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The role of FDG PET/CT radiomics in the prediction of pathological response to neoadjuvant treatment in patients with esophageal cancer

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ABSTRACT

Background: Attainment of a complete histopathological response following neoadjuvant therapy has been associated with favorable long-term survival outcomes in esophageal cancer patients. We investigated the ability of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) radiomic features to predict the pathological response to neoadjuvant treatment in patients with esophageal cancer.

Materials and methods: A retrospective review of medical records of patients with locally advanced resectable esophageal or esophagogastric junctional cancers. Included patients had a baseline FDG PET/CT scan and underwent Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) protocol followed by surgery. Four demographic variables and 107 PET radiomic features were extracted and analyzed using univariate and multivariate analyses to predict response to neoadjuvant therapy.

Results: Overall, 53 FDG-avid primary esophageal cancer lesions were segmented and radiomic features were extracted. Seventeen radiomic features and 2 non-radiomics variables were found to exhibit significant differences between neoadjuvant therapy responders and non-responders. An unsupervised hierarchical clustering analysis using these 19 variables classified patients in a manner significantly associated with response to neoadjuvant treatment ($p < 0.01$).

Conclusion: Our findings highlight the potential of FDG PET/CT radiomic features as a predictor for the response to neoadjuvant therapy in esophageal cancer patients. The combination of these radiomic features with select non-radiomic variables provides a model for stratifying patients based on their likelihood to respond to neoadjuvant treatment.

Key words: FDG PET/CT; esophageal cancer; radiomics; neoadjuvant therapy; pathological response

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Introduction

Esophageal cancer is an aggressive disease with a low survival rate of 15–20% [1]. Since the mid 1990s there has been a shift from a predominance of squamous cell carcinoma (SCC), which had accounted for 90–95% of all esophageal cancer [2] to adenocarcinoma which now accounts for 50-80% of esophageal cancer cases in Western countries [3, 4].

The outcomes of esophageal cancer have been improved by neoadjuvant approaches [5]. Neoadjuvant radiochemotherapy has resulted in downstaging of esophageal cancer, an increased rate of resection of advanced esophageal SCC, prolonged survival and improved quality of life [6]. However, as the clinical and imaging evaluation of esophageal cancer after neoadjuvant therapy can be inaccurate [7], histopathologic evaluation is performed using morphological criteria. Complete histopathologic response is a predictor of long-term survival in patients with esophageal cancer [8].

Esophageal cancer is currently staged using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), which provides additional important information beyond the standard staging methods (endoscopy, endo-luminal ultrasound, multi-detector CT), mainly in the detection of distant metastases [9–11].

Radiomics represents an emerging field within medical imaging that holds promise as a tool, impacting disease diagnosis and prognosis, particularly in oncology, facilitating the delivery of precision medicine. At its core, radiomics lies in its recognition of information embedded within medical images, including tumor pathology and biology, which may not be apparent to the human eye during routine clinical interpretation. By systematically extracting features and identifying patterns from conventional images, radiomics unveils valuable insights that may otherwise remain undetected. This process entails a stepwise approach involving data selection, image acquisition, segmentation, feature extraction, and data investigation and validation. In oncological contexts, radiomics finds application in classification tasks aimed at determining the probability of a sample belonging to a specific category (e.g., benign versus malignant), and prediction of clinical outcomes [12, 13].

Radiomics using PET parameters is a relatively new technique for extracting quantitative variables [14]. In patients with cancer, first-order histogram variables, such as tumor shape, heterogeneity, uniformity and texture, as well as second-order variables, such as gray-level co-occurrence matrix (GLCM) and gray-level dependence matrix (GLDM), can be used to characterize tumors [15–17] and have shown to be correlated with tumor aggressiveness [18] and prognosis [19].

The aim of this study was to evaluate the feasibility of utilizing radiomic features extracted from FDG PET/CT imaging to predict the pathological response of neoadjuvant therapy in esophageal cancer patients.

Materials and methods

This retrospective study was approved by the institutional ethics committee (approval number 8069-21-SMC). The requirement for patient informed consent was waived.

Patients

Consecutive records of adult patients (> 18 years) with a diagnosis of esophageal or esophagogastric junctional cancer who underwent FDG PET/CT scans for staging between 2015–2021 were retrieved. Then, a case-by-case search was performed using the Carestream Vue picture archive and communication system (PACS) version 12.1.5.1 (Carestream Health Inc., Rochester, NY, USA) to obtain cases showing FDG-avid esophageal cancer.

