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REVIEW

Clinical impact of FDG PET/CT in alimentary tract malignancies: an updated review

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Abstract

The use of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) is well established in the evaluation of alimentary tract malignancies. This review of the literature and demonstration of correlative images focuses on the current role of PET/CT in the diagnosis (including pathologic/clinical staging) and post-therapy follow-up of esophageal, gastric, and colorectal cancers. PET/CT provides utility in the management of esophageal cancer, including detection of distant disease prior to resection. In gastric cancer, PET/CT is useful in detecting solid organ metastases and in characterizing responders vs. non-responders after neoadjuvant chemotherapy, the latter of which have poorer overall survival. In patients with GIST tumors, PET/CT also determines response to imatinib therapy with greater expedience as compared to CECT. For colorectal cancer, PET/CT has proven helpful in detecting hepatic and other distant metastases, treatment response, and differentiating post-radiation changes from tumor recurrence. Our review also highlights several pitfalls in PET/CT interpretation of alimentary tract lesions.

Keywords FDG · PET/CT · Gastric malignancy · Esophageal malignancy · Colorectal · Malignancy

Introduction

PET/CT is a valuable imaging tool for the diagnosis, surveillance, and treatment monitoring of alimentary tract malignancies. This review of recent literature and correlative imaging examples is performed with emphasis on major advancements in the utilization of PET/CT, pathologic/clinical staging, and follow-up for esophageal, gastric, and colorectal cancers.

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PET/CT in the evaluation of esophageal cancer

Overview

Esophageal cancer is a common malignancy, with an estimated 17,000 cases occurring in the USA in 2017 [1]. It traditionally has had a poor prognosis because of its early spread through the esophageal wall and to adjacent lymph nodes, with an estimated 5-year survival of 17–34% [1]. The two major histological types of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which have different tumor biology, different prognoses, and possibly different treatments. Historically, throughout the world, 90% of esophageal carcinomas were ESCC. In the USA over the last three decades, there has been a progressive decline in ESCC, possibly due to reduction in smoking and alcohol consumption, while at the same time there has been a significant rise in the incidence of adenocarcinoma [2].

Only over the last decade has the EAC incidence begun to diminish. Greater awareness of the risks associated with Barrett's metaplasia, dietary factors, and smoking may have resulted in greater risk modification in some populations, and earlier detection of EAC. Further epidemiological data are needed to better understand these evolving trends [3]. ESCC can occur anywhere in the esophagus (with a proximal to mid-esophageal predilection), but EAC predominantly occurs in the distal esophagus, in a similar distribution to Barrett's esophagus. Esophagogastric (EG) junction tumors are generally esophageal adenocarcinoma, but if the EG junction is involved, and the epicenter is more than 2 cm below the EG junction, the tumor is more likely of gastric origin.

Recent research, including the CROSS trial and others have shown that preoperative neoadjuvant therapy improves outcomes in patients with resectable, locoregionally advanced esophageal cancer [4–7]. While there is still debate over the best form of preoperative treatment, the CROSS trial utilized chemoradiotherapy (CRT) (Carboplatin, Paclitaxel, and concurrent radiation therapy) prior to resection of the primary tumor versus surgery alone [6]. Both adenocarcinoma and squamous cell carcinoma histology were included in the series. Overall 5-year survival with preoperative CRT followed by surgery was 47% as compared to 33% with surgery alone. It appears that neoadjuvant CRT results in a more significant pathologic complete response and positive mean survival impact over surgery alone for ESCC (81 months vs 21 months) than EAC (43 months vs 27 months), but is of benefit for both histologies [6]. Ongoing trials will continue to look at issues like the best preoperative strategy, approaches to debilitated patients with co-morbidities, and whether esophagectomy is always necessary after successful CRT [8].

The initial tumor location, grade, and TNM staging of esophageal cancer (Table 1) are key elements in determining the optimal approach to treatment and prognosis. While TNM staging for EAC and ESCC are identical, the American Joint Committee on Cancer (AJCC) clinical staging differs based on histologic type due to stage-specific mortality rate differences [9, 10], and tumor location having less impact on EAC prognosis than ESCC prognosis. While the initial pretreatment tumor grade is important for both ESCC and EAC, it may be difficult to assess on some endoscopic biopsy specimens, especially if a stricture limits access to the lesion. Recall that the initial pretreatment tumor grade is critical, because post-neoadjuvant chemoradiotherapy biopsies may be even less accurate due to fibrosis or inflammation from radiotherapy. Clinical staging continues to be heavily dependent on imaging determining the extent of locoregional disease, which underscores the need for a consistent approach and paradigm.

Table 1 Pathologic TNM staging of cancers of the esophagus and esophagogastric junction (AJCC 8th edition) [11]

Tis	High grade dysplasia/carcinoma in situ
T1a	Involves mucosa only
T1b	Extends to submucosa
T2	Involves muscularis propria
T3	Beyond wall into adventitia
T4a	Resectable, invades adjacent pericardium, pleura, diaphragm
T4b	Unresectable, invades structures like trachea, vertebral body, aorta
N0	No positive nodes
N1	1–2 positive nodes
N2	3–6 positive nodes
N3	7 or more positive nodes
M0	No distant metastases
M1	Distant metastases

Diagnosis and initial staging

A multidisciplinary, multimodality approach to staging esophageal carcinoma with endoscopic ultrasound (EUS), contrast-enhanced CT (CECT) of the chest, abdomen, and pelvis, and PET/CT is key in deciding on the most effective individualized treatment, and identifying those patients with advanced unresectable tumors with distant disease. Following endoscopy and a positive biopsy for ESCC or EAC, there are three pathways:

1. If the esophageal lesion appears early/superficial, EUS may be done initially to determine if the patient is a candidate for endoscopic therapy. Non-invasive, superficial lesions (T1s or T1aN0 disease) may be successfully treated by endoscopic resection or photodynamic therapy [12].
2. For larger, more advanced appearing primaries on endoscopy or invasion on biopsy, CECT will be performed. If CECT shows advanced distant disease, EUS and PET/CT may not be needed if only palliative chemotherapy will be offered. In our institution, a baseline and post-chemotherapy PET/CT may be selectively performed, even in this setting. In addition to managing the symptoms and sequalae of the primary tumor, clinical assessment and PET/CT can determine if the palliative approach is effective. It also allows identification of new critical lesions (such as bony metastases to the hip or spine) that may require radiotherapy.
3. For larger, more advanced appearing primaries on endoscopy or invasion on biopsy, with no distant disease on initial CECT, EUS to assess the primary tumor invasion and adjacent nodes is strongly warranted. PET/

CT is also indicated to identify those patients with occult metastatic disease if not confidently excluded or characterized by CECT (Figs. 1, 2). Assuming the patient has no severe co-morbidities, and only local invasion and regional adenopathy (including supraclavicular or celiac nodal groups) is present, the patient would be a potential candidate for preoperative neoadjuvant chemoradiotherapy followed by esophagectomy. The presence of either distant metastases (lung, bone, liver, brain or distant lymph nodes), or stage T4b disease (involvement of aorta, trachea, or vertebral body), indicates non-resectability [13, 14]. (Figure 3)

In general we structure our esophageal carcinoma PET/CT reports around those findings that reflect the greatest value of PET/CT, and follow a TNM approach. The source and fused images almost always identify the hypermetabolic primary tumor, but cannot determine depth of tumor penetration through the esophageal wall. If, however, invasion into major adjacent structures (T4 disease) is present, it is reported and correlated with the non-contrast images (obtained for attenuation correction) and prior contrast-enhanced CT scans, when available. EUS is considered the most accurate procedure for preoperative local T staging of both ESCC and EAC due to its ability to determine the depth of penetration of the primary lesion. EUS may over-stage the tumor due to peri-tumoral fibrotic changes or understage lesions due to microscopic tumor invasion, but PET/CT, because of its slice thickness and resolution, does not address those shortcomings. CT is highly specific in detection of advanced esophageal cancer, especially when an obstructing esophageal mass is present, with invasion or encasement of adjacent structures/vessels. In this context there is usually good correlation with PET/CT. Caution should be exercised in over-interpreting "stranding" of the peri-esophageal mediastinal fat or loss of distinct fat planes as adventitial spread of tumor (T3 disease) on CT or PET/CT; it may be due to peri-tumoral inflammation, lymphatic obstruction, or fibrosis, even on images obtained prior to neoadjuvant CRT.

