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FDG-PET for Colorectal Carcinoma

By Harvey A. Ziessman, M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

1. Discuss the nonimaging workup diagnosis, staging, and detection of recurrent colorectal cancer.
2. Identify the contribution and limitations of conventional imaging to the initial diagnosis, staging, and detection of recurrent colorectal cancer.
3. Discuss the added benefit of F-18 FDG-PET in the diagnosis, staging, and detection of recurrent colorectal cancer.
4. Provide improved care to patients for the diagnosis, staging, and detection of recurrent colorectal cancer.

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Dr. Ziessman has no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and is not affiliated in any manner with any provider of any commercial medical or healthcare profession service.

Colorectal carcinoma is the second most common cancer in the U.S. accounting for 12% of all malignancies. Over 148,000 U.S. citizens are diagnosed annually and 56,000 deaths result.¹ At initial diagnosis, 20% of patients have metastases and 50% will develop metastatic disease.²

Most cancers of the large bowel are adenocarcinomas. Two-thirds are located in the rectum, rectosigmoid, or sigmoid colon; the other third are distributed throughout the rest of the colon. Many begin as adenomatous polyps. The progression from adenoma to carcinoma occurs by the sequential accumulation of genetic changes.

Initial Diagnosis

Diagnosis is usually made by a barium contrast study and/or colonoscopy with biopsy. Screening tests are recommended for asymptomatic patients 45 years and older, which include annual digital exam and stool guaiac testing. Colonoscopy is recommended at three- to five-year intervals starting at 50 years.

Staging Primary Colorectal Cancer

After detection, the extent of disease determines prognosis and directs therapy. Early stage disease is treated by surgery alone.

If regional or distant metastases are discovered, therapy with a combination of surgical and other therapeutic modalities is indicated.

Preoperative staging attempts to identify the extent of local infiltration, involvement of regional lymph nodes,

and the presence or absence of metastases. Patients with lymphatic spread from their primary cancer have decreased survival and are candidates for adjuvant chemotherapy. Table 1 summarizes accepted staging classifications. T (tumor size) N (lymph nodes) M (metastases) staging is increasingly being applied to patients with colorectal cancer. Unlike other solid tumor classifications, the T in colorectal cancer does not relate to the size of the lesion, but rather to the depth of penetration by the tumor into or through the bowel wall.³

Slightly more than one-third of new cases are diagnosed in the localized state. Five-year survival is greater than 90% for stage I lesions and greater than 70% for stage II lesions. Another third of cases are diagnosed with regional nodal involvement. Survival decreases as the depth of penetration into pericolic tissues and serosal involvement increases, as tumor grade and age increase, and as the number of involved regional involved nodes increase. Overall, five-year survival approaches 50% to 70%. In those with distant metastases, five-year survival is 10% or less.³ Liver metastases are found in 10% to 25% of patients at initial operation. Of these, 25% are candidates for surgical resection and postoperative prolonged survival occurs in up to 30%.

Table 1
Staging Classification of Colorectal Carcinoma

Stage 0	Tis, N0, M0	In situ
Stage I (Dukes A)	T1-2, N0, M0	Limited to bowel wall
Stage II (Dukes B)	T3, N0, M0	Involvement of all layers of bowel wall
Stage III (Dukes C)	Any T, N1-3, M0	Involvement of regional nodes
Stage IV (Dukes D)	Any T, any N, M1	Distant metastases

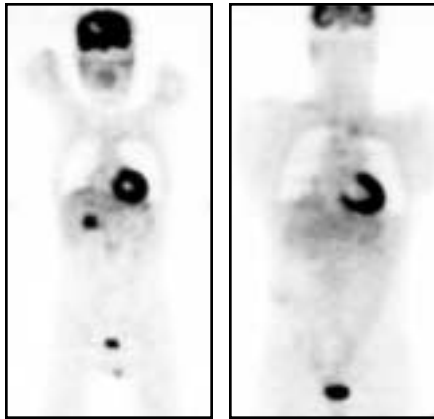


Figure 1. A: Preoperative whole-body FDG-PET scan. Coronal view: metastasis to the right lobe of the liver. B: Postoperative study. Negative whole-body PET scan.

