

Surgical treatment of liver metastases in patients with neuroendocrine tumors

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Abstract: Liver metastases occur in 75% to 80% of patients with neuroendocrine tumors (NETs), and are considered significant adverse prognostic indicators. Management of NETs liver metastases is challenging and requires aggressive therapy. Currently, there are many therapeutic options for metastatic NETs. However, there is considerable controversy regarding the optimal management. Although complete surgical resection remains the optimal therapy, a variety of other minimally invasive surgical and medical options are available, this includes thermal ablative techniques (e.g., radiofrequency ablation, microwave ablation, cryotherapy), embolization using transcatheter embolization, chemoembolization, or radioembolization, and medical therapy (e.g., chemotherapy, biotherapy with somatostatin analogues and interferon). Currently there is no evidence-based data directly comparing surgical versus alternative liver-directed treatment options. An aggressive surgical approach, coupled with additional liver-directed procedures is often recommended as it extends the overall survival. Optimal patient care should be directed by a multidisciplinary team to assure that all treatment options are explored for decision-making while treating this aggressive disease.

Key Words: Neuroendocrine tumor; liver metastases; laparoscopic resection; neuroendocrine carcinoma



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Introduction

Neuroendocrine tumors (NETs) are slow growing heterogeneous neoplasms, which are generally viewed with a favorable prognosis. This group of heterogeneous neoplasms defined as either non-functioning tumors often associated with liver metastases at the time of diagnosis, or functioning tumors that secrete peptide hormones. These hormones could cause characteristic patterns of symptoms, like flushing, diarrhea, and palpitation. NETs are comparatively uncommon, with an incidence range from 2.5 to 5.3 per 100,000 (1). Primarily, NETs arise from the gastro-entero-pancreatic neuroendocrine tract. Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) can be either carcinoid tumors, which arise from the endocrine cells of the gastrointestinal tract, or pancreatic neuroendocrine tumors (2).

In 2010, World Health Organization (WHO) and Tumor

Node Metastases (TNM) staging system of the European Neuroendocrine Tumor society (ENETS) and American Joint Committee on Cancer (AJCC) acknowledged a new classification system which identified three classes of tumors (G1, G2, G3) as defined by proliferative index (assessed by mitotic index and/or Ki 67). While the majority of NETs are recognized as well-differentiated tumors (G1, G2), neuroendocrine carcinomas belong to G3 category (3).

After the lymph nodes, the liver is the predominant site for NETs metastases. Synchronous liver metastases present in 75-80% of patients, which is a key adverse prognostic factor. When it is feasible, aggressive surgical management of both the primary tumor and the liver metastases improve overall survival rates extensively (4-6). Primary hepatic neuroendocrine tumors are extremely rare, and are diagnosed by exclusion of other primary tumors. As with metastases, the main treatment of primary hepatic NETs is

surgical resection (7,8).

Currently, there are many therapeutic options for metastatic NETs. This includes surgery (e.g., open resection, laparoscopic resection, liver transplant), medical therapy (e.g., chemotherapy, biotherapy with somatostatin analogues and interferon, thermal ablative techniques (e.g., radiofrequency ablation (RFA), microwave ablation, cryotherapy) and embolization using transcatheter embolization, chemoembolization, or radioembolization.

RFA is a palliative option aiming at debulking and controlling hormonal symptoms. Accordingly, Laparoscopic RFA was suggested when other treatment modalities including chemotherapy, somatostatin analogues, chemoembolization, and resection failed. *Akyildiz et al.* reported one of the largest prospective experiences with radiofrequency ablation of neuroendocrine liver metastases. *Akyildiz* recommended selection criteria for this study include maximum tumor size of 10 cm, maximum number of tumors of fifteen, and less than 20% liver involvement. Symptom relief was achieved in 97% of all patients treated with laparoscopic RFA (9). Additionally, *Berber et Siperstein* demonstrated that there was no significant increase in the morbidity with repeat ablation cases. This supports the concept that laparoscopic RFA can be performed in a repeated fashion in the case of recurrence (10).

In addition to histopathological analysis and clinical assessment, biochemical profile plays a major role in the NETs diagnosis. Serum 5-hydroxyindoleacetic acid (5-HIAA) a product of serotonin breakdown can be measured in a urine sample obtained over 24 hours, it is highly specific for NETs. However, 5-HIAA levels insensitivity necessitate measurement of other circulating peptide hormones such as Chromogranin A, Chromogranin A is 100% specific and highly sensitive marker for NETs (11-13). On the other hand, specific tumors are characterized with specific hormones such as pancreatic insulinoma, which is associated with elevated levels of Insulin and c-peptide; this is true as well in case of gastrinoma and Gastrin. Other markers are common to all NETs, such as synaptophysin, neuron-specific enolase (NSE) and calcitonin (4,14,15).