N staging with CT based on pathologic size criteria of lymph nodes may result in false-negative understaging of smaller nodes (Fig. 1) [15] or overstaging enlarged hyperplastic nodes. EUS with fine needle aspiration of sonographically abnormal lymph nodes is a well-accepted technique, and is most reliably performed on nodes abutting the esophageal adventitia. PET/CT is very successful for imaging metastatic adenopathy, but with one caveat; locoregional

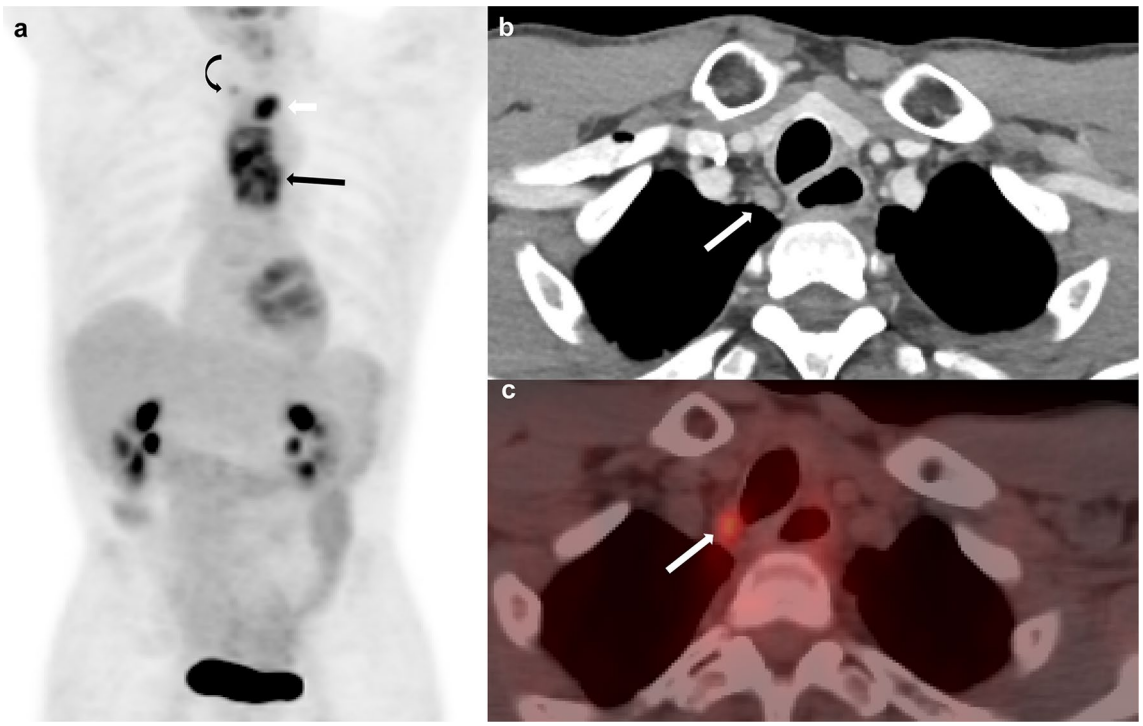

Fig. 1 Esophageal Carcinoma with nodal metastases. Maximum intensity projection (MIP) image (**a**) from a PET/CT scan reveals the primary esophageal mass (black arrow) within the upper-mid esophagus. A hypermetabolic metastatic lymph node is seen (white arrow) to the left of the trachea. Another even smaller metastatic lymph node is seen in the right paratracheal region (curved arrow). CECT slice and fused PET/CT image confirm the presence of a subcentimeter hypermetabolic right paratracheal, metastatic lymph node below the CT pathologic size criteria (b, c) (white arrow)

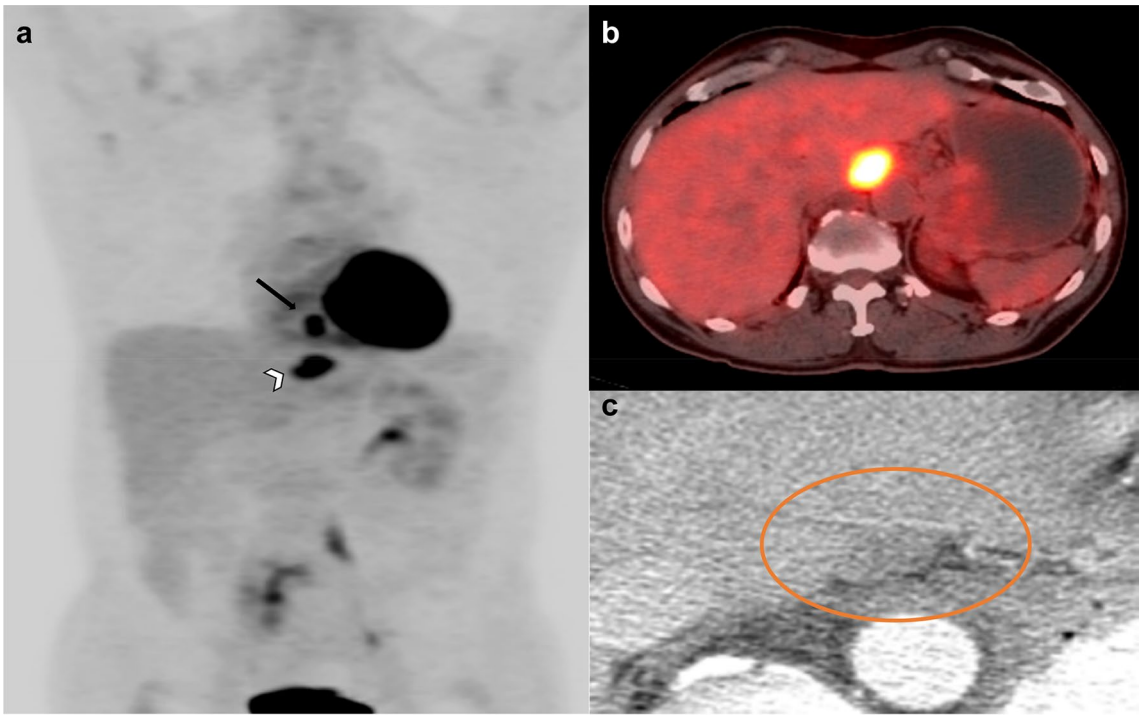

Fig. 2 Esophageal Carcinoma Metastatic Lymph Node. Maximum Intensity Projection (MIP) PET image (**a**) demonstrates hypermetabolic primary GE tumor mass (black arrow) with a second FDG-avid subhepatic lymph node (white arrowhead). Axial PET/CT (**b**) assists in accurate localization of hypermetabolic, metastatic lymph node. Axial post-contrast CT scan (**c**) shows the barely perceptable hypodense metastatic lymph node, below size threshold for pathologic CT criteria

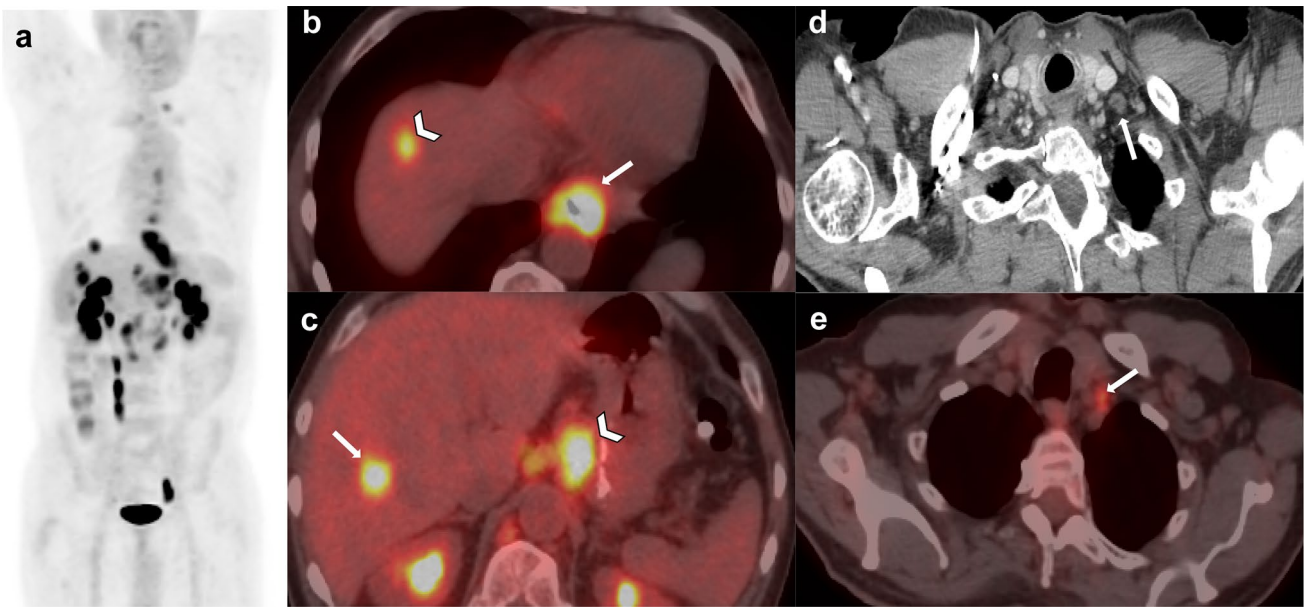

Fig. 3 Esophageal Carcinoma with nodal and distant metastases. MIP image (**a**) demonstrates primary distal esophageal tumor with liver and multiple lymph node metastases. Fused PET/CT image (**b**) shows hypermetabolic tumor at the GE junction (arrow) and a discrete focus of metastasis in the liver (arrow head). PET/CT slice at the level of the celiac axis (**c**) demonstrates hypermetabolic metastasis within the liver (arrow) as well as a hypermetabolic metastatic celiac axis lymph node (arrow head).CECT (**d**) shows a subcentimeter left supraclavicular lymph node (arrow), below the CT size criteria for pathology, which is clearly hypermetabolic on PET/CT (**e**), indicating a supraclavicular metastatic lymph node

nodes adjacent to very hypermetabolic primary tumors may be obscured by the activity in the closely applied esophagus [15, 16]. Lymph nodes further away from the primary tumor are more easily visualized with PET/CT. PET/CT is, therefore, a complementary technique to EUS. PET/CT excels at evaluating distant nodes in the mediastinum, supraclavicular and celiac regions. Lymph node metastasis is a very important prognostic factor; the presence of 7 or more involved nodes results in poorer prognosis [17].

