

REVIEW ARTICLE

Staging of cholangiocarcinoma: the role of endoscopyE. A. J. RAUWS¹, J. J. KLOEK², D. J. GOUMA² & T. M. VAN GULIK²¹*Department of Gastroenterology and* ²*Department of Surgery, Academic Medical Center, University of Amsterdam, The Netherlands***Abstract**

The main question for staging is resectability, which is reliant on vascular, longitudinal, and metastatic spread. Today, accurate staging of perihilar tumors is achieved by non-invasive diagnostic investigations. Direct cholangiography has been the gold standard as a diagnostic procedure in recent decades. Endoscopic retrograde cholangiopancreatography (ERCP) often only shows the ducts below the obstruction, and visualization of an obstructed part of the biliary tree is often not possible. Direct cholangiography reveals no information about local tumor extension, lymph nodes, or vascular involvement. Because of the given limitations, potential complications (cholangitis, sepsis) associated with direct cholangiography and reduction of the accuracy of subsequent cross-sectional imaging studies, these invasive techniques should only be used in the case of palliative interventions. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) can be used to assess the nature of biliary strictures and to derive information about the extent of periductal disease and the presence of lymph node metastases. In a study by Fritscher-Ravens, 44 patients with hilar strictures underwent EUS-FNA. The overall diagnostic accuracy, sensitivity, specificity, positive and negative predictive values were 91% (95% CI, 78.4–96.3%), 89% (95% CI, 73.3–96.8%), 100% (95% CI, 63.1–100%), 100% (95% CI, 88.8–100%), and 67% (95% CI, 34.9–90%), respectively. The planned surgical approach was changed in 27 of 44 patients. In 15–20% of cholangiocarcinoma, patients with unremarkable abdominal imaging studies have metastatic lymph node involvement according to EUS evaluation. Due to the risk of peritoneal seeding, however, EUS with FNA is not recommended in patients still with a potential curative tumor.

Key Words: *Cholangiocarcinoma, endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), staging*

Introduction

The staging of cholangiocarcinoma (CCA) of endoscopic cholangiography, endoscopic ultrasonography, intraductal ultrasound, brush cytology, biopsy, and fine-needle aspiration (FNA) is discussed in this article.

Diagnosis cholangiocarcinoma

If obstruction is secondary to a mass lesion, this lesion must be staged with cross-sectional imaging techniques before drainage procedures are performed [1]. If stents are inserted before non-invasive diagnostic investigations take place, the accuracy of subsequent cross-sectional imaging is reduced.

Staging cholangiocarcinoma

The main question for staging is resectability, which is reliant on vascular, longitudinal, and metastatic spread. Today, accurate staging of perihilar tumors is achieved ideally by non-invasive diagnostic investigations, including ultrasonography, computed tomography (CT) scan, and magnetic resonance cholangiopancreatography (MRCP).

The most common staging system describes the extent of tumor spread within the biliary system according to the Bismuth classification [2], but a main shortcoming of the Bismuth classification is lack of information on any vascular involvement. It is therefore not predictive of tumor resectability and patient survival.

Staging cholangiocarcinoma by endoscopic techniques

Cholangiography

Direct cholangiography has been the gold standard diagnostic procedure in recent decades. Endoscopic retrograde cholangiopancreatography (ERCP) often only shows the ducts below the obstruction, and visualization of an obstructed part of the biliary tree is often not possible. In addition, opacification of subsequently undrained liver segments puts the patient at risk for cholangitis. Percutaneous transhepatic cholangiography (PTC) for patients with non-communicating intrahepatic segments of the biliary tree often requires several punctures of the individual segments [3]. For obvious reasons, direct cholangiography reveals no information about local tumor extension, lymph nodes, and vascular involvement. Because of the given limitations, potential complications (cholangitis; sepsis) associated with direct cholangiography and reduction of the accuracy of subsequent cross-sectional imaging studies, these invasive techniques should only be used for palliative interventions.

Combined multiphase CT and direct cholangiography can be used for evaluation of the resectability of HCCA. The combined interpretation of CT and direct cholangiographic images resulted in an overall accuracy of 74.5% for the prediction of resectability [4].

A few minor studies [5–7] have compared MRCP with ERCP in patients with hilar strictures. MRCP and ERCP were both very effective in detecting the presence of biliary obstructions (each 100%), but MRCP was superior in investigating the anatomic extent and the cause of the obstruction compared with ERCP. MRCP was advantageous because it displayed the biliary tree proximal to the obstruction.

