Role of PET/Computed Tomography in Gastric and Colorectal Malignancies

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KEYWORDS

• Gastric cancer • Colorectal cancer • PET/CT • FDG

KEY POINTS

- 18F-FDG PET plays an important role in the evaluation of patients with cancer of the gastrointestinal tract both at the time of initial staging and at the time of subsequent treatment strategy
- Somatostatin-targeting radiopharmaceuticals have become key in the evaluation of patients with NETs
- Newer radiopharmaceuticals are being developed that may provide additional insights

INTRODUCTION

The glucose analog 2-deoxy-2-^{18}F-D-glucose (FDG) is the most widely used radiopharmaceutical for imaging of cancers using PET. ^{18}F-FDG is transported into tissues by glucose transporters (GLUTs) and is intracellularly phosphorylated into ^{18}F-FDG-6-phosphate. The greater glucose demand required to sustain anaerobic metabolism in tumor cells results in upregulation of non-insulin-dependent transporters, GLUT-1 and GLUT-3. Since most neoplasms have low concentrations of glucose 6-phosphatase, ^{18}F-FDG-6-phosphate accumulates in tumor cells, which results in enhanced tumor-to-background activity.

Gastric cancer (GC) is a prevalent gastrointestinal malignancy and is the fourth leading cause of cancer-related deaths worldwide.[1] Although less deadly, colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract and is the third most common malignancy worldwide. GC and CRC comprise several histologic types/subtypes, such as adenocarcinomas, neuroendocrine tumors (NETs), gastrointestinal stromal tumors (GISTs), lymphomas, mesenchymal tumors, and mixed tumor types. Histologic characterization is important to guide imaging and to determine if ^{18}F-FDG PET/CT is useful. For example, signet ring cell mucinous adenocarcinomas tend to have low ^{18}F-FDG avidity due to limited tumor cellularity. Intestinal adenocarcinomas and lymphomas of the gastrointestinal tissue are typically highly ^{18}F-FDG avid.[2]

Gastric and colorectal malignancies often spread first by local extension to adjacent organs, with subsequent peritoneal involvement and distant metastases (lymphatic or hematogenous).[3,4] Hematogenous spread is also common, typically to the liver, lungs, and bones.

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The goal of oncological imaging is detection and characterization of malignant disease, determining disease extent, staging, assessment of therapeutic response, recurrence, and prognosis.[5,6] Ultrasound, computed tomography (CT), and MRI are the most commonly used modalities for staging; if a biopsy is required, endoscopy or colonoscopy is typically needed. However, anatomic imaging is limited in differentiating benign from malignant nodal disease, post-therapy change from tumor recurrence, and even non-opacified bowel loops from metastasis. PET/CT with ^{18}F-FDG is a functional imaging modality that includes anatomic information (provided by CT). This is a powerful tool for the evaluation of gastric and colorectal carcinoma. This article focuses on the role of PET/CT in evaluating and managing GC and CRC. The authors start with describing the common aspects of imaging with ^{18}F-FDG, followed by tumor-specific discussions of gastric and colorectal malignancies. Finally, the authors provide a brief overview of non-FDG tracers including their potential clinical applications, and describe future directions in imaging these malignancies.

^{18}F-FDG PET TECHNIQUE

Several technical considerations are important for performing ^{18}F-FDG PET/CT in GC/CRC.[7,8]

Patient Preparation

Patients should fast for 4 to 6 hours before the scan to ensure optimal uptake of ^{18}F-FDG. Patients should also avoid strenuous physical activity before the scan. To improve imaging of the stomach, gastric distension is helpful and may be achieved by asking the patient to drink approximately 500 mL of water before scanning. The intravenous injection of 20 mg hyoscine butylbromide (antispasmodic) prior to imaging may be helpful.[9,10] When the scan is being performed for radiation therapy planning, a small amount of oral contrast may be used instead of the 500 mL of water. The use of negative oral contrast can help delineate the bowel and surrounding structures. Additionally, bowel preparation using an iso-osmotic solution given a day before the scan (cleansing) may decrease physiologic bowel uptake.

