Diagnosis

8

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The diagnosis of hilar cholangiocarcinoma is suspected clinically, but it is usually made with serum tumor markers and on medical imaging. Cytological and molecular techniques help in the diagnosis of difficult cases.

8.1 Clinical Manifestations

Hilar cholangiocarcinoma is usually asymptomatic, or occasionally associated with non-specific symptoms such as abdominal discomfort, anorexia and even weight loss in the early stage [1]. These symptoms are often vague and neglected, hence it is rarely detected at this stage. As the tumor grows and obstructs the common hepatic duct and/or biliary confluence, jaundice gradually develops. Most patients with hilar cholangiocarcinoma seek medical advice because of jaundice, which is commonly painless, progressive, and is accompanied by pruritus, clay-colored stool and dark urine [2]. Fever is uncommon and is due to acute cholangitis which happens in about 10 % of patients with hilar cholangiocarcinoma [3]. Patients then present with fever, chills and abdominal pain, in addition to jaundice.

Physical examination often reveals hepatomegaly with a firm consistency, but the gallbladder is usually impalpable. An enlarged gallbladder suggests a more distal biliary obstruction rather than at the hepatic hilum. In patients with pruritus, multiple excoriations of skin are frequently found.

In liver function tests, a markedly elevation of serum total bilirubin is usually shown, with the conjugated bilirubin being predominant. Simultaneous elevations of alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) are frequent [4].

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These clinical manifestations suggest obstructive jaundice. The differential diagnosis for obstructive jaundice is broad, and it includes a long list of hilar cholangiocarcinoma, ampullary carcinoma, duodenal carcinoma, pancreatic carcinoma, gallbladder carcinoma, choledocholithiasis, benign biliary stricture, etc. The presumptive diagnosis of hilar cholangiocarcinoma is usually based on serum tumor markers and medical imaging investigations. Brush cytology or forceps biopsy can offer a definite diagnosis. Its low sensitivity, however, limits its clinical role. Currently, a definitive diagnosis of hilar cholangiocarcinoma before an operation still remains a major challenge.

8.1.1 Serum Tumor Markers

Some serum tumor markers may be helpful in the diagnosis of hilar cholangiocarcinoma. Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) are the most widely used markers. They may be elevated in hilar cholangiocarcinoma, but they are non-specific and inadequately sensitive. CA19-9 and CEA can also be raised in many other malignancies, including gastric carcinoma, colorectal carcinoma, pancreatic carcinoma and gynecological carcinomas. In addition, CA19-9 can be elevated in some benign conditions, like cholangitis, choledocholithiasis and benign biliary stricture [5].

Patel et al. [6] compared the levels of CA19-9 in 36 cholangiocarcinomas without primary sclerosing cholangitis (PSC), 41 non-malignant liver diseases and 26 benign biliary strictures and found that a cutoff value of CA19-9 >100 U/ml had a sensitivity of 53 % for the diagnosis of cholangiocarcinoma, and a true negative rate of 76 % for non-malignant liver diseases and 92 % for benign biliary stricture. Other studies show in patients with PSC, CA19-9 at a cutoff value of >100 U/ml has a sensitivity of 75–89 % and a specificity of 80–86 % for the detection of cholangiocarcinoma [7–9]. A higher cutoff value improves its specificity [10], but impairs its sensitivity. Recently, Juntermanns et al. [11]

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analyzed retrospectively the CA19-9 level in 136 patients with hilar cholangiocarcinoma, and found that it was closely related to the tumor staging, being 253 ± 561 U/ml for UICC stage I, 742 ± 1,572 U/ml for stage II, 906 ± 1,708 U/ml for stage III and 1,707 ± 3,053 U/ml for stage IV.

