DISCUSSIONS IN PET IMAGING

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Evaluating Colorectal Cancer with PET and PET/CT

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LEARNING OBJECTIVES

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

- Discuss the nonimaging and imaging workup of colorectal cancer.
- Establish the diagnosis of CRC, determine the stage, and discuss surveillance and detection of recurrence.
- Identify the contributions and limitations of anatomic imaging and metabolic imaging.
- Evaluate the benefits of PET and PET/CT in diagnosis, staging, detection of recurrence, and therapy monitoring.

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In 2005, 145,290 new cases of colorectal carcinoma are expected in the U.S.—104,950 in the colon and 40,340 in the rectum—and approximately 56,290 patients will die from the disease. CRC is the third leading cause of cancer mortality, after lung and prostate cancer for men, and lung and breast cancer for women. Overall, CRC incidence and mortality rates are about 10% of all cancers. In absolute numbers, they are more than 35% higher in men than in women.

Between 1998 and 2001, incidence declined by 2.9% per year.[1] The highest U.S. incidence and mortality occur in African Americans, followed by whites and Asian Americans.[1] Most cancers of the large bowel are adenocarcinomas. Many begin as adenomatous polyps, and the progression to carcinoma occurs by accumulation of genetic changes.

DIAGNOSIS

The initial diagnosis is usually made by contrast studies of the bowel and/or colonoscopy, followed by biopsy. Screening is recommended for men and women over 50 years of age. Digital examination and fecal occult blood test or fecal immunochemical test should be performed every year and flexible sigmoidoscopy every five years.[1]

STAGING

After diagnosis, staging is indicated to direct therapy and determine prognosis. Early-stage disease can be treated by surgery alone, which is usually curative.

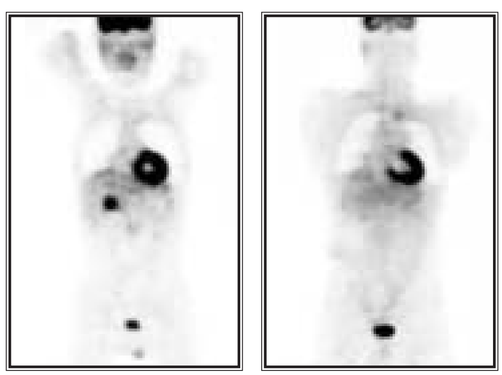

Figure 1. Left: Preoperative whole-body FDG-PET scan, coronal view. Metastasis to the right lobe of the liver. Right: Postoperative study. Negative whole-body PET scan.

If locoregional, hepatic, or distant metastases are discovered, a combination of various treatments is indicated, such as surgery, chemotherapy, and radiation therapy. Staging of newly diagnosed CRC attempts to identify the extent of local infiltration, involvement of regional lymph nodes, and presence of hepatic or extrahepatic metastases. Lymphatic spread of the disease leads to decreased survival.

Considerable effort has been invested in improving preoperative staging by using tomographic imaging. Anatomic modalities are excellent for detecting neoplasms but fail to reliably distinguish between benign and malignant tumors.[2,3] Molecular imaging with the glucose analog fluorine-18 FDG is used for staging in addition to anatomic imaging.

Table 1 summarizes the staging classification of T (tumor size), N (lymph node involvement), and M (distant metastasis). T staging in CRC relates to the depth of penetration of the tumor into the bowel wall.[4] Five-year survival between 1995 and 2000 was 90% for localized disease (stage I to II), 67% for regional metastases (stage III), and 10% for advanced disease with distant metastases (stage IV).[1] In general, survival decreases with increasing age. Liver metastases are found in 10% to 25% of patients at initial presentation. Of these, 25% are candidates for surgical resection, with prolonged survival in up to 30%.[4]

SURVEILLANCE

Recurrence rates after initial therapy are estimated to be 30%

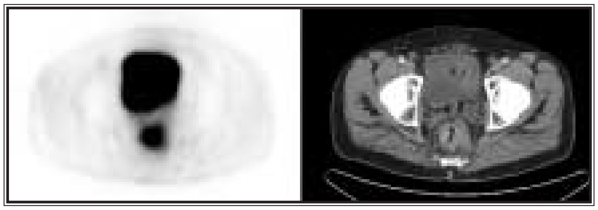

Figure 2. Primary rectal cancer in a 69-year-old man. Left: PET. Right: CT. Note hot bladder filled with excreted FDG.

