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Original article

To Compare and Determine the Diagnostic Accuracy of [^{18}F]-fluorodeoxyglucose Positron Emission Tomography Scan in Predicting Pathological Response in Operated Carcinoma Esophagus Patients after Initial Neoadjuvant Chemoradiation and Neoadjuvant Chemotherapy

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Abstract

The objective of this study was to determine whether [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) scan could predict the pathological response in esophageal carcinoma after surgery in patients receiving neoadjuvant concurrent chemoradiation (NACCRT) and neoadjuvant chemotherapy (NACT). A randomized prospective study was carried out from March 2014 to October 2016; thirty patients of histopathologically proven, locally advanced, potentially operable carcinoma esophagus comprising both squamous carcinoma and adenocarcinoma were randomized into NACCRT and NACT arms equally. Both groups had pretreatment FDG-PET-computed tomography (CT) scan and repeat scan after 5–6 weeks of neoadjuvant therapy (NAT). The change in mean %Δmaximum standardized uptake value (%ΔSUVmax) was compared with tumor regression grade (TRG) in the postoperative histology. Patients with TRG 1–2 were deemed responders and 3–5 were nonresponders. Pathologic response was correlated with percentage change in [^{18}F]-FDG uptake (%ΔSUVmax); receiver operating characteristics (ROC) analyses were done to assess sensitivity and specificity of FDG-PET to determine its diagnostic accuracy. The mean SUV in NACCRT group decreased from 15.47 ± 2.92 to 7.31 ± 4.07 ($P < 0.001$), while in NACT group, mean SUV decreased from 14.74 ± 3.95 to 8.60 ± 3.89 ($P < 0.001$). Comparison between NACCRT and NACT leads to mean SUV of 57.80 ± 22.40 and 45.92 ± 19.23, respectively ($P = 0.13$). In NACCRT and NACT, TRG had mean %ΔSUVmax values of 2.53 ± 1.25 and 2.93 ± 1.28 ($P = 0.393$). However, we found a statistically significant correlation between SUV% reduction and TRG ($P = 0.002$). ROC curve analysis for FDG-PET-CT suggested an area under the curve of 0.693 and sensitivity and specificity of 80% and 46.7%, respectively. NACCRT and NACT lead to a statistically significant reduction in mean %ΔSUVmax and with statistical significance correlation when compared with pathological response assessment. Hence, PET-CT can be used for differentiating responders and nonresponders to NAT.

Keywords: Esophageal cancer, neoadjuvant chemoradiation, neoadjuvant chemotherapy, positron emission tomography, response

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Introduction

Esophageal carcinoma is the sixth most common cause of cancer death worldwide and the fourth most common cause of deaths due to cancer in the developing countries.[1] Adenocarcinoma and squamous cell carcinoma (SCC) are the two major types of esophageal cancer.[2] Up until 10 years ago, the only treatment that offered an opportunity of healing was surgical resection. However, this therapeutic option presents mortality around 10% and is associated with high rates of local disease failure of approximately 58% and a dismal 5-year survival rate of 14%.[3,4] The current research data have demonstrated that neoadjuvant concurrent chemoradiation (NACCRT) or neoadjuvant chemotherapy (NACT) improves both disease-free survival and overall survival rates in this disease with dismal prognosis.

Positron emission tomography-computed tomography (PET-CT) has been shown to be of incremental value in the primary staging of esophageal cancer. Findings on the PET-CT examination can change patient stage in up to 40% of patients and change management in up to 34% of cases.[5] PET results can also provide prognostic information.[6] [^{18}F]-fluorodeoxyglucose (FDG) PET-CT examination results can affect patient management in approximately 22% of patients.[7] FDG-PET-CT imaging can be used to evaluate response to neoadjuvant therapy (NAT) as CT imaging is generally ineffective for determining pathologic tumor response. FDG-PET currently seems to be the best imaging modality for the assessment of response to NAT in esophageal cancer.[8] A decrease in FDG uptake has been found to be significantly greater in patients who are responding to therapy, and changes in FDG uptake occur before any change in tumor size. Effective assessment of tumor can be predicted as early as 14 days to 5–6 weeks, following initiation of neoadjuvant treatment.[9]

The patients who receive maximum benefit from neoadjuvant combination chemotherapy and radiation therapy (NACCRT) are those who achieve a pathological complete response (pCR), with no residual cancer cells in the primary tumor or lymph nodes. A pCR occurs in approximately 15%–30% of cases, and 3-year survival rates of approximately 60% irrespective of the applied protocol, type of histology, and tumor stage are achieved.[10] A further subdivision of pathological response to neoadjuvant regimens, the tumor regression grade (TRG),[11] may also identify patterns of incomplete response that may impact on treatment outcome, and the addition of the pathologic tumor-node-metastasis response to staging has been recently advocated.[12] We report, herein our study, the correlation between FDG uptake using standardized uptake value (SUV) before and after NAT and the histopathological response after surgery using TRG.