CEA alone has an unsatisfactorily low sensitivity and specificity for the diagnosis of cholangiocarcinoma [12]. Koea et al. [5] reported that CEA was elevated in only 2 out of 28 patients with hilar cholangiocarcinoma. Juntermanns et al. [11] found that the CEA level in patients with hilar cholangiocarcinma was related to the tumor staging, being 2.9 ± 3.8 U/ml for UICC stage I, 4.6 ± 6.5 U/ml for stage II, 18.1 ± 29.6 U/ml for stage III and 22.7 ± 53.9 U/ml for stage IV. A combination of CEA and CA19-9 improves the capability to detect cholangiocarcinoma. Siqueira and his associates reported that CEA > 5.2 ng/mL in combination with CA19-9 > 180 U/ml had a sensitivity of 100 % and a specificity of 78.4 % for the detection of cholangiocarcinoma in patients with PSC [13].

New markers, such as the human mucin subtypes A and C (mucin-5AC), trypsinogen and soluble fragment of cytokeratin 19, are now being investigated [14]. Bamrungphon et al. reported that mucin-5AC at a cutoff value of 0.074 had a sensitivity of 71 % and a specificity of 90 % for the diagnosis of cholangiocarcinoma [15]. The diagnostic values of these new markers still need to wait for large-scale clinical trials to assess.

8.1.2 Imaging Investigations

Imaging investigations play an essential role in the diagnosis and management of hilar cholangiocarcinoma. The commonly used imaging modalities include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), direct cholangiographies and positron emission tomography (PET).

8.1.3 Ultrasound

The widespread availability, convenience and low cost have made duplex ultrasound (DUS) of liver, biliary system and pancreas to be the most common first-step imaging study for patients with jaundice. DUS provides valuable diagnostic clues for hilar cholangiocarcinoma: firstly, DUS is sensitive and accurate in identifying biliary dilatation. Based on the distribution of biliary dilatation, the location of biliary obstruction can be precisely defined. Dilatation of intrahepatic bile ducts alone indicates a proximal biliary obstruction, and dilatation of both intra-hepatic and extra-hepatic bile ducts indicates a distal biliary obstruction. In a series of 429 patients with obstructive jaundice, the sensitivity and specificity of DUS in defining the location of biliary obstruction were 94 and 96 %, respectively [16].

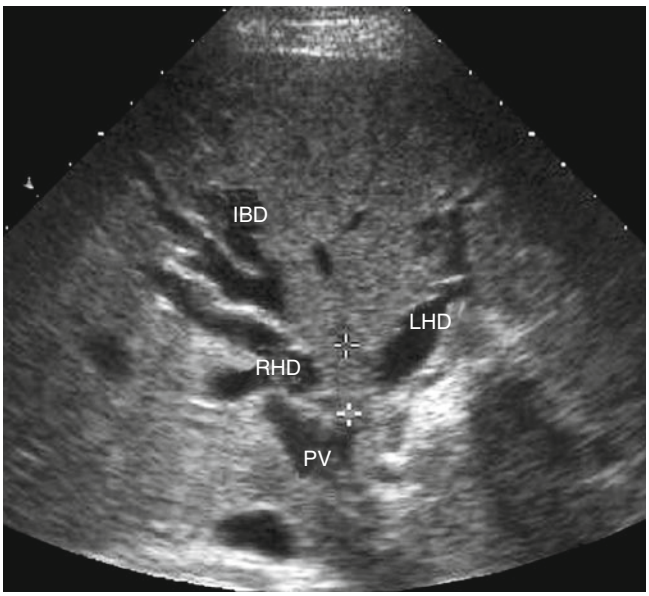

Fig. 8.1 A 49-year-old male with a hilar cholangiocarcinoma. Ultrasound examination reveals a mass inside the hepatic duct confluence (T) with dilatation of the intrahepatic bile ducts (*IBD*). Both the right hepatic duct (*RHD*) and the left hepatic duct (*LHD*) are not involved by the tumor, and the portal vein (*PV*) has an intact wall. The imaging features suggest a Bismuth-Corlett type II hilar cholangiocarcinoma

In the identification of etiology of the obstructive jaundice, DUS may directly show the bile duct tumor and its extention (Fig. 8.1). Hann et al. [17] reported in 39 patients with hilar cholangiocarcinoma, DUS detected bile duct tumors in 87 % of patients: as intra-ductal polypoid masses in 18 %, infiltrative lesions in 26 % and nodular mural thickening in 56 %. At the same time, it correctly evaluated the tumor extension in the bile duct in 87 %. Recently, contrast-enhanced ultrasound (CEUS) has been used in the diagnosis of hilar cholangiocarcinoma. The enhancement patterns of lesions are useful for the diagnosis and differential diagnosis of cholangiocarcinoma. In 30 patients with hilar cholangiocarcinoma, CEUS made a correct diagnosis in 93.8 % [18]. More large-scale clinical trials are still needed to assess its true role in the diagnosis of hilar cholangiocarcinoma.

