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Variants and Pitfalls in PET/CT Imaging of Gastrointestinal Cancers

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In the past two decades, PET/CT has become an essential modality in oncology increasingly used in the management of gastrointestinal (GI) cancers. Most PET/CT tracers used in clinical practice show some degree of GI uptake. This uptake is quite variable and knowledge of common patterns of biodistribution of various radiotracers is helpful in clinical practice. ^{18}F-Fluoro-Deoxy-Glucose (FDG) is the most commonly used radiotracer and has quite a variable uptake within the bowel. ^{68}Ga-Prostate specific membrane antigen (PSMA) shows intense uptake within the proximal small bowel loops. ^{11}C-methyl-L-methionine (MET) shows high accumulation within the bowels, which makes it difficult to assess bowel or pelvic diseases. One must also be aware of technical artifacts causing difficulties in interpretations, such as high attenuation oral contrast material within the bowel lumen or misregistration artifact due to patient movements. It is imperative to know the common variants and benign diseases that can mimic malignant pathologies. Intense FDG uptake within the esophagus and stomach may be a normal variant or may be associated with benign conditions such as esophagitis, reflux disease, or gastritis. Metformin can cause diffuse intense uptake throughout the bowel loops. Intense physiologic uptake can also be seen within the anal canal. Segmental bowel uptake can be seen in inflammatory bowel disease, radiation, or medication induced enteritis/colitis or infection. Diagnosis of appendicitis or diverticular disease requires CT correlation, as normal appendix or diverticulum can show intense uptake. Certain malignant pathologies are known to have only low FDG uptake, such as early-stage esophageal adenocarcinoma, mucinous tumors, indolent lymphomas, and multicystic mesotheliomas. Response assessment, particularly in the neoadjuvant setting, can be limited by post-treatment inflammatory changes. Post-operative complications such as abscess or fistula formation can also show intense uptake and may obscure underlying malignant pathology. In the absence of clinical suspicion or rising tumor marker, the role of FDG PET/CT in routine surveillance of patients with GI malignancy is not clear.
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Introduction

Gastrointestinal (GI) tract cancers accounted for nearly 213,690 cancer diagnoses and 118,320 cancer-related deaths in 2020.[1] Since the introduction of combined PET/CT scanners two decades ago, Positron Emission Tomography combined with Computed Tomography (PET/CT) has become an essential modality in the management of GI cancers, being used for diagnosis, staging, evaluation of treatment response, and assessment of prognosis.[2] This is particularly true for esophageal, gastric, and colorectal cancers.

Several radiotracers are used in clinical practice and in the research setting. The specific use of each radiotracer varies based on its metabolic pathway and intracellular stability. Cyclotron produced Fluorine-18 (^{18}F) with a physical half-life of 110 min allows adequate time for labelling as well as transport of radiopharmaceuticals to nearby locations. ^{18}F labeled Fluoro-deoxy-glucose (^{18}F-FDG) remains the most widely used radiotracer in molecular imaging. Carbon-11 (^{11}C) is a short-lived positron emitter with a physical half-life

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of 20 min that requires an on-site cyclotron. It can be used to label acetate, methionine, or choline for both oncological and non-oncological imaging. Generator-produced Gallium-68 (^{68}Ga) with a physical half-life of 68 min can be used for labeling somatostatin receptor binding compounds such as DOTATATE or DOTATOC (for imaging of neuroendocrine tumors) or small molecules binding to prostate specific membrane agent (PSMA) (for imaging of prostate cancer). Zirconium-89 (^{89}Zr, half-life: 3.3 days), Iodine-124 (^{124}I, half-life: 4.2 days), and Copper-64 (^{64}Cu, half-life: 12.7 h) labeled antibodies, targeting for instance A33 or HER-2/neu, are currently being evaluated in the research setting.

Most of the radiotracers used in the clinical and research setting show GI uptake to some extent (Fig. 1). As tracer accumulation within the GI tract is not specific for a single physiological process or pathology, it is imperative to understand physiological distribution of a given tracer within the normal GI tract and potential pitfalls in the interpretation of the imaging study. The purpose of this review is to convey the normal distribution pattern of commonly used tracers, highlight physiological variants, and emphasize pitfalls seen in PET/CT imaging of GI cancers.

Biodistribution of Commonly Used PET/CT Tracers

^{18}F-Fluoro-Deoxy-Glucose (FDG)

^{18}F-FDG is the most commonly used radiotracer in the evaluation of malignancy. One of the key advantages of this radiotracer is its high cellular uptake in many common tumors and its intracellular retention. It acts as a surrogate for glucose and is taken up in tissues with high

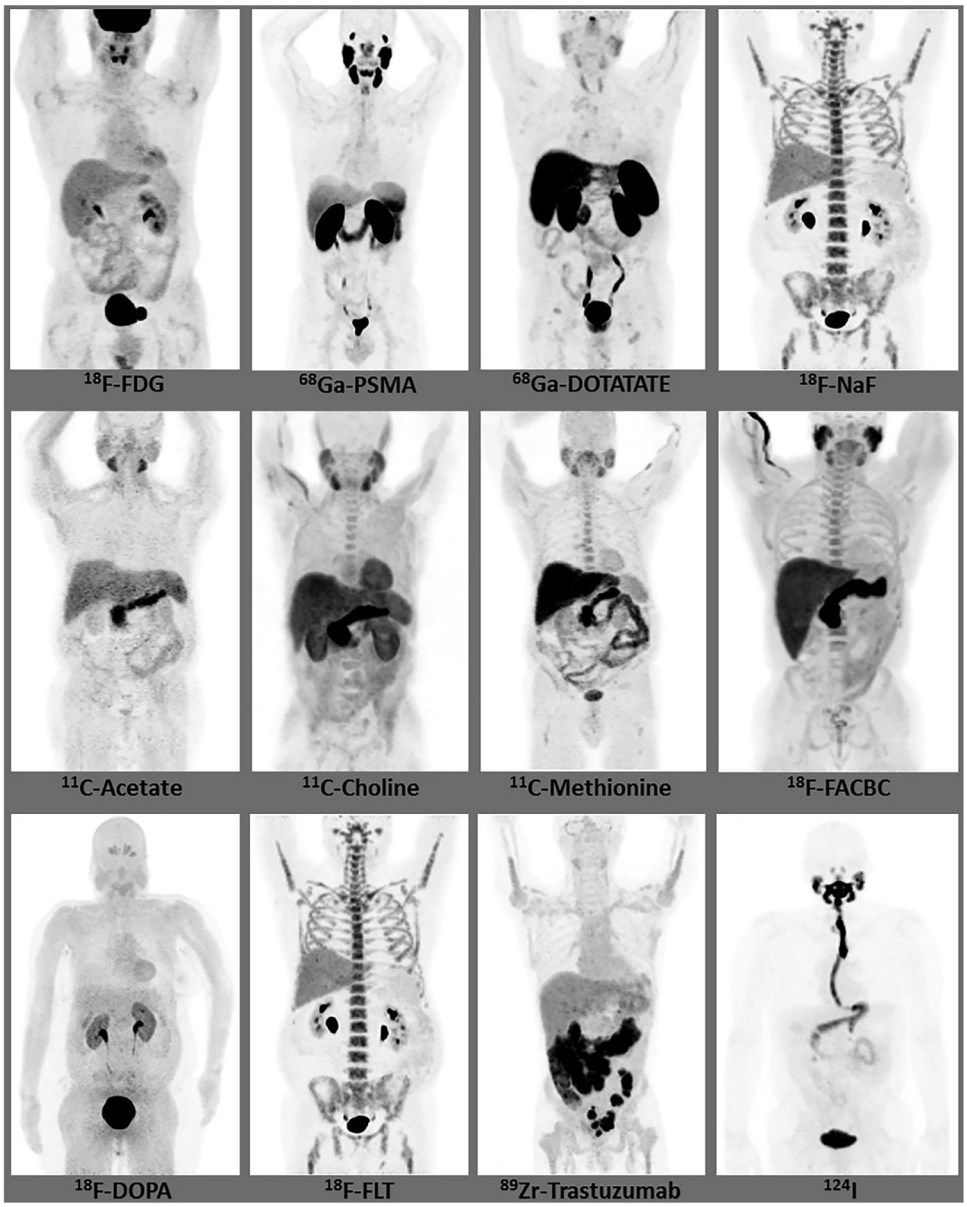

Figure 1 Maximum intensity projection (MIP) images depicting normal gastrointestinal biodistribution of various radiotracers.

transmembrane glucose transporter expression and hexokinase activity. ^{18}F-FDG uptake within the GI tract is quite variable and could be mild and diffuse, following the contours of the bowel, or intense and focal, mimicking malignancy. The exact mechanism by which ^{18}F-FDG accumulates in the GI tract is poorly understood. It is postulated that FDG is taken up by the GI muscle and is excreted into the bowel lumen. Other possible causes of GI uptake include swallowed secretions, colonic microbial uptake, mucosal uptake, and uptake by the normal lymphoid tissues, for instance in the terminal ileum.

