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Radiomics analysis of pre-treatment F-18 FDG PET/CT for predicting response to transarterial radioembolization in liver tumors

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ABSTRACT

Aim: To investigate the relationship between the textural features extracted from pre-treatment fluorine-18 fluorodeoxyglucose positron emission with computed tomography (F-18 FDG PET/CT) and the response to treatment in patients undergoing transarterial radioembolization (TARE) due to primary or metastatic liver tumors.

Material and Method: A total of 25 liver lesions from the pre-treatment F-18 PET/CT images of 14 patients were segmented manually. Standard uptake value (SUV) metrics and radiomics features were extracted for each lesion. Metabolic treatment response was determined according to PERCIST criteria in 18F-FDG PET/CT imaging performed 2 months after the treatment. Feature selection was done with recursive feature elimination (RFE). The association between selected features and treatment response was evaluated with logistic regression analysis.

Results: Eventually, 13 lesions responded to TARE, while 12 lesions remain stable or progressed. All standard uptake values and 27 out of 30 textural heterogeneity indicators were significantly higher in lesions that responded to treatment. SUVmax, kurtosis and dissimilarity features were selected by the RFE algorithm for the prediction of response to TARE. Logistic regression analysis revealed that all three parameters were significantly associated with treatment outcome.

Conclusion: Textural features extracted from pre-treatment F-18 FDG PET/CT in patients undergoing TARE due to liver tumors are promising biomarkers that can be potentially used to predict metabolic treatment response.

Keywords: PET/CT, radiomics, transarterial radioembolization, PERCIST

INTRODUCTION

Local treatments have been widely adopted into clinical practice for the treatment of primary and metastatic tumors of the liver that are not adequate for surgical resection. Transarterial radioembolization (TARE), one of these local treatment strategies, is an internal radiotherapy method performed by injecting beta-radiating radiolabeled microspheres into the tumor microcirculation through transarterial intervention of the hepatic artery branch. The rationale of this treatment is based on the fact that tumor cells are predominantly perfused through the arterial system and hepatocytes mostly from the portal venous system. By this means, radioactive microspheres can be selectively directed to the tumor and the tumor cells are exposed to high-dose radiation, while healthy liver parenchyma is minimally affected by radiation. TARE can be applied in all primary (hepatocellular cancer and cholangiocarcinoma) and metastatic (e.g., colorectal cancer and neuroendocrine tumors) malignancies of the liver that are not surgically resectable.

Tumor heterogeneity is a long-known phenomenon that determines treatment outcomes and prognosis in oncologic diseases (1). It is known that tumor biology varies between different regions in a lesion and between different lesions in a patient. Various molecular, genetic, epigenetic, and microenvironmental effects are thought to be among the causes of this entity (2). The biological nature of the liver malignancies was investigated in previous genotype studies and it was estimated that up to 60% of recurrent or metastatic tumors harbor

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subclones different from the primary tumor, and that up to 66% of single tumors demonstrate intratumoral heterogeneity (3).

Recent improvements in molecular imaging and medical informatics have promoted the weight of quantitative analyses and led to emergence of a novel research field called "radiomics". This approach is based on the extraction of quantitative characteristics of texture from medical images and originates on the premise that medical images hold quantitative data representing intratumoral heterogeneity. These relationships, which are otherwise invisible to the human eye, can be revealed with image analysis and may provide guidance for patient management (4-9). It has been previously reported that metabolic heterogeneity features extracted from fluorine-18-fluorodeoxyglucose positron emission with computed tomography (F-18 PET/CT) images can accurately predict prognosis in various malignancies (10,11). However, the number of studies investigating the role of radiomics analysis in PET imaging prior to TARE is limited.

In this context, we made radiomics analysis on the pre-treatment F-18 FDG PET/CT images of patients undergoing TARE due to liver tumors, and aimed to investigate the relationship between the PET textural features and response to treatment.

