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Temporal Analysis of Intratumoral Metabolic Heterogeneity Characterized by Texture Features for Cervical Cancer

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Abstract

Purpose—Aim of this pilot study was to explore temporal behaviors of intratumoral [¹⁸F] fluorodeoxyglucose (FDG) accumulation heterogeneity at a regional scale in patients with cervical cancer undergoing chemoradiotherapy.

Methods—Twenty patients with International Federation of Gynecology and Obstetrics stages Ib1 to IVa cervical cancer treated with combined chemoradiotherapy were included in this study. Patients underwent FDG-PET/CT before treatment, at weeks 2 and 4 during treatment, and at 12 weeks after completion of therapy. Patients were classified based on response to therapy including complete metabolic responders (CMR), partial metabolic responders (PMR), and patients with residual disease who developed new disease (NEW). Based on the presence of residual primary tumor following therapy, patients were divided into 2 groups, CMR and PMR/NEW. Temporal profiles of intratumoral FDG heterogeneity characterized by texture features at a regional scale were assessed and compared with those of the standardized uptake values (SUV) indices (SUV_{max} and SUV_{mean}) within the context of differentiating response groups.

Results—Texture features at a regional scale with emphasis on characterizing contiguous regions of high uptake within tumors varied significantly over time ($P_s < 0.001$) and further exhibited negative temporal trends in patients of CMR, while features describing contiguous regions of low uptake along with those measuring the non-uniformity of contiguous isointense regions within tumors exhibited significant temporal changes in patients of PMR/NEW ($P_s < 0.03$) but showed no persistent trends against time. Both SUV indices showed significant changes during the course of disease for either patient group ($P_s < 0.001$ for SUV_{max} and SUV_{mean} in patients of CMR; $P = 0.0109$ and 0.0136 respectively for SUV_{max} and SUV_{mean} in patients of PMR/NEW) and, moreover, demonstrated a constant descending temporal tendency in patients of CMR while a temporal profile characterized with a declining tendency up to the fourth week into treatment followed afterwards by a rising inclination in patients of PMR/NEW.

Conclusions—Results suggest that temporal evolutions of intratumoral FDG distribution heterogeneity characterized at a regional scale using image based texture features may provide an adjunctive or alternative option for understanding tumor response to chemoradiotherapy treatment and interpreting FDG accumulation dynamics in patients with malignant cervical tumors during the course of disease.

Keywords

Cervix; intratumoral heterogeneity; FDG-PET; texture analysis; temporal trend

Introduction

Cervical cancer is one of the most common types of female malignancies. Early-stage patients as graded in accordance with the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system as Ib and IIa can be cured on an average rate of 80%; nevertheless 30–50% patients with FIGO stages IIb to IVa at presentation experience treatment failure, indicating high mortality occurring in locally advanced cervical carcinoma [1,2]. Heterogeneity is a recognized characteristic of malignant cervical tumors. It emerges across multiple levels from genetic to macroscopic and has been described with respect to factors that influence resistance to therapy such as histological features including cellular proliferation, necrosis, non-cellular accumulations, physiologic features comprising degrees of vascularity, gene expression, energy metabolism, and oxygenation amongst others [3–11]. All of these aspects of intratumoral heterogeneity have implications for tumor biologic behaviors in patients, which may manifest as prognosis and treatment-response variability [12]. It is, therefore, of great importance to assess intratumoral heterogeneity before, during, and after the course of treatment, potentially allowing for tailoring personalized patient management and hence improvement of treatment outcome.

