Chapter 16

Secondary Liver Tumors

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Additional information is available at the end of the chapter

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1. Introduction

The liver is a common site of metastases. The most relevant metastatic tumor of the liver to the surgeon is colorectal cancer because of the well-documented potential for long-term survival after complete resection. However, a large number of other tumors commonly metastasize to the liver, including cancers of the upper gastrointestinal system (stomach, pancreas, biliary), genitourinary system (renal, prostate), neuroendocrine system, breast, eye (melanoma), skin (melanoma), soft tissue (retroperitoneal sarcoma), and gynecologic system (ovarian, endometrial, cervix). [1]

The high frequency of liver metastases is caused by: [2]

1. The liver's vast blood supply, which originates from portal and systemic systems.
2. The fenestrations of the hepatic sinusoidal endothelium may facilitate penetration of malignant cells into the hepatic parenchyma.
3. Humoral factors that promote cell growth and cellular factors, such as adhesion molecules, favor metastatic spread to the liver.
4. The liver's geographic proximity to other intra-abdominal organs may allow malignant infiltration by direct extension.

Not so long ago, oncologists were so pessimistic about the appearance of hepatic metastases that "no treatment" was often the recommendation. Advancing technology and improved surgical techniques now offer potential therapeutic options for patients with such lesions. Patient selection is the most important aspect of surgical therapy for metastatic disease in the liver and clinical follow-up of resected patients has identified those most and least likely to benefit. Therefore, realistic expectations and honest patient education is an important aspect of treatment. [1]

1.1. Clinical presentation

The clinical presentation of patients with liver metastases is variable and subtle. Most patients are asymptomatic; a minority may report abdominal pain, jaundice, or pruritus. Hepatic metastases from gastrointestinal carcinoid tumors are associated with release of vasoactive peptides and serotonin into the systemic circulation. Symptoms of the carcinoid syndrome, specifically flushing, sweats, and diarrhea, frequently occur in this setting. Liver metastases from neuroendocrine tumors can lead to significant symptoms caused by the production of functioning hormones. [1]

Physical examination may reveal hepatomegaly, a friction rub over hepatic metastases, or ascites caused by hepatic venous obstruction or peritoneal carcinomatosis. [2]

1.2. Histopathology

The histologic appearances of metastatic deposits in the liver may resemble those of the primary tumors; however, there can be marked differences. These differences exist because metastatic foci are derived from a select subpopulation of tumor cells. Cells that are capable of successful metastasis are believed to have specific characteristics, such as high motility, resistance to immune-mediated destruction, and a high concentration of matrix receptors or matrix-degrading enzymes.

Because the metastatic cell population may not be representative of the primary tumor, it can be difficult to determine the site of origin based on the histologic appearance of the metastases alone.

The initial light-microscopic findings can be used to categorize the tissue into one of three groups:

1. poorly differentiated carcinoma or adenocarcinoma,
2. well-differentiated adenocarcinoma, and
3. squamous carcinoma.

In most cases, immunohistochemical studies further differentiate these metastases. (Table 1) [3]

Tumor	Antigens
Colonic adenocarcinoma	CEA
Pancreatic carcinoma	CEA, pancreatic carcinoma-associated antigen
Lung carcinoma	CEA, cytokeratin, neuron-specific enolase
Breast carcinoma	CEA, milk-fat globulin, hCG
Thyroid carcinoma	Thyroglobulin
Prostate carcinoma	Prostate-specific acid phosphatase, PSA
Melanoma	S-100, vimentin, neuron-specific enolase
Carcinoid	Chromogranin, neuron-specific enolase
Lymphoma and leukemia	CLA
Sarcoma	
Smooth muscle	Type IV collagen, vimentin, desmin
Skeletal muscle	Myoglobin, vimentin, desmin
Neurogenic	S-100, myelin basic protein
Cartilage	S-100, vimentin
Bone	Vimentin
Germ cell tumors	α-fetoprotien, α1-antitrypsin
Trophoblastic tumors	hCG, α-Fetoprotein

Table 1. Immunohistochemical antigens for the identification of primary tumors.

Abbreviations: CEA, carcinoembryonic antigen; CLA, common leukocyte antigen; hCG, human chorionic gonadotropin; PSA, prostate-specific antigen.

1.3. Biochemical Laboratory Tests

The laboratory tests that are available for liver function assessment are not very sensitive. CEA remains the most sensitive test for metastatic colon cancer, but even this test can be normal in the presence of liver metastases, especially with minimal hepatic disease.

1.4. Imaging Techniques

The choice among the various techniques, and the sequence with which they are used, should be guided primarily by the clinical indication, taking into account the primary type and the different possible treatments, which also depend on the general status of clinical history of the patient. Dedicated liver imaging is not needed in patients diagnosed with disseminated, inoperable disease. [4]

1.4.1. Ultrasonography

1.4.1.1. Transabdominal ultrasonography (US)

US presents several advantages, including low cost, absence of irradiation, wide availability, and portability. Transabdominal ultrasound generally has a lower sensitivity for tumor detec-

tion than does CT scan or MR imaging, especially for lesions less than 2 cm in size. US is most commonly used for screening for metastases because of its wide availability. Hepatic metastases may be hypoechoic, hyperechoic, cystic, or of mixed echogenicity on ultrasound. Hyperechoic masses are observed more commonly in vascular tumors, such as renal cell and islet cell tumors. Hypovascular lesions, such as lymphoma, appear as hypoechoic masses. [5]

1.4.1.2. Contrast-enhanced US

Contrast-enhanced US, using intravascular microbubble contrast agents, has shown similar accuracy compared to CT and MR. An advantage of contrast-enhanced US is the potential for characterization of liver lesions based on morphologic evaluation as well as temporal vascular enhancement pattern. During the portal venous phase, benign lesions typically enhance more than the liver, whereas malignant lesions enhance less. [6]

1.4.1.3. Endoscopic ultrasound (EUS)

EUS is a well-established tool for diagnosing and staging various gastrointestinal tumors, especially pancreatic cancer; however, it is not used often for hepatic imaging. A few reports in the literature address the use of EUS in the evaluation of hepatic metastases. EUS can detect lesions that are not seen on conventional CT scanning and allows for tissue sampling using fine-needle aspiration. [4]

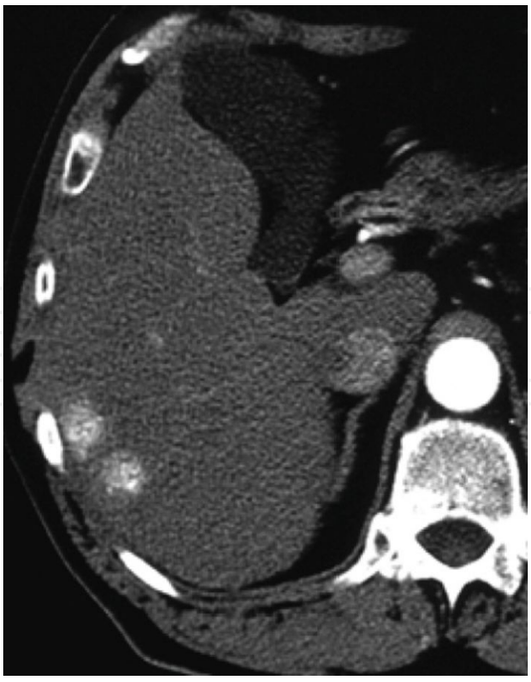

Figure 1. Computed tomography of hypervascular liver metastases from a renal primary tumor at the arterial phase.

