Surgery for Hepatic Neuroendocrine Tumors: A Single Institutional Experience in Japan

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Background: Surgical resection has been advocated as an effective treatment for hepatic neuroendocrine tumors (HNETs) in Western countries, but few data are available to define its indications. We evaluated the results of Japanese patients to determine the prognostic factors and the feasibility of our aggressive surgical approach.

Methods: The records of all consecutive patients who underwent surgical resection for HNETs at our institution were retrospectively reviewed. Patients were selected for surgery if all tumors were deemed resectable, regardless of their extent.

Results: A total of 21 patients were identified. Bilobar disease was present in 13 patients (62%). Eleven patients (52%) underwent major hepatectomy, which included right trisectionectomy, extended right or left hepatectomy and right hepatectomy. No in-hospital death occurred. The overall 1-, 3- and 5-year survival rates were 95, 68 and 41%, respectively, with a median follow-up of 34 months. Metastatic HNETs from bronchopulmonary primaries exhibited significantly poor outcome compared with other primary sites (P = 0.04). Patients who underwent curative resection had an improved overall 5-year survival rate of 73% compared with palliative resection (0%, P = 0.01). The longest survival in the latter group was 57 months. Complete symptom resolution rate was 92%.

Conclusions: This is the first study from Asia demonstrating the safety of aggressive hepatic resection for HNETs. Significant symptom relief and long-term survival were achieved irrespective of the extent of disease or the magnitude of operation. Metastatic HNETs from bronchopulmonary primaries may represent a more lethal subset of tumors.

Key words: neuroendocrine tumors – neoplasm metastasis – hepatectomy

INTRODUCTION

Neuroendocrine tumors are rare neoplasms that arise from the primitive gut with an indolent natural history, for which prognosis is significantly better than adenocarcinomas developing in the same organs (1–6). It is estimated, however, that 50–90% of patients with neuroendocrine tumors may develop liver metastases, which can lead to incapacitating endocrinopathies and eventually cancer-related death (7–13). These tumors may also metastasize to regional lymph nodes, adjacent organs, bones and brain (1,3,4). Patient presentation is heterogeneous, varying from classical carcinoid syndromes arising from small tumors, to asymptomatic patients with nearly total hepatic replacement by the tumor (1,7,8,10,12). With improved safety of liver resection, surgery has been advocated as the mainstay of treatment for hepatic neuroendocrine tumors (HNETs), being the only potentially curative therapy to improve survival as well as to provide outstanding relief of symptoms. Nevertheless, all sporadic reports come from Western countries and the data are limited (4–18). Further patient accrual is imperative to establish precise guidelines regarding the appropriate surgical management.

The aim of this study was to review our own experience in treating 21 consecutive Japanese patients with HNETs in which we employed an aggressive surgical approach in an attempt to remove all detectable tumors. We analyzed short- and long-term outcomes, and identified the factors that were associated with survival. The results of this study support the recommendation for an aggressive surgical approach to HNETs in Japan.
long-term results to evaluate the feasibility of the procedure and identify predictive factors that influence survival.

PATIENTS AND METHODS

We reviewed the medical records of all consecutive Japanese patients who underwent hepatic resection for HNETs from 1976 to 2004 at the National Cancer Center Hospital, Tokyo, Japan. Patients were selected for operation when they fulfilled one condition: removal of all lesions including the primary tumor and extrahepatic metastases was considered possible, regardless of its extent. The hospital charts, operation records and pathology reports were analyzed. Two pathologists reviewed all resected specimens to confirm the diagnosis of neuroendocrine tumors according to the current criteria (19,20).

Patients were considered to have synchronous disease when identification of the liver metastases and the primary tumor was simultaneous, or if the primary tumor site could not be detected. The tumors were categorized as primary HNETs (or of unknown origin) only after an exhaustive work-up failed to identify an extrahepatic primary site. Carcinoid syndrome was diagnosed by the presence of diarrhea, flushing and bronchospasm. None of the patients had right-sided heart disease. The extent of disease was defined by ultrasonography and computed tomography. Sites of extrahepatic metastases included locoregional lymph nodes and tumors in the remnant pancreas or the retroperitoneal space. To assess the consistency of medical care throughout the study interval, patients were divided into two groups according to the year they were operated on, whether in the recent 10-year period (from 1995 to 2004) or in the earlier period (before 1995).