Furthermore, DUS can accurately assess the status of the portal vein. In the study by Hann et al. [17], DUS correctly predicted the involvement of portal veins in 86 % of the 21 portal veins which were invaded by tumor in 16 patients. In another study, Bach et al. compared the accuracy of DUS and angiography combined with CT during arterial portography (CTAP) for the evaluation of portal vein involvement by tumor. The results showed that DUS detected 38 of 41 involved portal veins in 63 patients who received hepatectomy, with a sensitivity of 93 %, specificity of 99 %, positive predictive value of 97 % and negative predictive

value of 98 %. The results were similar to those obtained by angiography combined with CTAP [19].

The role of DUS in the diagnosis of hilar cholangiocarcinoma has been well established. However, its sensitivity, specificity and accuracy are operator-dependent. Hence, other imaging investigations are usually needed following ultrasound examination.

8.1.4 Computed Tomography (CT)

Triple-phase CT scanning plays an important role in the diagnosis and staging of hilar cholangiocarcinoma, since it can provide information regarding to the location of the biliary obstruction, tumor extension along the bile duct axis, vascular invasion, hepatic lobar atrophy, lymph node involvement and distant metastases. Its accuracy has been remarkably improved with the application of high-resolution multidetector-row CT scanners.

On Triple-phase CT scanning, hilar cholangiocarcinoma appears as an hyperattenuating intra-ductal mass, focal mural thickening or lumen obliteration at the hilar bile duct with dilatation of the intra-hepatic bile ducts (Fig. 8.2). The sensitivity of triple-phase CT for the diagnosis of hilar cholangiocarcinoma reaches up to 90–100 % [4], with an accuracy of 92.3–95 % [20, 21]. However, it has a tendency to underestimate the horizontal extension of tumor along the bile duct axis, with an accuracy of 77–80.9 % [21, 22].

CT is accurate in assessing the status of the portal vein and hepatic artery (Fig. 8.2). In 18 patients with hilar

