Metastatic Neuroendocrine Hepatic Tumors

Resection Improves Survival

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Background: The optimal treatment for hepatic metastases from neuroendocrine tumors remains controversial because of the often indolent nature of these tumors. We sought to determine the effect of 3 major treatment modalities including medical therapy, hepatic artery embolization, and surgical resection, ablation, or both in patients with liver-only neuroendocrine metastases, with the hypothesis that surgical treatment is associated with improvement in survival.

Design: Retrospective study.

Setting: Tertiary care center.

Patients: Patients with metastatic liver-only neuroendocrine tumors were identified from hospital records.

Interventions: Patients were subdivided into those receiving medical therapy, hepatic artery embolization, or surgical management.

Main Outcome Measures: Effect of treatment on survival and palliation of symptoms was analyzed.

Results: From January 1996 through May 2004, 48 patients with liver-only neuroendocrine metastases were identified (median follow-up, 20 months), including 36 carcinoid and 12 islet cell tumors. Seventeen patients were treated conservatively, which consisted of octreotide (n=7), observation (n=6), or systemic chemotherapy (n=4). Hepatic artery embolization was performed in 18 patients. Thirteen patients underwent surgical therapy, including anatomical liver resection (n=6), ablation (n=4), or combined resection and ablation (n=3). No difference was noted in the percentage of liver involved with tumor between the 3 groups. An association of improved survival was noted in patients treated surgically, with a 3-year survival of 83% for patients treated by surgical resection, compared with 31% in patients treated with medical therapy or embolization (P=.01). No difference in palliation of symptoms was noted among the 3 treatment groups (P=.2).

Conclusion: In patients with liver-only neuroendocrine metastases, surgical therapy using resection, ablation, or both is associated with improved survival.

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Patients with liver-only neuroendocrine tumor metastases may survive for long periods, even without definitive treatment.1 Because of this, controversy has existed regarding the role of definitive surgical procedures to treat these rare tumors. During the last few decades, the morbidity and mortality of liver surgery has decreased, such that in most large series, the operative mortality is less than 5%. Because of this, surgeons have become more willing to perform aggressive resections in patients with isolated hepatic neuroendocrine tumors. In addition, it is clear that surgical resection, ablation, or both offer the only potential for cure.2-4

See Invited Critique at end of article

Multiple treatment methods are available for patients with neuroendocrine hepatic metastases, including hepatic resection, ablative procedures using heat or cold, hepatic artery embolization, and chemotherapy. However, the optimal treatment is controversial because of the indolent course of these tumors and the lack of level I evidence regarding therapy for this uncommon neoplasm. Unfortunately, because of the rarity of this malignancy and the lack of equipoise for physicians caring for these patients, there will likely never be a randomized controlled trial evaluating surgical resection compared with medical treatment or embolization for patients with surgically resectable disease. We sought to evaluate outcome in patients with isolated hepatic neuroendocrine tumors treated with medical therapy, hepatic artery embolization, or surgical management at a single institution.

METHODS

PATIENT POPULATION

From January 1996 through May 2004, patients with liver-only metastatic neuroendocrine tumors treated at the University of Wis-
cinsin Hospital, Madison, were evaluated. Patients were identified from the University of Wisconsin tumor registry prospective database, interventional radiology prospective database, and hospital records. Patient demographics and tumor characteristics were recorded. Neuroendocrine tumors were characterized as either carcinoid or islet cell. Patients were identified as symptomatic from the neuroendocrine tumor if they had flushing, diarrhea, or abdominal pain. This study was approved by the University of Wisconsin Institutional Review Board.

**IMAGING EVALUATION**

Standard imaging that was obtained to stage patients with neuroendocrine tumors included abdomen/pelvis computed tomography and octreotide scan. All patients also had a chest radiograph; some patients had a chest computed tomogram. Computed tomographic scans obtained at the initial diagnosis of hepatic metastases were reviewed by a single radiologist (N.S.) to determine the percentage of tumor involvement within the liver. Tumor burden was rated as being less than 50%, 50% to 75%, or greater than 75%. In addition, the extent of liver involvement was categorized as lobar or bilobar and the size of the largest hepatic metastasis was recorded.