Hepatic resection was classified as major when two sectors or more were resected. Sectionectomy, segmentectomy, limited resection and enucleation were categorized as minor resection. Complete resection (curative intent) was attained only when the surgeon removed all primary and metastatic disease, including lymphatic spread. When unresectable residual tumor existed in the remnant liver or elsewhere in the body, or if liver tumors were treated with radiofrequency ablation (RFA) or ethanol injection, the operation was defined incomplete (palliative intent).

Outcome measures included complication rate following resection, operative and in-hospital mortality, symptom resolution rate, overall survival and disease-free survival. Survival time was calculated as the period from the date of hepatic resection until death or the most recent clinic visit, with none of the patients lost to follow-up.

Data are presented as percentages, median and range. Fisher’s exact probability test was used to determine the correlation between two categorical variables with two levels. Survival rates were analyzed with the Kaplan–Meier actuarial method and the log-rank test was applied to compare survival between different groups. Statistical significance was defined as a P value of less than 0.05. All statistical analyses were performed using SPSS statistical software (SPSS Inc., Chicago, IL).

RESULTS

A total of 21 patients comprised the subjects of this study. Patient demographics, tumor characteristics and extent of disease are summarized in Table 1. In the patients with metachronous disease, the median interval from the resection of the primary tumor to the development of hepatic metastases was 68 months (range: 25–265 months). The types of
resection included right trisectionectomy \( n = 3 \), extended right hepatectomy \( n = 2 \), right hepatectomy \( n = 3 \) and minor resection \( n = 10 \). Concurrent non-hepatic procedures included lymph node dissection \( n = 5 \), pancreatoduodenectomy \( n = 2 \), distal pancreatectomy \( n = 1 \) and bowel resection \( n = 3 \). No operative or in-hospital death had occurred. The median operative time was 380 min (range: 262–1195 min) and the median amount of blood loss was 970 ml (range: 344–6650 ml). Post-operative complications were observed in four patients (19\%), including intra-abdominal abscess \( n = 1 \), pancreatic leakage \( n = 1 \), peritonitis associated with renal failure \( n = 1 \) and myocardial ischemia \( n = 1 \). The median length of post-operative stay was 24 days (range: 12–106 days). Complete resolution of clinical symptoms was accomplished in 11 of 12 (92\%) symptomatic patients prior to surgery. One patient showed a partial response, but none of these 12 patients experienced recrudescence of their symptoms.

Median follow-up for all patients was 34 months (range: 8–234 months). The overall 5-year survival rate was 41\% with a median survival of 54 months (Fig. 1A). Metastatic HNETs from the lung or the bronchus had a significantly decreased outcome compared with other primary sites or unknown origin \( P = 0.04 \). None of the patients in this group survived over 5 years, while the median survival of the latter subset was 95 months (range: 13–234 months) (Fig. 1B).

Fourteen patients (67\%) who underwent complete resection had a significantly improved prognosis compared with the incomplete resection group \( P = 0.01 \) (Fig. 1C). In the former group, the median disease-free interval was 49 months (range: 10–234 months) and eight patients experienced tumor recurrences (57\%). Among the seven patients (33\%) who underwent incomplete resection, the longest overall survival was 57 months; resolution of symptoms after surgery was complete in five, partial in one, and one was asymptomatic pre-operatively. Other factors such as the resection status of the primary tumor, the extent of operation, tumor burden, or the period of operation had no impact on overall or disease-free survival (Table 2).

Of all 21 patients, five are currently disease-free and two are alive with recurrence in the remnant liver. Thirteen patients have suffered tumor-related death (12 widespread hepatic recurrences and one multiple brain metastases) and one has died of other causes.

**DISCUSSION**

Our results suggest that aggressive resection for HNETs can be safely performed, that it provides substantial relief of symptoms and allows long-term survival. Because all previous reports come from Western countries, this series is important as being the first to describe surgical outcomes for Asian patients, contributing to the body of data to reach a...
worldwide consensus in the treatment of this rare, intriguing disease.

