

Hepatocellular carcinoma with obstructive jaundice: diagnosis, treatment and prognosis

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Abstract

Obstructive jaundice as the main clinical feature is uncommon in patients with hepatocellular carcinoma (HCC). Only 1-12 % of HCC patients manifest obstructive jaundice as the initial complaint. Such cases are clinically classified as "icteric type hepatoma", or "cholestatic type of HCC". Identification of this group of patients is important, because surgical treatment may be beneficial. HCC may involve the biliary tract in several different ways: tumor thrombosis, hemobilia, tumor compression, and diffuse tumor infiltration. Bile duct thrombosis (BDT) is one of the main causes for obstructive jaundice, and the previously reported incidence is 1.2-9 %. BDT might be benign, malignant, or a combination of both. Benign thrombi could be blood clots, pus, or sludge. Malignant thrombi could be primary intrabiliary malignant tumors, HCC with invasion to bile ducts, or metastatic cancer with bile duct invasion. The common clinical features of this type of HCC include: high level of serum AFP; history of cholangitis with dilation of intrahepatic bile duct; aggravating jaundice and rapidly developing into liver dysfunction. It is usually difficult to make diagnosis before operation, because of the low incidence rate, ignorant of this disease, and the difficulty for the imaging diagnosis to find the BDT preoperatively. Despite recent remarkable improvements in the imaging tools for diagnosis of HCC, such cases are still incorrectly diagnosed as cholangiocarcinoma or choledocholithiasis. Ultrasonography (US) and CT are helpful in showing hepatic tumors and dilated intrahepatic and /or extrahepatic ducts containing dense material corresponding to tumor debris. Direct cholangiography including percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) remains the standard procedure to delineate the presence and level of biliary obstruction. Magnetic resonance cholangiopancreatography (MRCP) is superior to ERCP in interpreting the cause and depicting the anatomical extent of the perihilar obstructive jaundice, and is particularly distinctive in cases associated with tight biliary stenosis and along segmental biliary stricture. Choledochoscopy and bile duct brushing cytology could be alternative useful techniques in the differentiating obstructions due to intraluminal mass, infiltrating ductal lesions or extrinsic mass compression applicable before and after duct exploration. Jaundice is not necessarily a contraindication for surgery. Most patients will have satisfactory palliation and occasional cure if appropriate procedures are selected and carried out safely, which can result in long-term resolution of symptoms and occasional long-term survival. However, the prognosis of icteric type

INTRODUCTION

Jaundice presents in 19 % to 40 % of patients with hepatocellular carcinoma (HCC) at the time of diagnosis and usually occurs in later stages. In most situations, it is due to diffuse tumor infiltration of liver parenchyma, hilar invasion, or progressive terminal liver failure (advanced underlying cirrhosis)^[1]. Obstructive jaundice as the main presenting clinical feature is uncommon. Only 1-12 % of HCC patients manifest obstructive jaundice as the initial complaint^[2]. Identification of this group of patients is clinically important, because surgical treatment may be beneficial.

Mallory *et al.* described the first such case in 1947, in which HCC invaded the cystic duct and gave rise to obstructive jaundice caused by hemobilia from the tumor thrombi^[3]. Thereafter, there have been few and scattered reports of such presentations of HCC in English literatures^[4-11]. In 1975, Lin *et al.* clinically classified such cases as "icteric type hepatoma", which manifested as obstructive jaundice in the early stage before the tumor became discernible or palpable^[12]. Okuda classified these patients as "cholestatic type of HCC"^[13].

Thrombus in bile duct (BDT) is one of the main reasons of obstructive jaundice. The incidence was 1.2-9 % in previous report^[4,12-15]. Huang *et al.* collected the cases from the newly diagnosed HCC patients of the admission registration database, and found the incidence of this type HCC was only 0.53 %^[16]. Variation in the biological behavior of HCC may partly account for the difference in incidence. It is reported that the incidence is increasing in patients with HCC, and transcatheter arterial chemoembolization (TACE) therapy could increase the possibility of common bile duct obstruction of tumor thrombi^[17].

