords: PET/CT ; Texture ; Shape ; Radiomics ; Machine learning ; Lung cancer

1. Introduction

Lung cancer is the second most common type of cancer in men and women worldwide, with an estimated lifetime prevalence of about 1/15 and 1/17, respectively, for the two genders[1]. In Italy, there were ≈42,500 new cases in 2019, accounting for ≈11% of all the newly diagnosed cancers in the same year[2]. Five-year survival rates of patients with lung cancer vary considerably depending on the type and stage of the disease, and they range between a dismal 3% for distant small-cell lung cancer (SCLC) to 60% for localized non-small-cell lung cancer (NSCLC)[3]. Timely detection and correct management are therefore essential to improve the clinical outcome of patients with lung cancer.

In the last few years, computerized analysis of 3D scans from Computed Tomography (CT), Positron Emission Tomography (PET), and Magnetic Resonance Imaging (MRI) has received a great deal of attention as a means to improve the clinical management of a number of disorders. It is believed that radiomics has the potential to improve on traditional, manual interpretation by detecting features and patterns that otherwise would go unnoticed to the human eye[4][5]. By leveraging on large datasets (hence the suffix '*-omics*') and artificial intelligence techniques, radiomics may help predict the type of disease, survival, and response to therapy[6][7]. There are also a number of logistic advantages in this approach, such as providing nearly real-time results and not requiring any invasive procedure for the patient. Furthermore, compared with standard biopsy, radiomics can offer not only a full-field analysis of one lesion but also of more lesions within the examined area, and, depending on the protocol used, of the whole body too[8].

Fluorine 18 (^{18}F) fluorodeoxyglucose Positron Emission Tomography–Computed Tomography (PET/CT) is nowadays the mainstay in the management of lung cancer, having greatly improved patient diagnosis, staging, and follow-up [9]. The role of radiomics in this context has therefore attracted increasing interest in recent times[10][11][12][13][14]

2. Methodology

The overall workflow in radiomics involves six well-defined steps as described below.

2.1 Acquisition

This is the procedure whereby the scans are obtained, and includes both the examination itself and the patient preparation protocol. The output is a three-dimensional matrix of intensity values (voxel model), which in the remainder we refer to as the raw data. A wide range of parameters intervene in the acquisition process, among them tube current and voltage (for CT); spatial resolution (voxel size), reconstruction algorithm and related settings both for CT and PET. All these variables may have a significant impact on the radiomics features computed[6][15], with certain features being affected more than others[16].

2.2. Pre-Processing

Pre-processing may involve spatial filtering, windowing, and/or resampling. The objective of the first can be either to reduce noise or emphasize features at different scales. Common tools for this task are Butterworth smoothing[17], Gaussian filters [18], and Laplacian of Gaussian filters[19]. Windowing consists of applying a lower and upper threshold to the intensity values of the raw data, this way defining a range of acceptable values. Resampling amounts to changing the

number of bits used for the encoding, which is commonly 12 or 16 for the raw data. This is typically reduced to eight, six, or four before feature extraction [17][20][21]. Pre-processing is a crucial step in the workflow and may significantly affect the overall outcome, as numerous experiments have demonstrated[16][17].

2.3. Segmentation

Segmentation (delineation) is the process whereby the part of the scan that is relevant for the analysis (*Region of Interest*—ROI) is separated from the background. The output of this step is a binary (boolean) matrix the same size of the raw data, where 'true' (1) indicates that the voxel belongs to the ROI, 'false' (0), otherwise. Segmentation is a time-consuming and rather complex step, for many lesions will show unclear and ill-defined borders. The process is also complicated by the presence of areas such as necrosis, atelectasis, and/or inflammation, whose role in the radiomics work-flow is not fully understood yet. Although a number of automated (e.g., adaptive thresholding[22], convolutional networks) and semi-automated (e.g., level-set[23], region growing[24]) methods have been proposed, manual delineation is still regarded by many as the gold standard[6].