Previously, assessment of distant lymph nodes was thought to be essential in determining whether esophageal carcinoma was inoperable. In earlier versions of the AJCC classification, distant nodes (e.g., in the celiac or supraclavicular regions, depending on primary tumor location), were classified as metastatic disease. However, with changes in the AJCC classification 8th edition [11], all nodes, regardless of location, fall within the N category, not the M category. Therefore, while node location may not adversely impact outcome or survival, it is important to correctly identify nodes outside the mediastinum, so that they will be included in the radiotherapy port at the time of neoadjuvant therapy. Coronal fused PET/CT images are useful not only for localizing nodes, but determining adjacent anatomic landmarks to help the radiotherapist develop their treatment plan.

Finally, the greatest strength of PET/CT is in determining the M stage and detecting distant metastatic disease from esophageal cancer, that may be occult or equivocal on prior contrast-enhanced CT scanning (Fig. 3). Careful comparison of PET/CT with prior CT is valuable in differentiating suspected metastatic disease from benign incidental findings that may mimic tumor on CT. In addition to reviewing the attenuation corrected PET and PET/CT images, careful review of the non-attenuation corrected PET images of the lungs is important in detection of possible metastatic lung nodules.

Evaluation of response to treatment

Most patients with locoregionally invasive ESCC and EAC receive preoperative neoadjuvant CRT [18]. PET/CT has proven valuable in identifying patients who respond to neoadjuvant CRT (usually performed 6 weeks after CRT completion) who will then go on to definitive/curative esophagectomy [18]. Specifically, PET/CT is useful in excluding new distant disease that developed during CRT, that would preclude esophagectomy. Bruzzi et al. performed a retrospective study on patients with potentially resectable esophageal cancer who underwent neoadjuvant CRT followed by PET/CT for distant disease, and found 8% of their cohort developed new metastatic disease [14]. Including PET/CT in the post-neoadjuvant therapy evaluation will further identify those patients who would benefit from definitive treatment and spare others from non-curative resections [19]. In patients with significant co-morbidities, imaging is also useful in identifying responders, who may benefit from more conservative management (i.e., without esophagectomy) after their initial complete or partial response to CRT. Finally, PET/CT has been found to be a valuable tool in follow-up after surgical treatment for the timely detection of tumor recurrence [20].

Various studies evaluated PET/CT parameters such as maximum standard uptake value (SUV max), change in SUVmax, and total lesion glycolysis (TLG) as factors in prognostication [21]. They found that higher baseline SUVmax may predict poorer survival. Elimova et al. showed in a prospective phase II study that PET/CT is a powerful prognostic tool in predicting longer median overall survival in esophageal cancer patients after CRT by using baseline TLG value [2]. Change in SUVmax during or after CRT may not predict outcome, but additional quantitative measures derived from SUV may allow more precise prognostication in the future.

Limitations

PET/CT is most useful in the assessment of lymph nodes in tumors with a high probability of nodal disease and with higher pathologic grade on EUS guided biopsy such as T1b disease [16]. PET/CT is not found to be useful in initial evaluation of primary esophageal carcinoma and detection of locoregional disease in patients with superficial tumors (Tis and T1a) and in fact may falsely upstage patients with lower grade disease on EUS due to inflammation from endoscopy or tumors with low volumes below the resolution of PET/CT. Acute inflammation due to radiation injury after CRT may result in abnormal FDG uptake. Radiation esophagitis and radiation hepatitis (Fig. 4) may both lead to false-positive interpretations and be mistaken for tumor. Knowledge of the location of the patient's radiation port and the timing of recent radiotherapy is of importance in accurate interpretation. Waiting 6 weeks after CRT is generally accepted, but ideally the patient will undergo post-CRT endoscopy prior to PET/CT. If residual post-CRT inflammation is present on endoscopy, the significance of residual activity in the tumor and adjacent esophagus should be interpreted with caution.

Role of PET/CT in the evaluation of gastric cancer

Overview

The incidence of gastric cancer has gradually decreased worldwide, however, its prognosis remains poor with an estimated 5-year survival of 20–25% [22]. Gastric

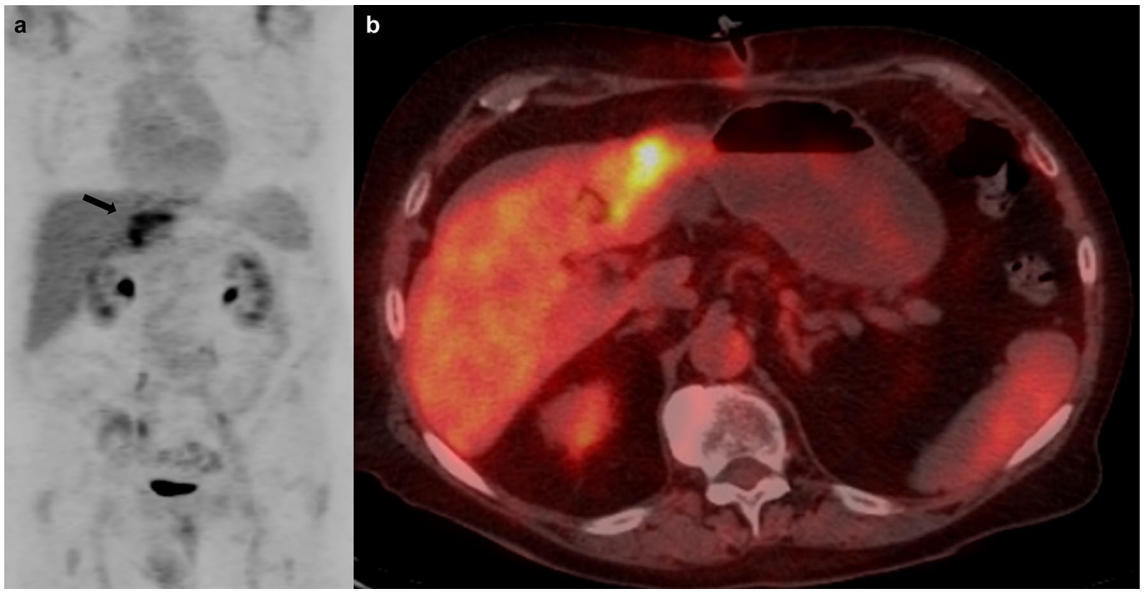

Fig. 4 Esophageal carcinoma patient with radiation hepatitis after neoadjuvant treatment. A patient with distal esophageal adenocarcinoma who was treated with external beam radiation therapy underwent follow-up PET/CT imaging 8 weeks after therapy. MIP (**a**) and fused PET/CT (**b**) images reveal a hypermetabolic focus in the left hepatic lobe. Liver ultrasound failed to demonstrate discrete metastatic lesion(s) in this area. Biopsy of the hypermetabolic liver segment revealed radiation hepatitis, a finding that can be encountered due to the radiation portal being extended inferiorly to include the lower GE junction and the celiac nodal region

adenocarcinoma (GAC) is the most common gastric cancer, accounting for 95% of all gastric malignancies. The major histologic types of primary GAC include intestinal (tubular) adenocarcinoma (often related to chronic autoimmune gastritis or chronic H. pylori associated gastritis) and diffuse (mucinous or signet ring) adenocarcinoma. Other malignancies of the stomach include mucosa-associated lymphoid tumor (MALT) lymphoma, other more aggressive lymphomas, gastrointestinal stromal tumors (GIST), and less frequently sarcomas and carcinoid tumors.

Gastric cancer remains a cause of significant morbidity and mortality, more commonly seen in Eastern European and Asian countries and, to a lesser extent, within the USA [23]. In the west, most patients have a poor prognosis at diagnosis, with approximately 80% having advanced disease (Fig. 5) [24]. Even after curative resection, gastric cancer can recur distantly due to abundant lymphatic channels within the gastric walls and lymphatic drainage away from the stomach which may result in skip lesions [25].

The initial TNM staging (Table 2) and histopathologic grade of GAC are key elements in determining the optimal approach to treatment and prognosis. While tumor markers (such as CEA and CA 19-9) may be of value, in general they have not been shown to have independent prognostic value.

