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Editorial

Measuring tumor metabolic heterogeneity on positron emission tomography: utility in cervical cancer

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18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) is valuable for cervical cancer in assessing prognosis, monitoring treatment response to chemoradiation, posttherapy tumor marker elevation with negative or equivocal computerized tomography/magnetic resonance imaging, restaging at documented recurrence, and evaluating response to salvage treatment [1]. Intratumoral heterogeneity is a common feature of malignant tumors and is related to proliferation, metastasis, resistance to therapy, and recurrence [2]. Measuring intratumoral metabolic heterogeneity by imaging to reflect tumor heterogeneity is an appealing hypothesis. Many researchers have tried various techniques on ^{18}F-FDG PET image data to investigate their potential roles for prognosis and predicting treatment response in many malignancies including cervical cancer [1,3]. Kidd and Grigsby [4] used the derivative (*dV/dT*; V=volume; T=threshold) of the volume-threshold function from 40% to 80% to quantify tumor heterogeneity in a prospective study of 72 cervical cancer patients and found that there was a significant correlation between tumor volume and heterogeneity (*dV/dT*; R^2=0.881). Besides, heterogeneity was significantly associated with lymph node metastasis at diagnosis (p=0.0009) and response to chemoradiation (p=0.0207). In a pilot study with 20 cervical cancer patients treated with concurrent chemoradiation (CCRT), Yang et al. [5] found certain texture parameters of heterogeneity decreased significantly with time in the complete metabolic response group during the course of CCRT, while no persistent trends with time were observed in the partial metabolic response or new lesion group. In this issue, Chung et al. [6] retrospectively reviewed 85 patients with International Federation of Obstetrics and Gynecology (FIGO) stage IB to IIA cervical cancer who had ^{18}F-FDG PET images before radical surgery. The median follow-up was 32 months, and 14 patients developed recurrences. Intratumoral FDG uptake heterogeneity (IFH) was defined by coefficient of variation (CV) (the ratio between the standard deviation of the standardized uptake value [SUV] and the SUV_{avg} within the automatically delineated tumor volume calculated using each SUV threshold from 2 to 4). In multivariate analysis, IFH was found to be the sole independent risk factor (p=0.028) for recurrence, while other PET (SUV_{tumor}, metabolic tumor $volume_{tumor}$ [MTV_{tumor}], total lesion $glycolysis_{tumor}$ [TLG_{tumor}], SUV_{LN}) or histopathological (FIGO stage II) parameters were significant by univariate analysis but not significant in the multivariate analysis. However, because IFH was highly correlated with primary tumor size, depth of cervical invasion, SUV_{tumor}, MTV_{tumor}, and TLG_{tumor}, the problem of multicollinearity will cause the regression model unstable [7].

Many techniques have been used to characterize tumor heterogeneity on PET including visual evaluation, CV of SUV, area under the curve of the cumulative histogram, and fractal or textural feature analysis [8]. A study analyzed 555 pretreatment ^{18}F-FDG PET images of cancer patients (45 cervix, 101 lung [non-small cell], 139 head and neck, 112 esophagus, and 158 breast) using four robust texture feature parameters. The relationships between metabolically active tumor volume and texture features were similar across the different tumor types. Stage, volume, and heterogeneity were independent prognostic factors for non-small cell lung cancer for instance [8].

The texture analysis involved multiple approaches, such as histogram-based methods. The heterogeneity descriptors (HDs) disregard the inherent spatial relationship between voxel values, and reflect the voxel-value frequency distribution using first-order statistics [3]. Other approaches account for the spatial arrangement of the voxel values within the tumor using second-order gray level co-occurrence matrix or higher-order statistics, such as gray-level run length matrix, gray-level size zone matrix, or neighboring gray-level dependence matrix, to represent the spatial arrangement of intensities in a 3D volume of interest [3,5]. However, same descriptor name may be used for descriptors calculated from different definitions resulting in confusions, therefore, a plea to standardize the HDs is called [3]. Despite significant results are noted by applying numerous parameters that characterized PET heterogeneity, the biological correlation demands further investigation.

In conclusion, measuring tumor metabolic heterogeneity on PET data is potentially useful for clinical oncology practice. Type I error is unavoidable in studies investigating many HDs in a limited set of patients and outcome events. Further prospective, large-scale studies have to be performed with the well-defined HDs to validate their true utility in the management of cervical cancer.

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