MATERIAL AND METHOD

The study was approved by the Ankara City Hospital No. 1 Clinical Researches Ethics Committee (Date: 14.10.2020, Decision No: E1-20-1180). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

This retrospective observational study included 14 patients that underwent baseline F-18 FDG PET/CT imaging and received Y-90 resin microsphere TARE due to primary or metastatic liver tumors. Exclusion criteria were having non-FDG avid lesions in the pre-treatment PET/CT and inaccessibility of follow-up data. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

PET/CT Imaging Protocol

PET/CT imaging was performed with a 6-slice CT-integrated PET scanner (GE Discovery IQ PET/CT, Milwaukee, WI, USA). After fasting for at least 4 hours, 444-629 MBq (12-17 mCi) 18F-FDG was injected intravenously while blood glucose level was below 150 mg/dL. Patients rested in a quiet room for 1 hour for adequate biodistribution of the radiopharmaceutical. Following the scout scan, CT (120 keV, 10-90 mA) and PET (3 minutes/bed) images from vertex to mid-thigh were acquired. Sagittal, coronal, and transverse slices and MIP images were obtained by iterative reconstruction (ordered subset expectation maximization, 14 subsets, 6 iterations), attenuation correction and model-based scatter correction on PET images.

Texture Analysis Protocol

The segmentation of lesions and extraction of radiomics features were performed using Local Image Features Extraction (LIFEx) software (12). Lesions with increased FDG uptake were manually segmented into a 3D volume of interest (VOI) by a nuclear medicine physician with 5 years of experience. Standard uptake values were discretized to 64 grey levels at a bin size of 0.3125. Multiple radiomics parameters (shape, histogram and textural features derived from gray-level co-occurrence matrix (GLCM), neighborhood gray-level different matrix NGLDM, gray-level run length matrix (GLRLM) and gray-level zone length matrix (GLZLM) were extracted for each lesion.

Assessment of Response to Therapy

Metabolic response was assessed on a lesion level using the PERCIST criteria (13). Accordingly, complete metabolic response was defined as normalization of SUV adjusted for lean body weight (SUL). Partial response and progression were defined as the decrease or increase of at least 30% in SULpeak, respectively. Lesions that neither responded partially nor progressed were interpreted as stable. Eventually, lesions with complete or partial response were classified as responsive, and those that remained stable or progressed were classified as non-responsive.

Statistical Analysis

Normally distributed numerical variables are presented as mean (standard deviation), and non-parametric variables were presented as median (min-max). Categorical variables are presented as numbers and percentages. The selection of the most discriminant features was made with recursive feature elimination (RFE), a feature selection method that fits a model and removes the weakest feature until the specified number of features is reached. Independent predictors of response to TARE were determined with multivariable regression models built on the selected features. Statistical analyses were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) and Stata/MP 16 (Stata Corporation, College Station, Texas, USA) software. A p-value below 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 25 liver tumors from 14 consecutive patients were included in the final analyses. The mean (SD) age was 57 (17) years. Eight patients had one single lesion, whereas 7 patients had multiple lesions varying between 2 and 4. Twelve patients (48%) were diagnosed with primary hepatocellular carcinoma (HCC), and 12 patients had metastatic liver tumors (10 colorectal cancer, 2 neuroendocrine tumors and 1 cholangiocarcinoma). The mean time between pre-treatment PET and application of TARE was 32 (19) days, and the mean time between TARE and response assessment was 75 (31) days. Characteristics of the study population are presented in **Table 1**.

Table 1. Characteristics of the study population and analyzed lesions

	All Patients (n=14)
Gender	
Male	9 (64%)
Female	5 (36%)
Age, years	57 (17)
Time Between Baseline PET and TARE, days	32 (19)
Time Between TARE and Response Assessment, days	75 (31)
	All Lesions (n=25)
Pathology	
HCC	12 (%52)
Metastatic	13 (%48)
Tumor Volume, mL	570.46 (1001.11)
Tumor/Background Ratio	2.48 (1.75)
Administered Activity, GBq	1.19 (0.67)
Absorbed Tumor Dose, Gy	183.18 (113.70)
Response to TARE	
Complete response	7 (28%)
Partial response	6 (24%)
Stable	10 (40%)
Progression	2 (8%)

Data are presented as mean (SD) for continuous variables, and n (%) for categorical variables

Characteristics of Responsive and Non-Responsive Lesions

In total, 13 lesions metabolically responded to TARE (7 complete response, 6 partial response), while 12 lesions either remained stable or progressed. The mean values of SUV metrics and textural features according to responsive and non-responsive lesions are shown in **Table 2**. Most of the extracted features were significantly different between responsive and non-responsive lesions. Indicators of intratumoral heterogeneity (e.g., contrast, correlation, entropy dissimilarity) were significantly higher in responsive lesions. Accordingly, indicators of lower intratumoral heterogeneity (e.g. homogeneity and correlation) were significantly higher in non-responsive lesions. **Figure 1** shows the pre-treatment and post-treatment PET images of a lesion that responded partially and another lesion that remained stable.