Image Acquisition

Images are usually acquired approximately 60 minutes after the intravenous injection of ^{18}F-FDG (~0.15 mCi/kg) with the patient lying supine. Additional static and delayed images maybe acquired to differentiate physiologic ^{18}F-FDG uptake in the bowel from that due to malignancy.[11] Intravenous diuretic administration for faster emptying of the urinary bladder may be considered in select cases with rectal carcinoma to increase the signal-to-noise ratio in the pelvis. Obtaining additional delayed images at 100 to 150 min post injection can be helpful in select patients to improved differentiate between inflammatory versus neoplastic etiologies.[12,13]

Image Quantification and Interpretation

For semiquantitative analysis, regions of interest (ROI) can be drawn to obtain standardized uptake values (SUVs). The maximum SUV is the most commonly used metric, although others such as the SUVpeak, SUVmean, and the lean body mass–adjusted SUV have shown to be of benefit.[14] Additional derived parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), although not routinely calculated, may have prognostic significance.[15] Image interpretation is typically qualitative and takes into account both the metabolic features on PET and the morphologic features on CT or MRI. As with other oncologic indications, it is important to be aware of infective and inflammatory conditions that can mimic a malignancy on ^{18}F-FDG PET/CT.[2,16] The major limitations of evaluation of GC and CRC with ^{18}F-FDG PET/CT include:

- Variable physiologic uptake in the gastrointestinal tract. Additionally, metformin can lead to an intense ^{18}F-FDG uptake in the small intestine and the colon.
- Infective/inflammatory conditions—Bacterial and fungal infections, enterocolitis, inflammatory bowel disease, diverticulitis, and post-surgery or post-radiation therapy inflammation.
- Small liver lesions may be missed due to physiologic FDG uptake in the liver, unless the lesional avidity leads to a significantly high tumor to background activity.
- Mucinous-type malignancies, well-differentiated NETs.

^{18}F-FDG PET/CT findings should be interpreted in conjunction with other imaging modalities and clinical information to ensure accurate staging and treatment response evaluation. Timing in relation to treatment received is important along with reviewing previous studies and correlation with other imaging and tumor markers.

GASTRIC CANCER

Epithelial tumors are the most common histologic type, accounting for over 80% of gastric tumors, with the predominant subtype being adenocarcinoma.[17] Gastric adenocarcinoma is further

classified into intestinal and non-intestinal (diffuse and indeterminate) subtypes based on the Lauren classification.[18] Using a different classification scheme, the World Health Organization (WHO) classification of gastric adenocarcinoma includes papillary, tubular, and mucinous subtypes (equivalent to the Lauren intestinal subtype), signet-ring cell and other poorly cohesive carcinomas (equivalent to diffuse subtype), and rare subtypes (eg, mixed, squamous, adenosquamous) equivalent to the Lauren indeterminate subtype.[19] Mesenchymal and NETs account for the second and third most common types of gastric malignancies, respectively, followed by gastric lymphoma.[18] (**Fig. 1**).

CLINICAL INDICATIONS OF PET/COMPUTED TOMOGRAPHY IMAGING

Diagnosis

Histopathologic evaluation of gastric tissue, following endoscopic biopsy is the gold standard for the diagnosis of GC. ^{18}F-FDG PET/CT has variable and often limited sensitivity in detecting primary GC due to interference from physiologic FDG uptake in the stomach and ^{18}F-FDG-avid non-neoplastic and benign pathology such as gastritis and leiomyoma.[20,21] Correlation with multimodal imaging, endoscopy, and clinical features is recommended in patients with diffuse or focal increased ^{18}F-FDG uptake in the stomach. There is variability of ^{18}F-FDG uptake among the various histo-types, with the intestinal subtypes having a higher ^{18}F-FDG avidity and mucincous subtypes having low ^{18}F-FDG avidity due to their pauci-cellular nature.

