Surgery ■■ (2017) ■■–■■

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/ymsy

American Association of Endocrine Surgeons

Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors

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ARTICLE INFO

Article history:
Accepted 26 May 2017

Background. Recently, there has been a move toward decreasing the threshold for liver debulking for metastatic carcinoid tumors from 90% to 70%. The debulking threshold and factors that predict outcomes of liver debulking operations specifically among pancreatic neuroendocrine tumors are not well defined.

Methods. Records of patients with pancreatic neuroendocrine tumors undergoing liver debulking with a threshold of 70% from 2006 to 2016 were reviewed. Extrahepatic metastases and positive margins by enucleation were allowed. Liver progression-free survival and overall survival were calculated by the Kaplan-Meier method for various factors and compared by log-rank. Factors also were correlated with liver progression-free survival and overall survival by multivariate regression analyses.

Results. Forty-two patients underwent 44 operations, of which 24 resulted in 100% debulking, 12 resulted in ≥90% debulking, and 8 resulted in ≥70% debulking. Median liver progression-free survival was 11 months. The 5-year overall survival rate was 81%. There were no significant differences in outcome based on percent debulked. Only liver metastasis ≥5 cm correlated with liver progression-free survival and overall survival.

Conclusion. Consideration should be given to expanding the criteria for liver debulking in pancreatic neuroendocrine tumors to include a new threshold of >70% debulking, intermediate grade tumors, positive margins, and extrahepatic metastases; these criteria yield results indistinguishable from complete resection. Using these expanded criteria will increase the number of patients eligible for an operation and maintain high survival rates.

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms that frequently metastasize to the liver. When compared with pancreatic adenocarcinoma, PNETs are relatively slow growing but remain associated with substantial morbidity and mortality. Functional pancreatic tumors secrete hormones, including insulin, gastrin, vasoactive intestinal peptide, glucagon, and somatostatin, which can be the source of debilitating endocrinopathies and death. The detection of nonfunctional PNETs has increased markedly in recent years in association with increased use of various cross-sectional imaging technologies for assessment of other abdominal complaints.[1] The majority of patients with PNETs, however, continue to present with advanced disease; indeed, 64% of patients have liver metastases at the time of diagnosis.[2] These patients frequently have bilobar disease with numerous metastases and often are deemed ineligible for resection by standard criteria. In fact, it is estimated that only 5% to 15% of patients with PNETs are considered resectable.[3-5] The most common cause of death in patients with neuroendocrine liver metastases is liver failure due to gradual replacement of normal liver parenchyma with tumor.[6]

Debulking neuroendocrine liver metastases has been shown to be associated with improved survival in a number of studies.[7-10] Most series, however, have reviewed mixed groups of neuroendocrine tumors of various primary locations, combined to generate adequate power to assess these procedures. In a recent series of patients with carcinoid liver metastases, our institution examined expansion of operative criteria that supported decreasing the threshold for liver debulking from 90% to 70%, allowing extrahepatic metastases, and performing resection by parenchyma-sparing techniques with positive margins allowed.[11] A threshold of 70% for debulking and use of parenchyma-sparing techniques was supported by a subsequent series of small intestinal neuroendocrine tumors that included 18 PNETs.[12] These expanded criteria, however, have not been examined in a dedicated series of only PNETs. Some series suggest that patients with PNETs have lesser survival rates than patients with other neuroendocrine tumors,[2] with other reports indicating that PNETs are associated with more aggressive behavior without commenting specifically on survival.[13,14] Therefore, the

Presented at the 38th Annual Meeting of the American Association of Endocrine Surgeons, Orlando, FL, April 2–4, 2017.

Conflict of interest: R.F.P. and S.J.P. (spouse) have disclosures to report: R.F.P. serves as a consultant for Novartis Oncology Pharmaceuticals and Ipsen.

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https://doi.org/10.1016/j.surg.2017.05.030
0039-6060/

threshold for debulking and the prognostic factors associated with operative intervention in these patients warrant additional examination.

Methods

Records of patients with PNETs, including duodenal gastrinomas, undergoing liver debulking by a single surgeon from January 1, 2006 to December 31, 2016 were reviewed retrospectively. The Oregon Health & Science University Institutional Review Board approved the study; review of the medical record was exempted from informed consent by the board. Data collection and storage were compliant with HIPAA 1996. Data collected included age; sex; site of the primary tumor; functional status of the tumor; preoperative, perioperative, and postoperative use of octreotide; number, location, and size of tumors resected; tumor grade (determined by number of mitoses/high-powered field and percent Ki-67, according to the guidelines of the North American Neuroendocrine Tumor Society)[15]; presence and location of extrahepatic disease; resection of extrahepatic metastases; duration of hospital of stay; date of liver progression; other treatment of liver metastases (either before or after liver debulking); status at last follow-up; and cause of death. Liver progression was determined by radiographic findings every 3 months, according to Response Evaluation Criteria in Solid Tumors, version 1.1.[16]

Operative data collected included type of liver resection performed. Positive margins by parenchyma-sparing enucleations were allowed. The percentage of liver disease debulked was estimated by the surgeon at completion of operation, based on visual, radiographic, and intraoperative ultrasonographic assessment. Patients were classified into 3 groups based on percent of gross hepatic metastases resected: ≥ 70%, ≥90%, and 100%. Additionally, status of resection of the primary tumor was recorded.

