Liver Surgery for Neuroendocrine Tumors

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20.1 Introduction

Neuroendocrine tumors (NETs) comprise approximately 10% of metastatic liver lesions. Formal hepatic lobectomy is rarely indicated because approximately 80–90% of metastases are multifocal and bilateral. The most frequent cause of death in patients with metastatic NETs is liver failure resulting from hepatic replacement by tumor [1, 2]. Five-year survival in patients with liver metastases has been reported at 30–50%, but 5- and 10-year survival rates greater than 80% can be achieved with aggressive surgical and multimodal therapy [3]. The goals of therapy should be prolongation of survival, objective tumor control, symptom control and biochemical control of functional tumors, and improvement in quality of life. Hepatic cytoreductive surgery performed for a curative or palliative intent can provide long-lasting benefit.

Because most metastases are bilateral, formal hepatic lobectomies are rare. To preserve the maximum amount of normal hepatic tissue, multiple segmentectomies or subsegmentectomies are more commonly performed. Nonanatomical metastectomies, enucleation, radiofrequency or microwave ablation, and irreversible electroporation are also used to cytoreduce tumor burden, either singly or in combination. Selectively, liver transplantation may be an option if extrahepatic disease can be controlled or eliminated. Multivisceral transplants (en bloc liver, stomach, intestine, and pancreas) are now being performed for metastatic disease at the mesenteric root with liver and pancreatic metastases.

The choice of specific technique and its timing should be ascertained by a multidisciplinary consensus when evaluating the patient with liver metastases [2, 4]. Every effort should be made to resect the primary tumor initially or at the time of liver resection. A certain percentage of patients with “unknown primaries” will have their primary discovered at the time of liver resection. Simultaneous resection of the primary tumor should be performed in healthy patients. In patients with advanced disease who have intestinal obstruction and/or ischemia and malnutrition, the intestinal obstruction and intestinal ischemia should be addressed first. After nutritional rescue, the patient may then safely undergo major hepatic cytoreduction [2].

Selection criteria for surgical resection should include having less than 50% of the liver parenchyma involved with tumor. The presence of tumor abutting or encircling vascular or biliary structures is not an absolute contraindication to surgery. Many times the tumors will displace these structures without invasion. When major vascular or biliary structures are encased, we have successfully used irreversible electroporation (IRE) to avoid collateral damage from the heat generation that occurs with radiofrequency ablation or microwave energy. Radiofrequency ablation, microwave ablation, or IRE is best reserved for tumors 3 cm or less in diameter [3].

Preoperative preparation is critical to successful hepatic surgery in patients with functional NETs. A relative contraindication to liver resection is the presence of right-sided heart failure, a condition more likely to occur in patients with carcinoid syndrome and elevated 5-hydroxyindoleacetic acid (5HIAA) levels. In addition to addressing malnutrition and fluid and electrolyte losses from the gastrointestinal tract, attention must be given to the prevention of carcinoid crisis intraoperatively. Manipulation of a functional serotonin-producing tumor can lead to cardiovascular collapse unless somatostatin analogue blockade is initiated preoperatively. We recommend an intravenous bolus of octreotide (250–500 μg) followed by a continuous infusion of 250–500 μg per hour. Using this protocol, we have limited the incidence of carcinoid-induced hypotension to less than 3% in our last 220 liver resections [5]. Volume expansion, antihistamines, H2 blockers, and steroids serve as adjuncts to block the serotonin response intraoperatively, and they can also reduce carcinoid-induced asthma [2]. We recommend avoiding vasopressors such as epinephrine, which can precipitate massive serotonin release and irreversible carcinoid crisis. We have successfully used low-dose dopamine, vasopressin, and

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phenylephrine hydrochloride (Neo-Synephrine) when pressor support was required after the initiation of high-dose octreotide therapy.

In cases of bilobar disease, there usually will be several dominant, large lesions and several smaller lesions. In an effort to achieve at least a 70–90% debulking, the larger lesions can be individually excised and the smaller lesions (usually less than 3 cm) can be treated with radiofrequency ablation or IRE. In the case of a diminutive left lobe, a staged procedure is used. The left lobe can be debulked initially and the right portal vein embolized, causing some regression of the right hepatic lobe and hemihypertrophy of the left, followed by resection of the right hepatic lobe 6 weeks after embolization [4].

20.2 Radiofrequency Ablation and Microwave Ablation

Although the wavelength energies are different, we will consider radiofrequency ablation (RFA) and microwave ablation together. Both rely on high-frequency (radio wavelength) alternating current to generate heat in excess of 100 °C in a defined space dictated by the "antenna" probe placed directly into the tumor. We use this technology when faced with small tumors (3 cm or less) deep within the hepatic parenchyma, to spare normal hepatic tissue that would otherwise be lost by a large resection. We use this method when the tumors are not near hilar structures, in order to avoid collateral heat injury to those areas.