Initial Staging

The role of ^{18}F-FDG PET/CT is limited for T- and N-staging gastro-esophageal junction tumors and GC. The primary role is detecting distant metastases, that is, M-staging per the tumor, node, and metastasis (TNM) staging system.[21–23] The National Comprehensive Cancer Network (NCCN) guidelines for esophageal and gastro-esophageal junction tumors recommend endoscopic ultrasound (EUS) and CT for T and N staging, and ^{18}F-FDG PET/CT for staging occult distant metastases on CT.[24] ^{18}F-FDG-PET/CT does not have a major role in early-stage tumors (T1) due to the low likelihood of distant metastases and the false-positive PET/CT findings resulting in additional investigations that are often low yield and potentially delay treatment.[25] Similar to gastro-esophageal junction tumors, the NCCN guideline recommends EUS and CT for initial staging of gastric cancer. The NCCN guidelines permit use of ^{18}F-FDG PET/CT in GC with the following indications: staging if there is no evidence of M1 disease (may not be appropriate for T1 disease) and if clinically indicated; for the evaluation of response to neoadjuvant and adjuvant chemotherapy or chemoradiation, and for surveillance following neoadjuvant or adjuvant therapy in stage I-III disease.[26]

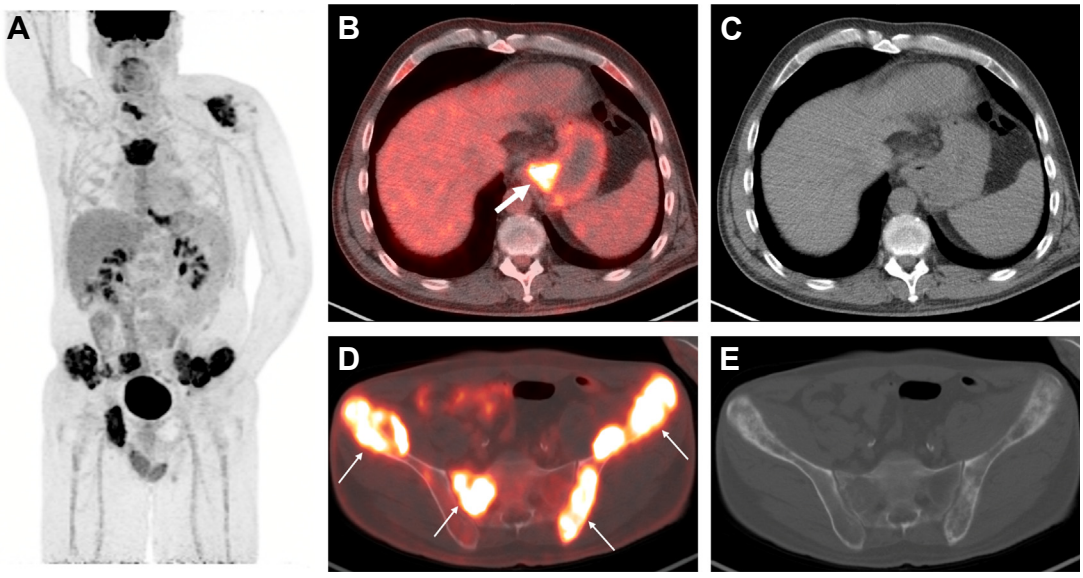

Fig. 1. A 52-year-old-man with gastric adenocarcinoma. ^{18}F-FDG PET/CT maximum intensity projection image (*A*) shows extensive hypermetabolic metastatic disease. The trans-axial fused PET/computed tomography (CT) and CT images show the hypermetabolic primary lesion involving the gastric cardia and the distal esophagus (*thick arrow*; *B, C*) with multifocal osseous metastases, including both the iliac bones and the sacrum (*thin arrows*; *D, E*).

Radiation Treatment Planning

Analogous to the incorporation of CT-based radiation treatment planning in the 1990s, the current incorporation CT through FDG PET/CT can improve target delineation and reduce acute (eg, diarrhea, constipation, bleeding, mucositis, etc.) and late (eg, small-nerve neuropathy, accelerated atherosclerosis, strictures, fistulas, etc.) radiation toxicities, thereby decreasing overall patient morbidity and mortality. Traditionally radiotherapy delivery was done using an anteroposterior conformal technique; currently, with increasing accessibility to newer technology, multi field techniques are more commonly used. Multi field techniques (eg, 3D-Conformal Radiation Therapy, Intensity Modulated Radiation Therapy) allow increased flexibility in determining which regions including normal tissue are likely to be incidentally irradiated. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) criteria establishe dose-volume constraints for organs at risk (OAR) when irradiating cancer. The OARs during radiotherapy planning for GC are the heart, kidneys, esophagus, liver, and spinal cord. The gross tumor volume (GTV) is defined as the region containing known disease (ie, stomach, colon, rectum) as seen in the planning CT (ie, CT simulation). Clinical target volume (CTV) is the GTV plus an extension contour that includes anatomic regions likely involved with microscopic disease. A third extension is then made to the CTV to create the planning target volume (PTV) margins; these expansion margins are based on set-up uncertainty and internal organ motion so as to ensure the CTV receives the full prescription dose during each fraction.[27] Dose-volume constraints are then used in routine inverse dose planning to optimize the therapeutic ratio of the radiotherapy prescribed to the PTV.[28] As PET-avid regions help define the GTV, fusing or co-registering an FDG PET/CT with a CT simulation helps to improve GTV delineation for gastric and colorectal cancers, optimizes the therapeutic ratio between the OARs and PTV, and allows for dose variation in different areas of the tumor [5]. The value of FDG PET/CT may also be seen in GTV delineation of oligometastatic disease for stereotactic body radiotherapy, where tighter dose constraints are required. Further, the NCCN increasingly recognizes the usefulness of FDG PET/CT in radiation treatment planning [27].

