Original Article

# Role of Textural Analysis of Pretreatment $^{18}$F Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Response Prediction in Esophageal Carcinoma Patients

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## Abstract

**Introduction:** Positron emission tomography/computed tomography (PET/CT) is routinely used for staging, response assessment, and surveillance in esophageal carcinoma patients. The aim of this study was to investigate whether textural features of pretreatment 18F-fluorodeoxyglucose ($^{18}$F-FDG) PET/CT images can contribute to prognosis prediction in carcinoma oesophagus patients. **Materials and Methods:** This is a retrospective study of 30 diagnosed carcinoma esophagus patients. These patients underwent pretreatment 18F-FDG PET/CT for staging. The images were processed in a commercially available textural analysis software. Region of interest was drawn over primary tumor with a 40% threshold and was processed further to derive 92 textural and radiomic parameters. These parameters were then compared between progression group and nonprogression group. The original dataset was subject separately to receiver operating curve analysis. Receiver operating characteristic (ROC) curves were used to identify the cutoff values for textural features with a $P < 0.05$ for statistical significance. Feature selection was done with principal component analysis. The selected features of each evaluator were subject to 4 machine-learning algorithms. The highest area under the curve (AUC) values was selected for 10 features. **Results:** A retrospective study of 30 primary carcinoma esophagus patients was done. Patients were followed up after chemo-radiotherapy and they underwent follow-up PET/CT. On the basis of their response, patients were divided into progression group and nonprogression group. Among them, 15 patients showed disease progression and 15 patients were in the nonprogression group. Ten textural analysis parameters turned out to be significant in the prediction of disease progression. Cutoff values were calculated for these parameters according to the ROC curves, GLZLM_long zone emphasis (Gray Level Zone Length Matrix)_long zone emphasis (44.9), GLZLM_low gray level zone emphasis (0.006), GLZLM_short zone low gray level emphasis (0.0032), GLZLM_long zone low gray level emphasis (0.185), GLRLM_long run emphasis (Gray Level Run Length Matrix) (1.31), GLRLM_low gray level run emphasis (0.0058), GLRLM_short run low gray level emphasis (0.005496), GLRLM_long run low gray level emphasis (0.00727), NGLDM_Busyness (Neighborhood Gray Level Difference Matrix) (0.75), and gray level co-occurrence matrix_homogeneity (0.37). Feature selection by principal components analysis and feature classification by the K-nearest neighbor machine-learning model using independent training and test samples yielded the overall highest AUC. **Conclusions:** Textural analysis parameters could provide prognostic information in carcinoma esophagus patients. Larger multicenter studies are needed for better clinical prognostication of these parameters.

**Keywords:** *Carcinoma esophagus, positron emission tomography/computed tomography, response prediction, textural analysis*

## Introduction

The global burden of cancer is increasing day by day. The reason could be the growing population and cancer-causing habits.[1] Esophageal cancer is among the top ten cancers in the world.[2] Esophageal cancer is usually associated with high mortality. The outcome is usually dependent on the extent of the disease on presentation.[3]

Esophageal cancers could be localized or metastatic. Localized disease is limited to mucosa and submucosa. The localized disease could be best treated surgically.[4] When the tumor crosses the submucosa, there is an increase in the risk of spread to the lymph nodes. This leads to a decrease in the survival rate. The patients who present with a tumor that has penetrated the submucosa have a 5-year survival rate of 20%–30%.[3]



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In the case of advanced esophageal cancers, neoadjuvant chemotherapy and/or radiotherapy is performed. The main goal is to downsize the tumor, so as to decrease the tumor burden.[5] Most of the patients have locally advanced esophageal cancer or distant metastases at presentation. In locally advanced esophageal cancer, adjuvant chemotherapy or chemoradiotherapy will improve survival in patients responding to therapy. However, the patients who do not respond to therapy may be unnecessarily affected by the toxicity of therapy.[6] Therefore, it could be beneficial to noninvasively predict the response to therapy early in the course of treatment to allow the personalization of treatment.