In addition to being widely employed in tumor diagnosis and staging along with monitoring therapy response, positron emission tomography (PET) imaging with [^{18}F]fluoro-2-deoxy-d-glucose (FDG) with providing added values on functional variation within tumors, has also been under intense investigation for use in characterizing intratumoral heterogeneity towards prediction of treatment outcome. Predominant indices derived from FDG-PET used in studies of this type consist of the mean and the maximum standardized uptake values (SUV) within the delineated tumors [13–17]. However, simple SUV measurements that can be affected by several factors such as magnitude of FDG dose and the length of the FDG uptake period after administration may not sufficiently be indicative of tumor behavior [18]. In addition, other tumor characteristics such as perfusion, hypoxia, aggressiveness, and proliferation rate can affect the degree and also the heterogeneity of tumor FDG uptake. Given these inherent vulnerabilities of SUV measurements, alternative strategies have been sought after for intratumoral heterogeneity characterization. Given that FDG activity distribution is reflective of underlying tumor biological heterogeneity, characterizations of variations in FDG distribution have been lately advocated using various image characteristics, especially with texture features. Appraisal of spatial heterogeneity based on metrics deviation from an idealized ellipsoid structure on the pre-treatment FDG-PET scans of sarcoma patients was shown to be significantly associated with survival [12]. Texture features at multiple scales ranging from local and regional to global were applied on baseline FDG-PET scans of patients with esophageal carcinoma to characterize FDG uptake heterogeneity [19]. In patients with cervical cancer, promising results with respect to characterizing tumor uptake heterogeneity for prediction of treatment outcome were shown using texture features based on co-occurrence matrix extracted from baseline FDG-PET [18]. However, temporal behaviors of tumor heterogeneity characterized with texture features during the course of disease have never been assessed.

The hypothesis of this pilot study was that FDG uptake heterogeneity characterized by textural features evolves during the course of therapy. The values of each feature parameter extracted from FDG-PET scans of patients with cervical carcinoma acquired before treatment, after 2 and 4 weeks of treatment, and at 12 weeks after the completion of

treatment are not static. We believe that the changes in tumor heterogeneity over time during therapy may be a better predictor of outcome in comparison with a single measurement prior to therapy.

Patients and Methods

Patient Description

Twenty patients with a clinical diagnosis of cervical cancer treated with exclusive chemoradiotherapy between 2008 and 2010 were included in this study. The study was approved by the Washington University Human Research Protection Office (HRPO 08-0804). Written informed consent was obtained from all patients. Table 1 summarizes the demographics of all patients investigated. The mean age at the time of diagnosis was 47.8 ± 11.5 year (median, 44 year; range, 25–74 year). Patients were staged clinically according to the FIGO staging system with the distribution as follows: 1 patient with stage Ib1, 1 with stage Ib2, 1 with stage IIa, 7 with stage IIb, 1 with stage IIIa, 8 with stage IIIb, and 1 patient with stage IVa. Histopathological examinations of all the tumors showed squamous cell carcinoma in 16, adenocarcinoma in 3 and clear cell carcinoma in 1. In addition, 13 patients had lymph node metastasis at diagnosis. All patients underwent a pre-treatment clinical whole-body FDG-PET/CT. All patients were treated with concurrent radiotherapy and cisplatin chemotherapy. FDG-PET/CT imaging was used to define the extent of the metabolic activity of the lesion for radiation treatment planning. The radiation was based on standard treatment practices of external IMRT irradiation and high-dose-rate (HDR) intracavitary brachytherapy for cervical cancer at our institution [20]. Chemotherapy consisted of weekly administration of cisplatin with a dose of 40 mg/m^2 for six cycles. During treatment, two research FDG-PET/CT studies of the pelvis were performed respectively at weeks 2 and 4 during therapy. A post-treatment whole-body FDG-PET/CT was used for assessing treatment response and detecting any residual or progressive disease at week 12 after completion of therapy [13,21]. Patients were subsequently classified as complete metabolic responders (CMR), partial metabolic responders (PMR), and new disease (NEW) for patients with residual disease at the primary site that also developed new disease based on the post-treatment PET scans. At the end of therapy, there was no residual primary tumor in patients with CMR, but residual primary tumor was present in patients with PMR and NEW, thus, we divided our patients into 2 groups, CMR and PMR/NEW.

PET/CT Protocol

FDG-PET/CT was performed in all patients with a hybrid PET/CT scanner (Siemens Biograph 40 TruePoint). Patients were fasted for a minimum of 4 hours before injection of FDG. The administered dose of FDG ranged from 10 mCi to 15 mCi (median, 14.3 mCi), depending on patient weight, and the uptake period after injection was on average 1 hour. The uptake time of PET studies during treatment was matched to that for the pretreatment study. CT was conducted in the craniocaudal direction from the base of skull through the proximal thighs at 120 kVp and 111 effective mAs with 5 mm slice thickness. PET was performed within the same anatomic extent with imaging times of 2 to 4 min/bed position. Serum glucose levels ranged from 86 to 152 (median, 103). Urinary tract activity was minimized by placing a Foley catheter before injection of FDG and by administration of furosemide and i.v. fluids after injection of FDG. The PET images were reconstructed according to the manufacturer guidelines.

