Efficacy of Detection Methods for Metastatic Gastrointestinal Cancers

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Gastrointestinal cancers metastasize to regional lymph nodes by direct extension, via the portal circulation and, ultimately, anywhere in the body. A search for metastatic disease is important at the time of original presentation of these cancers since the presence of metastases often changes the treatment plans. After initial treatment, follow-up strategies are often used to detect subsequent metastases, even though (with the notable exception of colorectal metastases in the liver) the discovery of metachronous metastases has prolonged the lives of only a small number of patients.

The detection of metastases from gastrointestinal cancers in asymptomatic patients is determined in three ways: imaging techniques, tumor markers, and tissue sampling with immunocytological cell staining or molecular biological methods.

Imaging Techniques

Computed tomography (CT) is the primary tool used to stage patients with gastrointestinal malignancies. The identification of metastatic disease with CT scans is dependent on the type of cancer and location of the metastasis.

Esophageal Cancer

Esophageal cancer metastasizes to regional lymph nodes in the chest or abdomen, to the liver, and by direct extension. The accuracy of CT detection of direct invasion into the aorta, trachea, bronchi, pericardium, or diaphragm is 88% to 94%. CT is less useful in determining lymph node metastasis. Although CT cannot determine whether a node contains cancer, lymph node enlargement (usually >1.5 cm) is the primary criterion for detection of malignancy. The sensitivity for detection of mediastinal lymph nodes is 48% to 70%; for subphrenic lymph nodes, the sensitivity is 61% to 80%. The specificity of enlarged nodes is high (>90%). Nodes cannot be detected when they are immediately adjacent to or incorporated in a primary tumor. CT appears to be comparable to endoscopic ultrasound for the detection of regional lymph node metastases.

Gastric Cancer

Gastric cancer metastasizes to regional lymph nodes by direct extension, to the peritoneal cavity (Blumer’s shelf), ovary (Krukenberg tumor), and to the liver. Although endoscopic ultrasound has proved useful for detection of primary tumor invasion of the gastric wall, it is no more helpful than CT in detecting regional lymph node metastases. CT sensitivity for the detection of malignancy in regional lymph nodes is reported to be 40% to 60% and is comparable to magnetic resonance imaging (MRI). CT is quite accurate for the detection of ovarian metastases but is inefficient at detecting peritoneal disease.

Colon Cancer

Colon cancer metastasizes to regional lymph nodes by direct extension and to the liver, lung, bone, and brain. Accuracy of detection of tumor in lymph nodes is 40% to 70%. A recent prospective, multi-institutional trial comparing MRI and CT found CT to be more accurate at determining the extension of tumor through the bowel wall (74% vs 58%). CT and MRI were found to be comparable for the detection of lymph node metastases (62% vs 64%) and liver involvement (62% vs 70%).

Liver Metastases

Liver metastases are detected by spiral CT quite efficiently. It has been reported that 91% of liver lesions greater than 1 cm in size can be detected with portal-phase contrast CT. Spiral CT has largely supplanted CT arterial portography as the least expensive and invasive assessment of the liver. The ability of CT to correctly predict operative findings in patients undergoing exploration for liver malignancies has been studied. The sensitivities for CT, delay CT, and CT portography are listed in the Table. Follow-up CT scans are most useful when compared to previous, or baseline, scans. CT of the chest is the most useful way to examine the lung fields for metastases.

<table>
<thead>
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<th>Extrahepatic Disease: CT Imaging Values</th>
<th>CT-C</th>
<th>CTAP</th>
<th>CT-D</th>
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<tr>
<td>Total</td>
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</table>
Pancreatic Cancer

Imaging techniques are most useful for determining resectability of primary pancreatic cancers. Accuracy of predicting lymph node metastases is similar to that described above.

Magnetic Resonance Imaging

MRI is a commonly used modality for the detection of metastases from gastrointestinal malignancies. MRI cholangiopancreatography and MRI with gadolinium are especially useful for the detection of hepatic metastases and the differentiation of metastatic disease from benign liver lesions. Hepatic metastases usually have low signal intensity on T1-weighted images. A central high-intensity area may represent hemorrhage or necrosis. Heavily weighted T2 images with dynamic gadolinium enhancement help to differentiate malignant lesions in the liver from cysts and hemangiomas. Focal nodular hyperplasia and fatty infiltration of the liver, sometimes difficult to distinguish from metastatic lesions on CT, are usually correctly diagnosed using MRI techniques.

Tumor Markers

A wide variety of tumor-associated molecules have been described in gastrointestinal malignancies. The use of serum measurements of these molecules has been used to assess patients prior to initial surgery and to follow patients under surveillance for recurrence. In the early 1950s, Owen Wangensteen, recognizing that as many as 50% of patients with colorectal cancer operated on for cure died of recurrent disease, proposed the idea of a “second-look” operation to assess and resect residual or recurrent disease. Reoperation typically took place six months after definitive surgery. He found that 50% of eligible patients were operated on without finding cancer and that most who had cancer were not resectable. Only 6.2% of patients with cancer survived for five years, and the concept was largely abandoned. By the 1980s, however, CT scanning and carcinoembryonic antigen (CEA) assay had become available, and the idea of a “second-look” operation was given a second look.

