Original Article

Role of (F-18) Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Prediction of Response to Neoadjuvant Therapy in Esophageal Cancer: Correlation with Pathological Response and Survival

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Abstract

Purpose: The purpose of this study is to assess the correlation between metabolic response with fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) and pathological response in patients with locally advanced esophageal cancer treated with neoadjuvant chemoradiotherapy and to study FDG-PET parameters for the prediction of pathological response and outcome. **Methods:** Twenty-five patients with locally advanced esophageal cancer underwent two FDG-PET/CT scans for initial staging and after neoadjuvant chemoradiotherapy. FDG uptake in the primary tumor was calculated in both scans (SUVmax, SULpeak, and TLG). Metabolic response was assessed according to the reduction of PET parameters: complete response (mCR = 100%), partial response (mPR ≥50%), and no response (mNR ≤50%). Pathological response was also classified as complete (pCR), partial (pPR), or no response (pNR). Patients were followed up (range, 8–99 months) determining free-disease interval (FDI) and overall survival (OS). **Results:** Two patients were excluded due to exitus for nonesophageal-related causes. The metabolic response was observed in 18/23 remaining patients (3mCR, 15 mPR), of which 12/18 patients showed a pathological response (3 pCR, 9 pPR). A major discrepancy was observed in 2 mNR patients who achieved pPR. FDI and OS were longer in patients with metabolic response than nonresponders, but no statistical difference was found. No significant correlation was found between PET parameters and pathological response, FDI, and OS. **Conclusions:** FDG-PET/CT is a useful technique to assess response to neoadjuvant chemoradiotherapy in esophageal cancer. Although in this preliminary study, no correlation between metabolic and pathologic response was found and no statistical differences between responders and nonresponders were observed, a tendency of longer FDI and OS was apparently found in responders patients.

Keywords: *Esophageal cancer, fluorodeoxyglucose, metabolic response, neoadjuvant therapy, outcome, positron emission tomography*

Introduction

Esophageal cancer is currently the 9th most prevalent neoplasm worldwide, the third among those of gastrointestinal origin, constituting the 6th cause of death by cancer. Its incidence varies widely depending on geographic location, from 5 cases per 100,000 inhabitants in most Western countries to 16 times higher in countries such as South Africa, China, Turkey, or Iran.[1,2]

It is the neoplasm that has increased its incidence the most in Western countries over the last three decades, multiplying it by 6.[3] Furthermore, it associates a bad prognosis and a mortality rate close to 85%–90%.[4]

In early stages of the disease, the treatment of choice is surgical resection. However, esophageal cancer is usually detected late, already in the symptomatic phase, which implies diagnosis at an advanced stage. In Western countries, 70% of patients diagnosed with esophageal cancer are already stage III disease (T3-T4 N+) of the World Health Organization TNM classification. In these cases, survival at 5 years postresection is <15%. Therefore, it is necessary to use multimodal therapies that contemplate the

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Table 1: Bivariate analysis for positron emission tomography metabolic parameters of this study

Table: DFS Bivariate

	No event	Event	2* HR	2*p.ratio	2*p.overall
PETpreTSUVmax	18.9 (9.51)	16.8 (5.27)	0.97 [0.90;1.05]	0.478	0.478
PETpreTSULpeak	11.3 (7.11)	9.74 (2.67)	0.96 [0.86;1.08]	0.529	0.529
PETpreTTLG	238 (179)	169 (93.2)	1.00 [0.99;1.00]	0.378	0.378
PETpostTSUVmax	4.80 (3.26)	5.78 (3.84)	1.05 [0.89;1.24]	0.535	0.535
PETpostTSULpeak	2.76 (1.78)	3.05 (2.03)	1.04 [0.77;1.41]	0.804	0.804
PETpostTTLG	28.0 (32.8)	33.2 (32.3)	1.01 [0.99;1.02]	0.525	0.525
DSUVmax	70.4 (20.9)	65.2 (19.1)	0.99 [0.96;1.02]	0.472	0.472
DSULpeak	71.1 (21.5)	68.3 (17.9)	1.00 [0.97;1.02]	0.748	0.748
DTLG	83.4 (14.5)	75.8 (19.1)	0.97 [0.94;1.01]	0.121	0.121

