18F-FDG PET/CT Metrics Are Correlated to the Pathological Response in Esophageal Cancer Patients Treated With Induction Chemotherapy Followed by Neoadjuvant Chemo-Radiotherapy

Nicola Simoni1*, Gabriella Rossi1, Giulio Benetti2, Michele Zuffante3, Renato Micera1, Michele Pavarana4, Stefania Guariglia2, Emanuele Zivelonghi2, Valentina Mengardo5, Jacopo Weindelmayer5, Simone Giacopuzzi5, Giovanni de Manzoni5, Carlo Cavedon2† and Renzo Mazzarotto1†

1 Department of Radiation Oncology, University of Verona Hospital Trust, Verona, Italy, 2 Department of Medical Physics, University of Verona Hospital Trust, Verona, Italy, 3 Department of Nuclear Medicine, University of Verona Hospital Trust, Verona, Italy, 4 Department of Oncology, University of Verona Hospital Trust, Verona, Italy, 5 Department of General and Upper G.I. Surgery, University of Verona Hospital Trust, Verona, Italy

Background and Objective: The aim of this study was to assess the ability of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) to provide functional information useful in predicting pathological response to an intensive neoadjuvant chemo-radiotherapy (nCRT) protocol for both esophageal squamous cell carcinoma (SCC) and adenocarcinoma (ADC) patients.

Material and Methods: Esophageal carcinoma (EC) patients, treated in our Center between 2014 and 2018, were retrospectively reviewed. The nCRT protocol schedule consisted of an induction phase of weekly administered docetaxel, cisplatin, and 5-fluorouracil (TCF) for 3 weeks, followed by a concomitant phase of weekly TCF for 5 weeks with concurrent radiotherapy (50–50.4 Gy in 25–28 fractions). Three 18F-FDG PET/CT scans were performed: before (PET1) and after (PET2) induction chemotherapy (IC), and prior to surgery (PET3). Correlation between PET parameters [maximum and mean standardized uptake value (SUVmax and SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)], radiomic features and tumor regression grade (TGR) was investigated.

Results: Fifty-four patients (35 ADC, 19 SCC; 48 cT3/4; 52 cN+) were eligible for the analysis. Pathological response to nCRT was classified as major (TRG1-2, 41/54, 75.9%) or non-response (TRG3-4, 13/54, 24.1%). A major response was statistically correlated with SCC subtype (p = 0.02) and smaller tumor length (p = 0.03). MTV and TLG measured prior to IC (PET1) were correlated to TRG1-2 response (p = 0.02 and p = 0.02, respectively). After IC (PET2), SUVmean and TLG correlated with major response (p = ...
Advantages and therefore should be used, and in "bad responders", in which CRT could be unnecessary or even detrimental due to possible adverse events. In this unfavorable group, surgery should not be further delayed or, alternatively, a change in systemic therapy should be adopted.

Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT), combining functional PET information with anatomical CT images, is routinely used for diagnosis, radiation treatment planning, and response evaluation in various gastrointestinal malignancies (10–13). In particular, the role of 18F-FDG PET/CT for baseline staging, restaging before surgery, and recurrence/distant metastases detection during follow-up in EC is well established (14, 15). Furthermore, it represents a useful, non-invasive tool to assess the response to neoadjuvant chemotherapy and chemoradiotherapy. Several traditional PET parameters, such as maximum and mean standardized uptake value (SUVmax and SUVmean), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), have demonstrated the ability to provide functional information useful in predicting pathological response to nCRT in EC patients (16–18). More recently, radiomic features are emerging as promising tools to stratify patients in "good" or "bad" responders. Some studies have investigated different first, second and high-order features, in EC patients, demonstrating that PET radiomic parameters can predict the response to nCRT (19–25). In addition, Chen et al. postulated that using a combination of traditional and radiomic PET parameters can provide a better stratification of patients into different prognostic subgroups (26).

Based on this background, we performed a novel analysis to evaluate the ability of 18F-FDG PET/CT metrics to predict histological tumor regression in patients with EC treated with an intensive nCRT protocol.