^{68}Ga-Prostate Specific Membrane Antigen (PSMA)

Prostate specific membrane antigen (PSMA) is structurally similar to glutamate carboxypeptidase II and folate hydrolase I. Although PSMA was first identified in the prostate, it is now known to occur in various tissues.[3] Its expression within the stomach is weak to moderate, including weak expression in gastric carcinomas. Small bowel enterocytes are strongly positive to PSMA on immunostaining, whereas intestinal adenocarcinoma shows moderately intense PSMA immunostaining. PSMA expression within both normal colonic mucosa and colonic adenocarcinoma is weak to moderate.[4] This pattern of immunostaining is reflected on ^{68}G-PSMA imaging where the proximal small bowel shows intense tracer uptake compared to rest of the GI tract. Uptake is also noted within the celiac, cervical, and sacral ganglia, which can mimic a lymph node metastasis.[5,6] Excretion into the saliva may result in esophageal uptake. Hepatobiliary clearance may result in activity within the bowel lumen.[7]

Somatostatin Receptor Scintigraphy (SRS)

Somatostatin receptor (SSTR) subtypes 1−5 are widely distributed throughout the body. SSTR-1 is expressed at the highest level in the stomach and jejunum, with low levels seen in the colon. The distribution of SSTR-2 is different from SSTR-1 and is seen in low levels within the jejunum and colon.[8] Gallium-68-DOTA-Dphe1, Tyr3-Octreitate (Ga-68 DOTATATE) is a somatostatin analog with high affinity for somatostatin receptor-2 (SSTR-2) and is used in neuroendocrine tumor imaging. The GI uptake of the tracer is quite variable. A decreasing proximal to distal gradient with high physiologic uptake is generally seen in the stomach, moderate uptake in the jejunum and ileum, and mild uptake in the colon and rectum.[9] This may be explained in part by the diminishing density of somatostatin receptors along the GI tract.[10] Salivary excretion of the radiotracer into the GI tract may also contribute to GI activity.

^{18}F-Sodium Fluoride (NaF)

^{18}F-NaF is a bone-seeking positron emitting radiotracer that is similar in action to ^{99m}Tc-MDP but has better resolution, high bone-to-background ratio, and improved sensitivity.[11] It provides image quality and extent of disease evaluation superior to that of ^{99m}Tc-MDP. The major route of excretion is via the kidneys. The exact mechanism of uptake within the bowels is not known and is quite varied, ranging from minimal to intense uptake.[12]

^{11}C-Acetate

^{11}C-acetate is a biomarker for lipid synthesis and can be used for the study of myocardial perfusion and oxygen consumption as well as for the imaging of various malignancies such as hepatocellular carcinoma, prostate cancer, renal cancer, and bladder cancer.[13,14] The distal esophagus may show prominent tracer uptake, and excreted (usually low-grade) activity can be seen in the small and large bowel.[15,16] Metastatic disease to the bowel from HCC, though rare, may be missed on C11-acetate imaging.[17]

^{11}C/^{18}F-Choline

Choline is a precursor of phosphatidylcholine, which is an important element of cell membrane and a marker for lipogenesis,[18] and can be labeled with ^{18}F (^{18}F-methylcholine; ^{18}F-FCH and ^{18}F-ethylcholine; ^{18}F-FECH) or ^{11}C (^{11}C-choline). These agents have been investigated for their utility in imaging prostate cancer, hepatocellular carcinoma, and brain tumors such as glioblastoma.[19-21] ^{11}C-choline has predominant hepatic metabolism that may result in early accumulation within the bowel, compared to ^{18}F-FCH or ^{18}F-FECH, which are primarily excreted via the kidneys.[22] In general, colonic activity is lower than small bowel activity, in contrast to ^{18}F-FDG, for which colonic uptake is more prominent than small bowel uptake.[23] Intense choline uptake can be seen in inflammation, such as esophagitis, and in colonic adenomas.[18,24]

Amino Acid Tracers

Some of the commonly used amino acid tracers include ^{11}C-methyl-L-methionine (MET), Anti-1-amino-3-^{18}F-Fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC; commercial name: Axumin), ^{18}F-Fluoro-L-dihydroxyphenylalanine (F-DOPA), and ^{18}F-Fluoro-ethyl-L-Tyrosine (FET).

Methionine is an essential amino acid that plays an important role in the synthesis of polypeptide chains and formation of S-adenosylmethionine (SAM) required for methylation of DNA, RNA, and protein.[25] MET is a biomarker for amino acid transport, which can be used for the imaging of CNS tumors, prostate cancer, and bladder cancer.[13,26,27] It shows variable and high accumulation within the bowel, limiting its use in GI and pelvic malignancies.[28] The stomach wall uptake rapidly increases during the first 4.5 min and the mean SUV of the stomach wall is usually higher than that of large bowel loops.[29] There is some excretion of MET activity from the pancreas into the duodenum, and this has been used to assess pancreatic exocrine function.[30] FACBC is a non-natural synthetic L-leucine analog used in the assessment of prostate cancer, breast cancer, and brain tumors.[31,32]

Mild to moderate esophageal uptake is frequently seen, particularly within the distal esophagus and the gastroesophageal junction, and may indicate inflammation similar to that seen with FDG uptake. Mild to moderate FACBC uptake is also seen within the stomach, small bowel, and colon.[33] F-DOPA is a radiolabeled analog of the amino acid L-DOPA and is predominantly used in the imaging of brain tumors and neuroendocrine tumors.[34-36] Mild uptake may be seen the esophagus. The bowel may show no or mild diffuse uptake. Less frequently, mild uptake may be seen within the duodenum.[34]

^{18}F-Fluorothymidine (FLT)

^{18}F-FLT is a biomarker of cell proliferation and thymidine kinase-1 activity. It has been used in non-invasive assessment of cell proliferation activity of several cancers as well as for prediction and monitoring of therapy response.[37] Due to the presence of rapidly proliferating mucosal cells within the GI tract, physiological uptake is expected within the intestines and is usually mild and variable. Low background activity results in high tumor-to-background uptake, enabling detection of primary GI neoplasms such as gastric cancers.[38]

Human Epidermal Growth Factor-2 (HER2) Targeted Imaging

The antibodies trastuzumab and pertuzumab can be radiolabeled (for instance with ^{89}Zr or ^{67}Cu) and used for HER2 imaging, for instance in breast and gastric cancers. Bowel activity can be seen one to two days after injection, reflecting the primary excretion route of this agent.[39-42]

Iodine-124 (^{124}I)

^{124}I is a positron emitter with a half-life of 4.2 days; one of the advantages of PET imaging for thyroid cancer is the ability to perform lesional dosimetry.[43,44] The isotope can also be used to label various antibodies, peptides, and amino acids.[45,46] For lesional dosimetry studies in thyroid cancers, it is administered orally. Normal activity is seen in salivary glands and stomach; lower GI activity may also occur.

Maximum intensity projection (MIP) images that depict the normal biodistribution of the above tracers are shown in Fig. 1. Mechanism of action, use, and biodistribution of some of the commonly used radiopharmaceuticals in the clinical and research setting are presented in Table 1.

Technical Artifacts in Imaging

Technical artifacts occur irrespective of the radiotracer used and can lead to inaccurate interpretation. Most relevant for this topic are CT-related and patient-related factors.