DFS: Disease free survival, HR: Hazard ratio

Table 2: Bivariate analysis for positron emission tomography metabolic parameters of this study

Table: OS Bivariate

	No event	Event	2* HR	2*p.ratio	2*p.overall
PETpreTSUVmax	19.2 (9.25)	16.2 (5.13)	0.97 [0.89;1.05]	0.415	0.415
PETpreTSULpeak	11.3 (6.87)	9.61 (2.76)	0.96 [0.85;1.09]	0.546	0.546
PETpreTTLG	232 (174)	171 (97.6)	1.00 [0.99;1.00]	0.444	0.444
PETpostTSUVmax	4.50 (3.37)	6.31 (3.54)	1.10 [0.93;1.30]	0.278	0.278
PETpostTSULpeak	2.59 (1.85)	3.33 (1.88)	1.13 [0.83;1.54]	0.443	0.443
PETpostTTLG	26.3 (32.5)	36.2 (32.1)	1.01 [0.99;1.02]	0.450	0.450
DSUVmax	72.3 (21.5)	62.0 (16.4)	0.98 [0.96;1.01]	0.256	0.256
DSULpeak	72.9 (22.0)	65.5 (15.6)	0.99 [0.96;1.02]	0.431	0.431
DTLG	84.4 (14.6)	73.6 (18.4)	0.96 [0.93;1.00]	0.069	0.069

OS: Overall survival, HR: Hazard ratio

administration of chemoradiotherapy in neoadjuvant mode before esophagectomy. Neoadjuvant therapy is used to eradicate lymph node micrometastases and also to reduce the size of the primary tumor, facilitating curative surgery. Complete pathological response rates of 10%–43% and 30% overall survival (OS) at 3 years were reported in patients treated with multimodal therapy regimens.[4]

[F-18]-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) plays an important role as part of the multidisciplinary protocol for initial staging and assessment of response to neoadjuvant therapy in esophageal cancer. FDG-PET is able to evaluate early response to neoadjuvant treatment with greater sensitivity than CT to determine viable residual tumor. The reduction in size and metabolism of the target lesions is interpretable in terms of tumor response since it has been shown to be related to pathological response and prognosis. The absolute value of FDG uptake, measured in the postneoadjuvant PET, can reflect the volume of residual tumor after the induction treatment, with its consequent prognostic value.[5]

SUV_{max} is the most used metabolic parameter in PET-CT, since its numerical values and their variation during the treatment seem to correlate with the pathological response to neoadjuvant therapy.[6] Multiple retrospective survival analyses have been performed, taking as a reference the postsurgical pathological results, aiming to find an optimal threshold of SUV_{max} reduction between baseline and after therapy PET-CT, to help discriminate responders from nonresponders.

Assessing the pathological response according to the Mandard system (percentage of viable tumor cells after treatment: >10% in nonresponse, 0%–10% in partial response and 0% in complete response), a 30%–60% reduction of SUV_{max} of the primary tumor corresponds to partial response, while a ≥20% SUV_{max} increase in a ≥1 cm region is considered

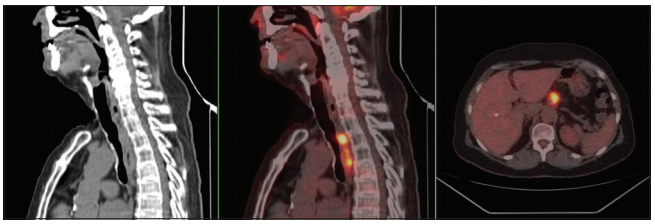

Figure 1: Staging positron emission tomography/computed tomography in a64 year-old male patient with squamous carcinoma of the upper thoracic third of the esophagus and nodal involvement in the left gastric artery. Proposed staging: T3N + M0

tumor progression. Other metabolic parameters such as SULpeak and TLG have been described as solid alternatives for the quantification of metabolic response.[7]

The aim of our study was to assess the correlation between metabolic response, measured with [F-18]-FDG PET-CT using parameters of tumor uptake and volume (SUVmax, SULpeak, and TLG), and pathological response in patients with locally advanced esophageal cancer treated with neoadjuvant chemoradiotherapy (QT-RT), as well as to study PET parameters of metabolic activity to predict disease-free interval (DFS) and OS.