Imaging techniques have a significant role in the diagnosis and management of patients with liver metastases, this includes somatostatin receptor scintigraphy, CT scan and MR imaging. These techniques help in detecting the presence of liver metastases estimating the mass characteristics, distribution, and location to major vessels. Unfortunately, all of these techniques were unsuccessful to identify undersized liver metastases (i.e., tumors <0.5 cm in diameter).

This discussion focuses on surgical treatments of NETs liver metastases and examines all forms of surgical resection, as well as liver transplantation.

Open surgical resection

In general, NETs patients with liver metastasis present in one of two manners: (I) considerable liver disease with carcinoid syndrome in need of debulking or (II) limited disease potentially curable with aggressive curative resection. Numerous studies have confirmed complete hepatic resection for liver metastases has significantly improved long-term survival compared to other conservative treatments (5,6,16-18).

Aggressive surgical resection increases the 5-year survival of NETs with solitary liver metastasis to 100%. Where disseminated metastatic NETs suffer a 51% 5-year survival rate after surgical resection (19). Multiple factors including primary tumor site, histological grade and metastatic sites other than liver play a major role in the overall survival (20,21). The surgical approach used depends on the distribution of metastases. In unilobar metastasis, resection of the primary tumor and liver metastasis can be completed synchronously, while bilobar metastasis often requires incomplete left lobe resection and right portal vein ligation, followed by right lobe resection in a two-step approach (22).

Resection of the primary tumor and the adjacent mesenteric lymph nodes confer significant increases in the survival rate. The principle concern over aggressive surgery is patient safety, hepatectomy in conjunction with abdominal resections can be associated with significant morbidity and mortality especially synchronous pancreatectomy (23). Improved survival has been reported by *Hill et al.* when liver resection is coupled with pancreatic NETs resection. However this study has been criticized for significant selection bias (24).

Significant reductions in biomarkers are associated with symptoms relief and disease control. However, in case of multiple non-resectable hepatic metastases, no clinical trial advocates surgery over other modalities. Additionally, disease recurrence was reported after hepatic metastasis resection (25).

Operative management with SSAs is indicated to avoid intra and post-operative carcinoid crisis. This is especially critical in the case of metastatic functioning tumors often characterized by carcinoid syndrome (26).

Prophylactic cholecystectomy during abdominal exploration is indicated in NETs patients with liver metastases. This strategy is indicated to avoid gallstones

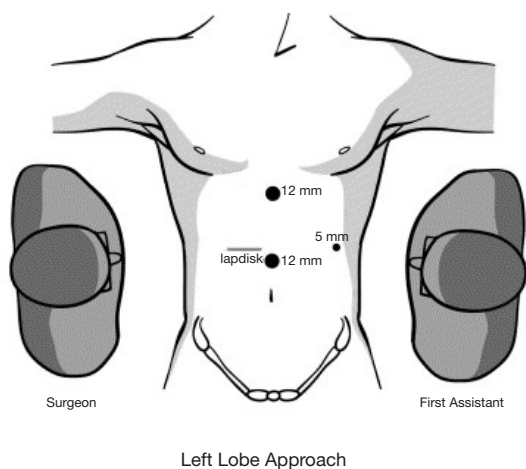


Figure 1 Port placement and surgeon positioning for laparoscopic liver resection (left-sided resection)

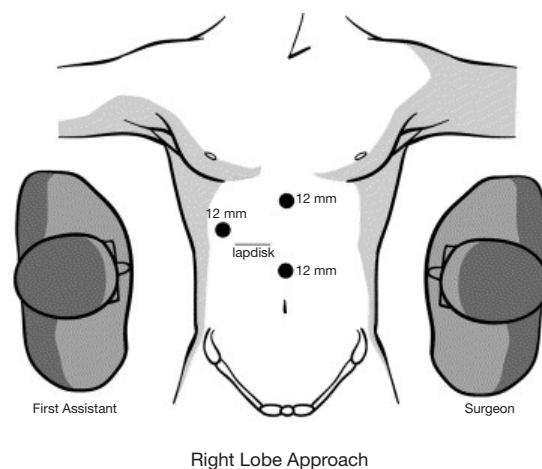


Figure 2 Port placement and surgeon positioning during laparoscopic liver resection (right-sided resection)

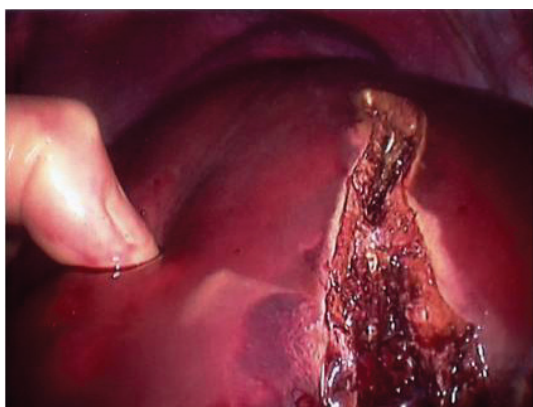


Figure 3 The use of an ultrasonic dissector to incise Glisson's capsule before major hepatic transection is essential before placement of endovascular staplers

associated with somatostatin long-term treatment, and prevent gallbladder necrosis due to hepatic artery embolization for liver metastases (27).