$^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) is known to have better sensitivity and specificity in detecting distant metastasis. It is used in the initial staging of esophageal cancer.[7] It is also used in therapy response assessment and assessing the prognosis of patients.[8]

In FDG PET/CT, F-18 fluorodeoxyglucose, a glucose analog is used as a tracer. It represents the lesion glycolytic activity. The most widely used parameter is the maximum standardized uptake value ($SUV_{max}$). It is valuable in the prognosis and response prediction of therapy in esophageal cancer patients.[9] The parameters such as metabolic tumor value (MTV) and total lesion glycolysis (TLG) have been shown to provide a better assessment of tumor burden. They have higher predictive values for tumor response.[10]

The role of $^{18}$F-FDG PET/CT has been well established in staging of the esophageal carcinoma patients. It is associated with a better sensitivity and specificity than combined use of CT and echoendoscopy, especially regarding the detection of distant metastasis. $^{18}$F-FDG PET has been also used to assess response to therapy and patient outcome prognosis. Within this context, few studies have explored the potential prognostic value of pretreatment $^{18}$F-FDG PET, demonstrating that the level of activity concentration on preoperative PET, although not statistically significant, tends to predict overall survival.

The FDG uptake in the tumors is not homogeneous. The FDG uptake is variable at places due to necrosis, hypoxia, cell proliferation, and microvessel density.[11] The tumor heterogeneity is shown to be associated with disease progression and aggressive behavior of the tumor.[12]

Intratumor heterogeneity is also identified as a potential source of treatment failure.[13]

The conventional parameters such as $SUV_{max}$, TLG, and MTV, even though they are valuable in predicting tumor response and prognosis of patients, they don't take into account the spatial distribution of the radiotracer and the heterogeneity of the tumor. This leads to limitations in characterizing the biological behavior of the tumor.

The concept of textural analysis is based on the spatial arrangement and distribution of voxels in a region of interest (ROI).[14] Textural analysis characterizes tumor heterogeneity in the form of PET image-derived quantitative indices. These indices could be used in predicting therapy response or as prognostic factors. There have been several studies demonstrating the predictive value of the textural indices in cases of lung cancer,[15] breast cancer,[16] sarcoma,[17] lymphoma,[18] and rectal cancer.[19]

This study was performed to assess the role of textural analysis indices in predicting the tumor response to therapy in patients with esophageal cancer.

## Materials and Methods

### Patients

Thirty patients with newly diagnosed esophageal cancer were retrospectively analyzed who underwent $^{18}$F-FDG PET/CT for staging and response assessment. Written and informed consents were taken from the patients at the time of scanning. These patients were treated with chemotherapy (with alkylating agents) and external-beam radiotherapy from October 2019 to June 2022. These patients underwent $^{18}$F-FDG PET/CT as a part of the staging procedure before CRT. The mean age of the patients at the time of diagnosis was 52.8 years (median 50 years, range 26–71 years) and 73% of the patients were male. Most of the tumors were squamous cell carcinoma (18 patients). These tumors originated from the middle and lower esophagus. All patients were treated with external-beam radiotherapy and chemotherapy. One month after the completion of treatment, patients were assessed with follow-up PET/CT using PERCIST criteria. Depending on the response, patients were classified as progressive disease, complete responders, partial responders, and stable disease. The institutional review board has approved this retrospective study and the requirement to obtain informed consent was waived.

### Imaging technique

All the PET/CT scans were performed using GE DISCOVERY MIDR PET/CT scanner (GE Healthcare, Milwaukee, USA) for staging. All the patients were instructed to fast for >6 h before the scan. The fasting blood glucose was checked before the scan. If the glucose levels were in the normal fasting range, patients were injected with an $^{18}$F-FDG injection. The injections were done according to the weight of the patients. At $^{18}$F-FDG injection, the mean plasma glucose level was 100 mg/dl. CT from the brain to mid-thigh was performed before the PET scan using a 16-slice CT scanner. Whole body PET was performed covering an identical area to that covered by CT. Acquisition time was 1–2 min per bed position, with 7–8 bed positions. Images were reconstructed with the three-dimensional (3D) row-action maximum-likelihood algorithm using standard clinical protocol parameters (2

iterations, relaxation parameter of 0.05, and 3D Gaussian postfiltering of 5 mm in full width at half maximum). The obtained images were then exported to LIFEx software.[20]

### Image analysis

The focal FDG uptake in the primary lesion was visually interpreted in consensus by two board-certified nuclear medicine physicians. They were blinded to clinical, pathological, and other imaging information. The tumors were delineated manually and ROI were drawn over the tumors. The ROI was then delineated with 40% thresholding. Forty percent threshold was used conventionally. Then, the ROI was processed to obtain the textural indices. All the parameters were extracted from the delineated tumor. Only primary tumors were considered, as textural analysis cannot be reliably performed on small lesions as the number of voxels involved would be less. Hence, the lymph nodes and distant metastasis were not involved in the ROI.