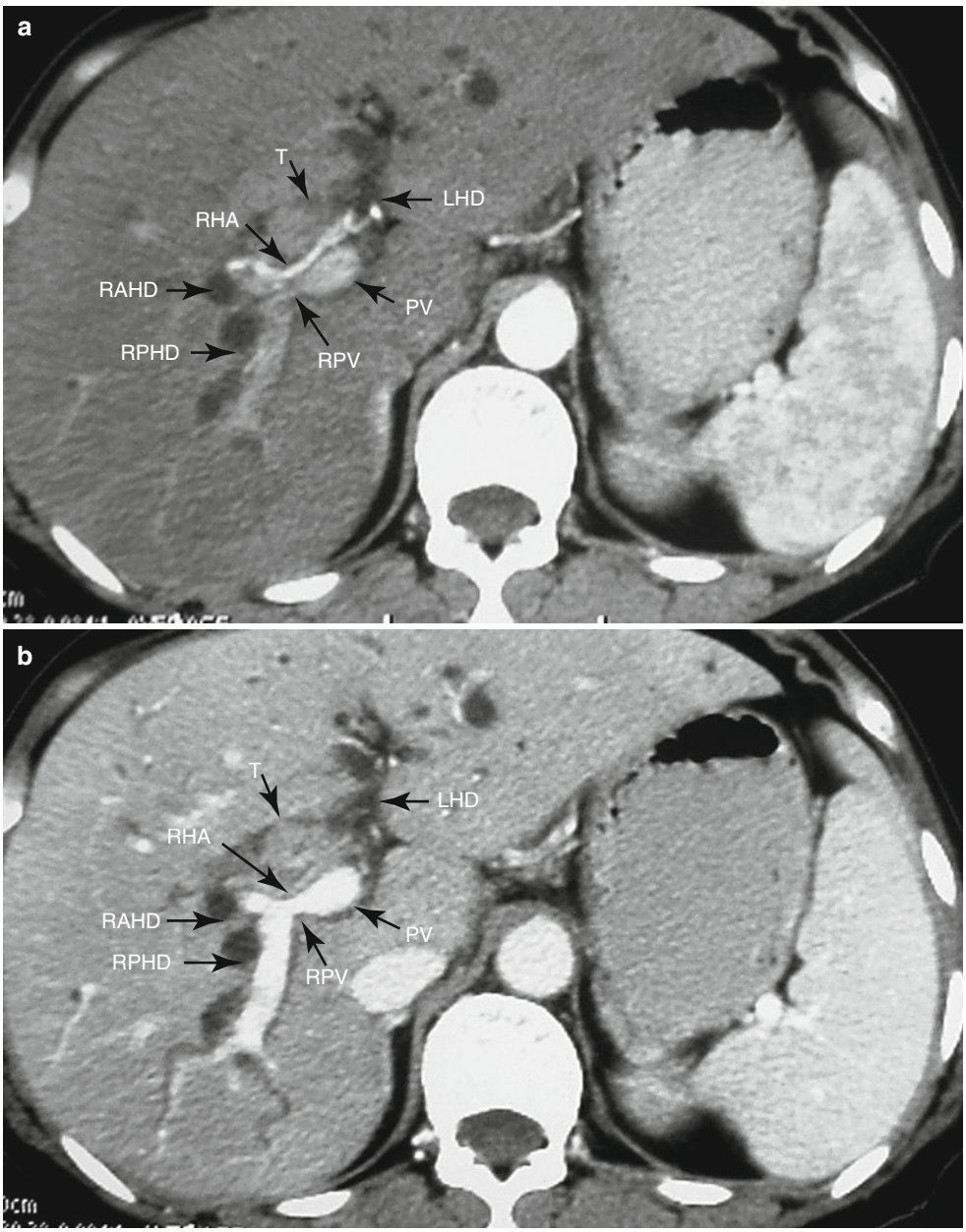

Fig. 8.2 A 56-year-old female with hilar cholangiocarcinoma. Triple-phase CT scanning shows a contrast-enhanced mass (*T*) inside the hepatic duct confluence at the arterial phase (**a**). The tumor presents with washout at the portal phase (**b**). The right hepatic duct is invaded by the tumor up to the confluence of the right anterior sectoral duct (*RAHD*) and right posterior sectoral duct (*RPHD*), and the left hepatic duct (*LHD*) remains intact (**a** and **b**). Part of the wall of the right hepatic artery (*RHA*) is not clear (as shown by an *arrow* in **a**), and the right portal vein (*RPV*) is markedly stenotic (as shown by an *arrow* in **b**), suggesting that both of these vessels have been invaded by the tumor. *PV* portal vein

cholangiocarcinoma, it correctly detected portal vein involvement in 47 of 51 invaded portal veins, with a sensitivity of 92.3 % and a specificity of 90.2 %. Its sensitivity and specificity for the detection of hepatic artery involvement were 100 and 90 %, respectively [23]. In another study involving 55 patients with hilar cholangiocarcinoma, CT had an accuracy of 85.5 % in detecting portal vein invasion and 92.7 % in detecting hepatic artery invasion [24].

Additionally, CT is useful in detecting hepatic lobar atrophy, lymph node involvement and distant metastases. Atrophy of one liver lobe is usually accompanied with hypertrophy of the contra-lateral lobe. This condition presents in hilar cholangiocarcinoma when the tumor invades one portal branch and causes atrophy of the ipsilateral liver lobe. Compensatory hypertrophy causes the contra-lateral liver lobe to enlarge. In the detection of lymph node involvement, CT has a sensitivity of 35–63 % [21, 25] and a specificity of 75–95 % [21, 24]. CT is also useful in detecting distant metastases, such as liver metastases and peritoneal metastases, but it is not sensitive enough to detect sub-centimeter metastatic lesions.