to 40%, and recurrence usually occurs within the first two years of follow-up. Recurrence is locoregional in one-third of patients, who are eligible for resection. Appropriate patient selection is essential, because only 20% to 30% of patients are curable with secondary surgery. The most common site of metastasis is the liver (30%), followed by locoregional (20%), lung (20%), intra-abdominal (15%), and retroperitoneal (10%).[4]

Serial measurements of serum carcinoembryonic antigen are used for surveillance. The sensitivity for detecting recurrence is a low 59%, with a specificity of 84%. Management of patients with an isolated increase in serum CEA and minimal symptoms who have a negative workup by conventional imaging poses a clinical problem. In these patients, laparotomy leads to a definitive diagnosis in 90% of cases, but 12% to 60% of these patients are unsuitable for resection.

Six months after resection, as many as 20% of patients show evidence of metastatic disease. Approximately one-quarter of patients who develop hepatic metastases will have disease limited to the liver. Of these, only 10% to 20% will be candidates for surgical resection. Hepatic metastatectomy prolongs survival and is curative in some cases (Figure 1). The outcome of untreated liver metastases is poor, with a median survival of less than 12 months. After resection of hepatic metastases, the five-year survival rate is 25% to 35% and median survival time 30 to 40 months. This compares with a median survival time of 12 to 18 months for patients with liver metastases treated with chemotherapy alone.[5]

Distant metastases outside the liver are usually considered a contraindication to resection of hepatic metastasis. Portal, hepatic, or celiac lymph node metastases are associated with decreased survival. Patients with isolated lung metastasis in addition to hepatic metastasis may do well with resection of both. Poor prognosis is associated with the presence of thoracic lymph node metastasis, a short disease-free survival interval, and high preoperative serum CEA level.

A solitary liver metastasis is no longer the only indication for hepatic resection. However, as the number increases from one to four, prognosis and survival decrease. All disease must be resected with negative surgical margins in order to improve survival.

STAGING OF RECURRENT CRC

Restaging and subsequent therapy depend on localization of the recurrence and differentiation of isolated resectable disease from distant metastasis.

Colonoscopy can rule out extension of recurrent tumor and detect metachronous primary cancer, which is seen in about 10% of cases. Anatomic and molecular imaging are required for accurate staging. Determining the presence or absence of extrahepatic disease is critical to discern those patients who will not benefit from abdominal surgery.

ANATOMIC IMAGING

Conventional radiological imaging has uses and limitations in several areas.

• *Diagnosis.* Double-contrast studies of the colon are the standard method for diagnosing primary colorectal cancer. Virtual colonoscopy has been shown to be equally effective in the university hospital setting, but it is still cumbersome and not in widespread use.

• *Staging primary CRC.* Local infiltration can be assessed with CT, particularly with advanced tumors, but sensitivity is not high (a reported 55% to 70%). The accuracy of CT and MR for detecting and characterizing transmural penetration in stage I to II tumors is considerably lower. Endo-anal ultrasonography is useful for rectal cancers. Laparoscopy directly visualizes the peritoneal surface, but it is invasive and requires general anesthesia. Intraoperative ultrasound, although helpful, is not widely used.

CT can detect lymph node involvement and intra-abdominal extrahepatic metastases with an overall accuracy of 25% to 73%.[6] Sensitivity for malignant lymphadenopathy is 45% for CT, and 40% for MR. Extrahepatic abdominal metastases are often missed on CT, and both CT and MR imaging have difficulty in differentiating post-surgical changes from tumor recurrence.[2,3]

Hepatic metastases can be detected with CT, with reported sensitivities of 55% to 85% in series that studied PET and CT in the same patients. The lower sensitivities come from single-slice CT, while multislice CT has a sensitivity over 80%. Intraoperative ultrasound has improved detectability of liver metastasis but is not routinely used.

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

• *Surveillance of recurrent CRC.* Routine follow-up with CT imaging is standard, but it is neither sensitive nor specific. The sensitivity of contrast-enhanced CT is 50% to 80%, and it declines for lesions less than 1 cm in diameter.[6] The ability to detect peritoneal implants or low-volume local recurrence is limited. CT portography has a better sensitivity for the detection of hepatic metastases (85% to 95%), but it requires a contrast injection into the superior mesenteric artery, and the false-positive rate is 15%. MRI is used to differentiate metastases from benign lesions such as cysts and hemangiomas.