CT Factors

High-density oral contrast material may cause significant attenuation, leading to overcorrection on attenuation corrected PET images and the appearance of apparent FDG-avid lesions and overestimation of SUV[47] (Fig. 7C). Metallic implants such as lumbar fixation hardware or intraluminal bowel stents can cause streak artifact and degrade the quality of the CT images. They can also result in overestimation of local tracer uptake. Assessment of the non-attenuation corrected PET images identifies the artifact and clarifies interpretation.[48,49]

Patient Factors

Patient motion during image acquisition of imaging can lead to PET vs. CT misregistration. PET is usually acquired over a duration of 2 to 3 min at each bed position, whereas CT is acquired over a few seconds. The effect is particularly seen in the peristaltic bowel, which could change its position between the CT and PET acquisition. Respiratory motion can result in misregistration of organ activity in the upper abdomen, possibly giving the appearance of an FDG-avid hepatic metastasis due to misplaced colonic activity on the fused images. Similarly, misregistration within the pelvis can occur due to different filling status of the urinary bladder, shifting the position of bowel loops and the uterus between CT and PET acquisitions. Arms by the side of the patient can cause significant streak and attenuation artifact.

Physiologic and non-physiologic radiotracer uptake that can mimic malignancy and pitfalls in PET/CT imaging of various GI malignancy are presented in Table 2.

Esophagus

Based on location, esophageal tumors can be divided into cervical, upper thoracic, middle thoracic, lower thoracic, and gastroesophageal junctional tumors. Gastroesophageal junctional tumors have epicenters no more than 2 cm off the cardia.[50] Squamous cell carcinomas (SCC) and adenocarcinomas (AC) are the two major subtypes of esophageal cancers.

Physiologic FDG uptake within the esophagus could be caused by swallowed saliva or metabolic activity within the esophageal smooth muscle due to peristalsis and can be seen as low-grade linear uptake along the length of the esophagus (Fig. 2E).

Variable moderate to intense, diffuse, or focal radiotracer uptake can be seen in esophagitis due to various causes such as gastroesophageal reflux disease, recent radiation therapy, medication, or infection (Fig. 2A-D). Benign esophageal leiomyoma (Fig. 2F) and glycogen acanthosis are also known to show FDG uptake.[51,52] Uptake within the distal esophagus and gastroesophageal junction, similar to FDG uptake with reflux disease, can be seen with ^{11}C-acetate and ^{18}F-FACBC [33]. ^{68}Ga PSMA has shown to have uptake within achalasia.[53]

Table 1 Mechanism of Action, Use, and Biodistribution of Radiopharmaceuticals Commonly Used in Clinical and Research Settings

Radiotracers	Property	Mechanism of Action	Use	GI Biodistribution
^{18}F-Fluoro-Deoxy-Glucose (FDG)	Glucose analog	Glucose analog	Majority of the oncological imaging	Variable, mild or intense, diffuse or segmental, throughout the GI tract
^{68}Ga-Prostate specific membrane antigen (PSMA)	Similar to glutamate carboxypeptidase II and folate hydrolase I	PSMA expressed on cell membrane, internalized on ligand binding	Prostate cancer	Intense uptake within duodenum and jejunum, variable low-grade uptake within the remainder of the bowel loops
Somatostatin receptor Scintigraphy (SRS)	Somatostatin receptor analog	Binds to somatostatin receptor (SSTR) subtypes	Neuroendocrine tumor	More intense within the proximal bowel loops compared to the distal bowel
^{18}F-Sodium Fluoride (NaF)	Analog for hydroxyl group in in the bone matrix	Localization in the hydroxyapatite crystal	Osseous metastases	Not common, if present, it is variable, predominantly with the small bowel
^{11}C-Acetate	Substrate for synthesis of acetyl Co-A	Biomarker for cell membrane lipid synthesis	Myocardial perfusion and oxygen consumption various malignancies, such as hepatocellular carcinoma, prostate cancer, renal and bladder cancers	May have prominent esophageal uptake, low-grade within the small and large bowel
^{11}C/^{18}F-Choline	Precursor of phosphatidylcholine	Biomarker for lipogenesis and biosynthesis of cell membrane	Prostate cancer, hepatocellular carcinoma and brain tumors	Variable but generally colonic uptake is less than the small bowel uptake
^{11}C-methyl-L-methionine	Essential amino acid	Protein synthesis	CNS tumor imaging, prostate and bladder cancers	Variable and intense, stomach uptake higher than in large bowel loops
FACBC; commercial name: Axumin	Non-natural synthetic L-leucine analog	Amino acid transporter	Prostate cancer, breast cancer and brain tumors	Variable mild to moderate uptake within the GI tract, more prominent with in the esophagus
^{18}F -Fluoro-L-dihydroxyphenylalanine (F-DOPA)	L-DOPA analog	Precursor for catecholamines	Brain tumors and neuroendocrine tumors	Mild uptake within the esophagus. Minimal or no uptake within the bowel loops
^{18}F-Fluoro-ethyl-L-Tyrosine (FET)	Neutral amino acid analog	Amino acid transporter	Brain tumor	Minimal or no uptake
^{18}F-Fluorothymidine (FLT)	Pyrimidine analog	Biomarker for cell proliferation and thymidine kinase -1 activity	Several cancers for prediction and monitoring of therapy response	Variable, usually low-grade
Human Epidermal Growth Factor-2 (HER2) targeted imaging	Humanized mAb against HER2 Receptor	Binds to HER2 receptor	Breast and esophagogastric cancer	Seen one to two days after administration and moves distally over time
Iodine-124 (^{124}I)	Positron Emitting Iodine	Functions as Iodide	Thyroid	Seen one to three days after ingestion and decreases over the time

Table 2 Variants and Pitfalls of PET/CT in GI Cancers

Site	Tracer Used	Benign Conditions That Can Mimic Malignancy	Malignant Conditions With Unreliable or Low-Grade Uptake
Esophagus	FDG	Esophagitis, leiomyoma	T-staging is unreliable Early-stage adenocarcinoma can be low-grade with low PPV for Stage 1 disease Radiation induced fibrosis or inflammation versus residual disease can have similar appearance
Stomach	FDG	Physiologic uptake, particularly within the fundus, gastritis, schwannoma, leiomyoma	Distal gastric tumors ca be low-grade compared to proximal tumors Decreased sensitivity for LNs Decreased sensitivity for diffuse-type cancers such as Signet ring cell cancers Decreased sensitivity for some indolent NHL such as gastric MALT Response assessment not possible for non-avid or minimally avid tumors Higher sensitivity for determining treatment failure than to predict response for GIST Role is unclear in routine follow up Can have false positive results
Small Bowel	FDG	Physiologic uptake, IBD, enteritis,	Can be low-grade for MALT lymphoma and neuroendocrine tumors (NET)
	Ga-DOTATATE		High proliferation index and poorly differentiated NETs and neuroendocrine carcinomas
Colon and Rectum	FDG	Physiologic uptake, metformin bowel, colonic or ileostomy stoma, polyps, diverticulitis, IBDs, colitis, Inflammatory pseudotumor, sarcoidosis, normal appendix	May not be helpful in staging of localized disease without metastases Mucinous tumors can be low-grade
		Anastomotic uptake – physiological and inflammation Post-operative changes and complications such as fistula Radiation induced inflammation	Can have false positive results for response assessment in neoadjuvant setting
			Not recommended for routine follow up; can have false positive results
Anal Canal	FDG	Physiological, hemorrhoids, anal fistulas	Not for local staging of primary tumor
		Radiation induced inflammation	Can be false positive if performed soon after chemoradiotherapy Role in follow up unclear – uptake within the anal canal on follow up does not necessarily indicate recurrence
Peritoneum	FDG	Benign conditions as such mesenteric panniculitis, post-operative changes, TB peritonitis Splenules, transposed ovaries, sarcoidosis, portal vein thrombosis, mesh prosthesis, hernia repair plug,	Decreased sensitivity for small-volume disease, predominantly cystic disease, ascites, multicystic peritoneal mesothelioma, pseudomyxoma peritonei
		Post hyperthermic intraperitoneal chemotherapy (HIPEC) or operative changes	Response assessment and recurrence – PET/CT may underestimate disease