### Standardized uptake value analysis

Activity in a lesion is reported in terms of the $SUV_{max}$. $SUV_{max}$ is the value of the most intense pixel in the ROI. This allows the exclusion of low counts from the areas of necrosis adjacent to normal structures. SUVmean is an average of all counts in the ROI, which may be more representative because a spurious single hot area will not cause incorrect data to be recorded. SUV peak is the average of the counts from a circular volume surrounding the hottest pixel. The SUV peak may more accurately represent maximal tumor metabolism with a higher degree of statistical significance than the $SUV_{max}$. MTV refers to the metabolically active volume of the tumor. TLG is the product of MTV and SUV mean. All these values are provided by the software automatically.

### Textural analysis

Once the images are processed, the software provides different types of textual indices and matrices. There are three different types of textural features-first order, second order, and higher order textural features. First-order textural features are statistics based on the gray level distribution of the image but do not consider relative positions of gray levels. They quantify intensity variations between each voxel and its immediate neighbors. Second and higher order textural features do consider relative positions of gray levels and therefore allow quantification of heterogeneity.

### First-order parameters

First-order parameters quantify intensity variations between each voxel and its immediate neighbors. These are intensity-based and histogram-based parameters. They include parameters such as entropy, skewness, and energy.

Entropy reflects irregularity in the gray level. A completely random distribution would have very high entropy.

Energy reflects the uniformity of the distribution.

Skewness reflects on the asymmetry of the gray-level distribution.

Kurtosis reflects the shape of the gray level distribution relative to normal distribution.

### Second-order parameters

These are regional heterogeneity parameters. They are calculated through analysis at the level of groups of boxes and areas of various sizes and intensities. They include:

#### *Gray level zone length matrix*

It provides information on the size of homogeneous zones for each gray level in three dimensions. From this matrix, 11 textural indices can be computed. They depend on the size of the zone if it is a long zone or short zone and the level of intensity; if it is a low gray level or a high gray level.

#### *Gray level run length matrix*

It gives the size of homogeneous runs for each gray level. The matrix is computed for the 13 different directions in 3D and for each of the 11 textural indices derived from the matrix. They depend on the size of the run if it is a long run or short run and the level of intensity; if it is a low gray level or a high gray level.

### Higher order parameters

These parameters tell us about spatial interrelationships and frequency distributions of the gray levels. They include matrices like-neighborhood gray level difference matrix and gray level co-occurrence matrix.

#### *Neighborhood gray level difference matrix*

It corresponds to the difference of gray level between 1 voxel and its 26 neighbors in three dimensions. Three textural indices are computed from this matrix.

a. NGLDM_Coarsness: Is the level of spatial rate of change in intensity
b. NGLDM_Contrast: Is the intensity difference between neighboring regions
c. NGLDM_Busyness: This is the spatial frequency of changes in intensity.

#### *Gray level co-occurrence matrix*

It takes into account the arrangements of pairs of voxels to calculate textural indices. Six textural indices are computed from this matrix.

a. Gray level co-occurrence matrix (GLCM)_homogeneity: Is the homogeneity of gray level voxel pairs
b. GLCM_Energy: Is the uniformity of gray-level voxel pairs
c. GLCM_Contrast: Is the local variations in the GLCM

d. GLCM_correlation: Is the linear dependency of gray levels in GLCM
e. GLCM_Entropy: Is the randomness of gray-level voxel pairs
f. GLCM_Dissimiliarity: This is the variation of gray-level voxel pairs.

### Response evaluation

Response to chemoradiotherapy was assessed after 1 month of completion of treatment. Follow PET/CT was used to assess tumor response. Tumor response was classified as complete response, partial response, stable disease, or progressive disease according to the response evaluation criteria in solid tumors. Patients with a complete response and partial response were considered responders and patients with stable disease or progressive disease were considered nonresponders.

### Statistical analysis

This is a retrospective study of 30 diagnosed carcinoma esophagus patients. These patients underwent pretreatment $^{18}$F-FDG PET/CT on GE DISCOVERY MIDR PET/CT scanner for staging. The images were processed in LIFEx software. ROI was drawn over the primary tumor with a 40% threshold and was processed further to derive 92 textural and radiomic parameters. These parameters were then compared between the progression group and the nonprogression group. Receiver operating characteristic (ROC) curves were used to identify the optimal cut-off values for the textural features with a $P < 0.05$ for statistical significance using SPSS version 22.0 (IBM Corporation in Armonk, New York). software. Specificity and sensitivity (including 95% confidence intervals) for each of the studied parameters were derived using ROCs curves measuring associated areas under the ROC curves (area under the curve [AUC]). Feature selection was done with principal component analysis. The selected features of each evaluator were subject to 4 machine-learning algorithms. The highest AUC values were selected for 10 features. Textural results were compared with those of $SUV_{max}$ and SUV mean for their ability to distinguish between responders and nonresponders.

