Article published online: 2022-04-22

Original Article

Using positron-emission tomography–computed tomography for predicting radiotherapy-induced tumor regression in carcinoma esophagus in an Indian population

ABSTRACT

Carcinoma esophagus is a common malignancy of the Indian subcontinent. The role of positron-emission tomography–computed tomography (PET-CT) in the assessment of response to radiotherapy has been widely studied and accepted. However, its precise use as a predictive tool for actual histopathological response to radiotherapy needs further evaluation, especially in an Indian population. The aim of this study was to identify a quantum of metabolic response on PET-CT that can also predict for a good pathological response. Forty-four patients of carcinoma esophagus treated with neoadjuvant chemoradiotherapy followed by surgery were included in the study. All patients underwent a PET-CT before starting treatment as well as at 4–6 weeks after completion of radiotherapy. The percentage change in pre and posttreatment maximum standardized uptake value (SUV_{max}) value (ΔSUV%) of the primary tumor was correlated against histopathological tumor regression grade (TRG) as per the Mandard's system. Seventy-five percent of the patients with a significant metabolic response, i.e., a ΔSUV% of 60% or more, also had a good pathological response to treatment. Thus, by considering a ΔSUV% of 60%, we could predict for a good pathological response (TRG of 1 or 2) to chemoradiotherapy in our patient set with a sensitivity of 95.45% and a specificity of 72.72%.

Keywords: Carcinoma esophagus, positron-emission tomography–computed tomography, radiotherapy

INTRODUCTION

Carcinoma esophagus is the eighth most common cancer in the world with a very poor survival (overall ratio of mortality to incidence of 0.88).[1] In the cancer registry of Pune district in India, it is the fifth most common cancer overall.[2] The standard of care for the management of locally advanced disease remains multimodality therapy with neoadjuvant chemoradiotherapy followed by surgery. Although the magnitude of benefit with neoadjuvant therapy remains unclear, several studies have shown the prognostic significance of pathological response and histopathological tumor regression after neoadjuvant therapy in both squamous carcinoma and adenocarcinoma of the esophagus in terms of improved disease-free survival (DFS) and overall survival (OS) in patients with pathological complete response (pCR) compared to patients with partial or no pathological response.[3-6] The rate of R0 resections is also seen to be the highest in the subset of patients with pathological response in these studies (94%–100% in responders vs. 64%–88% in nonresponders).[5,6] Postoperative

Sankalp Singh, Niharika Bisht[1], Arti Sarin[1], A. V. S. Anil Kumar[2], Samir Gupta[1], Amul Kapoor[1], Prabha Shankar Mishra[3]

Department of Radiation Oncology, Command Hospital (CC), Lucknow, Uttar Pradesh, Departments of [1]Malignant Disease Treatment Centre, [2]Nuclear Medicine and [3]Pathology, Command Hospital (SC), Pune, Maharashtra, India

Address for correspondence: Dr. Niharika Bisht, Command Hospital (SC), Pune - 411 040, Maharashtra, India. E-mail: niharikabisht@gmail.com

Submission: 14-12-2018 **Accepted:** 11-04-2019 **Published:** 18-12-2019

How to cite this article: Singh S, Bisht N, Sarin A, Kumar AA, Gupta S, Kapoor A, *et al*. Using positron-emission tomography–computed tomography for predicting radiotherapy-induced tumor regression in carcinoma esophagus in an Indian population. World J Nucl Med 2019;18:361-5.

Access this article online	
Website: www.wjnm.org	Quick Response Code
DOI: 10.4103/wjnm.WJNM_114_18	

tumor stage has also been shown to be the best predictor of survival outcome in patients of carcinoma esophagus and gastroesophageal junction who have undergone preoperative chemoradiotherapy followed by surgery.[7] Although several tumor regression grading systems have been proposed, the three-tier system proposed by Wu *et al*. has been reported to have an excellent interobserver agreement in grading the residual tumor in patients of esophageal carcinoma.[8]

Positron-emission tomography–computed tomography (PET-CT) has also been used extensively in the assessment of treatment response, and the prognostic significance of metabolic response postneoadjuvant chemoradiotherapy in patients of locally advanced carcinoma esophagus has been established in several studies.[9-13] However, there still remains uncertainty about the timing of the PET-CT scan after chemoradiation (2–6 weeks),[11,14] as well as the reduction in the maximum standardized uptake value (SUV_{max}) that should be considered significant (varies from 35% to 80% in studies)[11,14-16] in terms of predicting pathological response.

