Identification of Unknown Primary Tumors in Patients With Neuroendocrine Liver Metastases

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Background: For patients with neuroendocrine tumor (NET) liver metastases, resection of the primary tumor may prevent local complications (obstruction, ischemia, and bleeding) and improve survival. Despite preoperative evaluation, the primary tumor location may remain unknown.


Setting: Academic medical center.

Patients: One hundred twenty-three patients with NET liver metastases.

Main Outcome Measures: Successful identification and resection of the primary tumor.

Results: Fifteen patients underwent surgical exploration. The primary tumor was located in 13 patients (86.7%) in the small intestine and resected in 12 patients. Primary tumors in the small intestine found during surgical exploration were significantly smaller than those identified preoperatively (1.38 vs 1.91 cm, P = .03) and were often multifocal (54.2% [n = 15]). Computed tomography (34.6% [n = 78]) and somatostatin receptor scintigraphy (26.2% [n = 42]) were not sensitive in locating a primary NET in the gastrointestinal tract. Colonoscopy was sensitive in detecting colonic NETs (86.7% [n = 15]).

Conclusion: For patients with NET liver metastases and unknown primary tumor, surgical exploration effectively identifies and resects occult primary tumors that are often located in the small intestine. Primary tumors are usually small and multifocal, so careful palpation of the small intestine is essential. Before patients are considered for surgery, a multidisciplinary team assessment and evaluation consisting of computed tomography, somatostatin receptor scintigraphy, and upper and lower endoscopy should be done.

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advocate that the primary tumor be localized and resected, even in asymptomatic patients with unresectable NET liver metastases.\(^6\)\(^,\)\(^9\)

A recent epidemiological study of NETs that included almost 20,000 patients showed that approximately 11% to 14% had metastatic disease with unknown primary tumor.\(^1\) Nevertheless, there are no clear recommendations on how best to identify unknown primary tumors in patients with NET liver metastases. Previous studies\(^11\)–\(^14\) have suggested a limited role for computed tomography (CT), somatostatin receptor scintigraphy, enteroclysis, or capsule endoscopy for detecting the primary NET. An evolving technique, magnetic resonance imaging enteroclysis, identified small intestinal NETs in 8 of 12 patients.\(^13\) Recently, surgical exploration was used to successfully localize and resect occult primary NETs in 17 of 22 patients (77%), but the use of preoperative evaluations in identifying the primary tumor was not described.\(^4\) The 2-fold purpose of our study was to determine the use of preoperative evaluation for detecting the primary tumor in a larger number of patients with well-differentiated NET liver metastases and whether laparoscopic or open surgical exploration is effective for identifying and resecting an unknown primary tumor in patients with NET liver metastases.

**METHODS**

We performed a retrospective review of the University of California, San Francisco (UCSF) pathology database to identify all patients with a tissue diagnosis of well-differentiated NET liver metastases from January 1, 1993, to August 15, 2008. Demographic, clinical, radiographic, procedural, and pathological data were obtained from electronic medical records. The UCSF Committee on Human Research approved the study. Statistical comparisons were calculated using the \(t\) test.

**RESULTS**

We identified 123 patients with NET liver metastases confirmed by biopsy (Table 1 and Figure 1). Nearly two-thirds (64.2%) presented to UCSF with NET liver metastases, and 27.6% presented with localized disease that subsequently metastasized to the liver. The most common primary tumor sites were the pancreas (35.0%), small intestine (26.8%), and colon (12.2%).

Of the 79 patients who presented with NET liver metastases, 8 had no further workup because of extensive disease or comorbid conditions. The 71 remaining patients underwent evaluations to localize the primary tumors at the discretion of the treating physicians. Each patient underwent at least 1 CT scan, and most (59.2%) underwent somatostatin receptor scintigraphy. Many patients underwent upper and lower endoscopy (29.6% and 59.2%, respectively) to identify the primary tumor and to assess for synchronous neoplasms. Rarely, ultrasonography, positron emission tomography, magnetic resonance imaging, small-bowel series, and capsule endoscopy were done.

All patients with NETs arising from the GI tract and pancreas had their diagnosis confirmed by tissue biopsy. This meant we could retrospectively evaluate the sensitivity of different diagnostic methods for detecting the primary tumor, although our data did not permit us to determine specificity. We found that for patients with NET liver metastases and a primary tumor of the pancreas, CT successfully localized the primary tumor in every case, probably because the average size of the primary tumors of the pancreas (7.98 cm) was much larger than that of the small bowel (1.70 cm, \(P < .01\)) and large bowel (3.75 cm, \(P < .01\)). In contrast, for patients with NET liver metastases and primary tumors in the GI tract (ie, stomach, small intestine, colon, or rectum), CT successfully identified the primary tumor just 34.6% of the time, and somatostatin receptor scintigraphy localized it even less frequently (Table 2). It was not always possible to determine from the records whether every ileal primary tumor was located in the terminal ileum and potentially amenable to colonoscopic detection. Thus, we likely underestimated the ability of colonoscopy to identify primary tumors in the ileum.