**TREATMENT GROUPS**

Patients were grouped according to the initial treatment they received: medical therapy, hepatic artery embolization (HAE), or surgical management. Patients treated with curative intent were considered to have surgically resectable disease if they had isolated hepatic metastases that were amenable to complete resection, ablation, or both. The number and size of hepatic metastases were less important than consideration for whether the entire tumor could be resected or ablated. In patients submitted to surgery for palliation only, resection was considered if 90% or more of the tumor volume could be removed.

Medical therapy consisted of observation, octreotide treatment, and/or systemic chemotherapy. Hepatic artery embolization was performed with or without chemotherapy. Generally, patients were referred for HAE for control of symptoms, including symptoms due to hormone secretion or abdominal pain. Surgically treated patients included those who underwent hepatic resection, ablation, or both. No patient in the medical treatment or HAE group was subsequently treated surgically.

**STATISTICAL ANALYSIS**

Comparisons between groups were tested using χ² or t tests as appropriate. Univariate analysis of survival was performed using log-rank analysis for categorical variables and Cox regression for continuous variables using SPSS software version 11.0 (SPSS Inc, Chicago, Ill). Survival was calculated from the time of diagnosis of liver metastases for all groups. Differences were considered statistically significant if P<.05.

**RESULTS**

**PATIENT DEMOGRAPHICS AND TREATMENT GROUPS**

Forty-eight patients (18 females and 30 males) with liver-only neuroendocrine hepatic metastases were identified. The median age was 56 years (age range, 27-85 years). There was no difference in age and sex between treatment groups (P>.05). The median follow-up for surviving patients was 20 months. Symptomatic patients presented with symptoms of flushing (n=6), diarrhea (n=6), and abdominal pain (n=17).

Seventeen patients were treated medically, which included octreotide only (n=7), observation (n=6), or systemic chemotherapy (n=4). Eighteen patients underwent HAE, including 16 bland and 2 chemoembolizations. The remaining 13 patients were treated surgically with curative intent, including anatomical liver resection (n=6), ablation (n=4), or combined resection and ablation (n=3).

Specific operations consisted of anatomical liver resection including lobectomy or extended hepatectomy (n=6), radiofrequency ablation (n=2), cryoablation (n=2), or combined segmentectomy or wedge resection and concomitant cryoablation (n=3).

In 9 of 13 patients, the primary lesion had been resected prior to liver resection. In 3 of the 13 patients, the primary tumor was resected at the time of the liver resection, including the following operations: right hemicolectomy, resection of a presacral mass, and pancreateoduodenectomy. In 1 patient, the liver was the only site of neuroendocrine tumor at the time of diagnosis and with continued follow-up.

Only 1 patient who was treated with octreotide was not an operative candidate because of significant comorbidities. All patients who had liver metastases amenable to resection, ablation, or both were treated surgically.

**TUMOR CHARACTERISTICS**

Thirty-six patients (75%) had metastatic carcinoid tumors; 12 patients (25%) had islet cell tumors. There were no differences in primary tumor type between the 3 treatment groups, with 71% carcinoid tumors in the medical group (n=12), 78% in the HAE group (n=14), and 77% in the surgical group (n=10) (P=.8). No patient had a diagnosis of multiple endocrine neoplasia. The location of primary tumors was primarily in the gastrointestinal tract (n=19) and pancreas (n=15), with fewer tumors in other sites, including the lung and retroperitoneum. No primary tumor site was identified in 2 patients. There was no difference in the ratio of patients in each treatment group with synchronous manifestation of hepatic metastases: medical treatment group (10/17 [59%]), HAE (12/18 [67%]), and surgical (6/13 [46%], P=.5).

Twelve (92%) of 13 patients undergoing surgery were treated with curative intent. In the single patient with residual disease present after surgery, postoperative chemoembolization was performed to treat a single site of tumor.

**EXTENT AND SIZE OF LIVER METASTASES**

Based on the calculated percentage of liver involvement, no difference was noted in the extent of liver metastases between the surgically and nonsurgically treated groups. In the surgically treated patients, 80% of patients had less than 50% of the liver involved with tumor, compared with 63% of the nonsurgically treated patients (P=.5). However, when the HAE group was compared with the medically and surgically treated groups, patients in the HAE group had a greater degree
of liver involvement (P = .02). In addition, there were more patients with bilobar liver involvement in the medically treated (13/17) and HAE groups (16/18) than in the group undergoing surgical treatment (5/13, P = .003).