Methods

Procedure

Over a period of 5 years, 25 patients with a diagnosis of locally advanced esophagus neoplasia in stage III were included in the study (22 men and 3 women, mean age 59 years, range from 45 to 79). All of these patients were candidates to neoadjuvant therapy followed by radical surgery and had previously undergone endoscopy, biopsies, and contrast-enhanced CT as part of the diagnosis and staging protocol. Fifteen of these patients were diagnosed with adenocarcinoma (ADC) and 10 with squamous cell carcinoma (SCC) [Figure 1].

All patients underwent two [F-18]-FDG PET-CT (0.1 mCi/Kg), for staging and response assessment, in the same Discovery ST equipment (GE Healthcare). Full-body images were obtained, usually from orbit to mid-thigh, acquired between 50 and 70 min after the intravenous injection of [F-18]-FDG.

The first PET-CT was performed to complete the initial tumor staging protocol and the second for response assessment, approximately 4 weeks after concluding neoadjuvant chemotherapy (cisplatin and 5-fluorouracil) and radiotherapy (45 Gy).

Both PET-CT studies were analyzed by a medical specialist in nuclear medicine using the PETVCAR tool (G. E.), assessing parameters of metabolic activity in the primary tumor (SUV_{max}, SULpeak, and TLG). The variables used for these parameters were the pretreatment absolute values, posttreatment absolute values, and the differential between both of them, calculated as the percentage of the reduction attributable to the effect of neoadjuvant therapy.

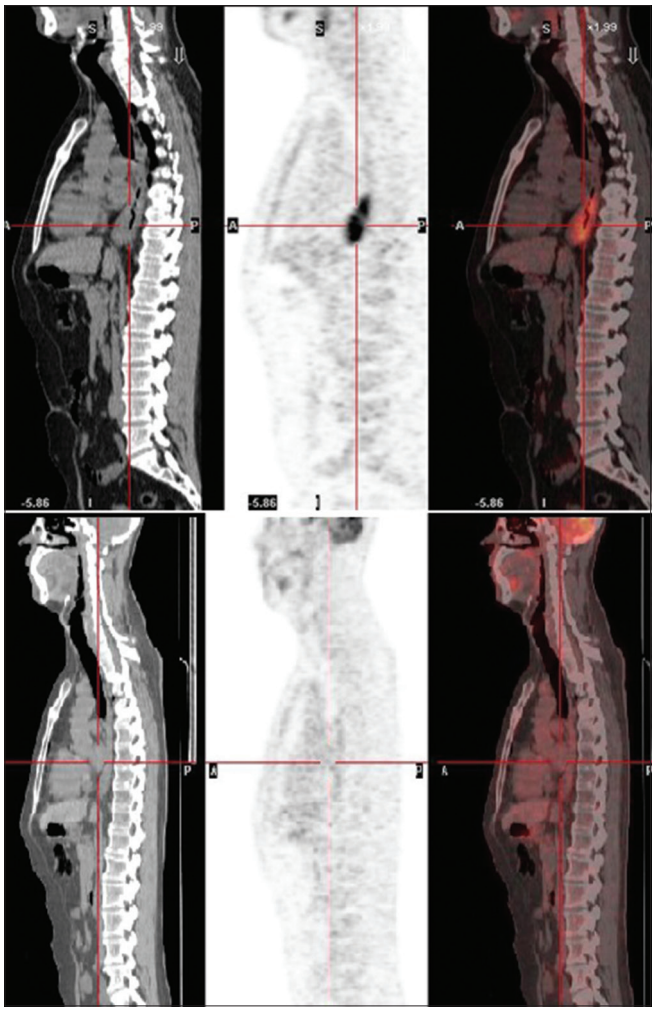

Figure 2: Fifty-five-year-old male patient. Squamous cell carcinoma of the esophageal middle third, with complete metabolic response after neoadjuvant therapy. The patient also achieved pathological complete response