PATHOLOGICAL FEATURES

HCC may involve the biliary tract in several different ways: tumor thrombi, hemobilia, tumor compression, and diffuse tumor infiltration. Infrequently, jaundice may also result from the external compression on the major bile ducts by direct tumor encasement or by the metastatic lymphadenopathy at the porta hepatis^[18,19].

BDT might be benign, malignant, or a combination of both. Benign thrombi could be blood clots, pus, or sludge. Malignant thrombi could be primary intrabiliary malignant tumors, HCC with invasion to bile ducts, or metastatic cancer with bile duct invasion. HCC invasion into bile duct may be due to one of the three mechanisms: (1) a distal tumor may grow continuously until it fills the entire extrahepatic biliary system; (2) a fragment of necrotic tumor may separate from the proximal intraductal growth, migrate to the distal common bile

duct and cause an obstruction; (3) hemorrhage from the tumor may partially or completely fill the biliary tract with tumor-containing blood clots^[4, 14-16, 20, 21]. In this type of HCC, blood clots are inevitably mixed with fresh tumor debris. However, Shimoji *et al.* reported one case suspected recurrent HCC during the choledochotomy after left hepatectomy for HCC, no HCC was detected by either macroscopic or intra-operative ultrasonographic examination. The course of hemobilia thus remained unclear until the autopsy was performed. Hemorrhage from a ruptured branch of the portal vein into the intrahepatic bile duct, filling the entire common bile duct with solid casts of blood, is uncommon. The hemorrhage into intrahepatic bile duct may be secondary to a portal vein rupture from: (1) a rupture of the engorged or variceal proximal portal vein leading directly into the intrahepatic duct; (2) necrosis of a cirrhotic liver nodule adjacent to both the intrahepatic bile duct and the vein; or (3) either cholangitis or an abscess in the proximal intrahepatic bile duct. Despite the remarkable recent improvements in various diagnostic modalities, hemobilia is still often incorrectly diagnosed as biliary tract carcinoma or stones. The etiologic diagnosis of jaundice in patients with cirrhosis, either with or without HCC, is thus of great clinical importance^[22].

Fragments of tumor in the bile duct, as described by Edmondson and Steiner, are usually fragile, fleshy, and grayish-white, having the appearance of chicken fat^[23]. BDT often grows faster than the primary cancer. The parenchymal tumor could be not continuous with the extrahepatic bile duct tumor. The bile duct tumor might attach to the mucosa of the bile duct with a thin stalk, without invasive growth into the submucosa^[24]. Most of the primary tumors are pathologically confirmed as HCC, however, the growth of mixed type of liver cancer (HCC and cholangiocarcinoma) into the common bile duct (CBD) has also been found, which may differ from the underlying mechanism of the development of icteric type HCC^[25].

In most cases, hepatic tumors can not be palpated from the liver surface because they are deep-seated and small, or because the liver is cirrhotic^[12, 18, 21, 26]. Intraductal HCC growth is mostly caused by direct invasion from the primary lesion and occasionally from an adjacent massive tumor thrombus in the portal vein^[27]. Icteric type HCC may occur even with no primary detectable lesion^[21, 28]. Most primary lesions of icteric type HCC patients are grossly infiltrative type or mixed infiltrative and nodular type. Usually, no tumor capsule formation could be found in the primary tumors. The infiltrative nature of this particular type of HCC may in part explain their invasion of the biliary tree and portal veins early in their growth without regard to tumor size or type^[19, 29].

CLINICAL MANIFESTATION AND DIAGNOSIS

Clinical features

The common clinical features of this type of HCC include: high level of serum AFP; the history of cholangitis with dilation of intrahepatic bile duct; aggravating jaundice and rapidly developing into liver dysfunction. It is usually difficult to make diagnosis before operation, because of the low incidence rate, ignorant of this disease, and the difficulty for the imaging diagnosis to find the BDT preoperatively.

