Hepatic Metastases of Gastroenteropancreatic Neuroendocrine Tumors: Safe Hepatic Surgery

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Abstract. Liver metastases of neuroendocrine tumors are usually slow-growing, and cytoreductive hepatectomy can help reduce the effects of endocrinopathies and increase life expectancy and symptom-free survival. However, it has yet to be fully investigated how hepatectomy for metastatic neuroendocrine tumors can be performed safely. Here we report the results of 13 patients with neuroendocrine liver metastases operated on in our institution and those of a French multicentric study that included 131 patients. Preoperative patient selection and appropriate surgical technique, sometimes combined with preoperative portal embolization and local tumor destruction (radiofrequency and cryotherapy), may increase the resectability and the safety of the procedure. The mortality rate after hepatectomy was 0% (2.3% in the French study); the 3- and 6-year survival rates were 91% and 68%, respectively, in our institution (the mean survival time was 66 months in the French multicentric survey). Significant prolonged survival with complete palliation of symptoms can be obtained after liver metastases resection with low mortality.

Slow-growing malignant gastroenteropancreatic neuroendocrine tumors commonly send metastatic deposits to the liver. Although numerous symptomatic, cytotoxic, immunologic, and isotopic therapies have been developed, only complete surgical resection offers definitive cure. With improvements in hepatic resection techniques (gained mainly from colorectal experience) [1], curative liver resection of metastatic neuroendocrine tumors has been proposed to be the most valuable therapeutic option, with improved long-term survival. Because of tumor size-related symptoms, cytoreductive surgery has gained acceptance as a potentially palliative option in symptomatic patients.

The safety of surgical management for liver metastases from gastroenteropancreatic neuroendocrine primary lesions is very important. Indeed, the natural history of these tumors is long (mean 5–10 years) [2], and mortality after liver resection is therefore not acceptable. Our aim was to answer the following four questions: Is resection of metastatic disease justified? How is safety defined for hepatic resection? What are safe indications and safe operative procedures? Is it possible to increase the indications for safe hepatic resection? We report our own experience with 13 patients treated between January 1986 and December 1998 and the results of a French multicentric survey that included 131 patients.

Is Resection of Metastatic Disease Justified?

The natural history of metastatic neuroendocrine carcinomas is well established. Moertel [3] and Thompson et al. [4] reported an overall 5-year survival of 30% to 40% and a median survival of 3 to 4 years for untreated patients or patients unresponsive to nonsurgical therapies. Madeira et al. [2] confirmed these results and classified metastatic patients into two groups according to the progression of hepatic metastases [more or less than a 25% rise in tumor volume after 6 months delay evaluated by computed tomography (CT)]. The 5-year survival was significantly different in the two groups: 34% for the fast-growing tumors versus 100% for the slow-growing tumors. Results obtained after liver resection of metastatic neuroendocrine carcinomas [5] showed an increase in overall survival (73% vs. 30–40% four-year survival) and median survival (6 years vs. 4 years). Furthermore, surgery provided effective, prompt, and complete palliation of symptoms in about 90% of cases. These findings suggest that curative or palliative hepatic resection of neuroendocrine metastases is justified.

How Is Safety Defined for Hepatic Resection?

Safe minor or major hepatic resection at the end of the twentieth century could be achieved with minimal mortality ($< 5\%$ or even $< 1\%$) and low morbidity ($< 20\%$) (Table 1), avoiding specific complications such as hemorrhage, liver failure, or bile leakage. This perspective can be obtained by selecting "good" candidates for surgery, adequate preoperative evaluation, appropriate surgical techniques, and adequate anesthesiology and postoperative management. With improved surgical techniques most of the patients undergoing hepatectomy do not need blood transfusion.

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Table 1. Mortality and morbidity after resection of colorectal or neuroendocrine hepatic metastases.

Study	No.	Mortality (%)	Morbidity (%)
Adson [6]	141	0–4[a]	—
Fortner [7]	65	7	27
Nordlinger [1]	1818	2.4	24
Scheele [8]	434	4.4	16
Que [5][b]	74	2.7	24
Miyagawa [9][c]	172	2.9	37
Taylor [10]	173	0	28
Harmon [11]	110	4	34

[a]Minor hepatectomy 0%, major hepatectomy 4%.
[b]Only neuroendocrine hepatic metastases included.
[c]Including cirrhotic liver.

Table 2. Primary site and type of tumor.