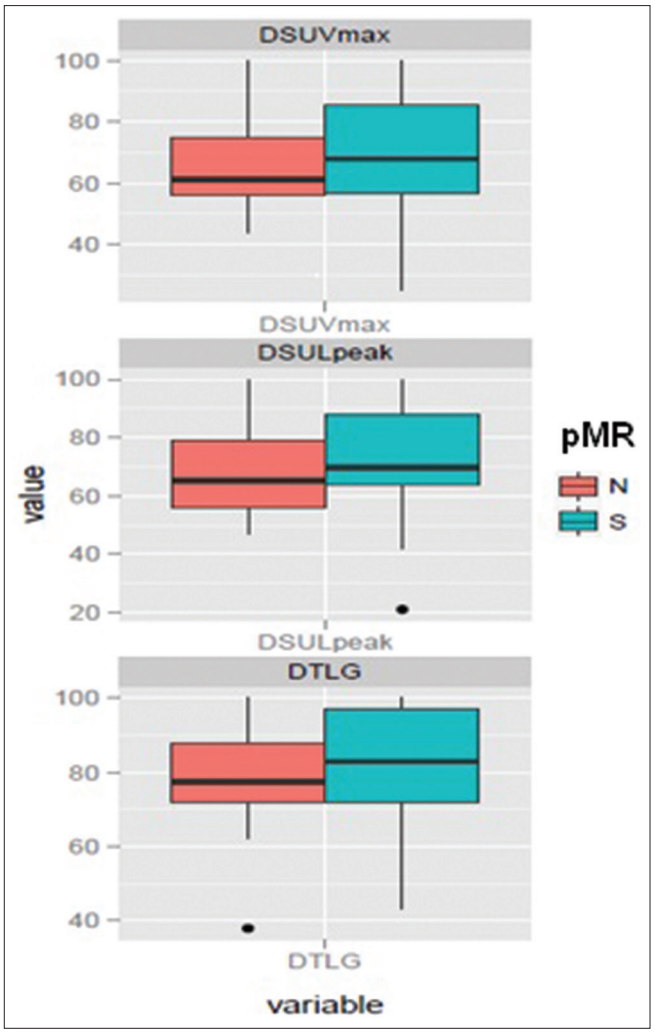

Figure 3: Correlation between reduction of metabolic response positron emission tomography parameters and pMR

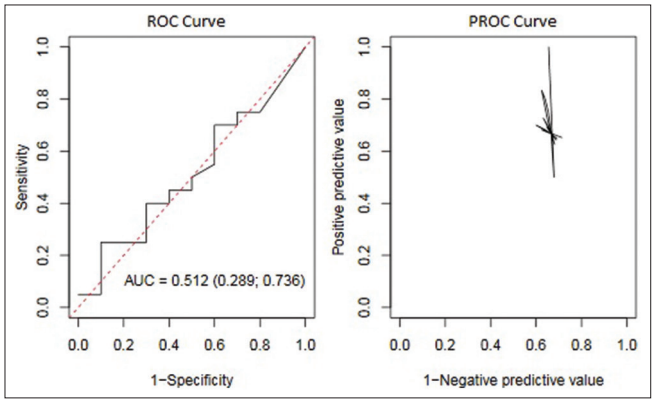

Figure 4: Positron emission tomography post TSUVmax versus pMR: Receiver operating characteristic and PROC curves