Just as other types of HCC, no specific symptoms could be found in the early stage. Only when intraductal tumor growth occurs in the common hepatic duct and/or the common bile duct does obstructive jaundice become a clinical concern. Hemobilia due to intraductal tumor growth is occasionally observed.

Besides jaundice, right upper quadrant pain is one of the major presenting features. In cirrhotic patients, unexplained hemobilia could be the initial complaint without any

manifestation of primary tumor, which can reveal a small, potentially curable, HCC that has spread to the biliary tree^[30]. Sometimes, this kind of patient is manifested as acute pancreatitis^[31].

The serum total bilirubin level can rise very rapidly and correlates well with ALP and GGT levels^[16, 32]. It is important to evaluate carefully when dealing with patients with intrabiliary tumor thrombi, even though they may show negative for viral hepatitis infection.

There are still difficulties and challenging problems in differential diagnosis of this type of HCC. The presence of an elevated AFP level and positive HBV markers are helpful to establish the diagnosis. The absence of these findings, especially with no primary hepatic tumor being detected, a variety of other diagnoses will be entertained. Despite remarkable recent improvements in the imaging tools for diagnosis of HCC, such cases were still incorrectly diagnosed as cholangiocarcinoma or choledocholithiasis^[4, 14-16, 21, 33, 34]. Ultrasonography (US) and CT are helpful in showing hepatic tumors and dilated intrahepatic and/or extrahepatic ducts containing dense material corresponding to tumor debris.

Ultrasonography (US)

Abdominal US is valuable as an initial investigation and for differentiation of patients with these presentations. Using US, it is able to suspect patients with icteric type HCC, even before other diagnostic strategies. Dilatation of proximal biliary tracts developed inevitably with time. Distension of the gallbladder was occasionally seen if the thrombus was located below the common hepatic duct (CHD). Tumor thrombi of bile duct could be easily identified on US as low-, iso-, or high-echogenic masses. At times, vascular signals could be detected on a Color Doppler sonography (CDS). Regarding biliary tract tumor thrombi, icteric type HCC should be strongly suspected whenever liver tumors exist. Moreover, pathological proof of thrombi can be obtained with an US-guided approach.

CDS is a non-invasive method in liver hemodynamic studies. Because HCC is known to be a hypervascular tumor, CDS is useful in detection of blood flow in HCC and helpful in differentiating it from other liver tumors. For the detection of tumor vascularity, spectral Doppler sonography guided by CDS is shown to be useful in the differential diagnosis of liver tumors. It is also useful in detection of blood flow within portal vein thrombosis in liver cirrhosis. It is a useful method for differentiating malignant from benign portal vein thrombi in liver cirrhosis, with 45-90 % sensitivity and 95-100 % specificity^[35]. Wang *et al.* found blood flow in bile duct tumor thrombi in 7 of 8 patients (87.5 %) with HCC and bile duct infiltration. Power Doppler sonography, a technique based on the integrated power of the Doppler spectrum, is more sensitive than CDS in depicting vascular flow in HCC. Its utility in detection of vascularity of bile duct tumor thrombi in patients with HCC might be more sensitive than that of CDS^[36].

Endoscopic sonography could show a tumor thrombus with central echogenicity and a "nodule-in-nodule" pattern, could provide more accurate evidence for the correct diagnosis^[37].