Diagnosis and initial staging

A multidisciplinary, multimodality approach to staging GAC with endoscopic ultrasound (EUS), contrast-enhanced CT (CECT) of the chest, abdomen, and pelvis, and PET/CT is key in deciding on the most effective individualized treatment, as well as identifying those patients with advanced unresectable tumors with distant disease. The approach is similar to that described above for esophageal carcinoma. There are some caveats worth noting: (1) Use of EUS is increasingly prevalent for T staging in clinical practice, despite improvements in CT (and MRI) such as greater gastric distension with negative oral contrast agents. Use of anatomic landmarks to standardize the orientation of EUS images for correlation with CECT and PET/CT is also increasingly useful. (2) Unlike for esophageal cancer, neoadjuvant treatment is far more controversial for GAC, but may be of benefit for tumors at the EG junction (see below). (3) While TNM staging is well accepted for GAC, clinical staging as it relates to prognosis and survival is still evolving.

The only effective curative treatment of GAC is complete resection of the primary tumor and adjacent lymph nodes. When interpreting PET/CT for esophageal cancer, the focus is identifying nodes to be included in the treatment port. For GAC, the exam needs to be focused on directing resection. In

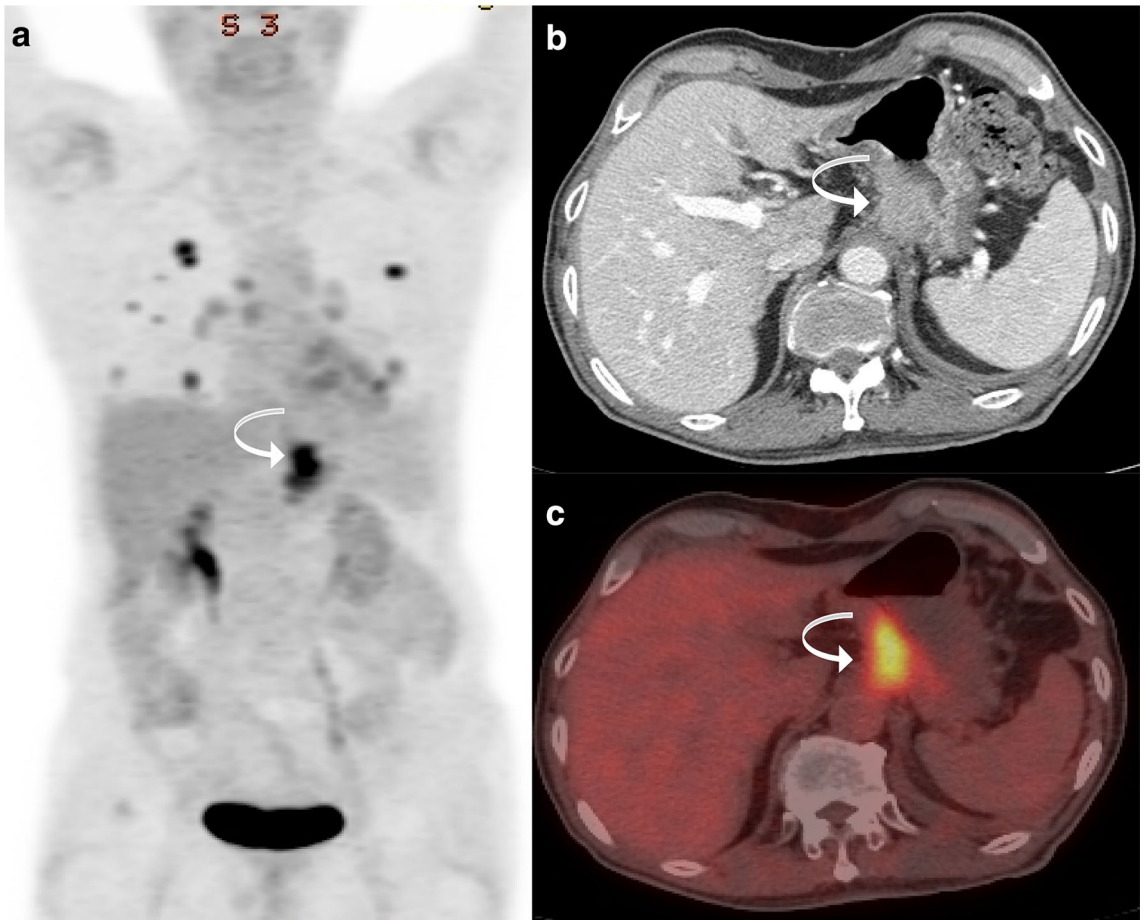

Fig. 5 Patient with gastric carcinoma and lung metastases. MIP image (**a**) demonstrates the gastric mass (curved arrow) along with widespread lung metastases in a patient with primary gastric adenocarcinoma. CECT (**b**) shows enhancing gastric wall thickening (curved arrow) extending beyond the lesser curvature of the stomach and fused PET/CT (**c**) shows a significantly hypermetabolic primary gastric mass (curved arrow) at the proximal stomach (Max SUV = 10.4)

Table 2 Pathologic TNM staging of gastric adenocarcinoma (AJCC 8th edition)

Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
M0	No distant metastases
M1	Distant metastases

general, as many nodes as possible should be removed at surgery to allow for accurate pathologic staging and prognosis. The AJCC 8th edition suggests that 30 nodes is preferable to the older standard of 16 [11]. When describing the N stage on PET/CT (or CECT), the radiologist should be mindful of the D classification (D1–4) for extent of nodal dissection. D1–2 lymphadenectomy includes dissection of perigastric nodes, and nodes along the celiac axis and splenic artery. This is the standard surgical approach in countries with a high prevalence of gastric cancer. D3–4 lymphadenectomy is more extensive, and refers to dissection of nodes at the root of the mesentery, around the middle colic vessels and para-aortic nodes [26]. It is worthwhile for the imager to highlight and report specific regions of hypermetabolic adenopathy to optimize sampling and possibly prognosis.

Also, unlike staging for esophageal cancer (except possibly those at the EG junction), peritoneal cytology is commonly assessed inpatients with GAC. Positive peritoneal cytology constitutes distant metastatic disease, and is positive in up to 16% of patients with locally advanced disease, in the absence of other distant metastases [27]. EUS and CECT remain the most reliable modalities for preoperative T staging of gastric cancer [28]. PET/CT has a limited role in T staging due to factors such as variable physiologic FDG uptake in the gastric mucosa, gastric motility during scanning and the low spatial resolution of PET/CT [29]. Since FDG uptake is physiologically greater in the proximal portion of the stomach, increased uptake in the distal stomach should raise suspicion. Diffuse vs. focal uptake does not particularly help differentiate benign from malignant lesions, as there can be considerable overlap. It is especially difficult to discern abnormal uptake in a non-distended stomach, therefore, a negative oral contrast agent, preferably of low molecular weight, is often helpful for PET/CT as well as CECT.

The relatively low spatial resolution of PET/CT also makes it challenging to discriminate perigastric nodal disease from the adjacent primary tumor. Fortunately, this may not significantly impact the treatment approach given that almost all patients with gastric cancer undergo at least D1 dissection [30]. Despite its low sensitivity, data support the high specificity of PET/CT in detection of N2 or N3 nodal disease, which is more impactful on treatment since it may help decision-making regarding D2 to D4 lymphadenectomy or preventing needless surgery [30]. PET/CT is also superior to CT in detection of metastatic disease in smaller lymph nodes, not deemed pathologic by CT size criteria, especially near the hepatoduodenal ligament, posterior peripancreatic region, mesenteric, middle colic, and para-aortic lymph nodes. This significantly impacts surgical approach.

The major utility of PET/CT in GAC is detection of sites of hematogenous metastases, most frequently the liver, by way of the portal venous drainage [31]. Other common sites of distant disease may involve the lung, adrenals, bone, peritoneum and ovaries (Krukenberg tumor) due to peritoneal or lymphatic spread (Fig. 5) [32]. PET/CT has shown comparable specificity but higher sensitivity, compared to CT, MRI or ultrasound, when evaluating for solid organ metastatic disease [31]. The literature suggests change in management based on PET/CT result is variable, with impact on decision-making in 14–52% of cases [33].

Evaluation of response to treatment

The MAGIC trial is the most widely known neoadjuvant chemotherapy (NAC) trial in gastric and EG junction adenocarcinoma. Pre- and early post-operative neoadjuvant chemotherapy was given in addition to gastrectomy and node resection versus gastrectomy and node resection alone [34]. While the addition of NAC showed a survival benefit, the heterogeneity of the patients included in the trial has created controversy. Similarly, the data regarding use of PET/CT to predict early response to NAC are promising, but thus far not sufficiently conclusive to guide therapy [35]. Following definitive gastrectomy and NAC, there are also mixed results for the utility of PET/CT as a tool for detecting recurrence [36]. Post-surgical inflammatory uptake at the surgical anastomosis, diminutive size of peritoneal metastases, technical difficulty distinguishing vascular uptake from nodal uptake, and urinary tract FDG avidity may all limit accurate interpretation. After surgery, CECT is the most common modality for surveillance. There are conflicting data as to whether PET/CT should be included in post-surgical surveillance for detection of tumor recurrence, given the additional expense and comparable sensitivity and specificity to CECT [37]. Although a meta-analysis performed by Zou et al. found 86% sensitivity and 88% specificity of PET/CT for detection of recurrence after surgical resection, multiple reports exist revealing the low sensitivity of PET/CT in detecting peritoneal metastases where CT is more sensitive [22, 33, 38, 39]. FDG uptake patterns that should increase suspicion for peritoneal metastases are: diffuse, indistinct uptake throughout the abdomen and pelvis rendering it difficult to delineate visceral outlines and random, well circumscribed, focal uptake outlining the peritoneal cavity.

