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Extrahepatic spread of hepatocellular carcinoma: a pictorial review

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Abstract Although extrahepatic spread of hepatocellular carcinoma (HCC) is uncommon, it can be found anywhere in the body. Most extrahepatic metastases of HCC occur in patients with advanced-stage intrahepatic tumor, but incidental extrahepatic lesions have also occasionally been found in patients with early-stage intrahepatic HCC. The detection of extrahepatic metastatic disease is crucial when planning therapy for patients with HCC and should be used to avoid unnecessary surgical intervention. In this study we illustrate the radiologic findings of extrahepatic metastases of HCC involving various sites. The presumed mechanism of extrahepatic extension of HCC is also discussed.

Keywords Hepatocellular carcinoma · Metastases · Liver neoplasms · Liver

Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy. It has a very aggressive clinical course, with a mean survival rate of much less than a year if left untreated. Because of its rapid clinical course, the extrahepatic spread of HCC is uncommon, but longer survival may also lead to an increased incidence of metastasis in patients who respond to treatment. Hepatocellular carcinoma metastasizes to anywhere in the body by way of the blood, direct spread, or lymphatic spread. If HCC is limited in the liver, curative surgical therapies, such as surgical resection or orthotopic liver transplantation, may be offered, but the patient will be left with only palliation if extrahepatic spread exists; thus, recognition of extrahepatic metastasis is important for planning treatment. Most extrahepatic metastases of HCC occur in patients in an advanced stage of intrahepatic tumor, but incidental extrahepatic lesions have occasionally been found in patients with early-stage intrahepatic HCC. Knowledge of the location and radiologic appearance of the extrahepatic spread of HCC is important in order to assure the choice of the most appropriate therapy and therefore to assure patients the best chance for longer survival [1, 2, 3, 4, 5].

In this article we discuss the radiologic findings of the extrahepatic spread of HCC involving various sites.

Pulmonary and circulatory system involvement

The most frequent site of HCC metastasis is the lung [1]. The most common manifestation consists of one or more nodules within the lung parenchyma (Fig. 1). These are usually derived from small tumor emboli lodging in peripheral pulmonary arteries or arterioles, with subsequent extension into the adjacent parenchyma. There are multiple nodules that tend to be more numerous in the lower lobe basal segment of the lung, reflecting the gravity-induced preferential blood flow. Tumor cells are carried to the lungs in the blood stream through the inferior vena cava or lymph draining from the main or right thoracic duct [1, 2, 3].

Tumor thrombus in the right atrium tends to extend continuously from the liver tumor through the inferior

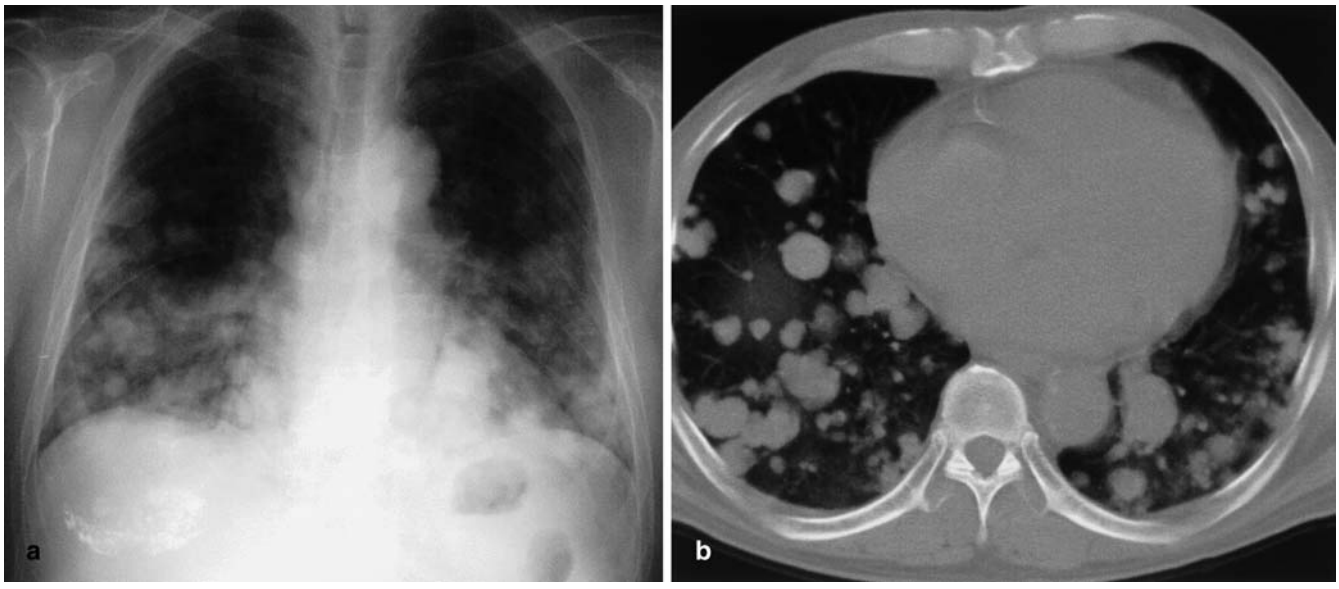

Fig. 1a, b Lung metastases. **a** Chest radiography and **b** chest CT show numerous nodules in both lungs. The nodules tend to be more numerous in both lower lungs than in the upper lungs. Note a parse Lipiodol-laden mass in the liver on chest radiography