Tumor Extraction and Image Preprocessing

For each patient, PET/CT images were reviewed for abnormal FDG uptake at the primary tumor site, lymph node regions, and distant sites. The primary tumor was identified and then delineated using the 40% thresholding method with the threshold determined by optimized

correlation with the CT dimensions of the primary tumor [22]. In order to avoid misinterpretation of different intensity values and to obtain meaningful statistical comparisons during texture analysis across patients and over time, voxel intensity values (I) within the delineated tumor volume underwent a linear rediscrretization process:

$$\hat{I}(x) = \left\lceil 2^N \times \frac{I(x) - \min(I(x))}{\max(I(x)) - \min(I(x)) + 1} \right\rceil, \quad (1)$$

where $\hat{I}$ denotes the resultant intensity values inside the delineated tumors and 2^N represents the number of rediscrrete levels with N equal to 8 in the current study. In this study, only the primary tumors were considered for analysis, as texture analysis cannot be reliably performed on small lesions such as nodal and distant metastases due to the very limited number of voxels involved in these structures.

Texture Analysis

Two types of volumetric texture encoding methods with emphasis on characterizing regional heterogeneity, as listed in the left column of Table 1, were employed in this study and the following provides a brief description of each method.

Gray-Level Run Length Encoding Method

The gray-level run length encoding method is based on computing the number of gray-level runs of various lengths [23]. A gray-level run is a set of consecutive and collinear voxels possessing the same gray-level value, and the length of a run is the number of the voxel in the run. A Gray-Level Run-Length Matrix $GLRLM(\theta)$ is defined as follows: each element $GLRLM(i, j/\theta)$ represents the number of runs with voxels possessing gray-level intensity equal to i and length of run equal to j along a specific orientation θ . The size of the matrix $GLRLM(\theta)$ for a given delineated tumor is N by K with N identical to the maximum gray level inside the tumor and K equal to the longest run length possible within the tumor. Orientation θ in 3D contains 13 different angular directions, and therefore 13 gray-level run-length matrices were generated for a given tumor with each matrix computed for one direction. A total of 11 texture features, as listed in the right column of the second row in Table 2, were extracted from each of these 13 matrices and for each feature the average value of the 13 directions was taken.

Gray-Level Zone Size Encoding Method

Instead of counting the number of voxels with the same gray-level intensity along various orientations as in the grey-level run length encoding method, the gray-level zone length encoding method takes account of the number of gray-level zones of various sizes [24]. A gray-level zone is a contiguous region with voxels having the same intensity value, and the size of a zone is the number of the enclosed voxel. A gray-level zone size matrix $GLZSM$ is formed with each entry $GLZSM(i, j)$ denoting the number of zones of gray-level intensity equal to i and of size equal to j . The number of rows of the resultant matrix for a given delineated tumor is equal to the maximum gray level inside the tumor and the number of column is identical to the size of the largest zone possible within the tumor. Once the matrix was obtained, the 11 texture features as listed in the second column of the last row in Table 2 were computed for each delineated tumor.

Standardized Uptake Value (SUV) Analysis

In view of their widespread use in characterizing FDG uptakes for therapy response monitoring together with the prevailing role they have been playing in the context of FDG-PET-based therapy-response prediction investigations, standardized uptake value (SUV)

indices including maximum SUV (SUV_{max}) and mean SUV (SUV_{mean}) were measured for all the identified tumor volumes, with each of these SUV normalized by the decay-corrected injected activity together with the patient's body weight at the date of PET exam, as most commonly used in clinical practice. Temporal evolution of the SUV_{max} and SUV_{mean} during the course of disease was assessed for each patient group. In addition, the ability of the SUV_{max} and SUV_{mean} at baseline to differentiate patients with regard to treatment outcome was also explored and further compared with that of the texture features being investigated.

Statistical Analysis

The difference of each feature extracted from PET scans at different time points along the course of disease was interrogated with the Friedman's ANOVA test [25]. The capacity of each feature at baseline to distinguish patients with respect to treatment outcome was investigated with using the Mann-Whitney test [26]. *P* values of less than 0.05 were considered statistically significant. Trend analyses for features exhibiting significant temporal changes during the course of disease were carried out using first order linear regression.

