
Debulking of Extensive Neuroendocrine Liver Metastases

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Introduction

The incidence of neuroendocrine tumors (NET) primarily in the mid-gut, but also of the pancreas, has increased significantly over the past two decades. The cause for this increase in incidence is not clear. Patients with mid-gut NET may present with symptoms of diarrhea as well as flushing, but a large number of patients, despite volume disease and elevated secretory products, may be asymptomatic. Similarly, patients with pancreas NET often present as asymptomatic lesions of the liver. These malignancies frequently metastasize to the liver and nowhere else. Patients who die from this malignant disease typically succumb to liver failure.

Patients with NET metastatic to the liver frequency have large numbers of lesions distributed evenly throughout the liver. The approach to these patients surgically is very different from the approach employed in the more well-defined patient population of metastatic colorectal cancer to the liver. Specifically, in treatment of colon cancer metastasis, there are clear guidelines related to numbers of lesions as well as the importance of doing a negative margin resection. For debulking of metastatic neuroendocrine tumors to the liver, there is no limitation in terms of number of lesions, and it is not important to have negative margins. In fact, it is more appropriate to resect lesions right on their capsule. Also, it is felt that

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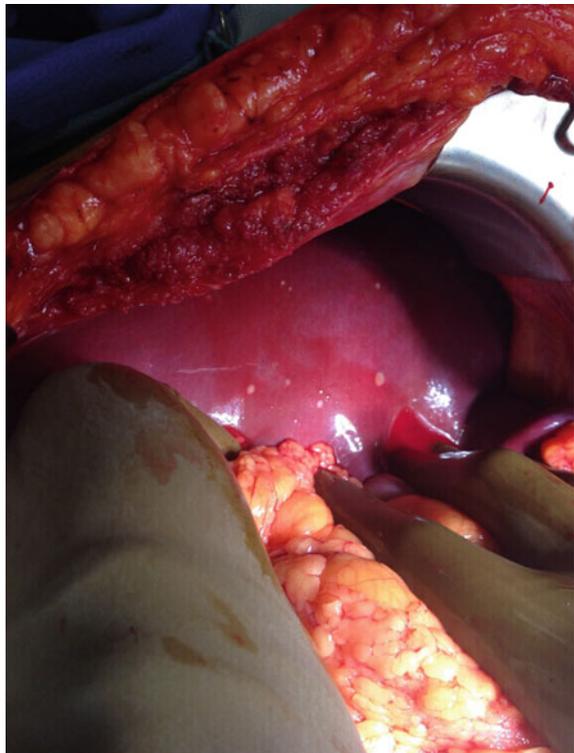
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surgical debulking is beneficial to patients even if up to 30% of the disease is not able to be treated.

Case 1: Mid-Gut Neuroendocrine Tumor Metastatic to the Liver

The patient is a 62-year-old man with a past history of papillary thyroid cancer 6 years earlier, in complete remission, who presented with flushing and a change in bowel habits with going from one bowel movement per day to two to three loose bowel movements per day. He had imaging with CT scan that showed a dominant 6 cm right inferior segment hepatic lesion, additional lesions up to 3 cm in the right hepatic lobe, a 3 cm caudate metastasis, and small lesions in the left liver (Fig. 2.1). The pancreas appeared normal, and the official reading said there was no evidence of any small bowel lymphadenopathy or lesions in the small intestine. A biopsy was performed of the large level 6 lesion and it showed a metastatic neuroendocrine tumor. Twenty-four hour urinary 5HIAA was elevated at 13 mg/24 h (upper limits of normal 7.5). He was treated with Sandostatin, with resolution of his flushing and improvement in his bowel function. No other efforts at treatment and no endoscopic

Fig. 2.1 Intraoperative picture of left lobe of liver in patient with metastatic small bowel NET to the liver. Large 8 cm lesion in inferior right lobe with other lesions in right lobe and caudate. Multiple small lesions in left liver make it clear that there is no curative option, and also demonstrates why right hepatectomy is not indicated due to extensive contralateral disease



studies were performed at an outside institution. An initial interval scan at 6 months showed an increase in size of his right segment 6 hepatic metastasis from 6 cm up to 8 cm. The remaining lesions were stable, and no new lesions appeared and there were no other findings. He was referred to our multidisciplinary neuroendocrine tumor group.