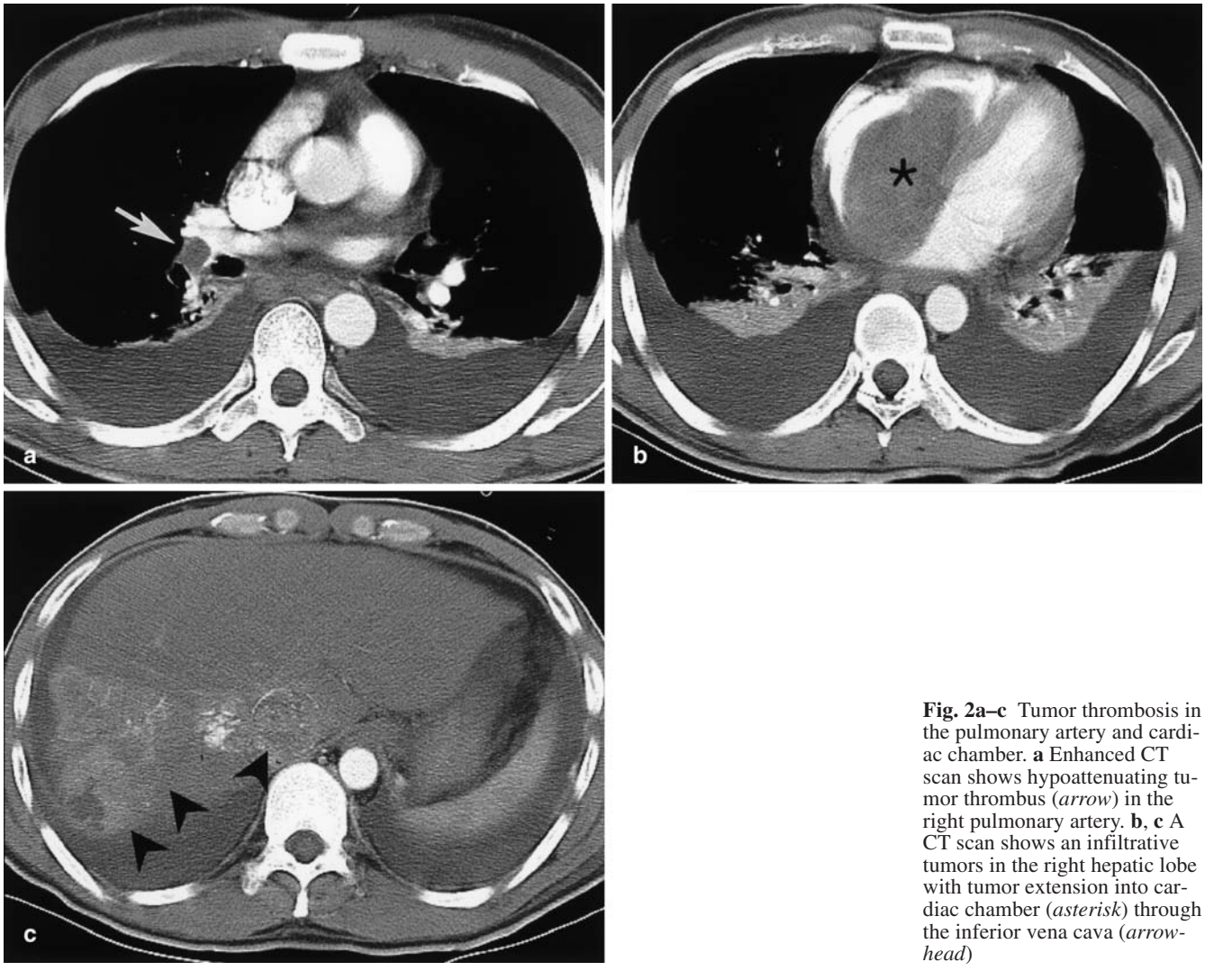

Fig. 2a–c Tumor thrombosis in the pulmonary artery and cardiac chamber. **a** Enhanced CT scan shows hypoattenuating tumor thrombus (*arrow*) in the right pulmonary artery. **b**, **c** A CT scan shows an infiltrative tumors in the right hepatic lobe with tumor extension into cardiac chamber (*asterisk*) through the inferior vena cava (*arrowhead*)

