Abstract Although radiographic studies usually provide accurate preoperative staging information in colorectal cancer patients, intraoperative frozen section evaluation of extracolonic tissues may be requested in order to confirm the diagnosis of a metastasis or ensure its complete resection. The liver represents the most common site of distant organ metastases from colorectal cancer. Several benign lesions may simulate liver metastases, most notably von Meyenberg complexes and bile duct hamartomas. Peritoneal carcinomatosis is also an important intraoperative finding that may alter the surgical management of colon cancer patients. A number of mimics of peritoneal carcinomatosis are encountered in the frozen section laboratory.

Keywords Metastasis · Liver · Bile duct hamartoma · Peritoneal carcinomatosis

Introduction

Radiographic studies provide accurate preoperative staging information for most colorectal cancer patients, although surgeons may observe unsuspected abnormalities during exploratory laparotomy that warrant intraoperative consultation. Frozen section evaluation of extracolonic tissues may be requested by the surgeon in order to
confirm a diagnosis of metastasis, ensure complete resection of a metastatic deposit, or to make a diagnosis on a newly discovered lesion. Thus, it is important for pathologists to be familiar with the morphologic characteristics of colorectal carcinoma, as well as those of a variety of entities that may simulate the appearance of a metastasis.

Liver Metastases

**Gross Features**

The liver is the most common site of distant organ metastasis from colorectal cancer, and up to 25% of patients with colon cancer have liver metastases at the time of surgery. However, unlike many cancer patients, some individuals with colorectal carcinoma may undergo resection of limited liver metastases, since this procedure improves outcome in a subset of patients. The aim of surgery is complete tumor resection with maximal preservation of liver function [1]. Therefore, intraoperative evaluation may be required to determine the adequacy of hepatic resection [2]. Hepatic metastases of colorectal carcinoma typically appear as one, or more, relatively well-circumscribed tan, white nodules unassociated with cirrhosis (Fig. 2.1). They may have a depressed, variegated cut surface owing to the presence of extensive necrosis.

**Microscopic Features**

Colorectal cancer metastases usually consist of overtly malignant infiltrative glands, many of which contain abundant necrotic luminal debris (Fig. 2.2). Most show a variable amount of desmoplastic stroma surrounding tumor cells, although the stroma may show hyalinization, particularly when patients have received prior chemotherapy. Tumors that have been treated with embolization may be entirely non-viable.
Metastatic colorectal cancer deposits are *pale yellow*, or *white*, with a loculated rim. They may contain depressions that reflect tumor necrosis. The amount of resected liver is largely determined by the anatomic location of metastases, although margins may be close in order to maximally preserve hepatic function.

**Differential Diagnosis**

Several benign liver lesions may simulate colorectal cancer metastases [3–8] (Table 2.1). Most are detected during laparotomy and, thus, may prompt intraoperative consultation. The most common entities to consider in the differential diagnosis of metastatic carcinoma include von Meyenberg complexes (bile duct hamartomas) and biliary adenomas [2]. Both types of lesions appear as small, tan-white nodules, which may be multiple (Fig. 2.3). Bile duct hamartomas are well-circumscribed proliferations of variably cystic ductules enmeshed within hyalized stroma. The ducts are lined by flattened, or cuboidal, epithelium without cytologic atypia and may contain bile plugs (Fig. 2.4). Biliary adenomas contain a proliferation of small bile ductules within compact, cellular stroma. The ductules are lined by bland cuboidal epithelial cells with mild cytologic atypia and generally do not contain bile (Fig. 2.5).
Fig. 2.2 Metastatic colorectal cancer deposits are composed of malignant glands that contain abundant luminal necrotic debris (a) or are enmeshed within desmoplastic stroma (b).
Table 2.1  Mimics of metastatic colorectal carcinoma in the liver

- Von Meyenberg complex
  - Often multiple
  - Firm, white subcapsular nodules
  - Cystic ducts lined by bland, flattened epithelium
  - Dense, hyalinized stroma
  - Bile often present in ductules
  - No atypia, mitoses, or necrosis

- Biliary adenoma
  - Often multiple
  - Well-circumscribed, firm, grey-white subcapsular nodules with central depression
  - Compact proliferation of small tubular ducts with abundant cytoplasm and pale nuclei
  - Lack cystic dilatation and bile
  - No atypia, mitoses, or necrosis

- Hemangioma

- Multifocal fatty infiltration
  - Multiple radiographically apparent spherical densities
  - Macrovesicular steatosis in liver biopsy material

- Solitary necrotic nodule of the liver
  - Necrotic core surrounded by hyalinized fibrotic tissue