Limitations

Even though many GAC primary tumors and metastases significantly take up FDG, others may not be strongly FDG avid due to their histopathology. Mucinous, signet cell, poorly differentiated adenocarcinomas, and gastric adenocarcinoma of intestinal type typically have low FDG uptake

[36]. Diffuse type gastric tumors also have low uptake, likely due to diffuse infiltration of adenocarcinoma cells resulting in relatively low level homogeneous uptake with low expression of the glucose transporter 1 (GLUT-1) and an increase in inert mucous content [30, 40]. FDG uptake in the gastric mucosa from a variety of infectious, inflammatory, post-operative, post-radiation or physiologic processes may result in false-positive findings decreasing the specificity of PET/CT. Finally, smaller gastric cancers are not accurately detected by PET/CT. One study showed that PET/CT has a sensitivity of 76.7% for gastric cancers > 3 cm but only 16.8% for those < 3 cm [41].

Several technical factors may also hinder accurate interpretation of PET/CT images such as misregistration of PET and CT images due to respiratory diaphragmatic motion in the upper abdomen. This can result in misregistration of abnormal uptake in the abdomen to the chest and lungs. Misalignment can be minimized by obtaining images during shallow breathing or mid-expiration.

GIST and diffuse large B-cell lymphoma

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors and represent up to 3% of gastrointestinal cancers, occurring most frequently in the stomach (60%) [42]. Almost all patients with GIST express c-kit receptor tyrosine kinase, hence tyrosine kinase inhibitors such as imatinib mesylate are the mainstay of treatment for patients who are not surgical candidates [38, 39]. GIST are well evaluated by PET/CT, particularly in monitoring response to tyrosine kinase inhibitors (Fig. 6) [43]. GIST may actually increase in size after imatinib mesylate treatment due to cystic changes or necrosis which occurs in the early stages of regression [44]. CECT may underestimate the therapeutic effect of imatinib mesylate if solely anatomic criteria (Response Evaluation Criteria in Solid Tumors, i.e., RECIST) are used (Fig. 7) [43]. CT may especially underestimate significant partial response to imatinib treatment when the requirement that tumor size must be reduced by at least 30% is used as the sole interpretive criteria [45].

Gayed et al. found that CT and FDG PET/CT have comparable sensitivity and positive predictive value in initial staging of malignant GISTs. They further concluded that CT scans had better anatomic resolution of the sites of lesions, however, PET/CT scans were able to predict response to imatinib mesylate therapy 2 months earlier than CT [43]. They, therefore, suggested the addition of PET/CT to CECT in diagnosis and staging as well as evaluation of recurrence in GIST [43]. PET/CT detects metabolic activity, while CECT not only assesses lesion size, but tumor enhancement. Drug resistance is a common problem following imatinib treatment for GIST. Data suggest that up to half of all patients that respond to imatinib treatment may develop resistance after approximately 2 years of therapy [46]. PET/CT may be helpful in identifying resistance to imatinib or development of resistant cell lines which allows some lesions to grow, while others regress simultaneously in the same patient (Fig. 7). Further studies are needed to establish its accuracy in this context, and the optimal timing of imaging.

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin Lymphoma worldwide, with

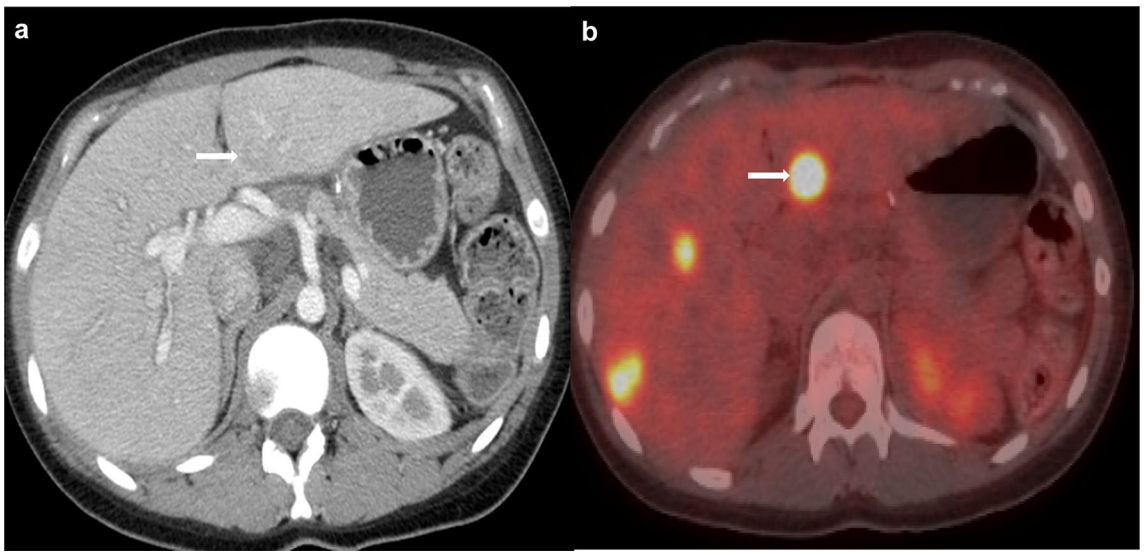

Fig. 6 Patient with metastatic GIST tumor. CECT (**a**) in a patient with previously resected GIST. There is a barely perceptible metastasis from a gastrointestinal stromal tumor in the left lobe of the liver (arrow). It is much better appreciated as an intensely FDG-avid lesion (arrow) on fused PET/CT image (**b**) than on CT. Other liver metastases are also present

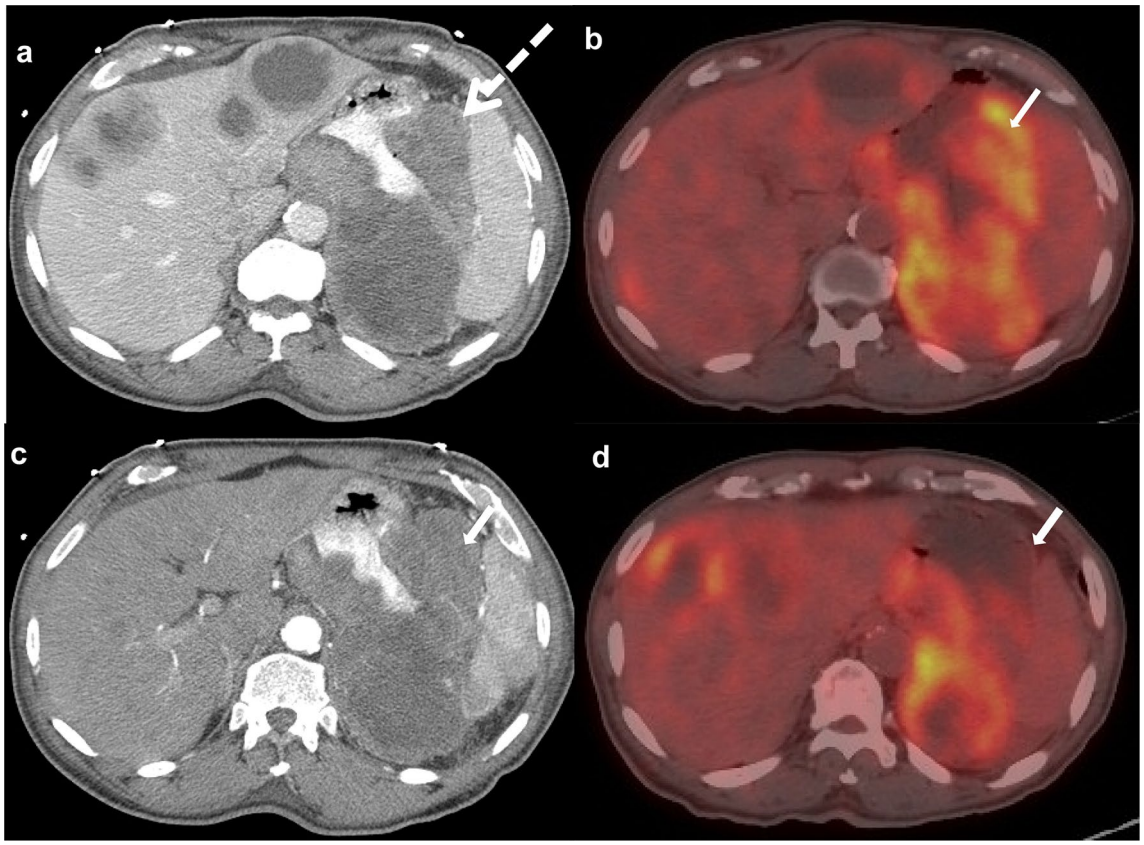

Fig. 7 Treatment response in metastatic GIST tumor. Patient with metastatic GIST pre- and post-imatinib treatment. Pretreatment CECT (**a**) and fused PET/CT image (**b**) at the level of the stomach demonstrates hypermetabolic GIST along the border of the stomach (arrow) with hypodense, hypoenhancing thickened regions of the gastric wall. Additionally, there are peripherally hypermetabolic thick-walled metastases in the left lobe of the liver. Post-treatment CECT (**c**) and fused PET/CT (**d**) demonstrate increased thickening of the gastric wall yet significant decrease in metabolic activity along the greater curvature (arrow), consistent with partial treatment response. The interval increase in hypermetabolic liver lesions may indicate another subset of cell lines that have developed relative resistance to imatinib