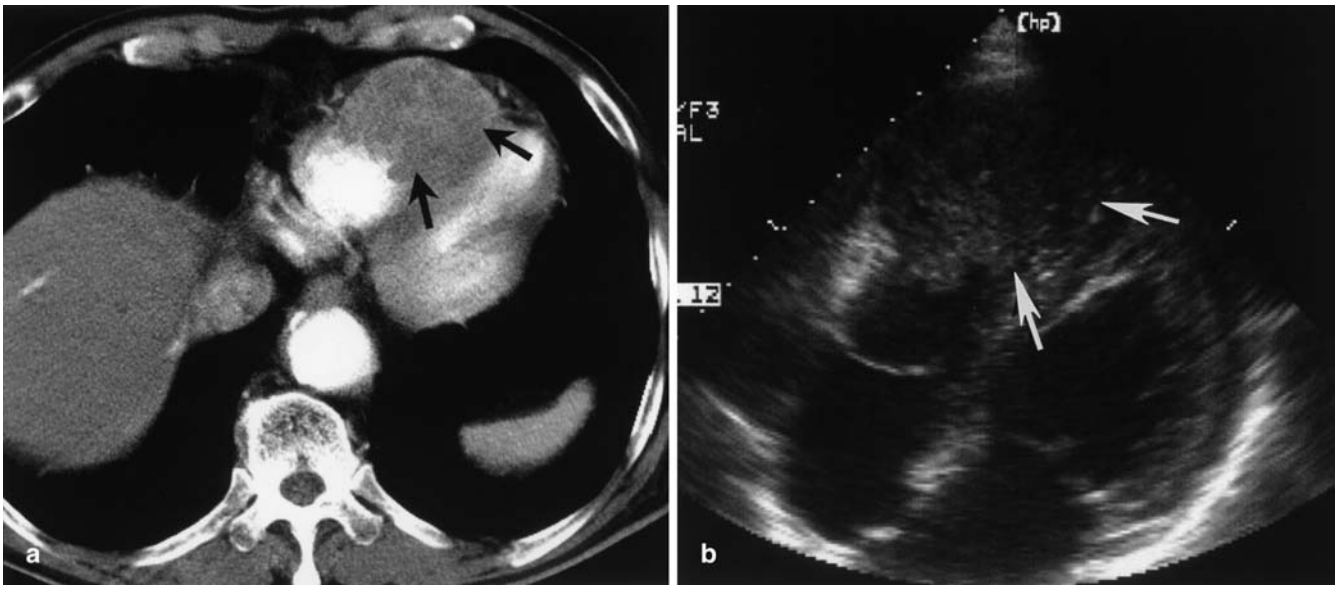

Fig. 3a, b Heart metastasis. **a** Enhanced CT scan shows an irregular hypoattenuating mass (*black arrows*) in the right ventricle. **b** Echocardiography shows an ill-defined hypoechoic mass (*white arrows*) in the right ventricle

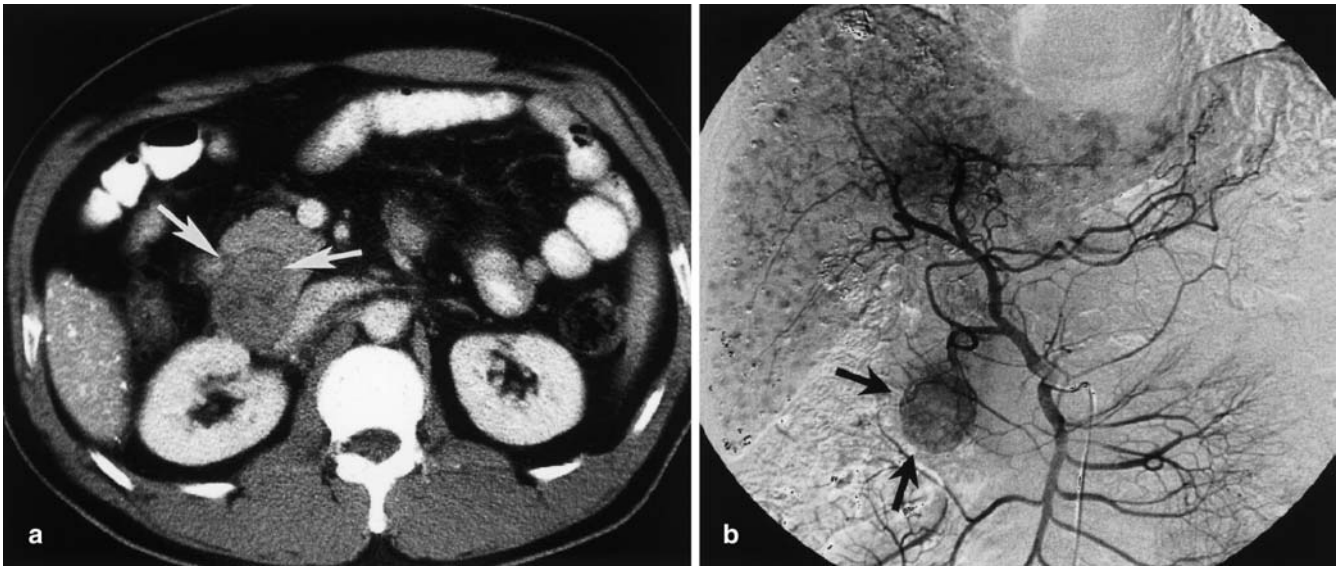

Fig. 4a, b Lymph node metastasis. **a** Abdominal CT scan shows an enlarged lymph node with heterogeneous low attenuation (*arrows*) in the peripancreatic space. **b** Celiac arteriography shows hypervascularity at the peripheral portion of the enlarged lymph node (*arrows*). Multiple small tumor stainings are seen in both lobes of the liver

vena cava and may also invade the cardiac muscles (Fig. 2). The most frequent route of HCC metastasis to the lung is the transvenous route of extension of the tumor thrombus into the right atrium via the inferior vena cava; thus, the right atrium and ventricle are more common than the left side of the heart or the pericardium and tends to be accompanied by lung metastasis [6]. Another usually rare condition is HCC metastasis in the cardiac muscles (Fig. 3). The possible routes of rare metastasis to the heart and pericardium are via lymphatic channels in the mediastinum, which produces tumor implants on the epicardial space. In the presence of metastatic cardiac tumors, it is important to evaluate the relationship between the tumor and the cardiac muscles and valves [6].