Table 2. SUV metrics and textural features of lesions according to their respond to TARE

	Responsive (n=13)	Non-Responsive (n=12)	p-value
SUVmax	10.90 (4.64)	4.30 (1.59)	<0.001
Skewness	0.48 (0.36)	-0.05 (0.89)	0.059
Kurtosis	2.65 (0.75)	3.90 (0.92)	0.001
Sphericity	0.84 (0.07)	0.82 (0.09)	0.56
Surface Area (mm^2)	4276.14 (3270.22)	7406.02 (6072.16)	0.12
Compacity	4.34 (1.31)	5.54 (2.13)	0.10
Homogeneity	0.36 (0.17)	0.63 (0.11)	<0.001
Correlation	0.02 (0.03)	0.08 (0.04)	<0.001
Contrast	43.92 (40.93)	3.61 (6.11)	0.003
Correlation	0.44 (0.15)	0.54 (0.16)	0.12
Entropy	2.01 (0.41)	1.30 (0.28)	<0.001
Dissimilarity	4.60 (2.74)	1.12 (0.89)	<0.001

Data are presented as mean (SD)

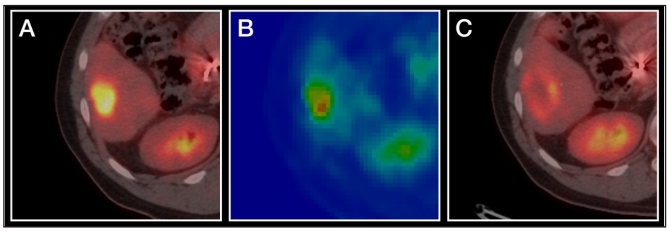

Figure 1. Example of a highly heterogeneous lesion with partial metabolic response to TARE (A) Pre-treatment PET/CT; SUVmax: 14.76, Entropy: 8.01, Kurtosis: 1.83 (B) Textural representation of the tumor (C) Post-treatment PET/CT.

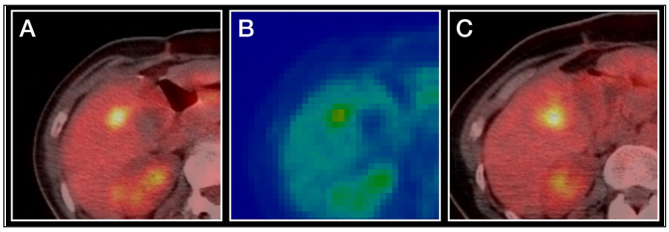

Figure 2. Example of a homogeneous lesion that was not responsive to TARE (A) Pre-treatment PET/CT; SUVmax: 7.34, Entropy: 5.75, Kurtosis: 5.78 (B) Textural representation of the tumor (C) Post-treatment PET/CT.

Predictors of Response to TARE

SUVmax, kurtosis and entropy were selected by the RFE method as highly discriminant features for predicting metabolic response to TARE. Association between these features and treatment response were confirmed with logistic regression analysis (**Table 3**). The odds ratio SUVmax, kurtosis and dissimilarity were 0.53 (0.33 – 0.86, p: 0.011), 10.71 (95% CI: 1.50 – 76.42, p: 0.018) and 0.35 (95% CI: 0.16 – 0.78, p: 0.010), respectively.

Table 3. Logistic regression analysis for predicting response to TARE

Variable	Odds Ratio	95% Confidence Interval	p-value
SUVmax	0.54	0.33 – 0.87	0.011
Kurtosis	6.53	1.52 – 28.13	0.012
Dissimilarity	0.35	0.16 – 0.78	0.010

DISCUSSION

The current study indicates that radiomics analysis in pre-treatment F-18 FDG PET/CT images could be a useful approach to predict treatment response in patients undergoing TARE. Textural features are known to be associated with response to therapy in various tumor types (14-20). However, to the best of our knowledge, this is the first study to investigate predictive potential of radiomics analysis on baseline F-18 FDG PET/CT for predicting metabolic tumor response after TARE. According to our results, multiple heterogeneity parameters were significantly higher in the lesions that responded to treatment. SUVmax, entropy and dissimilarity were the three prominent parameters for predicting the metabolic response.