Tumors of the small intestine detected on CT were significantly larger than tumors that were not (2.09 vs 1.60 cm, \(P = .05\)) (Table 3). In contrast, the ability to detect primary tumors in the colon on CT did not correlate with size. As for endoscopy, the primary tumors in the colon that were not seen actually tended to be larger, although there were only 2 such patients (Table 2). Finally, the ability of somatostatin receptor scintigraphy to locate the primary tumor did not seem to depend on size.

Despite extensive evaluation, 17 patients (13.8%) had occult primary tumors, 2 of whom underwent surgery for reasons other than to locate the primary tumor. One patient underwent a hepatectomy to resect NET liver metastases. The other had laparoscopic radiofrequency ablation of NET liver metastases. In the operative reports, there was no description of a careful surgical exploration for the pri-

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**Table 1. Characteristics of 123 Patients With Metastatic Neuroendocrine Tumor of the Liver**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>57.0 (18-96)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66 (53.7)</td>
</tr>
<tr>
<td>Female</td>
<td>57 (46.3)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>91 (74.0)</td>
</tr>
<tr>
<td>Black</td>
<td>9 (7.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (6.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>12 (9.8)</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>43 (35.0)</td>
</tr>
<tr>
<td>Small intestine(^a)</td>
<td>33 (26.8)</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>15 (12.2)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (4.1)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Presacral</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Unknown(^b)</td>
<td>22 (17.9)</td>
</tr>
</tbody>
</table>

\(^{a}\) Includes patients who initially had occult primary tumors that were later identified on surgical exploration.

\(^{b}\) Unknown owing to inadequate records, or lack of workup secondary to the extent of disease or other comorbidities, or failed workup.

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mary tumor. The 15 remaining patients underwent surgical exploration to locate the occult primary tumor and to achieve other operative goals, such as cholecystectomy in anticipation of long-term octreotide therapy and/or resection of NET liver metastases. Seven of 8 laparotomies and 6 of 7 laparoscopic explorations were successful in locating the primary tumor (total, 86.7% success). In 1 patient, resection was not attempted owing to extensive mesenteric fibrosis. For 2 patients in the laparoscopic group, conversion to an open surgical procedure was required to resect the mesenteric disease safely.

All primary tumors found on surgical exploration were in the small intestine; 12 were in the ileum, and 1 in the jejunum. When compared with small-intestine tumors located on preoperative evaluation, the 13 occult lesions found on surgical exploration were significantly smaller (1.91 vs 1.38 cm, \( P = .03 \)). No differences were noted in demographics, symptoms, multifocality, or biochemical levels between tumors identified during surgical exploration and those found preoperatively. For patients with small-intestinal primary tumors, most (13 of 24 [54.2%]) had multifocal disease, and most (20 of 24 [83.3%]) had documented mesenteric fibrosis.

**COMMENT**

This study sought to determine the use of preoperative evaluation for detecting the primary tumor in a large number of patients with well-differentiated NET liver metastases and whether laparoscopic or open surgical exploration is effective for identifying an unknown primary tumor in patients with NET liver metastases. To our knowledge, our series of 71 patients is the largest to date. We found that preoperative evaluation fails to identify the primary tumor in 21.1% of patients, which agrees with the findings of another study.1 Moreover, we show that laparoscopic or open surgical exploration is effective for identifying an unknown primary tumor in patients with NET liver metastases. Our high success rate (86.7%) in identifying the occult primary tumor in patients with NET liver metastases is the highest reported (22%-77%).6,12-16 We believe our experience with this rare condition will help other surgeons manage patients with NET liver metastases.

Among 123 patients evaluated at UCSF with NET liver metastases, the pancreas was the most common primary site identified (35.0%). In every case, CT detected the primary liver disease.
tumor of the pancreas, which was large (mean size, 7.98 cm). Our findings may not be surprising, given the retrospective nature of the pancreas and likelihood for nonfunctioning pancreas NETs to cause symptoms until reaching a threshold size. However, we believe our results suggest an important point: it is highly unlikely that an occult primary tumor of the pancreas is present in patients with NET liver metastases. Therefore, our findings also suggest that endoscopic ultrasonography to look for a subcentimeter tumor in the pancreas is unwarranted in a patient with NET liver metastases.

In our series, CT and somatostatin receptor scintigraphy were the most commonly used methods for detecting tumors. Both had low sensitivity for detecting the primary tumor in the stomach, small intestine, and colon/rectum (CT, 34.6%; somatostatin receptor scintigraphy, 26.2%). The small size of primary NETs in the GI tract makes preoperative detection challenging. Indeed, reported sensitivities for detection of primary NETs are low: CT, 0%-22%; capsule endoscopy, 38%-45%13; CT enteroclysis, 50%;14 and double balloon enteroscopy, 33%.16 In our series, the average size of primary NETs in the small and large intestine was only 1.84 cm. Not unexpectedly, the small-intestine tumors discovered on CT were significantly larger than those that were not detected. Although somatostatin receptor scintigraphy had a low sensitivity for detecting primary NETs, in conjunction with CT, somatostatin receptor scintigraphy can help to determine the extent of disease (eg, in lymph nodes, liver, and bone), which may provide useful prognostic information.