During cancer staging, FDG PET-CT is not sufficiently accurate to assign the T-stage, as it cannot reliably assess esophageal wall definition or the depth of tumor invasion. Lowe et al. reported that ^{18}F-FDG PET accurately staged the T category in 43% of patients, compared to 71% by endoscopic ultrasound.[54] ^{18}F-FDG PET-CT is of limited value in the assessment of early-stage adenocarcinoma when the endoscopy and biopsy indicate cTis and cT1 disease.[55] In a meta-analyses by Shi et al., FDG PET/CT had a sensitivity of 55–62% and a specificity of 76–96% for detection of

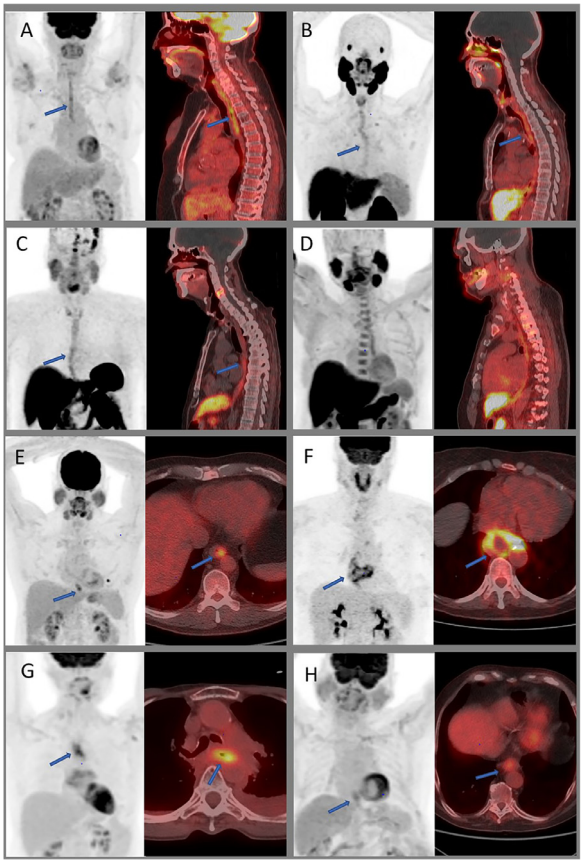

Figure 2 Physiologic and non-physiologic radiotracer uptake within the esophagus. MIP and fused sagittal images demonstrating mild to moderate diffuse uptake of benign esophagitis on 18F-FDG PET/CT (A), ^{68}Ga-PSMA PET/CT (B), ^{68}Ga-DOTATATE PET/CT (C), and 18F-FACBC PET/CT (D). MIP and axial fused images of the chest showing benign focal uptake within the distal esophagus (E), moderately intense peripheral uptake within a benign leiomyoma (F), post-radiation inflammation within the mid esophagus (G), and low-grade uptake within a biopsy proven esophageal adenocarcinoma (H).

regional lymph node metastasis.[56] Interim FDG PET/CT after induction chemotherapy may differentiate responders from non-responders early in the course of treatment. A decrease in 35% of initial FDG uptake has been shown to predict clinical response in patients with locally advanced adenocarcinoma of the gastroesophageal junction with sensitivity and specificity of 93% and 95%, respectively.[57] However, the value of FDG PET/CT after completion of chemoradiotherapy remains unclear. In the post-chemoradiotherapy setting, the esophagus may have a very heterogeneous appearance due to radiation induced inflammation and fibrosis (Fig. 2G). FDG tends to perform worse in adenocarcinomas than in squamous cell carcinomas[57,58] (Fig. 2H). In a systematic review, FDG PET/CT showed pooled sensitivity and specificity of 62% and 73%, respectively, for detecting pathological complete response in primary tumor and regional lymph nodes; the authors noted that this was not sensitive enough to guide treatment decisions.[59]

FDG PET/CT has proven useful in the detection of recurrent esophageal cancer. In a meta-analysis, the pooled sensitivity and specificity were 96% and 78% for detecting recurrence after primary treatment with curative intent.[60] Of note, pretest probability matters, and the positive predictive value of FDG PET/CT was lower for patients with initial stage I disease compared to those with initial stage II or III disease.[61]

Stomach

Most gastric cancers are adenocarcinomas, followed in prevalence by lymphoma and gastrointestinal stromal tumors (GIST). Gastric carcinoid and gastric metastases are rare. Some precancerous pathologies such as H. pylori infection, autoimmune gastritis, and atrophic gastritis are known to precede the development of the intestinal type (Lauren's classification) of gastric adenocarcinoma, which include the tubular (most common), mucinous, and papillary subtypes. Poorly cohesive carcinoma, which includes signet ring cell carcinoma, belongs to the diffuse type (Lauren's classification) of gastric cancer.[62] The stomach is the most common site of primary extranodal non-Hodgkin lymphoma (NHL), accounting for nearly 60–75% of cases, with diffuse large B-cell lymphoma (DLBCL) and mucosa associated lymphoid tissue (MALT) the most prevalent subtypes.[63]

The mechanism of physiologic gastric FDG uptake is unclear, ranging from intense and localized to the fundus/cardia to mild to moderate and diffuse throughout the stomach (Fig. 3A). Koga et al. postulated that FDG uptake may be related to number of parietal cells in each region of the stomach, with higher mean FDG uptake in the upper part of the

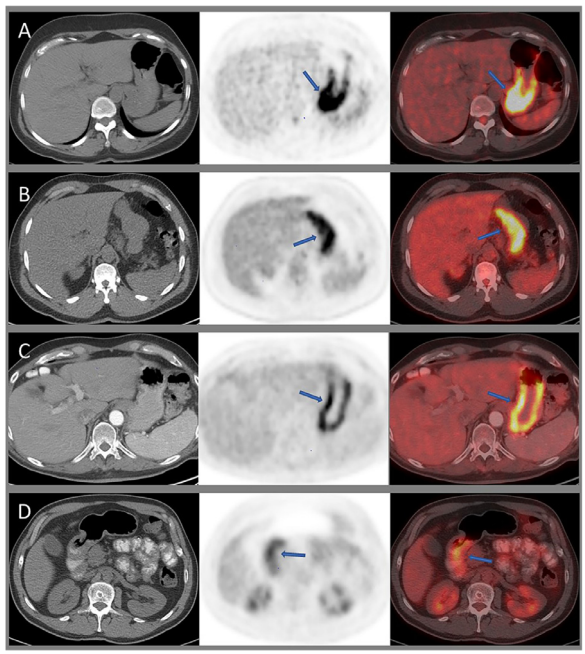

Figure 3 Axial CT, PET, and fused images of 18F-FDG PET/CT demonstrating intense, predominantly proximal, physiologic gastric uptake (A); moderately intense diffuse uptake in H. pylori infection (B) and chronic inactive gastritis (C); mild diffuse uptake within the pylorus post-radiation (D).

stomach, where the parietal cells are most numerous.[64] The uptake is usually within the wall, but it is not understood whether it is in the smooth muscles of the gastric wall or within the layers of the gastric mucosa. Use of gastric distension using water or carbonated liquids and an antimotility agent such as Buscopan was shown to be an effective tool in discriminating patients with physiological uptake in up to 64% of cases.[65] However, in most cancer treatment centers, it is not a routine practice to use this protocol for patients undergoing FDG PET-CT without a known gastric pathology. Physiologic FDG uptake can also be related to the normal lymphoid tissues.

Benign pathologies of the stomach include mucosal ulcerations, for example secondary to peptic ulcer disease or H. pylori infection (Fig. 3B); benign polyps such as hyperplastic, adenomatous, or inflammatory polyps; and diffuse mucosal abnormalities such as acute gastritis, medication, or radiation induced gastritis and chronic and atrophic gastritis (Fig. 3C and D). All of these can cause variable gastric FDG uptake and can mimic primary gastric malignancy. Elevated gastric FDG uptake can be seen in H. pylori infection and chronic atrophic gastritis. Benign pathologies such as xanthogranulomatous gastritis and benign tumors such as gastric schwannoma and leiomyoma can mimic GIST on PET/CT[66–68] (Fig. 4A and B).