The RFA needle is typically placed under ultrasound guidance, and the tines are deployed to the desired length depending upon lesion size and desired margin (Figs. 20.1 and 20.2). After ablation, we retract the tines, rotate the probe 45°, redeploy, and repeat the ablation to increase cell killing in all fields defined by the probe. Track ablation is used as the needle is withdrawn to achieve hemostasis and decrease the risk of seeding along the needle track.

Microwave ablation uses a different probe with a slightly larger diameter (14 gauge *vs* 18 gauge) with a single straight needle; no tines are deployed. The size of the ablation is directly related to the length of time the device is energized and the power setting. A longer ablation time means a larger zone of ablation. Some manufacturers also provide for ablation of the track as the needle is removed.

The main limitations of both technologies are size and location of tumors near vital structures within the liver. It is difficult to achieve complete killing in tumors larger than 3 cm, and when ablations are performed near larger blood vessels, a heat sink phenomenon can occur. The rapid flow of blood near an ablation site will cool the tissue to sublethal temperatures, and incomplete killing may occur. The phenomenon occurs more commonly with RFA, while microwave tends to continue to heat (and potentially injure or destroy) these blood vessels and associated bile ducts. One can at least partially prevent this heat sink effect by using the Pringle maneuver during ablation to obtain more even heat distribution. We usually pretreat the patient with mannitol and induce a brisk diuresis prior to ablation to minimize renal injury from tumor lysis syndrome. If multiple ablations are performed, the patient's core temperature may rise considerably and the heating blanket must be turned off. Postablation scanning usually displays avascular lesions remaining within the liver (Fig. 20.3).

Figure 20.1

Radiofrequency ablation (RFA). (**a**) Probe being advanced into the lesion, usually under ultrasound guidance. (**b**) Deploying the tines to the just beyond the edges of the lesion. (**c**) Zone of ablation extending beyond the tumor

20.3 Irreversible Electroporation

Irreversible electroporation (IRE) is a new technology that uses very high voltage (1500 V/m^2) at very low direct current (nanoamperes) passing through tissue between the positive and negative electrodes for multiple brief pulses (nanoseconds). The flow of electricity creates irreparable holes in cell membranes, inducing apoptosis. This technique does not produce heat or destroy stromal framework, so it is desirable for use near intrahepatic blood vessels and bile ducts, where significant heat generation would produce collateral damage. Normal bile duct and endothelial cells repopulate along the remaining stromal framework. We employ IRE (NanoKnife®, AngioDynamics, Latham, NY, USA) when RFA would be too close to hilar structures to avoid damage to main bile ducts, usually for tumors of 3 cm or less. Two to four electrodes are placed into or near the tumor to create an electric current field of sufficient size to ablate the tumor (Fig. 20.4a).

Ultrasound or CT guidance is used to place the 18-gauge needles (Fig. 20.4b). It is important to place the electrodes parallel to each other in multiple planes to produce the desired current flow and maintain uniform tissue impedance. Placing needles 2.5 cm apart appears to be optimum spacing (Fig. 20.4c). It is also important to place the electrodes parallel to major vascular structures so as not to traverse the lumens with the needles, which will increase the risk of post-procedure thrombosis.

20.4 Tumor Enucleation

Often midgut NETs metastatic to the liver are surrounded by a pseudocapsule, and these tumors are very dense. They can be enucleated (Figs. 20.5 and 20.6) by crushing the hepatic parenchyma near the tumor with a hemostat, clipping the feeding structures with fine hemoclips, and tying the larger vessels prior to division. Alternatively, an energy resective device such as the LigaSure™ (Medtronic–Covidien, Minneapolis, MA, USA) can be used. Enucleation preserves the greatest amount of normal intervening liver and is useful for multiple or single superficial tumors of the liver. It also can be done laparoscopically. Despite positive margins of resection, recurrence rates remain low using this technique.

20.5 Segmental and Lobar Resections

More formal segmental or lobar resections are performed along the Couinaud resection lines (Fig. 20.7a) following the venous system. Ultrasound is used to note the location of the veins within the liver. The larger trunks are not amenable to sealing and dividing with the energy devices currently available (LigaSure™; Harmonic® scalpel, Ethicon Endo-Surgery, Cincinnati, OH; Aquamantys®, Medtronic, Minneapolis, MN), but the smaller branches entering the segments can usually be adequately sealed with these devices. The crush and clip or tie technique and/or an energy device is used to divide the hepatic parenchyma. Liver compression sutures of 2-0 chromic on a blunt needle are used as an adjunct for hemostasis along resection lines (Fig. 20.7b). Intraoperative ultrasound should be employed to map out the larger vascular structures; these can be divided with the endoscopic vascular stapler inserted directly into the hepatic parenchyma (Fig. 20.7c), or by conventional suture ligature. This technique is best applied to superficial lesions. Despite tumor cells at the margin, recurrence rates are generally low.