Assessment of Treatment Response

Apart from initial staging, the NCCN guidelines recommend ^{18}F-FDG PET/CT for assessment of treatment response in esophageal and GE junction tumors following neoadjuvant or definitive chemoradiation.[29] The curative treatment of gastric cancer includes surgical resection of tumor and lymph node dissection. Studies show that perioperative chemotherapy or radiochemotherapy can improve relapse-free and overall survival in patients with gastric cancer.[30,31] So, the evaluation of the therapy response is important in management. There is evidence that ^{18}F-FDG PET/CT can be effective in response evaluation in gastric cancer.[32–34] In a study performed on 40 gastric cancer patients, the tumoral FDG uptake reduction 2 weeks post chemotherapy was significantly different between responding and non-responding tumors with 35% FDG uptake reduction as optimal cutoff of differentiation.[34] Another study evaluating response to neoadjuvant chemotherapy found FDG PET superior to response evaluation criteria in solid tumors (RECIST) evaluation by CT in predicting the median time to disease progression and overall survival.[32]

Re-staging and Surveillance

Distant lymphatic and peritoneal metastatic disease can be detected in up to 40% of patients approximately 2 to 3 years after definitive treatment of locally advanced GC.[20,35,36] Both the NCCN and the European Society for Medical Oncology guidelines support the use of FDG PET/CT to detect disease dissemination.[37]

Colorectal Cancer

Colorectal cancers (CRC) can be found from the cecum to the rectum, with the rectosigmoid being the most common location for colorectal adenocarcinoma.[38] In less than 10% of patients, CRC is associated with familial syndromes including familial adenomatous polyposis, hereditary nonpolyposis colon cancer syndrome, and Peutz–Jeghers syndrome. The most common histologic subtype comprising more than 90% of colorectal cancer is adenocarcinoma, originating from epithelial cells of colorectal mucosa.[39] Other subtypes include mucinous carcinoma of the colon, neuroendocrine, squamous cell, adenosquamous, spindle cell, lymphoma, and undifferentiated carcinomas. As discussed previously, the mucinous subtypes commonly show poor uptake on FDG due to low cellularity and high mucin content of the tumor mass. These tumors frequently produce cystic or calcified hepatic metastases and have widespread intraperitoneal metastases.[40] Among large bowel lymphomas, diffuse large B-cell lymphoma is the most common.[41] In comparison with adenocarcinoma, colonic lymphoma often presents with circumferential wall thickening,

and, can affect longer as well as multiple colonic segments.[42] Another major histologic category of colorectal malignancies are the family of neuroendocrine neoplasms (NENs) of the large bowel, with a predilection for the rectum.[43] These include indolent well differentiated NETs to poorly differentiated carcinomas which are highly aggressive. The majority of NETs express somatostatin receptors that can be targeted in diagnostic imaging and therapy (theranostics).[44–46]

CLINICAL INDICATIONS OF PET/COMPUTED TOMOGRAPHY IMAGING

Diagnosis

Colonoscopy is the modality of choice for initial diagnosis as it allows evaluation of the entire large intestine and the capability to take biopsies/resection of polyps in a single session.[47] Focal ^{18}F-FDG uptake in the bowel on PET/CT, especially when correlating with a mass on CT, suggests a malignant lesion and requires further evaluation with colonoscopy. PET/CT can also identify incidental synchronous/metachronous primary tumors, affecting management. However, ^{18}F-FDG PET/CT has low specificity as premalignant lesions such as adenomas, and focal infection/inflammation also show increased ^{18}F-FDG uptake and can be found incidentally in PET. Thus, a single time point PET/CT alone cannot reliably differentiate between benign and malignant disease.[48] (**Fig. 2**).