Overall, the resectability of hilar cholangiocarcinoma as assessed by preoperative CT has a sensitivity of 94–100 %, a specificity of 48–79 %, and an accuracy of 60–88 % [26].

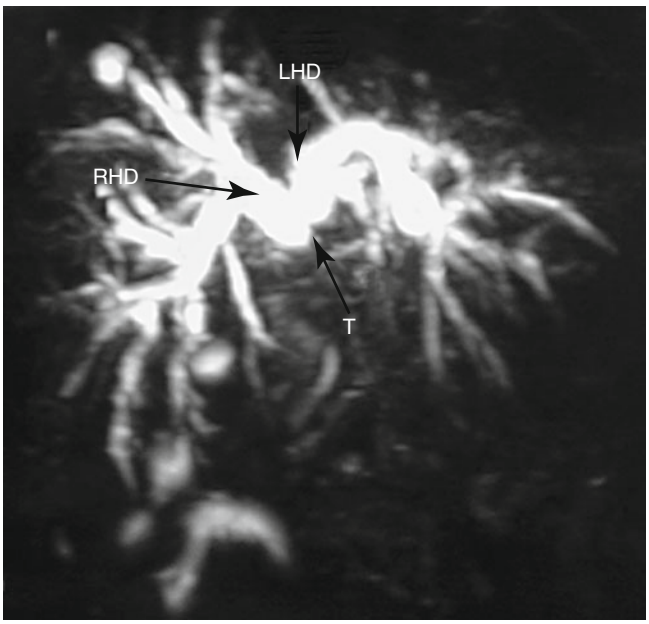

Fig. 8.3 A 50-year-old female with a hilar cholangiocarcinoma. MRCP shows a complete biliary obstruction at the confluence of the hepatic ducts (*T*), but both the right hepatic duct (*RHD*) and the left hepatic duct (*LHD*) are intact. The features suggest a Bismuth-Corlett type II hilar cholangiocarcinoma

8.1.5 Magnetic Resonance Imaging (MRI)/Magnetic Resonance Cholangiopancreatography (MRCP)

MRI combined with MRCP is another excellent imaging modality for the diagnosis and staging of hilar cholangiocarcinoma. Like CT scanning, MRI/MRCP provides reliable information regarding the level of biliary obstruction, extent of biliary ductal involvement, vascular invasion, hepatic lobar atrophy, lymph node involvement and distant metastases.

MRI has an accuracy of 66 % for the detection of lymph node involvement [27], a sensitivity of 78 % and a specificity of 91 % for portal vein involvement, a sensitivity of 58–73 % [28] and a specificity of 93 % for hepatic arterial involvement [29]. In addition, MRCP offers a two-dimensional or three-dimensional reconstruction of the entire biliary tree, which is valuable for precisely defining the longitudinal tumor extension within the bile duct (Fig. 8.3). The accuracy of MRCP in defining the extent of biliary ductal involvement in hilar cholangiocarcinoma reaches 71–96 % [25]. Compared with direct cholangiographies, including percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP), MRCP has a similar diagnostic accuracy in hilar cholangiocarcinoma but with the advantages of non-invasiveness, convenience and no risk of procedure-related cholangitis [4].

Park et al. [30] compared MRI/MRCP versus CT with direct cholangiographies in the evaluation of 27 patients with bile duct cancer. The accuracies of MRI/MRCP or CT with direct cholangiography were 90.7 % vs. 85.1 % in defining the involvement of bilateral secondary biliary confluence, and 87 % vs. 87 % in defining the involvement of intra-pancreatic common bile duct. Both had a similar accuracy in assessing vascular invasion and lymph node metastases.

Overall, MRI/MRCP has been extensively used in the diagnosis and staging of hilar cholangiocarcinoma, with an accuracy of 72–83 % in predicting its resectability [26].