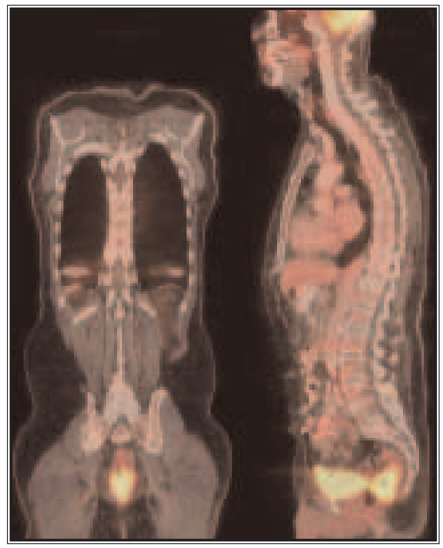

Figure 3. Fused PET/CT images. Note presacral mass with intense FDG uptake. Left: Coronal image through middle of tumor. Right: Sagittal image through midline.

• *Monitoring of treatment response.* CT can detect complete or partial resolution of tumor masses. However, it cannot reliably distinguish residual or recurrent tumor masses from necrotic or fibrotic masses resulting from successful treatment. MRI has similar difficulties.

MOLECULAR IMAGING WITH PET AND PET/CT

Performing PET or PET/CT imaging requires administration of a positron-emitting radiopharmaceutical for PET (contrast for CT if requested), a dedicated scanner for the detection of high-energy photons for PET (and low-energy photons for CT), and computers and monitors with necessary hardware and software for image acquisition, tomographic reconstruction, image processing, and display.

PET is a volumetric imaging modality requiring dedicated detectors for the annihilation radiation emitted after a positron interacts with an electron and all mass is converted into two 511-keV photons emitted in opposing directions. Positron-emitting nuclides, such as carbon-11, nitrogen-13, and oxygen-15, have short half-lives, whereas F-18, with a half-life of 110 minutes, can be distributed commercially by a central radiopharmacy.

• *Imaging of glucose metabolism with FDG.* For oncologic applications, the best known PET radiopharmaceutical is the glucose analog F-18 FDG. Like glucose, FDG is transported into the cells and phosphorylated by hexokinase-II to FDG-PO_4. The next enzyme in the pyruvate pathway has no affinity for FDG-PO_4, and this metabolite is trapped inside the cell. Malignant tumors have increased glucose utilization and are less dependent on insulin than normal tissues. After prolonged fasting, normal tissues will have low FDG uptake, whereas most tumors still have enhanced FDG uptake. Cerebral cortex is an exception, because it uses glucose exclusively under basal conditions.

Thus, increased FDG uptake signifies enhanced glucose metabolism. The uptake varies greatly for different tumor types, but a high uptake is usually associated with a high number of viable tumor cells and high expression of glucose transporter 1 (GLUT-1). Lung cancer has a high expression of GLUT-1 and is therefore readily detectable, whereas renal cell cancers show the opposite trend.[7] In general, CRC is FDG-avid.

Increased FDG uptake is not specific for neoplasms, however. Inflammatory processes also have increased uptake, and false-positive results have been reported for tuberculosis, fungal infections, sarcoidosis, nonspecific granulomas, suture granulomas, acute postoperative changes, radiation changes, abscesses, pancreatitis, and fractures. Kubota et al have studied the uptake of FDG in macrophages and granulation tissue as well as tumors.[8,9]

CT, MR, and ultrasound are anatomic imaging modalities that distinguish abnormalities based on structural and morphologic tissue changes. Suspected malignant lymphadenopathy is diagnosed by lymph node enlargement, but tumor may reside in normal-sized lymph nodes, or enlargement may occur in benign inflammatory disease. FDG-PET, on the other hand, detects metabolic changes, which usually occur earlier than structural changes. After treatment, anatomic imaging cannot distinguish residual or recurrent tumor from necrosis or fibrosis, but metabolic imaging does have this ability.

FDG-PET has two limitations: false-positive results may occur, and small lesions may be missed. Regarding size, it is not only the spatial resolution that limits PET but also the contrast resolution (i.e., the difference in metabolic activity between the lesion and its surroundings). Thus, very hypermetabolic lesions of 5 mm have been detected with FDG-PET.

