Preoperative Positron Emission Tomography to Evaluate Potentially Resectable Hepatic Colorectal Metastases

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Hypothesis: Positron emission tomography (PET) influences clinical management in the preoperative evaluation of patients with hepatic metastases from colorectal cancer.

Design: Prospective cohort study.

Setting: Academic tertiary care center.

Patients: From January 1, 2000, through December 31, 2002, 71 consecutive patients referred with potentially resectable hepatic metastases based on conventional imaging findings underwent PET or PET with computed tomography in the subsequent preoperative evaluation.

Intervention: Performance of hepatic resection was based on the results of the overall preoperative evaluation.

Main Outcome Measures: Concordance with conventional imaging findings, identification of additional findings, and change in clinical management were analyzed.

Results: The PET findings confirmed the lesions identified by conventional imaging techniques in 64 (90%) of the patients. Additional lesions were identified on PET in 23 patients (32%). The information obtained by PET resulted in a change in clinical management in 17 cases (24%). False-positive PET findings occurred in 6 patients (8%), whereas false understaging occurred in 11 (15%). In no cases did PET findings have an adverse impact on patient outcome.

Conclusions: Positron emission tomography provides useful information in the selection of patients with hepatic metastases from colorectal cancer being considered for surgical therapy. Such improved selection may serve to reduce the number of unnecessary surgical explorations and result in improved long-term survival in patients undergoing resection. Positron emission tomography should be integrated into the routine preoperative evaluation of patients being considered for hepatic resection of colorectal metastases.

Arch Surg. 2006;141:1220-1226

Each year, more than 50,000 Americans develop hepatic metastases from colorectal cancer.1 A large body of evidence supports the implementation of hepatic resection as a curative treatment in selected patients.2-6 Through advances in surgical planning, operative techniques, and postoperative care, the perioperative mortality for this procedure is commonly less than 2%.7 With improvements in patient selection and adjuvant therapy, long-term survival for patients undergoing resection is also improving, with 5-year survival rates exceeding 50% in some reports.7 Despite improvements in preoperative assessment, intraoperative identification of unresectable disease occurs in 10% to 20% of cases.8 In addition, most patients will develop recurrent disease after apparent complete resection, both within and outside the liver.8

The standard algorithm for the preoperative evaluation of patients with potentially resectable hepatic colorectal metastases relies on conventional diagnostic modalities (CDMs) such as magnetic resonance imaging (MRI) or computed tomography (CT). Positron emission tomography (PET) has emerged as a complementary imaging modality to detect metastases not evident on CDM findings.9-11 In PET, patients are injected with a fluorine-18-labeled glucose analogue fludeoxyglucose F 18 (FDG), which is selectively taken up by metabolically active cells. Images are gen-

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erated on the basis of the functional characteristics of the tissues, enabling PET to detect malignancy before it has become anatomically apparent. In PET-CT, PET is coupled with CT images to localize areas of increased FDG uptake within corresponding anatomic structures.

Despite these favorable results, PET has not been universally accepted as the standard of care for preoperative evaluation of patients undergoing hepatic resection for colorectal metastases. The purposes of this study were to determine the effect of incorporating PET or PET-CT with CDMs on the clinical management decisions in patients being considered for surgical therapy for colorectal liver metastases and to identify discordances between PET or PET-CT and CDMs according to intraoperative findings, pathological findings, and follow-up.

METHODS

PATIENT POPULATION

During a 3-year period (January 1, 2000, through December 31, 2002), 71 consecutive patients with hepatic colorectal metastases were entered into a prospective preoperative assessment algorithm at The Johns Hopkins Hospital, Baltimore, Md. In accordance with this protocol, patients were included in the study if they were identified as surgical candidates on the basis of CDM findings. In all cases, CDMs included triple-phase helical CT, contrast-enhanced MRI, or both. Patients were eligible if they were believed to be surgical candidates for complete (R0) resection or radiofrequency ablation. Patients then underwent whole-body PET as part of their preoperative evaluation (Figure 1). Patients were excluded from the study if they had undergone PET before surgical consultation. During this period, few patients had undergone PET before surgical referral. These patients were excluded to remove a potential bias, because patients with PET studies demonstrating unresectable disease would be unlikely to undergo surgical referral. Operative findings and patient follow-up were obtained from office records and the hospital tumor registry, with approval from the hospital institution review board.