Gastric GIST has been detected on PSMA PET,[69,70] and ^{18}F-choline uptake has been reported in gastric neuroendocrine tumors.[71]

The variable, sometimes intense physiological FDG uptake within the stomach wall can lead to difficulty in detection of primary gastric malignancies. T-stage cannot be assessed reliably due to limited spatial resolution. Smyth et al. reported lower FDG avidity in distal gastric tumors than in proximal cancers (59% vs. 81%), as well as lower FDG avidity in diffuse-type gastric cancers than in those of intestinal subtype (44% vs. 97%).[72] In terms of nodal staging, FDG PET/CT has a lower sensitivity than EUS (50% vs. 73%), and again, its accuracy is lower for diffuse-type than for intestinal/mixed-type tumors (49% vs. 59%).[73] FDG is not reliable for the assessment of signet ring carcinoma subtype (SRCC); these tumors show lower FDG uptake than tumors of other histology and may be missed completely (Fig. 4C). Interestingly, high ^{68}Ga PSMA uptake was reported in signet ring cell gastric cancer.[74]

The reported detection of gastric MALT of FDG PET/CT varies widely, ranging from 50–71%; in general, FDG uptake in gastric MALT is lower than in more aggressive lymphomas[75-78] (Fig. 4D).

As noted above, FDG PET/CT has been used for response assessment at different time points during and after completion of therapy. Long term results of a prospective study showed sensitivity and specificity of interim FDG PET/CT in predicting responders of 69% and 82%.[79] A pilot study showed an improvement in disease-free survival among metabolic non-responders when the neoadjuvant chemotherapy was switched to a non-cross resistant regimen.[80]

The exact role of FDG PET/CT in detecting recurrent gastric cancer is still unclear. One study evaluated its role for surveillance in asymptomatic gastric cancer patients after curative surgery. In patient-based analysis, sensitivity and specificity were 84% and 88%, with no clear difference when stratified by early vs. advanced gastric cancer or time between surgical resection and PET scan. However, false positive FDG uptake was observed in 11% of patients, resulting in low positive predictive value (PPV) of only 43%.[81] In a recent meta-analysis, the pooled sensitivity and specificity of the FDG PET/CT for detecting recurrent gastric cancer were reported to be 81% and 83%.[82]

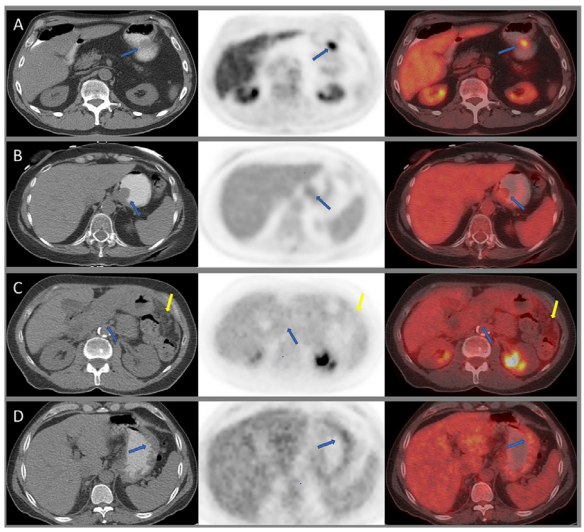

Figure 4 Axial CT, PET, and fused images of 18F-FDG PET/CT demonstrating intensely avid gastric schwannoma along the greater curvature of the stomach (A), mildly avid leiomyoma at the gastroesophageal junction (B), diffuse low-grade uptake within an infiltrating poorly differentiated adenocarcinoma with signet ring cell features (blue arrows) and peritoneal carcinomatosis (yellow arrows), (C) and mild diffuse uptake within a biopsy proven gastric MALT lymphoma (D).

Small Bowel

Primary tumors of the small bowel such as adenocarcinomas, GIST, lymphoma, and neuroendocrine tumors (NET) are relatively uncommon, accounting for about 5% of all GI malignancies.[1] Some tumors have predilection for certain parts of the small bowel; for example, adenocarcinomas are more frequently found in the duodenum, and NET are more commonly found in the distal ileum.[83,84]

The majority of commonly used radiotracers show physiologic small bowel avidity, either due to hepatobiliary excretion, active secretion into the lumen, or swallowed activity moving along the GI tract. Physiologic FDG uptake in the terminal ileum/caecum can be very intense (Fig. 6A). As the small bowel is quite mobile within the peritoneal cavity, misregistration of PET and CT images is not uncommon, which may make it difficult to localize FDG activity.

Of note, PSMA shows high uptake within the duodenum and the proximal part of the jejunum where there is abundance of brush borders (microvilli) showing increased PSMA immunostaining[85,86] (Fig. 1).

Inflammatory FDG uptake can be seen in inflammatory bowel disease (IBD), radiation or medication induced enteritis, or infection. Usually, this uptake appears linear, along the length of involved segments or portions of the bowel, rather than focal.[87] Louis et al. reported a sensitivity of 72.9% in the assessment of IBD when compared with endoscopy. The overall specificity was only 55.3%, increasing to 72.3% when the FDG uptake was associated with CT changes such as bowel wall thickening.[88] Intussusception can be associated with increased FDG uptake. In adults, the underlying cause of intussusception is tumor-associated in up to 77% of patients.[89]

Small bowel adenocarcinomas usually show increased FDG uptake with CT features of a mass (Figs. 5C and 6C). However, benign adenomas can present in similar fashion (Figs. 5A and 6B). Like in the stomach, involvement of the small bowel by high-grade lymphoma, most commonly DLBCL, is associated with intense FDG uptake. However, indolent lymphomas may show diffuse mild uptake.[90] Small bowel GIST can be intensely FDG-avid (Fig. 5B). In contrast, small bowel NET can be missed easily (FDG sensitivity 36%), in particular when showing a low proliferation index of less than 2%.[91]

^{68}Ga-DOTATATE is the standard imaging test for the evaluation of well-differentiated NET,[92] with a high sensitivity (>94%) and high specificity (>92%), particularly within the midgut.[93] For G3 tumors and those with higher proliferation index (>20%), as well as poorly differentiated neuroendocrine carcinomas, assessment with FDG PET/CT is proposed.[94] Focal ^{68}Ga-DOTATATE in the liver secondary to hepatocellular carcinoma can mimic NET metastases.[95]

Among the other PET radiotracers, PSMA uptake has been reported in duodenal adenocarcinoma[96] and in ileal GIST.[97]

Colon and Rectum

Two major distinct precursor pathways are noted for the development of colorectal cancer: the adenoma to carcinoma pathway and the serrated neoplasia pathway.[98] Most colon cancers arise from adenomatous polyps (adenoma to carcinoma sequence).[99] Adenomas progress through sequential genetic mutations and chromosomal instability, resulting in microsatellite stable tumors. The serrated neoplasia pathway occurs most often due to BRAF and KRAS mutations and may result in either microsatellite stable (MSS) or unstable tumors.[98] Microsatellite instability (MSI) due to defective DNA repair is also seen in Lynch syndrome. Right-sided colon cancers tend to have more genetic mutations and microsatellite instability, which contributes to the inferior prognosis of advanced stage in right-sided colon cancers compared to left-sided colon cancers.[100]

Physiological FDG uptake within the cecum, ascending and sigmoid/rectosigmoid colon (usually segmental and of mild to moderate intensity) is frequently greater than in other sections of the large bowel.[48,101] Attempts to improve colonic imaging on FDG PET/CT by prior administration of cleansing agents[102] may be counterproductive by inducing inflammation with resultant increased uptake.