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1.4.1.4. Intraoperative US (IOUS)

IOUS involves a direct scan of the liver, allowing the use of higher-frequency transducers with higher resolution. IOUS can also be useful at detecting small, deep hepatic metastases not palpable. IOUS is more accurate than conventional CT scanning or MR imaging for delineating liver lesions and is regarded as an important tool in determining resectability and prognosis. [7]

1.4.2. Computed Tomography

1.4.2.1. Noncontrast Computed Tomography

Contrast CT is sometimes not possible because of contrast allergic reactions or renal impairment. Although the sensitivity and specificity of noncontrast CT is far reduced as compared to contrast CT, it may help in identifying hypervascular metastases (especially carcinoid tumors, islet cell tumors, and renal cell carcinomas) or visualizing calcifications or hemorrhage. Noncontrast CT often fails to distinguish hypovascular tumors from the liver parenchyma. Nonenhanced blood vessels may also appear as low-attenuation masses and be confused with metastases. [4]

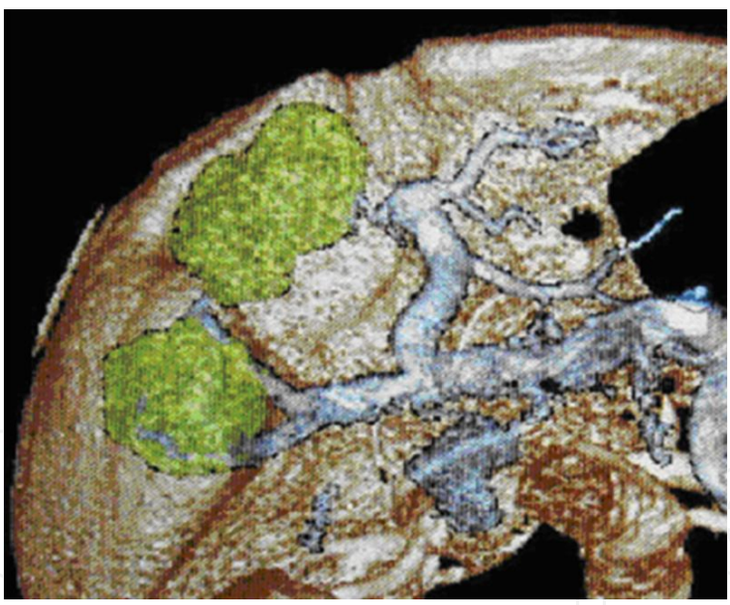

Figure 2. Computed tomography 3-D reconstruction before surgical showing liver metastases (http://c2i2.digithalamus.com/winter2003/Imaging%20update%20in%20metastatic%20liver%20disease.asp).

1.4.2.2. Contrast Computed Tomography

The CT appearance of liver metastases varies according to the pathologic type of the primary tumor. Most lesions are seen best in the portal venous phase, and some lesions are best seen in delayed venous and occasionally arterial phases. Metastases from melanomas, sarcomas, neuroendocrine tumors, and renal cell carcinomas (fig. 1) are hypervascular and there-

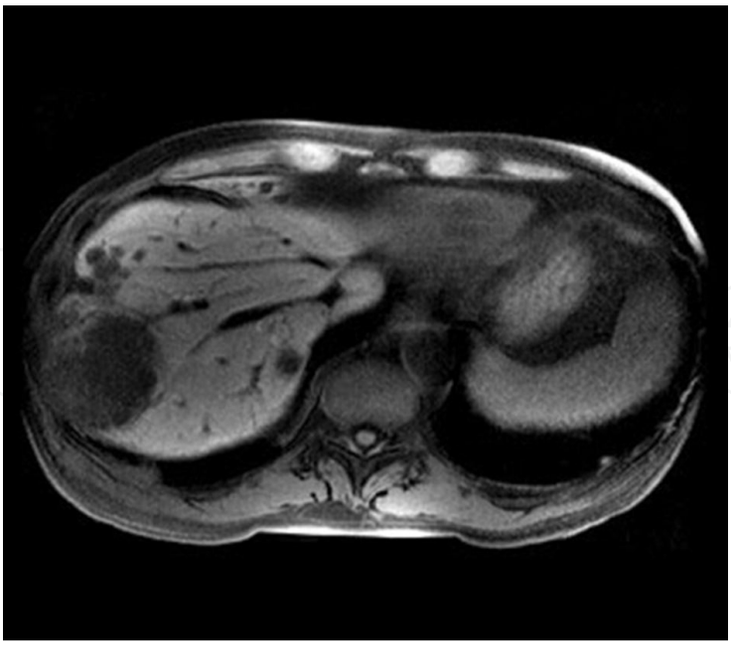

Figure 3. Liver metastases after Mn DPPD or mangafodipir injection.

fore better visualized during the hepatic arterial phase. Metastases from colorectal cancer are hypovascular and therefore better visualized during the portal venous phase. [8]

1.4.3. Magnetic Resonance Imaging (MRI)

T1-weighted images generally show hepatic metastases as low-intensity lesions, whereas T2-weighted images show these lesions to be areas of increased signal intensity. Dynamic, breath-hold MR imaging with a gadolinium-based contrast material is considered to be the most sensitive MR technique for detection of hepatic metastases (fig. 3). Similar to CT, MR angiography can be used as a noninvasive method to evaluate hepatic vasculature. Novel MR contrast agents have the potential for improving detection of liver metastases. [8, 9]

1.4.4. Positron Emission Tomography (PET)

PET, in which a radioactively labeled tracer is administered to the patient and the scanner collects the emitted positron radioactivity to generate an image, allows imaging of cellular processes (such as cellular proliferation (18F-labeled thymidine), hypoxia (18F-labeled Miso), and blood flow ([15O]water) to be visualized. The majority of clinical experience relies on the uptake and use of glucose in human cells. 18F-Fluorodeoxyglucose 18FDG, the most commonly used marker in PET imaging, is an analogue of glucose in which a carbon atom is replaced by a radioactive fluorine isotope. 18FDG is transported into cells, where it accumulates to create an intense signal on PET imaging. Malignant lesions typically have increased 18FDG uptake because of the increased expression of glucose transporter proteins and elevated levels of glycolysis. [10, 11]