Methods

This randomized prospective study has been carried out in thirty consecutive patients; 15 in each arm including both males and females of carcinoma esophagus middle and lower one-third of both histologically proven squamous carcinoma and adenocarcinoma from March 2014 to October 2016 in the Department of Radiation Oncology of our Institute after obtaining written informed consent from the patients. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The sample size was calculated keeping in view at the most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). However, consideration of the past data, which give idea of variation in the variables, played an important role in calculating the sample size. The sample size estimation was done by calculating intake of locally advanced esophageal cancer, satisfying all inclusion criteria at our center from previous year's hospital records.

Eligibility criteria

For the patients included in the study, the length and width of the tumor were not exceeded 8 and 5 cm, respectively. Only patients with tumors of clinical stage T1N1 or T2-3N0-1 with no clinical evidence of metastatic spread, according to the International Union against Cancer Tumor-Node-Metastasis classification, were enrolled. Eligible patients were 18–75 years of age, had a World Health Organization performance status score of 2 or lower (on a scale of 0–5, with 0 indicating fully active, 1 unable to carry out heavy physical work, and 2 up and about more than half the day but unable to work), and had lost 10% or less of body weight. Patients also had to have adequate hematologic, renal, hepatic, and pulmonary function, as well as no history of other cancer or previous radiotherapy (RT) or chemotherapy.

Randomization and treatment

Patients were randomized into two groups using a piece of paper method. The terms NACCRT NACT were written separately on each piece of paper, and the patients were asked to pick up a random piece of paper at the registration counter in the presence of a blind observer. The patients were assigned to a particular group according to the respective piece of paper picked up by them. In both groups, patients were evaluated with [^{18}F] FDG-PET CT scan in addition to upper

gastrointestinal endoscopy (UGIE) and biopsy. After initial work-up, the patients in NACCRT arm received five cycles of weekly chemo-RT intravenous (IV) injection carboplatin targeted at an area under the curve (AUC) of 2 mg/ml/min and injection paclitaxel 50 mg/m^2 of body surface area (BSA) for 23 days with concurrent RT 41·4 Gy, given in 23 fractions of 1·8 Gy on 5 days/weeks followed by surgery. In NACT arm, the patients received two cycles of 3 weekly chemotherapy with injection paclitaxel 175 mg/m^2 and injection carboplatin targeted at an AUC 5 mg/ml/min.

Postneoadjuvant therapy evaluation

In both groups, a repeat work-up involving UGIE and FDG-PET-CT was performed to assess the response to NAT after 5 weeks of NACCRT and NACT before patients were taken up for surgery. Whole-body FDG-PET-CT scan spanning base of skull to mid-thigh was done 45 min after IV injection of 370 MBq (Millibequerel) of [^{18}F] FDG using a whole-body full ring dedicated lutetium oxyorthosilicate PET-CT scanner. CT images were obtained using 130 KV and 90 mA (mean) without administration of IV or oral contrast. SUVs were determined with a small fixed-dimension region of interest (ROI), 8 mm in diameter; the value was determined using the highest activity inside this area. SUVs were calculated after correction of radioactive decay according to the following formula: SUV = ROI activity (MBq/ml)/injected dose (MBq/body weight g). ROIs were drawn at every level where tumor tissue was detectable, and maximal SUV was the highest detectable value inside the tumor. SUV of the primary tumor was determined at baseline and after therapy. Maximal SUV of the pretreatment scan was labeled as SUV1 and the posttreatment scan as SUV2. Change percentage (SUVΔ%) was expressed as ([SUV1 − SUV2]/SUV1) × 100.

