Pictorial Essay

Role of Positron Emission Tomography/Computed Tomography in Gastrointestinal Malignancies: A Brief Review and Pictorial Essay

Abstract

Positron emission tomography/computed tomography (PET/CT) is increasingly becoming a mainstay in diagnosis and management of many malignant disorders. However, its role in the assessment of gastro-intestinal lesions is still evolving. The aim of this review was to demonstrate the areas, where PET/CT is impactful and where it has limitations. This will allow for us to reduce unnecessary investigations and develop methods to overcome the limitations.

Keywords: *Gastrointestinal malignancies, gastrointestinal stromal tumors, lymphoma, neuro-endocrine tumors, positron emission tomography/computed tomography*

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Introduction

Positron emission tomography/computed tomography (PET/CT) has become an essential component of management guidelines in many diseases such as lung, breast, and lymphoproliferative malignancies. The ability to image metabolic processes like glucose metabolism adds to the information provided by structural imaging, especially in the context of treatment monitoring, where metabolic changes can often precede structural changes.

This brief review will touch on the role of this modality in various gastrointestinal malignancies, including its strengths and limitations.

Esophageal Cancer

There are two major variants of esophageal cancer, namely squamous cell carcinoma and adenocarcinomas. This cancer has a very high mortality, with a 5-year survival of ~20%; which ranges from ~47% in patients with localized disease to <5% in patients who present with distant metastases.[1] Therefore, it is imperative that diagnosis is made at localized stage, so that curative and more aggressive treatment options can be made available to the patients.

At the time of baseline staging, both CT and PET/CT do not seem to have any significant role in T-staging as they cannot accurately assess the extent of tumor invasion and therefore endoscopic ultrasound (EUS) continues to be the most important investigation.[2,3] It also allows for sampling, which is necessary for confirmation of the disease. 18F-FDG-PET/CT has additional limitations in that it is unable to reliably differentiate confounding changes like inflammation from actual malignant pathology. However, in confirmed cases of esophageal malignancy, the semi-quantitative parameters derived from PET/CT (like SUV_{max}, metabolic tumor volume [MTV], and total lesion glycolysis [TLG]) can predict a locally advanced tumor in the preoperative period with good accuracy.[4] High SUV_{max} has also been shown to predict early recurrence and low survival.[4]

Similar to the T-staging, CT and PET/CT do not seem to offer any distinct advantage over EUS in the detection of locoregional lymph nodal metastases, especially when involved lymph nodes are small or in close relation to the primary disease.[2,3]

In contrast to little benefit shown in T and N-Staging, cross-sectional imaging with either CT or PET/CT does have a role in the detection of nonregional lymph nodal and distant metastases [Figure 1]. For these indications, PET/CT, with its ability to combine metabolic information with structural imaging, is superior to

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conventional modalities.[5] In comparison with CT imaging, PET/CT was shown to change management in ~40% of the patients, principally through detection of new metastases or ruling out false positives in CT.[6] Therefore, 18F-FDG-PET is recommended in patients, who are candidates for radical treatment.[7]

Although PET/CT has an intermediate sensitivity (pooled 0.62) and specificity (pooled 0.73) in the detection of pathological complete response;[8] changes in SUV_{max} and TLG can predict pathological complete response after neoadjuvant chemoradiotherapy.[9] However post RT changes such as esophagitis and ulceration can complicate reliable detection of residual disease.,[2,7] Still, its role in RT planning and mid-radiotherapy imaging (for prognosis) has shown some promise.[10,11]

Finally, 18F-FDG-PET/CT has been shown to be a reliable investigation for the detection of recurrent disease, with very high sensitivity and good specificity [Figures 2 and 3].[12,13]

Gastric Cancer

Like esophageal cancers, gastric cancers have a low 5-year survival of ~30% and most cases (36%) are detected with distant metastases at baseline.[14] For all practical purposes, gastroesophageal junction tumors behave similarly to the esophageal tumors and the above-mentioned concepts are