Gastrointestinal system or intraperitoneal involvement

The second most common metastatic site of HCC, after the lung, is the regional abdominal lymph nodes. Regional lymphadenopathy can occur in the portohepatic, peri-

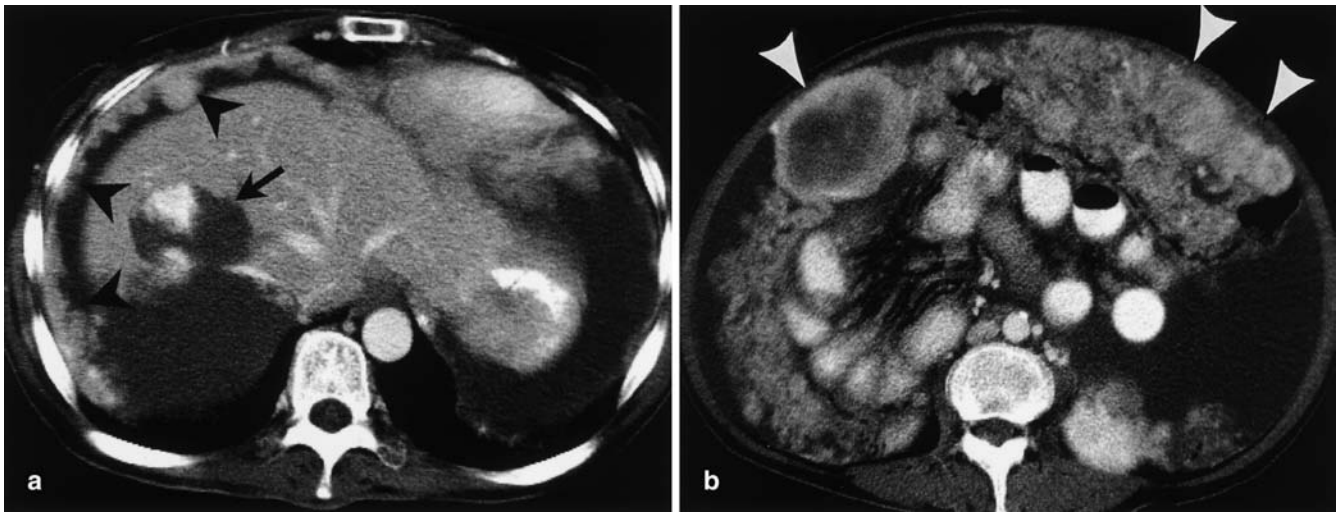

Fig. 5a, b Peritoneal metastases. The CT scan shows multiple conglomerated nodules in the peritoneal cavity (*arrowheads*). Note a hemangioma (*arrow*) in the right lobe dome of the liver

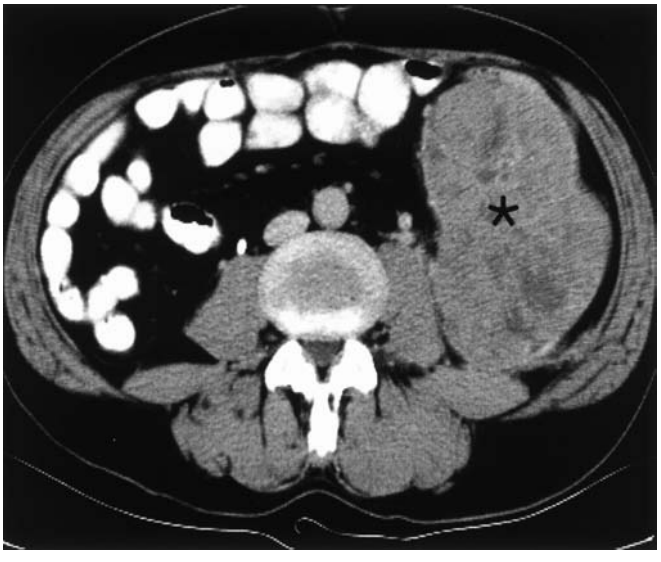

Fig. 6 Peritoneal metastasis. The CT scan shows a lobulated mass with central necrotic area in the left lower abdomen (*asterisk*)

pancreatic, gastroduodenal, portacaval, aortocaval, and para-aortic nodal sites within the upper abdomen. Most regional lymphadenopathy has been seen in the peri-celiac and the portohepatic lymph nodes (Fig. 4) [1].

The incidence of peritoneal implantation from HCC has been reported to be 2–16%, and it is markedly lower than that of peritoneal metastases from other primary hepatic malignancies. The pathway of peritoneal seeding from HCC is thought to be a rupture of exophytic HCC into the peritoneal cavity and subsequent seeding of metastatic deposits. Radiologic manifestations of the intraperitoneal spread of HCC are single or multiple discrete masses located in the peritoneal cavity [7]. The

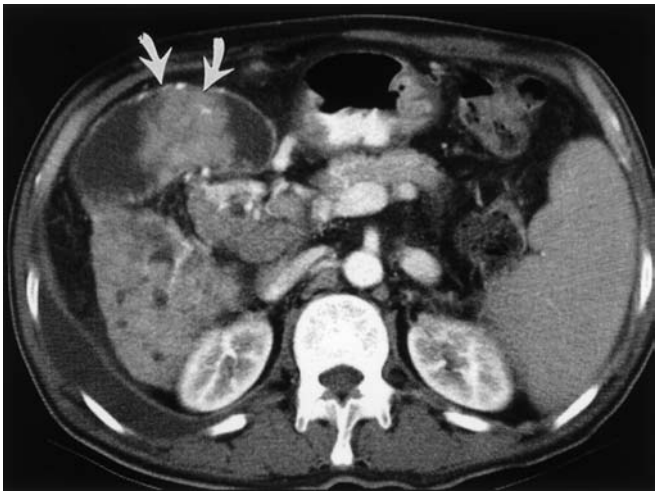

Fig. 7 Gallbladder metastasis. The CT scan shows a well-enhancing mass (*arrows*) in the gallbladder