Surgery and histological analysis

The patients in both NACCRT and NACT arms underwent surgery preferably within 5–6 weeks of neoadjuvant treatment. A video-assisted thoracoscopic surgical (VATS) esophagectomy approach was adopted for tumors involving middle and lower one-third. For tumors involving the lower one-third where VATS was not possible, a transhiatal resection was performed. As per histology, the specimens were separated into two groups as per Mandard classification with or without regressive changes, while the regressive changes included the stromal changes and cytological alterations.[11] Basing on these changes, the tumor regression was classified into five histological TRGs based on vital tumor tissue at the ratio of fibrosis: TRG 1 was defined as complete regression fibrosis without detectable tissue of tumor; TRG 2 was defined as fibrosis with scattered tumor cells; TRG 3 was fibrosis and tumor cells with preponderance of fibrosis; TRG 4 was fibrosis and tumor cells with preponderance of tumor cells; TRG 5 was tissue of tumor without changes of regression. Patients with TRG 1–2 were considered responders while 3–5 were considered nonresponders.

Statistical analysis

All analysis was performed with SPSS version 17.0 (Chicago). All quantitative data were expressed as medians (ranges). The diagnostic accuracy of [^{18}F]-FDG-PET-CT was calculated by the receiver operating characteristics (ROC) curve test. The area under the ROC curve (AUC) provides a measure for the accuracy of a diagnostic test. It ranges from 0.5 to 1.0. The optimum cutoff value for differentiation of responding and nonresponding tumors was defined by the point of ROC curve with minimum distance from the 0% false positive rate and 100% true positive rate. The correlation between the SUV% and TRG was compared between NACCRT and NACT groups using a paired *t*-test.

Results

The basic demographics are shown in Table 1. The median age was 58 years; there was a male preponderance. Of 30 patients, 27 (90%) patients had squamous histopathology with involvement of middle one-third of the esophagus. Most patients had stage III disease.

Change in standardized uptake values postneoadjuvant treatment in responders and nonresponders

In NACCRT group, in 33.3% responders, the SUV fell from 12.58 ± 1.68 to 2.36 ± 0.52 ($P < 0.0002$), while

Table 1: Patient characteristics

Factor	*n* (%)
Male/female	24/6
Mean age (years)	58
Pathology	
SCC	27
Adenocarcinoma	3
Stage	
IIB	2
IIIA	16
IIIB	12
Site	
Middle 1/3rd	17
Lower 1/3rd	5
Middle and lower 1/3rd	8
Regional distribution	
North India	16
South India	3
Western India	9
Eastern India	2

SCC: Squamous cell carcinoma

in 66.7% nonresponders, SUV fell from 16.92 ± 2.24 to 9.78 ± 2.19 ($P < 0.0001$) [Table 2]. In NACT group, in 20% responders, SUV fell from 9.7 ± 0.85 to 2.0 ± 0.43 ($P < 0.005$), while in 80% nonresponders, SUV fell from 16.0 ± 2.53 to 10.25 ± 2.09 ($P < 0.0001$) [Table 3]. The mean SUV in NACCRT group fell from 15.47 ± 2.92 to 7.31 ± 4.07 ($P < 0.001$) [Figure 1] while in NACT group fell from 14.74 ± 3.95 to 8.60 ± 3.89 ($P < 0.001$) [Figure 2]. Although there was a statistically significant reduction in SUV in both groups after neoadjuvant treatment, a comparison between the NACCRT and NACT arm leads to a mean SUV of 57.80 ± 22.40 and 45.92 ± 19.23, with a nonsignificant $P = 0.13$. This concluded that both treatments result in a significant metabolic response; however, one does not outperform the other in a statistically significant manner.

Table 2: %ΔSUV values and tumor regression grade in NACCRT group

SUV_{max} uptake		%ΔSUV	Tumor regression grade (Mandard)
Before NACCRT	After NACCRT		
12.4	2.1	83.06	3
19.5	12.4	57.25	3
16.3	9.3	42.94	2
17.6	10.6	39.72	3
21.5	14.2	33.95	4
16.2	9.8	39.50	4
11.4	1.8	98.2	1
14.5	9.1	37.24	4
16.5	10.3	37.57	3
15.2	8.6	43.42	2
10.8	2.3	91.8	1
14.3	7.2	49.65	1
17.6	8.3	52.84	3
15.1	2.4	84.10	2
13.2	3.2	75.75	1

SUV_{max}: Maximum standardized uptake value

Table 3: %ΔSUV values and tumor regression grade in neoadjuvant chemotherapy group

SUV_{max} uptake		%ΔSUV	Tumor regression grade (Mandard)
Before NACT	After NACT		
10.5	2.2	79.04	2
8.8	1.5	82.95	1
9.8	2.3	76.53	3
17.5	11.1	36.57	4
18.6	12.8	31.18	3
16.8	10.5	37.5	2
19.1	13.6	28.79	5
12.5	6.4	48.8	3
16.5	10.8	52.77	2
17.5	9.8	44.00	1
15.3	12.1	20.91	2
12.4	8.6	30.64	3
11.5	7.5	34.78	4
16.8	10.4	38.09	4
17.5	9.4	46.28	4

