Problems in staging of pancreatic and hepatobiliary tumours

Bruno M. Schmied, Kaspar Z'graggen, Claudio A. Redaelli and Markus W. Büchler

Department of Visceral and Transplantation Surgery, Inselspital, University of Bern, Bern, Switzerland

Introduction

Surgery plays a key role in the therapy of hepatobiliary and pancreatic cancer and 80–90% of patients undergo surgery at least once. Although it is at present the only modality with a chance for long-term survival, curative surgery can be performed in only 40–50% of patients referred to specialised surgical institutions. Staging is an essential step in the management of patients with hepatobiliary and pancreatic tumours. Preoperative staging should ideally distinguish resectable from unresectable disease and sort out candidates that are best managed by palliative non-surgical treatment. Intraoperative staging determines resectability and the adequate surgical procedure for a specific patient and finally postoperative and histopathological staging (pTNM) may indicate the appropriate adjuvant therapy and should predict outcome.

Metastatic and locally invasive hepatobiliary and pancreatic malignancy is, with a few exceptions, not amenable to resection and less so to curative surgery. Therefore the detection of tumour spread into distant organs or locally into vessels is a crucial part of staging procedures to determine resectability. So far, this issue was often answered during explorative laparotomy but recent advances in radiological techniques and diagnostic laparoscopy improved assessment of tumour extension before laparotomy. This article discusses the problems in the preoperative staging and detection of local invasion and metastases in hepatobiliary and pancreatic cancer.

Preoperative staging

Percutaneous and endoscopic ultrasound

The majority (70–90%) of patients with pancreatic or hepatobiliary carcinoma present with obstructive jaundice and ultrasonography (US) is often used as the first imaging modality. The accuracy of US can exceed that of computed tomography (CT) and the application of endoscopic ultrasound (EUS) promises further improvement for small lesions that are anatomically close to the stomach and the duodenum [1]. In experienced hands, well-defined structures can be traced down to less than 10 mm [2]. US is an excellent technique to determine the level and aetiology of a bile duct obstruction and provides information about the extension of an obstructive mass such as a cholangiocarcinoma. In patients with hepatocellular carcinoma (HCC) US is a reliable and routinely used screening tool and often allows the detection of solitary tumours without (T1) and with invasion into the hepatic or portal veins (T2, T3) and multifocal lesions (T4). For surgical purposes we advocate an additive use in conjunction with CT.

The main disadvantages of sonography are its observer dependency and its limitations in obese patients. Moreover quality EUS is currently not available in all institutions. Many surgeons have also difficulties creating virtual three dimensional images of tumour extension and prefer CT and/or MRI. Therefore, sonography is often used in screening and for specific questions, such as the vicinity of a tumour to portal veins in hilar cholangiocarcinoma. Vascular involvement (T4) of hepatobiliary cancer can be assessed by colour Doppler US with high accuracy (91%) [3] and in combination with endosonography (ES) [4] infiltration of duodenum and peripancreatic tissue (T3) can be detected in pancreatic cancer. Lymph node size is not a reliable indicator for the presence of metastasis and differentiation between reactive and malignant lymph nodes is notoriously difficult. Moreover the presence of lymph node metastasis does not change treatment or exclude a patient from potentially curative surgery [5]. Small liver (<3–5 mm) and peritoneal metastases may be missed by US in more than 15%.

Computed tomography scan (CT)

Progress of diagnostic imaging techniques especially standardisation of the spiral abdominal CT clearly

improved tumour staging of pancreatic and hepatobiliary cancer and became the current gold standard for preoperative staging [6]. Nevertheless, CT is often used in combination with other techniques. Its accuracy to diagnose pancreatic cancer is more than 90% [7] because benign non-cystic pancreatic tumours are rare. The distinction between malignancy and an inflammatory mass of the pancreatic head in a patient with chronic pancreatitis may be difficult [8]. In a recent study, it allowed to predict tumour resectability in 72% and its sensitivity and specificity for irresectability was 78 and 76%, respectively [9,10]. Although its predictive value for vascular infiltration was 88% in a recent publication [10], the radiological assessment of local tumour extension, e.g. the degree of vascular encasement and institutional resectability rates are variable [11–13]. Tumours in the head of the pancreas can also originate within the ampullary tissue (papilla, distal common bile duct, duodenum) and these cancers represent different tumour biologies with a more favourable outcome. The prognostic value of CT in these patients is therefore limited.

CT is capable to detect solitary, multifocal or diffusely infiltrating HCC. Small HCC (less than 1–2 cm in diameter) can be difficult to diagnose using dynamic intravenous-contrast enhanced CT with a detection rate of only 50–58% [14]. More advanced modalities such as CT during arteriography or CT following injection of Lipiodol may increase the diagnostic accuracy for early HCC to 90–96% [14]. Portal vein invasion in large HCC is demonstrated in up to 57% of cases using dynamic incremental scanning [15] and invasion of hepatic veins is common (T2–T4). The indication for surgery, however, is often not limited by the extension of HCC into the hepatic vein, but rather by the presence of multifocal tumours, infiltration of the portal pedicle or a reduced functional hepatic reserve in patients with liver cirrhosis [16].