Surveillance and Detection of Recurrence

Recurrence rates after initial therapy are estimated to be 30% to 40% and usually occur within the first two years of treatment. The recurrence is localized in up to 30% of cases making the patient a candidate for resection. To minimize morbidity and mortality, appropriate patient selection is essential, because only 20% to 30% are curable. The most commonly reported metastatic site is the liver (30%), followed by locoregional (20%), lung (20%), intra-abdominal (15%), retroperitoneal (10%), and intraluminal sites (5%).³

Serial serum measurement of serum carcinoembryonic antigen (CEA) is used for surveillance and detection of asymptomatic recurrence. Its sensitivity for detection of recurrence is low (59%). Specificity is 84%. Management of patients with an isolated increase in serum CEA who have minimal symptoms and normal conventional imaging poses a clinical dilemma. Second-look laparotomy leads to a definitive diagnosis in 90% of cases, however, 12% to 60% of patients are unsuitable for resection.

As many as 20% of patients show evidence of metastatic disease within six months of resection. Of those who develop liver metastases, one-fourth will have disease limited to the liver. Of these, only 10% to 20% will be candidates for surgical resection. Surgical resection of hepatic metastases prolongs survival and is curative in some patients. The outcome of untreated hepatic metastases is poor, with a median survival of less than 12 months. With hepatic resection, five-year survival is 25% to 35%, 10-year survival 20%, and median survival 30 months to 40 months. This compares to a median survival of 12 months to 18 months for patients with hepatic metastases treated with chemotherapy alone.²

Extrahepatic metastases, excluding potentially resectable anastomotic recurrence, are usually considered a contraindication to hepatic resection. Portal, hepatic, or celiac lymph node metastases are associated with decreased survival, thus, a contraindication to liver resection. Patients with

isolated lung metastases in addition to hepatic metastasis may do well with resection of both. Poor prognosis is associated with the presence of malignant thoracic lymph nodes, a short disease-free interval, and high preoperative CEA level. More than one liver metastasis is not necessarily a contraindication to surgery. However, as the number of liver metastases increases from one to four, prognosis and survival decrease. All disease must be resected with negative surgical margins to increase survival.

Staging of Recurrent Colorectal Cancer

Restaging and subsequent therapy depend on localization of the recurrent tumor and differentiation of isolated resectable disease from distant metastases. Colonoscopy can rule out extension of recurrent tumor and detect metachronous primary cancer, seen in up to 9% of cases. Radiologic imaging methodologies are required to adequately stage patients and are discussed below. Determining the presence or absence of extrahepatic disease is critical for identifying patients who can be spared an unnecessary abdominal exploration.

CONVENTIONAL RADIOLOGIC EVALUATION

Initial Diagnosis

Double contrast studies of the colon are the standard radiologic method for diagnosis of primary colorectal cancer. Three-dimensional CT reconstruction (virtual colonoscopy) is on the horizon, but requires further development.

Staging Primary Colorectal Cancer

•**Local infiltration.** CT can assess for local infiltration, particularly with advanced tumors, although sensitivity is not high (55% to 70%). CT and MRI accuracy for detecting and characterizing transmural penetration in low-stage tumors is considerably poorer. Endoanal ultrasonography is useful for evaluation of rectal cancers. Laparoscopy directly visualizes the peritoneal surface, but is invasive and requires general anesthesia. Intraoperative ultrasonography, although helpful, is not widely used.