NACT: Neoadjuvant chemotherapy; SUV_{max}: Maximum standardized uptake value

Tumor regression grade 1–2 versus tumor regression grade 3–5 in NACCRT and neoadjuvant chemotherapy group

In NACCRT group of 15 patients, 7 (46.6%) had achieved a complete or near-complete response (TRG 1–2) while 8 (53.4%) had less or no response (TRG 3–5), while in NACT group of 15 patients, 6 (40%) had TRG 1–2 while 9 (60%) had TRG 3–5. In NACCRT group, TRG had a mean value of 2.53 ± 1.25, while in NACT group, TRG had a mean value of 2.93 ± 1.28, with a nonsignificant difference, $P = 0.393$ [Figures 3 and 4]. This concluded that there is no statistically significant difference between the NACCRT and NACT groups as far as TRG is concerned.

Correlation between standardized uptake value percentage reduction and tumor regression grade

In our study, we found a significant correlation between the %ΔSUVmax reduction and TRG after analyzing the data of all thirty patients in both NACCRT and NACT groups with a significance value of 0.002, where correlation is significant at a value of 0.01 level (two-tailed) [Figures 5 and 6].

Receiver operating characteristics curve analysis

The sensitivity and specificity of [18F] FDG PET scan was 80% and 46.7% respectively determined by ROC Curve Analysis having an AUC of 0.693.

Discussion

Carcinoma esophagus constitutes a major portion of upper gastrointestinal tract pathologies, enforcing a significant health-related burden on the society around the world. Over the last few decades, the world is seeing

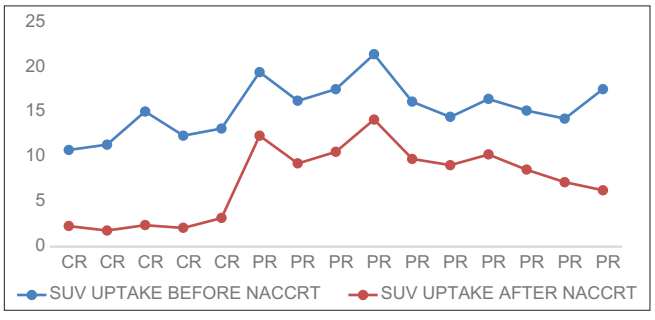

Figure 1: Response assessment post-NACCRT by standardized uptake value

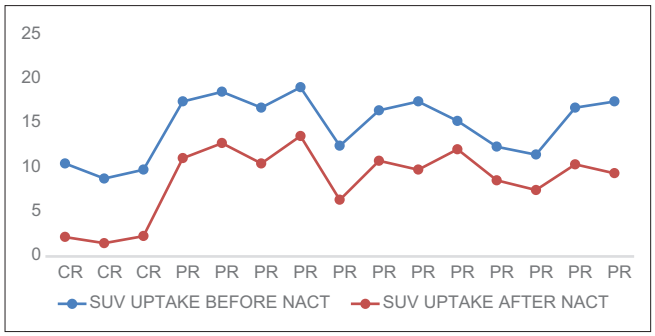

Figure 2: Response assessment postneoadjuvant chemotherapy by standardized uptake value uptake

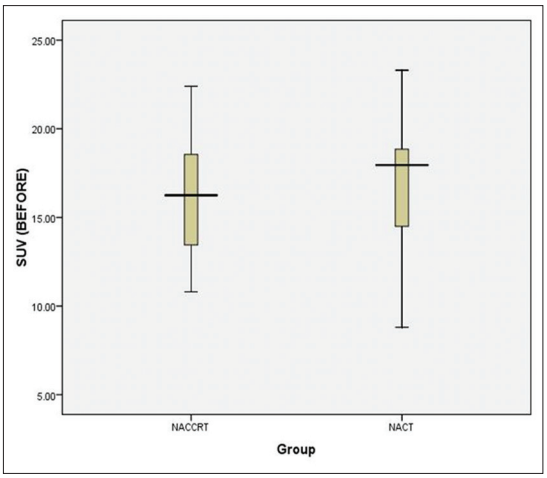

Figure 3: Box and Whisker representation of pretreatment standardized uptake value values in NACCRT and neoadjuvant chemotherapy groups