Results

Patient characteristics, including age, FIGO stage, histology, lymph node status at diagnosis, and response on the 3-month posttherapy PET are listed in Table 2. The mean tumor volume at diagnosis was 62.75cm^3 (median, 36.64cm^3 ; range, $10.38\text{--}248.33\text{cm}^3$). At 3 months posttherapy, 15 patients were considered to have a CMR, 3 patients had a PMR, and 2 patients had new (NEW) disease.

For each patient, we performed texture analysis for the primary tumors as delineated on PET scans at each time point to examine how the extracted texture features evolved during the course of disease. Median values for each feature derived from *GLRLM* are compared in Table 3 for the two patient response groups (i.e., CMR and PMR/NEW). Comparison of texture features based upon *GLZLM* between the two patient response groups is presented in Table 4. Note that for the CMR group, no abnormal FDG uptake in the region of the original tumor renders the corresponding entries in Tables 3 and 4 as voids. For features derived from *GLRLM*, the Friedman's ANOVA test revealed that HGRE, SRHGE, and LRHGE demonstrated statistically significant temporal changes during the course of disease in patients with CMR (P s < 0.001), while LGRE, SRLGE, LRLGE, GLNU, and RLNU exhibited significant temporal changes in patients with PMR/NEW during the course of disease (P = 0.0189, 0.0189, 0.0189, 0.0293, and 0.0070, respectively). Results of the Friedman's ANOVA test on features based upon *GLZLM* show that SZE, HGZE, SZHGE, LZHGE and ZP manifested statistically significant temporal changes during the course of disease in patient with CMR (P = 0.0013, 0.0004, 0.0004, 0.0004, and 0.0128, respectively) whereas LGZE, SZLGE, LZLGE, GLNU, and ZSNU exhibited significant temporal changes in patients of PMR/NEW during the course of disease (P = 0.0189, 0.0189, 0.0189, 0.0293, and 0.0136, respectively). As for the two SUV indices examined, their median values at different time points during the course of disease are summarized in Table 5 for the two response groups. Statistical interrogation with the Friedman's ANOVA test evinced significant temporal changes of both indices in either response group during the course of disease (P s < 0.001 for SUV_{max} and SUV_{mean} in patients of CMR; P = 0.0109 and 0.0136 respectively for SUV_{max} and SUV_{mean} in patients of PMR/NEW).

Among those showing significant changes during the course of disease, six texture features (i.e., HGRE, SRHGE, and LRHGE derived from *GLRLM* and HGZE, SZHGE and LZHGE derived from *GLZLM*) were observed with an overall temporal trend in patients with CMR. The temporal characteristics of the three *GLRLM*-based features and the three *GLZLM*-

based features in patients with CMR are presented in Figures 1 and 2. Results from first order linear regressions show that all the six features exhibited high negative correlations with follow-up time (R -squared = 0.945, 0.946, 0.943, 0.999, 0.968, and 0.893 for HGRE, SRHGE, LRHGE, HGZE, SZHGE, and LZHGE, respectively). No persistent temporal trends were observed from those texture features that exhibited significant temporal changes in the PMR/NEW patient group.

Temporal characteristics of SUV_{max} and SUV_{mean} in patients of CMR are presented in Figure 3. It can be seen that both indices were highly correlated with follow-up time (R -squared = 0.913 and 0.999 for SUV_{max} and SUV_{mean} , respectively) and demonstrated an overall descending tendency over the course of disease for this particular group of patients. Temporal characteristics of the SUV indices for the patient group with PMR/NEW are presented in Figure 4. Although no persistent overall temporal trends were observed from either index over the entire course of disease, both indices did manifest high negative correlations with follow-up time through to the fourth week after treatment initiation (R -squared = 0.762 and 0.817 for SUV_{max} and SUV_{mean} , respectively).

Distributions of various features extracted at baseline, including SUV_{max} and SUV_{mean} along with two example metrics taken for each of the two texture encoding categories (LGRE and HGRE for *GLRLM*-based scheme; LGZE and HGZE for *GLZLM*-based scheme), are compared for the response groups of CMR and PMR/NEW in Figure 5. Results of the Mann-Whitney test show that at baseline neither the examined SUV indices nor the texture features being investigated was capable of differentiating the two response groups at the statistical significance level of 0.05 (P = 0.1513 and 0.2870 for SUV_{max} and SUV_{mean} , respectively; P s range from 0.0577 to 0.287 for *GLRLM*-based texture features; P s range from 0.0577 to 0.4313 for *GLZLM*-based texture features).