significant uptake of FDG in 90-95% of cases. PET/CT is used as a standard imaging modality for the staging, prognostication, and assessment of extranodal disease extent in DLBCL. In primary gastric lymphoma, the lymphomatous cell type involving the stomach often determines FDG avidity (Fig. 8), with DLBCL typically displaying high levels of FDG avidity.

Aggressive DLBCL has significantly more uptake and intensity than low grade mucosa-associated lymphoid tissue lymphoma (MALT), which is typically of low FDG avidity (Fig. 9). It is well established that apart from assessing disease spread, PET/CT is also useful in determining response to chemotherapy in DLBCL. While DLBCL of the stomach may arise spontaneously, some research suggests that DLBCL in the stomach may arise from the transformation of long standing MALT lymphoma [47]. This should be considered when modest uptake in a MALT lymphoma markedly increases on follow-up scans.

Role of PET/CT in the evaluation of colorectal cancer

Overview

Colorectal carcinoma is the third most common malignancy and third leading cause of cancer mortality in the USA, with approximately 150,000 new cases and 50,000 attributable deaths annually. The overall 5-year survival rate is around 65% but varies with disease stage at the time of diagnosis [1]. Resection of the primary tumor combined with adjuvant or neoadjuvant therapy in selected patients, is the only proven curative treatment. More recently, chemoablation and radioablation have been added in cases of isolated liver or lung metastases for curative intent. Accurate preoperative staging and follow-up surveillance is critical in determining the most effective therapy.

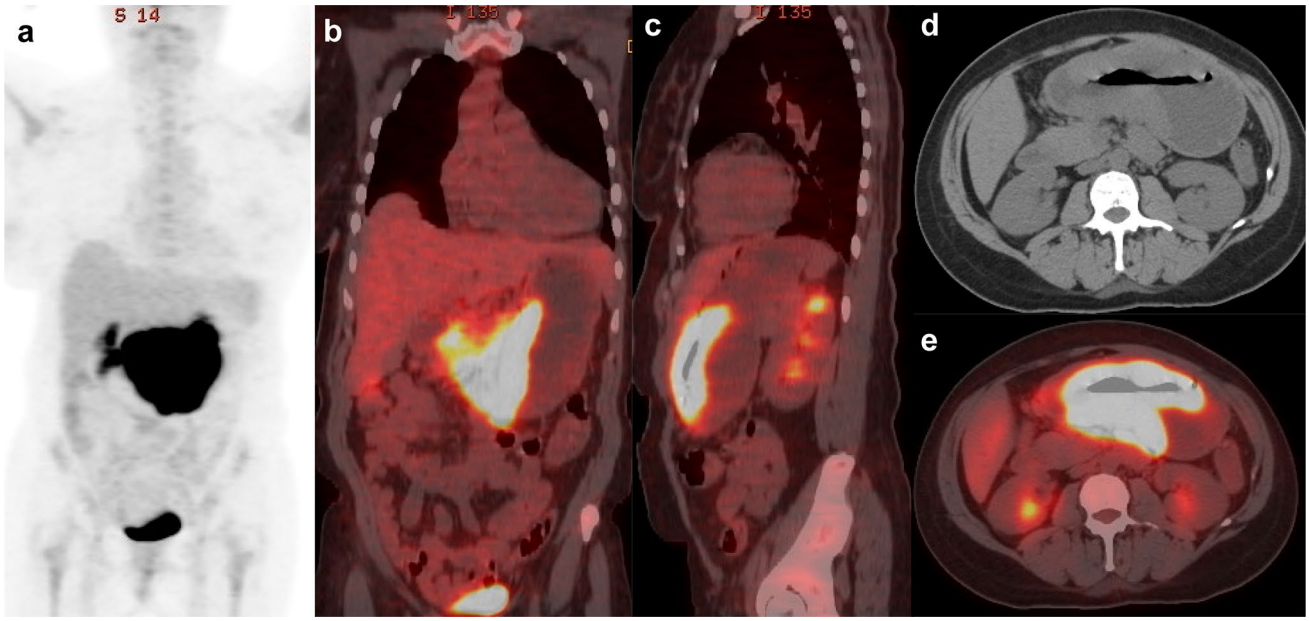

Fig. 8 Patient with gastric DLBCL. MIP image (**a**) and coronal/sagittal-fused PET/CT images (**b**) show circumferentially and significantly hypermetabolic gastric wall thickening along the gastric antrum. Axial fused (**c**) and CECT (**d**) demonstrates mass-like gastric wall thickening along the antrum

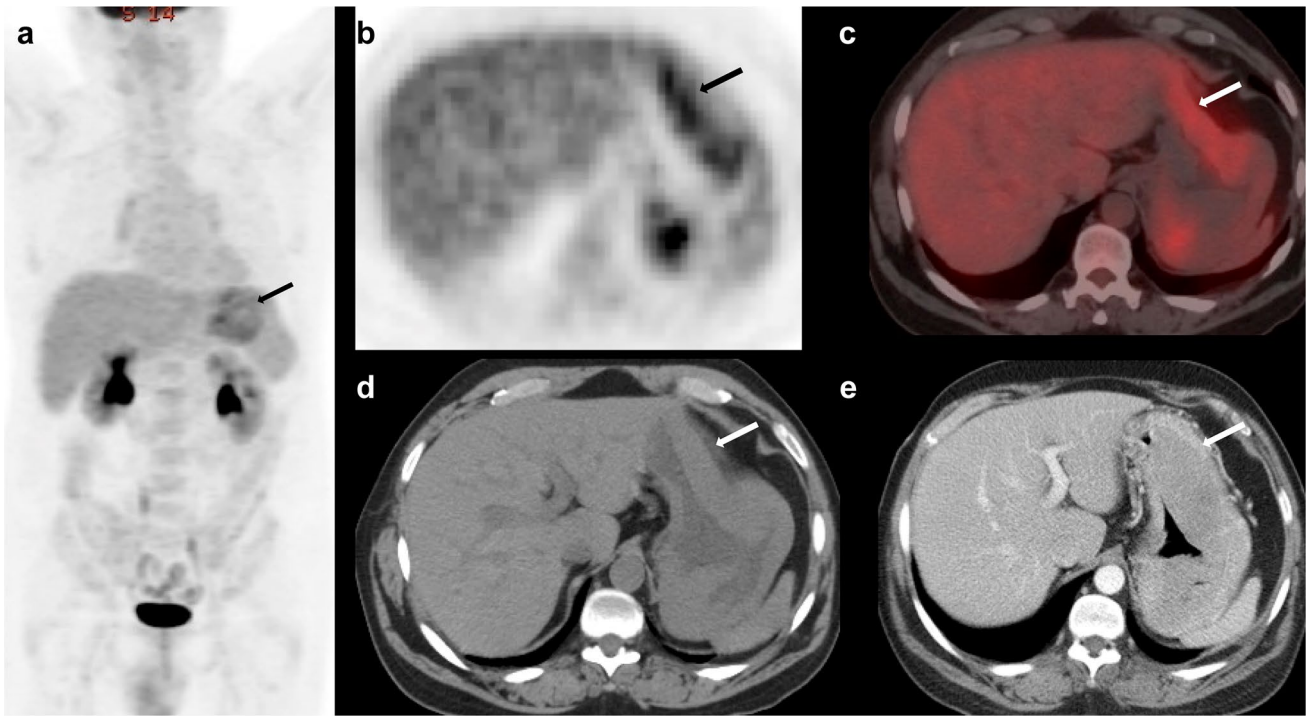

Fig. 9 Patient with gastric MALT. MIP image (**a**) and PET (**b**) and fused PET/CT (**c**) image demonstrate only minimally increased FDG uptake (Max SUV = 4.0) in the thickened gastric wall. Axial non-contrast (**d**) and CECT images (**e**) demonstrate thickened gastric wall with some enhancement, corresponding to the site of mild FDG uptake depicting the low FDG avidity of MALTomas (relative to DLBCL)

TNM staging based on pathology and imaging is applied in colorectal cancer, but the nodal staging, however, differs somewhat from other gastrointestinal tumors. Nodal involvement is very closely linked to reduced survival, and, therefore, within the N stage, the designation N1a–c is included to reflect the need for more precise nodal pathologic information (Table 3).