## Results

Patients were evaluated 1 month after the completion of combined radiochemotherapy. There were a total of 30 patients who were eligible for analysis. All the patients' characteristics are described in Table 1. Among them, there were 15 responders and 15 nonresponders. Responders constituted patients who had a partial response or complete response. Nonresponders constituted patients who had a stable metabolic disease or disease progression.

ROC analysis revealed 10 parameters which were significantly correlated to outcome ($P < 0.05$). Most features in the original dataset were redundant due to multicollinearity and were removed while preferentially preserving the parameters with $P < 0.05$ in the ROC analysis. This resulted in a feature set of 10 parameters.

These parameters were then separately passed through a principal component analysis algorithm and a standard scaling algorithm. Four different algorithms for a creating a machine learning model were tested on the previous mentioned interactions of the data including one unchanged set as well. The best and most consistent combination was the Standard scaled data with a logistic regression model with an accuracy of 83% ($\kappa$ =0.666, mean squared error [MSE] = 0.16, MSE error = 0.408, $f$ = 0.857, Matthews correlation co-efficient = 0.707 and perirhinal cortex = 0.958). Similar results were found with K-nearest neighbor model and least accuracy was given by the adaboost model.

Neither $SUV_{max}$ nor SUV mean was significantly different between responders and nonresponders. MTV and TLG were also not significant in predicting therapy response. Nonresponders show significantly higher MTV and TLG than responders. By textural analysis, the area under the ROC curves (AUC) values were calculated for all the different parameters.

In the case of first-order parameters, none of the parameters were significant in predicting response to the therapy. The AUC values for these parameters were below 0.7. Among the first-order parameters, SUVkutosis and SUV_Excess kurtosis have a max AUC value of 0.68.

Among the second-order parameters, four parameters from the GLRLM matrix and four parameters from the GLZLM matrix were significant in predicting the response. They were GLZLM_long zone emphasis (LZE), GLZLM_low gray level zone emphasis (LGZE), GLZLM_short zone low gray level emphasis (SZLGE), GLZLM_long zone low gray level emphasis (LZLGE), GLRLM_

**Table 1: Characteristics of patients**

| Characteristics | Number of patients |
|---|---|
| Sex | |
| Males | 22 |
| Females | 8 |
| Location of the tumor | |
| Upper 1/3$^{rd}$ esophagus | 4 |
| Middle 1/3$^{rd}$ esophagus | 11 |
| Lower 1/3$^{rd}$ esophagus | 15 |
| Type of carcinoma | |
| Squamous cell carcinoma | 18 |
| Adenocarcinoma | 12 |
| Metastases | |
| Present | 12 |
| Absent | 18 |
| Response to therapy | |
| Responders | 15 |
| Nonresponders | 15 |

long run emphasis (LRE), GLRLM_low gray level run emphasis (LGRE), GLRLM_long run low gray level emphasis (LRLGE), and GLRLM_short run low gray level emphasis (SRLGE). The cutoffs were calculated for these parameters. The cutoffs are given in Table 2 and the AUC values are described in Table 3.

These parameters tell about the distribution of the size of homogeneous zones for each gray level in three dimensions.

In the case of higher-order parameters [Figure 1], GLCM homogeneity and NGLDM_Busyness were significant in predicting the tumor response. GLCM homogeneity represents the homogeneity of the tumor. NGLDM_Busyness represents the spatial frequency of changes in intensity.

Other higher parameters like contrast, coarseness, etc., in the NGLDM and GLCM matrix were not statistically significant predictive factors of response.

The AUC for GLCM_homogeneity is 0.729 and the cut-off was calculated to be 0.37. NGLDM_Busyness was also significant in predicting the tumor response in carcinoma esophagus patients. The AUC value for NGLDM_Busyness is 0.75. The cut-off was calculated to be 0.309.

Based on ROC analysis of textural parameters, textural parameters can identify the nonresponders group of patients better than the SUV-based measurements. This could be demonstrated by their respective AUC values. For example, $SUV_{max}$ has an AUC of 0.258.