Discussion

Assessment of intratumoral metabolic heterogeneity as manifested on FDG-PET may be of importance in both treatment outcome prediction and biologically adapted strategies. Although tumor heterogeneity in FDG distribution has been demonstrated previously, there have been very few reports with regard to the temporal characteristics of tumor FDG uptake heterogeneity changes during the course of disease. In the current work, intratumoral heterogeneity of FDG uptake depicted by texture features at a regional scale was evaluated at four different time points including baseline, 2nd week and 4th week during therapy, and 12th week after the completion of treatment to explore the temporal behaviors of tumor metabolic heterogeneity for patients with cervical cancer who underwent chemoradiotherapy.

In the cohort of 15 cervical cancer patients with CMR, six texture features, namely HGRE, SRHGE, and LRHGE derived from *GLRLM* and HGZE, SZHGE and LZHGE derived from *GLZLM*, demonstrated statistically significant differences at the time points examined and were further observed with a negative temporal trend when applying first order linear regression analysis of the mean score of each of these six features against time. For the three *GLRLM*-based features, HGRE underscores runs identified within a tumor that possesses high gray-level values, and the other two, i.e., SRHGE and LRHGE, depict high gray-level runs too but with emphasis respectively on runs of short length and long length. Similarly for the three *GLZLM*-based texture features, except gray-level zones instead of gray-level runs are employed in describing the contiguous regions of constant intensity appearing inside a tumor. Thus, it can be seen that all six texture features showing significant temporal changes in patients with CMR characterize, though through different aspects, the isointense continua of high activity inside a tumor. Negative temporal trends revealed using linear

regression analysis in the six features indicate that contiguous regions of constant high activity appearing in baseline tumors of patients with CMR might undergo either shrinking in size and/or diminishing intensity in response to chemoradiotherapy, and thereafter evolve into low-activity regions. This is also evidenced by the ascending temporal trends of texture features that describe low-intensity regions, such as LGRE, SRLGE, and LRLGE derived from *GLRLM* and LGZE, SZLGE, and LZLGE derived from *GLZLM*. For patients with PMR/NEW, there is also a certain number of texture features derived from one of the above texture encoding schemes showing significant statistical changes over the time points examined. These features are mainly those characterizing the contiguous regions with constant low gray-level values appearing within a tumor and those measuring the non-uniformity in either the sizes or the gray-level values of the contiguous regions with constant intensity inside a tumor. However, no persistent overall temporal trends were observed from them.

SUV indices including SUV_{max} and SUV_{mean} were also appraised for the studied patient population to examine how they evolved during the course of disease for each response group. In the cohort of patients with CMR, both SUV indices showed statistically significant differences among the time points examined and, moreover, evinced descending tendencies against time. As for the patient group with PMR/NEW, both indices exhibited significant changes during the course of disease too nevertheless instead of constant temporal tendencies as in patients of CMR the two indices demonstrated temporal profiles characterized with a declining tendency up to the fourth week into treatment followed afterwards by a rising inclination as seen in Figure 4. Considering SUV indices derived from FGD-PET as an indicator for tumor metabolism, the persistent descending temporal trends of both indices seen in CMRs may be an indication of the progressive eradication of lesion cells along the course of treatment consequent to the systemic suppression from chemotherapy in conjunction with the simultaneous targeted attack from radiations; and on the other hand for the patient group with response of PMR/NEW, the declining tendency of either index demonstrated during the early stage of treatment may reflect the successive elimination of the susceptible tumor cells as the cocurrent chemoradiotherapy started and proceeded while the rebound of either index at the post-treatment PET exam may correspond to, but not necessarily limited to, the recovery along with the repopulation of those tumor cells that were resistant to the administered treatment.