Metformin is an oral biguanide molecule which accumulates preferentially in the intestinal mucosa, increasing glucose turnover in the splanchnic bed, decreasing hepatic glucose uptake, and reducing fatty acid utilization.[103] It causes activation of AMP activated protein kinase, resulting in upregulation of GLUT-1, 2, and 4 transporters.[104] The drug may cause significantly higher FDG uptake in the colon (as well as in small bowel)[105] (Fig. 7A). Discontinuation of metformin 48 h prior to FDG PET/CT is insufficient to

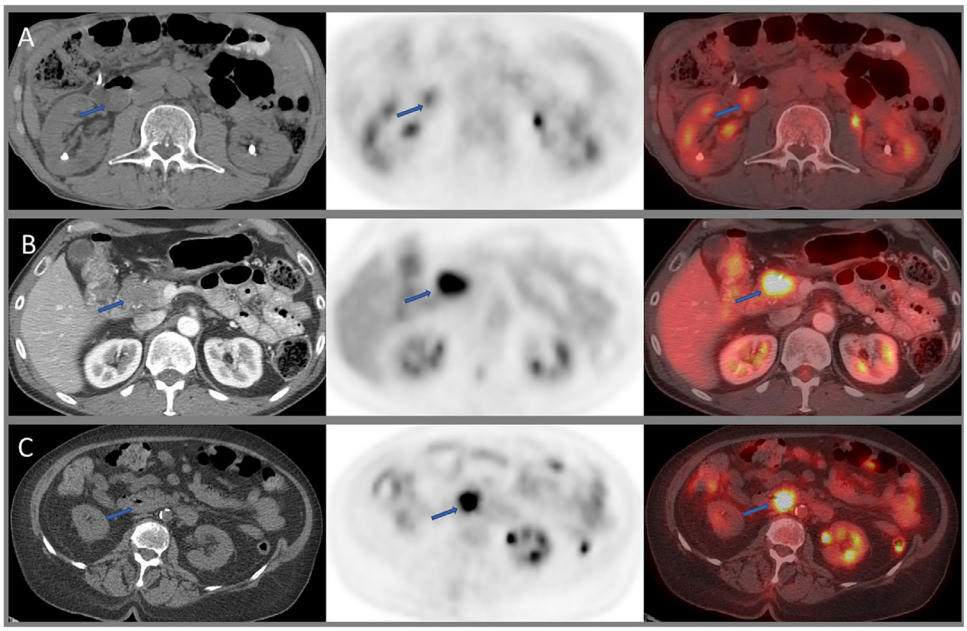

Figure 5 Axial CT, PET, and fused images of 18F-FDG PET/CT demonstrating low-grade uptake within a duodenal tubulovillous adenoma (A), intensely avid gastrointestinal stromal tumor (GIST) of the duodenum (B), and duodenal carcinoma (C).

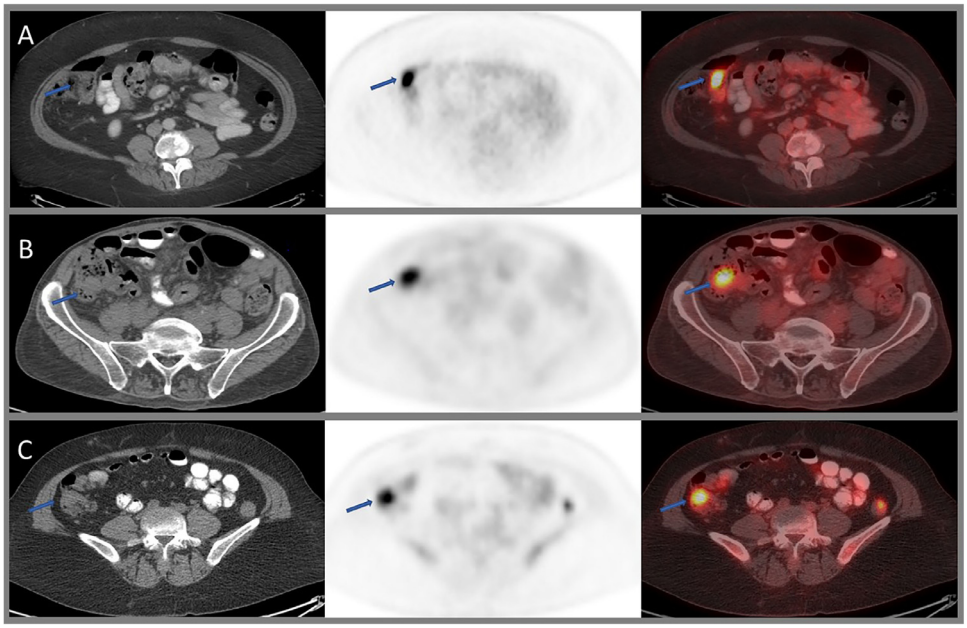

Figure 6 Axial CT, PET, and fused images of 18F-FDG PET/CT through the lower abdomen showing intense physiological uptake within the ileocecal junction (A), benign sessile tubular adenoma (B), and metastatic deposit at the ileocecal junction from patient's known poorly differentiated gastric adenocarcinoma with signet ring cell features (C).

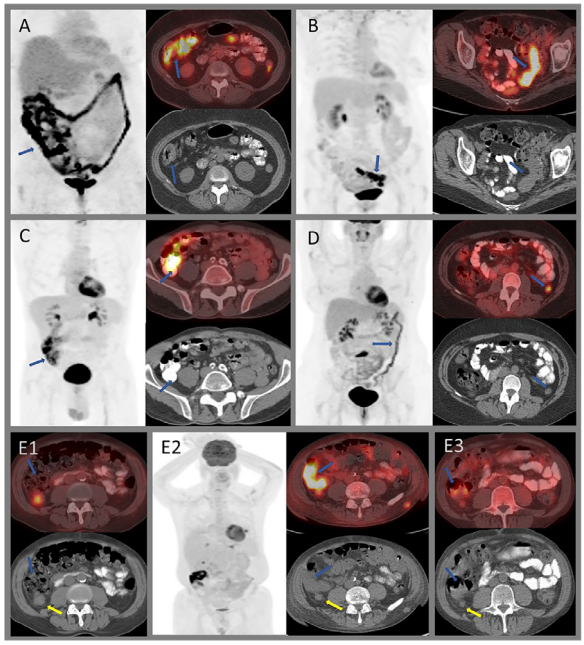

Figure 7 Variable FDG uptake within the colon. A) Intense diffuse uptake throughout the large bowel in patient on metformin. B) Segmental intense uptake within the sigmoid colon with bowel wall thickening in a patient with known ulcerative colitis without active symptoms. C) Intense uptake secondary to attenuation artifact from oral contrast media. D) Moderately intense diffuse uptake within the distal large bowel in a patient with active ulcerative colitis. Incidental note is made of intensely avid L4 vertebral body metastasis from patient's primary breast cancer. E) Post-radiation colitis of the hepatic flexure (E2) in a patient who underwent radiation therapy for a moderately intense right posterior peritoneal metastasis (E1; yellow arrows). Post-radiation, the nodule decreased in size; however, intense uptake is seen within the adjacent hepatic flexure (E2; blue arrows). Bowel uptake resolved on subsequent imaging with residual low-grade uptake within the peritoneal nodule (E3).

suppress this prominent bowel uptake, although uptake is lower than in patients with continued medication.[106]

Non-physiological benign FDG uptake within the colon can be focal (*e.g.*, due to polyp or diverticulitis), segmental (*e.g.*, in Crohn's disease, radiation colitis) (Fig. 7E1-E3), or diffuse (*e.g.*, in ulcerative or pseudomembranous colitis)[107-109] (Fig. 7B and D).