Computed tomography (CT)

Although CT is useful in patients with obstructive biliary disease, axial CT is not an effective method of demonstrating biliary anatomy. Because of the cross-sectional orientation of the CT images, the anatomy is fragmented and CT alone is less accurate in providing information of complex anatomic relationships. 3D CT cholangiography demonstrated the dilated bile ducts but could not depict nondilated peripheral bile ducts not seen on 2D axial images. On 3D CT cholangiography with miniIP, grades for anatomic details of biliary system were over

grade 4: visualization up to third-order branches. 3D CT cholangiography with miniIP determined the cause and level of all patients. Grades for anatomic visualization of the biliary tree corrected with an attenuation difference between bile ducts and enhanced hepatic parenchyma. Therefore, maximal hepatic parenchymal enhancement is one of the most important factors for 3D cholangiography with miniIP. Appropriate dilatation of the biliary tree is also necessary to extract pixels of bile ducts for 3D cholangiography. Focal disruptions of peripheral bile ducts were in all patients. However, the limitation of resolution in demonstrating a normal size of bile duct and focal disruption do not interfere with the determination of the level of obstruction, contiguity of ducts between different hepatic segments, and the presence or absence of isolated hepatic segment. 3D CT cholangiography correctly show the presence of biliary obstruction. Moreover, there is complete agreement between 3D CT cholangiography and PTC in the determination of obstruction level and cause in all patients. Spiral CT cholangiographic findings were also in agreement with those of direct cholangiography with regard to the site and extent of obstruction^[38].

Direct cholangiography

Although sonography and CT are sensitive in detecting biliary tract obstruction, direct cholangiography including percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) remains the standard procedure to delineate the presence and level of biliary obstruction. Nevertheless, direct cholangiography is operator dependant and invasive, with a higher complication rate in patients (up to 9 %) with obstructive jaundice^[39,40]. The complications, such as pancreatitis, sepsis, hemobilia, and bower proliferation, can be life threatening and can delay or even diminish the chance of managing the primary disease. ERCP and PTC are useful in the diagnosis of intrabiliary thrombi, and intraductal filling defects resulting in partial or complete obstruction and ductal dilatation are shown in 70 % of bile invasion by HCC. However, these cholangiographic features are not diagnostic for bile duct invasion by HCC; therefore, ERC and PTC are limited in their usefulness for characterization of BDT.

Magnetic resonance cholangiopancreatography (MRCP)

The MR features of intraductal tumors, bile duct obstruction with an associated hepatic mass or localized intrahepatic duct dilatation within wedge-shaped areas, indicated intraductal tumor extension. The enhancement of intraductal masses on dynamic MR images shows an extension of HCC rather than blood clots. MR cholangiography is recently shown to be superior to ERCP in detecting the presence of biliary obstruction, but it is relatively ineffective for interpretation of icteric-type HCC.

MRCP was introduced in 1991 by Wallner *et al*^[41]. It is an absolutely noninvasive imaging modality, allowing demonstration of the biliopancreatic system by means of data acquisition and images post-processing reconstruction presenting at the coronal planes similar to conventional cholangiography. It requires neither contrast medium injection, nor biliary endoscopic intervention; therefore, it completely avoids the formidable complications inherent to conventional cholangiographic examinations. Both primary liver tumors and dilatation of biliary system could be demonstrated in MRCP. Recent studies have demonstrated that MRCP can accurately depict abnormalities in the hepatobiliary system, and claimed a high accuracy in depicting various biliary and pancreatic disease entities, with reported sensitivities approaching 90-95 % for biliary and pancreatic ductal dilation and stricture^[42].