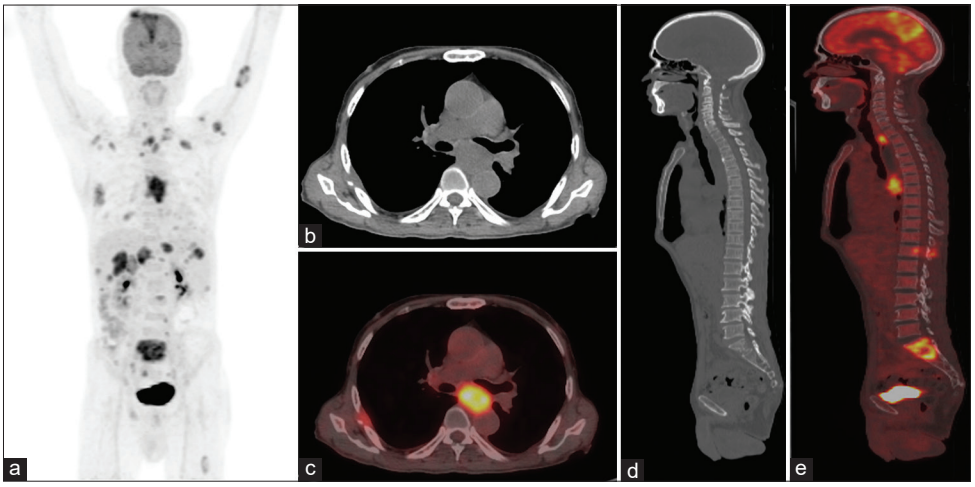

Figure 1: Case of 70-year-old male who presented with dysphagia and upper gastro intestinal endoscopy and subsequent fine-needle aspiration cytology revealed squamous cell carcinoma. The patient was referred for baseline staging in FDG Positron emission tomography/computed tomography and MIP (a), Axial computed tomography (b), Axial positron emission tomography/computed tomography (c), Sagittal computed tomography (d) and Sagittal positron emission tomography/computed tomography (e) are shown. While positron emission tomography/computed tomography played a minimal role in assessment of primary disease (b and c) in terms of local extent and regional lymphadenopathy; it was much superior to other modalities in detection of distant metastases. This was especially significant in this patient where there was a single paratracheal lymph node and no pulmonary metastases. The positron emission tomography/computed tomography was able to identify extensive distant metastases to axial and appendicular skeleton (a, d and e)

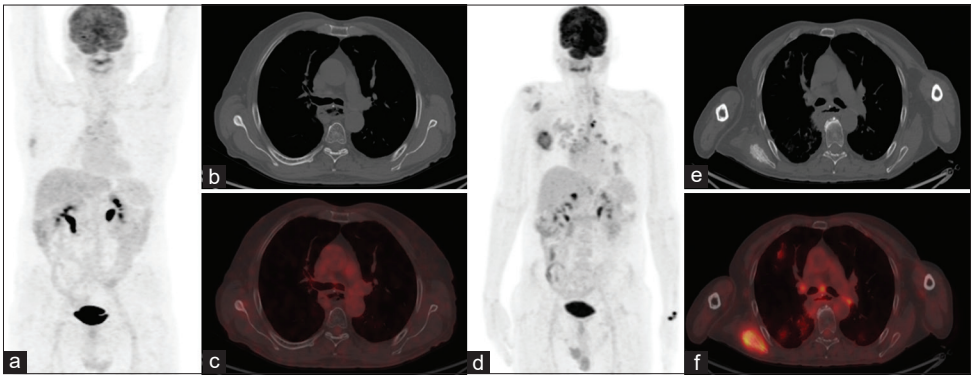

Figure 2: Case of 65-year-old male who underwent chemo-and radio-therapy for squamous cell carcinoma of the esophagus. The patient underwent surveillance FDG positron emission tomography/computed tomography (a [MIP], b [Axial computed tomography] and c [Axial Positron emission tomography/computed tomography]) 3 months after treatment, which showed no significant metabolically active residual disease at the site of the primary. However, an area with mildly increased radiotracer uptake was noted in relation to the lateral border of the scapula, with minimal sclerosis in the corresponding computed tomography images (a-c). Follow-up FDG Positron emission tomography/computed tomography (at 6 months from baseline) revealed progressive disease involving the right scapula (d [MIP], e [Axial computed tomography] and f [Axial Positron emission tomography/computed tomography]). Also note the areas of increased uptake in the both lungs and mediastinal lymph nodes, which were infective in origin. This case shows the sensitivity of Positron emission tomography/computed tomography in detection of even minimal residual disease (a-c), which might have otherwise been missed in computed tomography (due to minimal structural changes)

applicable to those lesions. On the other hand, nonjunctional tumors can show variable 18F-FDG avidity; with higher avidity in tumors having larger size, nonsignet cell histology and Glucose transporter-1 expression.[15] While, some studies have shown higher uptake and sensitivity of 18F-FDG-PET/CT in intestinal type lesions and in lesions with lesser mucin content;[16] others have shown avidity to be independent of Lauren classification.[17] Still, in our practical experience, the former is true in most cases [Figures 4 and 5].

In baseline imaging/initial staging, analogous to esophageal cancers, EUS is superior to both CT and PET/CT in the assessment of tumor depth (T-staging) and regional local nodal evaluation.[18,19] 18F-FDG PET/CT is inferior to CECT for some indications, due to low 18F-FDG avidity in some pathological variants. Still, uptake in the primary and lymph nodes has been shown to be associated with pathological stage.[20] Similarly, PET/CT is worse than CECT in loco-regional lymph nodal staging.[21] Still, 18F-FDG avidity in lymph nodes can be a marker of incurable disease and worse prognosis.[17]

The saving grace for PET/CT is its superiority in detection of distant metastases, which aids in the reduction in the number of unnecessary invasive procedures and radical treatments in patients who are unlikely to benefit from these [Figure 4].[18]

In the context of response assessment, PET/CT seems to contribute little in the detection of complete response; however, it can reliably identify nonresponders to neo-adjuvant chemotherapy, thereby aiding in selection of patients who should proceed to immediate resection/other multi-modal therapies.[22] Expectedly, the utility of PET/CT in response assessment of lesions with low 18F-FDG avidity is limited.