MATERIAL AND METHODS

Study Design

This is a single-center retrospective analysis of prospectively collected data, approved by the Institutional Review Board of our Hospital. Inclusion criteria were: a) patients treated with an intensive nCRT protocol for locally advanced resectable SCC or ADC of the esophagus or EGJ (Siewert I and II); b) availability of 18F-FDG PET/CT scans performed before and after induction chemotherapy, and before surgery; c) surgical resection; d) availability of resection specimens for pathological analysis. Exclusion criteria were: a) chemo-radiation therapy approaches other than the nCRT protocol (e.g., CROSS scheme); b) Siewert III type (candidates for peri-operative chemotherapy) and SC cervical tumors (treated with definitive CRT); c) upfront resectable (cT1 or cT2N0) or metastatic disease; d) non-execution of at least one of the three 18F-FDG PET/CT scans; e) no surgical resection; f) unavoidability of resection specimens.
**nCRT Protocol and Surgery**

The nCRT protocol consisted of a first phase of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TCF) for 3 weeks (days 1-22), followed by a second phase of concurrent chemotherapy (TCF) and radiotherapy for 5–6 weeks (days 29-63), as previously described (9). Radiation therapy (RT) was delivered with volumetric modulated arc therapy (VMAT), prescribing 50-50.4 Gy in 25-28 fractions. Figure 1 describes the nCRT protocol schedule. Sample VMAT plans are presented in Figures S1 and S2 (Supplementary Material).

After restaging, surgery with radical intent was performed 8 weeks after nCRT completion. Tri-incisional subtotal esophagectomy (McKeown procedure), partial esophagectomy (Ivor-Lewis procedure) or total gastrectomy with distal gastrectomy were performed based on tumor characteristics.

**18F-FDG PET/CT Method and Metrics**

Three 18F-FDG PET/CT scans were performed: the first (PET₁) at baseline, before the start of the induction phase and the second (PET₂) before the concomitant phase (week 4 of nCRT protocol). PET₁ and PET₂ were performed with the patient in RT treatment position, as simulation for volume delineation and treatment planning. The third 18F-FDG PET/CT (PET₃) was performed during restaging prior to surgery. Figure 2 shows 18F-FDG PET/CT relative time points.
were extracted from both PET1 and PET2. These parameters were: maximum and mean standardized uptake value (SUV\textsubscript{max} and SUV\textsubscript{mean}), metabolic tumor volume (MTV) and total lesion glycolysis (TLG), defined as the product of MTV and SUV\textsubscript{mean}.

**Radiomic Feature Extraction**

Radiomic features were extracted from PET\textsubscript{1} and PET\textsubscript{2} without applying any gray-level normalization nor voxel resampling. Indeed, according to the IBSI guidelines, calibrated gray levels should not be further standardized and the cubic voxel spacing was the same for the whole dataset. The DICOM files (volumes and RT Structures) were converted to the nii format through dcmrtstruct2nii (27). Since the gradient-based contouring algorithm, used to define the VOI, tends to exclude the most peripheral zones of the lesion, with the consequent inclusion of a limited number of voxels, the VOIs were dilated by 1 voxel (4 mm) in each direction. This was performed by using the built-in BinaryDilateImageFilter method of SimpleITK (v1.2.4) (28), implemented in Python (v3.7.6) under conda (v4.8.2) environment. In addition to increasing the number of voxels included in the lesion, dilating the VOI also allows the analysis to be performed on the low-enhancement region of the tumor, potentially adding information on how the uptake decreases on the lesion boundary. Radiomic features were extracted through pyradiomics (v3.0), an open-source python package (29). All the available features implemented in pyradiomics were extracted: Shape, First Order, GLCM, GLDM, GLRLM, GLSZM, and NGTDM [the meaning of these acronyms can be found in Zwanenburg et al. (30)]. For gray-level discretization, a fixed bin-count of 64 bins was adopted. A hundred and five features were extracted from both PET\textsubscript{1} and PET\textsubscript{2}.

**Pathological Analysis**

Post-surgical pathology examination provided macroscopic and microscopic description of the primary tumor and retrieved nodes. Post-resection staging was assessed following ypTNM categories according to the International Union against Cancer (UICC, 7\textsuperscript{th} edition, 2010). The degree of pathologic response was scored using the tumor regression grade (TRG) classification according to a modified Mandard score system: TRG\textsubscript{1} = no residual cancer cells; TRG\textsubscript{2} = residual cancer cells scattered through fibrosis; TRG\textsubscript{3} = increased residual cancer cells with predominant fibrosis and TRG\textsubscript{4} = including TRG\textsubscript{4}, residual cancer predominant fibrosis, and TRG\textsubscript{5}, no regressive changes within the tumor, of the Mandard score system (6). Patients were grouped according to the pathological response to nCRT in two classes of outcome. Major pathologic response was defined as TRG\textsubscript{1–2} while non-response as TRG\textsubscript{3–4}.