Endoscopic retrograde cholangiopancreatography (ERCP)

Clinically jaundiced patients with hepatobiliary and pancreatic malignancies often undergo ERCP that allows definition of biliary pathology and alterations of the main pancreatic duct and its side branches with an accuracy of 95% [17]. ERCP is the gold standard in the detection of subtle pancreatic and biliary abnormalities (Tis, T1) but its value for tumour staging is low [4]. The possibility to biopsy ductal pathology, collect samples for cytological analysis and to place stents or nasobiliary drains to relief obstructive jaundice are often used in patients with hepatobiliary and pancreatic malignancy. The physiologic changes induced in a patient with obstructive jaundice have to be included in the risk assessment. Although the use of preoperative biliary drainage is a controversy, we routinely use endoscopic stent placement in patients with cancer of the pancreatic head or extrahepatic bile duct tumours if bilirubin levels are >100 μmol/l [18].

Magnetic resonance imaging and angiography

Magnetic Resonance Imaging (MR) including MR cholangiopancreaticography and MR-angiography [19] has the potential to replace CT in combination with diagnostic ERCP as the primary staging examination. It allows in some patients the detection of tumours smaller than 1 cm in diameter [20]. However, since many hepatobiliary and pancreatic tumours are not diagnosed in screening exams, the sensitivity for small non-symptomatic tumours is not its main advantage. The ability of MR to define tumour extension towards vascular structures non-invasively makes MR attractive for preoperative assessment. The reduction of cost and time of examination compared with CT will facilitate its routine application. MR-angiography also replaced conventional angiography, a technique that was regularly used in many patients with hepatobiliary and pancreatic cancer.

Diagnostic laparoscopy

Since all non-invasive staging examinations have a false negative rate of 10–30% for small liver and/or peritoneal metastases, diagnostic laparoscopy has been advocated to avoid unnecessary laparotomy and/or to prove the malignant nature of hepatobiliary and pancreatic tumours by biopsy. Its routine use has been advocated for patients with pancreatic cancer, predominantly of the pancreatic body and tail. Laparoscopy can improve tumour staging but its value for the determination of resectability is questioned. In pancreatic cancer detection of metastatic lesions by laparoscopy has been reported in 10% to 35% [21–23]. The value of concurrent peritoneal lavage cytology and immunohistochemical examination that approximately doubles the detection of minimal peritoneal tumour spread has not been defined conclusively. We use laparoscopy selectively in patients with locally advanced non-metastatic cancer because in more than 75% of our pancreatic cancer patients laparoscopy did not change course of treatment and allowed detection of abdominal metastases in only 10%.

Discussion

A balanced preoperative assessment of patients with hepatobiliary and pancreatic tumours includes staging of the malignancy but also registration of operative risks, particularly pre-existing cardiopulmonary disease to determine whether curative or palliative treatment should be attempted. Potentially curative surgery is defined by a radical resection (R0) of the primary tumour and may include, lymphadenectomy and in exceptional cases resection of mono- or oligotopic metastases. Since morbidity and mortality rates decreased to a minimum in many centres, more radical resections to improve long-term survival can be performed [24–26]. While this approach significantly improved survival of patients with hepatobiliary cancer [27], further studies on radical surgery in pancreatic cancer are planned and needed. Preoperative staging of tumours includes primarily radiologic techniques but analyses of functional reserve capacity of the affected organ, particularly the liver [16], molecular biological examinations of tumour-associated antigens, monoclonal antibodies, cytokines, genetic markers and the detection of minimal cancer spread in blood, bone marrow and the peritoneal cavity are currently under investigation and may in the future improve staging.

New diagnostic tools have improved preoperative staging and allow a more accurate definition of local tumour extension and further technical developments can be expected. When distant spread of cancer has been excluded, surgical exploration is often indicated since resectability is defined intraoperatively and resection is possible in many cancers of the liver, bile duct and the pancreas. Therefore, the important information for the surgeon collected by the above mentioned studies, pertains to the presence of metastases and definitive signs of irresectability, such as a complex infiltration of vascular structures [28].

Advances in surgical technique such as the safe resection and reanastomosis of portal structures, multivisceral resections, segmental liver resection with preservation of functional hepatic capacity, have extended the spectrum of surgical indications towards more advanced tumours. In addition to a considerable reduction of both, morbidity and mortality [24] the long-term survival of hepatobiliary cancer after radical surgery increased during recent years and even for ductal adenocarcinoma of the pancreas 5-year survival of 15–30% are reported.

We therefore conclude that although preoperative staging certainly increased in accuracy, surgical exploration and resection are still essential in patients with hepatobiliary and pancreatic malignancies. The addition of biological markers and molecular staging may improve ability to treat these patients more specifically and at an earlier stage, and new treatment modalities may in the future allow to have effective treatment of advanced stages and local tumour extension.

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