PET/CT imaging in the diagnosis, staging, and follow-up of colorectal cancer

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Abstract

Colorectal cancer is a common malignancy that afflicts many in the western world. Imaging studies are frequently used to evaluate patients in the screening, staging and surveillance of colorectal cancer. Cross sectional imaging studies such as ultrasound, computed tomography and magnetic resonance imaging provide anatomic and morphologic information about tumor and patterns of spread. Positron emission tomography (PET) differs in that it provides information about tumor metabolism. [18F]Fluorodeoxyglucose PET has been clinically used for the evaluation of patients with a wide variety of cancers since most malignancies, including colorectal cancer, typically show increased glucose metabolism. This review present the positron emission tomography/computed tomography imaging findings that may be encountered in the diagnosis, staging and follow-up of patients with colorectal cancer.

Keywords: Colorectal cancer; positron emission TOMOGRAPHY; computed tomography.

Introduction

Colorectal cancer is a common malignancy that afflicts many in the western world. Approximately 150,000 new cases will be diagnosed in the United States in 2008 and approximately 50,000 deaths will be attributed to the disease this year[1]. Most patients are diagnosed with colorectal cancer in the sixth and seventh decade of life[1]. Approximately 30% of colorectal cancers occur in the sigmoid, 25% occur in the rectum and 25% occur in the cecum and ascending colon. Histologically, colon cancers are adenocarcinomas that form moderately to well-differentiated glands that secrete varying amounts of mucin[2].

Imaging studies are frequently used to evaluate patients in the screening, staging and surveillance of colorectal cancer. This review presents the positron emission tomography (PET)/computed tomography (CT) imaging findings that may be encountered in the diagnosis, staging and follow-up of patients with colorectal cancer.

Screening

The adenoma—carcinoma sequence theory is well established and suggests that many colon cancers develop directly from adenomatous polyps. The malignant potential of a polyp is largely determined by its size. Polyps greater than 2 cm in size have a greater than 40% risk of being cancerous, while those less than 0.5 cm are essentially at no risk for harboring malignancy. Other features of a polyp that predispose to malignancy are villous architecture and degree of cellular atypia and dysplasia[3].

The cumulative risk for developing invasive carcinoma in unresected polyps has been reported to be 2.5% at 5 years, 8% at 10 years and 24% at 20 years[4].

With the knowledge that colon cancers develop slowly over time, most often from preexisting adenomas, screening is of great importance for prevention of colon cancer. The ideal screening test should be safe, accurate and inexpensive. While there are several screening methods currently in use, such as fecal occult blood testing, optical
colonoscopies and imaging studies such as barium enema or CT colonography, none of them meets all of these criteria at the present time. While imaging studies generally provide an anatomic or structural snapshot of abnormalities, PET imaging differs in that it provides information about metabolic activity and function.

\[ ^{18}\text{F}\] Fluorodeoxyglucose (\[^{18}\text{F}-\text{FDG}\]) PET has been clinically used for the evaluation of patients with a wide variety of cancers since most malignancies, including colorectal cancer typically show increased glucose metabolism. The greatest difficulty in using PET for colonic abnormalities is the presence of physiologic uptake in the gastrointestinal tract. The exact etiology of FDG uptake in the colon is not entirely clear. Some suggest that increased FDG uptake is due to uptake into mucosal structures. Differences in the histology of the intestinal glands in the ascending colon, descending colon, rectum, and small intestine can cause regional differences in FDG uptake and standard uptake value (SUV) readings. The presence of lymphoid tissue in the colon may contribute to FDG uptake. Increased activation of glandular structures in the ascending colon compared with other regions could induce increased FDG uptake or even excretion into the lumen\cite{5}. Muscular activity with peristalsis may be another minor contributor to physiologic colon uptake.

Aside from normal colonic uptake of FDG, both benign and malignant colonic lesions can be detected by FDG-PET. A study by Yasuda et al. looked at 110 patients and found that precancerous adenomatous polyps can be detected incidentally on whole body images performed for other indications with a sensitivity of 24\%\cite{6}. The investigators in this study showed that benign colonic adenomas with FDG uptake could not be distinguished from FDG avid carcinomas of the colon. Lesion size was an important consideration in this study. The positivity rate for PET rises with increasing polyp size, with 90\% positivity in lesions greater than 13 mm\cite{6}. Another study by van Kouwen et al. showed similar findings with higher detection rates with increasing size (72\% sensitivity with size >11 mm) and grade of dysplasia of the adenomatous polyps\cite{7}.

Since colonic uptake is frequently seen on FDG-PET imaging, it is important to determine whether the process is focal or diffuse to help distinguish physiologic from pathologic activity. While the measurement of SUV does not allow the differentiation of benign from malignant processes of the colon, the presence of focal colonic FDG uptake as an incidental finding on PET/CT justifies a colon screening examination and PET/CT fusion can be particularly helpful for localization of lesions (Fig. 1)\cite{8}. FDG-PET may also identify inflammatory diseases of the colon such as inflammatory bowel disease or diverticulitis (Fig. 2).