Aim

It was our endeavor in this study to try to identify a quantifiable degree of metabolic response seen on 18F-fluoro-2-deoxyglucose positron-emission tomography–computed tomography (18-FDG PET-CT) in patients of carcinoma esophagus treated with neoadjuvant chemoradiotherapy that may be predictive or indicative of histopathological response seen postradical surgery in an Indian population.

MATERIALS AND METHODS

This was a retrospective analysis of patients of locally advanced carcinoma esophagus treated with neoadjuvant chemoradiotherapy followed by surgery. After requisite approval from the departmental ethical committee, medical records of all patients of carcinoma esophagus (squamous or adenocarcinoma) treated with curative intent at a tertiary cancer hospital between January 2015 and June 2017 were retrieved and analyzed. Only patients who were treated with neoadjuvant chemoradiotherapy followed by radical surgery were selected. All patients were planned on a Nucletron conventional simulator using conventional two-dimensional planning techniques and were treated on a Theratron 780E telecobalt machine. All patients received a dose of 4500 cGy in 25 fractions at 180 cGy per fraction. The concurrent chemotherapy regimens used were paclitaxel + carboplatin, cisplatin + 5-fluorouracil, cisplatin + capecitabine, or cisplatin alone. Four patients received radiotherapy alone due to expected poor tolerance to concurrent chemotherapy either due to an existing comorbidity or due to a poor performance status.

It was mandatory for the patient to have undergone a whole-body PET-CT scan before starting (PET1) and at 4–6 weeks after completing (PET2) radiotherapy to be included in the study. The percentage change in SUV_{max} for the primary lesion between PET1 and PET2 was calculated for all patients and was termed ΔSUV%. All patients with 60% or more reduction in SUV_{max} of the primary lesion between PET1 and PET2, i.e., a ΔSUV% of 60% or more, were defined as having a good metabolic response (GMR). The value of 60% for ΔSUV% was decided upon after a thorough and extensive literature review which showed the range of reduction in SUV_{max} before and after radiotherapy in carcinoma esophagus to vary between 35% and 80%.[11,14-16] The various parameters considered in the study are defined in Table 1.

On the basis of tumor regression grade (TRG) reported in the final histopathology report, the patients were classified into good pathological responders (GPRs) and poor pathological responders (PPRs). The Mandard's system[17] [Table 2] was used for reporting TRG. Patients with TRG score of 1 or 2 were included in the GPR group and those with TRG score of 3, 4, or 5 were placed in the PPR group. The list of patients in the GMR group and those in the GPR group was compared, and the concordance between the two lists was analyzed to see

Table 1: Parameters used in the study

Parameter	Definition
PET1	PET-CT done before commencement of NACCRT
PET2	PET-CT done at 4-6 weeks after completion of NACCRT
ΔSUV%	Percentage decrease in SUV_{max} of primary lesion between PET1 and PET2
GMR	Good metabolic response - Value of ΔSUV% ≥60%
TRG	Tumor regression grade (Mandard's system for reporting TRG used)
GPR	Good pathologic response - TRG score of 1 or 2
PPR	Poor pathologic response - TRG score of 3, 4, or 5

PET: Positron-emission tomography; CT: Computed tomography; GMR: Good metabolic response; TRG: Tumor regression grade; GPR: Good pathological responders; PPRs: Poor pathological responders; SUV_{max}: Maximum standardized uptake value; NACCRT: Neo Adjuvant Concurrent Chemo Radiotherapy

Table 2: Mandard's system for reporting tumor regression grade

TRG	Histopathological description
TRG 1	No viable cancer cells, complete response
TRG 2	Single cells or small groups of cancer cells
TRG 3	Residual cancer outgrown by fibrosis
TRG 4	Significant fibrosis outgrown by cancer
TRG 5	No fibrosis with extensive residual cancer

TRG: Tumor regression grade

whether a correlation existed between the ΔSUV% and the histopathological response.