Presence of intraluminal soft tissue at the bile duct, and enhancement of the intraluminal soft tissue in the arterial phase are two typical features of HCC with tumor thrombi in bile duct. Sometimes, the simultaneous presence of an intraluminal tumor in the portal trunk and CHD could be found in this type of patients. Three different MRCP features could be found: (a) an oval defect in the hilar bile duct(s) with dilated intrahepatic ducts. A bulky intraluminal-filling defect resulting from either tumor fragments or blood clots obstructing the major bile duct is the most common cholangiographic finding of icteric type HCC. This feature has been reported in about 70 % of this type of patients. It most frequently occurs in the hepatic or common bile ducts, causing partial or complete obstruction. The bile ducts containing tumor fragments are visualized because the impacted tumor appears dark on MRCP and there is no surrounding bile. A comparison of direct cholangiography with MRCP showed that the non-visualized bile duct in type I MRCP corresponded well in size, contour, and location to the intraluminal filling defect on conventional cholangiography; (b) dilated intrahepatic ducts with missing major bile ducts, and (c) localized stricture of the hilar bile duct(s). It is an unusual cholangiographic feature of icteric-type HCC, and an incidence of 9-15 % has been reported. The stricture is short, smooth, and confined to the porta hepatis, in contrast to the multiple, long segmental dilatations and "rat-tail" stricture seen in cholangiocarcinoma. The localized stricture is probably the result of bile duct encasement by the large infiltrative tumor in the caudate lobe and hepatic hilum and the enlarged hilar lymph nodes. However, it may be very difficult to differentiate from hilar cholangiocarcinoma or cystic duct cancer in a patient presenting with type III MRCP, because of the very similar cholangiographic appearance. Other imaging modalities are required for additional information about the extent of the tumor, the extraluminal tumor compression, and the presence of enlarged lymph nodes. The presence of one or more of the following features in multiplanar MRI and MRCP help to identify this rare, specific type of HCC: (a) the presence of an intraluminal tumor in both the portal trunk and the common hepatic duct, (b) enhancement of the intraluminal tumor in the CHD on the arterial phase, (c) type I MRCP feature, and (d) hemobilia, blood clot within the gallbladder, and/or type II MRCP feature^[29, 42-45].

Both ERCP and MRCP are excellent for confirming the presence of malignant perihilar biliary obstruction that has been suggested by sonography and CT. Nevertheless, MRCP is obviously superior to ERCP in interpreting the cause and depicting the anatomical extent of the perihilar obstructive jaundice. It is particularly distinctive in cases associated with tight biliary stenosis and along segmental biliary stricture. For this kind of patients, an undue pressure and retention of contrast medium imposed on a diseased biliary tree might deteriorate the pre-existing biliary tract infection. Therefore, the amount of injected contrast agents given is below the optimal dose needed to appropriately visualize the biliary tree cephalad to the lesion site. Complementary PTC is warranted to remedy this problem. Certainly, the procedure-related risk increases synergically. Furthermore, in cases with separate biliary obstruction, detailed opacification of the intrahepatic biliary system may have necessitated multiple PTC sessions before the MRCP era. For deeply jaundiced patients with renal insufficiency, an iodinated contrast material is particularly dangerous; whereas MRCP is also satisfactorily delineate the dilated biliary system irrespective to the serum bilirubin level and renal function. In addition, the nonopacified area on the direct cholangiography, such as a sequestered bile duct or gallbladder as a result of tumor invasion, can be depicted clearly by MRCP.

Icteric type HCC represents the most difficult disease entity to correctly diagnose using either MRCP or ERCP. The

characteristic cholangiographic feature of bile duct involvement by a ruptured HCC is a large expanding intraluminal filling defect with an irregularly lobulated outline and ground-glass radiolucency of the filling defects, which may be smooth or irregular, usually seen in the common hepatic duct^[14,44,45]. The differential diagnoses of this type of cholangiography include papillary type cholangiocarcinoma, intraductal polyps or mucin-hypersecreting intrahepatic biliary neoplasm. It still relies on other information, such as the presence of liver cirrhosis, hepatitis markers, tumor markers (AFP, CEA), the fluctuation of jaundice, and hemobilia. The presence of an encapsulated mass with a central scar or internal fat may also be helpful to diagnose icteric HCC. MRCP and direct cholangiography provide the equivalent diagnosis information that segmental bile ducts are not visualized and the CHD is partially opacified because of migrating tumor thrombi. Furthermore, by means of T2-weighted axial and coronal plane of MR images, tumor thrombi that ruptured from the primary tumor into both intrahepatic and extrahepatic bile ducts could be perfectly depicted. This novel diagnostic modality makes the diagnosis of icteric HCC more straightforward and certain than ever before^[46].