PET AND PET-CT TECHNIQUES

All PET studies were performed at a single center (The Johns Hopkins Hospital) using standard imaging protocols. The PET findings were acquired on an Advance scanner (GE Medical Systems, Waukesha, Wis), and germanium-gallium attenuation correction was performed. Approximately midway into the study, PET-CT was used preferentially to PET alone. These tomograms were obtained on a dedicated in-line PET-CT scanner (Discovery LS PET-CT scanner; GE Medical Systems). The patients fasted for at least 4 hours before the study, and blood glucose levels were checked to ensure they were below 200 mg/dL (<11.1 mmol/L) before the injection of FDG. Patients who underwent combined PET-CT received oral but not intravenous contrast. Emission data were acquired for 5 minutes per field of view with a total of 5 to 7 fields from the base of the skull to midthigh 60 minutes after administration of FDG in both techniques. On the basis of the PET and CDM findings, management was determined at the discretion of the treating physicians, including whether to proceed with surgical therapy.

IMAGE INTERPRETATION

Evaluation of the PET findings was based on the retrospective review of the nuclear medicine clinical report and not a second review of the PET findings because the report represented the information available to the surgeon when the clinical decision was made. This controlled for any bias of interpretation that could result from reviewing the studies after a pathological diagnosis had already been determined. The PET findings were assigned a numeric score from 0 to 4 as described previously12: scores were based on the degree of suggestion of malignancy, where 0 indicates definitely benign; 1, probably benign; 2, equivocal; 3, probably malignant; and 4, definitely malignant. Scores of 0 to 2 were defined as a negative finding, while those of 3 or 4 were recorded as a positive finding. These results were analyzed to determine the following characteristics: the CDM-PET concordance rate, the diagnosis of additional disease sites by means of PET, the rates of false upstaging and understaging by PET findings, and the impact of the PET findings on surgical management. Concordance rates were determined by comparing the CDM and PET findings. The findings were considered to be discordant if PET failed to identify the index lesion(s) identified by CDMs. In cases where PET identified lesions that were missed on CDM findings or when CDM findings identified a false-positive lesion, the findings were verified through surgical exploration, biopsy, or follow-up imaging (minimum of 6 months). Based on this information, the rates of false upstaging and understaging were determined. We reviewed the medical records to characterize cases in which information obtained by means of PET resulted in a change in clinical management.

For each of the end points listed in the preceding paragraph, we used a χ² test to make statistical comparisons between the following subgroups of patients: examination during the first 18 months vs the last 18 months of the study period, PET vs PET-CT, mucinous vs nonmucinous pathological findings, and preoperative chemotherapy (>3 months after surgery) vs no chemotherapy. P<.05 was considered statistically significant.
PATIENT DEMOGRAPHICS

Seventy-one consecutive patients underwent PET (n=33) or PET-CT (n=38) for the preoperative evaluation of colorectal metastases to the liver during the 3-year study period. Patient characteristics are summarized in the Table. The patients consisted of 49 men and 22 women ranging in age from 32 to 90 years (mean age, 61 years). Patients had a median of 2 liver metastases, with a median tumor diameter of 4.5 cm. Primary tumors were located in the rectum in 16 patients (23%), the right or transverse colon in 31 (44%), and the left or sigmoid colon in 31 (44%). Moderately differentiated pathological findings predominated (55 patients [77%]), and 6 patients (8%) had mucinous tumors. The average serum carcinoembryonic antigen level at the time of presentation was 28 ng/dL, with 19 patients (27%) having extrahepatic disease in the iliac and hilar lymph nodes that was missed on CT findings of the chest, abdomen, and pelvis. Of the 229 lesions that were identified using all types of imaging, 30 (13%) were seen on CDMs but not PET, 46 (20%) were seen on PET but not on CDMs, and 153 (67%) were seen on both. Of the 30 metastases discovered on CDM findings but missed on PET, only 4 (2.2% of all lesions seen on CT) were determined to be false-positive findings. Although data related to the size of metastases were not universally available in the radiology reports, PET missed lesions ranging from 1 to 3 cm in 5 patients.

Thirty-eight percent of the 71 patients in the study underwent PET-CT, with the remaining 62% undergoing standard PET (Table). In the first 18 months of the study, 1 (3%) of 34 patients had PET-CT, compared with 26 (70%) of 37 having PET-CT in the second 18 months (P= .005). There was no statistically significant difference in concordance rates between patients studied during the first 18 months and those studied during the last 18 months of the study (P=.78). Similarly, comparisons of concordance rates between patients who underwent PET vs PET-CT (P= .49), those who had mucinous vs nonmucinous pathological findings (P= .30), and those who received preoperative chemotherapy vs those who did not (P= .20) failed to reach statistical significance.