Figure 20.1

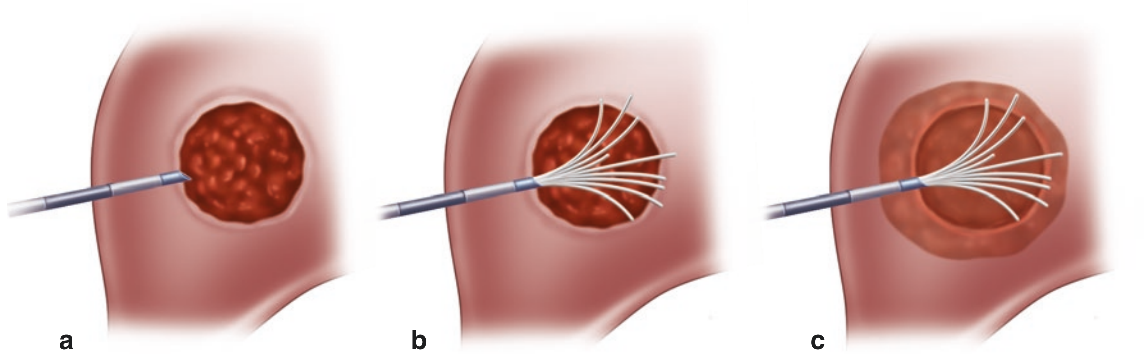


Figure 20.2

Image obtained under ultrasound during radiofrequency ablation. Note the needle advanced into the tumor in the posterior portion of the liver, with the white portion being the area within the tumor that has reached >100 °C