**Statistical Analysis**

The association between clinical/radiomic data and response to treatment was first analyzed by means of the chi-square test or Fisher’s exact test for categorical parameters, and Student’s T-test for continuous quantities (age and length of tumor). The association between PET/CT metabolic parameters and response to treatment (defined as a dichotomous variable) was assessed by means of logistic regression and ROC analysis. For logistic regression analysis, quantitative metabolic parameters were logarithmically transformed to meet the assumption of linearity on the logit scale, as in van Rossum et al. (18). Quantitative variables were described as median and interquartile range (IQR) or mean and standard deviation (SD), and categorical variables were summarized as counts and percentages. Statistical analysis was performed using R version 4.0.2 (https://www.R-project.org/) and MATLAB version R2019a (The Mathworks, Inc.; Natick, Massachusetts, USA). The significance level of the radiomic analysis was computed at p < 0.05/N, where N = 210 is the number of the tested features considering both PET\textsubscript{1} and PET\textsubscript{2} (Bonferroni correction). Two features were considered strongly correlated (i.e. redundant) when the pairwise Pearson’s correlation coefficient was higher than 0.90; in this case, the feature with the highest average correlation with all the other features was removed. The significance level for all tests was assumed at p < 0.05.

**RESULTS**

**Study Population**

Ninety-eight patients with biopsy-proven locally advanced esophageal squamous cell carcinoma (SCC) or adenocarcinoma (ADC), who underwent neoadjuvant chemo-radiotherapy at our Institution between January 2014 and December 2018, were retrospectively identified. Forty-four patients were excluded from the study for the following reasons: preoperative approach other than nCRT protocol (n=31); no surgery (n=8); lack of at least one \(^{18}\)F-FDG PET/CT scan (n=5). The remaining 54 patients were considered eligible for analysis. Among them, 41 (75.9%) showed a major pathologic response (TRG\textsubscript{1–2}) and 13 (24.1%) a non-response (TRG\textsubscript{3–4}) to nCRT.

All patients completed the nCRT planned program. PET\textsubscript{1} was performed immediately before (median 8.5 days, IQR 6–14) the start of IC, while PET\textsubscript{2} was performed during the 4th week (median 25 days, IQR 22–28) of the nCRT protocol schedule. PET\textsubscript{3} was performed 5 weeks (median 5.1 weeks, IQR 4.0–5.4), and surgery 8 weeks (median 7.9 weeks, IQR 6.6–9.1) after nCRT completion.

At the last follow-up, 33 patients (61.1%) were alive. The median follow-up of the entire cohort was 32.5 months (IQR 26.0–45.0 months). The median overall survival (OS) and disease-free survival (DFS) of the TRG\textsubscript{1–2} group at the time of last follow-up were 34.7 months (IQR 27.5–49.7 months) and 30.7 months (IQR 17.1–47.7 months), respectively, while the corresponding figures for the TRG\textsubscript{3–4} group were 28.0 months (IQR 23.4–30.8 months) and 18.1 months (IQR 10.4–30.7 months), respectively (p < 0.01).

**TRG and Baseline Characteristics**

Table 1 reports the results of the analysis of the association between baseline parameters and response to the nCRT protocol. Parameters that statistically correlated to outcome were histological subtype (p = 0.02) and tumor length (p = 0.03). All other parameters evaluated were not statistically linked to treatment outcome.
TRG and Metabolic Parameters

Table 2 reports the results of the analysis of the association between metabolic parameters of PET1 and PET2 with tumor regression grade class (TRG1-2 vs. TRG3-4). Relative differences between the parameters at the two subsequent PET/CT scans are also reported. At baseline, MTV (AUC 0.74) and TLG (AUC 0.69) were statistically correlated to histological tumor regression. In addition, at PET2, SUVmean (AUC 0.67) and TLG (AUC 0.64) were significantly related to a higher chance of major pathologic response (Figure 3). No significance was detected when relative differences were considered. Interestingly, none of the post-CRT PET metrics resulted significantly correlated with the outcome measured (average SUVmax was 5.01 vs. 5.09, SUVmean 2.81 vs. 2.75, and MTV 8.74 ml vs. 8.74 ml, in TRG1-2 vs. TRG3-4 patients, respectively; all p > 0.05). Therefore, additional analysis, relative to PET3 metrics, was not conducted. Figure 4A reports the boxplot distribution of the MTV at PET1, the parameter most correlated to treatment outcome at logistic regression analysis.