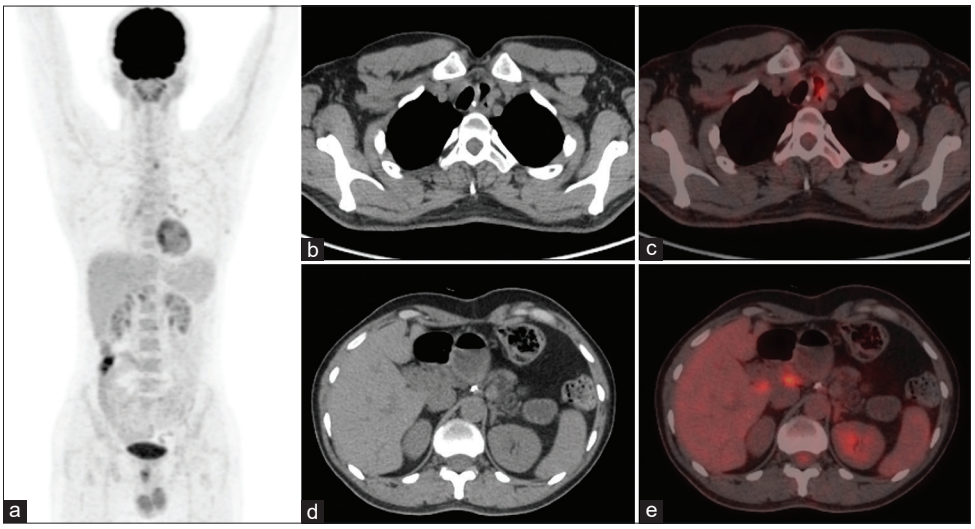

Figure 3: Case of 47-year-old male who underwent chemoradiotherapy and surgical resection (with gastric pull-up) for squamous cell carcinoma of the esophagus. The patient underwent surveillance FDG Positron emission tomography/computed tomography (a [MIP]; b, d [Axial computed tomography]; and c, e [Axial Positron emission tomography/computed tomography]) 6 months after treatment, which postsurgical recurrence in the para-esophageal lymph node (b and c) and peri-, porto-caval lymph nodes. Also note that all nodes were subcentimetric with low tumor burden, which further emphasizes the sensitivity of 18F-FDG Positron emission tomography/computed tomography

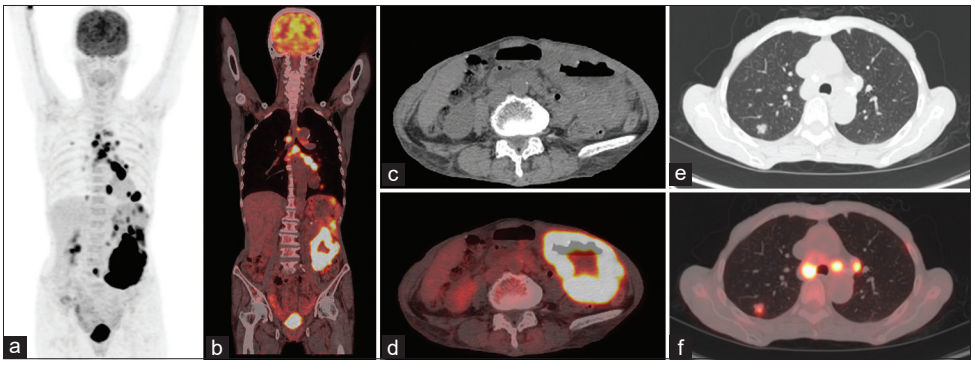

Figure 4: Case of 72-year-old female who was diagnosed as having adenocarcinoma of the stomach. Due to extensive nature of the primary disease, she underwent 18F-FDG Positron emission tomography/computed tomography for metastatic work-up (MIP [a], coronal positron emission tomography/computed tomography [b], Axial computed tomography [c and e], Axial positron emission tomography/computed tomography [d and f]). Apart from the bulky primary disease involving distal stomach and pylorus (b-d), extensive intensely FDG avid lymph-nodal (a, b, f) and pulmonary metastases were also found (e and f). Note must be made that this was "intestinal-type" variant, which explains the intense FDG avidity of the primary as well as metastatic disease

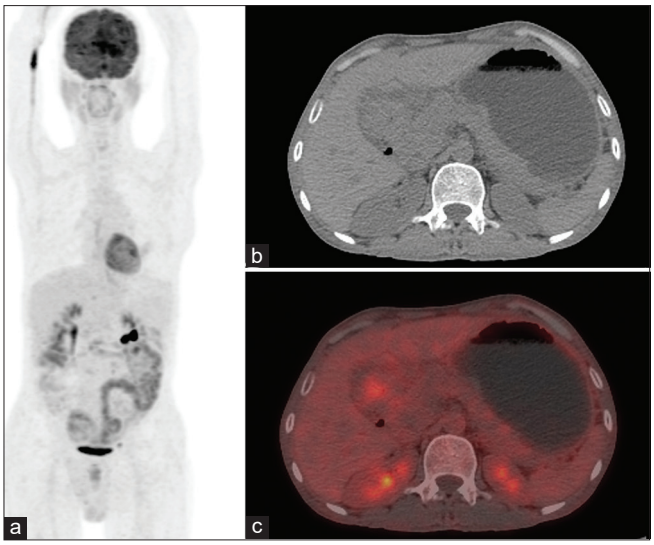

Figure 5: Case of 52-year-old male who presented with features of gastric outlet obstruction and was referred for 18F-FDG positron emission tomography/computed tomography for baseline evaluation (MIP [a], Axial computed tomography [b], Axial positron emission tomography/computed tomography [c]). Positron emission tomography/computed tomography showed a circumferential thickening involving the distal pylorus (b) and gastro-duodenal junction, but showing minimal to mild FDG uptake (a and c). The patient was later diagnosed as having Signet cell adenocarcinoma of the stomach, which have not been shown to be very 18F-FDG avid

In addition to 18F-FDG uptake in the primary and lymph-nodes, other parameters quantifying metabolic burden of disease like MTV and TLG have been used for prognostication after curative resection.[23]

Finally, bone-marrow uptake in postsurgical patients has been shown to be a marker of worse recurrence-free and overall survival.[24] It may be a marker for systemic inflammatory response.[25]