Focal incidental uptake in the large bowel is seen in approximately 2% of all patients undergoing FDG PET/CT [110]. In a substantial number of cases, this may be due to malignant or premalignant conditions, and therefore further evaluation with colonoscopy is often recommended[24,109,111] (Fig. 8C). In a systematic review, the rate of neoplastic, benign, and inflammatory pathologies in incidentally detected focal colorectal FDG uptake were 76%, 19%, and 5%.[110] FDG intensity as measured by SUV shows considerable overlap between benign, premalignant, and malignant focal colorectal incidentalomas.[111] In asymptomatic adults undergoing cancer screening with same day FDG PET/CT and colonoscopy, Hwang et al. reported a sensitivity and specificity of 6% and 97% for detecting colonic carcinoma and adenoma. The sensitivity increased to 29% in lesions greater than 1 cm.[112] Gollub et al. reported that the sensitivity of FDG PET to detect advanced adenoma was 49% and concluded that PET cannot be relied upon for accurate identification of these patients.[113]

Colonic diverticular disease ranges from asymptomatic diverticulosis to symptomatic uncomplicated diverticular disease, uncomplicated diverticulitis, and complicated diverticulitis (including perforation, abscess, bleeding, fistula, peritonitis, or stenosis).[114] Focal intense FDG uptake may be seen throughout the spectrum of diverticular disease and should have correlating CT findings for diagnosis[115,116] (Fig. 8B). Inflammatory pseudotumor or colon sarcoidosis can

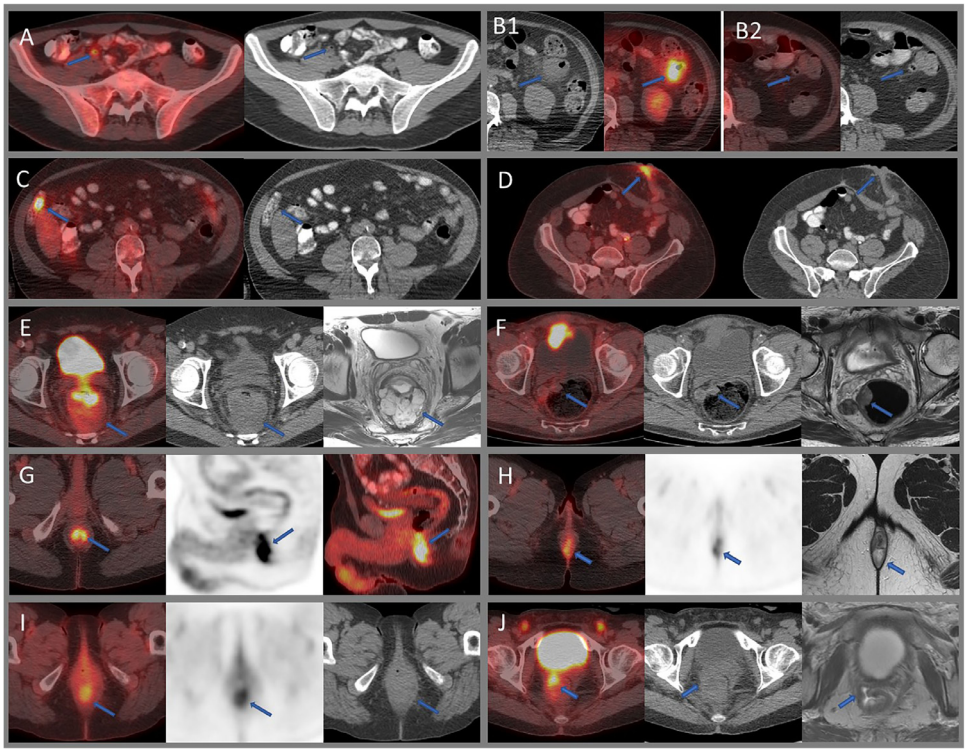

Figure 8 Benign and malignant FDG uptake within the bowel. A) Moderately intense uptake within a gas filled normal appendix. B) Intensely avid diverticulitis within the descending colon (B1), which resolved on follow up imaging two weeks later (B2). C) Intensely avid hepatic flexure tubule-villous adenoma. D) Benign intense uptake within a left anterior abdominal wall stoma. E) Rectal cancer with a mildly avid large mucinous component as seen on axial T2W MRI. F) Mildly avid right lateral wall rectal neuroendocrine tumor. G) Physiologic intense uptake within the anal canal in a patient undergoing 18F-FDG PET/CT for head and neck cancer. H) Moderately avid internal/external hemorrhoids at the anal verge as seen on MRI and also noted on clinical examination. I) Moderately intense radiation proctitis. J) Intense uptake along the rectovaginal fistula as seen on MRI.

mimic colonic carcinoma or lymphoma on FDG PET/CT.[117,118] Acute appendicitis can be intensely FDG-avid. However, for diagnosing appendicitis on imaging, there should be correlating CT findings, such as thickened appendix, peri-appendiceal inflammatory changes, abscess, or appendicolith, as even normal appendix can sometimes show high FDG avidity[119,120] (Fig. 8A).

The primary role of FDG PET/CT in the pre-surgical evaluation of newly diagnosed patients with colorectal cancer is to confirm limited (potentially operable) disease and to evaluate patients with unclear or unsatisfactory conventional imaging, including those with allergy to intravenous contrast.[121,122] Compared to CT or MRI, FDG PET/CT offers little added value in establishing the local extent of the primary tumor in patients without metastases. Mucinous tumors can show minimal or no FDG uptake, leading to a false negative rate as high as 41%[123] (Fig. 8E). In a meta-analysis, the pooled sensitivity and specificity of FDG PET for detecting regional lymphadenopathy were 43% and 88%, and 72% and 71% when addressing rectal tumors only.[124] Neuroendocrine tumors can show low-grade uptake depending on their proliferation index (Fig. 8F).

Neoadjuvant treatment is used in patients with locally advanced rectal cancer and those with potentially resectable metastatic disease.[122] No current imaging modality can reliably determine complete pathologic response to select patients for non-surgical management.[125] In a meta-analysis, FDG PET/CT had a pooled sensitivity of 52%, which was lower than that of MRI (86%).[126] However, FDG PET/CT may help to identify non-responders early and thereby change treatment management. Generally, PET/CT is performed 5–6 weeks after neoadjuvant treatment. Further prolongation of the scan up to 12 weeks after therapy completion does not seem to improve sensitivity or specificity.[127]

Post-surgically, complications such as intrabdominal fluid collection and fistulas may show intense FDG uptake due to inflammation/infection. FDG uptake can also be quite variable at a colonic or small bowel anastomosis or at the stoma (Fig. 8D). One study showed increased FDG uptake around the anastomosis in 27 of 70 patients, of which 41% had local recurrence; FDG PET/CT was highly sensitive (100%) with suboptimal specificity (73%),[128] and SUV measurements did not help in differentiating between recurrence and benign uptake when the post-operative period was less than 12 months. However, another study reported that early post-operative FDG PET/CT detected occult metastases in 6 of 49 patients and changed management in up to 14% of patients in the pN2 subgroup of patients with stage III colorectal cancer.[129] Others have reported a false positive rate of 21% in

patients with stage III colorectal cancer undergoing early post-operative PET/CT.[130]

In the absence of clinical suspicion of relapse, there is no significant difference between the diagnostic performance of PET/CT and conventional follow up.[131] However, FDG PET/CT is useful in detecting relapse in patients with rising CEA. A meta-analysis including 510 patients reported a pooled sensitivity and specificity of 94% and 77%.[132] FDG PET/CT can also provide valuable information in patients with clinical suspicion of relapse, even if the CEA is within normal limits.[133] Post-treatment complications such as rectovaginal or rectovesical fistulas show intense FDG uptake and should be differentiated from recurrent disease (Fig. 8J). In one study, post-operative surveillance PET/CT of rectal and sigmoid cancer showed FDG uptake to be benign in 13 of 43 hypermetabolic pelvic lesions, including fistulae, anastomotic sinus, perirectal inflammation, and abscess.[134]

Anal Canal

Anal squamous cell carcinoma (ASCC) is the most common histological type, followed by anal adenocarcinoma (AAC).[135] There has been an increasing trend in the incidence of ASCC and the risk factors include HPV infection, HIV positive patients, chronically immunosuppressed patients, and organ transplant patients.[136]

Variable physiological FDG uptake within the anal canal can be due to smooth muscle uptake, lymphatic tissue uptake, or fecal microbes[137] (Fig. 8G). Very often, intense physiological uptake within the anal canal is caused by increased metabolic activity of the internal and external sphincter [48]. Anal FDG uptake is unrelated to sex, age, or blood glucose levels.[137]

Intense benign FDG uptake has been reported in hemorrhoids,[138] either due to inflammation, thrombosis, or vascular proliferation within the hemorrhoids[139] (Fig. 8H).