Computed tomography may be useful in detecting mesenteric masses that may result from extension of the primary NET or lymph node metastases with associated fibrosis, suggesting a small-intestine primary tumor. In our database search, we identified 5 patients who presented with a mesenteric mass seen on CT (2 of whom have NET liver metastases and are included in our study cohort). Four of these patients had primary NETs in the small intestine; 1 had NET in the right colon.

Our patient cohort underwent a total of 42 colonoscopies, with 20 successfully detecting the primary tumor. However, only 33 were done in patients who were later confirmed to have a primary NET in the colon or ileum. In the 9 other patients, the primary NETs were in locations not amenable to colonoscopic detection. Thus, the true sensitivity of colonoscopy in this patient group is at least 60.6% (20 of 33 patients). We were unable to determine if all patients marked as having ileal NETs in our database actually had terminal ileal disease that would have been amenable to colonoscopic detection. Colonoscopy was especially effective in locating NETs in the colon (86.7%).

In the 15 patients in our series who had NET liver metastases and an unknown primary tumor, we successfully identified the primary NET in 13 (86.7%), all of which were located in the small intestine. We found that laparoscopy readily detected the primary NET in the small intestine since it typically causes a dimpling of the serosa (Figure 2). Because most patients had multifocal primary tumors (54.2%), which are often pea-sized, we believe careful palpation of the entire small intestine is essential. During laparoscopic surgery, we used the soft-tissue wound retractor (Alexis Wound Retractor; Applied Medical, Rancho Santa Margarita, California) or the hand-assisted laparoscopic device (GelPort; Applied Medical) to aid in the exteriorization of the bowel to permit palpation. If laparoscopic exploration fails to identify the primary tumor, we do not believe open surgical exploration is indicated since careful palpation of the small bowel and preoperative upper or lower endoscopy should detect most primary tumors in the GI tract that are likely to cause symptoms.

As a retrospective analysis of a cohort from a single institution, our study had no control subjects and is subject to selection and referral bias. Therefore, although ours is the largest series to date, the following recommendations must be offered cautiously. For patients with well-differentiated NET liver metastases, localization and resection of the primary tumor should be considered to treat and prevent complications (ie, pain, obstruction, ischemia, or perforation) and, perhaps, improve survival.9,10 Computed tomography and somatostatin receptor scintigraphy should be obtained to identify the primary tumor and assess the extent of disease. If no pancreatic tumor is seen on CT, our study suggests that an occult primary tumor of the pancreas is unlikely and that up-
Figure 2. Primary ileal neuroendocrine tumor. Note the tumor is characteristically white and dimpls the serosa.

per and lower endoscopy should be done to search for the primary tumor and to rule out synchronous neoplasms. Synchronous or metachronous neoplasms can occur in an estimated 20% of patients with NET. In our cohort, we identified 4 patients with synchronous and 5 with metachronous disease.

If the patient is a suitable candidate for surgery, even if he or she has unresectable NET liver metastases, laparoscopy with careful palpation of the entire small intestine should be done to identify the primary NET. Frequently, there are multifocal primary tumors that are often very small. Laparoscopic resection is preferred but may be infeasible if the regional adenopathy, fibrosis, or both extend into the root of the mesentery. Importantly, even in the absence of a desmoplastic mesenteric mass, a wide mesenteric dissection encompassing regional lymph nodes is required; if the surgeon cannot achieve this laparoscopically, then an open approach should be taken. Perioperative octreotide infusion should be given to prevent carcinoid crisis. At the time of surgery, a cholecystectomy should be done to prevent gallstone-related complications associated with long-term somatostatin analog therapy and to prevent gallbladder necrosis from hepatic artery embolization.

In conclusion, for patients with NET liver metastases and an unknown primary tumor, surgical exploration effectively identifies and resects occult primary tumors that are often located in the small intestine. Primary tumors are usually small and multifocal, so careful palpation of the small intestine is essential. Before a patient is considered for surgery, a multidisciplinary team assessment and evaluation consisting of CT scan, somatostatin receptor scintigraphy, and upper/lower endoscopy should be done.

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Author Contributions: Drs Wang and Parekh contributed equally to this article. Drs Wang, Parekh, and Nakakura had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wang, Parekh, and Nakakura. Acquisition of data: Wang and Parekh. Analysis and interpretation of data: Wang, Parekh, and Nakakura. Drafting of the manuscript: Wang, Parekh, and Nakakura. Critical revision of the manuscript for important intellectual content: Wang, Parekh, Zuraek, Venook, Bergsland, Warren, and Nakakura. Statistical analysis: Parekh. Study supervision: Nakakura.

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REFERENCES