Initial Staging

The NCCN guidelines recommend CT and MRI for the initial staging of colorectal carcinoma. ^{18}F-FDG PET/CT is useful for detecting lymph node involvement and distant metastases. There is limited added value of ^{18}F-FDG PET/CT in the local staging of CRC, and it is thus not routinely performed for pre-operative staging.[49,50] Around 30% of patients with CRC have distant metastases at initial presentation, including involvement of the liver, lungs, and bones.[51] In patients with suspected metastatic disease, ^{18}F-FDG PET/CT is useful for determining overall stage and prognosis as the management and long-term outcomes are heavily influenced by the initial stage of the disease. Surgical resection of limited metastatic disease with curative intent has demonstrated favorable long-term outcomes.[12–15]

Radiation Therapy Planning

NCCN guidelines recognize the usefulness of ^{18}F-FDG PET/CT in radiation therapy planning.[52] ^{18}F-FDG PET/CT helps improve tumor delineation, minimizing exposure to non-tumor areas, allowing for radiation dose adjustment to different areas of the tumor.

Assessment of Treatment Response

Anatomic changes lag behind metabolic changes when assessing response to therapy.[6] ^{18}F-FDG uptake is proportional to the number of viable cells; hence, reduction in FDG uptake usually denotes treatment response which precedes changes in tumor size.[14] ^{18}F-FDG PET/CT can assess treatment response in the early course of therapy, which can help guide treatment decisions and predict prognosis.[53] Treatment response is frequently assessed using both qualitative (visual analysis) and quantitative methods including parameters such as standardized uptake value (SUV).[54] Other volumetric PET parameters like metabolic tumor volume (MTV) and total lesion glycolysis (TLG) can also be used.

^{18}F-FDG PET/CT has been utilized for response assessment in a variety of treatment settings, including neoadjuvant and adjuvant chemotherapy, radiation therapy, and metastasis-directed therapies, including selective internal radiation therapy (SIRT), radiofrequency ablation, and transcatheter arterial chemoembolization, predominantly in locally advanced disease, oligometastatic disease, or potentially resectable metastatic disease.[55,56] It also helps in the optimal selection of patients for surgical resection and early identification of non-responders.

Multiple studies have been performed using different treatment regimens, imaging timepoints, and assessment criteria for analyzing the role of ^{18}F-FDG PET/CT after neoadjuvant chemotherapy.[57,58] Assessment of response using ^{18}F-FDG PET utilizing parameters like SUVmax, MTV, and TLG are predictors for long-term outcomes, but there is a lack of uniform, ideal timing of PET during and after neoadjuvant chemotherapy for CRC.[59] PET response criteria in solid tumors (PERCIST) has been established as the metabolic response criteria for the assessment of treatment response in solid tumors, predominantly in a clinical trial setting.[14]

Immunotherapy is an emerging treatment modality for advanced CRC. Assessing treatment response after immunotherapy is challenging as the post-treatment changes in the tumor microenvironment can mimic progression of disease, a phenomenon also known as “pseudoprogression.”[60] A few immunotherapy-specific response assessment criteria have been described based on FDG PET/CT; however, most lack validation in large cohorts.[61–64]