Small Intestinal Malignancies

In contrast to above-mentioned malignancies, small intestinal malignancies are usually detected earlier and have a better survival.[26] Survival improves significantly with curative resection and therefore accurate staging is paramount.[27] As with other gastrointestinal malignancies, PET/CT by itself is insufficient for assessing tumor depth and hence T-staging. Dedicated studies on the use of 18F-FDG PET/CT in small intestinal malignancies are rare and most literature has focused on lymphomas and neuroendocrine tumors. Both these indications will be discussed in a separate section. Still, PET/CT seems to provide an advantage in the assessment of metastatic sites, particularly distant metastases because of whole-body imaging and sensitivity of 18F-FDG to metabolic changes.[27] Furthermore, the use of PET/CT enterography can improve the assessment of primary disease, by improving rater confidence and reducing false positives.[28]

Colorectal Malignancies

Colorectal malignancies are usually detected at an earlier stage and consequently have a good 5-year survival.[29] As with other gastrointestinal malignancies, the role of PET/CT in the evaluation of T-stage is limited by its lower resolution, inadequacies in the assessment of true depth of involvement, physiological 18F-FDG activity, and confounding inflammatory lesions.[30] The combination of PET with CT colonography can improve specificity and allow for noninvasive assessment of obstructive lesions, where colonoscopic examination is not feasible.[28,30,31] However, PET/CT colonography has a limited role in assessment of small polyps (<10 mm).[32] Recently, PET/magnetic resonance imaging (MRI) has been shown to improve both local and distant staging, when compared to PET/CT.[33] Similar to T-staging, in N-staging its role is limited to the evaluation of suspicious lymph-nodes detected by other modalities.[30] Finally, the role of PET/CT in evaluation of distant metastases is not certain. It has been shown to offer no significant benefit over CT or contrast-enhanced EUS in detection of hepatic metastases, while it is inferior to MRI.[34] Furthermore, the use of PET/CT in patients with liver metastases has not translated into any significant improvements in OS or PFS,[35] and also has not been found to impact patient management in a meaningful way [Figure 6].[36] PET/CT also underestimates the extent of peritoneal carcinomatosis in both mucinous and nonmucinous tumors.[37] All in all, preoperative PET/CT may change surgical management in a small number of patients but does not impact recurrence rates or survival.[38] However, in a subgroup of patients with recurrent but resectable colorectal cancers, 18F-FDG PET/CT can change management and improve PFS and OS [Figure 7].[39] Another domain, where PET/CT seems to have some role is in prognosis; as SUV measurements in metastatic lymph nodes, hepatic metastases and bone marrow have been correlated with recurrence free survival.[40-42] However, in a recent multi-center randomized trial, the use of PET/CT for monitoring post curative resection patients only added to costs, without impacting management.[43]

Lymphoma

The avidity of 18F-FDG in the lymphomas is dependent on the subtype. Many gastrointestinal lymphomas including MALTomas, Diffuse large B-cell type, Follicular type, and T-cell type show significant 18F-FDG uptake.[44-49] Lymphomas can account for nearly a fifth of gastrointestinal malignancies and this involvement can be primary or secondary.[27] In primary lesions, 18F-FDG PET/CT allows for the assessment of extent of involvement and in secondary lesions, it can detect other sites of involvement. Because of its sensitivity, PET/CT is able to aid in accurate staging both at baseline and follow-up (residual disease) [Figures 8 and 9].[27] In addition, parameters like TLG have shown promise as prognostic markers.[44] For the purpose of staging and restaging, PET/CT is superior

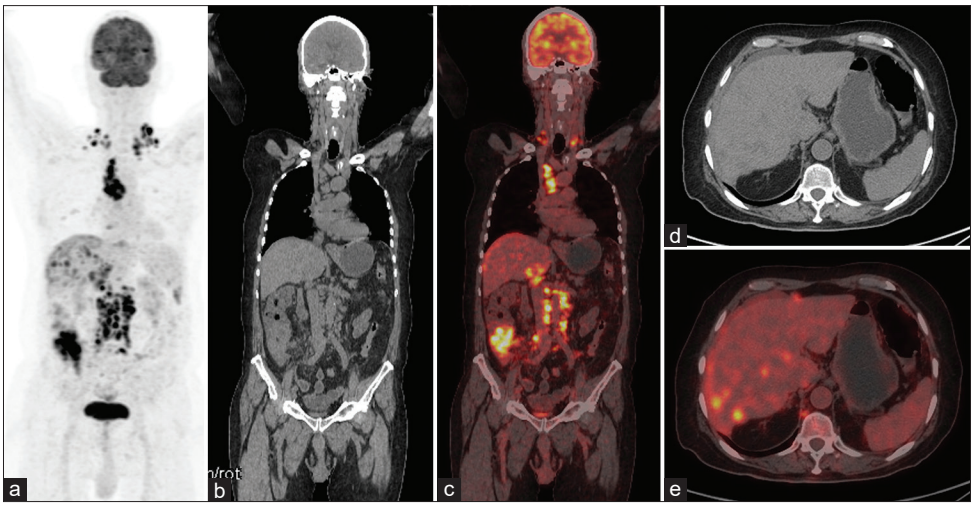

Figure 6: Case of 73-year-old male who was diagnosed with adenocarcinoma of the caecum with hepatic and retro-peritoneal lymph nodal metastases. He was referred for 18F-FDG positron emission tomography/computed tomography for metastatic workup (MIP [a], Coronal computed tomography [b], Coronal positron emission tomography/computed tomography [c], Axial computed tomography [d] and Axial Positron emission tomography/computed tomography [e]). Positron emission tomography/computed tomography showed a FDG avid mass involving the caecum and ascending colon with metabolically active retroperitoneal lymphadenopathy (b and c) and liver metastases (d and e) (all of which had already been identified). In addition, positron emission tomography/computed tomography was able to detect involvement of cervical and mediastinal lymph-nodes (a-c). These additional sites of involvement did not impact the management in this patient