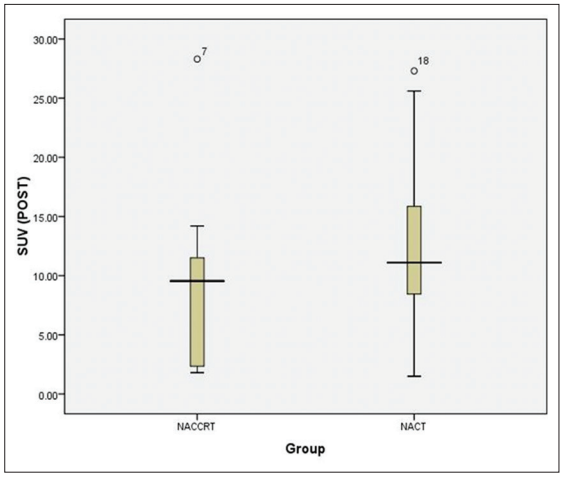

Figure 4: Box and Whisker representation of posttreatment standardized uptake value values in NACCRT and neoadjuvant chemotherapy groups

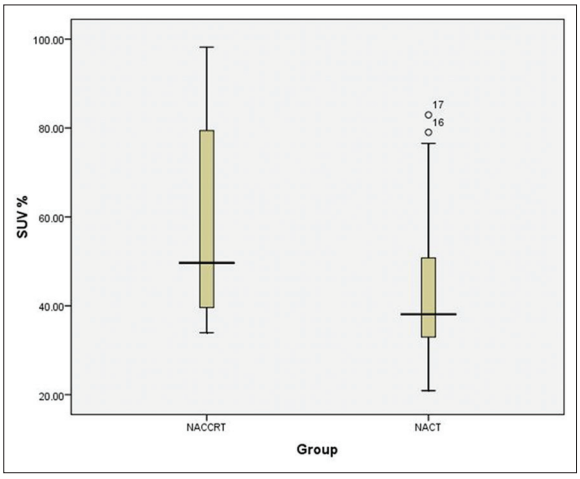

Figure 5: Box and Whisker representation of standardized uptake value % change in NACCRT and neoadjuvant chemotherapy groups

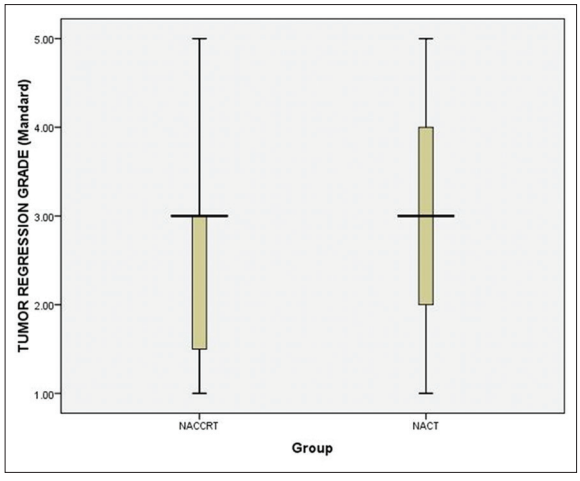

Figure 6: Box and Whisker representation of tumor regression grade in NACCRT and neoadjuvant chemotherapy groups

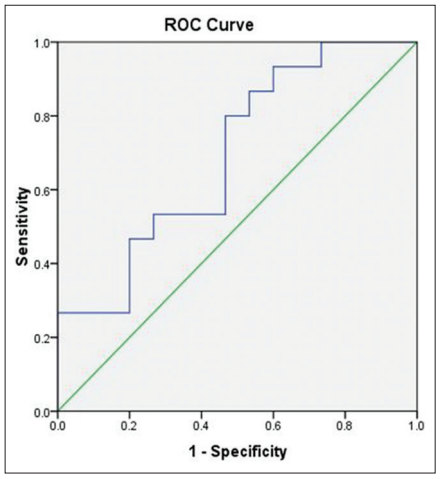

Figure 7: Receiver operating characteristics curve analysis for prediction of histopathological response by maximum standardized uptake value percentage change after neoadjuvant therapy

a dramatic shift in the location of lesion from upper and middle portion to lower one-third and esophagogastric junction (EGJ). Eastern Europe and Asia harbor most cases of SCC, while adenocarcinoma predominates in North America and Western Europe. Tobacco and alcohol abuse are major risk factors for SCC, whereas

the use of tobacco is a moderately established risk factor for adenocarcinoma.[2] Barrett's esophagus, obesity, high body mass index, and gastroesophageal reflux disease seem to be the major risk factors for development of adenocarcinoma of the esophagus or EGJ.[3] Males constitute the dominant sex being affected by this disease. In the early 1900s, RT was the primary treatment of cancer of the esophagus, but cure was considered a rare event. Since the 1930s with progress in anesthetic and surgical techniques, esophagectomy became the treatment of choice with localized disease. However, with the introduction of concurrent chemoradiation protocols, regardless of the use of platinum, it offers a clear advantage when compared to RT alone.[13,14]