Figure 20.3

CT images of necrotic avascular tumors after RFA

Figure 20.2

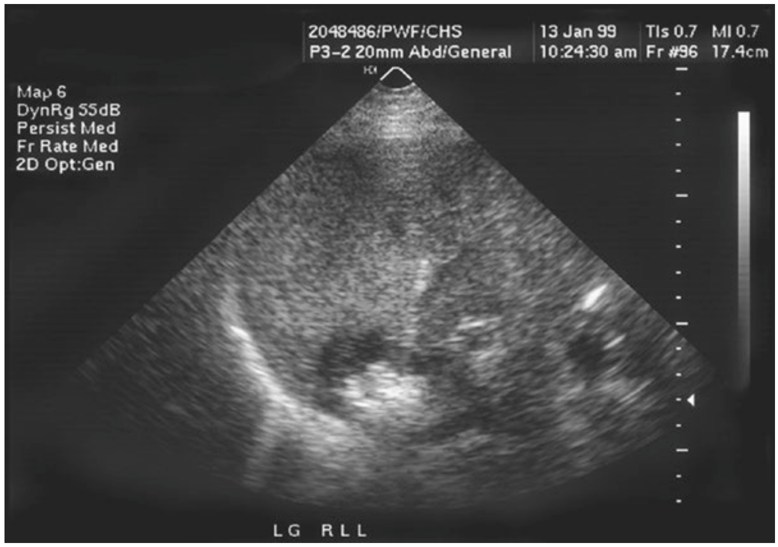


Figure 20.3

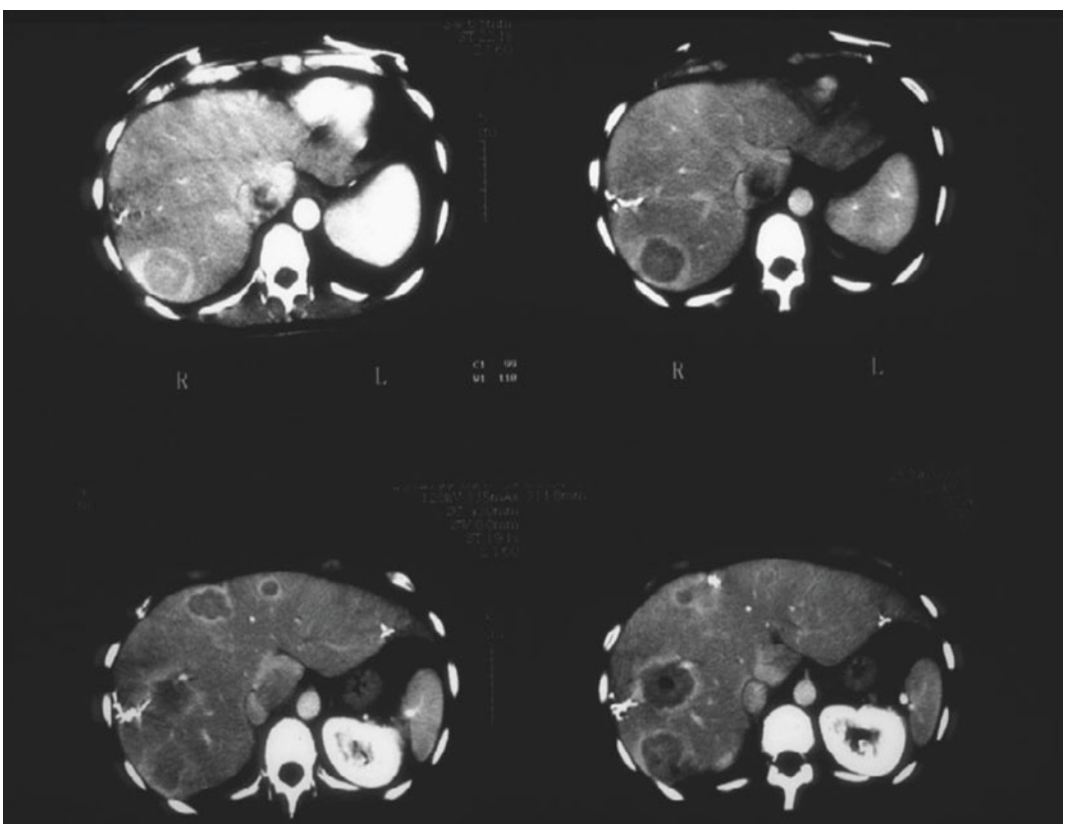


Figure 20.4

(**a**) Irreversible electroporation (IRE) electric field generated around the tumor. (**b**) Initial needle placement seen on CT scan for percutaneous technique. (**c**) Needle spacing