An octreoscan was obtained and it showed activity in the hepatic metastasis; no activity in the small bowel mesentery, small bowel, or pancreas. Serum serotonin was elevated at 1,433 ng/mL (normal range 85–220). We performed upper endoscopy and colonoscopy, which showed no lesions. He had a capsule endoscopy which was negative.

He was seen in surgical consultation and was recommended to have an exploration with liver debulking, including intraoperative identification of his mid-gut primary and planned resection. He had been receiving monthly Sandostatin injections, and an intravenous Sandostatin drip was prepared for infusion as needed for carcinoid storm. The approach was right subcostal incision with extension to the left side. The lateral aspects of the subcostal incision was not curved superiorly as is typical for right hepatic lobectomy, but rather went more inferiorly to allow exploration of the abdominal cavity for his primary to facilitate exploration of the abdominal cavity for a primary lesion. The initial part of the operation was to assess the primary. It was found immediately on palpation of the distal small bowel which was in the pelvis. The hepatic flexure of the colon and area of the ileo-cecal valve was completely mobilized with some tethering of the primary lesion and palpable lymph nodes in a loop of distal small bowel mesentery in the pelvis. This distal small bowel was brought up into the subcostal incision and there was careful palpation of the bowel from the ligament of Treitz to the ileocecal valve. The solitary lesion approximately 8 cm proximal to ileocecal valve was the only mass palpated. This had not been visualized by colonoscopy.

For mid-gut NET that are more than 20% proximal to the ileocecal valve, every effort is made to try to preserve the ileocecal valve and do a segmental small bowel resection. At this site and with the location of the lymph node metastasis necessitating resection of the right colic trunk, a right hemicolectomy with resection of segment of small bowel and nodal metastasis was performed with standard anastomosis. Once the bowel resection and anastomosis was completed, the retractors were completely shifted from exposing the lower aspect of the abdomen to exposing the liver. The liver was completely mobilized and assessed by palpation and intraoperative ultrasound. The dominant segment 6 lesion was easily felt, there were four to five additional lesions in the right lobe > 1 cm and a large palpable caudate mass. The left and right liver had multiple small palpable metastases (Fig. 2.2). A cholecystectomy was performed. In this case, it was not necessary to remove the gallbladder to address any of the hepatic nodules, but for patients with NET with a laparoscopic approach, or certainly with an open approach liver metastasis, it is mandatory to remove the gallbladder as long-term use of Sandostatin will lead to formation of gallstones and ability to approach the gallbladder laparoscopically is compromised after such an extensive hepatic debulking procedure. To address the dominant lesion in the right segment 6, the right hepatic lobe

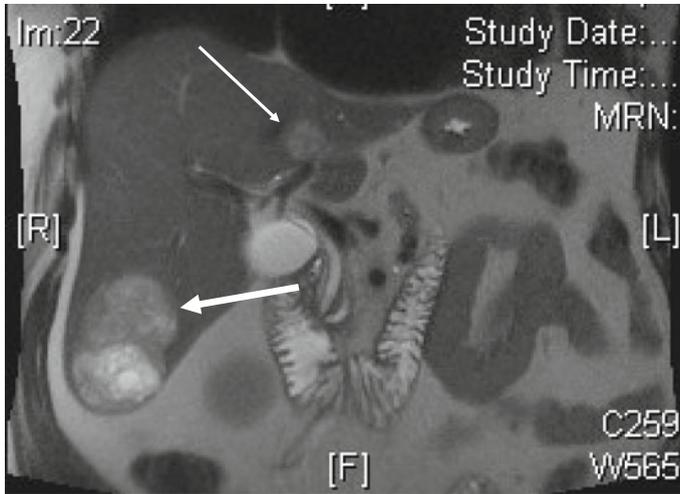


Fig. 2.2 Axial MRI of patient with metastatic NET to liver. Large right segment 6 lesion has grown significantly over 6-month interval (*large arrow*). Caudate lesion is second largest tumor (*small arrow*). At laparotomy, attempts were made to remove this lesion, but concerns over damaging left portal triad resulted in radiofrequency ablation of this tumor

