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Original paper

Investigating multi-radiomic models for enhancing prediction power of cervical cancer treatment outcomes

Baderaldeen A. Altazi[a,b,c,*], Daniel C. Fernandez[a,b], Geoffrey G. Zhang[a,b], Samuel Hawkins[a,b], Syeda M. Naqvi[a,b], Youngchul Kim[a], Dylan Hunt[a,b], Kujtim Latifi[a,b], Matthew Biagioli[d], Puja Venkat[a], Eduardo G. Moros[a,b]

[a] H. L. Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33612, USA
[b] University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620, USA
[c] King Fahad Specialist Hospital at Dammam, Saudi Arabia
[d] Florida Hospital, 2501 N Orange Avenue, Orlando, FL 32804, USA

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ABSTRACT

Quantitative image features, also known as radiomic features, have shown potential for predicting treatment outcomes in several body sites. We quantitatively analyzed ^{18}Fluorine–fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography (PET) uptake heterogeneity in the Metabolic Tumor Volume (MTV) of eighty cervical cancer patients to investigate the predictive performance of radiomic features for two treatment outcomes: the development of distant metastases (DM) and loco-regional recurrent disease (LRR). We aimed to fit the highest predictive features in multiple logistic regression models (MLRs). To generate such models, we applied backward feature selection method as part of Leave-One-Out Cross Validation (LOOCV) within a training set consisting of 70% of the original patient cohort. The trained MLRs were tested on an independent set consisted of 30% of the original cohort. We evaluated the performance of the final models using the Area under the Receiver Operator Characteristic Curve (AUC). Accordingly, six models demonstrated superior predictive performance for both outcomes (four for DM and two for LRR) when compared to both univariate-radiomic feature models and Standard Uptake Value (SUV) measurements. This demonstrated approach suggests that the ability of the pre-radiochemotherapy PET radiomics to stratify patient risk for DM and LRR could potentially guide management decisions such as adjuvant systemic therapy or radiation dose escalation.

1. Introduction

Based on the 2017 estimates of the American Cancer Society (ACS), cervical cancer is the third most commonly diagnosed gynecological malignancy in the United States, with an estimated incidence of 12,820 new cases and estimated deaths of 4,210 [1]. The widespread implementation of early detection screening with the Pap smear test and subsequent treatment of precancerous lesions played a vital role in decreasing the cervical cancer incidence rate by half between 1975 (14.8 per 100,000) and 2012 (6.7 per 100,000). Subsequently, mortality rate also declined by half between 1975 (5.6 per 100,000) in comparison to 2012 (2.3 per 100,000). However, in less developed countries where screening is less prevalent or nonexistent, the burden of cervical cancer is much greater. This leads to cervical cancer being the fourth most common cancer in women worldwide, with an estimated global incidence of 528,000 new cases and 266,000 deaths in 2012 with the vast majority of these cases in less developed countries [2].

The ability to predict treatment outcome for patients, especially those at high risk of responding poorly to standard therapies, is of great interest. Such ability could help clinicians modify their treatment plan, or modality, to improve patient's response to treatment. At present, recent research in the expanding field of functional imaging has put a high emphasis on the investigation and development of quantitative noninvasive biomarkers given the increasing need of robust treatment outcome predictors. ^{18}Fluorine–fluorodeoxyglucose (^{18}F-FDG) PET imaging has been widely used in oncology as a functional imaging technique to define the gross tumor volume, assess its response, and for cancer staging. One of the most common semi-quantitative metrics for FDG-PET is the standardized uptake value (SUV) where the maximum

* Corresponding author.
E-mail addresses: Deen.Altazi@moffitt.org (B.A. Altazi), Daniel.Fernandez@moffitt.org (D.C. Fernandez), Geoffrey.Zhang@moffitt.org (G.G. Zhang), Samuel.Hawkins@moffitt.org (S. Hawkins), Syedamahrukh@health.usf.edu (S.M. Naqvi), Youngchul.Kim@moffitt.org (Y. Kim), Dylan.Hunt@moffitt.org (D. Hunt), Kujtim.Latifi@moffitt.org (K. Latifi), Matthew.Biagioli@flhosp.org (M. Biagioli), Puja.Venkat@moffitt.org (P. Venkat), Eduardo.Moros@moffitt.org (E.G. Moros).

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SUV (SUV_{MAX}) reportedly predicted for overall survival [3], treatment response [4], and lymph node involvement [5].

On the other hand, several studies [6,7] questioned utilizing SUV_{MAX} as an independent prognostic metric due to several measurement uncertainties that might be attributable to its sensitivity to variation in tumor volume, initial FDG uptake kinetics and distribution, inter-observer variability, and in-vivo metabolism. Therefore, one of the goals of this study was to examine the accuracy of the prediction of treatment outcomes based on observed differences in the SUV_{MAX} within the primary tumor volume. In addition to SUV_{MAX}, several studies proposed SUV_{PEAK} (defined as the maximum of all the mean values computed from placing a spherical kernel of approximately 1.2 cm in diameter to yield a $\sim 1\,cm^3$ sphere centered at each voxel within the tumor volume) as a potential robust alternative to SUV_{MAX} due to its minimum variability over time and relative insensitivity to image noise [8,9]. The predictive performance of SUV_{PEAK} was also investigated in this study.