ADDITIONAL FINDINGS IDENTIFIED BY PET

The PET studies detected additional disease in 23 patients (32%). Of these, 13 patients (57%) had extra-abdominal findings, whereas 10 patients had intra-abdominal findings, including 4 (17%) with intraperitoneal disease, 5 (22%) with extrahepatic disease, and 1 (4%) with both. Comparisons of subgroups failed to demonstrate a statistically significant advantage in detecting additional disease, including examination during the first 18 months vs the last 18 months (P=.13), PET vs PET-CT (P=.85), and preoperative chemotherapy vs no chemotherapy (P>.99). Although no difference was seen in lesion identification between patients with mucinous vs nonmucinous pathological findings (P=.80), the small number of mucinous tumors in this study makes a meaningful comparison difficult. Figure 2 illustrates a 56-year-old patient from our study who was found to have extrahepatic disease in the iliac and hilar lymph nodes that was missed on CT findings of the chest, abdomen, and pelvis. Figure 3 shows another patient from the study whose PET findings demonstrated disease in a portacaval node that was not evident on CT findings. This node was confirmed to be metastatic disease at laparotomy.

IMPACT OF PET ON CLINICAL MANAGEMENT

In 17 patients (24% of all cases), the PET findings significantly changed the clinical management of the disease. In 8 of these patients, extrahepatic or unresectable disease detected on PET findings resulted in canceling planned surgery. Importantly, the PET findings in these 8 patients were confirmed to be true-positive in all cases. Therefore, no patient was denied resection on the basis of false-positive PET results. In 9 patients, PET findings were used to diagnose additional disease that significantly altered the surgical approach. For example, 1 pa-

Table. Summary of Characteristics in 71 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>61.3 (32-90)</td>
</tr>
<tr>
<td>No. of liver metastases</td>
<td>2.5 (1-7)</td>
</tr>
<tr>
<td>Size of largest tumor, cm</td>
<td>4.4 (1-10)</td>
</tr>
<tr>
<td>Disease-free interval, mo</td>
<td>17 (0-76)</td>
</tr>
<tr>
<td>Sex, M/F %</td>
<td>49 (69)/22 (31)</td>
</tr>
<tr>
<td>Imaging modality, PET-CT/PET</td>
<td>27 (38)/44 (62)</td>
</tr>
<tr>
<td>Distribution of disease, %</td>
<td>27 (38)/44 (62)</td>
</tr>
<tr>
<td>Preoperative chemotherapy within 3 mo,</td>
<td>47 (66)</td>
</tr>
<tr>
<td>Mucinous pathological findings, %</td>
<td>8</td>
</tr>
<tr>
<td>Poorly differentiated, %</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; PET, positron emission tomography; PET-CT, the combination of PET and CT.

*Unless otherwise indicated, data are expressed as mean (range).
tient underwent pulmonary resection in addition to hepatic resection for metastatic disease. Two patients had evidence of a PET finding in the region of the primary tumor resection and underwent concomitant bowel resection for what proved to be local recurrences. In both of these cases, the local recurrences were not identified on preoperative colonoscopy findings and would not have been identified as part of a routine surgical exploration.

Figure 2. Imaging findings in a 56-year-old man with known liver metastasis. Whereas computed tomography (CT) (A, C, and E) showed apparently resectable liver metastases and normal-sized nodes (red circles), the combination of positron emission tomography (PET) (B) and CT (PET-CT) (D and F) detected additional abnormal uptake, including 2 additional lesions in the liver, in the iliac and hilar nodes, and abnormal uptake in the area of the anastomosis (red circles). FDG indicates fludeoxyglucose F 18.
The PET findings in 3 patients detected suspected periportal nodal disease not evident on CDM findings. All underwent exploration and resection or radiofrequency ablation of liver metastases along with resection of the involved periportal nodes. In addition to the 17 patients in whom clinical management was changed on the basis of PET findings, 8 showed PET evidence of metastatic disease that was ignored by the surgeon or ruled out by other diagnostic test results. In 2 of these cases, the PET findings were in fact confirmed on postoperative follow-up to represent true metastases. The other 6 were confirmed to be false-positive findings.