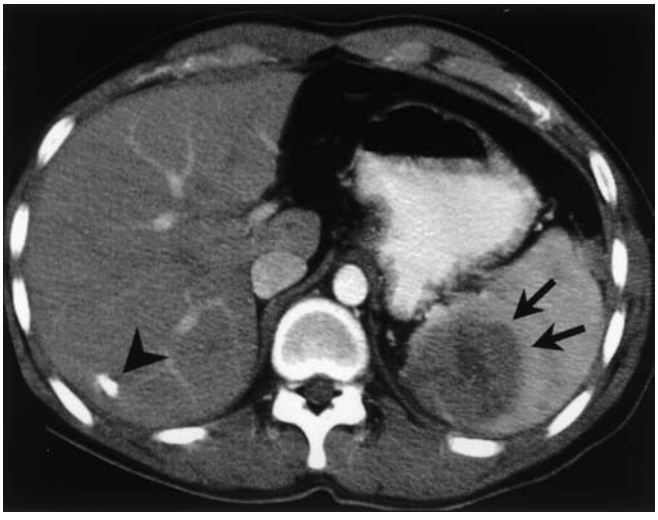

Fig. 8 Splenic metastasis. The CT scan shows a round hypoattenuating mass (*arrows*) in the spleen. Note a small Lipiodol-laden nodule in the right lobe of the liver (*arrowhead*)

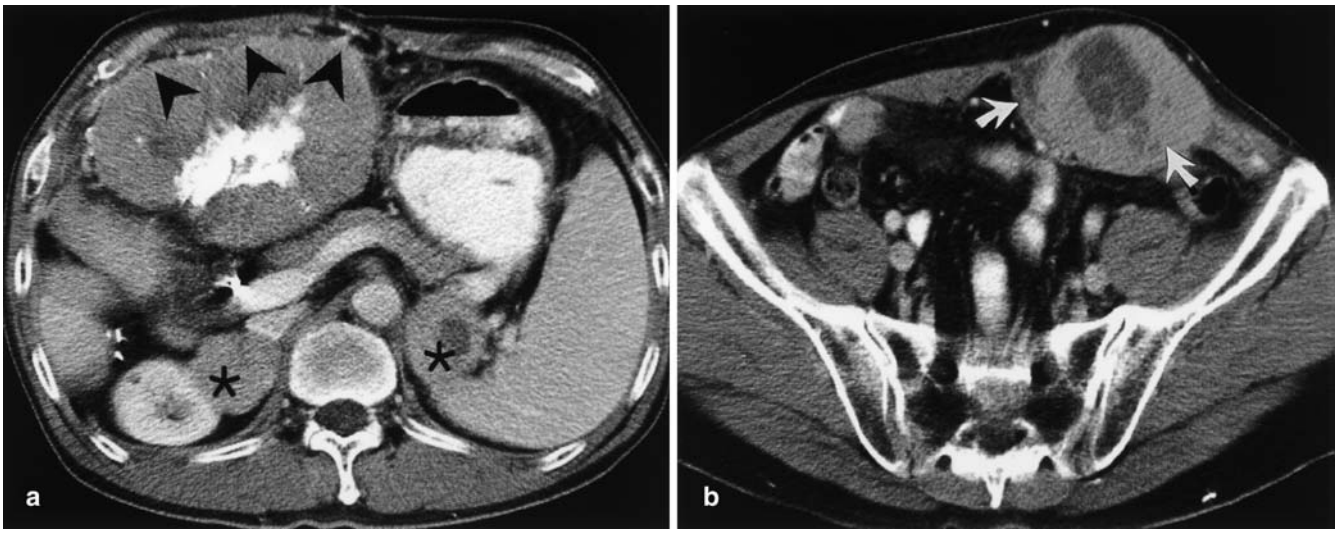

Fig. 9a, b Adrenal gland and abdominal wall metastases. **a** The CT scan shows round, well-defined masses in the bilateral adrenal gland (*asterisks*) and exophytic-growing tumor from the left lobe of the liver (*arrowheads*). **b** The CT scan shows a well-enhanced mass with central necrosis (*arrows*) in the abdominal muscle

Fig. 10 Kidney metastasis. The CT scan shows a hypoattenuating mass (*asterisk*) in the right lobe of the liver and a contour-bulging mass with heterogeneous low attenuation (*arrows*) in the right kidney. An enlarged lymph node in the lateral aortic or aortocaval space is also noted (*arrowheads*)

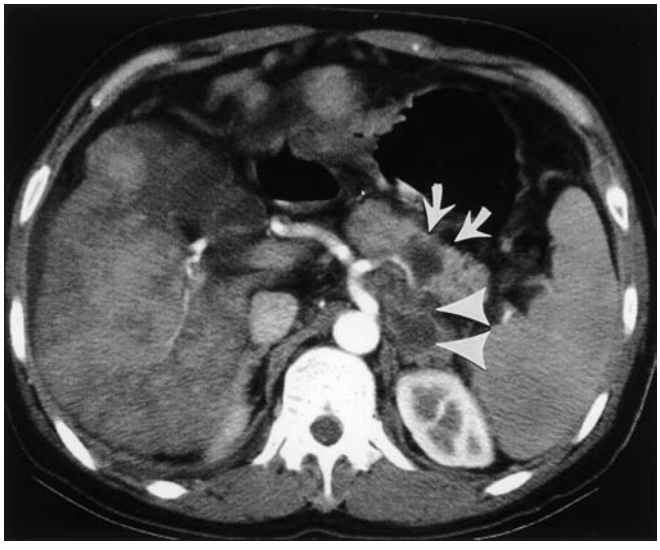

Fig. 11 Pancreas metastasis. The CT scan shows an irregular mass (*arrows*) in the pancreatic tail and a hypoattenuating mass in the left adrenal gland (*arrowheads*)

internal heterogeneity and necrosis frequently seen in intraperitoneal masses reflect the characteristics of hepatic HCC. Intraperitoneal masses are hypervascular, such as primary hepatic masses, and are most commonly supplied by the omental branches (Figs. 5, 6) [7, 8].