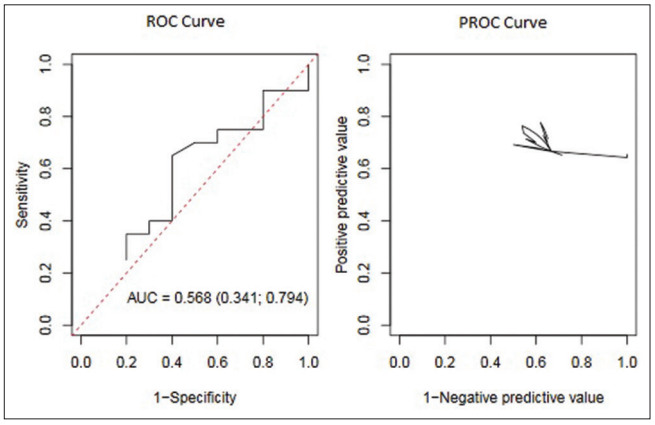

Figure 5: SUVmaxDR versus pMR: Receiver operating characteristic and PROC curves

Based on this reduction percentage, the metabolic response was classified as:

- Complete metabolic response (mCR), when normalization of esophageal metabolic activity was achieved, with FDG uptake similar to background mediastinal uptake [Figure 2]
- Partial metabolic response (mPR), in those patients in whom the three metabolic parameters under study were reduced by more than 50% but still had mild esophageal uptake suggestive of tumor persistence. Also included in

this group were those patients who showed a reduction of their metabolic parameters >50% but presented inflammatory uptake due to esophagitis that prevented from confirming a complete metabolic response
- No metabolic response (mNR), in those patients who did not reach a reduction >50% in the three parameters or showed signs of tumor progression (increase of metabolic activity or appearance of new lesions).

All patients included in the study underwent surgery between 2 and 7 weeks after completing neoadjuvant therapy, performing radical esophagectomy using the Ivor Lewis or McKeown techniques. Pathological response to neoadjuvant treatment was determined after histopathological assessment of the surgical specimen (primary tumor) and was classified as:
- Complete pathological response (pCR): no evidence of neoplasia in the surgical specimen
- Partial pathological response (pPR): presence of <10% of viable tumor cells in the surgical specimen and/or reduction of T classification of initial TNM, with only remaining tumor in the esophageal wall ≤ T1
- No significant pathological response (pNR): presence of ≥10% of viable tumor cells in the surgical specimen and/or absence of significant reduction of T classification of initial TNM, persisting tumoral involvement at the esophageal wall ≥ T2.

We qualified as a major pathological response (pMR) those patients with pCR or pPR.

After surgery, a follow-up of all patients was performed, determining if recurrence had occurred, its location, the DFS (DFS: months between surgery and the date of recurrence, or the date of last recorded visit with Oncology in those cases with no recurrence) and OS (OS: months elapsed between diagnosis of esophageal cancer and the last recorded visit with Oncology). This follow-up period ranged from 8 to 99 months. Considering survival parameters, patients were classified as:
- Status 1: Patient alive, free from disease
- Status 2: Patient alive with evidenced recurrence
- Status 3: Patient deceased in relation to recurrence of known esophageal neoplasm
- Status 4: Patient deceased by reasons not related to esophageal neoplasm.

Statistical bivariate analyses were performed with all the available response variables. Receiver operating characteristic (ROC) curves were performed to identify sensitivity, specificity, positive predictive value, negative predictive value, and under the curve area, calculating cutoff points and threshold value for the different metabolic parameters in relation to pathological response results and survival. Cox multivariate analysis was planned for the variables with statistically significant relationship in the bivariate analysis. Survival was calculated by the Kaplan–Meier method with curves for OS and DFS parameters.

Results

Two patients were excluded from the study due to death for reasons unrelated to recurrence of esophageal neoplasm (status 4).

Of the 23 remaining patients, 18 showed metabolic response by reduction of the three metabolic parameters assessed in the primary tumor. Of these patients, 3 showed mCR and 15 mPR. Five patients in the study did not show a clear metabolic response in the second PET-CT (mNR), four of them due to stability of the disease and one due to progression.