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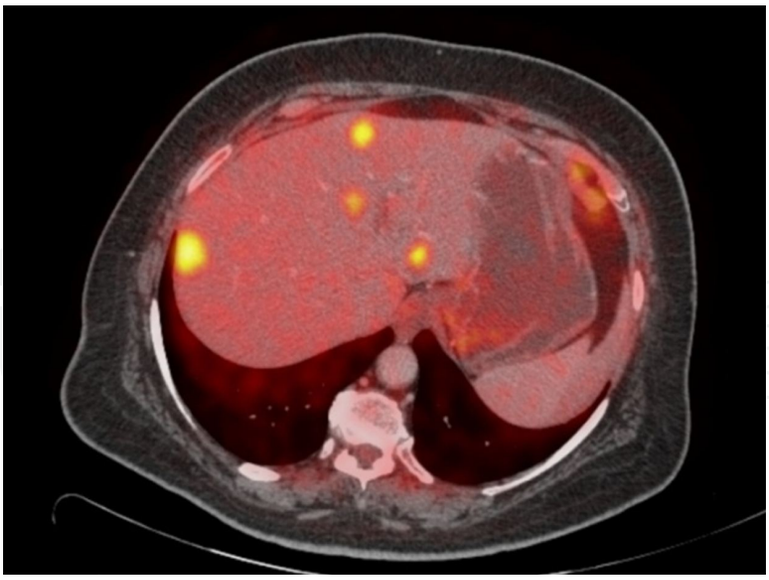

Figure 4. PET/CT Cancer pancreas with liver metastases (http://www.radrounds.com/photo/petct- -2context).

1.4.5. PET/CT (fig. 4)

Despite excellent clinical results with FDG PET, the technique is intrinsically limited by the lack of precise and reliable anatomic information. Foci of increased uptake that are clearly located in the liver parenchyma are readily identified and usually correspond to metastases, but the bowel uptake is highly variable and may be focally increased in regions close to the liver, and therefore be mistaken with peripheral liver lesions. Combined PET/CT scanners allow the precise localization of the abnormal areas of uptake. Modern PET/CT devices are equipped with high-end CT scanners, fully capable of performing full diagnostic CT studies. [11]

2. Colorectal Liver Metastases (CLM)

The liver is the most common site for hematogenous metastasis from colorectal cancers (CRC). A quarter of patients with primary colorectal carcinoma are found to have synchronous hepatic metastasis. Nearly half of patients who undergo resection of the colorectal primary eventually develop metachronous liver metastasis. [2]

CRC principally spreads through two mechanisms:

1. Via portal venous drainage.
2. To regional lymph nodes and then through central lymphatics into the systemic circulation or

2.1. Prognostic Variables and Staging Systems

All patients with colorectal metastases by definition are grouped as stage IV in the TNM staging system, but considerable diversity exists within this group. The prognosis of a pa-

tient with a solitary liver metastasis found years after resection of a node-negative right colon cancer is different from the prognosis of a patient with synchronously discovered diffuse bilateral liver metastases at the time of operation for a perforated node- positive colon cancer. A classification system that can discriminate between these patients and provide meaningful prognostic information is essential. This classification system must enable the comparison of patients from diverse publications and facilitate patient selection for adjuvant therapy or clinical trials. [2, 12]

2.1.1. Independent predictors of prognosis include [2]

1. the presence of extrahepatic disease,
2. a positive resection margin,
3. nodal metastases from primary cancer,
4. a short disease-free interval,
5. largest tumor greater than 5 cm,
6. more than one liver metastasis, and
7. CEA greater than 200 ng/mL.

- The first two parameters are data that are determined intraoperatively only because preoperative evidence of extrahepatic disease and inability to obtain negative margins would be relative contraindications to surgery. There is no role for surgical debulking in this setting.
- Using the last five criteria, a preoperative clinical risk score (CRS) system was created with each positive criterion counting as 1 point.
- This CRS is a simple, easily remembered staging system for classifying patients with liver-exclusive metastatic colorectal cancer

2.1.2. Prognostic Scoring System for Hepatic Colorectal Metastases: Clinical risk score (CRS)

- Node-positive primary tumor
- Disease-free interval <12 mo between colon resection and appearance of metastases
- Size of largest lesion >5 cm
- >1 tumor
- CEA >200 ng/dL

Sum of points with 1 point assigned for each positive criterion

- The presence of any one of these characteristics still was associated with a 5-year survival.
- No single criterion can be considered a contraindication to resection.
- The total score out of 5 is highly predictive of outcome.

- A score of 2 or less places a patient in a good prognostic group, for whom resection is ideal.
- For scores of 3 or 4, outcome is less favorable, and patients should be considered for aggressive trials of adjuvant therapy.
- For a score of 5, long-term disease-free survivors rarely are encountered, and resections in this high-risk group should be accompanied by trials of adjuvant therapy.
- This CRS proved useful in selection of patients for neoadjuvant therapy and ablative therapies and in stratification of patients enrolled in clinical trials
- A high CRS has been associated with sufficiently high incidence of occult metastatic disease that fluorodeoxyglucose positron emission tomography (FDG PET) can be justified as a preoperative test
- The yield from laparoscopy in the preoperative staging of patients with hepatic colorectal metastases also has been correlated with the CRS.
- For patients with a high CRS, a laparoscopy can save patients with disseminated disease from having a laparotomy, minimizing morbidity and hospital stay, whereas patients with a low CRS can avoid the added anesthesia and operating room time associated with a negative laparoscopy. [2, 12]

2.1.3. Molecular Determinants of Outcome

There are reports that molecular characteristics that predict response to chemotherapy, such as tumor thymidylate synthase levels or levels of the transcription factor E2F-1, are important in predicting the outcome It is likely that these and other molecular determinants will be incorporated into postoperative prognostic scales in the future. [2]

2.2. Medical Treatment

Over the past 3 decades, the most widely used chemotherapeutic agent in the treatment of metastatic CRC has been 5-fluorouracil (5-FU), used either alone or in combination with other chemotherapies. [13]

Now, the most commonly used regimens are: FOLFOX, FOLFIRI, and FOLFOXIRI.

2.2.1. FOLFOX is a made up of the drugs

- FOL – Folinic acid (leucovorin), a vitamin B derivative used as a "rescue" drug for high doses of the drug methotrexate and that modulates/potentiates/reduces the side effects of fluorouracil;
- F – Fluorouracil (5-FU) fluorouracil (5-FU), a pyrimidine analog and antimetabolite which incorporates into the DNA molecule and stops synthesis; and
- OX – Oxaliplatin (Eloxatin) A platinum-based drug, usually classified as alkylating agents, although it is not actually alkylating groups (functions by a similar mechanism)

This regimen is recommended for 12 cycles, every 2 weeks. The recommended dose schedule given every two weeks is as follows:

- Day 1: Oxaliplatin 85 mg/m² IV infusion in 250-500 mL D5W and leucovorin 200 mg/m² IV infusion in D5W both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.
- Day 2: Leucovorin 200 mg/m² IV infusion over 120 minutes, followed by 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.FOLFOX4 regime.

Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.

FOLFOX4				
drug	dose	administration	time	term
Oxaliplatin	85 mg/m²	IV infusion	2 h	day 1
Folinic acid	200 mg/m²	IV infusion	2 h	day 1 + 2
Fluorouracil	400 mg/m²	IV bolus	2 min	day 1 + 2
Fluorouracil	600 mg/m²	IV infusion	22 h	day 1 + 2

Table 2.

2.2.2. FOLFIRI is is made up of the following drugs:

- FOL – folinic acid (leucovorin).
- F – fluorouracil (5-FU); and
- IRI – irinotecan (Camptosar), a topoisomerase inhibitor, which prevents DNA from uncoiling and duplicating.

The dosage consists of: Irinotecan (180 mg/m² IV over 90 minutes) concurrently with folinic acid (400 mg/m² [or 2 x 250 mg/m²] IV over 120 minutes).

Followed by fluorouracil (400-500 mg/m² IV bolus) then fluorouracil (2400-3000 mg/m² intravenous infusion over 46 hours).

This cycle is typically repeated every two weeks. The dosages shown above may vary from cycle to cycle.

FOLFOX and FOLFIRI are widely considered to be equivelent in the metastatic setting and are generally selected according to the toxicity profile. The FOLFOX regimen is characterized by a higher rate of grade 3 and 4 neurotoxicity and neutropenia. The FOLFIRI is associated with more nasuea and vomiting, mucositis, and alopecia.

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2.2.3. Folfoxiri

- irinotecan, oxaliplatin, fluorouracil, and folinate

FOLFOXIRI has been shown to have better results than FOLFIRI and FOLFOX in several studies.

2.2.4. Cetuximab (Erbitux) and panitumumab (Vectibix)

Both are monoclonal antibodies against the epidermal growth factor receptor (EGFR) and are now an important part of the treatment algorithm for unresectable colorectal metastases. Cetuximab is a chimeric monoclonal antibody approved for treatment of metastatic CRC in combination with irinotecan in patients with disease refractory to irinotecan or as a single agent in patients who cannot tolerate irinotecan or oxaliplatin. Panitumumab is a fully humanized monoclonal antibody and therefore appears to have a lower rate of serious infusion reactions compared with cetuximab. Like cetuximab, panitumumab is approved for single-agent therapy in patients who have progressed on standard chemotherapy. [2]

2.3. Regional treatment for metastatic colorectal cancer

The rationale for a regional approach to what normally would be thought of as a systemic process is based on the concept that tumor cells from gastrointestinal malignancies, especially colorectal cancer, spread hematogenously via the portal circulation, making the liver the first site of metastasis in most patients. This stepwise spread of cancer from primary site to liver and from there to other organs provides an opportunity to prevent dissemination of tumor to other sites by direct treatment of hepatic metastases. In this way, metastatic colorectal cancer differs from most other metastatic malignancies. In addition, the remarkable ability of the liver to regenerate after hepatic resection has enabled aggressive surgical options for hepatic metastases. There is no doubt that surgery alone can cure a subset of patients. [14]

Liver resection has become the standard treatment for metastatic lesions from colorectal primaries. With many series reporting long-term survival for these patients, even before the era of modern chemotherapy, 5-year, 10-year, and 20-year survivals with hepatic resection can be expected to reach 40%, 25%, and 20%. [2]

2.3.1. Preoperative evaluation

All patients with CLM benefit from evaluation by a multidisciplinary team comprising physicians (surgeons, medical oncologists, radiologists, pathologists), nurses, social workers, and research coordinators. The central tenets in the preoperative evaluation of patients for potential surgical resection of CLM are:

1. establishing the diagnosis,

2. anatomically defining the liver lesion for diagnosis and surgical planning, and

3. staging to rule out extrahepatic disease.

4. evaluation of the patient's fitness for operation;

5. estimation of an individual's tumor biology.

Preoperative biopsy of CLM is rarely indicated or beneficial for assessment of CLM, and has been associated with tumor dissemination and decreased survival. Preoperative biopsy may have usefulness for confirmation of extrahepatic disease when a change in therapy is planned based on the biopsy results. [1]

2.3.1.1. Evaluation of Fitness for Operation

A careful evaluation of a patient's physiologic capability to tolerate hepatic resection is necessary to ensure favorable outcomes after hepatectomy. History, physical examination, and routine laboratory studies (complete blood count, liver function testing, and coagulation studies) are relied on to screen for underlying liver dysfunction.The criteria for patient operability are similar to the criteria considered for any major laparotomy. A history of cardiac and pulmonary disease must be investigated because these patients are at significant risk for perioperative complications. Any previous liver disease that might have impaired hepatic function should be evaluated because this determines the volume of liver than can be resected safely. [2, 14]

2.3.1.2. Anatomic and Functional parameters

Determination of resectability is primarily based on preoperative imaging. High-quality cross-sectional imaging is critical for gauging the extent of disease, response to preoperative therapy, and for operative planning (The role of preoperative imaging was discussed above). [14]

Patients should be routinely reimaged after any course of systemic therapy; preferably within 4 weeks of planned resection. Meticulous preoperative attention to the relationships of CLM to arterioportal inflow, biliary drainage, and hepatic venous outflow is necessary and allows for an informed and efficient hepatectomy. Preoperative imaging may also help to identify the presence of concomitant parenchymal disease (eg, fibrosis/cirrhosis, portal hypertension, steatohepatitis) or extrahepatic disease. [2]

Resectability of CLM has been well defined by the American Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO) in a 2006 consensus statement as an expected margin-negative (R-0) resection resulting in preservation of at least 2 contiguous hepatic segments with adequate inflow, outflow, and biliary drainage with a functional liver remnant (FLR) volume of more than 20% (for healthy liver). [1, 14]

2.3.1.3. Tumor biology

Careful evaluation of all patients in a multidisciplinary setting allows for better identification of those patients most likely to benefit from surgical resection as opposed to those who would benefit more from nonoperative therapies, given their particularly aggressive disease. Consideration of this question is far from an exact science, but valuable information can be gleaned from factors such as [1]

1. the stage of primary disease,

2. number and distribution of CLM,
3. tumor histology,
4. response to chemotherapy,
5. rate of growth of CLM on serial imaging,
6. rate of increase in serum carcinoembryonic antigen (CEA).