It allowed the identification of the nonresponders with a maximum sensitivity of 43% and 14% specificity. The threshold used was 5.4. On the other hand, the textural parameter GLCM_homogeneity has an AUC of 0.72. It allowed the identification of the nonresponders with a sensitivity of 80% and specificity of 60%.

In the case of SUVmean, it has an AUC of 0.22. It allowed the identification of the nonresponders with a maximum sensitivity of 50% and 6% specificity. The threshold used was 3.5. On the other hand, the textural parameter GLRLM_LRE has an AUC of 0.702. It allowed the identification of the nonresponders with a sensitivity of 73% and specificity of 66%.

**Table 2: The cutoffs for GLZLM and gray level run-length matrix parameters**

| Parameter | Cut off |
|---|---|
| GLZLM_LZE | 44.9 |
| GLZLM_LGZE | 0.006 |
| GLZLM_SZLGE | 0.0032 |
| GLZLM_LZLGE | 0.185 |
| GLRLM_LRE | 1.31 |
| GLRLM_LGRE | 0.0058 |
| GLRLM_SRLGE | 0.005496 |
| GLRLM_LRLGE | 0.00727 |

LZE: Long zone emphasis, LGZE: Low gray level zone emphasis, SZLGE: Short zone low gray level emphasis, LZLGE: Long zone low gray level emphasis, LRE: Long run emphasis, LGRE: Low gray level run emphasis, SRLGE: Short run low gray level emphasis, LRLGE: Long run low gray level emphasis, GLZLM: Gray level zone length matrix

**Table 3: The area under the curve values for GLZLM and gray level run-length matrix parameters**

| Parameter | AUC values |
|---|---|
| GLZLM_LZE | 0.738 |
| GLZLM_LGZE | 0.742 |
| GLZLM_SZLGE | 0.720 |
| GLZLM_LZLGE | 0.773 |
| GLRLM_LRE | 0.702 |
| GLRLM_LGRE | 0.773 |
| GLRLM_SRLGE | 0.782 |
| GLRLM_LRLGE | 0.764 |

LZE: Long zone emphasis, LGZE: Low gray level zone emphasis, SZLGE: Short zone low gray level emphasis, LZLGE: Long zone low gray level emphasis, LRE: Long run emphasis, LGRE: Low gray level run emphasis, SRLGE: Short run low gray level emphasis, LRLGE: Long run low gray level emphasis, AUC: Area under the curve, GLZLM: Gray level zone length matrix

## Discussion

Currently increased interest is noted in the use of image-derived textural analysis parameters for quantification of intra-tumor heterogeneity. In this study, we assessed the potential role of textural indices in predicting the response of patients with esophageal cancer undergoing concomitant chemoradiotherapy. An established method to predict response after neoadjuvant chemoradiotherapy in esophageal cancer patients has not yet been defined. Assessment of tumor response to therapy plays a central role in patient clinical management. Accurate response prediction will lead to omitting surgical treatment in complete responders or avoiding chemoradiotherapy in nonresponders. At

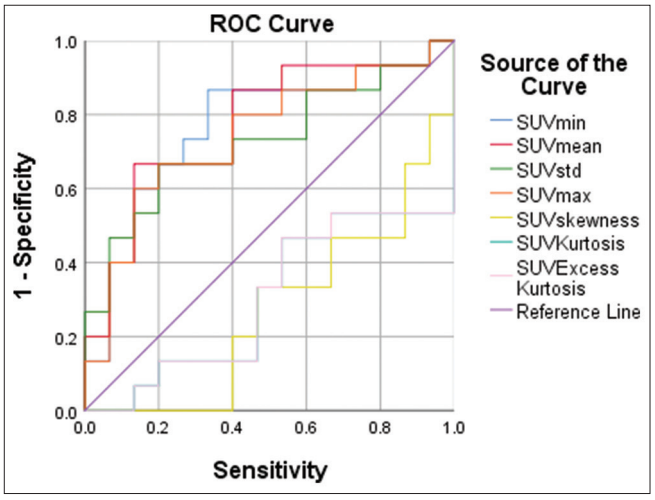


**Figure 1: ROC curves of SUV-related parameters and first-order parameters. ROC: Receiver operating characteristic, SUV: Standardized uptake value**

present, the response is mainly evaluated by measuring the size of the anatomical tumor and classifying the tumor shrinkage according to standard criteria. Since metabolic changes often occur before morphological changes, metabolic imaging seems to be a valuable tool for monitoring various treatments. $^{18}$F-FDG PET/CT has shown promising results in assessing response to therapy and prognosis. In Esophageal cancer, quantitative changes in FDG uptake 2 weeks after startup therapy have shown to correlate well with subsequent tumor shrinkage and patient survival.