Information on neoadjuvant therapy, tumor location, type of surgery, and post-surgery histology was obtained from the patients' medical records and post-surgery pathological records. Only records of patients with esophageal adenocarcinoma or SCC histology were included. Furthermore, only patients treated according to the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) protocol were included, since it represents the standard of care for locally advanced resectable esophageal or esophagogastric junctional cancers [20, 21].

The pathological response to neo-adjuvant therapy was categorized as: 1) complete pathological response or 2) partial or negligible pathological response based on the patients' post-surgery patho-

logical reports, which were categorized according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging [22].

Patients with non-FDG-avid lesions, patients without available medical/pathological information, patients diagnosed with non-esophageal cancer pathology, patients below 18 years of age, patients who did not receive neoadjuvant treatment, and patients who were not treated according to the CROSS protocol or did not complete surgery were excluded from the analysis.

FDG PET/CT acquisition

All PET/CT examinations were performed according to our institute's clinical scanning protocols. Diagnostic CT examinations were performed on a 64-detector-row helical CT scanner (Philips Vereos, Philips Medical Systems, Amsterdam, Netherlands). The field of view and pixel size of the PET images that were reconstructed for fusion were 57.6 cm and 4 mm, respectively, with a matrix size of 144 × 144. The technical parameters used for CT imaging were as follows: pitch 0.83, gantry rotation speed 0.5 s/rot,120 kVp, modulated tube current 40–300 mA, and specific breath-holding instructions. If not contraindicated, the patients received an intravenous injection of 5.18 MBq/kg after fasting for 4-6 hours. About 60 min after tracer administration, CT images were obtained from the vertex to the mid-thigh or for the whole body. An emission PET scan followed in three-dimensional (3D) acquisition mode for the same longitudinal coverage, 1.5 minutes per bed position. CT images were fused with the PET data to generate a map for attenuation correction, eventually generating reconstructed images for review on a computer workstation.

Image analysis

The images were analyzed using Carestream Vue PACS version 12.1.5.1 (Carestream Health Inc., Rochester, NY, USA). An experienced consultant radiologist and nuclear medicine specialist (L.D.) with a decade of experience in interpreting PET/CT scans assessed all scans. Utilizing the semi-automatic segmentation tool within the PACS system, a volume of interest (VOI) was delineated for each FDG-avid esophageal cancer lesion identified on the PET images (Fig. 1). Manual corrections were performed as needed to ensure accurate delineation.

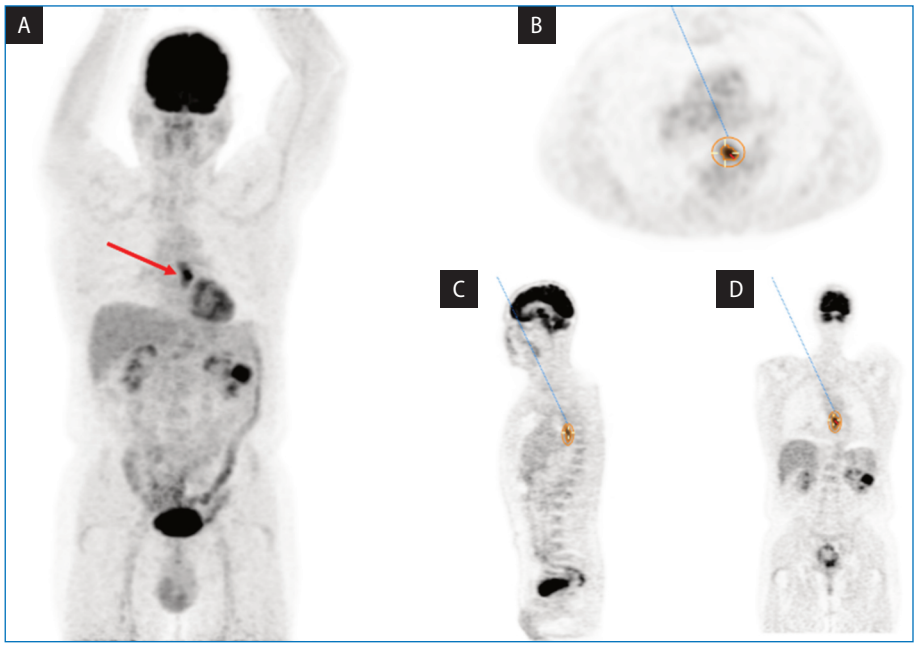

Figure 1. Example of ^{18}F-fluorodeoxyglucose (FDG)-avid esophageal cancer segmentation. **A.** A maximum intensity projection (MIP) image of the FDG positron emission tomography (PET) scan displays the lesion (indicated by the red arrow). The segmented lesion is indicated by the blue line on the axial (**B**), sagittal (**C**), and coronal (**D**) PET reconstructions