Type	Pancreas ($n = 7$)	Jejunum ($n = 3$)	Ileum ($n = 1$)	Unknown ($n = 2$)	Total
Nonfunctioning tumor	4	1	—	2	7
Carcinoid tumor	2	2	1	—	5
Glucagonoma	1	—	—	—	1

the inferior vena cava [16]. Residual hemorrhage of the transected parenchyma is controlled by meticulous ligatures. A bile leak test is carried out by injecting serum with methylene blue into the common bile duct via a transcystic drain. Perioperative care includes, if necessary, the use of frozen plasma, Trasylol (Aprotinine; Bayer, Puteaux, France), vitamin K, and albumin.

Is It Possible to Increase the Indications for Safe Hepatic Resection?

In the case of bilobar metastatic involvement, three methods are helpful for increasing the indications for safe hepatic resection of neuroendocrine tumors. The first is represented by a two-stage procedure: After resecting the deposits in the left lobe, percutaneous right portal embolization (or surgical ligation of the right portal vein) is performed. This procedure induces atrophy of the right lobe and functional hypertrophy and regeneration of the left vascularized part of the liver after 4 to 6 weeks, allowing a safe right hepatectomy [17, 18]. The second consists of combining liver resection and procedures of local tumor destruction (e.g., radiofrequency or cryotherapy). The third consists of repeat hepatectomies; this strategy is used successfully to treat recurrent liver metastases of colorectal cancer. We reported, with other groups [19, 20], that mortality, morbidity and long-term survival after repeated hepatectomies were similar to the results obtained after the first hepatectomy; iterative resections can be performed with great safety (less than 1% mortality).

Our Experience

Between 1986 and 1998 a total of 796 liver resections were performed in our department. Among these procedures only 13 (1.6%) were undertaken for liver metastases of neuroendocrine tumors. The gender ratio (M/F) was 7:6, and the mean age of the patients was 55 years (range 39–70 years). No patient had multiple neuroendocrine neoplasia syndrome. The primary tumor sites and types are listed in Table 2. The mean interval between the first symptom and the diagnosis was 13.7 months (range 2–60 months). The main symptoms at diagnosis included pain ($n = 6$), diarrhea ($n = 5$), flushing ($n = 4$), weight loss ($n = 3$), right cardiac failure ($n = 2$), and hypercalcemia ($n = 1$). One patient was asymptomatic. Primary tumor and hepatic metastases resection were synchronous in 11 patients and metachronous in 2 (4 and 6 years later).

Hepatic resections included right or left hepatectomy ($n = 2$), left lobectomy ($n = 2$), segmentectomy ($n = 16$), and nonanatomic resection ($n = 8$). These hepatic resections were undertaken under vascular occlusion in 12 patients. The mean durations of continuous ($n = 5$) or intermittent ($n = 7$) vascular occlusion were 34 and 39 minutes, respectively. Associated procedures included left splenopancreatectomy ($n = 4$), pancreaticoduodenec-

What Are Safe Indications?

"Good" candidates for surgery are symptomatic patients (mainly) and asymptomatic patients with a resectable primary tumor (but with liver masses unresponsive to nonsurgical treatments). They present without extrahepatic dissemination and without preoperative risk factors related to general health status [American Society of Anesthesiologists (ASA) score] or to associated diseases (e.g., right cardiac failure in carcinoid syndrome). After complete biologic evaluation of liver function (indocyanine green clearance) [12, 13] and extended radiologic estimation of residual nontumorous liver volume [magnetic resonance imaging (MRI), CT scan, three-dimensional CT scan] the type of liver resection(s) can be chosen.

What Are Safe Operative Procedures?

Unilobar or bilobar safe hepatic resection starts with an adequate abdominal approach (bilateral subcostal $\pm$ upper midline incision or J-shaped incision). Adequate retraction is needed for sufficient exposure of the operative field. After abdominal exploration the liver is mobilized by dividing the ligamentous attachments. Biopsy of the nontumoral hepatic parenchyma is performed for frozen section evaluation, and the importance of steatosis is assessed. Intraoperative ultrasonography is mandatory not only to detect unknown hepatic small lesions but also to appreciate tumor extension and its relation with pedicles. Based on this information the type of hepatic resection can be selected. On the basis of the segmental anatomy [14], liver transection is performed using a Kelly clamp ultrasound dissector under Pringle's maneuver. Intermittent clamping of the hepatoduodenal ligament for 15 minutes and reperfusion for 5 minutes seems to offer the best tolerance [15]. The hemihepatic or suprahilar selective (uni- or bisegmental) vascular occlusion technique may also be useful. The parenchymal dissection is performed along anatomic planes. Vessels and ducts are ligated using adsorbable clips, ultraligatures, and bipolar or argon coagulation. Ultrasonic dissection is of great help for isolating vessels in the liver parenchyma. Recently, waterjet dissection and ultracisor (Ultracision, Ethicon Endo-Surgery, Johnson & Johnson, Issy les Moulineaux, France) have also been used. Selective outflow clamping of hepatic veins (indicated for tumors that involve hepatic veins) offers the great advantage of preserving caval flow; it also avoids use of a venovenous bypass in case of hemodynamic instability, which may occur after clamping