FDG PET/CT is less sensitive than MRI in the local staging of primary anal tumors. However, it has a greater sensitivity for detecting metastatic lymph nodes and thereby can alter management.[140]

The primary mode of treatment for anal cancers is chemoradiotherapy. In a meta-analysis, PET changed the radiotherapy target volume definition in as many as 23% of patients,[141] although the impact on clinical outcome remained undefined.

In terms of response assessment, FDG PET/CT had a sensitivity and specificity of 92% and 85% for detecting residual tumor after chemoradiotherapy.[142] Test performance may be related to time after completion of therapy: at one month after end of treatment, sensitivity and specificity were 67% and 92%, but were higher at three months after therapy (100% and 97%),[143] probably due to persistent inflammation post-radiotherapy (Fig. 8I). Patients with complete metabolic response have a better prognosis than do non-responders.[144]

Post-treatment changes and complications associated with the anal canal can mimic malignancy. Kim et al. reported intense uptake in the presacral anastomotic sinus after low anterior resection mimicking recurrent disease.[145] In a study of 299 patients undergoing post-operative surveillance after low anterior resection, Kang et al. reported anastomotic sinuses and fistulas in 2.68% of the cases, with the majority of lesions demonstrating diffuse increased uptake.[146] Garg et al. demonstrated intense FDG uptake within a tubercular fistula-in-ano.[147]

There is limited evidence in the literature to support routine use of FDG PET/CT in the follow up of anal cancer patients in the post-chemoradiotherapy setting. Teagle et al. reported that a negative FDG PET/CT can exclude residual or recurrent disease in patients with anal cancer on follow up post-CRT.[148] On the other hand, presence of FDG uptake does not necessarily indicate recurrence. In the study by Teagle et al., 7.1% had false positive uptake and 21.4% had nonspecific uptake, which included low-grade uptake in the anal canal.[148]

Peritoneum

The peritoneum can be involved by primary malignancies such as peritoneal mesothelioma, primary peritoneal carcinoma, or pseudomyxoma peritonei. Metastatic involvement can occur from adjacent organs such as gastric, ovarian, or colorectal malignancies. Malignant spread within the peritoneum can be nodular, diffuse, military, along the serosal surface of the bowel loops, or solid viscera and ascites.

The peritoneum does not generally show physiologic uptake. However, several benign peritoneal conditions can show FDG uptake, such as mesenteric panniculitis, surgical clip granuloma, post-radiation ascites and hemoperitoneum, fat necrosis, epiploic appendagitis, and abdominal abscesses[149] (Fig. 9A, B and D). Mesenteric fat stranding associated with inflammatory pathologies can have an appearance similar to peritoneal carcinomatosis.

Post-surgical changes within the abdomen and pelvis may show variable degree of FDG uptake, which can make assessment of peritoneal malignancy difficult. Post-surgical mesh hernia repair may show focal, linear, or non-uniform FDG uptake with no relationship to the time from surgery to post-operative PET/CT or SUVmax[150] (Fig. 9C).

Splenules (post-surgical or post-trauma) can be FDG-avid and can be mistaken for peritoneal tumors (Fig. 9E). They do, however, reliably show uptake of radiolabeled heat−damaged red blood cells.[151] Unusual benign conditions such as transposed ovaries, sarcoidosis, abdominal histoplasmosis, or ectopic pregnancy can also show variable FDG uptake and mimic malignancies[152-155] (Fig. 9F). Portal vein thrombus can present with increased FDG uptake.[156]

FDG uptake in peritoneal carcinomatosis can be seen as focal intense uptake, irregular heterogeneous uptake, or nodular or curvilinear uptake along the surface of the viscera and/or diaphragm.[157] Kim et al. reported a pooled sensitivity and specificity of 87% and 92% for PET/CT in detection of peritoneal carcinomatosis.[158] Another study reported a false positive rate of 11% on a per patient basis among patients with suspected peritoneal carcinomatosis who underwent FDG PET/CT prior to cytoreductive surgery.[159] These may occur due to various causes such as misregistered uptake in

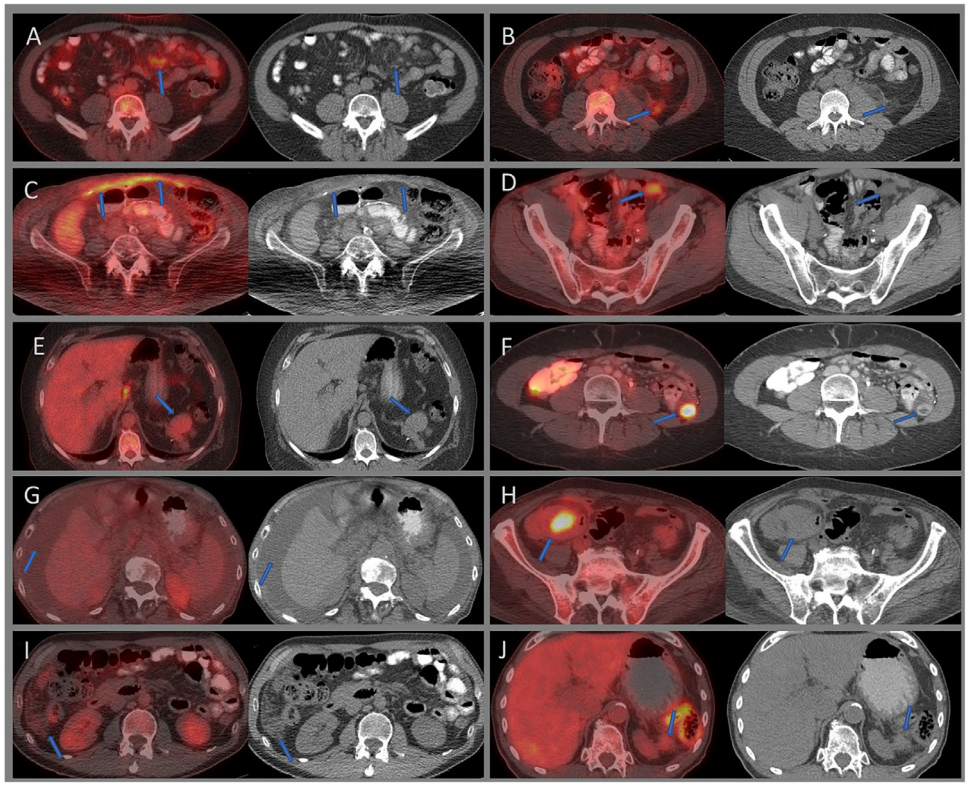

Figure 9 Axial fused and CT images of 18F-FDG PET/CT demonstrating moderately intense mesenteric panniculitis (A), left lower quadrant fat necrosis (B), intense uptake relating to surgical mesh hernia repair (C), moderately intense uptake with a hernia plug (D), mildly avid splenules at the pancreatic tail (E), intensely avid transposed ovary within the left paracolic gutter (F), low-grade malignant ascites from unknown primary (G), intensely avid post-surgical abscess adjacent to the ascending colon (H), minimally avid peritoneal mesothelioma within the right lilac fossa (I), and a minimally avid recurrent peritoneal metastatic deposit at the splenectomy bed from a pancreatic tumor (J).

normal bowel, benign mesenteric lymphadenopathy, non-malignant inflammatory pathologies such as foreign body reaction around mesh prosthesis, hernia repair plug, infections such as peritoneal abscess, and post-surgical changes (Fig. 9D and H). In general, FDG PET demonstrates reduced sensitivity for small-volume disease, predominantly cystic or low-grade disease, and ascites[160] (Fig. 9G and J). Multicystic peritoneal mesothelioma (MPM) may show mild or no uptake, whereas epithelioid peritoneal mesothelioma (EPM) is generally FDG-avid (Fig. 9I). In patients presenting with ascites as the first symptom, FDG PET/CT may detect the primary tumor in up to 80%[161] (Fig. 9G). FDG uptake is higher in malignant than in benign ascites, but with considerable overlap.[162]

Varied GI symptoms have been reported in patients with COVID-19. Most frequently, the GI symptoms include lack of appetite, diarrhea, vomiting, and abdominal pain.[163] CT appearances may include thickening of the bowel, pneumatosis, and, rarely, intussusception and ascites;[164] variable FDG uptake may be seen in these conditions.

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