Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients

Amanda N. Graff-Baker, MD,[a] David A. Sauer, MD,[b] SuEllen J. Pommier, PhD,[a,c] and Rodney F. Pommier, MD,[a,c] *Portland, OR*

Background. *Cytoreduction of carcinoid liver metastases typically aims for ≥90% debulking in patients without extrahepatic disease. Data on the impact of less-restrictive resection criteria and other clinical and tumor-specific factors on outcomes are limited.*

Methods. *Records of carcinoid patients undergoing liver debulking from 2007 to 2011 were reviewed. Debulking threshold was 70%, extrahepatic disease did not preclude cytoreduction, and positive margins were allowed. Kaplan-Meier liver progression-free (PFS) and disease-specific (DSS) survival were calculated and compared by log-rank analysis and statistical significance of differences in distributions of factors between patient groups was determined by chi-squared analysis.*

Results. *Fifty-two patients were identified. Complete resection of intrahepatic and extrahepatic gross disease was achieved in 12 patients. All primaries reviewed were low grade, but one third of patients had at least one intermediate-grade metastasis. Fifteen patients (29%) had liver progression; median PFS was 72 months. Five-year DSS was 90%, with all deaths from liver failure. Only age was an important prognostic factor for PFS and DSS. Five-year DSS for patients <50 years was 73% and was 97% for patients 50 or older (*P = *.03).*

Conclusion. *The use of expanded criteria for debulking resulted in 90% 5-year DSS. Although younger age portends a poorer prognosis, the favorable PFS and DSS justify also using expanded criteria in this subgroup. (Surgery 2014;156:1369-77.)*

From the Departments of Surgery[a] and Pathology,[b] and Division of Surgical Oncology,[c] Oregon Health & Science University, Portland, OR

Neuroendocrine tumors (NETs) are rare and slow-growing neoplasms that arise from cells of the neuroendocrine system. Carcinoid tumors originate in the enterochromaffin cells of the aerodigestive tract, with approximately 60% in the gastrointestinal tract and the small intestine is the most common site.[1]

Metastatic disease, most commonly in the liver, frequently is seen in patients with carcinoid tumors. This is particularly true among those patients with small bowel primaries, in whom 60–80% present with metastatic disease.[2] Patients who present with local or regional disease are at substantial risk of subsequently developing distant metastases.[1,3] Despite the slow-growing nature of these tumors, metastatic disease carries significant morbidity and mortality.[1,3] Patients with liver metastases frequently develop carcinoid syndrome secondary to the production of bioactive amines and polypeptide hormones; the degree of symptoms is often directly related to the hepatic disease burden. The most frequent cause of death is liver failure caused by hepatic replacement by tumor.[4,5]

Multiple retrospective studies have demonstrated that debulking of liver metastases can improve endocrine-related symptoms, as well as survival, in patients with metastatic NETs.[2,6-10] On the basis of the large series by Sarmiento et al,[10] a debulking threshold of ≥90% has been adopted by many centers. Although many operations are undertaken with curative intent, several series

Sources of financial support: OHSU Carcinoid Research Foundation.

Dr R. Pommier serves as a consultant for Novartis Oncology Pharmaceuticals and Pfizer, Inc.

Accepted for publication August 8, 2014.

Reprint requests: Rodney F. Pommier, MD, Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, L619, Portland, OR 97239. E-mail: pommierr@ohsu.edu.

0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2014.08.009

have found that the extent of hepatic and extrahepatic disease found at operation is underestimated in approximately 15% of cases.[2,7,9,10] Some authors report undefined or <90% thresholds for resection and included patients with extrahepatic disease,[2,7,8] but data on the impact of these inclusion criteria on outcomes are lacking.

Guidelines published by the North American NeuroEndocrine Tumor Society in 2010 indicate all NETs should be graded using the mitotic count and Ki67 index to delineate low-, intermediate-, and high-grade NETs.[11] Tumor grade often is solely determined from the primary tumor resection or biopsy of a single liver metastasis. Data on the heterogeneity of grade between primary and secondary tumors and among the frequently numerous liver metastases, and their impact on liver debulking outcomes, are also lacking.

In this study, we evaluated the impact of clinical and pathologic factors on liver progression-free and disease-specific survival in patients selected for liver debulking performed when inclusion criteria for liver resection were extended to include patients who could undergo ≥70% liver debulking, to those with extrahepatic disease, and to those with intermediate-grade liver metastases.

METHODS

Records of patients with carcinoid undergoing liver debulking by a single surgeon for the indications of improving symptoms and/or survival from January 2007 to December 2011 were reviewed. Data collected included age; sex; primary tumor site; functional status of the tumor; preoperative and postoperative use of octreotide; other treatments of liver metastases; number, location, and size of tumors resected; sites of extrahepatic disease; resection of extrahepatic disease; percentage of hepatic burden resected as estimated at the completion of the operation; length of stay; date of liver progression; status at last follow-up; and cause of death.

The study population included patients who underwent liver resection based on intraoperative visual and intraoperative ultrasonographic assessment by the surgeon that ≥70% of visible liver disease volume was resectable. The surgeon did not perform resection in patients in whom this was not possible. This threshold was selected on the basis of operative experience that when ≥70% is not resectable, substantial liver debulking is rarely technically possible. Positive margins via enucleation were allowed. Patients were further classified into three groups based on percent of gross hepatic metastases resected: 70–89%, 90–99%, and 100%. They were also classified into groups based on whether they had formal anatomic hepatic wedge resections, wedge resections, and those with bilobar resections. Patients who underwent resection of all gross intrahepatic and extrahepatic disease were defined as having a complete resection. Liver progression was determined by radiographic findings according to Response Evaluation Criteria in Solid Tumors, version 1.1.[12]

Pathology slides of primary tumors and liver metastases were reviewed for size and grade by a single pathologist. Grade was determined by number of mitoses/high-powered field (hpf) and percent Ki-67, when available, according to the North American NeuroEndocrine Tumor Society guidelines.[11] Tumors with <2 mitoses/10 hpf and <3% Ki67 index were low grade, tumors with 2–20 mitoses/10 hpf or 3–20% Ki67 index were intermediate grade, and tumors with >20 mitoses/10 hpf or >20% Ki67 index were high grade. At least 25 hpf were reviewed for each slide. If multiple slides were available for a single tumor, each slide was reviewed and the highest grade was recorded.

Statistical significance of differences in distribution of patients with liver-progression and stable hepatic disease among groups of patients with various categorical variables was determined by chi-squared analysis. Normally distributed and non-normally distributed continuous variables were compared with t test and Mann-Whitney U test, respectively. Liver progression and disease-specific times and rates were calculated with the Kaplan-Meier method and were compared by log-rank analysis. Statistical analyses were performed using the Statistical Package for the Social Sciences, version 22. Statistical significance was defined as a P value of ≤.05. The study was approved by the institution's investigational review board.

RESULTS

Fifty-two patients were identified. Patient characteristics are shown in Table I. After exploration at the time of liver resection, the primary tumor was localized in all but three patients. Thirty-seven patients received octreotide long-acting repeatable (LAR) as outpatients before resection; 88% of patients were maintained on octreotide LAR postoperatively. Liver-directed therapy had been used in seven patients before liver debulking; three had undergone liver radiofrequency ablation (RFA), two had received intra-arterial radioembolization, and two had undergone previous liver resection at another institution. Median length of stay after resection was 6 days.