In our series, 46 patients underwent liver resection alone, 14 underwent resection combined with radiofrequency ablation, and 3 underwent radiofrequency ablation alone. Five patients underwent exploratory laparotomy and were found to have metastatic disease that precluded complete resection or ablation. In 3 cases, the extent of liver resection or conversion to radiofrequency ablation was based on PET findings. In all of these cases, these additional metastases were identified by intraoperative ultrasonography.

**FALSE UPSTAGING BY PET**

Six patients (8%) had false-positive PET findings. Five of these patients underwent PET, whereas 1 underwent PET-CT. In 2 patients, the PET findings demonstrated additional intrahepatic disease that was found to be benign on operative evaluation. Pathological findings in the first of these demonstrated no carcinoma with foci of necrosis and chronic inflammation. However, because this patient was believed to have potentially resectable disease regardless, surgical exploration and liver resection were performed, and the PET findings did not contribute to inappropriate therapy in this patient. In the second patient, liver metastases diagnosed by PET were not appreciated after careful exploration with intraoperative ultrasonography at laparotomy. No resection was performed and no recurrence occurred at this site on subsequent follow-up imaging. Another patient had recently undergone radiation therapy to the pelvis, and PET findings showed FDG uptake at the sacroiliac joint. A subsequent MRI of the pelvis ruled out malignancy in this area. In 2 patients, negative extraabdominal PET findings were confirmed on subsequent follow-up CDM imaging. Another patient had FDG uptake in the pelvis (508 days after low anterior resection and radiation therapy) that did not correspond with metastatic disease at the time of laparotomy or at follow-up.

**FALSE UNDERSTAGING BY PET**

Disease was understaged by PET findings in 11 patients (15%) when compared with operative findings. In 7 of these cases, additional metastases were within the liver, less than 1 cm, and identified by intraoperative ultrasonography. Of these patients, 7 underwent more extensive resection or ablation, whereas 4 underwent exploratory laparotomy with biopsy. Comparisons between subgroups did not reveal a statistically significant tendency to understage, including examination during the first 18 months vs the last 18 months of the study period \( (P=.56) \), PET vs PET-CT \( (P=.37) \), and mucinous vs nonmucinous pathological findings \( (P=.09) \).
These data suggest that PET is useful in confirming lesions that are suspected of being metastases on CDM findings. Furthermore, PET can detect additional sites of metastatic disease that are missed on CDM findings. These advantages have direct implications for patient management, in that they can improve patient selection and limit the number of unnecessary surgical explorations in this setting. Based on these findings, we conclude that PET or PET-CT should be used routinely (when available) in the preoperative evaluation of patients with potentially resectable hepatic metastases from colorectal cancer.

The concordance rate between the PET and CDM findings was 90% in this study. This rate is comparable to those of previous studies that have demonstrated concordance as high as 99%13 and as low as 78% for extrahepatic disease (84% for intrahepatic disease).14 Although CDMs or PET may be more or less capable at detecting metastatic disease in specific situations and sites, it is most likely that both studies result in the greatest accuracy. In addition, CDMs provide anatomic detail not provided by PET alone, which is necessary when determining resectability and planning surgical therapy. Therefore, PET alone is not recommended for the preoperative evaluation. Perhaps, when PET-CT provides sufficient anatomic CT detail, possibly with the use of intravenous contrast, a single preoperative study may be all that is required. The accuracy when these 2 modalities are implemented in unison is excellent, but proper management depends on the clinician’s ability to interpret findings that conflict with each other in some patients.

The PET findings detected additional disease in 32% of the cases in our study. Although previous reports have demonstrated detection rates as low as 11%13 and as high as 86%,15 most studies report values ranging from 20% to 30%.16-19 Previous studies have advocated the use of PET on the basis of its ability to influence surgical management.13-20 In our experience, patient management was altered in 24% of cases owing to PET findings. Previous studies have reported a rate ranging from 14% to 61%. This variability is likely owing to the criteria used for defining a change in management.5,17-19,21 One might question the clinical relevance of a PET finding that would have been detected intraoperatively regardless and the procedure altered accordingly. In this study, altered surgical management was defined as a cancellation of the procedure or an alteration in surgical management that would not have happened without the PET findings. The only exceptions, perhaps, were the 3 cases in which surgery was performed for periportal involvement detected only on PET findings. Although nodal involvement would have been identified at operation, the decisions to proceed in these cases were based on the concern that PET findings alone may not be enough not to operate. It is not clear, in retrospect, that these patients benefited by resection in the face of nodal involvement.