Extraction of radiomic features

Before features were extracted, all images were normalized by standardization [centering to $\mu = 0$, standard deviation (SD) = 1] to ensure data analysis on the same scale (23). In total, 107 known radiomic features based on the Image Biomarkers Standardization Initiative histogram analysis [24] using the PyRadiomics toolkit (V3) [25] were extracted from the PET scans for each lesion. Radiomic features were classified as first-order (18 features), Gray Level Co-occurrence Matrix (GLCM) (24 features), Gray Level Dependence Matrix (GLDM) (14 features), gray level run-length matrix (GLRLM) (16 features), gray level size zone (GLSZM) (16 features), neighboring gray tone difference matrix (NGTDM) (5 features), and shape (14 features).

Univariate analyses

Although radiomics provides a means of analytically characterizing tumor phenotypes by extracting multiple quantitative image features, high dimensionality may degrade prediction and classification performance [26]. The process of feature selection aims to contend with the problem of high dimensionality by selecting the relevant features and removing the irrelevant and redundant ones [27]. Here we applied univariate analyses as a means for feature selection. For this purpose, 107 radiomic features and 4 non-radiomics variables (age, gender, tumor location, and reactive lymph node status) were compared between responders to neoadjuvant therapy and non-responders using two-sample t-tests for continuous variables and chi-squared tests for categorical variables. Variables showing $p < 0.1$ (one-sided, uncorrected) were included in further analyses. All analyses were performed using the R software (version 3.6.0, Boston, MA).

Hierarchical clustering

Unsupervised hierarchical clustering (UHC) analysis was performed to identify subgroups of patients with high radiomics similarity within each subgroup and a distinct radiomics profile between subgroups based on the similarity of the radiomic features calculated by Canberra distance. The UHC-derived patient dendrogram was split on the second level resulting in two clusters. Response to chemotherapy tumor type and gender were compared between UHC-derived groups by chi-squared test. UHC analysis was conducted using the "dendextend" R package.

Results

Patients

Of 245 cases of patients retrieved from the database, 192 were excluded due to treatments other than the CROSS protocol (n = 99), non-neoadjuvant therapy (n = 14), incomplete information (n = 54), and non-esophageal cancer (n = 25). The final cohort included 53 patients (66% males) with a mean age of 65 ± 9 years (range 40-78 years). Adenocarcinomas accounted for 64.1% of all lesions. Tumor locations included esophagogastric junctional cancer (39.6%), distal esophagus (37.7%), middle esophagus (20.7%), and upper esophageal cancer (2%). Notably, 39.6% of patients exhibited a complete pathological response after surgery (Tab. 1).

Univariate analyses

Of the 107 radiomic features and 4 non-radiomics variables (age, gender, tumor location, and reactive lymph node status) that were compared between responders and non-responders to neoadjuvant therapy, 19 variables showed $p < 0.1$ (one sided, uncorrected, Tab. 2). Additionally, tumor type was found to be significantly associated with response to neoadjuvant therapy, with patients with SCC showing greater response compared to those with adenocarcinoma [63% (12/19) *vs.* 26% (9/34), p = 0.02, by chi-squared test]. Overall,

Table 1. Patient demographics

Variable	Study population (n = 53)
Age, years, mean ± SD (range)	65 ± 9 (40–78)
Sex, n (%)	
Male	35 (66%)
Female	18 (34%)
Histology, n (%)	
Adenocarcinoma	34 (64.1%)
Squamous cell carcinoma	19 (35.9%)
Pathological response, n (%)	
Complete pathological response	21 (39.6%)
Partial/no pathological response	32 (60.4%)

SD — standard deviation

Table 2. Comparison between responders and non-responders to neoadjuvant therapy in esophageal cancer