In the current study, the overall survival rate at 5 years after hepatic resection was 41% during a median follow-up of 34 months. Although superior to historical controls of unresected HNETs (4,9,17,18,21,22), our result was somewhat lower than in recent reports (Table 3). Greater frequency of metastatic HNETs from the lung or the bronchus in our series may account for the decreased overall survival (Table 3). The significantly diminished prognosis of patients in this subset, with none of them surviving over 5 years, was a novel finding. The metastatic route to the liver is worth consideration. Theoretically, systemic spread is inevitable for bronchopulmonary primaries to provoke hepatic metastasis, while the liver is the initial organ to trap tumor cells dislodged from gastroenteropancreatic primaries via the portal vein. The highly proliferative nature of neuroendocrine tumors originating from foregut organs depicted by other authors (2,3) may also support the aggressive potential of bronchopulmonary primaries observed in this study.

Genetic diversity in the development of neuroendocrine tumors may be another explanation for the prognostic discrepancy. Through analysis of several large US databases, Modlin et al. (23) have discussed the race-related propensity toward carcinoids arising at specific primary sites, although the incidence of all carcinoid tumors between the Asian and non-Asian population was comparable (1–2 patients per 100,000 population per year). Soga et al. (24) also investigated the site-distribution difference of carcinoids among Japanese, US and European series. They found an approximately two-fold incidence of rectal and bronchopulmonary primaries in Japan. These data suggest a genetic-based protective or deleterious effect on each primary site, associated with a wide variety of metastatic potential and overall survival.

Although our experience was limited, the current series further revealed that neither the extent of disease nor the magnitude of operation had any influence on survival. This observation was contrary to other reports (4,10,16) that suggested HNETs with more than 50% liver involvement, bilobar disease, or massive metastatic pancreatic endocrine tumors were associated with poor prognosis. Extensive hepatic resections for HNETs have been anecdotal in the past, whereas 52% of our patients underwent major hepatectomies with low morbidity and zero mortality. Among the previous studies, this series appear to constitute the relatively aggressive surgical approach group treating a more advanced stage of disease (4–18, Table 3). The difference in patient selection may well also play some part in our rather disappointing overall survival rates despite the favorable short-term surgical outcomes.

Symptom control is another critical goal in treating HNETs, because endocrinopathies characteristic for these tumors can be incapacitating. The high complete symptomatic resolution rate of 92% in our study was in accord with previous reports (Table 3). It is of note that outstanding symptom control was achieved even in the palliative resection group, although the survival was significantly worse compared with curative resection (6). We conclude that as far as all HNETs (and extrahepatic lesions if present) are amenable to complete resection, irrespective of their extent, patients should undergo technically demanding liver resections in tertiary, high-volume centers where standardized strategies and treatments have been established (1,4,11,13).

The role of lymph node dissection in the surgical management of HNETs needs to be further addressed. At our institution, systematic lymph node dissection is not routinely performed at the time of hepatic resection for HNETs and is restricted to suspicious or definite cases of metastasis. Of the seven patients with extrahepatic disease, five underwent lymphadenectomy for peripancreatic or mesenteric nodal involvement. The presence of extrahepatic metastasis did not lead to a statistically significant decrease in survival (Table 2), which clearly represents the success of elective lymph node dissection. Our current strategy is supported by many authors stating that aggressive surgical resection is recommended whenever possible even in the presence of
extrahepatic disease for relief of symptoms and prolongation of survival (25–27).

The implications of palliative resection remain to be elucidated. The high recurrence rate (57%) in the curative resection group and the fact that 92% of tumor deaths resulted from multiple liver metastases in our study suggested that, ultimately, all of the patients would die from hepatic recurrence. The presence of occult metastatic lesions in the remnant liver is the rate-limiting factor for survival and attempts to achieve complete resection may merely entail attaining better disease control (13,14–18). The Mayo Clinic group has encouraged palliative resection provided that 90% of the tumor bulk could be resected (2,7,13). The definition of palliative surgery will be a cornerstone in the future treatment of HNETs, which may well evolve into a multimodality approach, incorporating resection, chemotherapy, TACE (transcatheter arterial chemoembolization), and RFA (3,4,13,18,28).

In conclusion, with our present study’s long post-operative follow-up and being the first report from Asia, the results from this series have indicated that aggressive surgical resection for HNETs, regardless of the extent of disease or the magnitude of operation, can be safely performed, offers excellent control of symptoms and yields long-term survival, if macroscopically complete resection is accomplished. The current series has yet again suggested that metastatic HNETs from the lung or the bronchus may have a significantly diminished survival.

**References**


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**Conflict of interest statement**

None declared.