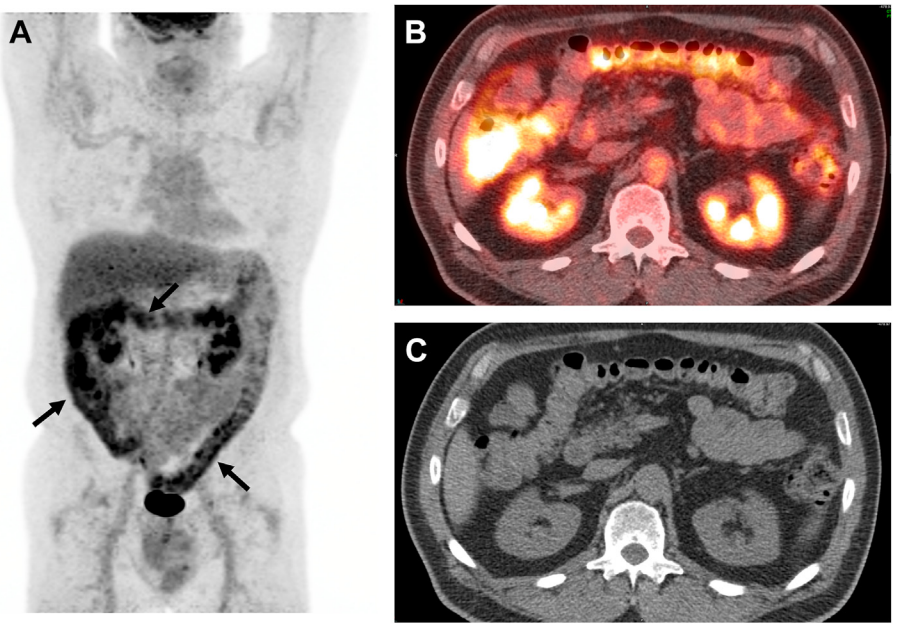

Fig. 2. A 58-year-old-man with adenocarcinoma of the sigmoid colon diagnosed on a colonoscopy biopsy. The maximum intensity projection (*A*) and the transaxial images (*B*, *C*) show diffusely increased FDG uptake throughout the colon (*arrows*) that limits the detection of the primary site. The patient had type 2 diabetes mellitus and was taking metformin at the time of the ^{18}F-FDG PET/CT study.

Re-staging and Surveillance

Disease recurrence is seen in up to 30% of patients within 2 years of initial resection, with the liver being the most common site for metastatic disease.[65,66] Guidelines recommend intensive follow-up during the first 3 to 5 years. Patients with rising serum carcino-embryonic antigen (CEA) levels without detectable disease on anatomic imaging pose a clinical challenge. Various studies have suggested the positive value of performing ^{18}F-FDG PET/CT in the evaluation of disease recurrence.[67–69] A few studies have evaluated the role of ^{18}F-FDG PET/CT for recurrent CRC with normal CEA levels, suggesting satisfactory sensitivities and specificities for detecting recurrence regardless of level of biomarkers.[70,71]

The major concern in detecting recurrence is differentiating recurrence from post-treatment scarring and radiation fibrosis. ^{18}F-FDG PET/CT has proven to be efficient and superior to both CT and MRI in this regard.[72] PET/CT can localize disease recurrence earlier than conventional imaging modalities with more accurate restaging, allowing for earlier intervention and potentially better outcomes. Accurate detection of loco-regional recurrence may be hindered by substantial distortion of anatomy post surgery.[73] The altered anatomy may limit the utility of structural imaging, but ^{18}F-FDG avidity can facilitate detection of disease sites. To increase the specificity of lesion characterization, dual time imaging can be done with ^{18}F-FDG by performing scans at 2 different time periods usually 1 to 3 hours apart. Increase of ^{18}F-FDG uptake with time favors a malignant etiology (**Fig. 3**).

OTHER RADIOPHARMACEUTICALS AND FUTURE DIRECTIONS

Fibroblast activation protein (FAP) is a type II transmembrane protease with dipeptidyl peptidase and endopeptidase activities that mainly exists in fibroblasts activated by cancer, chronic inflammation, and fibrosis.[74] A recently published meta-analysis of 148 patients with gastric cancer showed that ^{68}Ga-FAPI-04 PET/MRI or PET/CT was superior to ^{18}F-FDG PET/MRI or PET/CT in detection of the primary tumor, lymph node, and peritoneal metastases. There is low hepatic background with ^{68}Ga-FAPI-04 which may be advantageous for the detection of liver metastasis. Further studies are required to evaluate the sensitivity and specificity of ^{68}Ga-FAPI-04 PET in different pathologic types of gastric and colorectal malignancies.