Minimally invasive laparoscopic surgery

Obesity and fatty liver are often considered major obstacles in metastatic hepatic NETs surgical resection. Metastatic lesions are frequently numerous and extremely vascular, more than 90% of liver Metastatic lesions are supplied by the hepatic artery, making resection more technically challenging. This might explain the trend toward less invasive approaches to metastatic liver NET tumors such as

arterial embolization (28,29).

Laparoscopic liver resection has become the preferred surgical approach for many surgeons because of shorter operative time, decreased blood loss, and lesser blood transfusion, moreover, overall hospital stay was also drastically reduced, proving an earlier improvement and resumption of physiological functions (30-32). This is most notable in obese patients. Secondly, laparoscopic hepatectomy has been shown to be oncologically sound with equivalence to open surgery (32).

In laparoscopic liver resection the surgeons should maintain positions on opposite sides of the patient. In the case of left-sided tumors, the primary surgeon is on the patient's right side. This position allows the primary surgeon to place his right hand under the left lateral segment, which allows inferior retraction of the liver for incision and division of the coronary attachments. The hand-assist device is inserted in the right midabdominal quadrant adjacent to the midline port (*Figure 1*). During right hepatic resections, hand-assist port placement is in a more superior and lateral position, and the surgeon is positioned on the patient's left side and inserts his left hand (*Figure 2*). Selective vascular isolation is achieved through the stapler hepatectomy. During resection, the liver capsule is incised and the thickness of the parenchyma reduced with an ultrasonic dissector or tissuelink device (*Figure 3*). Once the initial 2 cm of the parenchyma is incised, the remaining resection is completed with an endovascular stapler. Homeostasis is subsequently achieved with an argon beam and completed with the use of biologic glues.

Recently, we have published our experience comparing laparoscopic to open liver resection for the management of NET liver metastases. Laparoscopic liver resection has a lower recurrence rate, 27% at mean interval of 14 months compared to 47% at a mean interval of 15.9 months in open resection. Laparoscopic resection has shorter operative time and hospital stays. The overall 3-year survival and 3-year disease free survival rate for the laparoscopic group 100% and 73.3%, respectively. Complications were lower in laparoscopic group compared to the open surgery group. In addition, laparoscopic surgery is considered safe and feasible in case of major, minor, atypical and even redo hepatectomy. However, metastases should not be more than four in number, and not require an extended hepatectomy to achieve negative margins (33).

Liver transplant

Liver transplantation should be considered another surgical option when both surgical and medical treatment fails to eradicate disease (34,35). Unfortunately, mortality after liver transplantations from recurrent liver disease remains a major concern. The five-year recurrence-free rates vary from 25-50% (36). Liver transplantation is a feasible option for young patients (<50 years old) with unresectable tumor, low ki-67 index and no extra-hepatic disease (15,37). Suspicious extra-hepatic lesions should be evaluated using exploratory laparoscopy or laparotomy prior to proceeding to liver transplant.

The primary tumor and lymph nodes must be resected before liver transplant. This will help to evade the high perioperative risks related to coupling of pancreatic or intestinal resections with the transplant operation (36,38). Furthermore, earlier primary tumor resection helps determining histopathological characteristics of the NET including Ki-67 index, and degree of differentiation, which are significant to patient selection for transplantation. Patients selection criteria includes patients with low grade tumor, G1, ten-percent or less Ki-67 index and 2 or less mitoses per high-power field (39).

Intractable carcinoid syndrome and hepatic failure Symptoms are all indications for liver transplantation. However, the selection criteria for transplantation should assure clinical improvement. Consequently, the improvement in patient's quality of life must exceed the considerable risks of both the liver transplant and the immunosuppression (36,40,41).

Even though Chemotherapeutics, arterial embolization,

and aggressive surgery for recurrent tumor may improve the survival rates (42), given the demand for donor organs and the need of fair selection criteria, liver transplantation is controversial (41).

Conclusions

There are a number of surgical options available for the treatment of NETs liver metastases. The choice of treatment depends on the symptoms, distribution of the metastases, and the histological features of the tumor. Nevertheless, there is no evidence-based data comparing surgery versus other liver-directed treatment options such as thermal ablation techniques, embolization, and somatostatin analogues in the management of patients with metastatic NETs. The future appears more encouraging with variable treatment options. Although aggressive surgical resection remains the gold standard for management, the laparoscopic option by experienced laparoscopic liver surgeons can be safe, feasible and provides earlier recovery and fewer complications. However, patients should be managed under the supervision of a multidisciplinary team to guarantee that all treatment options are explored both at diagnosis and follow-up.

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