A minimum of 12 lymph nodes must be recovered for lymph node staging to be considered accurate in curative resections. Metastases to non-regional lymph nodes outside of the drainage area of the tumor, i.e., those not found along vascular arcades of the marginal artery or pericolonic, perirectal or mesorectal nodes should be considered distant metastasis (M1a). Multiple metastases in an organ, even paired organs (ovaries, lungs), are still M1a disease (Table 3).

Diagnosis and initial staging

Since many patients with colorectal cancer undergo surgery for early disease, data on the utility of PET/CT in initial diagnosis and staging of colorectal cancer have been limited. CECT of the chest, abdomen, and pelvis is widely accepted for initial staging of a new colon cancer, if polypectomy results in a fragmented carcinoma specimen or positive margin. Although experience and national guidelines [48] do not support a primary role for PET/CT in this setting, it is beneficial for surgical planning in those patients with equivocal CT findings for advanced M1 disease, extensive regional nodes on CT outside of the local lymph node drainage, and/or significantly increased tumor markers (indicating a greater likelihood of distant disease). In rectal cancer, initial staging is performed with EUS and MRI to assess local invasion, and the anatomic relationship of the tumor and local nodes to the mesorectal fascia [49]. Initial staging PET/CT of rectal cancer is more commonly performed than for colon cancer, because of the greater likelihood of distant disease, but should be used selectively in patients who potentially have surgically curable M1 disease [50]. In general, PET/CT has high specificity for detection of metastatic lymph nodes and high sensitivity and specificity for liver metastases in patients with colorectal cancer [51, 52].

In spite of the need for expeditious surgery in colon cancer, recent studies including one by Petersen et al. have found that inclusion of PET/CT in initial staging of colorectal cancer results in change of treatment in 30% of the patients as compared to conventional CT imaging [53]. A change from palliative to curative treatment or vice versa was seen in almost 10% of the patients. Park et al. reported a 24% change in treatment plan in a similar prospective study [54]. In many of the published series, the change in treatment plan often was the result of the presence of liver metastases [55–58]. A meta-analysis by Niekel et al. reported that on a per-patient basis, the mean sensitivities of CT, MR, and PET/CT were 81.2%, 93.4%, and 94.2%, respectively, with the sensitivity of CT being significantly lower than PET/CT [57]. While the data are compelling, patients are generally referred

Table 3 Pathologic staging of colorectal cancer AJCC 8th edition

Tis	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosa)
T1	Tumor invades submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to other adjacent organs or structures
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	No regional lymph nodes are positive but there are tumor deposits in the subserosa, mesentery or non-peritonealized pericolic or perirectal/mesorectal tissues (associated with poor overall survival)
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
M0	No distant metastasis by imaging; no evidence of tumor in other sites or organs
M1	Distant metastasis
M1a	Metastasis confined to 1 organ or site without peritoneal metastasis
M1b	Metastasis to 2 or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

for preoperative PET/CT only if there is clinical or CT evidence of advanced disease. In patients with resectable disease with isolated liver metastases, resection or directed ablative treatment of the metastatic lesion along with perioperative chemotherapy can dramatically improve 5-year survival [55].

Evaluation of response to treatment

The primary curative treatment for early colorectal cancer is surgical resection. In an effort to downstage locally advanced tumors before surgery, neoadjuvant chemotherapy is used for colon cancer [59] and neoadjuvant CRT is used for rectal cancer [60]. In patients with colon cancer, neoadjuvant preoperative chemotherapy is reserved for patients with T4b disease (invasion of adjacent organs or structures). Usually CECT will suggest this invasion, but PET/CT may be performed to better assess regional and distant sites of tumor spread. Follow-up PET/CT will be performed 4 weeks after the conclusion of neoadjuvant chemotherapy for colon carcinoma (or neoadjuvant CRT for rectal carcinoma) (Fig. 10). A meta-analysis by Maffione et al. demonstrates high pooled accuracy for detecting early PET/CT response to neoadjuvant CRT 1–2 weeks after the start of treatment for rectal cancer [60]. This is encouraging, but in clinical practice the disease status is more commonly assessed 4 weeks after the conclusion of neoadjuvant treatment (assuming it was at least 6 weeks after surgery).

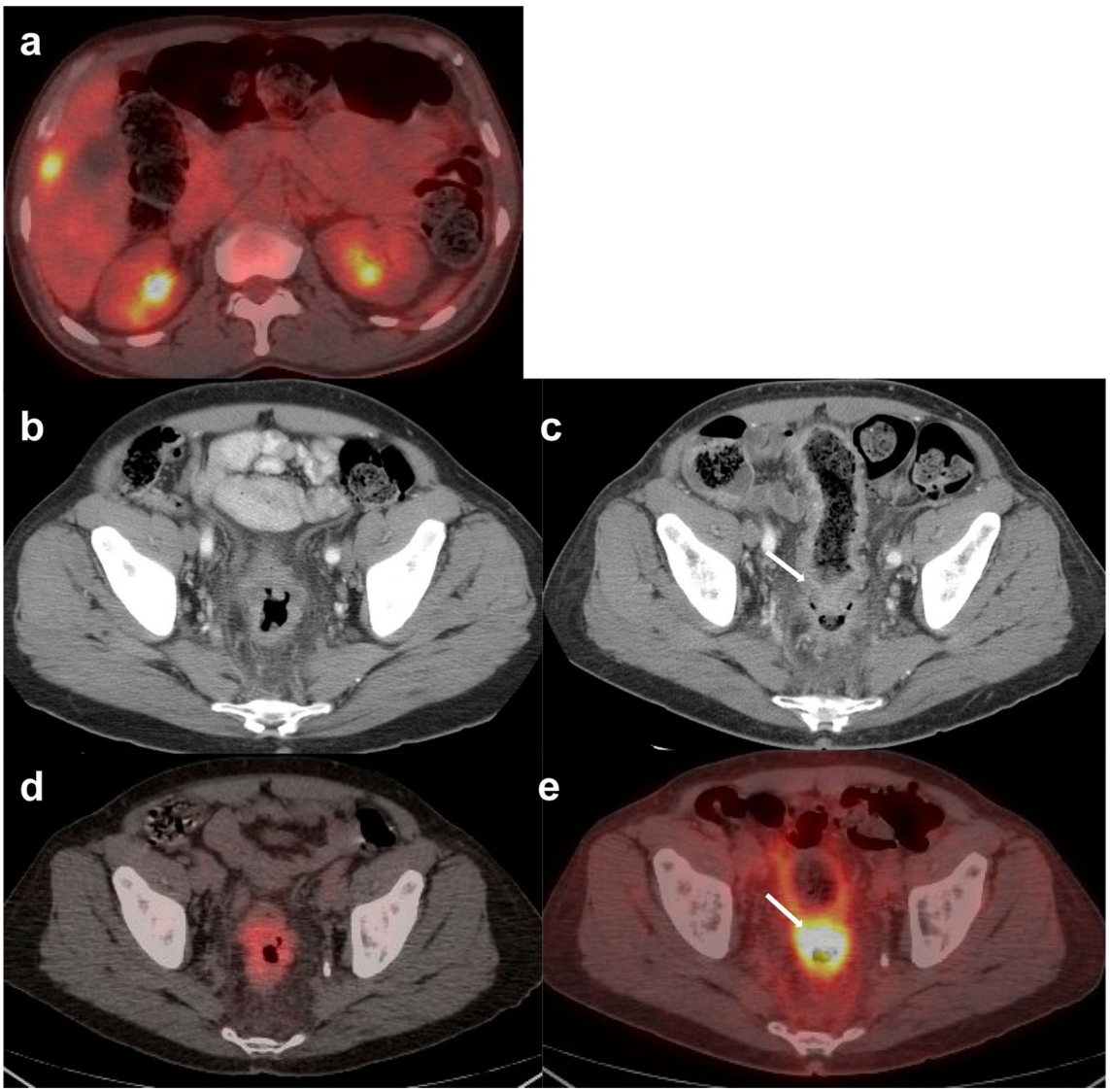

Fig. 10 PET-CT images of a patient with colorectal cancer M1 disease. PET-CT image (**a**) shows the liver metastasis. CECT before (**b**) and after (**c**) neoadjuvant chemotherapy show slight worsening of the colorectal mass which is now obstructive. PET-CT before (**d**) and after (**e**) neoadjuvant chemotherapy shows the suboptimal response with significant increase in metabolic activity of the colorectal mass