2.3.1.4. Diagnostic laparoscopy

Diagnostic laparoscopy has a role in staging those patients in whom preoperative imaging or high-risk scores suggest a high likelihood for finding intra-abdominal extrahepatic disease or for patients with indeterminate intrahepatic lesions that may be best characterized by IOUS. Laparoscopy is useful at identifying peritoneal disease or the involvement of periportal lymph nodes not apparent on preoperative imaging. When laparoscopy is employed, laparotomy can be avoided in patients with unresectable disease. [1, 2]

2.3.2. Operative technique

The goal should be a safe R-0 hepatectomy allowing for preservation of adequate FLR volume to avoid hepatic insufficiency. Given the significant decrease in survival between R-0 and R-1/2 resections, the ability to achieve R-0 resection, is paramount. The optimal width of resection margin is unclear, with no clear minimum margin established. A predicted margin width of less than 1 cm should not be used as an exclusion to resection. The extent of resection depends on the number and location of metastases relative to the portal triads and hepatic veins. Anatomic resections, which are facilitated by intraoperative ultrasound, are preferred to wedge resections. Anatomic resections permit excision of parenchymal areas distal to the tumor, where vascular micrometastases tend to occur, and, most importantly they are less likely to have positive margins. [14, 15]

The principles of hepatic resection are no different for colorectal metastases than for any other hepatic surgery. Technical details of liver mobilization and various anatomic hepatectomies have been well described elsewhere in this book. Most procedures can be divided into distinct stages: [1, 2, 14, 15]

1. exploration,
2. liver mobilization,
3. intraoperative ultrasonography,
4. inflow control,
5. outflow control,
6. parenchymal transection, and

7. hemo- and biliostasis.

The abdomen must be explored thoroughly for evidence of extrahepatic metastases. In particular, the celiac axis and portocaval and hilar lymph nodes must be palpated, and any suspicious nodes should be removed and examined by frozen section.

Most surgeons routinely use intraoperative ultrasound after mobilization of the liver. IOUS can delineate better the interior anatomy of the liver, including intrahepatic vessels, and hepatic resection can be performed more safely and in a more anatomically oriented fashion. In addition to the initial planning, the operation can be monitored by the repeated use of IOUS because the resection line is displayed in relation to the lesion and blood vessels. [14, 15]

2.3.3. Follow-up

Patients after hepatic resection usually are monitored in an attempt to identify early recurrence that may be amenable to further resection. Currently, most patients undergo serial physical examination, serum CEA level, annual chest x-ray, and CT of the abdomen and pelvis every 3 to 4 months for the first 2 years and then every 6 months for the next 5 years. [16]

2.3.3.1. Adjuvant Chemotherapy

1- Adjuvant Systemic Chemotherapy

Although the use of oxaliplatin-based or irinotecan-based chemotherapies in this setting is common, there are no clear data from comparative studies supporting such practice. [17]

2- Adjuvant Hepatic Arterial Infusion Chemotherapy

Regional chemotherapy, via the hepatic artery, is a theoretically attractive mode of adjuvant therapy, because the liver is the most common site for tumor recurrence after liver resection and is the sole site of recurrence in 40% of patients.

The rationale for HAI of chemotherapy is based on the concept that most metastatic liver tumors preferentially derive their blood supply from the hepatic artery, whereas normal hepatic tissue relies on the portal venous blood supply.

The ability of the hepatic parenchyma to extract and metabolize chemotherapy drugs to nontoxic metabolites offers a unique opportunity to administer highly toxic drug levels to tumor cells, while minimizing systemic toxicity. The most extensively studied agent is 5-fluorouracil-2-deoxyuridine (FUDR), an analogue of 5-FU that can be concentrated 100-fold to 400-fold in the liver because of a 95% hepatic extraction ratio. [17, 18, 19, 20]

2.4. Controversial issues

2.4.1. Downstaging of unresectable tumor and neoadjuvant chemotherapy.

Potential benefits of prehepatectomy chemotherapy include [2, 20]

1. the potential to render formerly unresectable patients resectable i.e. the possibility for downstaging liver metastases,
2. in vivo testing of chemotherapeutic efficacy,
3. identification of occult intra- or extrahepatic metastases, and
4. early exposure of subclinical microscopic metastases to systemic therapy.
5. with prudent monitoring and attention to comorbidities, allows for improved patient selection

Patients with tumor progression during preoperative chemotherapy have a significantly worse outcome CLM. Potential downsides of preoperative chemotherapy are largely related to hepatic toxicities that may be clinically relevant. Oxaliplatin has been linked to steatohepatitis and sinusoidal obstruction; irinotecan has been associated with steatohepatitis and periportal inflammation. A preoperatively treated liver is more fibrotic, often with perivascular adhesions. The planes of resection are difficult to dissect, making the procedure more challenging overall. Despite the operative complexity, the perioperative morbidity and mortality in the trials of resection after neoadjuvant chemotherapy do not seem to be higher than series of de novo hepatic resection. [1, 2]

One controversial issue is the treatment of a patient with a *complete clinical response* to neoadjuvant chemotherapy. When there is no visible tumor left to resect, should a blind resection, based on the site of previous metastasis, be undertaken? Suggested practice is to use intraoperative ultrasound to attempt to identify the lesion, and if this is not possible a hepatic resection of the area previously involved with tumor is performed. This is not, however, a universally accepted practice. [1, 2, 20]

Patients who present with liver lesions that are potentially resectable for cure should be offered a surgical resection because there are no definite data supporting a neoadjuvant chemotherapeutic approach.

2.4.2. Repeated resection for recurrent tumor

In the absence of extrahepatic disease and in a patient with a good performance status and adequate hepatic reserve, a repeat hepatectomy may be considered. Approximately one third of recurrence is amenable to further resection The presence of adhesions and the altered anatomy of the liver, particularly the position of the vasculature and biliary system, make this technically challenging.

There is a higher likelihood of further recurrence, however, and the study of adjuvant therapy should be encouraged in these patients. [21]

2.4.3. Synchronous Metastases

Synchronous CLM are noted in 20% to 30% of patients at the time of initial colorectal cancer diagnosis. Surgical management of this group of early metastases has been debated in terms

of disease biology, operative approach (staged vs. simultaneous colorectal and liver resection), the order of resection, and timing of chemotherapy. [2, 22]

Some suggests that synchronous diagnosis of metastases portends a worse prognosis, perhaps as a result of a failure to detect micrometastatic foci in the liver. Delaying hepatic resection may increase survival in the surgically resected group by selecting out the patients with aggressive tumor biology who would be unlikely to derive a survival benefit from resection. Although delayed resection does not seem to impair survival, it does increase the volume of resected liver, a factor that is predictive of postoperative complications. [22]

Potential benefits of simultaneous CLM resection include [2]

1. avoidance of morbidity of a second laparotomy and anesthesia, and
2. decreased time to initiation of chemotherapy.

Risks of simultaneous resection are related to the magnitude and complexity of the combined operation.

A selective approach to synchronous CLM should be based on careful consideration of the technical complexity and risks for the colorectal and liver resections, as well as judicious intraoperative decision making. Good judgment is required in selection of patients for a simultaneous or a staged resection in close coordination with medical oncologists and collaborating surgeons. [1]

2.4.4. Bilobar Metastases

Bilobar metastases are no longer an absolute contraindication to resection. Possible options include:

1. Extended hepatectomy,
2. 2-stage hepatectomy,
3. Combined hepatic resection and ablation.
4. For patients with insufficient FLR, portal vein embolization (PVE) may be a useful adjunct to increase the size of the FLR and allow for safe extended hepatectomy.