Radiomic Feature Analysis

Among the 210 radiomic features (105 for each PET scan), 14 resulted significant to the t-test with the adjusted significance threshold pTh = 0.05/210 = 0.00024 and none of them were extracted from the PET2 scan. Since many of these features are strongly correlated, as visible in Figure 5, the redundant information was removed resulting in three independent features. The three resulting features, highlighted in Figure 5 with bold fonts, are representative for the whole cluster and further reported in Figure 6 with the relative scatterplots and histograms. The boxplot of one of these three features is reported in Figure 4B.

DISCUSSION

Neoadjuvant chemo-radiotherapy (nCRT) has been widely accepted as the standard of care for the treatment of locally advanced, resectable esophageal cancer. However, a not negligible number of patients show a poor response to neoadjuvant therapy at the time of surgery (residual tumor on the resection specimen), as an expression of pre-existing intrinsic chemo- and radio-resistance. Notably, non-responder patients to nCRT have a significantly worse prognosis than responders.
Thus, there is an urgent need to early identify patients who could benefit or not from preoperative treatment, using prognostic and predictive tumor biology markers. This study demonstrated that $^{18}$F-FDG PET/CT metrics may be able to predict the degree of pathologic response, according to a modified Mandard tumor regression grade (TRG) score system, in patients undergoing induction chemotherapy (IC) followed by chemo-radiotherapy as an intensive neoadjuvant protocol.

Metabolic parameters, that were statistically correlated to treatment outcome, were the MTV (p = 0.02) at PET$_1$, and SUV$_{\text{mean}}$ (p = 0.03) at PET$_2$. The TLG was also significant at both time-points (p = 0.02 and p = 0.04, respectively). This can be interpreted as a consequence of the above, as TLG is defined as the product between MTV and SUV$_{\text{mean}}$. These results might suggest that the lesion volume, as determined before IC, and the average metabolic activity, as determined after IC, should be considered significant. In addition, at textural quantitative analysis, three independent radiomic features extracted from PET$_1$ images (JointEnergy and InverseDifferenceNormalized of GLCM and LowGrayLevelZoneEmphasis of GLSZM) were statistically correlated with major response (p < 0.0002). This indication could be important in view of a possible early prediction of outcome, with potential advantages to patients believed to benefit from the three-stage treatment. However, further investigations are necessary in order to obtain a reliable predictive model to be used in the clinical practice, especially if

**FIGURE 3** | Sagittal fused $^{18}$F-FDG PET/CT images obtained at baseline (PET$_1$) and after induction chemotherapy (PET$_2$). A significant response to induction chemotherapy (reduction in metabolic parameters) of the esophageal lesion can be observed. The patient was classified as TRG1 at final pathological examination. PET$_1$ parameters: SUV$_{\text{max}}$ 26.9, SUV$_{\text{mean}}$ 12.7, MTV 43.7 ml, TLG 553.9; PET$_2$ parameters: SUV$_{\text{max}}$ 6.7, SUV$_{\text{mean}}$ 3.2, MTV 15.9 ml, TLG 50.5.

**FIGURE 4** | Boxplot distribution of (A) MTV (ml) and (B) LowGrayLevelZoneEmphasis (GLCM) radiomic feature at $^{18}$F-FDG PET/CT scan taken before induction chemotherapy (PET$_1$). Classes are divided between major (TRG1-2) and non (TRG3-4) response (median, interquartile and full range are displayed).
the inclusion of radiomic features in the model is foreseen. In fact, additional validation is mandatory in the latter case since predictive models, based on radiomics, are more prone to overfitting compared to models based on conventional PET parameters.