In contrast to SUV indices exhibiting parallel temporal trends in both of the response groups during the early period of therapy (up to the fourth week after treatment initiation), the six texture features mentioned above that characterize the isointense continua of high activity inside a tumor showed significant temporal changes and demonstrated persistent temporal trends only in the response group of CMR over that specific period of time during therapy. It thus suggests, at least for the currently studied patient population, that temporal behaviors in the early phase of treatment for texture features with emphasis on characterizing the isointense continua of high intratumoral activity may be able to offer better predictive value on the outcome of therapeutic intervention than those of SUV indices. As for capabilities of differentiating response groups before treatment initiation, the Mann-Whitney examinations showed that both the studied SUV indices and the texture features being investigated failed to distinguish the two response groups at baseline, complying with our initial hypothesis that the changes in tumor heterogeneity over time during therapy may serve as a better predictor of response in comparison with a single measurement prior to treatment.

Despite a great number of well-behaved segmentation algorithms being proposed for automatic tumor delineation [27–30], a hard thresholding scheme with a cutoff value of 40% of the maximum activity was employed in the current study to define the lesion volume for the identified tumors by radiation oncologists on FDG-PET scans. This method has been

previously demonstrated to result in valid segmentations for cervical tumors with shown optimized correlations with the CT dimensions of the primary tumor along with the conformity of the resultant volumes to those revealed in surgical series [22, 31]. Given that radiation therapy treatments which patients of the current study underwent were planned with volumes derived through this fixed thresholding method as the targets, texture analysis was therefore only limited to the threshold defined volume for each FDG-PET scan. Considering the inability per se of fixed thresholding methods in handling FDG distribution heterogeneity exhibited in PET images, one may argue that adoption of such a strategy for texture analysis would give rise to the resulting texture parameters inaccurately and/or imprecisely describing actual underlying FDG accumulation heterogeneity. With acceding to this viewpoint, we nonetheless deem such a strategy relevant in the context of therapy-response prediction with the line of reasoning that it was to the target volume that radiation therapy was intended to be delivered and evaluation of FDG accumulation heterogeneity within this volume along with its evolution during the course of disease would be more pertinent to the appraisal of the impact of prescribed treatments on the final outcome. In addition, for a given delineated lesion texture analysis was preformed with its belonging voxels undergoing an intensity rediscritization procedure first as described above. It has been previously shown by Tixier et al. [19] that for texture categories studied in the current work the number of rediscritization levels does not make statistically significant differences on resultant parameter values. Given that a rediscritization procedure very similar to the one employed in Tixier et al.'s study was adopted in the current study, the effect of the rediscritization procedure on the observed temporal evolution of texture heterogeneity parameters would be expected to be limited, if any.

It must be stressed that there are certain limitations in the present study. In particular, it should be acknowledged that the presented results were based on a small cohort of patients, thus necessitating further validations of the current findings on a larger patient population and even distribution of tumor histology. Moreover, the presented temporal trends of various features were assessed with patient data at a small number of time points, thus only providing coarse temporal dynamics on the behaviors of tumor metabolic heterogeneity during treatment. In addition, treatment responses on posttherapy PET were derived in a subjective manner by nuclear physicians.

Future studies on temporal behaviors of intratumoral metabolic heterogeneity could include assessing the prognostic significance of the identified tumor heterogeneity temporal trends, exploring temporal behaviors of tumor heterogeneity described with other image-derived indices, and investigating the underlying biological mechanism responsible for the observed temporal characteristics of intratumoral heterogeneity as manifested on FDG-PET. These endeavors may lead to the ability to predict which patients will respond to a given treatment and prospectively target patients with high heterogeneity tumors for more aggressive therapy.

Conclusion

The current study is the first to reveal the temporal profiles of intratumoral heterogeneity of FDG accumulation at regional scale in patients with cervical cancer undergoing chemoradiotherapy. The results suggest image derived regional texture features may provide further characterization of intratumoral FDG distribution, which may lead to a better understanding of FDG accumulation in malignant cervical tumors and how this relates to response to treatment.

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Figure 1. Temporal characteristics of HGRE (High Gray-level Runs Emphasis), SRHGE (Short Runs High Gray-level Emphasis), and LRHGE (Long Runs High Gray-level Emphasis) in patients of CMR. The first column represents respective line plots of HGRE, SRHGE, and LRHGE scores prior to treatment, at weeks 2 and 4, and after completion of treatment in patients with CMR; corresponding error bar plots for each feature are summarized in the second column with linear trends over the course of treatment fitted in red.