Hautzel and Müller-Gärtner showed that even lower irradiation can increase tumor absorption and inflammatory changes can contribute to this increase; yielding inaccurate information about treatment response.[21] Within the same context, induced ulceration may also impair response assessment using PET.[22]

On the other hand, predicting the response prior to the start of treatment can be of great interest for optimal patient management. With similar endpoints, few authors have studied the predictive value of FDG uptake for therapy response.

Rizk *et al*. reported an SUV in excess of 4.5 as a reliable predictor of pathological response[23] whereas Javeri *et al*. demonstrated in a larger group of patients at the end of a higher response rate obtained after combined chemoradiotherapy in patients who have an initial SUV higher than 10.[24]

Some studies have already focused on the relationship between image analysis and tumor biology. Gillies *et al*. suggested that imaging can characterize longitudinal spatial variations of the tumor phenotype and its micro-environment so that the system dynamics over time can be quantitatively captured.[25] Segal *et al*. showed that contrast-enhanced CT image characteristics correlate with most of the liver's global gene expression profiles revealing cell proliferation, liver synthetic function, and patient prognosis.[26] Within the same context, Diehn *et al*. mapped neuroimaging parameters with gene expression patterns in glioblastoma,[27] whereas Strauss *et al*. combined dynamic pet kinetic parameters with gene array techniques.[28] Eary *et al*. previously demonstrated that a globally assessed FDG distribution heterogeneity in sarcoma is a potential prognostic factor.[29]

## Standardized uptake value-related parameters and first-order parameters

In this study, ROC analysis was performed on SUV-related parameters and first-order textural parameters [Figure 1]. The value of $SUV_{max}$, other SUV-based parameters, and first-order textural parameters was limited, possibly because it is extracted from a single voxel and does not characterize the total F18 FDG uptake. The AUC values for these parameters were not more than 0.7.

## Second order parameters

In this work, the second order and the higher order parameters were significant in predicting the tumor response in carcinoma esophagus patients.

The second-order parameters provide information on the size of homogeneous areas. 4 parameters from GLZLM [Figure 2] and GLRLM [Figure 3] matrix were significant.

## GLZLM matrix

The GLZLM matrix is a second-order parameter. It quantifies gray level zones in an image. A gray-level zone is defined as the number of connected voxels that share the same gray-level intensity. These are the regional heterogeneity parameters. In our study, four parameters from the GLZLM_matrix were significant in predicting the response in carcinoma esophagus patients posttreatment. They were GLZLM_LZE, GLZLM_LGZE, GLZLM_SZLGE, GLZLM_LZLGE. AUC value was more than 0.7 for these parameters.

GLZLM_LZE: Is a measure of the distribution of large area size zones, with a greater value indicative of more larger size zones and more coarse textures.

GLZLM_LGZE: Measures the distribution of lower gray-level size zones, with a higher value indicating a greater proportion of lower gray-level values and size zones in the image.

GLZLM_SZLGE: Measures the proportion in the image of the joint distribution of smaller size zones with lower gray-level values.

GLZLM_LZLGE: Measures the proportion in the image of the joint distribution of larger size zones with lower gray-level values.

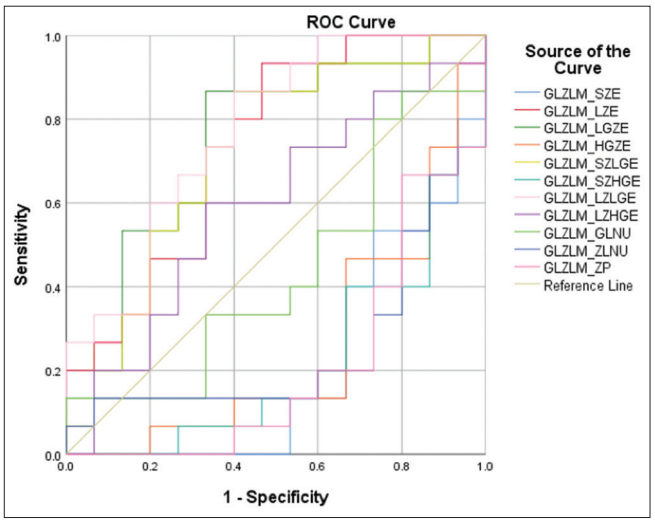


**Figure 2: ROC curves of textural parameters of GLZLM matrix. ROC: Receiver operating characteristics**

These parameters quantify the coarseness of the image. They map the areas with low gray levels and assess their sizes and arrangements. The response of the tumor to the chemotherapy depends on these gray levels and their arrangements. More the variation in the texture and gray level of the tumor, the more aggressive would be the tumor.