8.1.6 Direct Cholangiographies

PTC and ERCP are the two commonly used direct cholangiographies carried out by direct injection of contrast media into the biliary system. Both provide a clear delineation of the biliary tree and demonstrate precisely the location and extent of biliary obstruction. An abrupt, irregular and eccentric biliary stenosis with proportional dilatation of the proximal biliary tree usually implies malignancy (Fig. 8.4). The sensitivity, specificity and accuracy of ERCP/PTC for the diagnosis of malignant biliary obstruction are 58–85 % [31–33], 70–75 % and 72–81 % [32, 33], respectively. Compared with ERCP, PTC is more reliable to demonstrate the complex intrahepatic biliary tree in patients with hilar

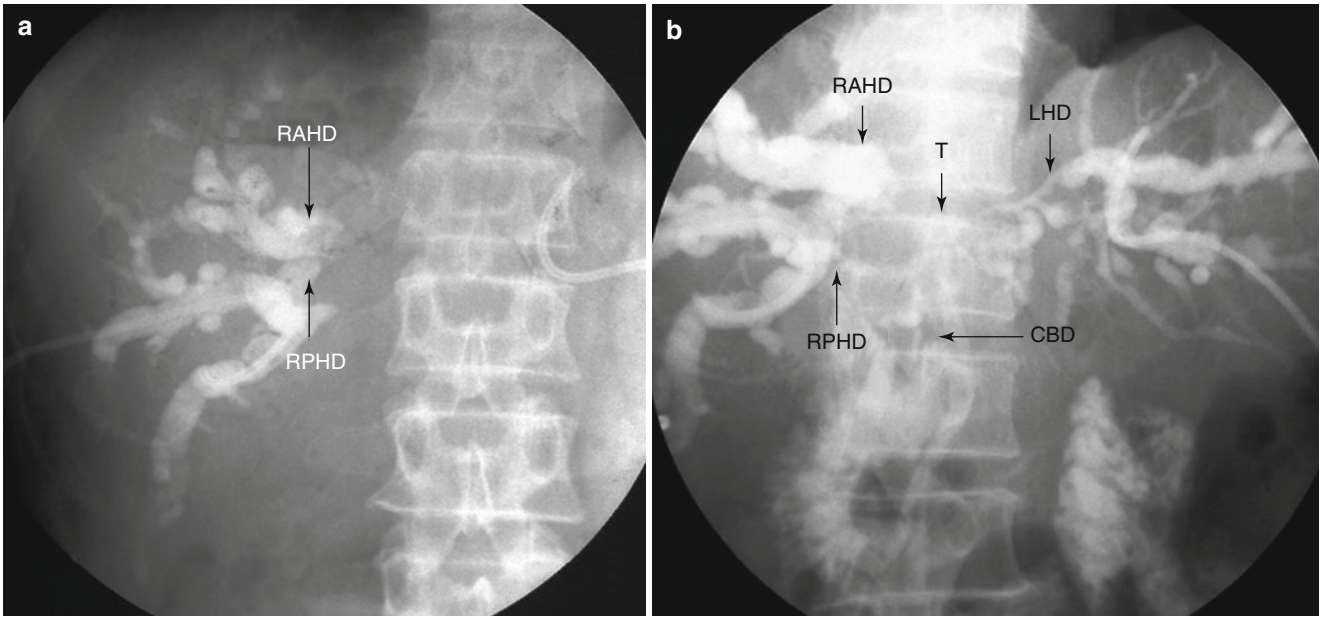

Fig. 8.4 A 60-year-old male with a hilar cholangiocarcinoma. Right PTC only delineated dilatation of the right anterior sectoral ducts (*RAHD*) and the right posterior sectoral duct (*RPHD*) with no visualization of the right hepatic duct (**a**). Subsequent left PTC shows dilatation of the left intrahepatic bile ducts with visualization of part of the left hepatic duct (*LHD*) and the common bile duct (*CBD*) (**b**). The features suggest the biliary obstruction (*T*) to involve the right hepatic duct, the hepatic confluence and part of the LHD (**b**)

cholangiocarcinoma, which is a pivotal factor for surgical planning. Hence, PTC is preferred than ERCP in most centers [34].