Of the 18 patients with metabolic response, 12 had pathological response in the surgical specimen analysis (3 pCR, 9 pPR). Of the 5 patients without a metabolic response, 3 did not present a significant pathological response of the esophageal tumor either. However, there was a discrepancy in the remaining 2 patients, that did not show significant decrease in PET uptake parameters but presented pPR in the assessment of the esophagectomy piece. The explanation for this fact may be the presence of inflammatory changes secondary to radiotherapy, which could hinder the assessment of visual response and quantitative PET analysis.

At the statistical analysis, no significant correlation was found between the reduction of metabolic response parameters by PET and pMR ($P > 0.05$) [Figure 3].

No cutoff points were found at ROC curves, with AUC results close to 0.5, with no diagnostic value: 0.43 in the ratio between SUV_{max} posttreatment and pMR, and 0.55 in the ratio between differential SUV_{max} and pMR [Figures 4 and 5].

Of all 23 patients, 11 had tumor recurrence during the follow-up period. Recurrences locoregional in 6 cases and distant in the remaining: liver (2), lung (3), pleura (2), peritoneum (1), retroperitoneum (1), brain (1), and penis (1). All recurrences occurred during the first 20 months after surgery. All patients who showed recurrence died (status 3). We found no relapses after those first 20 months of follow-up and no deceased patients after 35 months of follow-up.

DFS was higher in patients with metabolic response in PET (mCR or mPR) than in those who did not respond (median of 18.5 months vs. 12 months). OS was also higher in patients with metabolic response to neoadjuvant therapy (median 28 months vs. 20 months in nonresponders).

However, no statistically significant differences were found between both groups. Cox multivariate analysis was not performed since no variables with a statistically significant relationship were found in the bivariate analysis [Table 1 and 2].

At the time of the last follow-up, 61% of patients with metabolic response remained alive without disease (status 1) compared to 40% of the patients with an unfavorable metabolic response.

Conclusions

[F-18]-FDG PET-CT is a noninvasive diagnostic tool that has been proven to be useful in the evaluation of response to chemoradiotherapy treatment in tumors with known glucose avidity, as is the case of esophageal cancer in its two fundamental histological variants: SCC and ADK. In the course of neoadjuvant therapy, FDG-PET is able to reflect variations in the glucose metabolism of tumor cells, discriminating between viable tumor and posttreatment necrotic tissue, which provides fundamental information that seems to correlate with the pathological response.

Multiple studies have evaluated the usefulness of [F-18]-FDG PET-CT to determine response to neoadjuvant treatment in esophageal cancer by measuring parameters of metabolic activity in tumor cells of the esophageal wall. In these studies, several quantitative parameters have been evaluated; most commonly the absolute value of SUVmax after neoadjuvant therapy (SUVmaxpost) and the differential SUVmax between baseline and postneoadjuvant PET (SUVmaxDR). Other authors have proposed the use of metabolic tumor volume parameters referring optimal results.[8] However, the results of the studies have shown discrepancies, both in the existence of a correlation between metabolic response and pathological response or survival and in establishing consensus on which metabolic quantitative variable is most useful for predicting response. Thus, Rebollo *et al*.[9] in a metaanalysis of 7 studies with 248 patients in total, obtained very variable data of sensitivity and specificity for FDG-PET in primary tumour response assessment. Sensitivity ranged from 27.3% to 97.3% and specificity ranged from 41.7% to 95.2% among the various studies. The differences in the quantitative parameters between responders and nonresponders were mostly nonsignificant, as in our study.

In our study, we try to predict the response of various quantitative parameters related to metabolic activity and/or tumor volume (SUV_{max}, SULpeak, and TLG). Although it should be noted that it was a preliminary study with a small number of patients, the statistical analysis did not find a significant correlation between the metabolic response parameters and the pathological response or survival data. However, our results showed a tendency to a higher percentage of pathological response, lower recurrence rate, and greater survival in those patients who presented a reduction of PET uptake parameters.