Figure 20.5

Neuroendocrine tumor (NET) after enucleation

Figure 20.4

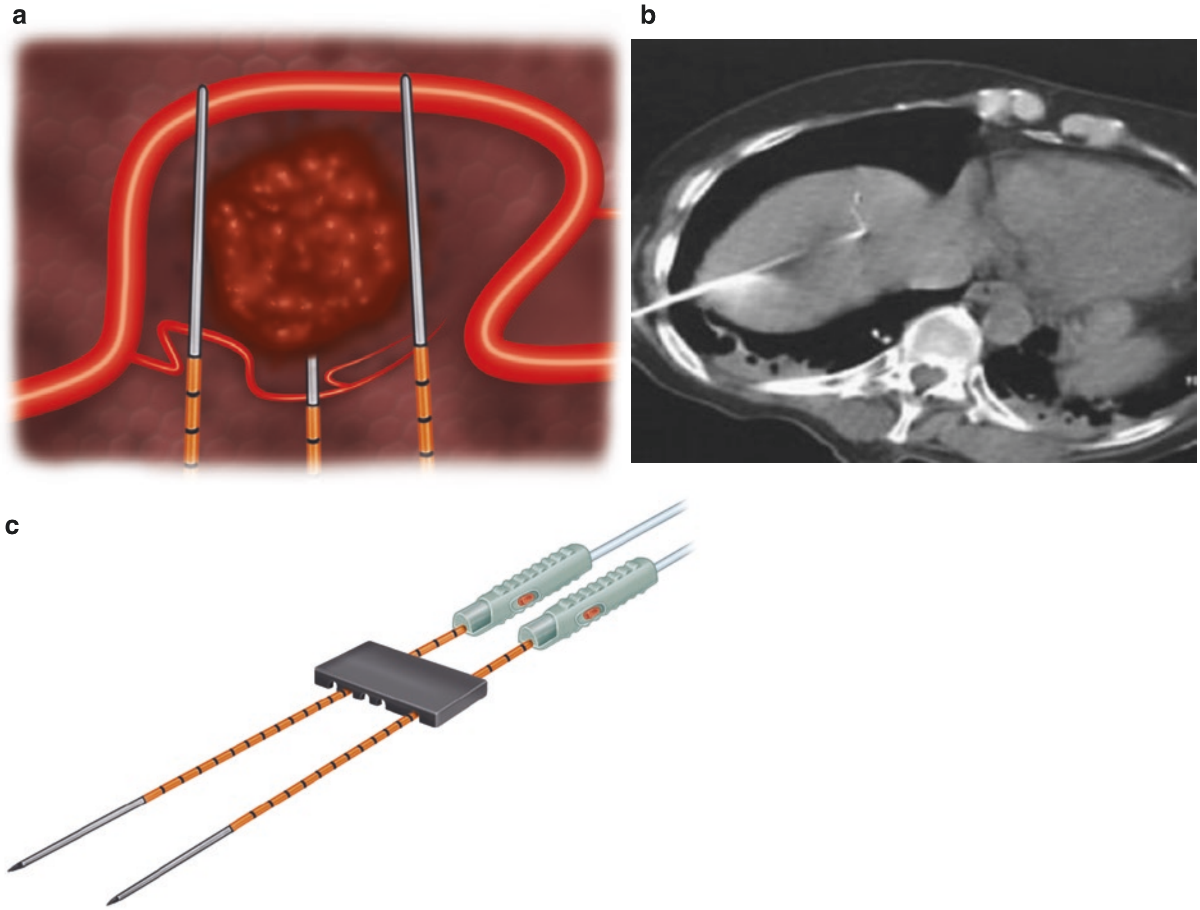


Figure 20.5

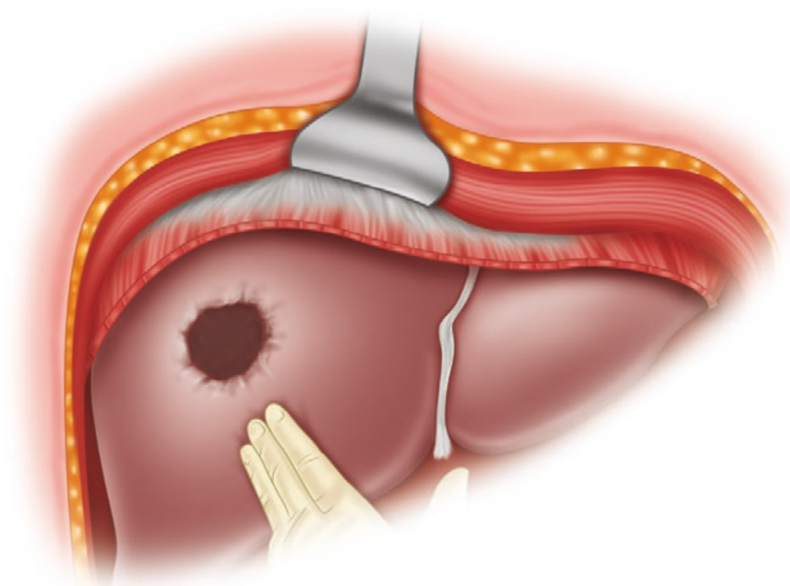


Figure 20.6

Enucleated NET specimen

Figure 20.7

(**a**) The Couinaud segmentation of the liver. (b) Liver compression sutures and parenchymal division with an energy device. (**c**) Use of an endovascular stapler in a left lateral segmentectomy