RESULTS

A total of 60 patients of carcinoma esophagus (excluding cervical esophagus) were treated between January 2015 and June 2017 in the radiotherapy department of our hospital. The ratio of males to females was 37:23. Fifty-two of the cases were squamous carcinoma, whereas only 8 were adenocarcinoma despite the preponderance of lower esophageal disease. There were 14 cases with upper third of the esophagus involved, 19 with middle third of the esophagus, and 21 with lower third of the esophagus and esophagogastric junction involvement. In 6 cases, more than one subsite of the esophagus was involved, and the origin of the primary was not discernible.

Six patients were metastatic and were offered palliative radiotherapy only. Two patients were referred after surgery and received postoperative radiotherapy, whereas 4 patients were treated with definitive chemoradiotherapy. A total of 48 patients were treated with neoadjuvant radiotherapy. Of these, one patient did not complete treatment and 3 were lost to follow-up. Thus, a total of 44 patients were available for the analysis and were included in the study.

The mean pretreatment SUV_{max} was 12.79 (5.8 to 25.25) and mean posttreatment SUV_{max} was 6.90 (12.2 to 0.0). The mean ΔSUV% was 54% (100% to 0%). Nearly 63.63% (28/44) of patients who underwent surgery showed a GMR. The percentage of patients who showed GPR was 47.72% (21/44). Figure 1 shows pre- and postradiotherapy PET-CT image of a patient who experienced a GMR.

All the 21 patients with a GPR had also shown a GMR; however, 7 (25%) patients with a GMR did not show a GPR. There was one case who did not show a GMR but had a very good response on histopathology with a TRG of 1.

A summary of the results is given in Table 3.

DISCUSSION

Although a vast number and variety of Western studies have been carried out on the use of PET-CT for response assessment and prognostication in esophageal cancer treated with chemoradiotherapy, the majority of cases in these studies are adenocarcinomas. In India and other Asian countries, squamous cell carcinomas tend to be the dominant histology,[18] as was seen in our study as well. The utility of FDG PET-CT should be re-examined in our patient population due to this variation in histology as 18-FDG has been shown to have differential uptake in squamous and adenocarcinomas.[19]

By correlating metabolic response as seen on serial PET scans with the final histopathological response to chemoradiotherapy, it may be possible to not only prognosticate patients accurately but also identify patients likely to have a complete response to neoadjuvant therapy and avoid radical surgery.

In our study, 64% of the patients had a significant metabolic response to chemoradiotherapy (≥60% reduction in SUV_{max}). Among these patients with significant metabolic response, 75% (21/27) had a TRG of 1 or 2 indicating good pathological response [Figure 2] and possible better prognosis (OS or DFS) compared to those who did not have a good pathological

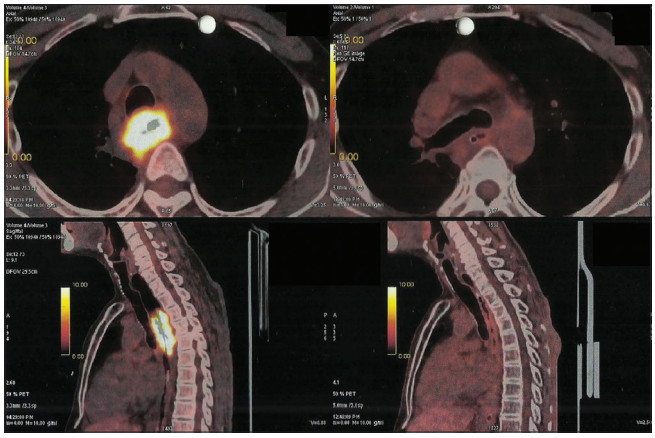

Figure 1: Pre- and postchemoradiotherapy positron-emission tomography–computed tomography scans showing complete metabolic response in a patient of carcinoma of the upper thoracic esophagus