• *Diagnosis.* A large study from Japan suggested a possible role for PET in screening for CRC.[10] Abnormalities were found in less than 3% of patients, however, and half were false positive. In other studies, a correlation was found between the size of polyps and the detection rate of CRC.[11,12] Clearly, screening for CRC with FDG-PET is not efficient or cost-effective.

• *Staging primary CRC.* In one report, FDG-PET was found to be superior to CT.[13] The CT results had a negative predictive value of 27%, suggesting that the patient population was biased. PET sensitivity for lymph node metastases is low and similar to CT, but detection of liver metastases is superior to CT. PET is not sensitive to local infiltration, but no data are available. Endo-ultrasound is the imaging modality of choice for rectal cancer.

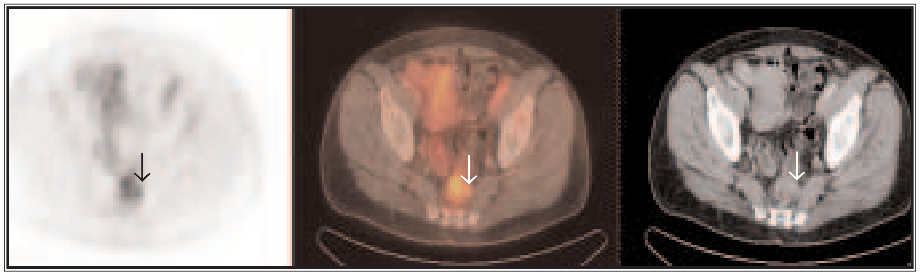

Figure 4. Lymph node left of rectum with increased FDG uptake (arrow). Axial images. Left: PET. Middle: Fused PET/CT. Right: CT image.

• *Recurrent CRC.* Numerous studies have shown that PET is superior to anatomic imaging for the detection of local recurrence, hepatic metastases, and distant metastases.[14,15]

Table 2 shows the average sensitivity and specificity of PET as computed in the meta-analysis by Huebner et al.[14] The meta-analysis does not specify the results of conventional imaging such as CT and ultrasound, and the comparison standard is not provided.

Pooling data from previously reviewed studies involving 301 patients with recurrent CRC between 1993 and 1997, the overall diagnostic accuracy of PET and CT was calculated.[16,17] The weighted average sensitivity was 95% for PET and 71% for CT. The weighted average specificity was 88% for PET and 85% for CT.

The sensitivity of FDG is lower for detecting mucinous carcinoma (58% versus 92% nonmucinous)[18] and for pure bronchioloalveolar cell carcinoma (33% versus 89% overall).[19] Detectability of hepatic metastasis is about 10% higher for PET than CT, but this difference is not statistically significant. With the current MSCT scanners, the difference is expected to become even smaller.

PET is clearly superior to CT for the detection of locoregional recurrence, which is mainly related to the difficulty of distinguishing fibrosis from recurrent tumor.

One of the first approved indications for FDG-PET imaging was an unexplained rise in serum CEA with negative conventional imaging. Several reports have shown excellent results, with PET sensitivity over 85% and a NPV of almost 100%.[15]

• *Staging recurrent CRC.* Many reports have shown that molecular imaging with FDG-PET is more accurate than anatomic imaging for staging of recurrent CRC.[20,21] The meta-analysis (Table 2) shows excellent sensitivity and specificity for PET.[14] Individual reports show a 20% increase in sensitivity and similar specificity for PET compared with CT.

Hepatic metastases are detected with higher sensitivity by PET than CT but with a specificity that is statistically not different. Extrahepatic metastases in the abdomen are also diagnosed with PET in higher numbers. The detection rate of unsuspected distant metastases is around 10%.

The five-year survival rate for resection of hepatic metastases has not changed and is still 30%. When a preoperative PET scan is performed, a subset of patients can be identified that will not benefit from surgery. Fernandez et al found a five-year survival rate of 58%.[22]

Many investigators have studied the clinical impact of staging recurrent CRC. Overall management is affected in 28% to 40% of patients through detection of unsuspected metastases after negative conventional workup, resulting in change of treatment (e.g., from surgical to medical treatment). In one-third of patients, PET led to downstaging, making surgical resection with curative intent possible.[23] The meta-analysis revealed an overall change in management in 29% of the 281 patients studied.[14]

A prospective Australian study revealed that the management plan was altered in 56% of 102 patients as a direct result of FDG-PET imaging.[24] Hepatic resection had a three-year survival of 45% with conventional imaging compared with 60% with PET imaging.

