

Measuring Intratumoral Metabolic Heterogeneity by Positron Emission Tomography in Cervical Cancer—A Review

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Abstract

Measurement of intratumoral heterogeneity by 18F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) is a valuable modality, which showed correlation to response of treatment and prognosis in various malignancies. PET-based texture analysis for tumor heterogeneity is a potential predictive factor for cervical cancer and related to lymph node metastasis, tumor volume, response of treatment, and pelvic recurrence. Although seemed promising in utility in oncology, a plenty of methods have been used for analysis of heterogeneity which led to confusion of definitions and comparing results challenging. Further larger sized prospective studies are needed for standardized heterogeneity descriptors and clinical applications.

Keywords: 18F-FDG PET; Positron emission tomography; Tumor heterogeneity; Texture; Cervical cancer

Introduction

Cervical cancer is one of the most common cancer and the leading causes of cancer-related death in women worldwide. The prognosis is depended on International Federation of Gynecology and Obstetrics (FIGO) stage, histology, Lymph Node (LN) metastasis, lymphovascular space involvement, positive surgical resection margins [1]. Clinical staging by pelvic examination, imaging studies, mainly Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are widely used for pretreatment evaluation and detection of recurrences/metastases.

Positron Emission Tomography

Positron Emission Tomography (PET), a functional imaging modality, which utilizes radiotracers, mainly 18F-fluorodeoxyglucose (18F-FDG), along or combined with CT or MRI, to detect metabolic processes, is beneficial in cervical cancer for evaluation of primary disease status, nodal metastasis, distant metastasis, prognosis, and recurrence [1,2]. Kidd et al. reported that prognostic nomograms composed with pretreatment 18F-FDG PET LN status, cervical tumor maximum standardized uptake value (SUVmax), and tumor volume could be a predictive model for recurrence free survival (RFS), disease-specific survival (DSS), and overall survival (OS) [3]. Liu et al. reported that patients with cervical squamous cell carcinoma (n=55), FIGO stage III-IVA or positive pelvic or para-aortic LN metastasis without other distant metastasis undergoing concurrent chemoradiation (CCRT), during-treatment SUVnode (P=0.001) and MTVratio of cervical tumor (P=0.004) were significant predictors for OS by multivariate Cox regression analysis [4].

Tumor Heterogeneity

Heterogeneity in tumor microenvironments is related to variation in tumor responsiveness to treatment, degree of vascularity, hypoxia, proliferation rates, and gene expression [5]. Intratumoral heterogeneity across the entire tumors measured by 18F-FDG PET showed predictive value of prognosis in many types of cancers, including sarcoma, esophageal cancer, rectal cancer, non-small cell lung cancer, and oropharyngeal cancer [5]. Beukinga et al. analyzed 97 pre-neoadjuvant chemoradiotherapy 18F-FDG PET/CT images of localized esophageal cancers, in which they used textural feature-derived parameters and compared with SUVmax. The results showed that the 18F-FDG PET derived textural feature 'long run low gray level emphasis', and the CT derived textural feature 'run percentage' were superior to SUVmax (area under the receiver operating characteristic curve (AUC of ROC): PET/CT texture 0.78 vs. SUVmax 0.58)[6].

Measuring Tumor Heterogeneity by PET in Cervical Cancer

Kidd and Grigsby prospectively studied 72 patients with FIGO stage IB1 to IVA cervical cancer patients treated with primary chemoradiation. The linear regression curves (one for each patient) took the form of the following general equation: $V=G-HT$, wherein V is tumor volume (cm^3), G is constant, T is threshold (%), H (dV/dT) is heterogeneity. They found there was a relationship with heterogeneity and tumor volume ($R^2=0.881$) and tumor heterogeneity was significantly associated with lymph node metastasis at diagnosis (P=0.0009), response to radiation (P=0.0207), risk of pelvic recurrence (P=0.0017), and risk of progression-free survival (P=0.03) [7]. Chung et al. retrospectively analyzed 85 patients with FIGO stage IB-IIA and found intratumoral FDG heterogeneity (IFH) was associated with primary tumor size, SUV tumor, MTV tumor, total lesion glycolysistumor (TLG tumor), and depth of cervical invasion. Multivariate analysis identified that IFH was the only independent risk factor for recurrence (P=0.028; HR, 756.997) while TLG tumor, MTV,