was completely mobilized off the inferior vena cava. The feeding vasculature from the inferior segmental portal triad was assessed by surgeon-directed ultrasound and entered the lesion at the inferior medial border of this mass. The approach was to identify the margin of this large hepatic metastasis in a lateral avascular area. As is typical, it was firm, white, and once we were on the capsule either with blunt dissection with a finger or with a right angle, the surrounding parenchyma was swept away. When bridging vessels were seen, they were controlled with clips or Aquamontys ablation. Intraoperative ultrasound-guided dissection to where the main trunk was plastered over this and a vascular stapler was used to divide the main trunk. This large lesion was removed with very little surrounding parenchyma and very little blood loss (Fig. 2.3a). The cut parenchyma of the base was controlled with argon beam laser. All other small nodules were then addressed. Any nodule larger than 5 mm on the surface was resected with cautery and some exophytic lesions sharply resected with the base treated with cautery. Lesions just under the surface in the range of 1–3 cm had a circular incision made with cautery right over the palpable nodule. Once the white capsule of the nodule was identified, again blunt dissection either with the finger or right angle clamp was used to go around this often resecting 3 cm lesions in under 30 s. Several small 2–4 mm lesions were controlled with Aquamontys ablation on the surface with the typical popping noise (Fig. 2.3b). Ultrasound revealed two lesions, one in the caudate that was medially posterior to the main left segmental portal triad (Fig. 2.1) and a second lesion that was deep anterior to the right portal triad. An attempt was made to enucleate the caudate lesion, but it was too close to the main left portal structures.

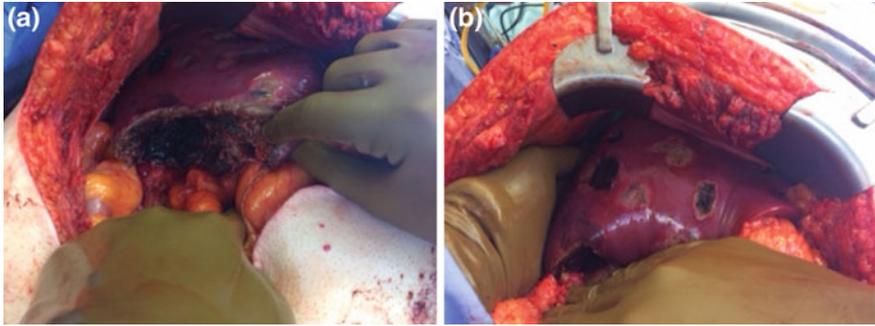


Fig. 2.3 Post-treatment photographs of patient with mid-gut NET. Panel **a** shows resection of 8 cm segment 6 lesion with hepatic parenchymal preservation. Panel **b** shows treatment of smaller lesions by enucleation (dark areas) or surface ablation (light areas)

These were treated with radiofrequency ablation with ultrasound guidance following standard ablation algorithms.

Postoperatively, the patient recovered with no significant change in hepatic functions postoperatively and was discharged on postoperative day 6 without complication. His pathology showed his small bowel lesion was a grade 1, 2.3 cm mass, solitary mid-gut primary with a Ki-67 of <1%. There were 4/22 lymph nodes with metastatic disease. All margins were negative. His large segment 6 lesion which at presentation had been 6 cm, was measured at 8.8 cm and had a Ki-67 of 9.7% with positive tumor margin as expected. There were five left liver nodules between 4 and 6 mm with Ki-67 of zero with no mitoses identified. There were 12 resected right hepatic nodules between 5 and 30 mm and had zero mitoses identified in these lesions.

This patient illustrates several aspects relevant to debulking of neuroendocrine lesions from a mid-gut primary. First, the patient had negative cross-sectional imaging and negative endoscopy in terms of the primary tumor in the terminal ileum and was labeled as an unknown or occult primary with extensive hepatic metastases. He had symptoms related to serotonin production and had an elevated 5HIAA. He had marked elevation of his serum serotonin, essentially confirming a mid-gut primary despite the negative imaging with colonoscopy, capsule endoscopy, and cross-sectional assessment of the bowel. Of note, his postoperative serotonin had dropped to near normal levels at 230 ng/mL. His primary lesion measured 2.3 cm in size despite the negative imaging, negative octreoscan, and negative capsule endoscopy. It was able to be palpated very easily on exposure of the bowel. This is very typical, and extensive efforts sometimes are costly to identify the primary and are not necessary with this clinical scenario. Also patients may sometimes be discouraged from undergoing surgical debulking of the hepatic metastases because of the occult primary and this should not be a hindrance, as again it can virtually always be identified by surgical exploration and treated simultaneously with debulking liver metastases.