Variable	Complete response	Partial response	p-value (complete *vs.* partial response)
	Mean ± SEM		
original_shape_LeastAxisLength	4.25 ± 0.26	6.37 ± 0.28	0.06
original_shape_Maximum2DDiameterRow	8.32 ± 0.65	11.69 ± 0.6	0.09
original_shape_MeshVolume	170.77 ± 27.92	463.6 ± 41.89	0.08
original_glrlm_LongRunEmphasis	6.61 ± 0.46	16.4 ± 1.13	0.06
original_glrlm_LongRunLowGrayLevelEmphasis	6.11 ± 0.56	16.21 ± 1.17	0.05
original_glrlm_RunLengthNonUniformityNormalized	0.36 ± 0.02	0.21 ± 0.01	0.08
original_glrlm_RunPercentage	0.51 ± 0.02	0.32 ± 0.01	0.06
original_glrlm_RunVariance	1.29 ± 0.1	3.49 ± 0.25	0.06
original_glrlm_ShortRunEmphasis	0.49 ± 0.03	0.29 ± 0.02	0.1
original_gldm_DependenceNonUniformity	12.78 ± 1.62	35.82 ± 4.85	0.07
original_gldm_LargeDependenceEmphasis	221.53 ± 15.1	378.67 ± 12.3	0.06
original_gldm_LargeDependenceLowGrayLevelEmphasis	201.96 ± 18.82	373.33 ± 14.23	0.05
original_gldm_SmallDependenceEmphasis	0.01 ± 0.001	0.0049 ± 0.0003	0.08
original_gldm_SmallDependenceLowGrayLevelEmphasis	0.01 ± 0.001	0.0044 ± 0.0002	0.06
original_glszm_LargeAreaEmphasis	13311.74 ± 3174.96	125643.67 ± 19330.29	0.03
original_glszm_LargeAreaHighGrayLevelEmphasis	18981.89 ± 7305.05	128097.01 ± 19293.06	0.02
original_glszm_LargeAreaLowGrayLevelEmphasis	11894.84 ± 2325.45	125030.33 ± 19361.8	0.04

SEM — standard error of the mean

smaller, more homogeneous lesions with finer texture, were associated with a complete response.

Hierarchical clustering

To explore the association between radiomic features and clinical outcomes, we performed a UHC analysis using the 19 variables that showed $p < 0.1$ (one sided, uncorrected, Tab. 2). As shown in Figure 2, two clusters were obtained: group A: 27/53 patients (50.9%) and group B: 26/53 patients (49.1%).

A significantly higher proportion of patients in group A achieved a response to neoadjuvant therapy compared to those in group B [59.3% (16/27) *vs.* 19.3% (5/26), $p = 0.007$). However, UHC segmentation was not significantly related to the tumor type [the percent of adenocarcinoma in group A *vs.* group B was 59.3% (16/27) *vs.* 69.2% (18/26), $p = 0.63$].

Discussion

Response to neoadjuvant radiochemotherapy is a strong predictor for long term survival in esophageal cancer (28, 29). Although esophageal cancer is currently staged using FDG PET/CT, the ability of this modality to predict treatment response is limited. Radiomics is a data analysis approach that is increasingly used to characterize tumor phenotypes by extracting quantitative imaging features. This approach had potential to individualize treatment strategies and optimize patient outcomes.

Here we set to use FDG PET/CT radiomic features to predict the pathological response to neoadjuvant treatment in patients with esophageal cancer. We used an unsupervised machine learning approach to demonstrate a significant association between response to neoadjuvant treatment and a radiomics-derived profile of patients.

Neoadjuvant radiochemotherapy is considered the gold standard for patients with loco-regional advanced esophageal cancer, with a 5-year overall survival of 36–47% compared to 23–34% in patients who had surgery alone [30]. However, only patients who achieved a major pathological response have shown improved survival [31]. The diversity in the effectiveness of neoadjuvant therapy might be explained, at least partly, by intratumor heterogeneity [32], which is well described in esophageal cancer [33]. Intratumor heterogeneity might be better analyzed using radiomics in which quantitative image features are derived on a pixel/vox-