SUV, and FIGO stage II were not [8]. Yang et al. analyzed 20 patients with stage IB1 to IVA cervical cancers and primary chemoradiation, who underwent 18F-FDG-PET/CT before treatment, during weeks 2 and 4 of treatment, and 12 weeks after completion of therapy. In this study, contiguous regions of high uptake in tumors decreased significantly with time in complete metabolic response group ($P < 0.001$) [9].

There are various methods and parameters for evaluation of tumor heterogeneity utilizing PET. Ho et al. prospectively studied intratumoral heterogeneity by FDG-PET and treatment outcome for 44 patients with bulky cervical cancer underwent definitive CCRT. In this study, pretreatment grey-level non-uniformity (GLNU) > 48 by grey level run length encoding method (GLRLM) textural analysis and intra-treatment decline of run length non-uniformity $< 55\%$ and the decline of TLG (Δ TLG) $< 60\%$ were associated with worse OS. In multivariate analysis, only Δ TLG was a significant variable ($P = 0.009$). Combining pretreatment with intra-treatment factors, they defined an initial GLNU > 48 and a Δ TLG $< 60\%$ as the high-risk group with significant worse non-complete metabolic response rate (83%), 5-year progression free survival (8% vs. 75%, $P < 0.001$), and 5-year OS (42% vs. 81%, $P = 0.001$) [10].

Yang et al. found that standardized spatial heterogeneity (SSH) ($P = 0.0026$), gray-level co-occurrence matrix (GLCOM)-based energy (ENGY) ($P = 0.0252$) and entropy (ENTR) ($P = 0.0240$), gray-level zone size matrix (GLZSM)-based GLNU ($P = 0.0234$) and zone size non-uniformity (ZSNU) ($P = 0.0188$) were significant predictive parameters of treatment response to CCRT in locally advanced cervical cancer ($n = 90$). Besides, SSH was associated with a larger AUC of ROC curve (0.782) compared with these four significant texture parameters (AUC = 0.659 for ENGY, AUC = 0.657 for ENTR, AUC = 0.659 for GLNU, and AUC = 0.665 for ZSNU) [11].

A pilot study of multiparametric 18F-FDG/18F-fluoromisonidazole (FMISO)-PET/MRI showed that a voxel-by-voxel analysis revealed only weak correlation between the MRI and PET parameters, indicating their complimentary roles of evaluation of tumor heterogeneity, hypoxia, cellularity, and neo-angiogenesis in locally advanced cervical cancer [12].

Challenges and Issues

Many approaches, such as histogram-based methods which reflects the voxel-value frequency distribution using first-order statistics, while SSH (which derived from multiplying Size Irregularity (SI) and Correction Factor (CF)), GLRLM, and GLZSM, which represent runs and zones with different grey-level values to describe contiguous regions of constant intensity in a tumor using higher-order statistics were used in the texture analysis [9-11,13]. Many potentially confounding issues have been identified, which are related to the complex workflow for the calculation of textural features, and the dependency of textural parameters on factors such as acquisition, image reconstruction, preprocessing, functional volume segmentation, and methods of quantifying correspondences with clinical metrics of interest [13]. Confusion of definitions of the descriptor names is noted and standardized heterogeneity descriptors are needed in the future applications [5].

Summary

Tumor heterogeneity is associated with prognosis in cervical cancer. Measuring intratumoral heterogeneity by PET in cervical cancer is

shown to predict response of treatment and prognosis. Although seemed promising in utility in oncology, a plenty of methods have been used for analysis of heterogeneity which led to confusion of definitions and comparing results challenging. Further prospective and large-scale studies have to be performed for better-defined heterogeneity descriptors for future routine clinical applications.

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