The results of the present study could lead to different considerations. Metabolic tumor volume (MTV) combines the information of SUV uptake and tumor volume, corresponding to the volume of tumor tissues with increased glycolytic activity. In our study, MTV in poor responders was significantly higher than in good responders (38.6 ml vs. 17.7 ml, p = 0.02). Since SUVmax and SUVmean did not differ significantly between the two groups (TRG1-2 vs. 3-4) at PET1, this figure appears to be consensual to the greater extent of the primary tumor in non-responder patients at the time of diagnosis (tumor length 6.8 cm vs. 5.4 cm in good responders, p = 0.02). This result is consistent with previous experiences reported in the literature (32, 33). This could suggest that the MTV of the primary tumor has the potential to become a valuable prognostic biomarker for response at baseline in EC patients. The other baseline parameter, significantly correlated with TRG class after nCRT, was squamous histological subtype (p = 0.02). This confirms the greater sensitivity to nCRT of the squamous histology compared to ADC, as reported in the literature (34). In this regard, whether surgery on demand is advisable in selected complete responder SCC patients after nCRT is currently under evaluation in the randomized SANO trial (35).

At PET2 evaluation, SUVmean represents the main predictor for pathological response (p = 0.03). The SUVmean provides information about intrinsic lesion characteristics, related to tumor grading, biological factors, and the presence of hypoxic or necrotic areas. Thus, it is reasonable to hypothesize that SUVmean after IC might be an effective predictor of the final response to nCRT. This post-induction chemotherapy assessment could help to guide a PET-adapted preoperative

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**FIGURE 5** Correlation matrix of all the radiomic features with high significance (p<0.0002) in t-test for patient response. The Pearson’s correlation coefficient identifies three disjointed clusters, in which the three representatives (Idn=InverseDifferenceNormalized, JointEnergy and LowGrayLevelZoneEmphasis) are highlighted in bold.
strategy in EC. Recently, a Memorial Sloan Kettering Cancer Center series tested the impact of changing concurrent chemotherapy, during radiotherapy, in PET non-responders after IC: no survival benefit was seen from this change in therapeutic strategy (36). On the other hand, in the MUNICON trial, after 2 weeks of IC, 18F-FDG PET/CT poor responders were referred to immediate surgery, while good responders continued with preoperative chemo-radiotherapy (37). The results of this trial suggested no decrement in survival outcomes with early termination of ineffective chemotherapy in PET non-responders, supporting a possible early discontinuation of preoperative treatment in this subset of patients. In the near future, the integration of 18F-FDG PET/CT traditional metrics as a predictor of response is undoubtedly intriguing, but requires further investigation.

The analysis of radiomic features revealed that textural characteristics of PET1 were more significantly correlated to treatment response compared to PET2, confirming the possible predictive value of PET1. Many radiomic features were correlated to each other, suggesting a redundancy of information that should be carefully taken into account if using radiomics in a predictive model. To this regard, extensive validation is necessary. However, the textural metrics, that correlate to treatment outcome, are associated to micro-variations of local metabolic activity thus indicating a possible role of spatial intra-tumor heterogeneity in predicting response (19). Relatively few studies have investigated the role of PET radiomic features in predicting response to nCRT in EC. As a whole, the results have highlighted a possible contribution of radiomic in the prognostic stratification of these patients (Table 3).

The predictive value of post-CRT 18F-FDG PET/CT functional informations has been largely evaluated, with conflicting results. Indeed, the utility of PET metrics after
TABLE 3 | Recent findings on the application of PET radiomics for the prediction of response in esophageal cancer patients treated with neoadjuvant chemo-radiotherapy (summary).