FDG-PET has been shown to be cost-effective for the clinical staging of recurrent CRC.[25] The main

TABLE 2. CLINICAL PERFORMANCE OF FDG-PET IN RECURRENT COLORECTAL CANCER

Body Region	Patients	Sensitivity	Specificity
Local	366	94.5%	97.7%
Hepatic	393	96.3%	99%
Whole Body	281	97%	75.6%

advantage of PET in oncology is that the whole body can be imaged in a tomographic mode with one injection and imaging session. The conventional approach with multiple CT or MR scans is more expensive than a single whole-body PET scan.[26]

- *Treatment monitoring.* Postsurgery evaluation with FDG-PET has proved to be more accurate than CT or MR imaging for differentiating scar tissue from local tumor recurrence. Postchemotherapy evaluation is similarly important to differentiate residual or recurrent tumor from scar/fibrosis. PET has also been used to monitor the effectiveness of chemotherapy.[27] Patients with the greatest reduction in FDG uptake showed the best clinical response. A European concerted action review found FDG uptake an adequate parameter for evaluating response and proposed that changes over 30% occur in responders to chemotherapy.[28]

Radiation therapy responses are more difficult to interpret. Initially, the inflammatory component may cause increased uptake. A German study revealed that increased uptake may be seen up to six months after radiation.[29] If complete response needs to be established, waiting six months is recommended. In order to discriminate responders from nonresponders, an interval of at least two months is recommended for RT and one month for chemotherapy.

The effect of preoperative radiation in primary rectal cancer showed a correlation between residual tumor volume, cell proliferation, and glucose utilization in a study by Schiepers et al.[30]

DUAL-MODALITY IMAGING WITH PET/CT

Combining standard PET and CT scanners into one device permits diagnostic-quality imaging. This setup allows for image fusion and perfect registration of the anatomic and metabolic images.[31] The lack of identifiable structures in an FDG-PET scan is thus circumvented, and CT can be used for attenuation correction as well. Software developments such as segmentation, iterative reconstruction, and scatter correction are now routinely applied, furnishing high-quality images of the whole body.

One of the main areas of contribution for PET/CT is the precise location of the bowel and lymph nodes, and association of FDG uptake with GI mucosa, which can be quite variable. This is even more important for restaging and therapy monitoring after surgery, when the anatomy has been changed. The contribution of breathing is less important for the abdomen than for the chest. Imaging artifacts caused by liver motion usually do not pose a problem in staging colorectal cancer. Non-attenuation-corrected tomograms and 2D projection images are always available to check for possible artifacts.

Cohade et al studied 45 patients with PET/CT and analyzed anatomic location and character of the lesion (benign versus malignant).[32] They found that the uncertainty in lesion localization decreased by 55% and in lesion type by 50%. Evaluating the stage of CRC with PET/CT increased accuracy of staging by 11%. As the authors point out, the gain by PET/CT is not tremendously high, as sensitivity and specificity of FDG-PET for staging of CRC is already quite high.[33]

As pointed out by Wahl, PET/CT is expected to be the imaging modality of choice for all abdominal and pelvic cancers.[34] The effect of intravenous and oral contrast, used for CT, on the PET images has been studied. Side by side interpretation of images corrected and not corrected for attenuation effects can solve interpretation difficulties in most clinical conditions. Accurate localization of muscle and brown fat uptake is another great contribution of PET/CT. These patterns are often found in young, tense, skinny, or shivering patients and are physiologic variants.

CONCLUSION

Molecular imaging with FDG using PET or PET/CT technology is essential in diagnosing, staging, and monitoring colorectal cancer. It is an approved indication, reimbursed by the Centers for Medicare and Medicaid Services. The most common referral indications are elevated serum tumor markers with negative anatomic imaging, restaging after treatment, and evaluation of the number and location of hepatic metastases. The introduction of dual-modality imaging with PET/CT has greatly enhanced the localization and characterization of lesions. Faster detectors and multislice acquisitions will provide an even more patient-friendly device, offering a single-session diagnostic examination for managing patients with CRC.

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