Two-stage hepatectomy for patients with bilobar metastases involves an initial hepatectomy with contralateral portal vein ligation or postoperative PVE, followed by chemotherapy. After restaging, a second hepatectomy is performed based on response to PVE/chemotherapy and ability to achieve resection with an adequate FLR. A proportion of patients will not be eligible for second hepatectomy because of disease progression, inadequate FLR, or perioperative or chemotherapy-associated complications. [23, 24]

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2.4.5. Extrahepatic Colorectal Metastases

In the past, extrahepatic disease has been labeled an absolute contraindication to resection of CLM. However, with the advent of more effective systemic therapies, a growing body of literature supports R-0 resection of CLM and extrahepatic metastases. [25]

- An assessment of tumor biology is critical to selecting patients for resection of CLM as well as extrahepatic metastases. For patients found to have extrahepatic metastases preoperatively, a short course of preoperative chemotherapy followed by reimaging is prudent to better define the disease biology.
- Intraoperative decision for previously unrecognized intra-abdominal extrahepatic metastases is difficult. The following should be considered:

1. the complexity and extent of the R-0 hepatic resection,
2. the complexity of resection of the R-0 extrahepatic metastases,
3. the physiologic age of the patient,
4. availability of postoperative chemotherapeutic options, and
5. the patient's risk of rapid progression with the additional finding of extrahepatic metastases.

3. Neuroendocrine Liver Metastases (NLMs)

The liver is the most common site of metastatic disease for neuroendocrine tumors. Nonoperative therapies for advanced neuroendocrine malignancies are associated with minimal response rates, short durations of disease stability, and no clear survival benefit. [26]

3.1. Pathology and Classification

Most NLMs are of gastrointestinal or pancreatic origin, or so-called gastroenteropancreatic (GEP) tumors GEP neuroendocrine tumors historically are divided into two broad types: carcinoid and noncarcinoid. Either type may or may not be associated with hormone production causing a clinical endocrinopathy (functional or nonfunctional). [26, 27]

Traditionally, gastrointestinal carcinoids have been classified by their site of origin—foregut (lung, thymus, stomach, duodenum, pancreas, bile duct, gallbladder, and liver), midgut (small intestine, appendix, and proximal colon), and hindgut (distal colon and rectum)—because of the various biologic and biochemical features shown within these groups. Pancreatic neuroendocrine tumors have been classified by whether they are functional or not. [26, 28]

Regardless of origin, neuroendocrine tumors are similar histopathologically. Many histologic and morphologic features may be shared by benign and malignant tumors. Histologically, neuroendocrine tumors typically are well differentiated, and atypia and mitoses are rare.

Neuroendocrine tumors stain positive for chromogranin A, neuron-specific enolase, and synaptophysin, which confirms neuroendocrine cell origin. Neuroendocrine tumors also stain positively for one or more endocrine hormones immunohistochemically. [27]

Morphologically, neuroendocrine tumors can be solitary or multiple and solid or cystic. Tumor size alone is not a reliable indicator of malignancy. Neuroendocrine tumors greater than 2 cm throughout the GEP tract have a greater probability of malignant behavior, however, than tumors less than 2 cm. Gross or microscopic vascular invasion may occur for any GEP neuroendocrine tumors, although major vascular invasion is most typical of pancreatic NECs. Only the confirmed presence of metastases confers an unequivocal diagnosis of malignancy. [28]

Regardless of whether NECs are classified as carcinoid or noncarcinoid, the natural history of patients with unresected or unresectable hepatic metastases generally has been similar. Overall, patients with unresected hepatic metastases from NEC have an approximately 30% 5-year survival The presence of liver metastases alone is the most significant factor adversely affecting outcome Five-year survival with and without liver metastases from NECs is approximately 30% to 40% and 90% to 100%. [26]

3.2. Treatment of NLMs

3.2.1. Liver resection

The treatment of hepatic metastases from NECs is aimed at reduction of the mass of malignant tissue (cytoreduction) chiefly for two reasons. [29]

First, metastatic gastrointestinal neuroendocrine tumors are usually indolent and slow growing because most are low-grade malignancies (WHO classification). Chemotherapeutic and radiotherapeutic regimens targeted at rapidly dividing cells are relatively ineffective, targeting only a paucity of the total population of malignant cells.

Second, symptoms secondary to expression and secretion of biologically active peptides by these tumors are directly related to overall mass of tumor, although production of peptides may be heterogeneous among individual metastases. Similarly, pain and debilitating decrease in performance status may have a negative impact on quality of life for nonfunctional NECs metastatic to the liver. Cytoreduction of the tumor is the most direct and immediately effective method to provide symptomatic relief.

These reasons, coupled with improved safety for hepatic resection, have prompted hepatic resection as a primary therapeutic option for patients with functional and nonfunctional metastatic GEP NECs. Currently, hepatic resection of NLMs is recommended if the primary tumor and regional disease are resectable or resected, and greater than 90% of hepatic metastases are resectable or ablatable.

The concept of hepatic resection for NLMs has grown because of several clinical observations: [30]

1. the protracted natural history of NECs compared with other gastrointestinal tract cancers,

2. the often prolonged duration of intrahepatic disease before evidence of extrahepatic progression,
3. the clinical impression that the severity of clinical endocrinopathies correlates with the intrahepatic volume of metastatic disease,
4. the frequent resectability of the primary and regional neuroendocrine tumors despite metastatic disease, and
5. the rarity of underlying concomitant hepatic disease (fibrosis or cirrhosis).

3.2.1.1. Debulking strategy

When complete resection of gross liver disease is not feasible or in the presence of unresectable extrahepatic disease, resection as a tumor debulking strategy should be considered in patients with extreme hormonal symptoms refractory to other treatments or with tumors in locations that would affect short-term quality of life, such as large lesions abutting the hepatic hilum (resulting in biliary obstruction) or the colon/duodenum (resulting in gastrointestinal obstruction). [31, 32]

3.2.1.2. Subsequent plan for treatment of recurrence. [26, 33]

1. For solitary recurrences, either resection or ablation is appropriate. Percutaneous ablative approaches often are preferable.
2. Repeat hepatic resection is advised for lesions in sites that preclude safe radiofrequency ablation (RFA) (i.e., surface metastases adjacent to bowel, near bile ducts, or near diaphragm).
3. Sequential ablation or resection is undertaken as recurrence is recognized until precluded by extent of recurrence within the liver.
4. Extensive recurrent intrahepatic metastases are treated by embolization or chemoembolization with or without systemic chemotherapy in the absence of extrahepatic disease and chemotherapy in the presence of extrahepatic disease.