•**Lymph node involvement and extrahepatic intra-abdominal metastases.** Overall accuracy of CT is reported to be 25% to 73%.⁴ CT sensitivity for malignant lymphadenopathy is 45% and MRI, 40%. Extrahepatic abdominal metastases are often

missed on CT. Both CT and MRI have difficulty in differentiating postsurgical changes from tumor recurrence. Immunoscintigraphy with Tc-99m labeled CEA has had mixed results. One report found it to be more sensitive for pelvic (74%) and intra-abdominal disease (66%) than CT (57% and 34% respectively).⁴ Others have noted a lower sensitivity.

•**Liver metastases.** CT has a reported sensitivity of 55% to 72% and underestimates the number of lobes involved in 33% of cases.⁴ MRI has similar results and cannot distinguish tumor from fibrosis.⁵ Intraoperative ultrasonography has improved detectability of liver metastases, but is not routinely utilized. Tc-99m CEA has been reported to detect metastases not seen on CT.

Surveillance and Detection of Recurrent Colorectal Cancer

Routine follow-up with CT is standard, however, it is neither sensitive nor specific. The sensitivity of contrast-enhanced spiral CT is 50% to 80% and declines dramatically for lesions less than 1 cm in size.⁴ Ability to detect peritoneal implants or low-volume locally recurrent disease is limited. CT arterial portography has a better sensitivity for detection of hepatic metastases, 85% to 94%,⁶ but requires contrast injection via catheter into the superior mesenteric artery. The false positive rate is

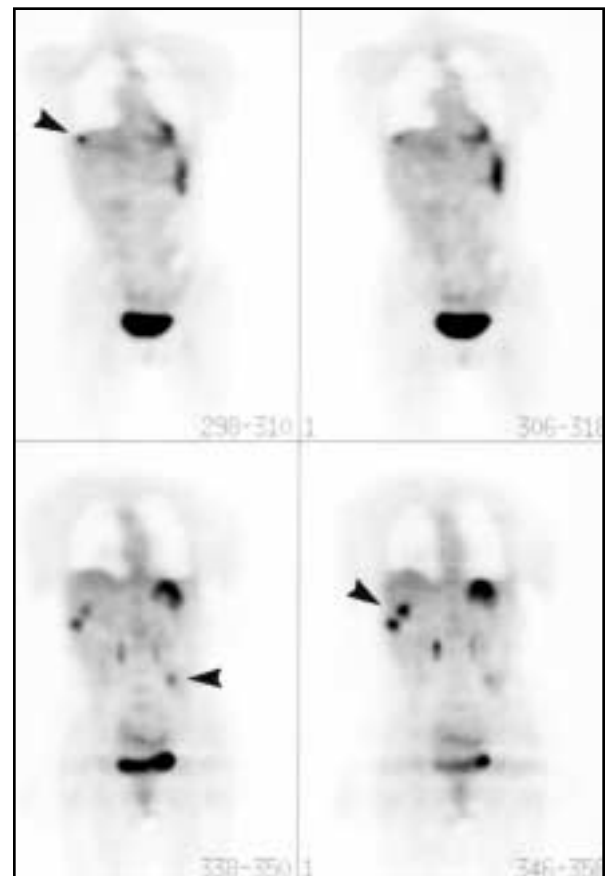


Figure 2. Four coronal FDG-PET images showing three metastases to the liver and a recurrence in the left abdomen at the site of prior resection (arrows).

15%. MRI is used to differentiate metastases from benign lesions, such as cysts and hemangiomas. Immunoscintigraphy with Tc-99m CEA for recurrent cancer has a sensitivity of approximately 90%.

Evaluating Treatment Response

CT can detect complete or partial resolution of tumor masses. However, it cannot reliably determine if residual masses are caused by persistent or recurrent tumor rather than necrosis and fibrosis. MRI has similar difficulty. Tc-99m CEA is superior to CT for differentiating scar from tumor in the pelvis.