In many cases, treatment of localized esophageal cancer relies on a multimodality approach. Routinely, in more locally advanced cases, use of chemotherapy in combination with radiation is used in a neoadjuvant fashion. The aim of NAT is to improve the control of both local and distant diseases while allowing for a more complete resection. Assessing response to NAT is important in providing information for planning further treatment. In the past, CT, magnetic resonance imaging, and endoscopic ultrasound have all been employed to assess response to NAT with mixed success. FDG-PET offers a functional alternative to anatomical imaging in assessing response to treatment. Moreover, the metabolic changes may precede structural changes, and this has been confirmed for certain solid tumors.[15]

There are very few studies which have compared both the forms of neoadjuvant treatments, i.e., NACCRT and NACT, and their correlation with metabolic response on FDG-PET-CT and TRG. The feasibility of [^{18}F]-FDG-PET-CT in predicting response to NACT in esophageal adenocarcinoma was presented in the MUNICON II trial by Lordick *et al*. They have shown how 35% regression of tumor FDG metabolism during neoadjuvant chemotherapy can serve to guide patients into either a neoadjuvant and surgery- or a surgery-only group. Their cutoff value of 35% had a sensitivity of 100% and specificity of 58%.[16] Our results of ROC analysis are in line with other studies with a cut off value of 38% which indicates a sensitivity and specificity of 46.7% respectively [Figure 7].

Kauppi *et al*. in their study in locally advanced adenocarcinoma of the esophagus found a > 67% change in baseline maximal SUV optimally predicted histopathological response(Sensitivity 79% and Specificity 75%) and they concluded that [^{18}F]-FDG-PET CT can distinguish a group of patients with worse prognosis after NACT.[17] In our study also, in NACT group, in responders (20%), SUV fell from 9.7 ± 0.85 to 2.0 ± 0.43 (P < 0.005), while in 80% nonresponders, SUV fell from 16.0 ± 2.53 to 10.25 ± 2.09 (P < 0.0001), suggesting a good correlation between change in SUV value and response.

In a study by Gillham *et al*., in the responders (28%), the SUV fell from 12.6 (±6.3) to 8.1 (±2.9) after 1 week of chemoradiation (P = 0.070), while in nonresponders (72%), the results were 9.7 (±5.4) and 7.1 (±3.8) (P = 0.003).[18] There were no significant differences between responders and nonresponders. The hypothesis that early repeat FDG-PET scanning may predict histomorphologic response was not proven in this study. In our study, in NACCRT group, in responders (33.3%), the SUV fell from 12.58 ± 1.68 to 2.36 ± 0.52 (P < 0.0002), while in 66.7% nonresponders, SUV fell from 16.92 ± 2.24 to 9.78 ± 2.19 (P < 0.0001), while we performed a FDG-PET-CT after 5–6 weeks of neoadjuvant treatment. In contrast, in our study, we found a significant correlation between change in SUV and TRG in both NACT and NACCRT groups (P = 0.002).

Conclusion

We could not find much literature even after extensive research where a head-to-head comparison has been done between NACT and NACCRT groups. In our study, we found that though there was a statistically significant reduction in SUV in both groups after NAT, a comparison between the NACCRT and NACT arm leads to a mean SUV of 57.80 ± 22.40 and 45.92 ± 19.23 with a nonsignificant difference, P = 0.13. This concluded that both treatments result in a significant metabolic response; however, one does not outperform the other in a statistically significant manner. An early marker of response offers the greatest potential clinical advantage, particularly if those not benefiting from treatment could be identified and offered alternative approaches, and this was the hypothesis evaluated in this study. However, the major drawback of this study was a small sample size. Despite that, we could conclude by this study that [^{18}F]-FDG-PET-CT is a good diagnostic modality for response assessment after NAT in locally advanced carcinoma esophagus patients and helps in differentiating between responders and nonresponders significantly.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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