3.2.2. Liver transplantation

Liver transplantation (OLT) has been employed increasingly to treat metastatic NEC. OLT may be indicated if the primary and regional NEC has been resected, and distal metastases have been excluded. While transplantation has the benefits of removing all hepatic disease burden, rapid disease recurrence is near universal. Long-term actuarial survival among patients transplanted for NLM is poor compared with overall patient and graft survival rates for all indications. At present, liver transplantation cannot be considered a viable option for unresectable NLM. OLT should be considered as an investigative treatment alternative in specialty centers. [34]

3.2.3. Radiofrequency Ablation

Radiofrequency ablation (RFA) can provide local control and short-term symptomatic relief from NLM when resection is not possible. Successful ablation typically occur in the treatment of small metastases (<5 cm). [35-38]

3.2.4. Ethanol Ablation

Percutaneous ethanol injection permits ablation of metastases located adjacent to structures at risk of damage by RFA. It can be performed on metastases located adjacent to vital structures (e.g., the hepatic flexure of the colon); adjacent to large vessels vulnerable to the heat-sink effect; and adjacent to central bile ducts, where subsequent biliary stricture may occur. [61]

3.2.4.1. Guidelines for Ablation

General guidelines in the ablation of liver metastases are analogous to the treatment of hepatocellular carcinoma and colorectal metastases. [35-38]

There are three clinical scenarios for ablation of neuroendocrine hepatic metastases:

1. adjunct to concurrent surgical resection of hepatic metastases,
2. treatment of limited hepatic metastases in patients unfit for operation, and
3. primary therapy when clinical expertise or intraoperative circumstances preclude safe resection.

3.2.5. Hepatic arterial therapy

Because neuroendocrine tumors usually are highly vascular lesions that predominantly derive blood supply from the hepatic artery (as opposed to the normal hepatic parenchyma that derive the majority of blood supply from the portal vein), opportunities exist for selected ischemia of NLM and/or delivery of directed chemotherapy via hepatic artery therapy. Hepatic arterial embolization with cyanoacrylate, gel foam particles, polyvinyl alcohol, and microspheres have all been used to achieve distal embolization without surgical ligation of the hepatic artery. Chemoembolization provides an intratumoral concentration of chemotherapy that is 10 to 20 times higher than systemic administration.

Complete response and long-term survival are not common after hepatic arterial therapy, as the periphery of the tumor is spared from ischemia or chemotherapy. Thus, embolization of lesions close to the hepatic hilum is generally unsuccessful, as the periphery of the tumor will still cause mass-effect associated symptoms. [39, 40]

The morbidity of embolization approaches include liver abscess, transient liver failure, pleural effusion, and postembolization syndrome, the latter consisting of fever, abdominal pain, leukocytosis, and a transient increase in liver enzymes and/or bilirubin. Multiple sessions of therapy are often needed with varying intervals between sessions. Contraindications to hepatic arterial therapy include hepatic failure, portal vein occlusion, uncorrectable coagulopathy, and renal failure. [40]

3.2.6. Medical treatment

A- Somatostatin Analogues

Short-acting somatostatin analogue therapy is used to prevent or to treat the carcinoid crisis periprocedurally for any intervention, including resection, transplantation, ablation, or embolization. Somatostatin analogue treatment generally is well tolerated. Steatorrhea, diarrhea, abdominal discomfort, and biliary sludge or gallstones can develop, but rarely preclude continued use. [41]

B- Chemotherapy

Systemic chemotherapy generally is reserved for patients with advanced or progressive disease in whom other treatment efforts have failed Streptozocin-based combinations with 5-FU and doxorubicin have resulted in objective responses. Carcinoid tumors may be less sensitive to cytotoxic agents because of the preponderance of low-grade malignant (well-differentiated) histology and low proliferation index. [24]

C- Interferon Alfa

Systemic interferon alfa may be used to treat advanced NEC. The mechanism of interferon alfa is mediated through direct inhibitors of the cell cycle (G1/S phase) and of protein and hormone production, through antiangiogenesis, and indirectly through increased immune stimulation. Adverse reactions to interferon alfa are common. Chronic fatigue and hematologic cytopenias are the most common side effects. [42]

3.3. Primary hepatic neuroendocrine tumors

NECs may arise primarily within the liver. The diagnosis presumes a thorough search and exclusion of an extrahepatic NEC. The cell of origin is unknown. Pancreatic heterotopia has been postulated as a source of these tumors. Some tumors may arise from intrahepatic biliary tract radicles because carcinoids of the extrahepatic biliary tract are more common. Primary hepatic neuroendocrine tumors may be metastases from an occult primary NEC or a primary NEC that had spontaneously regressed. [24]

4. Non-colorectal Non-neuroendocrine Liver Metastases (NCNNLM)

Except for gastrointestinal primaries, the liver is not the primary filter for venous blood. In other words, liver metastases from nongastrointestinal cancers indicate systemic tumor spread; this makes selection of patients a crucial factor to offer hepatic resection to patients who may benefit the most.

Tumor biologies among NCNNLM vary widely, and their treatment requires dedicated multidisciplinary teams with expertise in diverse areas including hepatic surgery, surgical

oncology, medical oncology, radiation oncology, diagnostic imaging, and interventional radiology. Patient care must be individualized, especially in the absence of data to clearly guide therapy. [43]

4.1. Treatment options

4.1.1. Resectional treatment

The potential utility of surgery in NCNNLM relates to several factors:

1. advances in chemotherapy have led to effective control of extra hepatic disease for certain tumor types, supporting a rationale for surgical resection of LM in the presence of presumed or de facto systemic disease;
2. improvements in patient preparation for surgery, surgical technique and perioperative care have reduced the perioperative risk of hepatic resection, tipping the risk–benefit ratio in favor of surgical resection in selected cases;
3. the increased emphasis on multimodality treatment approaches has improved patient selection and strengthened the role of hepatic resection as a key component of integrated multidisciplinary care in selected patients with NCNNLM.

Although it might appear that patients with isolated liver metastases can benefit from hepatic resection, the proper selection of patients that may potentially benefit from treatment remains the most critical issue. Patient selection criteria depend on the primary tumor type. After selection based on patient performance status and evaluation of comorbidities, staging studies are required not only to assess the overall disease status of the patient but also to characterize liver lesions and their precise location relative to intrahepatic vascular structures. Assessment of the liver volume that will remain after resection is an equally important component of surgical planning for extensive hepatectomy. [43, 45]

Patient selection and oncologic outcome of metastasectomy depends fundamentally on complete resection of all disease. Preoperative studies are essential in defining both the extent and the limits of surgical resection. Hepatic volumetry to assess the planned future liver remnant (FLR) volume is a critical tool for the selection of patients who will undergo major hepatic resection If the future liver remnant is of inadequate volume, preoperative portal vein embolization can be used to induce hypertrophy of the future liver remnant to allow safe resection. Liver tumors are deemed resectable if preoperative evaluation shows that complete resection of the tumor-bearing liver leaves an adequate remnant volume with adequate vascular inflow, outflow, and biliary drainage. The treatment of each individual tumor type requires expertise in staging, systemic therapy, and hepatic surgery. [43, 45]

4.1.2. Nonresectional treatment

Percutaneous and intraoperative ablative techniques may play a role in the treatment of many types of liver tumors because the therapy

1. can be performed percutaneously or with minimally invasive approaches,

2. is associated with low morbidity and mortality, and

3. can help preserve liver parenchyma in selected patients.