As with other imaging modalities, the utility of PET is limited by the radiologist’s ability to interpret the results definitively. Differentiation of true metastatic disease from benign regions of increased metabolism presents the greatest limitation to the accuracy of PET. Early experience at our institution (before September 2000) was characterized occasionally by ambiguous readings because of the difficulties inherent in interpreting the increase in radiotracer uptake. To obtain information that could more effectively guide clinical decision making, we developed a scoring system for interpreting results (described in the “Interpretation” subsection of the “Methods” section).

In 8% of cases, disease was falsely upstaged on the basis of PET information. Previous reports in the literature cite upstaging rates of 2%14 and 6.6%.13 The rate of false understaging was somewhat higher in our series at 15%. Previous studies have reported rates of 4%14 and 7.7%.13 These differences may be attributed to the patient population, the quality of the CDM, and institutional differences in the experience with and interpretation of PET data. Our experience suggests that the additional information gleaned from PET data must be tempered with a realistic view of the limitations of this technology for assessing intrahepatic disease. Three patients underwent unnecessary laparotomy on the basis of liver lesions that were seen on PET findings but subsequently found to be negative for tumor. In each case, the lesions were not confirmed by CT or by MRI findings. In these instances, additional diagnostic measures may have been beneficial. Although we did not find a significant difference in the accuracy of reported PET findings during the course of the study, we believe that the experience of the nuclear medicine team at reading these studies increases the accuracy and confidence (fewer equivocal reports) of the findings. Similarly, although we did not find a statistically significant difference in overall accuracy between PET and PET-CT, as others have shown,22 the correlation of PET with CT findings increases the confidence in a positive finding.

One intriguing finding was the difficulty with which PET identified intrahepatic disease in patients who had previously undergone chemotherapy. Of 7 patients with liver metastases that were missed on PET findings in our series, 5 underwent chemotherapy within 3 months of imaging. Because these patients did not undergo PET before chemotherapy, we do not know whether these lesions were initially undetectable on the PET findings or whether the findings became negative after a chemotherapeutic response. These data support the importance of obtaining a PET study before initiating chemotherapy in a patient who is a potential surgical candidate. Although PET will likely prove to be useful in monitoring the response to chemotherapy, perhaps one should rely more on the prechemotherapy PET study when determining extent of disease and resectability.

A limitation of this study is its applicability to other institutions where PET experience may not be as extensive compared with other types of imaging modalities. Interobserver variability of PET results remains a major obstacle to achieving widespread consistency between centers, and this may limit its usefulness in guiding clinical decision making. Nevertheless, as this technology continues to evolve and becomes more prevalent in smaller centers, it is likely that its potential advantages will become even clearer.
Taken together, these data suggest that adding PET to the diagnostic workup of patients with potentially resectable hepatic metastases from colorectal cancer may limit the number of unnecessary surgical explorations. Based on these findings, it is also likely that the improved patient selection with the addition of preoperative PET evaluation will contribute to improved patient outcomes after surgical therapy of hepatic colorectal metastases. Straßberg et al. reported improved survival in patients undergoing resection after preoperative PET staging compared with historical controls. However, these findings must be taken in the context of increased use of improved CT and MRI in patient selection, as well as improved chemotherapy and increasing use of salvage surgical therapy, which are likely to affect survival independent of preoperative PET staging. The best way to clearly define the value of this technology on long-term outcomes is through a randomized prospective trial comparing PET with alternative modalities. Unfortunately, such a study is unlikely to be feasible. Based on the findings of our report and other similar studies, the benefit of integrating PET into the preoperative evaluation appears too likely to propose such a randomized study.

Accepted for Publication: October 25, 2005.
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Author Contributions: This article represents original work by the authors. Study concept and design: Joyce, Schulick, and Choti. Acquisition of data: Joyce, Wahl, Patel, Schulick, and Choti. Analysis and interpretation of data: Joyce, Gearhart, and Choti. Drafting of the manuscript: Joyce and Choti. Critical revision of the manuscript for important intellectual content: Joyce, Wahl, Patel, Schulick, Gearhart, and Choti. Statistical analysis: Joyce and Choti. Obtained funding: Choti. Administrative, technical, and material support: Wahl and Choti. Study supervision: Schulick, Gearhart, and Choti. Image interpretation: Wahl. Financial Disclosure: None reported.

Previous Presentations: This study was presented previously as an abstract at the American Society for Clinical Oncology GI Symposium; February 25, 2004; San Francisco, Calif.

REFERENCES