To further clarify the extent of hepatic disease, we evaluated the number and size of the largest hepatic lesion present at the time of treatment. The mean±SD number of tumors for the medical, HAE, and surgical groups was 3.8±0.4, 4.7±0.2, and 2.3±0.5, respectively (differences between all 3 groups was statistically significant at P<.05). In evaluating the size of the largest hepatic lesion, there was no difference in size when the surgical group was compared with the nonsurgical group (mean tumor size, 4.5±2.3 cm for the surgery group compared with 6.3±5.4 cm for the nonsurgical group). However, there was a difference in the size of the largest hepatic lesion when all 3 groups were compared, with patients undergoing HAE having larger lesions (mean, 8.9±6.1 cm) than patients receiving either medical therapy (mean, 3.67±2.9 cm) or surgical therapy (mean, 4.5±2.3 cm, P = .03 HAE group compared with surgical group, and P = .006 HAE compared with medical group). The finding that patients who underwent HAE had a greater tumor burden, larger tumors, and a higher incidence of bilobar disease is likely a reflection of our treatment algorithm, which uses HAE primarily for symptomatic patients.

### SYMPTOM CONTROL

Of 48 patients with isolated hepatic neuroendocrine tumors, only 18 initially presented with tumor-related symptoms. In 12 (67%) of these 18 patients, symptoms were improved after treatment. There was no difference in palliation of symptoms between the treatment groups (percentage palliated per group: medical, 50% [5/10]; HAE, 83% [5/6]; and surgical, 100% [2/2]; P = .2).

### OVERALL AND DISEASE-FREE SURVIVAL

Median survival for the entire group of patients was 30.6 months. Univariate analysis of factors predictive of survival included age, time to presentation (synchronous vs metachronous), size of the largest hepatic metastasis, per-
Percentage of liver involvement, number of metastases, and location of lesion(s) (unilobar vs bilobar). Based on this analysis, only size of the largest hepatic metastasis was significant for predicting overall survival ($P = .02$, Cox regression, **Table 1**).

At a median follow-up of 19.5 months, overall survival for the medical, HAE, and surgical treatment groups was 34 months, 25 months, and not reached, respectively ($P = .03$). There was an association of prolonged survival in the surgically treated patients compared with the patients treated nonsurgically (Figure 1), with a 3-year survival of 83% for patients treated with surgical resection, compared with 31% in patients treated with medical therapy or HAE ($P = .01$).

For patients treated surgically, the median disease-free survival was 50.3 months (Figure 2). In the 5 surgically treated patients who developed recurrent disease, 2 were treated with octreotide and 1 was treated with bland HAE. There were no factors predictive of overall or disease-free survival for patients undergoing resection, although the analysis was limited by the small number of patients.

**Table 2. Summary of Recent Published Series Evaluating Outcome After Liver Resection for Hepatic Neuroendocrine Tumors**

<table>
<thead>
<tr>
<th>Source</th>
<th>Median Follow-up, mo</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Survival Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarmiento et al,2 2003</td>
<td>Not given</td>
<td>Surgery</td>
<td>170</td>
<td>75</td>
</tr>
<tr>
<td>Norton et al,1 2003</td>
<td>32</td>
<td>Surgery</td>
<td>16</td>
<td>82</td>
</tr>
<tr>
<td>Chamberlain et al,4 2000</td>
<td>27</td>
<td>Medical</td>
<td>18</td>
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<tr>
<td></td>
<td></td>
<td>HAE</td>
<td>33</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery</td>
<td>34</td>
<td>76</td>
</tr>
<tr>
<td>Chen et al,3 1998</td>
<td>27</td>
<td>Medical</td>
<td>23</td>
<td>29</td>
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<tr>
<td></td>
<td></td>
<td>Surgery</td>
<td>15</td>
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</tr>
</tbody>
</table>

Because of the varying presentation of patients with metastatic hepatic neuroendocrine tumors and the rarity of this disease, it is often difficult to define the ideal treatment approach based on the current literature. However, in patients with isolated hepatic disease, an increasing number of published findings demonstrate an association of improved survival in patients undergoing complete resection (Table 2).2,3,5-9 Our results show that an aggressive surgical approach is associated with an improvement in the 3-year survival to 83% for patients treated with surgical resection compared with 31% in patients treated medically or with HAE.