The initial strategy employed for this patient was a watch and wait with Sandostatin and although the majority of the lesions in his liver remain stable, he had a solitary lesion increase from 6 to 8 cm that then was 8.8 cm at the time of resection. This is somewhat unusual, but prompted a referral to a tertiary center which led to this successful debulking. The final pathology demonstrated that specific lesion had an intermediate and almost high grade Ki-67 of 9.7%, whereas both the primary lesion and the other liver metastases had Ki-67 of <1%. Clearly a secondary mutation had occurred in this specific lesion, leading to its rapid growth, and also demonstrating the importance of removing that before it became too large or it had metastasized outside the liver. This patient has been followed for over 12 months with no clear new lesions appearing, with complete resolution of the symptoms, and no postoperative complications.

Technical Pearls for Debulking Liver Metastases from Neuroendocrine Tumors

- Utilize cross-sectional imaging CT with contrast or MRI scans to assess for extent of hepatic metastasis. Plan a procedure to do as much hepatic parenchymal preservation with enucleation of lesions instead of anatomic resection even for large metastases.
- Approach neuroendocrine liver metastases with a blunt dissection on the firm white capsule of the lesion with the right angle or sometimes finger dissection. Make no attempt to obtain any hepatic margin. Use the argon beam laser or other energy devices such as cautery at high level or Aquamantys to burn the cut surface of the liver.
- Utilize surgeon-directed intraoperative ultrasound to guide resection of deeper nodules. Frequent use of ultrasound can identify approaches to lesions that are not even palpable in a vascular space, and then employ the blunt dissection technique once the metastasis is visualized to do an extraction.
- Reserve segmental resections for clusters of nodules at the lateral tip of the left lateral segment 2/3 or inferior right liver segment 6. Formal lobectomy is infrequently indicated due to distribution of metastases
- Use ablative techniques for deep lesions next to central portal structures in radiofrequency ablation and microwave ablation. Use energy such as high-level cautery or Aquamantys to burn surface nodules 4 mm or less and expect a popping sound as these are burned.

Case 2: Pancreas NET Metastatic to Liver

The patient is a 52-year-old man who worked at a steel mill and had a back injury. As part of his imaging for this injury he had an abdominal CT, which showed over 25 liver metastases in a bilobar distribution up to 3–4 cm in size and a 4 cm tail of the pancreas mass (Fig. 2.4a). Despite this bulky disease, his liver functions were completely normal. He had absolutely no abdominal or back pain related to his tumor burden. He had a percutaneous biopsy of a liver lesion which showed low-grade NET. He started on monthly long-acting Sandostatin shots and was treated with Everolimus. He had an interval 4-month scan which showed some progression of liver nodules. He underwent sequential bilobar Yttrium-90 embolizations and had a >80% response in his disease.

He sought out our multidisciplinary tumor group as his tertiary center, where he had been receiving treatment who did not recommend surgical debulking. At the time he was seen, it was an interval of 3–4 months after his radio-embolization and a repeat scan showed fairly significant progression back to the levels they were prior to embolization. On physical examination he looked completely healthy and well nourished and had absolutely no symptoms. The disease seemed to be almost too extensive to do a meaningful debulking, so he underwent another set of very closely spaced Yttrium-90 radio-embolizations at his home institution. He had a planned surgery date 3 weeks after the second one and he had a scan just 2 days prior to the surgery with another remarkable response again of >80% decrease in size of his bilobar lesions (Fig. 2.4b). His pancreas lesion has been stable throughout.