Gallbladder and splenic HCC metastasis are rare. Gallbladder involvement of HCC shows focal wall thickening, one or more polypoid masses, or replacement of the gallbladder by the neoplasm (Fig. 7). Splenic involvement of HCC produces single or multiple discrete nodules (Fig. 8). Most instances of metastastic cancer to the spleen result from hematogeneous spread of the disease via splenic arterial blood flow; however, HCC metastasis is believed to be able to spread to the spleen via the splenic vein in patients with portal hypertension or via the lymphatics in a retrograde fashion [1, 2, 3].

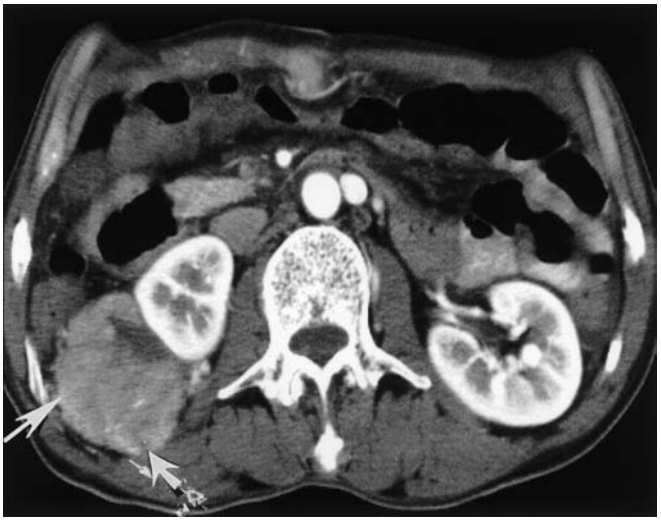

Fig. 12 Retroperitoneal metastasis. The CT scan shows anteromedial displacement of the right kidney due to a lobulated-contour, hypervascular mass (*arrows*) in the pararenal space

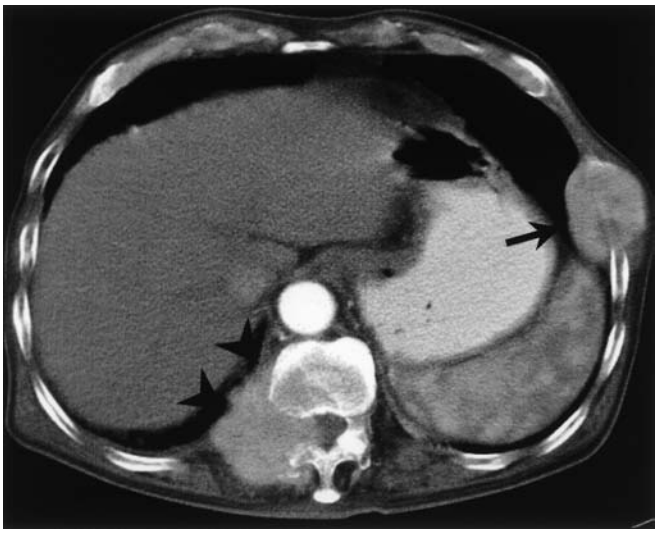

Fig. 13 Skeletal metastases. Abdominal CT scan shows an expansile hypervascular mass with bony destruction (*arrowheads*) in the lumbar vertebrae and chest wall (*arrows*)