One limitation of ERCP/PTC is their failure to display the full biliary tree in some patients with complete biliary obstruction. In such cases, PTC can only display the proximal intrahepatic biliary tree but not the distal biliary system. On the contrary, ERCP can only depict the distal biliary system but not the proximal intraheptic biliary tree. Neither can accurately assess the full extent of biliary involvement under such circumstances.

Another limitation is that they are invasive procedures and have their risks of associated complications, which include bile leakage, cholangitis, bleeding, pancreatitis and duodenal perforation [4, 12]. The PTC-related mortality ranges between 0.6 and 5.6 % [12].

Because of these limitations, ERCP/PTC has largely been replaced by MRCP in many centers [1]. However, ERCP/PTC has potential advantages. They can be used therapeutically for biliary drainage as well as for the collection of bile for cytological and molecular analysis.

8.1.7 Positron Emission Tomography (PET)

Positron emission tomography, using the radionucleotide tracer 18-fluorodeoxyglucose (FDG-PET), has been evaluated for the diagnosis and staging of hilar cholangiocarcinoma. An intensive focal accumulation of FDG at the hepatic hilum suggests hilar cholangiocarcinoma, but sometimes it is difficult to distinguish between malignancy from chronic biliary inflammation.

Preliminary studies show that the sensitivity of FDG-PET in the detection of hilar cholangiocarcinoma ranges between 59 and 100 % [35–38], with an accuracy of 67–100 % [35, 38]. FDG-PET shows no superiority to conventional triple-phase CT scanning in the detection of primary lesion of hilar cholangiocarcinoma [36]. FDG-PET is disappointing in identifying lymph node metastases, with a sensitivity between 13 and 42 % [36, 39, 40]. However, FDG-PET has been shown to be a promising modality to detect occult distant metastases. It is more accurate than conventional CT to identify distant metastases, with a sensitivity between 56 and 100 % [36, 40], and a specificity of 88 % [36]. FDG-PET leads to a change in the management in 17–24 % patients with cholangiocarcinoma [35, 40, 41]. More large-scale clinical trials are needed to evaluate the role of FDG-PET in the diagnosis and staging of hilar cholangiocarcinoma.

8.2 Cytological and Molecular Diagnosis

8.2.1 Brush Cytology and Forceps Biopsy

Currently the diagnosis of hilar cholangiocarcinoma is primarily based on imagings. The imaging-orientated diagnosis for hilar cholangiocarcinoma has some limitations. Sometimes it is difficult for imagings to discriminate

a malignant biliary stricture from a benign one when the imaging features are not characteristic. Moreover, even in patients with characteristic imaging features the diagnosis is only presumptive and not always correct [5, 42]. Hence, the imaging-based diagnosis for hilar cholangiocarcinoma is not adequate. To achieve a definite diagnosis of hilar cholangiocarcinoma, although clinically important, remains a major challenge.

Brush cytology and forceps biopsy via ERCP or PTC are the two most commonly used techniques to provide a definite diagnosis of hilar cholangiocarcinoma. Compared with forceps biopsy, brush cytology is less technically-demanding, less time-consuming and safer, and hence it is applied more widely. The detection of malignant cells in tissue specimens is diagnostic for malignancy. However, both brush cytology and forceps biopsy have a low sensitivity for diagnosing hilar cholangiocarcinoma since the tumor is usually abundant in fibrous stroma with only few cancerous cells [43]. The sensitivity of brush cytology and forceps biopsy for cancer detection in malignant biliary strictures ranges from 9 to 60 %, and 43 to 81 %, respectively [12, 44]. For hilar cholangiocarcinoma, the diagnostic sensitivity is between 41 and 50 % for brush cytology [42, 45], and 53 % for forceps biopsy [45]. A combination of brush cytology and forceps biopsy improves the diagnostic sensitivity to 60 % [45].

8.2.2 Endoscopic Ultrasonography-Guided Fine Needle Aspiration (EUS-Guided FNA)

In patients with a negative brush cytology and forceps biopsy, EUS-guided FNA is an alternative technique to provide a definite diagnosis of hilar cholangiocarcinoma. Good results have been reported in two small series of proximal biliary stricture, with a sensitivity of 77–89 % and a specificity of 100 %, for the detection of hilar cholangiocarcinoma [46, 47]. However, its negative predictive value was only 29 % [47]. This implies that a negative EUS-FNA does not necessarily exclude the possibility of hilar cholangiocarcinoma. EUS-guided FNA has other limitations that are technically demanding, and it is only feasible in patients with a focal mass or else its sensitivity sharply declines.