The statistical significance of differences in distribution of patients with stable liver disease, liver progression, or death among groups of patients with various categorical variables was determined by χ^2 analysis or Fisher exact test. Continuous variables were compared with a *t* test. Liver progression-free survival (LPFS) and overall survival (OS) were calculated by Kaplan-Meier method for clinical, operative, and pathologic factors and compared by log-rank analysis. Factors also were correlated with LPFS and OS by multivariate regression analyses. Patients who underwent >1 liver debulking were treated as separate cases for LPFS analyses and single cases for OS analyses.

Results

Clinicopathologic characteristics

Forty-two patients underwent 44 liver debulking operations. Patient characteristics are shown in Table I. The primary tumor location was the head of the pancreas in 17 patients (41%), tail of the pancreas in 17 patients (41%), duodenum in 7 (17%), and unknown in 1 patient in whom genetic testing (bioTheranostics, San Diego, CA) indicated a > 92% probability of a pancreatic primary. Thirty-three patients (75%) had liver metastases at diagnosis. Five patients (12%) had a functional tumor; there were 3 with Zollinger-Ellison syndrome, 1 insulinoma, and 1 VIPoma (vasoactive intestinal peptide). Thirty-five patients (83%) were receiving outpatient long-acting repeatable (LAR) octreotide before resection. Eleven patients had other therapies before liver debulking; 4 had prior liver resection, 4 received everolimus, 2 received 5-fluorouracil/streptozotocin, 2 received capecitabine/temozolomide,[17] and 1 each received cisplatin/etoposide, sorafenib, and underwent hepatic artery embolization with yttrium-90 (Y90) microspheres.

Operative characteristics

Sixteen patients (36%) had their primary tumor resected before liver operation, 5 (11%) had their primary tumor resected at the time of liver operation, 14 (33%) had their primary tumor resected after liver operation, and 9 (21%) did not have their primary tumor resected because they declined pancreaticoduodenectomy or were unresectable. Pancreaticoduodenectomies were preferably staged as separate operations after liver debulking to avoid liver abscesses due to worries of colonization of the biliary tree. Six patients (14%) had extrahepatic metastases, diagnosed intraoperatively in 4 patients and noted to be extra-abdominal in 1. These extrahepatic metastases were completely resected at the time of liver operation in 3 patients.

Thirty-one operations (70%) were for bilobar disease. There were 16 major hepatic resections performed (36%) and 28 parenchyma-sparing operations only were performed in 28 cases (64%). Mean estimated blood loss was 850 mL (range 50–4,000 mL). Transfusion was given during 7 operations (16%). The mean size of the largest resected liver metastasis was 4.5 cm (range 0.8–23.2 cm). The mean number of tumors resected per patient was 20 (range 1–101). Twenty-four operations (55%) resulted in resection of 100% of gross hepatic disease, 12 (27%) in resection of ≥90% of gross hepatic disease, and 8 (18%) in ≥70% resection of gross hepatic disease. The highest grade in any liver metastasis was grade 1 in 21 operations (48%) and grade 2 in 20 operations (46%); the grade was not determined in 3 operations (7%). Perioperative octreotide was administered during 42 of the 44 operations (95%). Hemodynamic instability consistent with carcinoid crisis occurred during 11 operations (25%), only in patients who did receive perioperative octreotide. Additionally, there was no correlation between functional tumor status and incidence of carcinoid crisis ($P = 1.0$). There were no operative deaths. Postoperative complications (Table II) occurred after 8 operations (18%) and did not correlate with carcinoid crisis ($P = .24$). Twenty-seven patients (64%) continued LAR octreotide postoperatively.

Outcomes

Follow-up status of all patients was known at the time of this writing. Median follow-up was 33 months. Eighteen patients (43%) met the criteria for liver progression after liver operation. The Kaplan-Meier curve for LPFS is shown in Fig 1. Median LPFS was 11 months, and the estimated 5-year LFPS was 4%. There were no significant differences in rate of progression according to percent of liver metastases resected (Table I). Three of 18 patients progressed in the ≥70% group, 6 of 12 in the ≥90% group, and 9 of 24 in the 100% group ($P = .75$ overall, see Table I for intergroup comparisons). Only the size of the largest resected liver metastasis and a formal hepatic resection correlated with liver progression on univariate analyses (Table I). The mean size of the largest resected metastasis was 6.4 cm in patients who had liver progression compared with 3.2 cm in patients with stable liver disease ($P = .03$). Formal hepatic resection was performed in 10 patients who developed liver progression compared with 6 patients with stable liver disease; there was a statistically significant correlation between formal hepatic resection and any liver metastasis ≥5 cm ($P = .02$). On multivariate regression analysis, only any resected liver metastasis measuring ≥5 cm correlated with progression ($P = .003$).

As the next treatment after liver progression, 6 patients underwent hepatic artery embolization with Y90 microspheres, 5 received everolimus, 3 resumed LAR octreotide, 3 received capecitabine/temozolomide,[17] 2 received sunitinib, and 2 had a second liver debulking (7 patients received 2 therapies).

The Kaplan-Meier curve for OS is shown in Fig 2. Five-year survival was 81%, with all deaths due to liver failure; median survival

Please cite this article in press as: Rosemary E. Morgan, SuEllen J. Pommier, and Rodney F. Pommier, Expanded criteria for debulking of liver metastasis also apply to pancreatic neuroendocrine tumors, Surgery (2017), doi: 10.1016/j.surg.2017.05.030