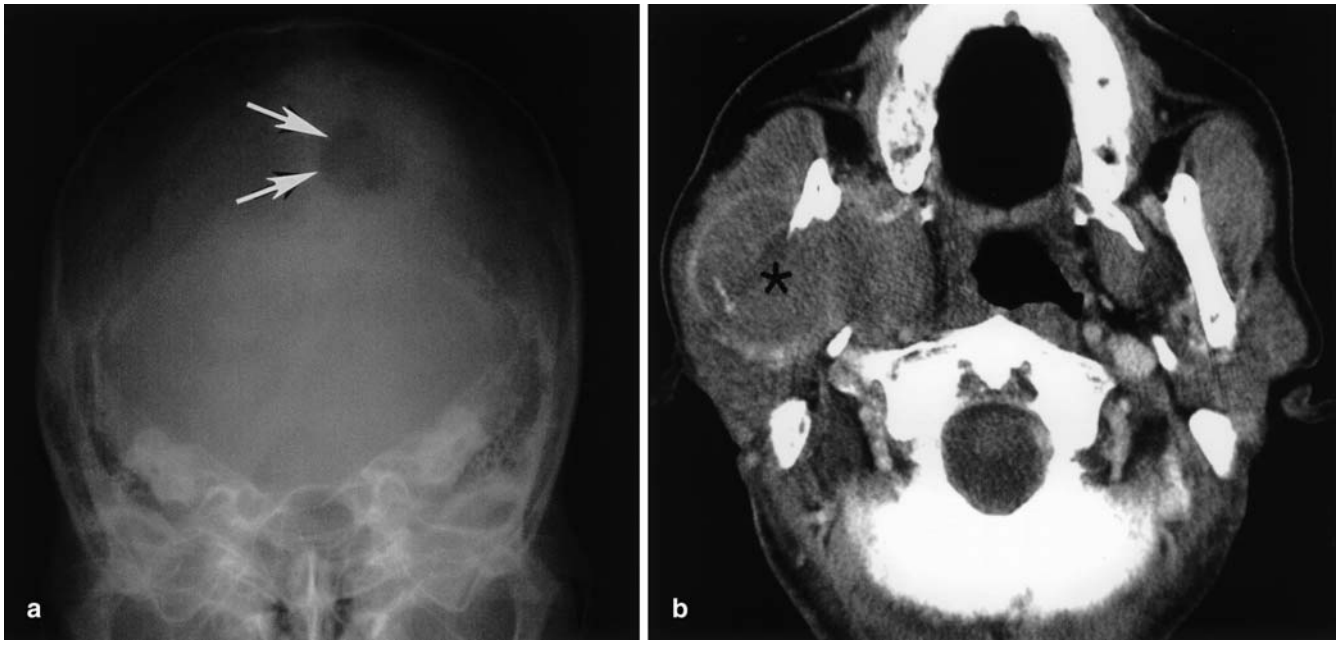

Fig. 14a, b Skull and mandible metastases. **a** Town's view shows an osteolytic lesion in the left parietal bone (*arrows*). **b** The CT scan shows a rim-enhancing mass with bony destruction in the mandibular body (*asterisk*)

Genitourinary system and retroperitoneal involvement

The reported incidence of adrenal metastasis at autopsy ranges from 1.2 to 21% [3]. Contrast enhancement characteristics vary from lack of enhancement to marked enhancement [1]. The right and left adrenal glands are equally affected. Strong enhancement during the arterial phase, when present, can be used to differentiate from adrenal adenoma (Fig. 9) [9].

Most renal metastases reach the kidney via a hematogeneous route. The common manifestations of renal metastases are small, multiple, and bilateral renal lesions. They usually show contrast enhancement and are best seen on post-contrast CT scans. Most lesions remain within the renal contour; however, larger metastases may project from the renal contour (Fig. 10).

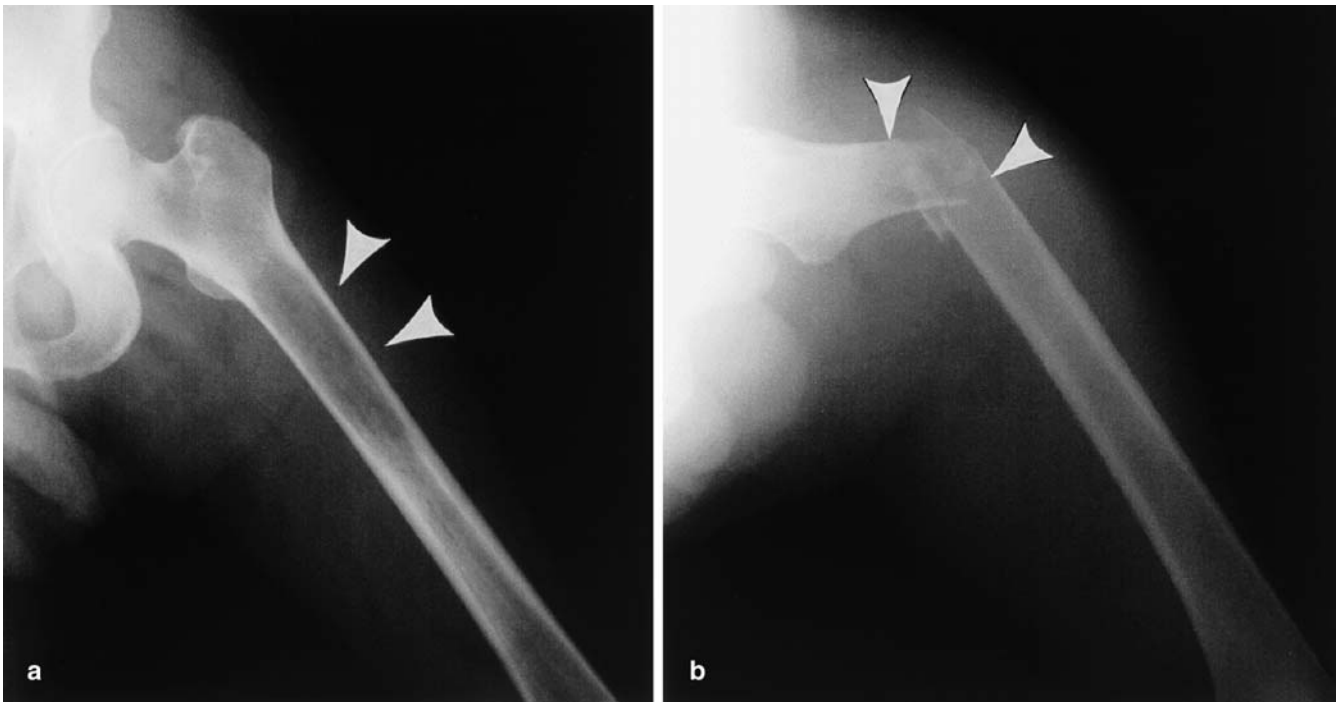

Fig. 15a, b Extremity metastasis. **a** Radiography of the femur shows an osteolytic lesion in the left femoral shaft. **b** Pathologic fracture occurred 3 months later (*arrowheads*)

Fig. 16 Acral metastasis. Hand radiography shows an osteolytic lesion (*arrows*) in the carpal bones

Metastases to the pancreas occur occasionally via hematogeneous spread [2]. The HCC pancreatic involvement is seen as unifocal or multifocal masses with contrast enhancement (Fig. 11).

Differentiation between a pedunculated HCC and a metastatic tumor to the retroperitoneal space is sometimes difficult, but it is important for exact preoperative localization and chemoembolization. The bare area is continuous from the perirenal space and the dropped HCC tumor cells in the retroperitoneum can subsequently form a retroperitoneal mass (Fig. 12).