A few studies have investigated the feasibility of combining FDG-PET with CT colonography (CTC), a relatively new technique that provides an endoluminal perspective of the colon. A prospective study by Gollub et al. evaluated 17 patients with a combined PET/CT examination after colonic cleansing and insufflation of the colon with carbon dioxide. These investigators found that PET/CTC was a feasible technique allowing

\begin{figure}
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\caption{Coronal MIP image (a) of an FDG-PET scan in a patient with a history of lymphoma who presented for routine surveillance shows focal uptake in the right lower quadrant (arrow) corresponding to a lesion in the cecum (arrow) on axial fused PET/CT (b) which proved to be a 3-cm adenomatous polyp at colonoscopy.}
\end{figure}
excellent image correlation in polyps measuring greater than 10 mm and showing promise in accurate anatomic correlation of both malignant and premalignant lesions of the colon[9]. Cost, availability and relative non-specificity make this technique less than feasible at the present time for widespread colorectal screening.

**Staging**

Once a diagnosis of colorectal cancer is established, staging becomes important for prognostication and to determine appropriate therapy. Complete surgical removal of tumor, along with regional lymphatics affords the best prognosis for patients with colorectal cancer. Recurrence rates are largely dependent upon the initial stage at diagnosis. Neoadjuvant or adjuvant chemotherapy and radiation therapy are therefore increasingly administered to decrease the incidence of recurrence[10]. In patients with rectal cancer, pre-operative therapy can help to downstage more advanced tumors, which allows sphincter preservation[10]. Once a tumor is invasive, it may extend through the layers of the colonic wall and invade adjacent structures[2,11]. Lymphatic, hematogenous and peritoneal spread may also occur.

PET can be a useful for pre-operative staging of colorectal cancer. The greatest value of PET lies in the fact that total body coverage allows detection of distant sites of disease. PET and PET/CT are clearly limited for T staging of the primary tumor due to limited spatial resolution and inability to distinguish the layers of the colonic wall. Transrectal ultrasound (US) and magnetic resonance imaging (MRI) provide much better anatomic resolution and are of greater value for T staging[11].

Nodal staging can be difficult with cross sectional imaging techniques such as US, CT and MRI. On cross-sectional imaging, size (greater than 1 cm) remains the primary criterion for predicting nodal metastasis, although it is well known that size is not an ideal indicator of disease. The advantage of PET lies in the ability to use metabolic activity to help distinguish benign from malignant adenopathy at sites away from the immediate vicinity of the primary tumor. Nodes in the immediate vicinity of the primary tumor are very difficult to detect with PET due to FDG activity of the primary which may obscure small lymph nodes. Small nodes are also not easily detected with PET. The overall sensitivity for nodal staging is therefore reported to be quite low, only 29%[12,13]. It is important not to confuse physiologic

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*Figure 2* Coronal MIP PET image (a) of an FDG-PET scan shows a focal area of uptake in the descending colon (arrow). Corresponding axial CT (b) image shows diverticulosis and surrounding stranding (arrow) compatible with diverticulitis.
activity in the urinary system with tumor spread in the retroperitoneum or pelvis and fused PET/CT has an advantage in anatomic localization over PET alone. Accurate staging also requires the detection of distant sites of metastatic disease (Fig. 3). This is important because limited disease spread such as to the liver may be resected for cure. Resection of colorectal cancer metastases with or without hepatic arterial perfusion therapy can lead to up to 60% 10-year survival in selected patients[14]. Therefore, pre-operative knowledge of tumor extent is very important to determine if curative resection is feasible. It has been suggested that FDG-PET is more sensitive than CT in the detection of hepatic and pulmonary metastases and in identifying other sites of intra-abdominal disease[13]. FDG-PET showed greatest accuracy in the detection of liver metastases with reported accuracy up to 99%, sensitivity up to 100% and specificity up to 98%[15]. It is important to keep in mind that lesion size is an important criterion for detection and small hepatic lesions are still not easily detected due to relatively high background liver activity. Also the limited spatial resolution of PET alone makes surgical planning difficult.

PET may also identify sites of disease that may preclude surgery or change the surgical approach. Several studies have shown that findings on PET and PET/CT results in change in stage and thereby alters management in up to 1/3 of patients[16–18]. In a study of patients with low rectal cancers, FDG-PET/CT altered treatment plans in 38% of patients largely through the detection of unsuspected inguinal adenopathy[19].

FDG-PET has also been used to predict response to pre-operative therapy and thereby predict outcome in several different malignancies including rectal cancer[20–24]. In a study by Guillem et al., 15 patients with locally advanced rectal cancer underwent FDG-PET imaging before and after completion of chemoradiation. All patients showed some degree of response to pre-operative therapy based on pathologic examination. The mean percentage decrease in SUVmax was 69% for patients that remained free of disease at a median follow-up of 42 months; the SUVmax decreased by only 37% in patients who eventually developed recurrence[20].