The current study compares patients with liver-only hepatic metastases from neuroendocrine tumors and compares outcome based on treatment. One strength of this study is the exclusion of all patients with extrahepatic disease, which has hampered interpretation of the results of other studies.5-6 The current study reveals an improvement in overall survival for patients who were treated with surgical resection compared with those receiving medical treatment or HAE in a selected group of patients with liver-only disease.

Clearly, the study is limited by its retrospective nature and resultant inherent selection bias. To assess the clinicopathologic characteristics of each of the treatment groups, the percentage of liver involvement was evaluated using preoperative computed tomography. There was no difference in the total percentage of liver involvement, with 80% of the surgically treated patients having less than 50% of the liver involved with tumor, compared with 63% of the nonsurgically treated patients. Although we found a larger percentage of patients had bilateral liver metastases in the nonsurgically treated patients, there was no difference in survival between patients with unilateral vs bilateral liver metastases. In addition, with continued experience in the use of ablative procedures, the presence of bilateral metastases should not limit the ability to treat patients operatively, either with ablation alone or with a combination of resection and ablation.

One limitation in directly comparing treatment groups was that patients with HAE had larger tumors and a greater number of tumors than the medically or surgically treated patients. This is likely because our treatment approach is to reserve HAE for those patients who become symptomatic, which is more likely as tumors increase in size or number. Therefore, the results of this study must be interpreted with some caution because of this finding.

These findings also reflect the marked selection bias that partially hinders our ability to compare treatment groups. Although resection is associated with an improvement in overall survival in patients with hepatic neuroendocrine tumors, the recurrence rate is as high as 75% at 5 years, even in patients who underwent complete resection.2 Sites of recurrence include the liver in most patients, with secondary sites of recurrence including the bone, brain, and lung.2 In our series, the disease-free survival was 58% at 3 years, with a median disease-free survival of 50 months. The difficulty in managing patients with recurrence is that there are few options for effective systemic treatment. Thus, there is a need for further investigation of systemic therapeutic agents for patients with metastatic neuroendocrine cancer.

The primary goal of surgical resection for patients with metastatic neuroendocrine cancer is improving survival. However, an equally important goal for patients with symptoms from hormone secretion by the tumor is palliation. Unfortunately, most series evaluating results of
liver resection in patients with hepatic neuroendocrine metastases have not evaluated quality of life measures after surgery. In one exception to this, Knox et al\textsuperscript{9} showed an improvement in quality of life as measured by Karnofsky performance score by postoperative month 3, which was sustained for more than 4 years after surgery. With regard to palliation of symptoms attributable to hormone secretion from tumor, systemic treatment with octreotide or regional treatment with HAE are both viable options to palliate symptoms.\textsuperscript{6,6} However, surgery is the only treatment option that can potentially improve survival and palliate symptoms. Therefore in patients who are symptomatic and appear resectable, complete resection or a combination of resection and ablation should be performed.

In patients with liver-only neuroendocrine metastases, surgical therapy with resection, ablation, or both is associated with improved survival compared with nonsurgical treatments. However, a multidisciplinary approach to patients with hepatic neuroendocrine tumors is necessary to optimally individualize treatment decisions.

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Author Contributions: Study concept and design: Musunuru, Chen, and Weber. Acquisition of data: Musunuru, Rajpal, Stephani, McDermott, Rikkers, and Weber. Analysis and interpretation of data: Musunuru, Chen, Holen, Rikkers, and Weber. Drafting of the manuscript: Musunuru, Rajpal, and Weber. Critical revision of the manuscript for important intellectual content: Musunuru, Chen, Stephani, McDermott, Holen, Rikkers, and Weber. Administrative, technical, and material support: Chen, Rajpal, and Rikkers. Study supervision: Chen, Holen, and Weber.

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REFERENCES