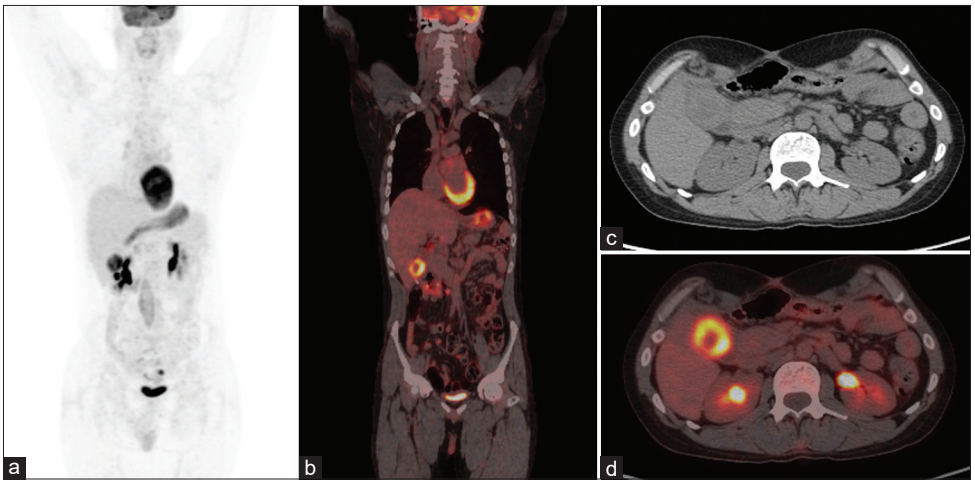

Figure 7: Case of 36-year-old male who was a postoperative follow-up case of adenocarcinoma colon. The patient had a suspicious mass in the region of hepatic flexure in ultrasound examination and was referred for re-staging Positron emission tomography/computed tomography (MIP [a], Coronal Positron emission tomography/computed tomography [b], Axial computed tomography [c] and Axial Positron emission tomography/computed tomography [d]). Positron emission tomography/computed tomography showed a FDG avid mass involving the hepatic flexure, in close relation to but not involving the liver (b-d). What was more important that identification of recurrence was absence of metastatic disease in Positron emission tomography/computed tomography (a). This made the patient eligible for re-surgery

to CECT,[49,50] primarily on account of its ability to detect metabolic changes in the absence of structural changes and in small lesions. Thereby, PET/CT plays an important role in decisions regarding extension or change in therapy [Figure 8].[27]

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors, which can involve any part of the gastrointestinal tract. The most common site of involvement is stomach followed by small bowel and colorectum. Endoscopy remains the mainstay of diagnosis as it also allows for histological and mutational analysis.[51] Since some sites may not be accessible through endoscopy, cross-sectional imaging is often needed. One of the major factors which weigh heavily on management is differentiation of benign from malignant lesions. The use of tumor diameter and Ki67 have not proven feasible in risk stratification.[51] However, in a recent systematic review, 18F-FDG PET/CT was found to have a pooled sensitivity of 0.88 in predicting the malignant potential of GIST lesions.[52] GIST lesions usually show high 18F-FDG avidity, which in turn correlates with stage, risk group, and mitotic index [Figure 10].[53] In addition, 18F-FDG

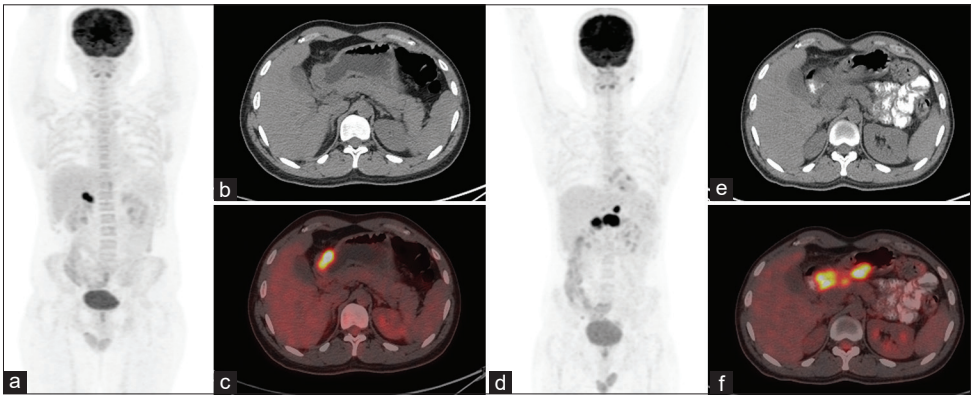

Figure 8: Case of 22-year-old male who was diagnosed with gastric lymphoma (B-NHL) and was advised Baseline Positron emission tomography/computed tomography (MIP [a], Axial computed tomography [b], Axial Positron emission tomography/computed tomography [c]); which revealed a metabolically active thickening involving the distal stomach and no other site of involvement; thereby confirming the diagnosis of primary gastric lymphoma and ruling out gastric involvement by systemic lymphomatous disease. He was started on chemotherapy and underwent Positron emission tomography/computed tomography after 3 months (MIP [d], Axial computed tomography [e], Axial Positron emission tomography/computed tomography [f]); which revealed increase in the extent of the earlier lesion as well as appearance of a new perigastric lymph nodal lesion– indicative of progressive disease