Skeletal system involvement

The incidence of metastasis to the osseous system from HCC ranges from 2 to 28%. The osseous metastasis is mostly osteolytic lesion with a hypervascular expansile soft tissue mass, more than two-thirds of which involve the lumbosacral or thoracic spine (Fig. 13). Osseous metastasis probably originates from blood-borne tumor emboli rather than from lymphatic spread; however, in most cases, metastases coexist in the bone and the neighboring lymph nodes. Bones with red marrow, such as vertebrae, ribs, skull, proximal femur, and humerus, are the preferential sites of metastatic deposits (Figs. 14, 15).

Occasionally, osseous metastasis occurs without involving the lungs or viscera. According to the experimental study by Batson, when pressure in the abdomen is increased, blood may bypass the caval systems into the vertebral plexus veins. Blood connects with the venous and sinusoidal systems of the bones of the spine,

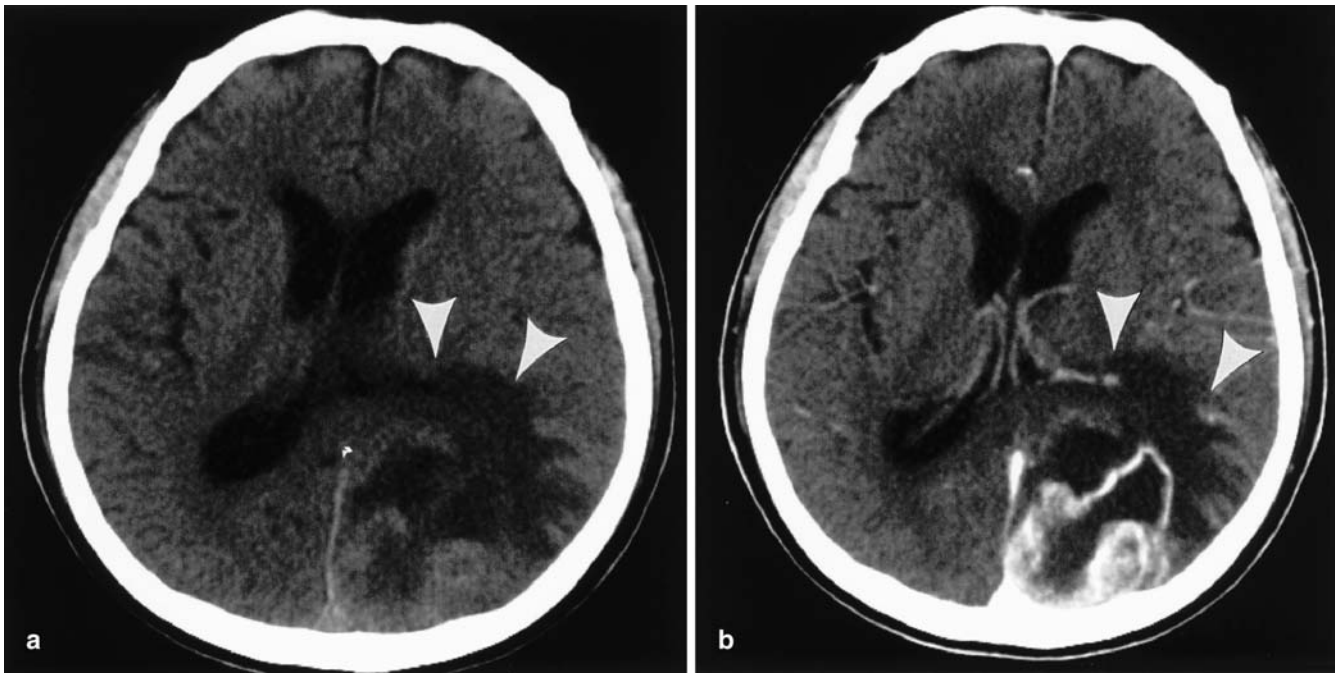

Fig. 17a, b Brain metastasis. **a** Unenhanced CT scan shows extensive edema (*arrowheads*) in the left parieto-occipital lobe with mass effect. **b** Contrast-enhanced CT scan shows a rim-enhancing mass in the left parieto-occipital lobe

shoulder, skull, and even as far as the region of the elbows or knees without having to flow through the heart or lungs.

Metastasis to the bones distal to the knees or elbows is known as acral metastasis and is extremely rare. Distal extremity and acral metastases are usually secondary to arterial dissemination related to a malignant tumor in the lung (Fig. 16).

The HCC involvement of the chest wall and paravertebral muscle is only infrequently seen (Fig. 13).

Central nervous system involvement

Metastasis to the central nervous system is uncommon with the incidence ranging from 0.6 to 7.7%. Brain parenchymal metastasis is the most common central nervous system manifestation of HCC. Intracranial metastases usually appear in the form of parenchymal lesions, rarely presenting with leptomeningeal seeding. Gray–white matter junction and watershed zonal predominance suggest hematogeneous metastasis and the frequent hemorrhagic tendency reflects tumor hypervascularity [10].

The CT findings include parenchymal hemorrhage in the watershed zone with a rim enhancement or an adjacent enhancing mass at the gray–white matter junction (Fig. 17).

Conclusion

Detection of the extrahepatic spread of HCC has increased with the improvement of imaging techniques and survival rates have improved due to recent progress in treatment. Understanding the frequent locations and typical radiologic findings of the extrahepatic spread of HCC is important in order to prevent unnecessary surgical resection or liver transplantation in patients with extrahepatic metastases.

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