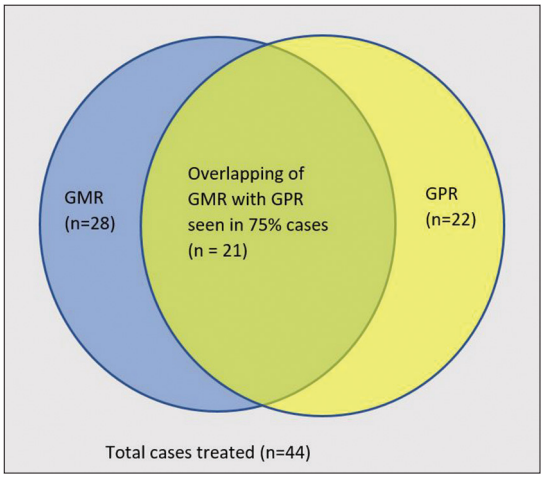

Figure 2: Venn diagram showing a 75% overlap between patients who showed a good metabolic response and those who also had a good pathological response

Table 3: A summary of the study observations

Parameter	Observation	
Total cases	60	
Sex ratio (male:female)	37:23	
Site-wise division of tumors (%)	Upper third - 14 (23) Middle third - 19 (32) Lower third - 21 (35)	6 tumors were multicentric with primary site not discernible
Histopathology (%)	52 squamous (87) versus 8 adenocarcinoma (13)	
Cases included for the study	44 (6 metastatic, 2 opted upfront, 4 treated with radical CRT, and 4 lost to follow-up)	
Mean pretreatment SUV_{max}	12.79 (5.8-25.25)	
Mean posttreatment SUV_{max}	6.90 (12.2 - 0.0)	
Mean ΔSUV%	54% (100% - 0%)	
GMR seen in	63.63% of cases (28/44)	
GPR seen in	50% of cases (22/44)	
Proportion of patients with GMR who also had GPR	75% (21/28)	
Proportion of patients with GMR who did not have GPR	25% (7/28)	
Proportion of patients who did not have GMR but had GPR	6.25% (1/25)	
Mean ΔSUV% in patients with GPR	85% (45%-100%)	

GMR: Good metabolic response; GPR: Good pathological responders; SUV_{max}: Maximum standardized uptake value

response. This is similar to what is previously published in the literature.[9-13]

In the remaining 25% though, the GMR did not translate into a good pathological response and their TRG varied from 3 to 5. The possible explanations for this lack of correlation between metabolic and histologic responses are as follows:

- Decreased FDG uptake after irradiation is mainly due to the reduced number of metabolically active tumor cells. However, a decrease of FDG PET does not always predict a good response because FDG can differentiate metabolically active cells from dead cells but cannot differentiate biologically viable from metabolically active cells[20]
- Variable 18-FDG uptake in residual hypoxic or necrotic tumor cells[21]
- Possible accelerated repopulation of residual tumor cells between time of second PET scan and surgery
- Respiratory motion artifact is greatest at the level of the diaphragm and can lead to misregistration of PET and CT images,[22] resulting in variation in the calculated SUV_{max} of up to 30%–50%.

Thus, by considering a ΔSUV% of 60%, we could predict for a good pathological response (TRG of 1 or 2) to chemoradiotherapy in our patient set with a sensitivity of 95.45% and a specificity of 72.72%. For the above cutoff of 60%, the positive predictive value for a GPR was 77.77% and the negative predictive value was 94.11%.

There was one patient who did not show a significant metabolic response but had a good pathological response. Radiation-induced local inflammation probably contributed toward preventing an adequate fall in SUV_{max} to be included in the GMR group. This is an established phenomenon[22] and should always remain a differential in a patient who has improved clinically but has a poor response on PET-CT.

CONCLUSION

Thus, our study was able to show that in an Indian population set, PET-CT can be a useful tool in identifying patients of carcinoma esophagus who are likely to respond to treatment and have potentially improved survival postchemoradiotherapy. However, the modality is far from infallible or error free, and the methodology requires further refinement. The subject certainly merits further research in the form of prospective studies and new innovations like more specific radionuclides for PET scans.

Fallacies

The authors concede that the study does suffer from certain fallacies. These are listed below:

- The study is a retrospective analysis
- There is variation in the radiotherapy and chemotherapy schedules used between patients
- The timing of the PET-CT scans is not uniform for all patients and varies between 4 and 6 weeks in the postneoadjuvant period
- The results are not statistically significant
- Lack of follow-up to determine whether the metabolic and PET response actually translated into OS or DFS benefit.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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