- Abscess

- Extrinsic compression by primary neoplasm or diaphragmatic implants

Peritoneal Disease

Peritoneal carcinomatosis describes widespread intra-abdominal metastases and, with the exception of low-grade appendiceal mucinous neoplasms, is not amenable to surgical debulking. In fact, detection of peritoneal metastases during exploratory laparotomy impacts the subsequent management of the patient and may alter the surgical procedure, so intraoperative evaluation plays a vital role in the care of patients with suspected tumor involvement of the peritoneal cavity [1, 9, 10]. Peritoneal carcinomatosis may appear as gray, or white, nodules within the peritoneal fat or studding the serosal surfaces of the viscera (Fig. 2.6). Colorectal cancers with mucinous differentiation disseminate in the form of implants comprised of pools of mucin that contain neoplastic
Fig. 2.3 Von Meyenberg complexes are round, *gray-white* nodules that may be multiple (*arrows*). Most are subcapsular and, thus, evident to the surgeon, who may submit them for frozen section analysis.

Fig. 2.4 Bile duct hamartomas contain mildly dilated tubules lined by cuboidal, or attenuated, epithelial cells without atypia. Occasional tubules may contain bile (*arrow*). The surrounding stroma is eosinophilic and rich in collagen, which may be hyalinized.
Fig. 2.5 Bile duct adenomas may closely simulate metastatic deposits of adenocarcinoma because they contain numerous proliferating tubules enmeshed within cellular stroma (a). However, the lesional cells are cytologically bland and contain abundant cytoplasm with uniform, pale nuclei (b)
Fig. 2.6  *Pale pink* or *gray* nodules on the visceral serosa reflect peritoneal carcinomatosis. Cancers with striking desmoplasia are firm and gritty, whereas those with mucin production are soft and gelatinous epithelial cells arranged singly or in nests and glands (Fig. 2.7). Tumor cells typically show marked cytologic atypia and mitotic activity, although mucinous neoplasms derived from the appendix may appear deceptively bland, resulting in considerable diagnostic confusion, as discussed in Chapter 6.

**Differential Diagnosis**

Two common mimics of peritoneal carcinomatosis may be encountered in samples submitted for frozen section analysis because both may grossly appear as one or more ill-defined gray, or white, nodules within peritoneal fat or on the intestinal serosa (Fig. 2.8). Mesenteric fat necrosis may simulate the appearance of metastatic poorly differentiated carcinoma, since the aggregates of macrophages display abundant cytoplasm and may show patchy cytologic atypia (Fig. 2.9a). Clues to the diagnosis include the presence of fat vacuoles surrounded by macrophages, mixed inflammation, dystrophic calcifications, and multinucleated cells
Fig. 2.7 Peritoneal deposits of mucinous carcinoma consist of dissecting mucin pools, some of which contain strips or clusters of malignant epithelium. Overtly malignant tumor deposits such as this one are not amenable to surgical debulking or peritoneal stripping.

Fig. 2.8 Fat necrosis may appear as yellow-white lobulated excrescences on the serosal surface (arrow).
Fig. 2.9 Sheets of macrophages in fat necrosis may simulate the appearance of carcinoma (a). Clues to the diagnosis include the presence of mixed background inflammation and variably sized vesicles of extracellular fat (b).
Papillary mesothelial hyperplasia is limited to the peritoneal surfaces and consists of an exuberant proliferation of mesothelial cells. Papillae contain loose fibrous connective tissue and are lined by a single layer of mesothelium (a). Mesothelial cells contain abundant eosinophilic cytoplasm and small, round nuclei without appreciable mitotic activity (b).
Intraoperative Evaluation for Extracolonic Disease

(Fig. 2.9b). Benign mesothelial proliferations, such as localized papillary mesothelial hyperplasia and reactive mesothelial hyperplasia, contain mildly atypical mesothelial cells that display complex architectural growth patterns (Fig. 2.10a). These lesions should be readily distinguished from metastatic colonic carcinomas, since the latter generally metastasize in the form of infiltrating glands and single cells. Most colorectal carcinomas also show overtly malignant cytologic features with nuclear irregularities and hyperchromasia, whereas mesothelial cells have abundant eosinophilic cytoplasm and uniform, round nuclei evident upon frozen section analysis (Fig. 2.10b). Epithelial cell proliferations of Mullerian derivation may simulate the appearance of peritoneal carcinomatosis and are discussed more fully in Chapter 3. Common benign mimics of metastatic carcinoma to the peritoneal cavity are enumerated in Table 2.2 [11–13].

Table 2.2  Peritoneal lesions that may simulate peritoneal carcinomatosis

- Mesenteric and omental fat necrosis
- Mesothelial lesions
  - Cysts
  - Localized papillary hyperplasia
  - Mesothelial hyperplasia with reactive atypia
- Peritoneal infections (Mycobacterium tuberculosis, Actinomyces)
- Endometriosis
- Florid endosalpingiosis

References