Gynecology & Obstetrics
ISSN: 2161-0932

Tang et al., Gynecol Obstet (Sunnyvale) 2017, 7:S5
DOI: 10.4172/2161-0932.S5:010

Review Article OMICS International

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

Yun-Hsin Tang[1,2] **and Chyong-Huey Lai**[1,2*]

[1]*Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan*

[2]*Gynecologic Cancer Research Center, Chang Gung Memorial Hospital, Taoyuan,Taiwan*

[*]**Corresponding author:** Chyong-Huey Lai, MD, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou, 5 Fu-Shin Street, Kueishan, Taoyuan 333, Taiwan, Tel: 886-2-27135211; E-mail: sh46erry@ms6.hinet.net

Received Date: December 01, 2016; **Accepted Date:** January 06, 2017; **Published Date:** January 12, 2017

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 (R2=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 (ΔTLG) <60% were associated with worse OS. In multivariate analysis, only ΔTLG was a significant variable (P=0.009). Combining pretreatment with intra-treatment factors, they defined an initial GLNU>48 and a ΔTLG<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].

This article was originally published in a special issue, entitled: **"Current Trends in Gynecologic Oncology"**, Edited by Tang YH and Lai CH

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.

Acknowledgements

Supported by grants from the Ministry of Science and Technology-Taiwan (MOST-104-2314-B-047-MY3), Chang Gung Medical Foundation (CRRPG3D0021 and CMRPG3B0061~3), and the Department of Health-Taiwan (DOHW105-TDU-B-212-113003).

References

1. Lai CH, Yen TC, Ng KK (2012) Molecular imaging in the management of cervical cancer. J Formos Med Assoc 111: 412-420.
2. Lai CH, Lin G, Yen TC, Liu FY (2014) Molecular imaging in the management of gynecologic malignancies. Gynecol Oncol 135: 156-162.
3. Kidd EA, El Naqa I, Siegel BA, Dehdashti F, Grigsby PW (2012) FDG-PET-based prognostic nomograms for locally advanced cervical cancer. Gynecol Oncol 127: 136-140.
4. Liu FY, Lai CH, Yang LY, Wang CC, Lin G, et al. (2016) Utility of (18)F-FDG PET/CT in patients with advanced squamous cell carcinoma of the uterine cervix receiving concurrent chemoradiotherapy: a parallel study of a prospective randomized trial. Eur J Nucl Med Mol Imaging 43: 1812-1823.
5. Lai CH (2016) Measuring tumor metabolic heterogeneity on positron emission tomography: utility in cervical cancer. J Gynecol Oncol 27: e12.
6. Beukinga J, Hulshoff JB, Dijk LV, Muijs C, Burgerhof J, et al. (2016) Predicting response to neoadjuvant chemoradiotherapy in esophageal cancer with textural features derived from pre-treatment 18F-FDG PET/CT imaging. J Nucl Med 116: 180-299.
7. Kidd EA, Grigsby PW (2008) Intratumoral metabolic heterogeneity of cervical cancer. Clin Cancer Res 14: 5236-5241.
8. Chung HH, Kang SY, Ha S, Kim JW, Park NH, et al. (2016) Prognostic value of preoperative intratumoral FDG uptake heterogeneity in early stage uterine cervical cancer. J Gynecol Oncol 27: e15.
9. Yang F, Thomas MA, Dehdashti F, Grigsby PW (2013) Temporal analysis of intratumoral metabolic heterogeneity characterized by textural features in cervical cancer Eur J Nucl Med Mol Imaging. 40: 716-727.
10. Ho KC, Fang YH, Chung HW, Yen TC, Ho TY, et al. (2016) A preliminary investigation into textural features of intratumoral metabolic heterogeneity in (18) F-FDG PET for overall survival prognosis in patients with bulky cervical cancer treated with definitive concurrent chemoradiotherapy. Am J Nucl Med Mol Imaging 6: 166-175.
11. Yang F, Young L, Grigsby P (2016) Predictive value of standardized intratumoral metabolic heterogeneity in locally advanced cervical cancer treated with chemoradiation. Int J Gynecol Cancer 26: 777-784.
12. Pinker K, Andrzejewski P, Baltzer P, Polanec SH, Sturdza A, et al. (2016) Multiparametric [18F]fluorodeoxyglucose/[18F]fluoromisonidazole positron emission tomography/ magnetic resonance imaging of locally advanced cervical cancer for the non-invasive detection of tumor heterogeneity: A pilot study. PLoS One 11:e0155333.
13. Hatt M, Tixier F, Pierce L, Kinahan PE, Le Rest CC, et al. (2017) Characterization of PET/CT images using texture analysis: the past, the present...any future? Eur J Nucl Med Mol Imaging 44: 151-165.