8.2.3 Fluorescence In Situ Hybridization (FISH) and Digitized Image Analysis (DIA)

Recently, sophisticated cytological techniques, including FISH and DIA, have been used to improve the sensitivity of brush cytology in cancer detection for malignant biliary strictures. FISH assay detects malignant cells by using fluorescent probes to identify chromosomal polysomy, and DIA detects malignant cells by using special stains to quantitate nuclear DNA and to identify aneuploidy [4]. Kipp et al. [48] compared the sensitivity and specificity of FISH and routine brush cytology for the detection of malignancy in 131 patients with biliary strictures, including 66 malignant and 65 benign biliary strictures. Compared with routine brush cytology, FISH markedly improved the sensitivity from 15 to 34 %. There was no significant difference in the specificity between FISH and routine brush cytology, being 91 % vs. 98 %, respectively. In another prospective study consisting of 100 patients with biliary stirctures, including 56 malignant and 44 benign biliary strictures, the sensitivity and specificity of DIA and routine brush cytology for the detection of malignancy were compared. DIA significantly improved the sensitivity from 18 to 39 %, but it simultaneously impaired the specificity from 98 to 77 % when compared with routine brush cytology [49]. However, these two studies were conducted on heterogeneous bilio-pancreatic carcinomas. The usefulness of FISH and DIA for the detection of hilar cholangiocarcinoma still awaits further evaluation.

8.2.4 DNA Hypermethylation

DNA hypermethylation of genes, such as the tumor suppressor genes and cell cycle regulation genes, is a common epigenetic change in malignancies, including cholangiocarcinomas. Hence, analysis the DNA methylation status of some important genes in the exfoliated cells of the bile provides diagnostic evidences for malignancy in patients with biliary strictures. We prospectively analyzed the methylation status of P16 and APC gene promoters of the exfoliated cells in the bile aspirates from 70 patients with biliary obstruction using methylation-specific PCR. Forty-eight of these patients were diagnosed to have malignant biliary obstruction (bile duct carcinomas in 36, pancreatic carcinoma in 8 and duodenal carcinoma in 4) by pathological examination, and 22 had benign biliary obstruction caused by cholelithiasis. Hypermethylation of P16 promoter was present in 72.9 % (35/48) of patients with malignant biliary obstruction, and in 9 % (2/22) of patients with benign obstruction ($P<0.05$). Hypermethylation of APC promoter was present in 56.2 % (27/48) of patients with malignant biliary obstruction, and in 9 % (2/22) of patients with benign obstruction ($P<0.05$). For malignant biliary obstruction, the sensitivity, specificity, positive predictivity and negative predictivity for the P16 gene were 72.9, 90.9, 94.6 and 60.6 %, respectively, and they were 56.2, 90.9, 93.1, 48.8 %, respectively, for the APC gene. Our results suggested that the methylation status of the P16 and APC gene promoters in the bile aspirate was valuable in the diagnosis of malignant biliary obstruction. The specificity was excellent. The P16 gene had a higher sensitivity than the APC gene [50]. The role of the DNA methylation status

in the diagnosis of hilar cholangiocarcinoma needs to be further assessed in large-scale clinical trials.

8.3 Summary

Despite improvements in diagnostic modalities in the past decade, differentiation between malignant and benign hilar biliary obstruction still remains a challenge. An accurate preoperative diagnosis is important for hilar biliary stricture to avoid inappropriately extensive resection. Although brush cytology and forceps biopsy are able to make a definite diagnosis, their sensitivity is low. EUS-guided FNA has a greater sensitivity for cancer detection, but it is only feasible for patients with a focal mass and it is technically demanding. Identification of molecular changes of the exfoliated cells in the bile, such as DNA methylation, may represent a novel approach for the diagnosis of hilar cholangiocarcinoma.

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