Figure 20.6

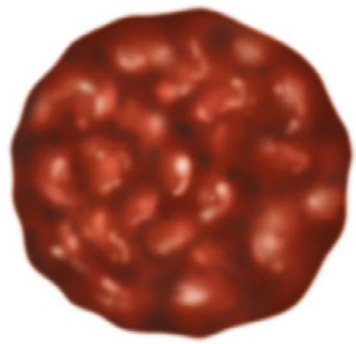


Figure 20.7

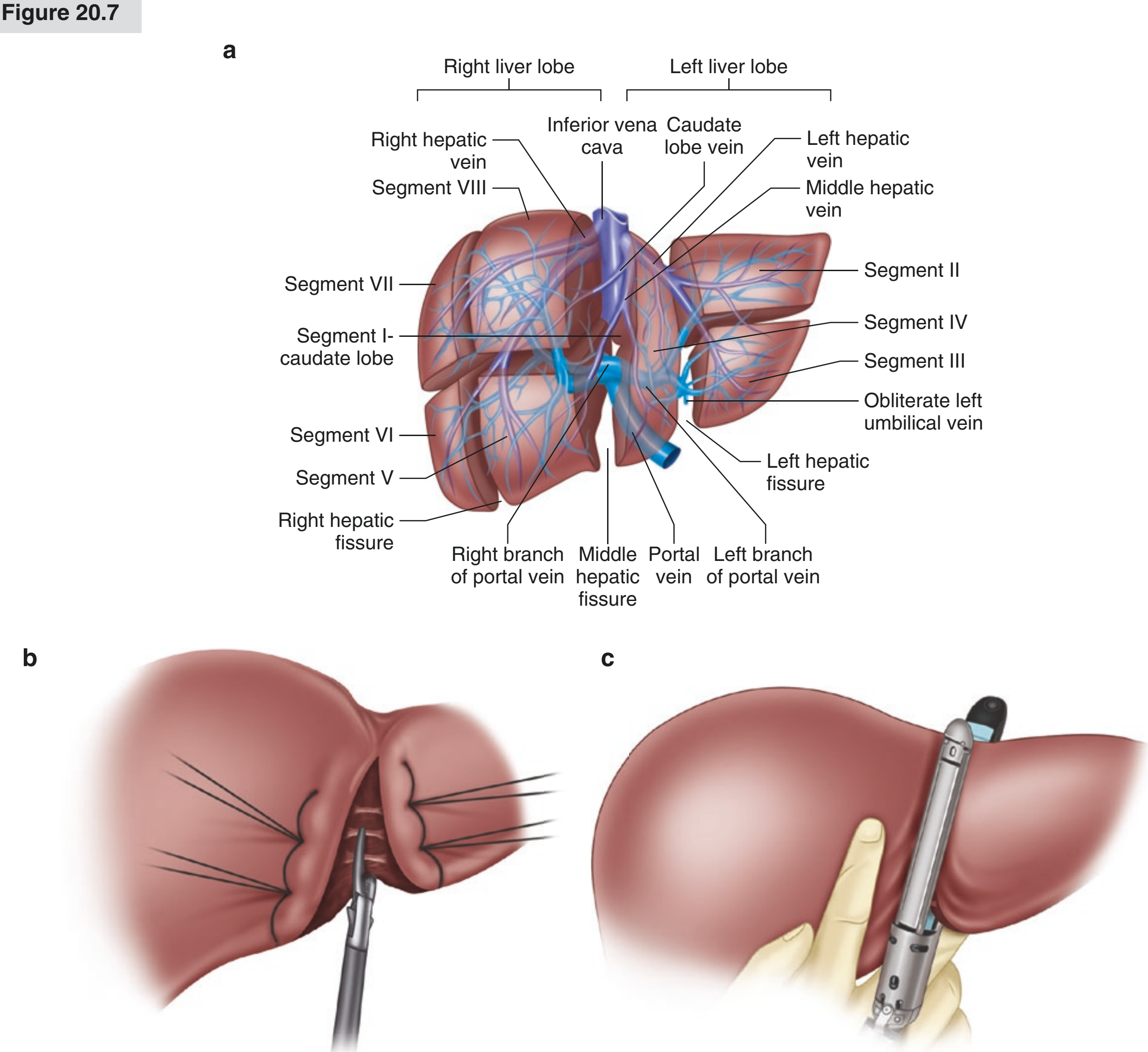
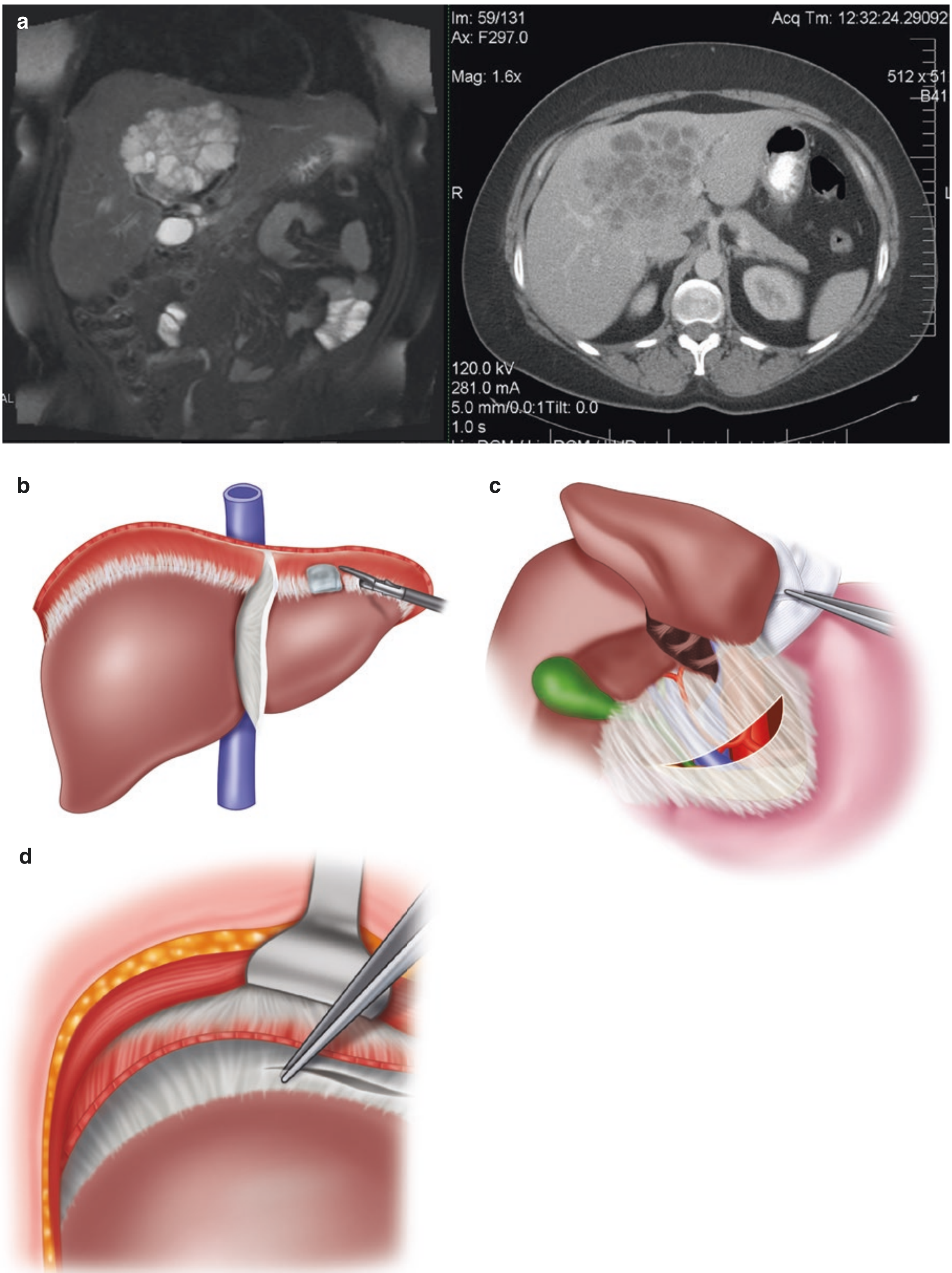


Figure 20.8

(**a**) A large central lesion splaying the portal veins, hepatic arteries, and biliary tree, as well as the left and right hepatic veins, in a patient with carcinoid syndrome. (**b**) Left lateral segment mobilization; the suprahepatic inferior vena cava (IVC) is to the left. (**c**) Division of the gastrohepatic ligament to expose the left side of the retrohepatic cava. The left lateral segment is rotated to the patient's right. (**d**) Right coronary ligament. Excessive traction prior to division will easily tear the liver capsule at this location