Figure 2. Temporal characteristics of HGZE (High Gray-level Zones Emphasis), SZHGE (Short Zones High Gray-level Emphasis), and LZHGE (Large Zones High Gray-level Emphasis) in patients of CMR. The first column represents respective line plots of HGZE, SZHGE, and LZHGE scores prior to treatment, at weeks 2 and 4, and after completion of treatment in patients of CMR; corresponding error bar plots for each feature are summarized in the second column with linear trends over the course of treatment fitted in red.

Figure 3. Temporal characteristics of SUV_{max} and SUV_{mean} in patients of CMR. The first column represents respective line plots of SUV_{max} and SUV_{mean} scores prior to treatment, at weeks 2 and 4, and after completion of treatment in patients with CMR; corresponding error bar plots for each SUV index are summarized in the second column with linear trends over the course of treatment fitted in red.

Figure 4. Temporal characteristics of SUV_{max} and SUV_{min} in patients of PMR/NEW. The first column represents respective line plots of SUV_{max} and SUV_{min} scores prior to treatment, at weeks 2 and 4, and after completion of treatment in patients with PMR/NEW; corresponding error bar plots for each SUV index are summarized in the second column with linear trends over the course of treatment fitted in red.

Figure 5.

Box-plot representation of features' values extracted at pre-treatment FDG-PET scans as a function of treatment outcome (CMR; PMR/NEW) for SUV_{max} ($P = 0.1513$) (1a), SUV_{min} ($P = 0.2870$) (1b), $LGRE$ (Low Gray-level Runs Emphasis) ($P = 0.0577$) (2a), $HGRE$ (High Gray-level Runs Emphasis) ($P = 0.1513$) (2b), $LGZE$ (Low Gray-level Zones Emphasis) ($P = 0.0577$) (3a), and $HGZE$ (High Gray-level Zones Emphasis) ($P = 0.1511$) (3b).

Table 1

Patient characteristics (n=20).

Age (years, mean±SD)	47.8±11.5
FIGO Stage	No. of patients
IB1	1
IB2	1
IIA	1
IIB	7
IIIA	1
IIIB	8
IVA	1
Tumor Cell Type	No. of Patients
Squamous	16
Adenocarcinoma	3
Clear cell	1
Lymph Node Status at Diagnosis	No. of Patients
None	7
Pelvic lymph node	9
Aortic lymph node	4
Treatment Response	No. of Patients
CMR	15
PMR	3
NEW	2

Table 2

Texture encoding schemes and associated features.

Encoding Scheme	Feature
Gray-level Run Length	Short Runs Emphasis (SRE)
	Long Runs Emphasis (LRE)
	Low Gray-level Runs Emphasis (LGRE)
	High Gray-level Runs Emphasis (HGRE)
	Short Runs Low Gray-level Emphasis (SRLGE)
	Short Runs High Gray-level Emphasis (SRHGE)
	Long Runs Low Gray-level Emphasis (LRLGE)
	Long Runs High Gray-level Emphasis (LRHGE)
	Gray-Level Non-Uniformity (GLNU)
	Run Length Non-Uniformity (RLNU)
	Run Percentage (RP)
Gray-level Zone Size	Short Zones Emphasis (SZE)
	Large Zones Emphasis (LZE)
	Low Gray-level Zones Emphasis (LGZE)
	High Gray-level Zones Emphasis (HGZE)
	Short Zones Low Gray-level Emphasis (SZLGE)
	Short Zones High Gray-level Emphasis (SZHGE)
	Large Zones Low Gray-level Emphasis (LZLGE)
	Large Zones High Gray-level Emphasis (LZHGE)
	Gray-Level Non-Uniformity (GLNU)
	Zone Size Non-Uniformity (ZSNU)
	Zone Percentage (ZP)

Table 3

Median values at different time points during the course of disease along with P-values resulting from Friedman's ANOVA test on temporal differences for *GLRLM*-based features compared between patients of CMR and PMR/NEW.