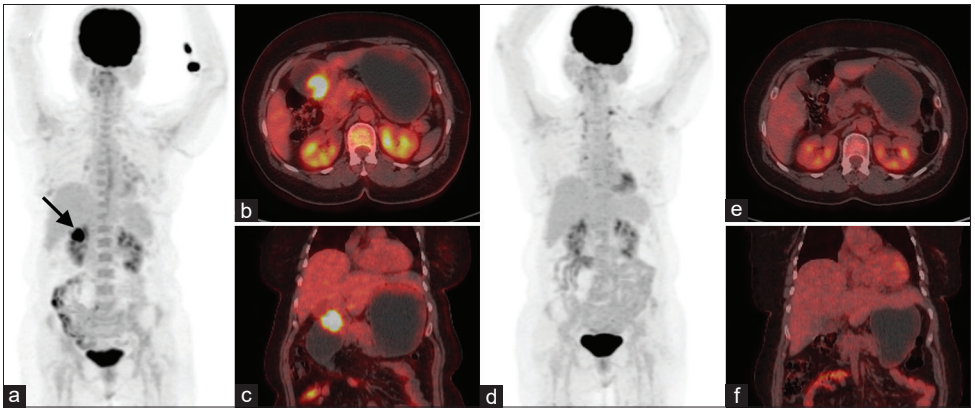

Figure 9: Case of 60-year-old female diagnosed with B-cell NHL. She underwent baseline Positron emission tomography/computed tomography (MIP [a], trans-axial Positron emission tomography/computed tomography [b], coronal Positron emission tomography/computed tomography [c]), which revealed intensely 18F-FDG-avid thickening in the pyloric region. She underwent follow-up positron emission tomography/computed tomography for response assessment after 3 months (MIP [d], transaxial positron emission tomography/computed tomography [e], coronal Positron emission tomography/computed tomography [f]), which showed complete metabolic response

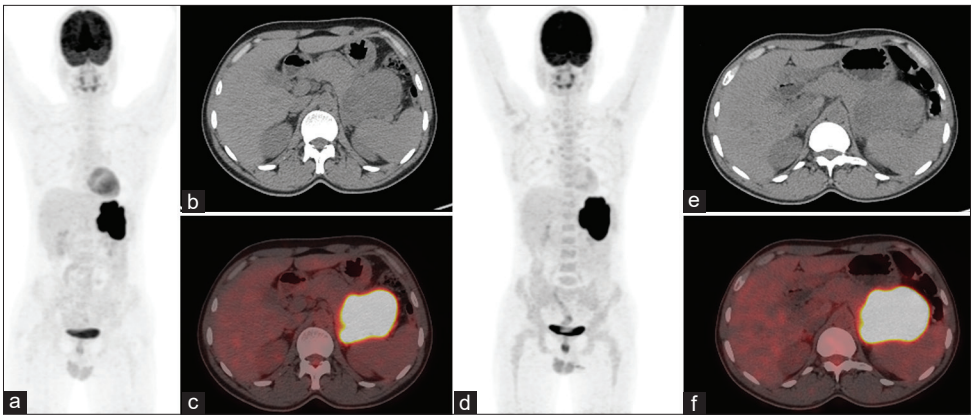

Figure 10: Case of 32-year-old male who diagnosed with Gastro Intestinal Stromal Tumor and underwent Baseline Positron emission tomography/computed tomography (MIP [a], Axial computed tomography [b], Axial Positron emission tomography/computed tomography [c]); which revealed a metabolically active mass involving the body of the stomach and no other site of involvement. The intense uptake was indicative of malignant nature of the disease. He was started on Imatinib based chemotherapy and underwent Positron emission tomography/computed tomography after 3 months (MIP [d], Axial computed tomography [e], Axial Positron emission tomography/computed tomography [f]); which revealed mild increase in the extent of the earlier lesion as well as metabolic uptake. Though the increase was not enough to satisfy the criteria of progressive disease and the patient was categorized as having stable disease, it ruled out possibility of surgery and the patient was considered for alternative treatment regimen

PET/CT influences management in patients when used for restaging by accurately detecting or ruling out local/distant recurrence with a sensitivity and specificity of 89% and 97%, respectively.[54] PET/CT is currently one of the most sensitive modalities for response assessment in GIST, with SUV_{max} (either at baseline or follow-up) being useful for both response assessment and prognostication in patients both sensitive or refractory [Figures 10 and 11] to Imatinib therapy.[55-57]

Neuroendocrine Tumors

Neuroendocrine tumors (NET) are rare tumors, many of which are nonfunctioning, i.e., the peptides secreted by them do not produce symptoms.[58] Thus, many patients present with symptoms related to local effects like obstruction or distant metastases. Both 18F-FDG and another radiotracer namely 68Ga-DOTA-peptides (which bind to somatostatin receptors) have been used for imaging this tracer. The choice of radiotracer depends on the differentiation and Ki67, with well-differentiated lesions showing avidity for 68Ga-DOTA-peptides and poorly differentiated ones being 18F-FDG avid [Figure 12].[59,60] 68Ga-DOTA-peptide-PET/CT has very high sensitivity and specificity for the detection of NETs (>90%) and has been shown to change management in as many as 50% of the patients [Figures 13 and 14].[61] Recently, the addition of CT enterography to PET imaging was shown to further improve sensitivity (to ~90%) in detection of unknown NET primaries.[60] Furthermore, the 68Ga-DOTA-peptide imaging is more sensitive than CECT for detection of both lymph nodal and distant metastases [Figure 14].[60] 68Ga-DOTA-peptide PET/CT imaging also has theragnostic applications. Recently, a dual tracer scoring system has been developed to prognosticate and to aid in treatment planning of metastatic NET [Figure 15].[62,63]