This statistically inconclusive trend is consistent with the results obtained by Vallböhmer *et al*.,[10] who in a study with 119 patients found a nonsignificant association between patients with a greater pathological response (<10% viable tumor cells) and those with a decrease in SUV_{max} in PET, without identifying a cutoff point with predictive value for histopathological response or survival in the studied metabolic parameters (SUV_{max} of the first PET, SUV_{max} of the second PET, SUV_{max} DR). Other authors such as Smithers *et al*., in a study with 45 patients, or Brink *et al*., in a study with 20 patients, also found no statistical association between FDG-PET response and histopathological response.[11,12]

On the other hand, the authors like Miyata *et al*., in a study with 211 patients, found a significant correlation between two PET parameters (SUV_{max} post and SUVmax DR) with pathological response, although they were unable to distinguish between complete and partial metabolic response. Both parameters were associated with a higher survival rate when SUVmaxDR >50% and SUVmaxpost <3.5, although only the SUVmax post was considered an independent prognostic factor.[5] This SUVmax DR decrease threshold >50% is the one that we used in the methodology of our study to classify the partial response versus no response groups and was previously validated by the authors such as Port *et al*.[13] or Brücher *et al*.,[14] who observed a correlation between SUVmax decrease and greater pathological response, with a sensitivity of 100% and specificity of 55%. Similar conclusions were reached by Weber *et al*., who proposed a cutoff point of 35% in the SUVmaxDR for differentiation of responders versus nonresponders.[15]

Recently, Caro *et al*., in a study with 64 patients, proposed a 6 threshold for the SUVmax post, which discriminated patients with a greater response from those with a poor response.[16] Other authors also found a significant relationship between major pathological response, metabolic response, and prognosis,[17] with cutoff values of SUVmaxpost to predict response around 4 g/ml.[18,19] Ott *et al*., on the other hand, found significant differences in survival at 3 years between responders and nonresponders by PET (70% vs. 35%, respectively).[20]

The reasons why no statistically significant results were found in our study could be related to the small number of patients included, especially in the subgroup of nonresponders, which limited the validity of the statistical analysis. Similarly, the short time elapsed between the completion of neoadjuvant radiotherapy and the performance of PET-CT response assessment (3–4 weeks, protocolized by the need to perform the surgical act as soon as possible), was a handicap for the determination of metabolic response, since many patients presented esophageal mural hypermetabolism due to posttreatment inflammatory changes that significantly affected the measurement of quantitative parameters and the calculation of metabolic tumor volume.

In our experience, the presence of radiation esophagitis is not usually a problem when it comes to identify if there has been downstaging or a trend toward tumor reduction since it presents a distinctive pattern easily identifiable in the visual assessment of PET-CT. Therefore, it is possible to distinguish patients who respond to neoadjuvant treatment, although it often makes it difficult to distinguish

between complete metabolic response and partial metabolic response. The influence of this inflammatory uptake in the calculation of posttreatment quantitative parameters could also be the key to explain the absence of statistically significant differences between the different groups of patients in our study, as well as the discrepancies found in the correlation with pathological response.

On the other hand, the statistical analysis of the present work focused exclusively on the metabolic parameters of the primary tumor at the esophageal wall. Lymphatic pathological uptake and its decrease after induction therapy were assessed by visual and quantitative analysis, but were not included among the variables analyzed in the statistical test. It would be desirable to extend the study by also evaluating these parameters of lymph node disease since the contribution of induction therapy to survival in esophageal cancer is closely related to the eradication of these lymphatic micrometastases, given that the primary tumor, independently of the degree of response, will be finally removed during esophagectomy.

In conclusion, FDG-PET is a noninvasive technique that has been shown to be useful in assessing response to neoadjuvant chemoradiotherapy in esophageal cancer in numerous studies. Although in this preliminary study, no statistically significant correlation was found between metabolic response parameters and pathological response, neither significant differences in survival between PET responders and nonresponders, there was a tendency to a lower recurrence rate and greater OS in patients who presented metabolic response. Broader analyses, including a larger number of patients, could yield statistically significant data that correlate metabolic and pathological responses, as demonstrated in previous publications.

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Conflicts of interest

There are no conflicts of interest.

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