SUVmax is the cornerstone parameter of oncologic PET imaging, and it is widely used for the objective assessment of metabolic activity. Considering that glucose is an essential molecule for cellular proliferation (21), PET imaging with F-18 FDG, a glucose analog, allows the identification of regions with increased proliferation, particularly malignant tumors (22,23). Lesions with a higher SUVmax on PET/CT are known to have an increased mitotic activity. This means that these lesions could demonstrate favorable response to radiation therapy when compared to lesions with lower SUV, since their exposure to radiation during cell division will be longer. This phenomenon was previously confirmed in several studies. Jo et al. (24) analyzed the pre-treatment F-18 FDG PET/CT images of 36 HCC patients and found that lesions with higher SUVmax demonstrated better response to radiotherapy. In a similar study including 35 HCC patients treated with RT, Kim et al. (25) analyzed the predictive value of baseline SUVs and found that the response of tumors with higher SUVmax was better than those in the lower SUVmax group. Pant et al. (26) reported that FDG-avid HCC lesions carry higher risk for metastasis than non-18F-FDG-avid primary tumors and HCC at higher stages was found more commonly in 18F-FDG-avid primary tumors. Tumors with a higher SUVmax will have a shorter doubling time. Thus, the response to radiation therapy is expected to be better in the lesions with higher SUV than those with lower. This finding is also in line with other studies (27-29) that investigated the relationship of SUV and treatment response in the tumors of the lung, esophagus, and nasopharynx, which reported that increased FDG uptake is an indicator of response to radiation therapy. Although the lesions with higher SUV are more radiosensitive to radiation therapy, they also tend to have more aggressive biological behavior. So in case of any residual tumor cells after TARE, lesions with higher SUVmax can potentially spread more rapidly.

An indicator of tumor aggressiveness other than SUVmax is the increased genotypic and phenotypic heterogeneity within the tumor, which can be non-invasively quantified with radiomics analysis. We have previously shown that there are strong correlations between the textural features extracted from PET images and the SUVmax values (30). Results of the current study indicate that two textural features, kurtosis and dissimilarity, were associated with treatment failure after TARE. Kurtosis is a relatively simple, histogram-based parameter that describes heterogeneity in a tumor. Lower values of kurtosis indicate a wider, flattened histogram. In other words, a decrease in kurtosis indicates a large spectrum of gray-levels and increased heterogeneity within the tumor. Kurtosis is reported to be a promising parameter for differentiating between cancer subtypes including renal cancer (31), gliomas (32), or discriminating pseudo-progression from tumor progression in glioblastomas (33). Dissimilarity, a textural feature derived from gray-level co-occurrence matrix, is an expression of intratumoral heterogeneity. Higher values of dissimilarity indicate increased inequality of intensity values between adjacent voxels. It has been previously reported for different patient groups that dissimilarity was significantly associated with response to treatment. Mosconi et al. (34) emphasized that the GLCM Dissimilarity feature extracted from CT images of intrahepatic cholangiocarcinoma patients undergoing transarterial radioembolization is a factor predicting treatment response. We previously found that increased dissimilarity in baseline F-18 FDG PET/CT images was associated with failure of first-line chemotherapy in diffuse large B-cell lymphoma (30). This feature was found to be associated with treatment response in non-small cell lung cancer as well (35). Dissimilarity was proposed as a prognostic biomarker for not only FDG PET, but also for PET imaging with other radiopharmaceuticals. Hotta et al. (36) conducted texture analysis on C-11 methionine PET and concluded that dissimilarity was the best feature to distinguish recurrent tumor from radiation necrosis in metastatic brain cancer patients.

Our findings should be interpreted in the context of several limitations. Firstly, this was a retrospective study that included a small population from a single center and imaged with the same PET/CT scanner. Lesions were

segmented manually, which could be prone to inter-observer variability. In future studies, segmentation methods can be compared to determine the preferred approach in this patient population. Lastly, considering the complex background of cancer biology, it should not be expected to get comprehensive outcomes based solely on textural analysis (37).

CONCLUSION

Radiomics features extracted from pre-treatment F-18 FDG PET/CT images in patients undergoing TARE are promising biomarkers that can be potentially used to for patient selection and predicting response to treatment. Future prospective multi-centric studies with larger cohort are needed to confirm these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara City Hospital No. 1 Clinical Researches Ethics Committee (Date: 14.10.2020, Decision No: E1-20-1180).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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