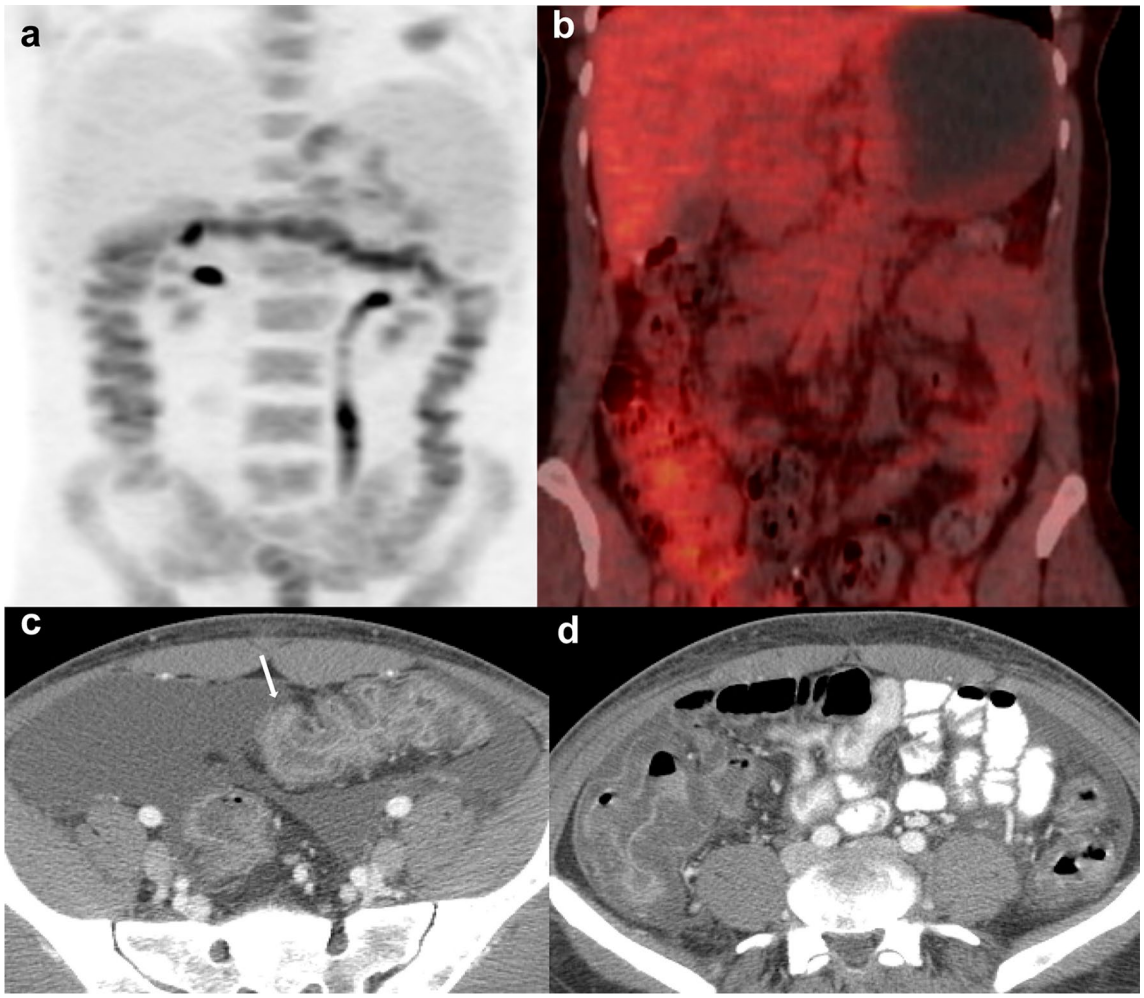

Fig. 11 MIP (**a**) and fused PET/CT (**b**) images demonstrate diffuse hypermetabolism involving the entirety of the colon in a patient with known pseudomembranous colitis. Corresponding CECT slices (**c**, **d**) demonstrate diffuse circumferential enhancing colonic wall thickening (arrow) with mucosal enhancement indicating inflammatory colitis

The vast majority of patients with colon cancer detected by screening colonoscopy or CT colonography will not present with advanced disease, and may not even be imaged preoperatively. At surgery, should T4 disease, regional or distant nodal involvement, or distant organ involvement be unexpectedly found, post-operative imaging including PET/CT would be likely performed in conjunction with the expectation that chemotherapy will be administered. After re-assessment with PET/CT [61], if complete remission occurs from a clinical and imaging perspective, subsequent follow-up will be largely clinical with serial CEA and CECT assessment. Serial screening PET/CT is not recommended. Serum CEA is used to monitor for recurrence, with a sensitivity of approximately 60-90% depending on the lowest normal limit (which can vary between 2.5 and 5 ng/mL) [62]. In the setting of rising CEA, PET/CT should be considered. When the CEA is elevated, imaging with PET/CT is more sensitive than conventional CT in identifying the site of recurrence [63]. A meta-analysis of PET/CT for recurrent colorectal cancer by Huebner et al. demonstrates a sensitivity of 97% and specificity of 76% for recurrent/metastatic disease in general, but with greater specificity (98%) for hepatic metastases [64]. PET/CT has also proven accurate in distinguishing viable tumor from scar tissue or radiation necrosis, especially in the pelvis and presacral region, after CRT for rectal cancer [65]. The overall change in clinical management for patients who undergo PET/CT for evaluation of response to treatment and restaging in colorectal cancer approaches 32% [64].

Limitations

When evaluating FDG uptake within the colon on PET/CT, the pattern of colonic uptake helps narrow the differential

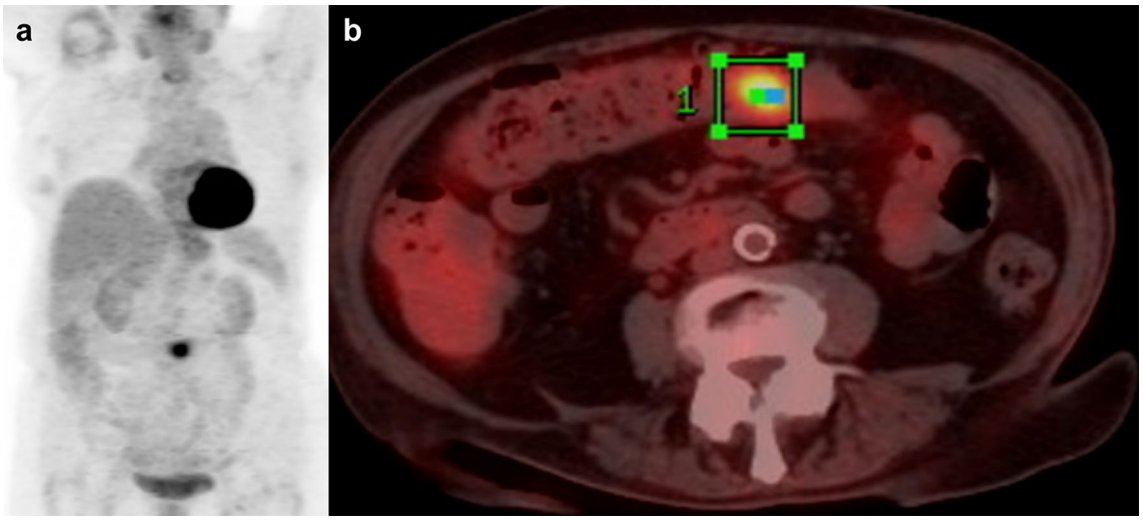

Fig. 12 MIP- (**a**) and axial-fused PET/CT (**b**) images demonstrate a focal area of increased uptake (Max SUV = 7.5, arrow) in the transverse colon. This represented an incidental finding in a patient not known to have colon cancer. Subsequent colonoscopic biopsy revealed a colon adenocarcinoma

considerations. Physiologic colonic FDG avidity is common, and due to mucosal, muscular, bacterial, or lymphocytic uptake, often most pronounced in the cecum and terminal ileum. The absolute values for physiologic colonic uptake are variable, with studies showing an average of maximum SUVs of 4–6 [66]. Other factors may also alter the FDG uptake pattern in the colon. Medications such as metformin for diabetes concentrate in the colonic mucosa to a much greater extent than the small bowel [67]. It can be withheld 48 h preceding the PET/CT to improve detection of abnormal colonic uptake. Segmental or diffuse colonic activity, in the absence of metformin use, should raise concern for infectious or inflammatory colitis (Fig. 11). Alternatively, incidentally detected focal areas of FDG uptake should raise concern for colonic adenoma or carcinoma (Fig. 12) [68].

Incidental focal colon uptake is associated with endoscopic lesions in 65.5% of cases [69]. In addition to carcinoma, Yasuda et al. found that approximately 90% of colonic adenomas > 13 mm in size also demonstrate focal FDG uptake [70]. These are generally more readily identified by PET/CT in the less mobile, fixed segments of the colon [64]. Incidentally detected focal (non-segmental) uptake in the colon should be evaluated further with colonoscopy. PET/CT may be less sensitive in detection of mucinous colorectal carcinoma compared to non-mucinous types (58% and 92%, respectively) [71].

In summary, PET/CT is a valuable tool for selective use in staging alimentary tract tumors, monitoring their response to treatment as well as detecting recurrence. Optimal evaluation is best achieved utilizing a multimodality and multidisciplinary approach.

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