## GLRLM matrix

The GLRLM matrix is a second-order parameter. It quantifies gray level runs, which are defined as the length in number of pixels, of consecutive pixels that have the same gray level value. These are the regional heterogeneity parameters. In our study, four parameters from the GLRLM matrix were significant in predicting the response in carcinoma esophagus patients posttreatment. They were GLRLM_LRE, GLRLM_LGRE, GLRLM_SRLGE, GLRLM_LRLGE. AUC value was more than 0.7 for these parameters.

GLRLM_LRE: Is a measure of the distribution of long run lengths, with a greater value indicative of longer run lengths and more coarse structural textures.

GLRLM_LGRE: Measures the distribution of lower gray-level size runs, with a higher value indicating a greater proportion of lower gray-level values and size, runs in the image.

GLRLM_SRLGE: Measures the joint distribution of shorter run lengths with lower gray-level values.

GLRLM_LRLGE: Measures the distribution of low gray-level values, with a higher value indicating a greater concentration of low gray-level values in the image.

Similar to the GLZLM matrix, the parameters from the GLRLM matrix quantify the heterogeneity of the tumor. More the heterogeneity, the more aggressive will be the tumor.

## Higher-order parameters

Higher-order parameters provide information about spatial interrelationships and frequency distributions of the gray levels.

## Gray level co-occurrence matrix

The GLCM takes into account the arrangements of pairs of voxels to calculate textural indices [Figure 4].

GLCM_Contrast is a measure of the local intensity variation. A larger value correlates with a greater disparity in intensity values among neighboring voxels.

GLCM_Correlation is a value between 0 (uncorrelated) and 1 (perfectly correlated) showing the linear dependency of gray level values to their respective voxels in the GLCM.

GLCM_Homogeneity is the homogeneity of gray level voxel pairs.

Among the higher-order parameters, GLCM homogeneity was significant in predicting the tumor response. The AUC value for GLCM homogeneity is 0.72. It represents the homogeneity of the tumor.

## NGLDM matrix

The NGLDM matrix quantifies the difference between a gray value and the average gray value of its neighbors [Figure 5].

NGLDM_Coarseness is a measure of the average difference between the center voxel and its neighborhood and is an indication of the spatial rate of change. A higher value indicates a lower spatial change rate and a locally more uniform texture.

NGLDM_Contrast is a measure of the spatial intensity change but is also dependent on the overall gray level dynamic range. Contrast is high when both the dynamic range and the spatial change rate are high, i.e., an image