The role of nonresectional ablative approaches for NCNNLM is not well defined. Data and experience are still accruing, and for now such treatment should be considered only in those centers that can provide the full spectrum of therapies for liver metastases. [43]

4.1.3. Hepatic arterial therapies

The utility of hepatic arterial therapies in the treatment of NCNNLM is not well understood. TACE, TAE, and hepatic artery infusion are not considered standard therapy for NCNNLM. For certain tumor subtypes, including unresectable soft tissue sarcomas (STS) and gastrointestinal stromal tumors (GIST), these approaches hold promise. [43, 45]

4.2. Specific tumor types

4.2.1. Gastrointestinal tumors

Overall reported survival rates for patients with NCNNLM from gastrointestinal tumors (esophageal, stomach, duodenum, pancreas, and small bowel) are worse than for those with nongastrointestinal LM.

4.2.1.1. Esophagus and stomach

Currently, there are no accepted indications for resection of esophageal cancer LM, either for palliation or cure. The justification for resection of gastric cancer liver metastases remains controversial. A few published series from Japan and Korea, where the incidence of gastric cancer is high, specifically address gastric cancer LM. Currently, hepatic resection for gastric adenocarcinoma cannot be recommended as standard of care. Data supporting hepatic resection in highly selected patients need confirmation by additional clinical studies. [43]

4.2.1.2. Small bowel

Metastases from small bowel adenocarcinoma are most often widespread and associated with a dismal outcome regardless of treatment. There currently are no data to support resection of small bowel LM except in highly selected cases. [43]

4.2.1.3. Anus

Liver metastases from anal adenocarcinoma are very uncommon, and a meaningful discussion of the indications for resection is difficult. [43]

4.2.2. Bile ducts and pancreas

4.2.2.1. Gallbladder, hilar bile ducts, and ampulla

There currently are no generally accepted indications for hepatic resection in patients with gallbladder cancer, cholangiocarcinoma, or ampullary carcinoma. Judicious recommendations should be made on a case-by-case basis. [43, 45]

4.2.2.2. Pancreas

Even for pancreatic carcinoma patients without LM, the overall survival is poor. LM from pancreatic adenocarcinoma occurs nearly always in the setting of disseminated systemic disease.. In the majority of cases, benefit cannot be expected from hepatic resection for this disease. [43, 45]

4.2.3. Breast

Although it has not been formally proven that liver resection prolongs survival for selected patients with liver metastases of breast cancer, recent studies suggest that with careful patient selection, resection of breast LM can produce long-term survival. Some authors also suggest that patients first should undergo systemic chemotherapy, and that only patients who do not progress should undergo liver resection. [45]

4.2.4. Genitourinary

4.2.4.1. Kidney

In patients with hepatic metastases of renal tumors in whom a complete resection seems possible, surgical exploration may be justified. The number of studies evaluating renal tumors including Wilms' tumors, renal cell adenocarcinomas, and nephroblastomas are few, and the cohorts of patients are small. [43, 45]

4.2.4.2. Testicle

Effective chemotherapeutic regimens are available for most reproductive tumors. Treatment with chemotherapy can lead to complete responses. Surgical resection is considered a necessary salvage treatment in the absence of complete radiographic response to systemic therapy, because residual teratomas have been known to degenerate into invasive carcinoma. [43]

"Salvage" hepatic resection may be considered because

1. resection is the only way to confirm a complete response in the residual liver masses,
2. teratomas may progress to malignant transformation in 30% of cases,
3. mortality and morbidity from hepatic resection is low, and
4. if feasible, concomitant resection of liver metastases and residual retroperitoneal disease is associated with favorable outcome.

Because of the small number of published cases, however, no general conclusions can be drawn.

4.2.4.3. Uterus and ovary

The concept of hepatic resection for LM from ovarian cancer has evolved from the fact that cytoreductive surgery can significantly alter the natural history of ovarian cancer metastatic to the peritoneum. Resection of ovarian LM may be considered in carefully selected patients that are candidates for complete cytoreduction after evaluation by a multidisciplinary team. [43]

4.2.5. Melanoma

Most patients with liver metastases of melanoma have unresectable disease owing to extrahepatic disease or disseminated hepatic metastases. Isolated liver metastasis from cutaneous melanoma is uncommon. Uveal melanoma is a distinct entity that seems to have a different tumor biology, and it commonly spreads to the liver.. Hepatic resection has been performed in both populations, although outcomes differ based on the primary site of origin. Hepatic resection for uveal or cutaneous melanoma should only be considered in a multidisciplinary setting and by experienced hepatic surgeons. [43, 45]

4.2.6. Adrenal

Hepatic resection can provide acceptable results in selected patients with limited adrenal metastases, particularly for palliation of symptoms in patients with secreting hepatic tumors. For patients with symptomatic disease who are not candidates for surgery, ablative therapy such as RFA may be an effective alternative therapy for symptom control. [43]

4.2.7. Soft tissue sarcoma and gastrointestinal stromal tumor

Hepatic resection for STS metastases is indicated for disease confined to the liver. Patients with retroperitoneal and intra-abdominal visceral STS and those with leiomyosarcomas are more likely to have liver-only metastatic disease than are patients with extra-abdominal STS.

The treatment strategy for patients with liver metastases from gastrointestinal stromal tumors has changed since the development of the targeted agent imatinib mesylate, which achieves dramatic tumor response rates. Imatinib is now the first-line treatment. Therapy with imatinib has revolutionized the treatment of patients with GIST and has been used alone and in conjunction with hepatic resection for GIST LM. “Complete” radiographic response assessed by CT or PET, including cystic changes after imatinib treatment of GIST, are not necessarily equivalent to complete pathologic response. Because hepatic lesions contain viable tumor in >85% of cases after chemotherapy and biologic therapy, the goal of surgical treatment is complete removal of all residual disease including small residual cystic lesions and “scars.” [43, 45]

4.2.8. Squamous cell carcinoma

Because the dataset is so heterogeneous, standard recommendations cannot be made, except that careful patient selection for hepatic resection is mandatory. [43]

4.2.9. Lung cancer

Resection of liver metastases of lung cancer has been reported, and in selected patients long-term survival has been achieved. [43]

4.2.10. Unknown primary cancer

Patients presenting with liver metastases from an unknown primary tumor are a challenge to manage because median overall survival is approximately 5 months. The treatment plan for these patients should be individualized and discussed in a multidisciplinary team. [43, 45]

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