**Surveillance**

Although most patients with colorectal carcinoma undergo surgery with the intent of cure, nearly 4 out of 10 patients experience relapse of disease[25,26]. Over the past decade, aggressive surgical approaches to metastatic disease are being practiced and nearly 30% of patients undergo resection of recurrent disease with increased long term survival[27]. With the use of newer chemotherapeutic agents, many lesions which are deemed unresectable can be downsized thereby allowing potentially curative surgery[28]. Even in patients who have surgically unresectable disease, increasing use of newer chemotherapeutic agents, when given early show improved survival[26,29].

Nearly 85% of recurrences occur within the first 3 years after surgery and nearly none occur after 5 years[27]. Hence most surveillance strategies focus resources on the first 3 years following surgery. Various approaches to surveillance are used by clinicians from the strategy of ‘call me if you have symptoms’ to the use of aggressive monitoring with regular clinic visits, periodic tumor marker assays, cross sectional imaging, ultrasound and endoscopy. Recognizing the benefit of early treatment in resectable metastases despite acknowledging the lack of sufficient data to determine the optimal frequency of tests, the American Society of Clinical Oncology (ASCO) in 2005 recommended that assay by carcinoembryonic antigen (CEA) be performed every 3 months for the first 3 years, CT scan of the chest, abdomen and pelvis be performed every year for the first 3 years and an endoscopy at 3 years in patients with stage 2 and stage 3 colorectal carcinoma[27].

In patients with a history of colorectal cancer, PET is commonly used as a problem solving tool when there is a high index of suspicion for recurrence as evidenced by a rising CEA but when the routine diagnostic work up is equivocal. Flanagan et al. reported that FDG-PET found disease in 15 of 22 patients with elevated CEA but negative diagnostic work up. They showed a positive
predictive value of 89% and a negative predictive value of 100%[30]. In a similar study, Flamen et al. report a sensitivity of 75% and a positive predictive value of 79% in a retrospective study of 50 patients[31]. However, these studies were done with stand alone PET instruments between 1993 and 1996 and between 1996 and 1999 respectively. Significant technical improvements providing hybrid images and images of a higher resolution and quality have taken place since that time.

Another common application of PET in patients with recurrent disease is in surgical planning, particularly in patients who develop resectable metastases in the liver or lungs. Identification of occult metastases in such patients would avoid unnecessary surgery in many and alter management significantly. In a meta analysis, Wiering and colleagues report that FDG-PET changed clinical management in 31.6% of patients[32]. PET in pre-surgical planning decreases the number of futile surgeries and, may also lead to increased survival by allowing for better patient selection[33,34]. FDG-PET also affords some benefit in rectal cancer patients who have been treated with surgery and chemoradiotherapy with subsequent development recurrence in the pelvis. Early identification of pelvic recurrence is necessary for surgery to be of any benefit and distinguishing tumor from post-treatment fibrosis can be a challenge for conventional cross sectional imaging studies; FDG-PET can be useful in this regard (Fig. 4)[35]. In patients who are candidates for curative resection of local recurrence, FDG-PET can show other sites of disease that would avoid unnecessary surgery.

It is important to be aware of some limitations of PET. FDG-PET has less spatial resolution when compared to other cross sectional imaging modalities such as CT and MRI. Currently, the resolution of most commercially available PET scanners is in the range of 1.3 to 1.5 cm and lesions smaller than this size may not be detected because of volume averaging[36]. Overall high background hepatic activity also makes PET for assessment of small hepatic metastases difficult. Despite a few reports of relative superiority of PET in detecting hepatic metastases compared to cross sectional imaging, the lack of clear anatomic landmarks and inability to detect small lesions are major limitations with PET alone. Another limitation of FDG-PET that must be kept in mind when imaging patients with colorectal cancer is the relative insensitivity for detection of mucinous tumors likely due to the paucicellularity of these tumors[37]. The use of neoadjuvant chemotherapy before surgery can also decrease the sensitivity of PET in lesion detection[38]. Serosal metastases on the surface of the large and small bowel may still be missed, due to physiological bowel activity. Pulmonary metastases, particularly small ones, may be missed because of partial volume artifacts amplified by breathing. In addition to all of the above mentioned false negatives on FDG-PET, it is important to keep in mind that inflammation can result in false positive FDG uptake.

**Conclusion**

In summary, FDG-PET has been used for detection, staging and surveillance of disease in colorectal cancer patients. Physiologic activity in the gastrointestinal tract can be problematic and careful correlation with fused CT images should be performed to improve specificity. FDG-PET also provides information for staging particularly with regard to the presence of distant metastatic disease. There is insufficient data to justify the routine use of FDG-PET in detecting recurrence in patients with colorectal cancer, mainly due to the lack of large randomized trials. PET is still considered a modality with emerging applications. In areas such as post-operative surveillance of colorectal carcinoma where the surgical treatment options and chemotherapy strategies are being constantly redefined, PET CT may find additional future applications, particularly with the development of new, more specific radiotracers.
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