POSITRON EMISSION TOMOGRAPHY

PET is a functional cross-sectional imaging modality requiring instrumentation quite different than conventional nuclear medicine gamma cameras because of the different physics of positron nuclear decay. Although many positron radionuclides have exciting potential as physiological radiolabels (e.g., C-11, N-13, and O-15) most have physical half-lives of only a few minutes. An onsite cyclotron is required. However, fluorine-18 (F-18) has a two-hour half-life, long enough for regional commercial distribution. PET has become an important clinical physiological imaging modality because F-18 is attached to a glucose analogue,

fluorodeoxyglucose (FDG). FDG uptake correlates with glucose metabolism. Malignant tumors have increased glucose metabolism compared to normal tissue and most benign processes. Thus, increased uptake on FDG-PET signifies active malignant tumor.

CT, MRI, and ultrasonography are excellent anatomical imaging modalities that make diagnoses based on structural/morphological tissue changes. Suspected malignant adenopathy is diagnosed by lymph node enlargement. However, tumor often resides in normal sized lymph nodes and enlargement may be caused by inflammatory disease. Physiological changes often occur within tissue before structural changes. FDG-PET detects the increased glucose metabolism of malignant tumors at an early stage. CT and MR cannot distinguish persistent or recurrent tumor from fibrosis and necrosis secondary to therapy. FDG-PET can distinguish between the two. A limitation of PET is its reduced sensitivity for detection of malignant lesions less than 1 cm in size. The most common cause for a false positive study is active inflammatory/infectious disease. Granulocytes and macrophages utilize glucose.

Initial Diagnosis

Two studies suggest a possible role for PET in

screening for colorectal cancer. In Japan, 110 asymptomatic health club members had both FDG-PET and colonoscopy. PET detected 14 of 59 adenomas (24%) in 30 subjects.⁸ Positivity rose with the size of the adenomas. Nine of 10 polyps ≤ 13 mm were detected. In the Netherlands, 39 patients referred for a wide variety of oncological and nononcological reasons had both colonoscopy and FDG-PET as part of their workup.⁹ When compared to colonoscopy, colorectal cancer was diagnosed by PET in 14 of the 39 cases, with a sensitivity of 74% and specificity of 84%. Four large adenomas were also detected.

Staging Primary Colorectal Cancer

Preliminary studies suggest a possible role for PET. In one study, FDG-PET was found superior to CT (positive predictive value [PPV] 93%, negative predictive value [NPV] 50%) versus CT (100% and 27% respectively).¹⁰ In another study of 48 patients, FDG-PET had a PPV and NPV of 90% and 100%, respectively. Sensitivity for lymph nodes metastases was 29%, similar to CT.¹¹ Detection of liver metastases was superior for PET (88% versus 38%). No data are available regarding the ability of PET to detect local infiltration. PET would not be expected to be very sensitive because of the small volume of tissue. On the other hand, synchronous tumors can be detected. Further data are needed.

Surveillance and Detection of Recurrent Colorectal Cancer

Numerous studies have shown FDG-PET to be superior to conventional imaging for detection of recurrent colorectal cancer. In 76 patients, the sensitivity of PET for detecting local recurrence was 93% versus 60% for CT.¹² In 105 patients suspected of having recurrent or metastatic colorectal cancer, the sensitivity/specificity of FDG-PET was 87%/68% compared to CT (66%/59%).¹³ However, the sensitivity of FDG-PET for detecting mucinous carcinoma of the colon is lower, 58%, versus nonmucinous carcinoma, 92%. Detectability of hepatic metastases was higher for PET than CT (89% versus 71%), while CT was better for detecting locoregional recurrence (94% versus 67%).