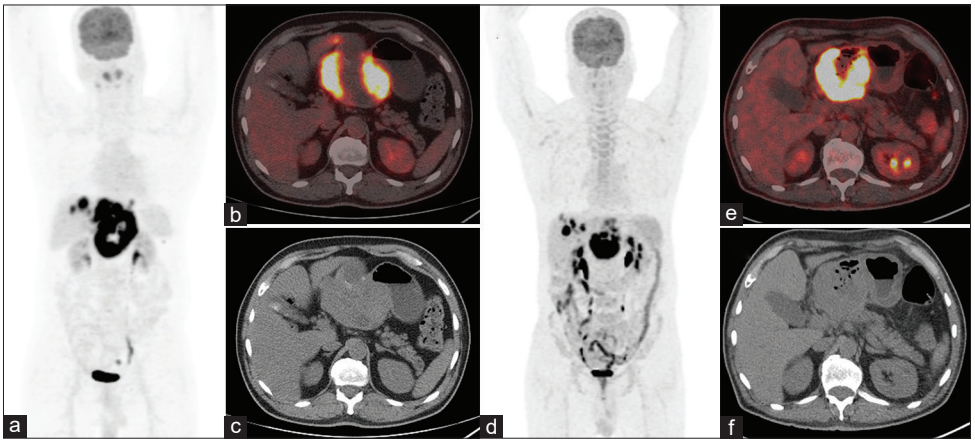

Figure 11: Case of 63-year-old male who underwent baseline 18F-FDG Positron emission tomography/computed tomography (MIP [a], Trans-axial Positron emission tomography/computed tomography [b], Trans-axial computed tomography [c]) for Gastro Intestinal Stromal Tumor, which revealed metabolically active primary disease in the pylorus, with metastases to the liver. The patient underwent follow-up Positron emission tomography/computed tomography after 4 months (MIP [d], Trans-axial Positron emission tomography/computed tomography [e], Trans-axial computed tomography [f]), which revealed reduction in the size and metabolic activity of the primary and the liver lesions, which was suggestive of partial response

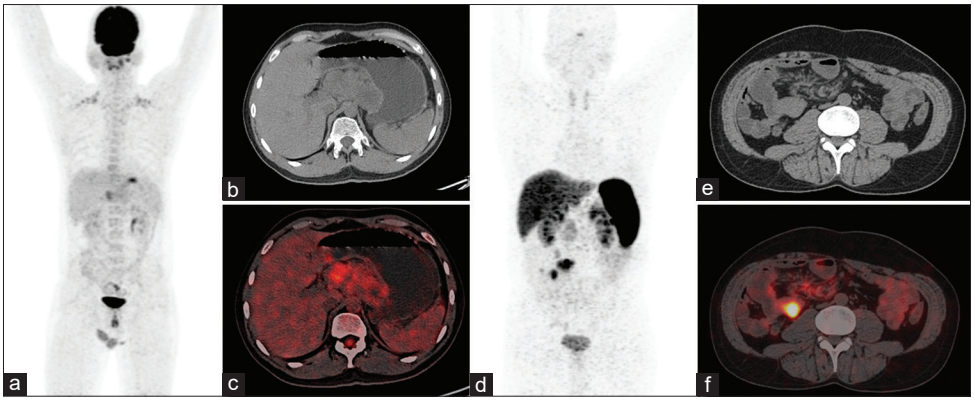

Figure 12: Case of 31-year-old male who diagnosed with Neuro-endocrine tumor (Grade 3) of the Distal stomach and underwent Baseline 18F-FDG positron emission tomography/computed tomography (MIP [a], Axial computed tomography [b], Axial Positron emission tomography/computed tomography [c]); which revealed a metabolically active mass involving the distal stomach and no other site of involvement. Also shown is the 68Ga-DOTANOC Positron emission tomography/computed tomography images (MIP [d], Axial computed tomography [e], Axial Positron emission tomography/computed tomography [f]) in a 48-year-old male with Grade 2 ileal carcinoid, showing increased tracer uptake in the primary mass as well as metastatic lymph node. Higher grade Neuro-endocrine tumors do not show adequate differentiation and hence Somatostatin Receptor expression, making 18F-FDG an ideal choice of tracer. On the other hand, low grade Neuro-endocrine tumors do show high expression of Somatostatin Receptor and are better visualized with Somatostatin Receptor imaging