2.4. Feature Extraction

Feature extraction is a pivotal step in the whole procedure and involves computing a set of quantitative parameters (image features or, simply, features) from the region of interest. The features should obviously correlate with the endpoint of the clinical condition investigated. At present, there are two main classes of features: the 'hand-designed' (or 'hand-crafted') ones and those based on Deep Learning (see Figure 1 for a possible taxonomy). Hand-crafted features are obtained via some suitable mathematical functions that are essentially designed by hand (hence the name). Most common among them are shape and texture features[25]. By contrast, Deep Learning features are obtained implicitly by training on large datasets of images.

Figure 1: A taxonomy of radiomics features

2.5. Post Processing

Post-processing consists of transforming the features through some suitable procedures, the most common being feature selection and feature generation. Feature selection consists of retaining a subset of the original features by selecting the most discriminative ones. This is crucial in radiomics, for some image features tend to be strongly correlated with one another[26]. Approaches to feature selection come in different varieties, such as correlation-based selection, reduction based on mutual information gain, recursive elimination, and Lasso regularization (see[27] for a review on this). Feature generation involves obtaining new features by combining of the original ones through some suitable transformations, such as Linear Discriminant Analysis (LDA), Principal Component Analysis (PCA), and Multi-Dimensional Scaling (MDS)[28][29].

2.6. Data Analysis

Data analysis comprises two separate steps: the first *(model building*), in which a classification and/or regression model is generated; the second, where the model is used to make predictions about the case or cohort of patients under evaluation. Model building involves (a) establishing the type of classifier or regressor to be used, and (b) feeding the model with a set of pre-classified cases—i.e., arrays of features/label pairs where the label indicates the clinical condition of the corresponding subject. This process of presenting the model with pre-classified cases is usually referred to as training. Crucial to this step, of course, is the availability of large enough datasets of pre-classified cases (ground truth).

3. Applications

Here below we present four typical applications of PET/CT radiomics in lung cancer.

3.1. Discrimination between Benign and Malignant Pulmonary Nodules

Solitary pulmonary nodules (SPN) are relatively common findings in the clinical practice, although the available data about the estimated prevalence at CT examination vary significantly[30][31]. Clinical management of SPN poses significant challenges, for a non-negligible fraction of them (estimated between 3.7% and 5.5%[32]) may represent malignant lesions. Traditionally, the evaluation involved manual assessment of some key image characteristics at CT that are considered strong indicators of benignity or malignancy[33]. In this scenario, recent studies have shown that prediction models based on quantitative imaging features can help differentiate between benign, malignant, and inflammatory pulmonary nodules[34][35][36][37].

3.2. Classification between Primary and Metastatic Lesions; Histological Subtyping

Detailed lesion characterisation has important implications for the management of patients with lung cancer. Differential diagnosis between primary and metastatic lesions, for instance, is crucial for stratification as well as for establishing the optimal treatment strategy[38]. Likewise, the correct identification of histological subtype has a strong influence on the outcome and determination of the most appropriate therapy[39][40].

3.3. Prediction of Survival

Prediction of survival plays an important role for triaging and, consequently, for determining the suitability of subjects for different treatment options. Survival studies, however, are notoriously difficult due to the long follow-up required and the presence of many confounding factors. It is not surprising then that results in this topic are less clear-cut than in the other potential applications[21].

3.4. Prediction of Response to Treatment

Predicting response to treatment—and in particular to chemotherapy, radiotherapy, and immunotherapy—is crucial to maximize the outcome, and, at the same time, minimize the side effects by avoiding the administration of inefficient treatments[19]. In previous studies textural features from PET/CT scans at the baseline were found to correlate with local recurrence and disease-specific survival in patients treated with radiotherapy[9][20]. Radiomic signatures from baseline PET/CT also proved useful to predict disease-free survival in NSCLC patients undergoing surgery[41].

4. Conclusions

Quantitative image analysis of PET/CT scans has attracted increasing research interest for the management of patients with lung cancer. There is growing evidence that radiomics can provide an added value to standard imaging analysis tools such as volume, SUV and density. However, the field is still at an early stage and further work is required to confirm the benefits and potential advantages in the clinical practice.

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