Figure 20.8


a
Im: 59/131
Ax: F297.0
Mag: 1.6x
Acq Tm: 12:32:24.29092
512 x 51
B41
R
120.0 kV
281.0 mA
5.0 mm/0.0:1Tilt: 0.0
1.0 s
b
c
d

20.6 Central Hepatectomy: Surgical Technique

Figure 20.8a shows a large central lesion splaying the portal veins, hepatic arteries, and biliary tree, as well as the left and right hepatic veins, in a patient with carcinoid syndrome. The middle hepatic vein is encased in tumor. To resect this tumor, the patient should be placed on high-dose octreotide infusion preoperatively. At operation, a 1-cm primary tumor was found in the terminal ileum and resected.

A key first step in all major hepatic resective surgery is to fully mobilize the liver for maximum exposure and ease of vascular control. All the ligamentous attachments of the liver are taken down. A laparotomy pad is placed behind the left lateral segment, and with downward traction on the liver, the ligament is divided with electrocautery, avoiding the left phrenic vein, with the pad protecting underlying structures (Fig. 20.8b). The gastrohepatic ligament is divided after rotating the lateral segment to the right (Fig. 20.8c). The coronary ligament and bare area of the liver are completely dissected off of the diaphragm by starting at the posterior inferior edge of the ligament (Fig. 20.8d). A Rumel tourniquet is placed around the porta hepatis for the subsequent Pringle maneuver. The hepatic veins are dissected and controlled (Fig. 20.9).

The anesthesiologist is instructed to maintain the central venous pressure at 0–4 mmHg and minimize crystalloid use during the resection. Urine output is maintained with mannitol infusion and albumin. The liver is mobilized off of the vena cava (Fig. 20.10).

The liver is scored with electrocautery circumferentially around the tumor, and dissection proceeds using crushing hemostats and hemoclips to divide the hepatic parenchyma immediately adjacent to the tumor. The dissection can be exceedingly difficult if the patient has had previous embolization therapy, because of the subsequent adhesions and neovascularity. The tumor is elevated off of the hilar structures and IRE is used to gain margins in this region without damage to the biliary or vascular structures. In a similar manner, adequate margins are obtained using IRE at the level of the hepatic veins with sacrifice of the middle vein. The Pringle maneuver is applied for 10 min with 5-min rest intervals for three applications during the deeper portions of the dissection as the tumor is excised from the liver substance and away from the hepatic and portal veins. After resection, additional hemostasis is achieved in the liver parenchyma using fibrin glue, direct pressure, and suture ligature when required (Fig. 20.11).

Figure 20.9

Dissection of the hepatic veins

20.7 Discussion

As have others, we have observed three major categories of metastatic disease of the liver:

- Type 1, a single metastasis of any size
- Type 2, isolated metastatic bulk accompanied by smaller deposits, always involving both lobes of the liver
- Type 3, disseminated metastatic spread with both liver lobes involved and little to no normal liver parenchyma

Most patients we see are of type 2. In addition, tumor biology is quite variable, ranging from indolent, slow-growing tumors with low mitotic index and low Ki-67 to poorly differentiated tumors with a high mitotic index and high Ki-67 score (mitotic index >20 mitoses per 10 high-power fields, and Ki-67 >20%). In general, patients who have rapidly growing tumors or rapidly progressing extrahepatic disease are not likely to benefit from aggressive surgery. Liver-directed embolic therapy such as bland embolization, chemoembolization, or yttrium-90 (Y-90) microsphere embolization should be considered in these patients [2, 4]. Patients who have slow-growing, indolent disease who have symptomatic tumors, patients who can be resected for cure, patients who have less than 50% of the hepatic parenchyma replaced with tumor in whom we can achieve 70% or better cytoreduction, and patients who have functional tumors are usually considered surgical candidates in our multidisciplinary program. We believe a team approach for decision making is key, as patients often are candidates for multiple forms of therapy not limited to surgical extirpation, including open or percutaneous ablative therapies, minimally invasive ablative therapies or resections, or liver-directed therapies such as chemoembolization or Y-90 microsphere embolization. In general, we do not recommend liver-directed embolic therapy in patients who have had biliary-enteric anastomoses, as they will have a high incidence of intrahepatic abscess formation after embolization. If we know a patient will require liver-directed therapy and biliary-enteric reconstruction as part of either liver resection or pancreatic head resection, we will recommend that the liver embolic therapy should be performed first, followed by subsequent hepatic resection or Whipple procedure. Liver-directed embolic therapy will make the hepatic dissection more difficult, as it engenders intense adhesions between the liver and the surrounding peritoneum. In addition, liver embolic therapy carries with it the risk of gallbladder infarction and acute cholecystitis. We recommend that all patients