Prostate-specific membrane antigen (PSMA) is a type II transmembrane receptor used primarily for imaging and therapy of prostate cancer.[75–79] In addition to the prostate cancer cells, PSMA is expressed in the tumor neovasculature of several non-prostate

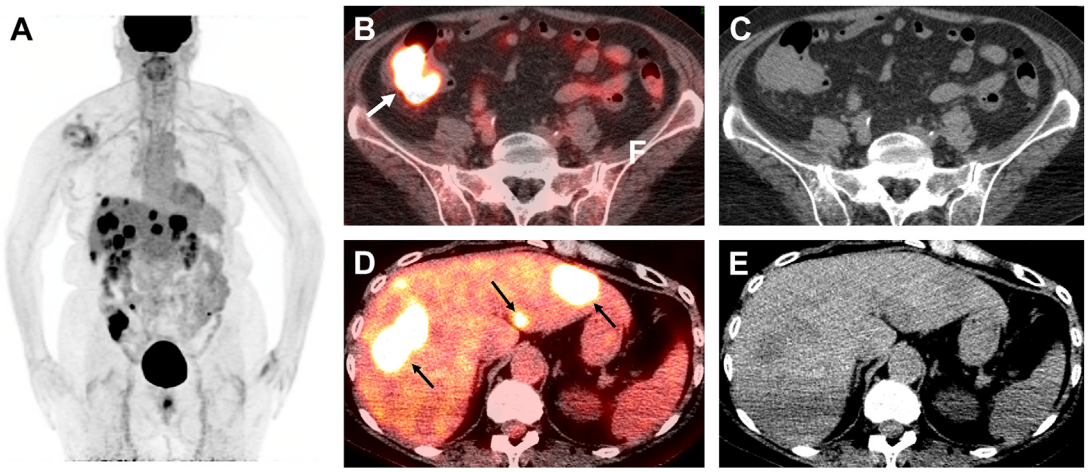

Fig. 3. A 78-year-old-woman with adenocarcinoma of the cecum. ^{18}F-FDG PET/CT maximum intensity projection image (*A*) and trans-axial fused PET/CT and CT images show (*B* and *C*) the hypermetabolic primary soft tissue mass at the cecum (*white arrow*) and (*D* and *E*) multiple hypermetabolic hypoattenuating lesions in the liver (*black arrows*) that were biopsy proven as metastases from the colorectal primary.

malignancies that can facilitate their diagnosis and potentially, therapy. These include several gastric and colorectal malignancies.[80–83] A prospective clinical trial has comparatively evaluated PSMA PET/CT to ^{18}F-FDG PET/CT of primary gastric and colorectal cancer; this study concluded with the feasibility of PSMA PET/CT for these aforementioned malignancies; however, ^{18}F-FDG PET/CT outperformed PSMA PET/CT due to the poor tumor-to-background ratio of latter, in the primary locations of these tumors.[84] Therefore, PSMA PET/CT may be better suited toward increasing the diagnostic certainty of imaging in the setting of metastatic disease.[85,86]

Somatostatin-targeting radiopharmaceuticals are excellent for the evaluation of NETs. Other radiotracers including ^{64}Cu-ATSM, ^{68}Ga-Pentixafor, ^{18}F-FLT, and ImmunoPET have been investigated as an alternative to ^{18}F-FDG PET. ^{18}F-FLT serves as a proliferative marker by reporting on the activity of thymidine salvage pathway.[87] A few pilot studies using ^{18}F-FLT have been performed for various indications in CRC, but has not gained much traction.[88] ^{64}Cu-ATSM is a promising theranostic agent with high tissue permeability and targeting of over-reduced state under hypoxia within tumors.[89]

SUMMARY

^{18}F-FDG PET plays an important role in the evaluation of patients with cancer of the gastrointestinal tract both at the time of initial staging and at the time of subsequent treatment strategy. While, to date, ^{18}F-FDG continues to be the most ubiquitous radiopharmaceutical used, somatostatin-targeting radiopharmaceuticals have become key in the evaluation of patients with NETs and it is likely that newer radiopharmaceuticals will become available in the near future, although their exact clinical indications remain to be determined.

CLINICS CARE POINTS

- 18F-FDG PET is useful in staging and subsequent treatment strategy of patients with gastrointestical and colorectal malignancies
- Somatostatin-targeting radiopharmaceuticals have become key in the evaluation of patients with NETs

DISCLOSURE

M.K. Ramirez-Fort is CEO of BioFort Corp. The other authors report no conflicts of interest related to gastric and colorectal cancer.

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