A large trial was reported in 1985 on data collected from 31 institutions. Of the 400 patients who were followed after curative surgery with serial serum CEA determinations, 130 (32.5%) had recurrences detected by symptoms or rising CEA. Seventy-five underwent second-look operation, and 39 had a curative procedure. Half of the operations and resections were done for symptoms and half for rising CEA. No tumors were found on five patients operated on for rising CEA, although two patients subsequently proved to have recurrences. Only 15 patients were disease free at the time of publication. In sum, only 4% of the original 400 patients had long-term benefit from the second-look procedure, and only 2% were affected by CEA result. The authors concluded that (1) patients with Dukes’ A colon cancer need not be followed with CEA because none of these patients in the study had a recurrence, (2) one quarter of patients with Dukes’ B1, B2, or C1 cancers had a recurrence and one half of Dukes’ C2 lesions recurrent, implying these patients should be followed with CEA determinations, (3) one to two-month intervals were most effective in detecting recurrent disease, and (4) reoperation should take place before CEA values exceed 11 ng/mL since the highest resectability and survival rates were noted in this group. Schneebaum et al studied the ability of CEA level to predict resectability of recurrence and concluded that although patients with higher CEA levels were less likely to be resected for cure, the large standard deviation in the values did not justify exclusion of patients from consideration of resection based on CEA levels alone.

Moertel et al studied 1,017 patients evaluated for resection based on symptoms or rising CEA levels and found that 2.9% benefitted from resection of tumor identified by rising CEA titer. In both studies of resection of colorectal cancer recurrence, the majority of the resected tumors were found in the liver or “wound seeds.”

Radioimmunoguided Surgery

Noting that 50% of patients with colorectal cancer develop recurrence, that the resectability of recurrences ranges from 12% to 60%, and that only 20% to 40% of patients resected for cure are disease free five years later, the Ohio State group employed a novel strategy to identify recurrent or persistent residual disease. This approach uses antitumor-associated glycoprotein murine monoclonal antibody tagged with I-125 that is injected into patients prior to exploration. At the time of operation, a hand-held gamma detection probe is used to locate the radioisotope. Two antibodies (B72.3 and CC49) were used in 131 patients, and 81 (63%) of them were found to be unresectable either by traditional surgical criteria or by radioimmunoguided surgery (RIGS). In 49 patients who were resected by a combination of traditional surgical assessment and RIGS criteria, 27 (55%) were alive at the time of publication, some two to eight years after exploration. Neither site of tumor resection nor Kaplan-Meier survival statistics were reported.

Cancer Cells in the Circulation and Bone Marrow

Bone Marrow and Peripheral Blood

Immunohistochemistry, flow cytometry, and polymerase chain reaction (PCR) techniques have been used to identify the presence of cancer cells in the peripheral blood.
blood and bone marrow of patients with gastrointestinal malignancies.

Using flow cytometry, O’Sullivan et al.24 found 28% of patients undergoing colon or rectum resection had bone marrow micrometastases. The percent of patients with micrometastases increased from 0% for B1 cancers to 45% for Dukes’ stage C. A total of 27% of patients with gastroesophageal junction cancers had positive flow cytometry. The presence of micrometastases at the time of resection did not correlate with conventional tumor markers (CEA or carbohydrate antigen 19-9). In a group of 20 colorectal cancer patients evaluated one to nine years after resection, 18 were free of disease and had negative bone marrows. Two had micrometastases, and one of these was found to have recurrence.

Using reverse transcription PCR, Soeth et al.25 evaluated both bone marrow and venous blood isolates from patients with gastrointestinal malignancies for evidence of micrometastases. They found 31% positive bone marrow and 17% venous isolates in patients with colorectal cancer. The presence of micrometastases correlated with stage of tumor. In gastric cancer and pancreatic cancer patients, a higher detection rate was found in the bone marrow when compared to peripheral blood. Survival in patients with PCR evidence of micrometastases was significantly shorter than in patients who tested negative.

To determine if micrometastases found in the bone marrow at the time of initial resection are evidence of shed cancer cells or a marker for metastatic potential, O’Sullivan et al.26 examined the bone marrows of carefully staged patients with gastrointestinal malignancies before and after they underwent “curative” surgery. Micrometastases were detected in 16 (22%) of 72 patients. In the 16 patients, subsequent bone marrow assessments were negative in 11 patients but persisted in five patients. This group represents a subset of patients with true residual disease. Detection of micrometastases postoperatively was associated with the discovery of overt metastasis during short follow-up (nine of 19 patients within 18 months), a highly significant finding when compared with patients who tested negative for micrometastases.

PCR techniques have been used to examine lymph nodes from the resected specimens of patients with gastrointestinal cancers. The expression of CEA mRNA in lymph nodes was assessed using a CEA-specific nested reverse transcriptase-PCR assay.26 In 117 lymph nodes from a variety of cancer patients, 30 were histologically positive for metastases and all were positive for CEA mRNA. Of 87 histologically negative nodes, 47 were positive for CEA mRNA.

References


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