Twenty-two patients with an unexplained rise in serum CEA level, but normal conventional imaging including CT, were evaluated with FDG-PET. PET had a PPV of 89% and NPV of 100%.¹⁴ A similar study reported PET sensitivity of 87%.¹⁵

Staging of Recurrent Colorectal Cancer

Over 20 published investigations have found that F-18 FDG-PET is more accurate than CT for staging recurrent colorectal cancer.^{12,16-17} In a large study of 155 patients, FDG-PET had an overall sensitivity of 93% and specificity of 98% compared to CT with a sensitivity of 69% and specificity of 96%.¹⁸ In a study of 61 patients, PET had a sensitivity of 93% and specificity of 89%, while CT had a sensitivity of 79% and specificity of 58%.¹⁹ Whole-body PET is particularly useful for detecting distant metastatic disease (e.g., abdominal nodal disease, pulmonary metastases, and differentiating

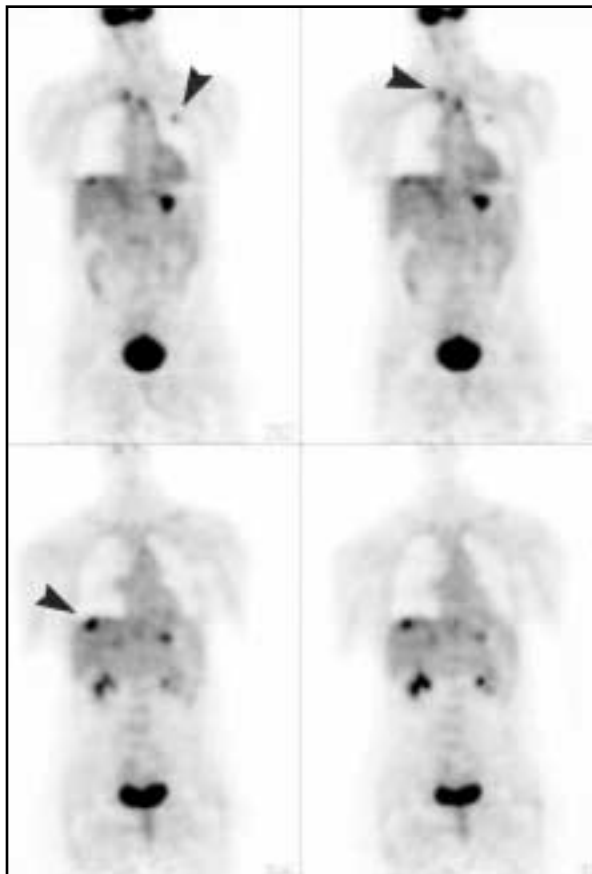


Figure 3. Four coronal FDG-PET images in a patient with recurrent colorectal cancer. Metastases to the liver, left upper lung, and right and left paratracheal nodes (arrows).

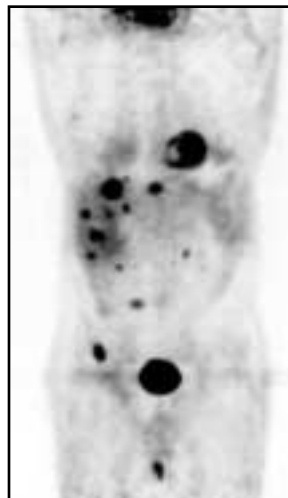


Figure 4. FDG whole-body PET. Recurrent colorectal cancer with multiple extensive metastases on FDG-PET to both lobes of the liver, mesenteric nodes, and right iliac crest.

postsurgical scarring from recurrent disease), which is difficult for CT.

•Hepatic metastases. PET is more sensitive for detection of liver metastases than conventional imaging. An early study of 76 patients found FDG-PET sensitivity/specificity for liver metastases (94%/98%) compared to CT/ultrasonography (85%/93%).¹² A more recent study of 54 patients found PET sensitivity for detection of hepatic metastases to be 91% compared to 81% for CT.¹⁹ Similarly, in 40 patients, FDG-PET had a higher sensitivity and specificity (95%/100%) compared to CT (74%/85%). PET also better delineated multiple liver lesions compared to CT.¹⁶

•Extrahepatic metastases. FDG-PET is particularly valuable for detecting metastases in the extrahepatic abdomen. One-third of PET-positive metastases in the extrahepatic abdomen and pelvis are CT negative.¹⁸ In a study of 34 patients, unsuspected extrahepatic disease was confirmed in 11 patients and clinical management changed in 10.¹⁹ In another study of 76 patients, PET detected 14 of 25 sites of extrahepatic metastases.¹² False positives were all in the thorax where granulomatous disease is known to cause false positives.