He was approached with a bilateral subcostal incision. He had two segmental resections, one of segment 2 in the left lateral area, where there was probably a

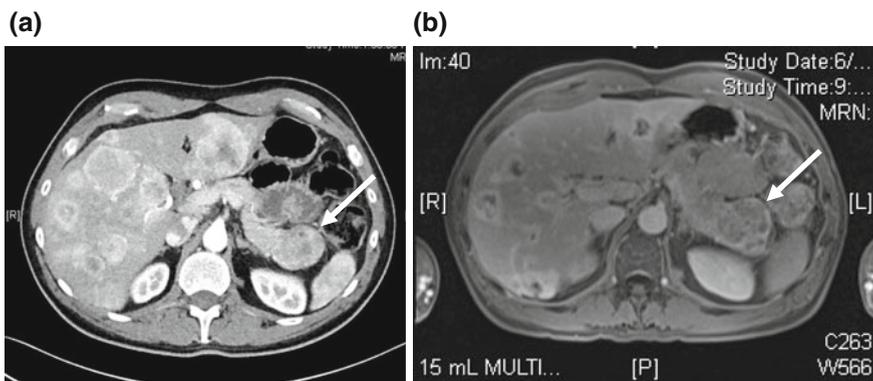


Fig. 2.4 Pretreatment and post-treatment CT and MRI of patient with metastatic pancreatic NET to liver. The patient had 5 cm primary in tail of pancreas (*arrow*) and large bilobar liver metastases (Panel **a**). After Yttrium-90 the liver lesions had an 80% response and appear necrotic (Panel **b**). The patient underwent distal pancreatectomy for the PNET primary and debulking of >95% of hepatic disease with no surgical complications

dozen tumor nodules all clustered, and another one in segment 5/6, with multiple tumor nodules. The other lesions were treated with enucleation on the capsule of the lesion, as well as five lesions treated with radiofrequency ablation by ultrasound guidance. He underwent a distal pancreatectomy with no evidence of extrapancreatic spread from his primary lesion. He did well postoperatively and was discharged on postoperative day 5 and flew across country back to his home institution on postoperative day 7. His pathology showed a well-differentiated intermediate-grade pancreas neuroendocrine tumor, 5.4 cm in size, with a Ki-67 of 5.9%. There was perineural invasion and lymphatic invasion, but there were 0/12 lymph nodes with metastasis. His left lateral partial hepatectomy showed more than 12 nodules between 4 mm and 21 mm, with 25% of the tumor viable. Similarly, his right inferior partial hepatectomy showed over 15 nodules between 4 and 20 mm, somewhat diffuse, with 20% of the tumor viable. He had over 10 left hepatic metastases resected between 4 and 24 mm, and over 15 right hepatic metastases resected between 4 and 25 mm.

This patient had removal of his primary, and probably debulking of greater than 95% of hepatic lesions with zero blood loss and completely normal hepatic functions postoperatively. Although the number of nodules were too great to completely render him disease-free, all of the Ki-67 indices in the liver metastases in the viable components were <2%, and the majority of these had been stable. Removing his intermediate-grade primary lesions to prevent further metastases and debulking of this large number of low-grade slow-growing lesions with an operation that causes minimal morbidity should improve his overall survival.

This case demonstrates the utilization of nonsurgical treatments to address bulky liver metastases, specifically in this case radio-embolization to optimally debulk with appropriate timing between the interventional radiology treatment and the surgical treatment.

These two cases illustrate that for the appropriately prepared patient, significant and sometimes bulky liver disease can be safely resected/ablated with minimal morbidity. If the primary is in place, this too can be safely resected at the time of liver debulking. Multiple lesions can be safely enucleated and segmental or sector resections should be reserved for areas of the liver where maximal debulking can be safely accomplished and the number of lesions exceeds that which can safely be enucleated. With the advent of systemic therapies that have shown activity for established disease, it may be possible to prolong the progression-free survival following maximal debulking of liver metastases.

Alternative Approach/Controversies in Management of Neuroendocrine Liver Metastases

- For extensive liver lesions with pathologically proven low Ki-67 (<2%), a “watch and wait” approach may be appropriate to assess the rate of growth supplemented by long-acting Sandostatin. Asymptomatic patients may be

followed with serial examinations for years with minimal change and good quality of life.