tomy ($n = 3$), right ileocolectomy ($n = 2$), portal vein resection ($n = 2$), hepatic artery reconstruction ($n = 1$), total gastrectomy ($n = 1$), and small bowel resection ($n = 2$). Combined surgical techniques included radiofrequency ($n = 1$) and cryotherapy ($n = 1$).

No deaths occurred, and no reoperations were needed. The mean hospital stay was 20 days (range 13–37 days). The hormonal effect was complete in five patients and partial in one. The mean follow-up was 42 months (range 12–75 months). Ten patients were alive at the time of this study, and three had died from recurrent disease (18, 43, and 75 months after hepatic resection, respectively). The overall survivals at 3 and 6 years were 91% and 68%, respectively; and disease-free survival was 69% at 3 years.

French Multicentric Survey

During the same period 131 patients from 10 French centers underwent liver resection for metastatic neuroendocrine tumors. Among these patients 50% had more than three liver metastases, and major hepatic resection was performed in 43% of cases (57 patients). The mortality was 2.3% (3/13 patients) and the morbidity 17%. After liver resection, disease-free survival ranged from 3 to 120 months (mean 41 months), and the overall survival ranged from 3 to 132 months (mean 66 months).

Conclusions

Metastatic neuroendocrine tumors frequently cause severe endocrinopathies and cancer-related death. Surgical resection of these metastases can be performed safely. Significant prolonged survival, sometimes with definitive cure or at least with fast and complete palliation of symptoms, can be obtained.

Résumé

Les métastases hépatiques des tumeurs neuroendocrines sont habituellement de croissance lente et la chirurgie dite «cytoréductive» peut s'avérer efficace dans la suppression des endocrinopathies, augmentant ainsi l'espérance de vie et la survie sans symptômes. Cependant, la technique d'hépatectomie la plus sûre pour l'ablation de tumeur neuro-endocrine métastatique reste discutée. Cette étude rapporte les résultats de 13 patients porteurs de métastases hépatiques, opérés dans notre institution, ainsi que ceux d'une étude française multicentrique comprenant 131 patients. La sélection préopératoire des patients et la technique chirurgicale appropriée, parfois combinée avec une embolisation portale préopératoire et/ou une destruction tumorale locale (par radiofréquence et/ou cryothérapie) peut améliorer le taux de résécabilité et la sûreté du procédé. La mortalité après hépatectomie a été de 0% (2.3% dans l'étude française), les taux de survie à 3-et à 6 ans ont été de 91% et de 68% dans notre expérience alors que la survie moyenne a été de 66 mois dans l'étude nationale française. Ainsi une survie prolongée importante fent être obtenue par résection hépatique avec palliation complète des symptômes et une mortalité très faible.

Resumen

Las metástasis hepáticas de los tumores neuroendocrinos usualmente son de lento crecimiento; la cirugía citorreductora puede reducir las endocrinopatías y aumentar la expectativa de vida y la supervivencia asintomática. Sin embargo, es necesario investigarmás a fondo la forma de realizar con mayor seguridad la hepatectomía por metástasis de tumores neuroendocrinos. En este artículo se informan los resultados en 13 pacientes con metástasis neuroendocrinas del hígado intervenidos en nuestra institución, junto con los de un estudio francés multiinstitucional que incluyó 131 pacientes. La selección preoperatoria de los casos y una depurada técnica quirúrgica, en ocasiones combinada con embolización portal preoperatoria y/o destrucción tumoral (radiofrecuencia y crioterapia), pueden incrementar la posibilidad de resección y la seguridad del procedimiento. La mortalidad consecuente a la hepatectomía fue 0% (2.3% en el estudio francés), con tasas de supervivencia a 3 y 6 aöns en el estudio francés). Con la hepatectomía se puede lograr una supervivencia prolongada con paliación total de los sínotomas y muy baja mortalidad.

Acknowledgments

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