Figure 20.9

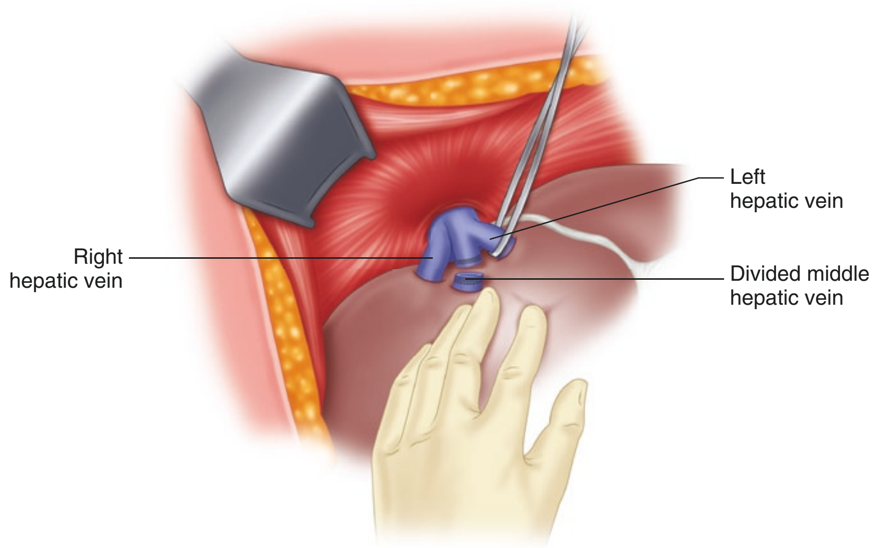


Figure 20.10

Mobilization of the liver off the vena cava

Figure 20.11

Postresection defect with exposed porta hepatis and hepatic veins within the liver

Figure 20.10

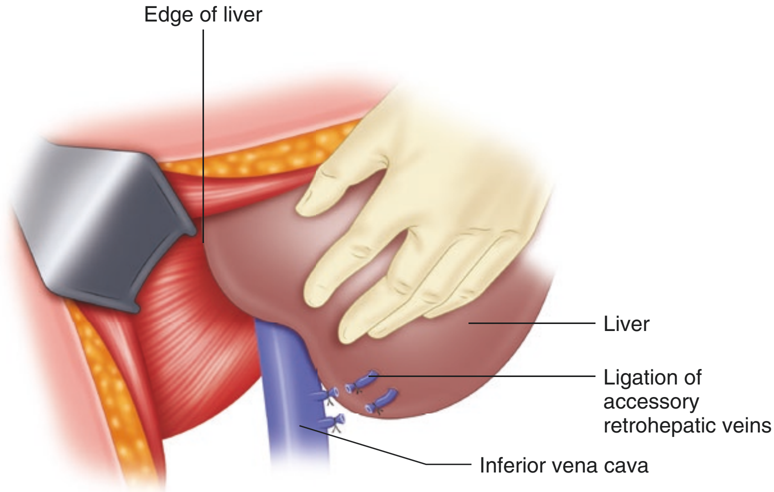
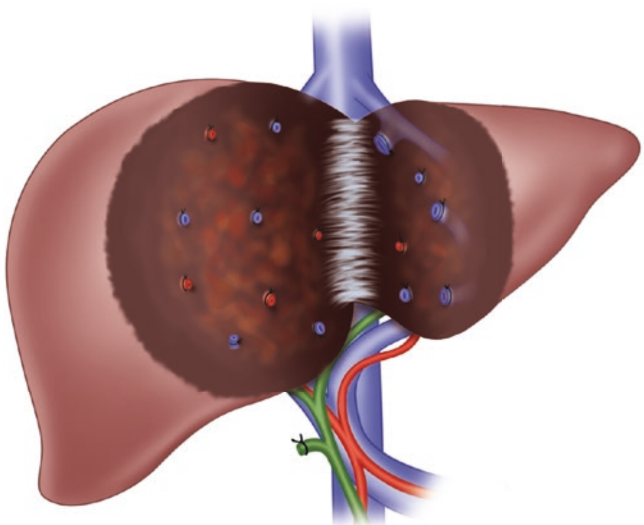


Figure 20.11



who are undergoing surgery should undergo cholecystectomy at the time of surgery if they are on long-term octreotide therapy or will undergo liver-directed embolic therapy. We usually perform liver-directed embolic therapy after all contemplated surgical procedures have been completed, but staging of different therapies is a highly individualized process, which certainly depends on the patient's comorbidities and overall nutritional status. Occasionally, liver-directed embolic therapy can downstage the patient's tumor burden to allow for successful resection, but it will make the mobilization of the liver more difficult. We do employ preoperative right portal vein embolization for diminutive left lobes, to cause hypertrophy of the left lobe. A dedicated team of hepatobiliary surgeons, medical oncologists, nuclear medicine physicians, gastroenterologists, radiologists, and endocrinologists is integral to the decision making process.

In our series of 229 procedures in 189 patients, an aggressive surgical approach has led to long-term survival (87% at 5 years, 77% at 10 years) [5]. In this group of patients with advanced liver disease, whose untreated 5-year survival is generally reported as 30–50%, we agree with others that an aggressive surgical approach is warranted for prolongation and improvement in quality of life [2, 4, 6, 7].

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