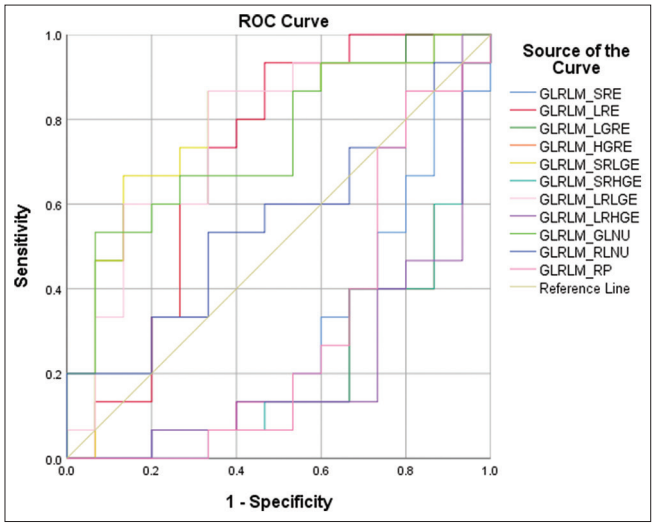


**Figure 3: ROC curves of textural parameters of GLRLM matrix. ROC: Receiver operating characteristic**

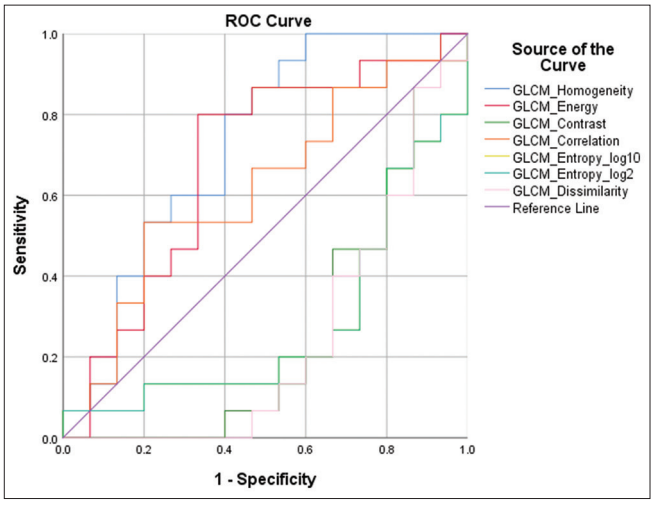


**Figure 4: ROC curves of textural parameters of GLCM matrix. ROC: Receiver operating characteristic. GLCM: Gray level co-occurrence matrix**

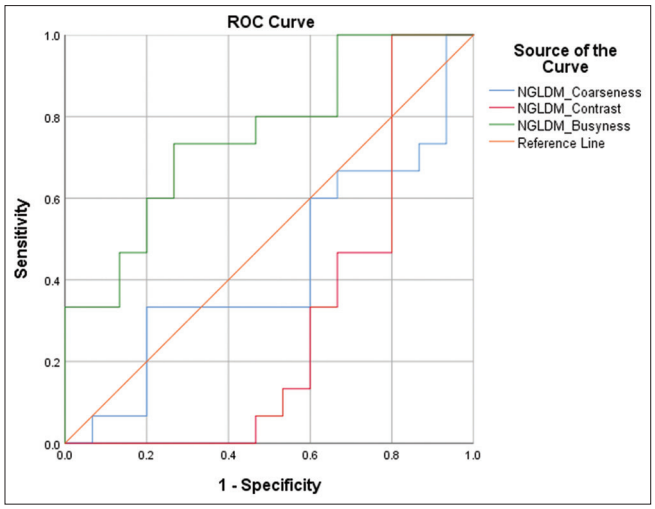


**Figure 5: ROC curves of textural parameters of NGLDM matrix. ROC: Receiver operating characteristic**

with a large range of gray levels, with large changes between voxels and their neighborhood.

NGLDM_Busyness is a measure of the change from a pixel to its neighbor. A high value for busyness indicates a "busy" image, with rapid changes of intensity between pixels and their neighborhood.

In this study, NGLDM_Busyness is significant in predicting the response. The AUC value calculated for NGLDM_Busyness is 0.75. The cutoff was calculated to be 0.309.

## Conclusions

In our study, the value of textual feature analysis was explored in the pretreatment FDG PET scans for predicting response to combined chemoradiotherapy. Global tumor metabolic features based on the intensity histogram were computed directly on the original image. Three orders of features were derived from the textual analysis: First order, second order, and higher order.

These features evaluated in this study highlighted tumor heterogeneity at a local and regional level characterized in several ways depending on the type of matrix used and the kind of feature computed on the matrix.

A single feature cannot be directly linked to a specific biological process. One could assume that a combination of textual parameters may be closely related to underlying physiological processes such as vascularization, perfusion, tumor aggressiveness, or hypoxia.[30,31] Therefore, textural features could be correlated to physiological processes related to response to combined radiochemotherapy.

For example, one could reasonably expect that the tumor exhibiting heterogeneous verses with a homogeneous FDG uptake may respond less favorably to a uniformly distributed radiotherapy dose. We could also hypothesize that underlying neoangiogenesis contributes to tumor FDG uptake heterogeneity. It is now widely accepted that neoangiogenesis is associated with the reduced effectiveness of conventional chemotherapy. However, the exact relationship between the proposed image-derived indices and the underlying tumor biology can be established only on carefully designed prospective studies.

### Limitations

The limitation of the present study is that it is retrospective, considering a relatively small patient cohort. Therefore, the potential of new image-derived indices characterizing tumor FDG distribution for the prediction of response to therapy studies in this work needs to be validated by a prospective study on a larger patient cohort.

### Key points question

Is there a role of textural and radiomic parameters derived from baseline $^{18}$F-FDG PET/CT in response prediction in esophageal carcinoma patients?

### Pertinent findings

A retrospective observational study of 30 primary carcinoma esophagus followed up postchemoradiotherapy and were divided into progression group and nonprogression group. Ten textural analysis parameters turned out to be significant in the prediction of disease progression.

### Implications for patient care

Textural analysis parameters could provide prognostic information in carcinoma esophagus patients.

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### Conflicts of interest

There are no conflicts of interest.

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