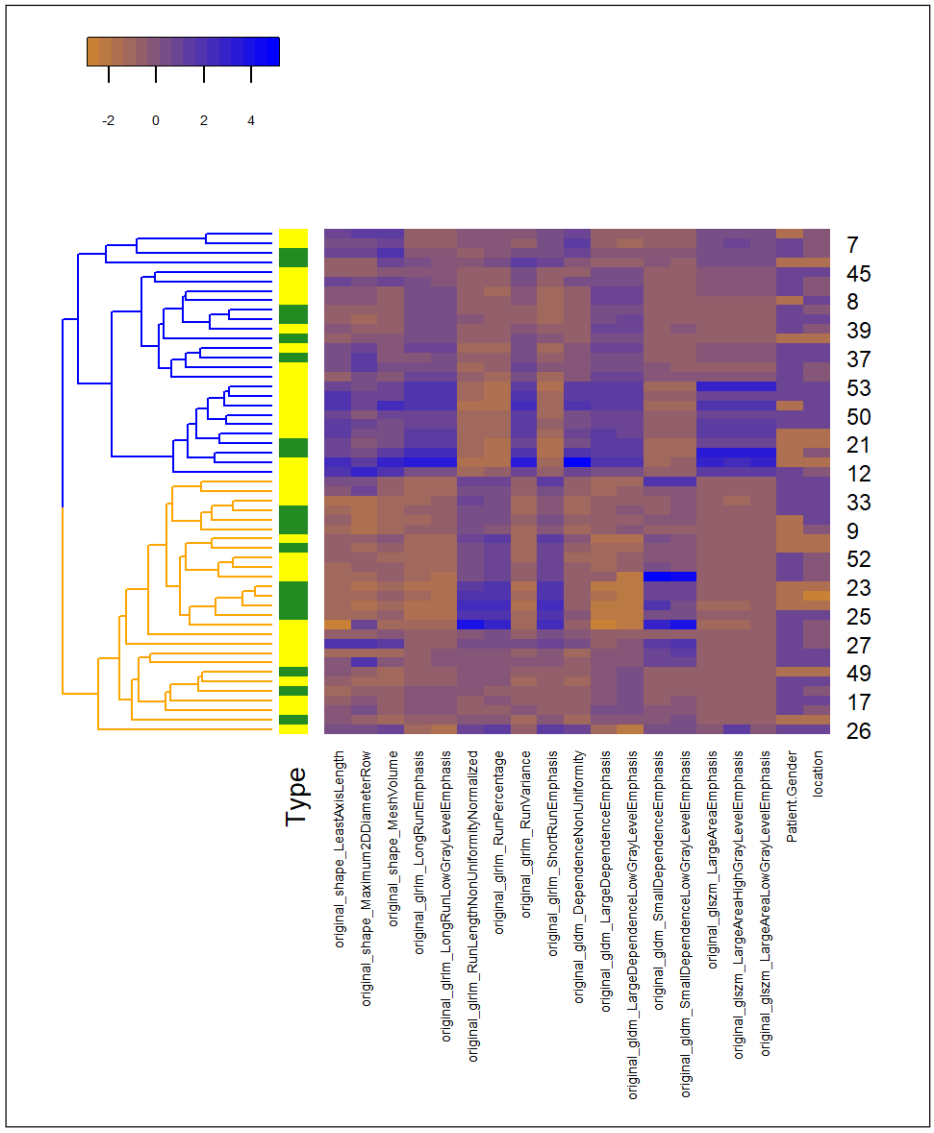

Figure 2. Unsupervised hierarchical clustering analysis of radiomic features of esophageal cancer. Seventeen radiomic features as well as gender and tumor location, identified by univariate analysis as having a correlation with response to neoadjuvant radiochemotherapy, were used to cluster 53 patients into two clusters (A — orange, B — blue) according to the similarity of the radiomic features. Type parameters are represented separately (green, yellow)

el-based analysis. Indeed, in our sample, smaller, more homogeneous lesions with finer texture were associated with a complete response. Comparably, the value of radiomic features in the prediction of pathologic response to neoadjuvant therapy has been investigated in several studies. Tan et al. [34] have shown in 20 patients with esophageal cancer that a tumor with higher skewness on pre-therapy FDG PET/CT is more likely to respond. Skewness is an intensity feature that measures the distribution of standardized uptake value (SUV) in relation to the mean value. Tixier et al. [35] evaluated 38 baseline PET features in 41 patients with esophageal cancer and showed that non-responders could be identified according to local tumor homogeneity and entropy. Moreover, features reflecting regional heterogeneity could differentiate partial responders from complete responders. Simony et al. [36] have shown that three radiomic features were correlated with major response to neoadjuvant chemoradiotherapy in 54 patients with esophageal cancer.

Our findings corroborate those of a previous study which showed that neoadjuvant response was related to tumor type, with SCC significantly associated with complete response [20]. However,

the UHC-derived segmentation was not related to tumor type, suggesting the radiomics-based profile was effective in classifying neo-adjuvant response across esophageal cancer tumor types, possibly representing features of general vulnerability and resilience to neoadjuvant treatment [37]. Future studies should include larger samples of histologically similar lesions to explore the profiles of neoadjuvant response unique to SCC and adenocarcinoma.

The study's limitations include its retrospective design. Secondly, the relatively small sample size precludes us from reaching definitive conclusions, specifically in terms of comparing the neoadjuvant response profiles of SCC and adenocarcinoma. Lastly, the study focused solely on analyzing the radiomics of FDG signals. Future studies should aim to incorporate both CT and FDG-derived radiomic features.

Conclusions

Our findings highlight the potential of FDG PET/CT radiomic features as a predictor for the response to neoadjuvant therapy in esophageal cancer patients. The combination of these radiomic features with select non-radiomic variables provides a model for stratifying patients based on their likelihood to respond to neoadjuvant treatment.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

None declared.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee (approval number 8069-21-SMC) and individual consent for this retrospective analysis was waived.

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