Feature	Pt Group	Pre-treatment	Week 2	Week 4	Post-treatment	P-value
SRE	CMR	0.994	0.994	0.995		0.2574
	PMR/NEW	0.993	0.992	0.993	0.995	0.1605
LRE	CMR	1.024	1.024	1.021		0.1092
	PMR/NEW	1.029	1.032	1.027	1.020	0.0772
LGRE	CMR	1.88E-3	1.88E-3	2.25E-3		0.7515
	PMR/NEW	6.57E-4	4.48E-4	1.32E-3	1.77E-3	0.0189
HGRE	CMR	2.67E+4	2.40E+4	1.82E+4		0.0004
	PMR/NEW	2.35E+4	1.92E+4	1.99E+4	2.21E+4	0.1176
SRLGE	CMR	1.88E-3	1.88E-3	2.25E-3		0.7515
	PMR/NEW	6.57E-4	4.47E-4	1.30E-3	1.77E-3	0.0189
SRHGE	CMR	2.65E+4	2.38E+4	1.81E+4		0.0004
	PMR/NEW	2.33E+4	1.91E+4	1.98E+4	2.20E+4	0.1176
LRLGE	CMR	1.88E-3	1.88E-3	2.25E-3		0.7515
	PMR/NEW	6.59E-4	4.51E-4	1.36E-3	1.77E-3	0.0189
LRHGE	CMR	2.75E+4	2.47E+4	1.85E+4		0.0004
	PMR/NEW	2.41E+4	1.97E+4	2.15E+4	2.25E+4	0.1176
GLNU	CMR	4.56	4.76	4.49		0.1353
	PMR/NEW	16.27	23.15	10.48	4.61	0.0293
RLNU	CMR	544.23	659.60	510.00		0.2231
	PMR/NEW	1797.14	2952.96	1226.32	598.83	0.0070
RP	CMR	0.992	0.992	0.993		0.1353
	PMR/NEW	0.991	0.990	0.991	0.993	0.1605

Table 4

Median values at different time points during the course of disease along with P-values resulting from Friedman's ANOVA test on temporal differences for *GLZSM*-based features compared between patients of CMR and PMR/NEW.

Feature	Pt Group	Pre-treatment	Week 2	Week 4	Post-treatment	P-value
SZE	CMR	0.980	0.976	0.981		0.0013
	PMR/NEW	0.975	0.972	0.970	0.983	0.3234
LZE	CMR	1.088	1.111	1.081		0.0617
	PMR/NEW	1.101	1.119	1.132	1.085	0.5642
LGZE	CMR	1.93E-3	1.94E-3	2.29E-3		0.5258
	PMR/NEW	6.72E-4	4.63E-4	1.37E-3	1.79E-3	0.0189
HGZE	CMR	2.66E+4	2.37E+4	1.81E+4		0.0004
	PMR/NEW	2.34E+4	1.92E+4	1.98E+4	2.21E+4	0.1176
SZLGE	CMR	1.93E-3	1.93E-3	2.28E-3		0.5258
	PMR/NEW	6.70E-4	4.60E-4	1.37E-3	1.78E-3	0.0189
SZHGE	CMR	2.59E+4	2.27E+4	1.78E+4		0.0004
	PMR/NEW	2.28E+4	1.87E+4	1.93E+4	2.18E+4	0.0772
LZLGE	CMR	1.93E-3	1.95E-3	2.29E-3		0.3951
	PMR/NEW	6.78E-4	4.77E-4	1.38E-3	1.79E-3	0.0189
LZHGE	CMR	2.96E+4	2.72E+4	1.95E+4		0.0004
	PMR/NEW	2.71E+4	2.11E+4	2.27E+4	2.33E+4	0.1447
GLNU	CMR	4.44	4.60	4.42		0.2231
	PMR/NEW	15.93	22.14	10.13	4.55	0.0293
ZSNU	CMR	509.07	610.43	484.68		0.2231
	PMR/NEW	1673.02	2634.21	1120.07	581.33	0.0136
ZP	CMR	0.973	0.966	0.974		0.0128
	PMR/NEW	0.968	0.963	0.959	0.975	0.5642

Median values at different time points during the course of disease along with P-values resulting from Friedman's ANOVA test on temporal differences for SUV indices compared between patients of CMR and PMR/NEW.

Table 5

Feature	Pt Group	Pre-treatment	Week 2	Week 4	Post-treatment	P-value
SUV _{max}	CMR	17.76	11.80	6.50		<0.0001
	PMR/NEW	22.34	12.71	9.89	10.01	0.0109
SUV _{mean}	CMR	10.97	6.98	3.58		<0.0001
	PMR/NEW	12.35	6.77	5.57	5.58	0.0136