The extraction of underlying information from medical images based on quantitatively derived features (Radiomics) is presented as a developing process in the field of medical oncological imaging [10,11]. The extracted radiomic features based on image textural and shape patterns have been used in tumor staging, the prediction for treatment outcome as well as in the process of classification and segmentation of tumor versus normal tissue. El Naqa et al. [12] reported several logistic regression models of radiomic features with good predictive power for treatment outcomes in cervical cancer patients treated with radiochemotherapy. However, the study suggested that further testing and validation using larger patient datasets were required. Tixier et al. [13] demonstrated that analysis of intratumor FDG uptake heterogeneity of baseline PET scans using radiomics differentiated, with higher sensitivity than SUV measurements, between esophageal cancer patients who showed partial- and no-response to chemoradiotherapy. Wei et al. [14] found a strong association between radiomic features extracted from baseline FDG PET and tumor staging in cervical cancer. This study focused on primary tumor volumes because of the limited resolution of PET images, which did not reproduce significant heterogeneity in the smaller lymph nodes. The preceding studies concluded that radiomic features have superior performance in comparison to SUV measurements regarding clinical outcome assessment and tumor heterogeneity description.

Accordingly, our motivation was to facilitate a comparison between our experience and previous studies in this field to analyze cervical cancer tumor heterogeneity on baseline FDG-PET scans retrospectively, and to investigate the ability of multi-radiomic regression models to predict for two major treatment outcomes, distant metastases (DM) and loco-regional recurrence (LRR).

2. Methods

2.1. Patient demographics

This retrospective study consisted of a cohort of eighty patients (Table 1) with an age range, at the time of diagnosis of 25–86 years (median: 50 years). All patients were diagnosed with cervical cancer and treated with definitive chemoradiotherapy between 2009 and 2015. Radiotherapy consisted of external beam radiation therapy (EBRT) to a dose range between 43.2 and 50.4 Gy (median = 45 Gy) and MRI-planned brachytherapy to a dose of 20–30 Gy (median = 28 Gy). All patients received concurrent cisplatin chemotherapy. The patients' disease was staged according to the classification of International Federation of Gynecology and Obstetrics (FIGO). The number of patients for FIGO stages IB, IIB, IIA, IIIA, IIIB, and IVA were 18, 33, 10, 1, 17, and 1, respectively. Most of the patients (89%) had tumor histology consistent with squamous cell carcinoma. The mean follow-up time at the start of the study was nineteen months. We aimed to examine the correlation between radiomic features and two treatment outcomes: the development of distant metastasis (DM) and loco-regional recurrence (LRR). In this work, both treatment outcomes are scalars conventionally assigned values 0 and 1. The event DM/LRR = 1 presents the complication after treatment and DM/LRR = 0 is the absence of that complication at the specific time point from the end of radiochemotherapy treatment. We set the start point of the follow-up time for each patient at the date of the initial pathological biopsy report, while the time to the clinical treatment outcome was reported based on the date of event occurrence. The institutional review board (IRB) at the University of South Florida, Tampa, FL., approved this study protocol.

Table 1
Patient characteristics.

Characteristic	All patients (n = 80)
Age at Diagnosis	Average: 50; Range: [25, 86] yrs.
Stage	
IB	18
IIB	33
IIA	10
IIIA	1
IIIB	17
IVA	1
Histology	
Squamous	72
Adenocarcinoma	8

2.2. PET imaging procedure and technique

All of the baseline PET/CT scans were performed using the same Discovery STE® hybrid PET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA) and institutional radiopharmaceutical administration protocol. All patients had to be fasting for 6 hours before being injected with an average activity of 363 MBq of ^{18}F-FDG. After the injection, a whole-body PET/CT scan in the supine position was acquired for cancer staging. Patient's weight (average weight = 87 kg) and blood glucose levels were recorded.

The PET static emission images were acquired after an average of 60 minutes post injection with an image slice thickness of 3.27 mm, row spacing of 5.47 mm, column spacing of 5.47 mm. The PET images were reconstructed using 3D maximum likelihood ordered subset expectation maximization (ML-OSEM) with two iterations and 28 subsets. All images were corrected for attenuation. Consequently, we converted the image intensity values to SUV units.

2.3. Method of metabolic tumor volume segmentation

Tumor volumes were segmented for this study (Fig. 1.a) using Mirada Medical DBx® software (Mirada Medical DBx®, Oxford, UK). A board-certified radiation oncologist manually delineated Metabolic Tumor Volumes (MTV), which contained both the cervical tumor and local direct extension in the uterus, parametrium, vagina, or other adjacent organs based on FDG uptake findings on PET and guided by CT, MRI, clinical examination findings, and patient-specific histopathological reports.

2.4. Radiomics analysis

We developed in-house software to process and quantify PET scans and to calculate the commonly implemented methods of feature extraction. In total, we extracted seventy-five radiomic features from each MTV (Fig. 1.a). Consequently, we divided the radiomic features based on their calculation method into six sets.