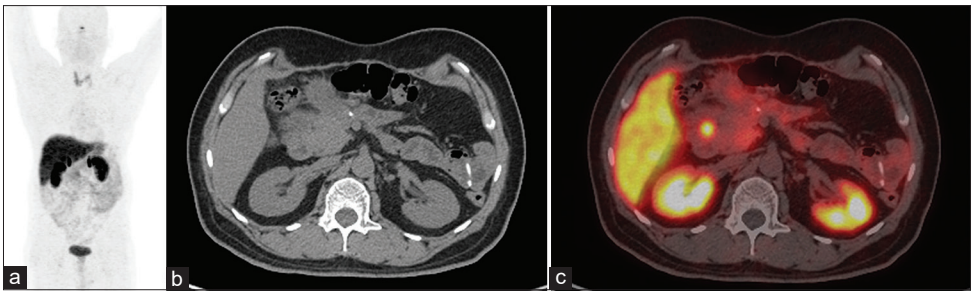

Figure 13: Case of 49-year-old male who was a follow-up case of Neuro-endocrine tumor (Grade 2) of the Pancreas (tail), post resection and hepatic metastectomy. The patient was sent for 68Ga-DOTANOC Positron emission tomography/computed tomography in view of rising Serum Chromogranin levels (MIP [a], Axial computed tomography (b), Axial positron emission tomography/computed tomography [c]); which revealed a Somatostatin Receptor expressing lesion in the second part of the duodenum and no other site of involvement. The 68Ga-DOTANOC Positron emission tomography/computed tomography was able to identify such low-burden recurrence at an early stage and patient was offered radical treatment

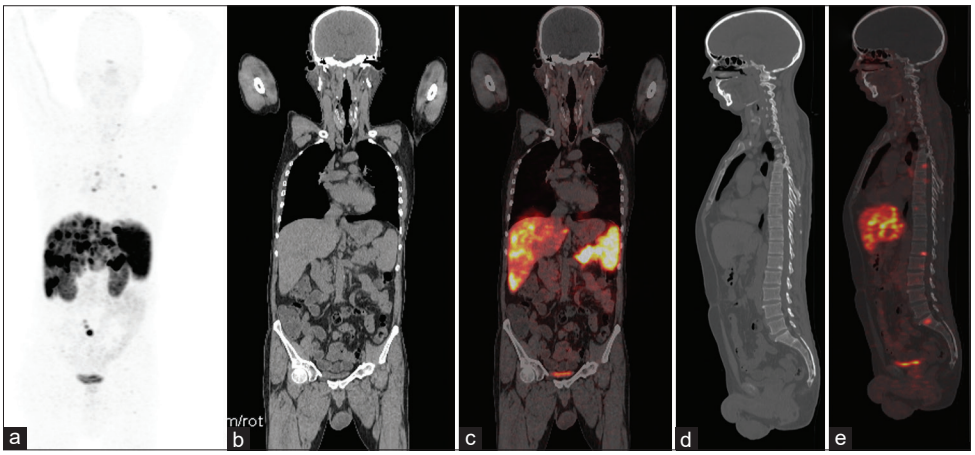

Figure 14: Case of 62-year-old male who was diagnosed with Neuro-endocrine tumor (Grade 2) of the Pancreas and was referred for Baseline 68Ga-DOTANOC Positron emission tomography/computed tomography (MIP [a], Coronal computed tomography [b], Coronal Positron emission tomography/computed tomography [c], Sagittal computed tomography [d], Sagittal Positron emission tomography/computed tomography [e]); which revealed a Somatostatin Receptor expressing metastases to the liver (b and c). Also noted were Somatostatin Receptor expressing skeletal metastases, some of which showed sclerosis in computed tomography (Lumbar lesion) and others did not (Thoracic and Sacral)

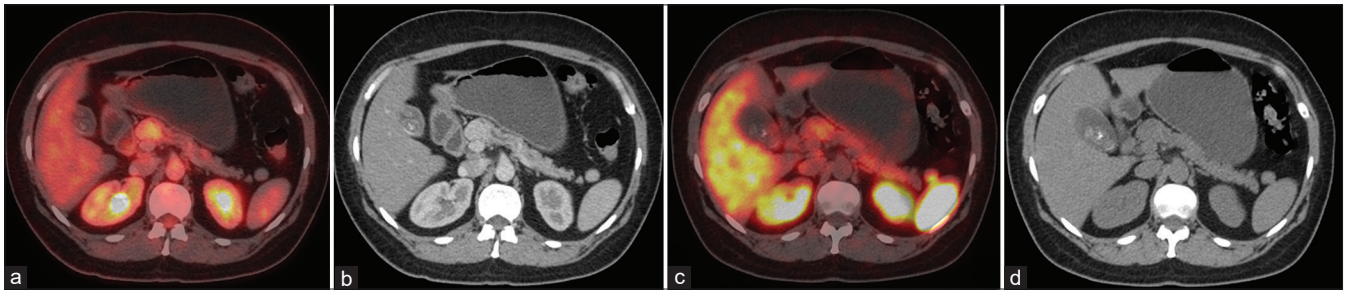

Figure 15: Case of a 45-year-old female, who was a diagnosed case of Neuro-endocrine tumors grade 2. The patient underwent 18F-FDG Positron emission tomography/computed tomography (Trans-axial Positron emission tomography/computed tomography [a] and computed tomography [b]), which revealed a mass in the head of the pancreas, with moderately elevated 18F-FDG uptake. The patient also underwent 68Ga-DOTANOC Positron emission tomography/computed tomography for treatment planning (Trans-axial Positron emission tomography/computed tomography [c] and computed tomography [d]), which also revealed mild-moderate activity in the mass lesion. Higher 18F-FDG uptake in this patient compared to 68Ga-DOTANOC (P4 in NETPET score) meant more aggressive phenotype and lower survival

Conclusion

PET/CT imaging is a very sensitive modality which allows for targeted imaging of metabolic processes and clubs these with structural changes. In most gastrointestinal lesions, it has been shown to improve detection of distant metastases, aid in prognostication, treatment planning, and posttreatment surveillance. Its limitations in local staging can be overcome to some extent through use of IV contrast/enterography/colonography.

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Conflicts of interest

There are no conflicts of interest.

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