In a prospective study, Coubière et al. [6] evaluated the diagnostic value of MRC with direct cholangiography in patients referred for suspected CCA. Direct cholangiography (percutaneous, $n=24$ or endoscopic, $n=25$) was performed within 7 days of the MRC. The concordance between MRC and direct cholangiography for the evaluation of surgical management was moderate with a kappa value of 0.55 (95% CI, 0.38–0.72), sensitivity of 84% (95% CI, 0.73–0.95), and specificity of 63% (95% CI, 0.49–0.77). The major limitation of this study was the evaluation of MR cholangiograms only, and the MRI potential of producing cross-sectional images of the liver and vascular structures was not used.

Brushing, endoscopic biopsy, and fine-needle aspiration

Both PTC and ERCP techniques allow bile sampling, brushing, and biopsies taken from the suspected stricture for diagnosis. ERCP-guided brushing is a very specific modality for diagnosis of carcinoma, but

it is not very sensitive. CCA is often desmoplastic, resulting in acellular sampling. Biliary cytology is positive for CCA in 30% of patients [8,9]. A combination of brushing with endoscopic biopsies increases the yield to 40–70% [10,11]. In one study, the sensitivity of routine brush cytology varied from 9% to 24% and specificity from 61% to 100%, reflecting a high degree of interpathologist variation [8]. Advanced cytology techniques for detection of aneuploidy (digital image analysis) (DIA) and aneusomy (fluorescence in situ hybridization) (FISH) increase sensitivity for the diagnosis of malignancy to 35–60% [12]. These sophisticated techniques are not widely available.

Endoscopic ultrasonography

Endoscopic ultrasonography-guided FNA (EUS-FNA) can be used for assessing the nature of biliary strictures and for providing information on the extent of periductal disease and the presence of lymph node metastases.

A few prospective studies [13–15] evaluated the role of EUS-FNA in biliary strictures. In the study by Fritscher-Ravens [13], 44 patients with hilar strictures underwent EUS-FNA. The overall diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 91% (95% CI, 78.4–96.3%), 89% (95% CI, 73.3–96.8%), 100% (95% CI, 63.1–100%), 100% (95% CI, 88.8–100%), and 67% (95% CI, 34.9–90%), respectively. The planned surgical approach was changed in 27 of 44 patients. In a study of 24 patients, EUS-FNA biopsy of suspected CCA has shown a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 77% (95% CI, 54–92%), 100% (95% CI, 15–100%), 100% (95% CI, 83–100%), 29% (95% CI, 4–71%), and 79% (95% CI, 58–93%), respectively [15]. The low negative predictive value does not permit the reliable exclusion of malignancy following a negative biopsy.

In 15–20% of CCA, patients with unremarkable abdominal imaging studies have metastatic lymph node involvement according to EUS evaluation [16]. Endoscopic ultrasound (EUS) with FNA from either the mass or the surrounding malignant-appearing lymph nodes appears to have a higher sensitivity than ERCP with brushing and biopsies [17]. The advantage of EUS guided FNA is the avoidance of contamination of the biliary tree as occurs with ERCP. EUS with FNA, however, is not recommended in patients still with a potential curative tumor due to the risk of peritoneal seeding.

EUS data are only reported from tertiary referral centres by specialists in ultrasonography. Lack of experience with EUS-FNA of biliary tree lesions leads to low sensitivities.

Intraductal ultrasound

If no mass is identified on CT scan or MRI, a biliary stricture is benign in 30–49% of patients [18–20]. In these patients, intraductal ultrasound (IDUS) can be used in combination with biliary brushing during cholangiography. IDUS is performed with high-frequency (15–30 MHz), thin-caliber (2.0–2.4 mm) probes. The depth of penetration is limited (2 cm), but sufficient to provide an accurate image of the bile duct wall, assess the depth of infiltration, and portal vein and right hepatic artery invasion. IDUS has limited value in assessing lymph node involvement because of the limited depth of ultrasonic penetration. EUS is superior to IDUS with respect to the detection of lymph node metastases [21]. An important limitation of IDUS is the inflammatory thickening induced when prior stenting of the biliary stricture has been performed [22]. The accuracy of IDUS in evaluation of the extent of a tumor has been reported as 86% [21,23]. When used in conjunction, IDUS increased the accuracy of ERCP from 58–60% to 83–90% in distinguishing between benign and malignant stricture [19,20]. The accuracy of IDUS in assessing tumor invasion to the right hepatic artery and portal vein is 92–100% [21]. However, visualization of the left hepatic and proper hepatic artery is poor (14–18%) due to anatomical features which cause ultrasound attenuation.

Consensus statements

- Staging cross-sectional imaging techniques should be performed before drainage procedures.
- Because of limitations and potential risks, direct cholangiography (percutaneous or endoscopic retrograde approach) should only be used for preoperative and palliative drainage.
- Brush cytology has a low sensitivity and negative predictive value and limits the ability to exclude malignancy.
- IDUS can be considered if staging cross-sectional imaging techniques are inconclusive.

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