- Utilize interventional radiology techniques prior to surgery to decrease the bulk of disease and facilitate surgical debulking. Specifically, bland embolization, TACE, or intra-arterial injection of radiospheres may lead to significant responses with appropriately timed surgical debulking.
- Utilize interventional radiology techniques such as percutaneous radiofrequency or microwave ablation or alcohol injection for residual or recurrent disease after extensive tumor debulking.

Overall Management of Patients with Extensive Neuroendocrine Hepatic Metastasis

- For patients with numerous bilobar lesions in the liver at presentation, a complete cure is unrealistic. Plan treatment strategies to maximize overall survival and minimize morbidity from the neuroendocrine tumor.
- For incurable patients, hepatic debulking may significantly increase the overall survival and may significantly increase the quality of life due to a decreased amount of secretory products from the neuroendocrine metastasis.
- Patients with extensive neuroendocrine metastases frequently present with unknown primaries. The most common location of the primary is mid-gut NET, and the second most common area is pancreas NET. Occasionally, patients present with chest NET or gastric carcinoids with bulky liver lesions. Work-up should include MRI/EUS for evaluation of pancreas, and a chest CT with the stomach assessed at the time of EUS. If all these studies are negative, virtually all patients have a mid-gut NET that can easily be felt and resected at the time of liver debulking. Assess cross-sectional imaging looking for distortion of the mesentery due to nodal metastases that are much more commonly visible than the primary NET in the small bowel.
- Utilize secretory products to assess for progression of disease as well as to assess the success of debulking treatment. Specifically, serum serotonin is far more reliable than chromogranin A for a marker for mid-gut carcinoid.
- Utilize nuclear medicine imaging including Indium octreoscan, MIBG, and gallium scan if available to look primarily for nonhepatic metastasis frequently occurring in bone or other unusual places.

Conclusion

In conclusion, surgical resection of metastatic neuroendocrine tumors to the liver is a completely different procedure than any other liver resection, and different than almost any resection for abdominal malignancy. Metastatic NET are basically “shucked out” on the margin of the tumor, with no attempt to get negative margins. Patients who would never be considered to be surgical candidates for any other type of malignancy can benefit from surgical debulking. It is imperative that this group of patients have their liver imaging reviewed by surgeons experienced in treatment of neuroendocrine tumors.

Treatment of Neuroendocrine Liver Metastases

1. Assess the volume and number of tumors on cross-sectional imaging.
 - a. Volume of metastatic lesions up to 50% of the overall liver volume may be debulked.
 - b. The number of lesions is not prohibitive if there is satisfactory residual hepatic parenchyma.
 - c. Goal may be to remove at least 70% (for mid-gut NET) and >90% to select pancreas NET.
2. Identify the primary NET and make plans to resect
 - a. For mid-gut NET:
 - i. Do segmental small bowel resection or right colectomy
 - ii. Palpate for multifocal primary lesion (>35%)
 - iii. Preserve the ileo-cecal valve if possible
 - iv. Remove bulky root of mesentery lymph nodes by resecting off vessels
 - b. For pancreas NET:
 - i. Distal pancreatectomy/splenectomy for body and tail pancreas PNET
 - ii. Assess head/uncertain primary PNET for well-defined margins and enucleate if a reasonable margin from the main pancreatic duct
 - iii. Consider pancreatico-duodenectomy for select patients (young, no co-morbidities) with complete excision of liver metastases.

c. Occult primary:

- i. Chest CT to rule out bronchial/thymic carcinoid.
- ii. EGD to rule out gastric and EUS/MRI to evaluate the liver. Carefully examine small bowel mesentery for signs of mid-gut carcinoid.
- iii. If all negative, palpate small bowel for primary mid-gut carcinoid.

3. Resection/Ablation of liver metastases

- a. Incision virtually along bilateral subcostal to allow mobilization of right lobe of liver.
- b. Assess deep lesions with IOUS.
- c. Plan resection ablation to normal hepatic parenchyma.
 - i. Enucleate any lesion away from major portal triad structures and major hepatic vein branches.
 - ii. Dissect bluntly right on the capsule of the metastasis
 - iii. Ablate deep lesions near major vessels
- d. Perform prophylactic cholecystectomy as patients will be on long-acting sandostatin
- e. For mid-gut NET have infusion of sandostatin available to prevent carcinoid crisis



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