Perhaps even more important than high accuracy for staging recurrent colorectal cancer, FDG-PET has repeatedly been shown to have a clinical impact in 28% to 40% of patients.^{18,19} This impact is often caused by detection of metastases unsuspected by conventional workup resulting in a change of planned therapy. In two-thirds of patients in one study, PET obviated the rationale for the prior planned curative resection. On the other hand, one-third of patients were down staged by PET, making surgical resection possible. In another study, significant additional diagnostic information was found in 20% of patients with

presumed resectable hepatic or pelvic recurrence and in 62% of patients with inconclusive conventional imaging or with elevated plasma CEA levels.²⁰ PET was particularly useful in detecting abdominal lymph node metastases and unsuspected extra-abdominal metastatic sites. In a recent prospective study, clinical management decisions were changed after FDG-PET in 29% of patients.²¹ A meta-analysis of 11 published articles and 281 patients reported an overall sensitivity of 97% and specificity of 76% for detection of recurrent colorectal cancer by whole-body FDG-PET and an overall change in management occurred in 29% of patients.²²

A recent prospective Australian study found that the management plan of 56% of 102 patients was significantly altered as a direct result of unexpected FDG-PET findings.²³ A prospective study of patients undergoing hepatic resection found that 3-year survival with conventional imaging was 45% compared to 60% when FDG-PET was added to the preoperative evaluation.²⁴ Another study found FDG-PET to be cost-effective when added to conventional imaging using a rigorous decision tree analysis.²⁵ A multicenter study of 267 patients who had been treated for colorectal cancer reported a potentially large economic savings caused by a reduction in unnecessary laparotomies performed and the increased number of resections with curative intent.²⁶

Evaluating Treatment Response

Post-surgery. FDG-PET has proved to be far more accurate than conventional imaging, including CT and MRI, (90% versus 65%) in the differentiation of post-surgical scar from local tumor recurrence.^{12,10,16}

Post-chemotherapy. An important appli-

cation of FDG-PET is its ability to differentiate residual disease or local recurrence from post-therapy changes.^{27,28} FDG-PET has also been used to monitor the effectiveness of chemotherapy. PET was able to discriminate responding from nonresponding patients with a sensitivity/specificity of 100%/90% four to five weeks after therapy.²⁹ A European collaborative study found FDG uptake a good method for evaluating response to chemotherapy.³⁰ Patients with the greatest reduction in FDG uptake showed the best clinical response.

Post-radiotherapy. The utility of PET has been evaluated for recurrent disease before and after radiotherapy. A significant decrease in FDG uptake was seen in 50% of patients who had a good palliative effect. This disappointing result was thought caused by inflammation secondary to radiation injury in many patients. They recommended a six-month observation to more effectively detect residual tumor activity. Two subsequent studies have shown FDG-PET can differentiate local recurrence from scarring after radiation therapy.^{27,28} Another study found PET more sensitive than measurements of CEA plasma levels for tumor recurrence.³¹

CONCLUSION

FDG-PET now plays a vital role in state-of-the-art diagnosis, staging, and restaging of colorectal cancer and has been approved for reimbursement by the Centers for Medicare & Medicaid Services (CMS). The most commonly requested indications for FDG-PET include localizing metastatic disease in patients with a rising CEA but normal conventional imaging, patients with an indeterminate lesion on CT, and those who are potential candidates for resection of localized metastatic recurrences.

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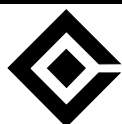
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