| Study, year (ref) | Sample size | nCRT protocol | PET time point | Main features evaluated | Results |
|------------------|-------------|---------------|----------------|------------------------|---------|
| Tixier et al. (19) | 41 (ADC 10, SCC 31) | 60 Gy + C or carboplatin/F | Pre-CRT | First order statistics (GLCM, RLM, GLSZM, NGTDM) | Tumor textural analysis (GLCM homogeneity, GLCM entropy, RLM intensity variability and GLSZM size zone variability) can identify NR, PR and CR with higher sensitivity (76%–92%) than any SUV measurement |
| Tan et al. (20) | 20 (ADC 17, SCC 3) | 50.4 Gy + C/F | Pre & Post-CRT | First order statistics (GLCM) | SUV\text{\textsubscript{max}} decline, SUV\text{\textsubscript{mean}} decline and skewness, GLCM inertia, correlation and cluster prominence, are predictors of CR (AUC 0.76–0.85) |
| Van Rossum et al. (21) | 217 ADC | 45–50.4 Gy + fluoropyrimidine/platinum or taxane | Pre & Post-CRT | First order statistics (GLCM, RLM, NGTDM) | At multivariate analysis baseline cluster shade, run percentage, GLCM entropy, and post-CRT roundness, correlates with CR |
| Yip et al. (22) | 45 (ADC 44, SCC 1) | 45–50.4 Gy + C, F, irinotecan/paclitaxel or carboplatin/paclitaxel | Pre & Post-CRT | Geometry, and texture parameters differentiate CR/PR from NR (AUC 0.71–0.76) |
| Beukinga et al. (23) | 97 (ADC 88, SCC 9) | 41.4 Gy + carboplatin/paclitaxel | Pre-CRT | First order statistics (GLCM, NGTDM) | Long runs (coarse texture) with low gray levels and homogeneity of runs (fine texture) higher in patients with CR |
| Nakajo et al. (24) | 52 SCC | 41–70 Gy + C/F | Pre-CRT | GLCM: Entropy, homogeneity, dissimilarity; GLSZM: Intensity variability, Size-zone variability, zone percentage | Texture features (GLSZM intensity variability and GLSZM size-zone variability), and volumetric parameters (MTV and TLG) can predict tumor response |
| Beukinga et al. (25) | 70 (ADC 65, SCC 8) | 41.4 Gy + carboplatin/paclitaxel | Pre & Post-CRT | Geometry, and local intensity (GLCM, GLSZM, NGTDM) | The combination of clinical T-stage and post-nCRT joint maximum predict CR |
| Chen et al. (26) | 44 SCC | 50 Gy + platinum-based regimen | Pre-CRT | SUV\text{\textsubscript{max}} decline, SUV\text{\textsubscript{mean}} decline and skewness, kurtosis, and entropy (NGTDM, TFCCM, NGTDM) | Pre-CRT primary tumor histogram entropy ≥ 3.69 predicts unfavorable response |

nCRT, neoadjuvant chemo-radiotherapy; C, cisplatin; F, 5 fluorouracil; NR, non response; PR, partial response; CR, complete response.

Radiotherapy remains controversial due to difficulties in distinguishing post-treatment inflammation from residual viable tumor (43, 44). In the present study, none of the PET metrics resulted significantly correlated with the pathological response to nCRT, confirming that metabolic parameters relative to post-CRT PET are poorly evaluable and potentially inaccurate, mostly due to post-radiation inflammatory-related uptake or the disappearance of detectable metabolic activity, both considered as confounding factors. On the other hand, the use of 18F-FDG PET/CT imaging before surgery, in appropriate combination with other restaging modalities, remains essential for the early detection of loco-regional and distant progression to nCRT.

Our study presents some limitations, including its retrospective nature. This is a single-center analysis; thus the results should be interpreted with caution. Moreover, different histologies (SCC and ADC) were considered, which potentially add heterogeneity to the outcomes measured. On the other hand, these limitations are counterbalanced by the analysis of one of the most homogeneous sample sizes for this topic so far, with patients undergoing the same intensive nCRT protocol, using a prospectively collected database, a standardized 18F-FDG PET/CT acquisition modality and a modern metabolic and radiomic parameter analysis.

In conclusion, our observations confirm that 18F-FDG PET/CT metrics are correlated with pathological response in EC. The analysis of PET traditional metrics and radiomic features may provide a new imaging perspective, moving from tumor staging to a promising role in disease stratification and prognostication. However, further studies are needed to justify a PET-guided strategy in the neoadjuvant approach to locally advanced EC. The integration with MRI data, as well as genomic and molecular analysis, might be useful as prognostic and predictive biomarkers for the selection of a tailored strategy improving the efficiency of neoadjuvant treatment for EC patients.
DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the datasets generated for this study are available on request to the corresponding author, subject to approval by the Institutional Review Board. Requests to access the datasets should be directed to NS, nicola.simon@avov.veneto.it.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato etico per la Sperimentazione Clinica (CESC) delle Province di Verona e Rovigo. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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AUTHOR CONTRIBUTIONS

Conceptualization, NS and CC. Methodology, NS, GB, and CC. Data curation, MZ, RMi, MP, EZ, and VM. Statistical analysis and radiomics, GR, GB, and CC. Validation, SGu, JW, and SGi. Writing—original draft preparation, NS, MZ, and CC. Writing—review and editing, GR, RMi, JW, and SGi. Supervision, GD and RMa. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.599907/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with one of the authors with several of the authors [NS, RMa].

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