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COMMENTARY

The promise and limits of PET texture analysis

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Abstract Metabolic heterogeneity is a recognized characteristic of malignant tumors. Positron emission tomography (PET) texture analysis evaluated intratumoral heterogeneity in the uptake of ^{18}F-fluorodeoxyglucose. There were recent evidences that PET textural features were of prognostic significance in patients with different solid tumors. Unfortunately, there are still crucial standardization challenges to transform PET texture parameters from their current use as research tools into the arena of validated technologies for use in oncology practice. Testing its generalizability, robustness, consistency, and limitations is necessary before implementing it in daily patient care.

Positron emission tomography (PET) texture analysis is a post-processing tool aimed at evaluating intratumoral heterogeneity in the uptake of ^{18}F-fluoro-deoxyglucose (^{18}F-FDG). There is an considerable recent evidence that PET textural features can provide significant prognostic information in patients with different solid tumors [1–4]. In general, first-order PET texture features used as prognostic factors are calculated based on histogram analysis, whereas the first-order texture features of maximum standard uptake values (SUV_{max}), mean SUV, or total lesion glycolysis are derived. Unfortunately, histogram-derived parameters cannot provide information about the spatial distribution of voxels with different intensities. For example, first-order texture features would be unable to distinguish between the different distributions depicted in Fig. 1, which reports a simplified model showing distinct patterns of intratumoral heterogeneity in ^{18}F-FDG uptake. Although the extraction of second-order textural features calculated from normalized gray-level co-occurrence matrices (NGLCM) may be helpful in distinguishing panel (A) from both panels (B) and (C), discrimination between panels (B) and (C) would still not be possible. Consequently, higher-order methods to classify textures [e.g., neighborhood gray-tone difference matrix (NGTDM), voxel alignment, or gray-level size-zone matrices] are required to achieve complete discrimination.

Metabolic heterogeneity is a recognized characteristic of malignant tumors. The analysis of different texture parameters is a useful tool in the field of biomedical image processing for quantifying tumor heterogeneity. Currently, the computation of tumor texture features is performed in a two-step process. First, the voxel intensities are resampled within the segmented tumors to obtain a limited range of values that are used for reducing the noise and normalizing the images. Second, the texture features are analyzed using different matrices. Unfortunately, there are still crucial standardization challenges to transform PET texture parameters from their current use as research tools into the arena of validated technologies for use in oncology practice and/or clinical trials. For example, different acquisition modes and reconstruction parameters of PET images may impair the reproducibility of textural feature measurements [5]. Moreover, it is still unclear whether the potential confounding effect introduced by the use of different scanners may limit the clinical usefulness of PET texture parameters as potential prognostic biomarkers. Future well-designed multicenter studies utilizing texture features

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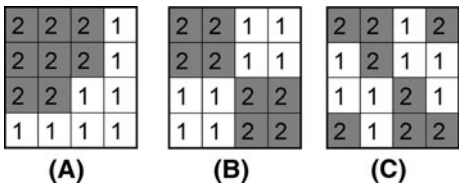

Fig. 1 A simple model showing three different patterns of heterogeneous ^{18}F-FDG distribution within an identical volume. The intensity value of each pixel is represented by a *number*. Each panel consists of 16 pixels; of them, 8 pixels have an intensity value of 1 and the remaining 8 have an intensity value of 2. Consequently, the mean and variance of intensity are the same for the three panels. The results of normalized gray-level co-occurrence matrix texture measurements indicate that panel (**a**) has the highest uniformity and the lowest entropy; however, panels (**b**) and (**c**) are characterized by the same uniformity and entropy. After application of the neighborhood gray-tone difference matrix to the central four core pixels, there is a stepwise decrease in coarseness from panel (**a**), through panel (**b**), to panel (**c**). Therefore, this technique allows a reliable differentiation between the three panels

derived from different PET scanners are warranted to address this issue.

Other potential sources of variability of the texture features include the settings used for image processing and the calculation methods. Concerning the issue of resampling, we have recently investigated the prognostic utility of PET textural features in patients with oropharyngeal carcinoma [4]. We found an evidence that uniformity calculated from NGLCM has a significant prognostic impact, but the predictive value of the texture parameters for clinical outcomes was dependent on the resampling size [4]. In order to achieve an optimal resampling size, the physical properties of the numerous different texture features should be carefully considered. For example, the parameters of "entropy" and "homogeneity" in NGLCM are by definition negatively correlated with each other. In presence of a positive correlation, an improper sampling size should be suspected. Similar correlations should be expected for "coarseness" and "busyness" in NGTDM. Hopefully, the use of inter-matrices correction techniques (e.g., correction between "entropy" in histogram analysis and "entropy" in NGTDM) may facilitate the identification of the most suitable resampling size. Further research in the field is eagerly awaited.

Notably, malignancies are characterized by numerous texture matrices that are not independent of each other. In this scenario, the generalizability of the calculation of PET textural features based on the use of different matrices should be improved. Moreover, different features should be integrated into a complex "texture signature" using bioinformatics techniques as commonly performed in genomics studies [6, 7].

Strikingly, there is a need to increase our understanding of the biological basis of PET texture parameters. Computed tomographic (CT) texture features of non-small cell lung cancer (NSCLC) have been shown to be associated with histological measures of hypoxia and angiogenesis [8]. However, it is still unclear whether PET texture parameters may reflect different biological features of the tumors. In general, there are complex and intricate relationships between textural features and tumor characteristics. For example, in patients with oesophageal cancer, increased entropy and decreased uniformity of CT images have been associated with poor response to therapy and shorter survival rates [9]. By contrast, a greater local heterogeneity of oesophageal tumors on PET images is associated with a better response to treatment [10]. In general, the prognostic significance of different texture features may vary according to the underlying malignancy. Oropharyngeal cancers with a higher coarseness tend to have a better prognosis [4], whereas an increased coarseness predicts worse survival in NSCLC [1]. Because malignancies have a very complex biology, it is clear that a single PET texture feature cannot provide sufficiently accurate information regarding clinical outcomes. The identification of panels of multiple multimodal biomarkers will hopefully implement the personalized prognostic stratification strategies. The success of this mission will depend on the development of multicenter collaborative research initiatives associated to robust bioinformatics evaluation of the imaging results using quantitative methodologies (i.e., "radiomics" [11]).

Besides its potential usefulness to shed more light on the biology of malignancies, texture analysis of PET images is a promising research tool in patients with solid tumors. However, testing its generalizability, robustness, consistency, and limitations are necessary before implementing it in daily patient care.

Conflict of interest None declared.

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