Choledochoscopy

Choledochoscopy is an alternative diagnostic technique applicable before and after duct exploration. Choledochoscopy can differentiate obstructions resulting from intraluminal mass, infiltrating ductal lesions or extrinsic mass compression. Yamakawa first introduced intra-operative fiber optic choledochoscopy (IOC), using an improved fiberoptic choledochoscope, in 1976. Chen *et al.*^[47] used IOC to visualize the nature of obstruction of the bile duct.

Characteristic cholangiographic findings of HCC invading into the bile duct include intraluminal expanding hilar mass density. Jan *et al.* found the main choledochoscopic findings were a yellowish intraluminal nodular mass and tumor thrombus in the CBD. These features may allow differential diagnosis from hilar papillary type cholangiocarcinoma^[44].

Bile duct brushing cytology

Bile duct brushing cytology is another useful technique in the diagnosis of malignant biliary strictures. In HCC with obstructive jaundice due to invasion of the biliary tract, a striking feature of the brushing is the prominent capillary vascular pattern associated with the tumor cells. This is a cytologic feature that has been noted in fine-needle aspirates of HCC as well, and is distinct from the expected findings in adenocarcinoma^[48].

TREATMENT STRATEGIES

Surgical treatment

Jaundice is not necessarily a harbinger of advanced disease and a contraindication for surgery. Patients with primary liver cancer and jaundice due to migrated tumor fragments in the bile duct may benefit from surgical resection. Most patients will have satisfactory palliation and occasional cure if the appropriate procedures are selected and carried out safely, which can result in long-term resolution of symptoms and occasional long-term survival.

The goals of operative intervention are biliary decompression with removal of tumor debris or tumor-containing blood clots, and, if possible, curative resection of the hepatic tumor. The commonly used operative methods are lobectomy (including the primary tumor and the tumor thrombi in bile duct), hepatectomy plus thrombectomy, choledochotomy with T-tube drainage alone, internal biliary stenting, or biliary diversion. The ideal treatment of these patients is hepatic resections^[18,33,34,49-51].

“Curative” resection is possible in some patients with obstructive jaundice. The overall survival of patients with HCC with obstructive jaundice might be similar to those patients who present with no clinical detectable jaundice, and is much better than those with jaundice due to hepatic insufficiency^[52].

There are numerous techniques that can be employed for biliary decompression and drainage^[26]. The decision to perform what kind of operations or interventions should be based on the nature and location of the main tumor mass, severity of the symptoms, associated neoplastic strictures, the patient's overall status, and the experience of the surgeon. Wang *et al.* reported 10 cases with gross evidence of tumor thrombi in the bile duct were treated with different resection methods and interventions. Eight out of the 10 patients underwent exploratory laparotomy (right lobectomy with extrahepatic bile duct resection in 2 cases, right lobectomy with tumor thrombectomy in 2 cases, left lobectomy and caudate lobectomy with extra-hepatic bile duct resection in 2 cases including T-tube drainage in 1 case and biopsy only with post-operative internal biliary stent in 1 case). Survival time of these patients was 39 months (still alive); 38 months (still alive); 8 months (died); 8 months (died); 8 months (still alive); 1 month (still alive); 14 months (died); 8 months (died), respectively. Of the 2 non-surgical cases, 1 underwent PTBD only and the other had endoscopic removal of the thrombi. Their survival time was 18 days (died) and 24 months (still alive with recurrence), respectively. The 4 cases, with right lobectomy or left lobectomy including extrahepatic bile duct resection, had relatively long-term disease-free survival (39 months, 38 months, 8 months and 1 month after operation, respectively). However, there were no differences in survival between the partial hepatectomy procedure with removal of tumor thrombi and the simple drainage procedure without tumor resection. So, they suggested that, for the improvement of survival, it was necessary to perform major hepatic resection with removal of the extrahepatic bile duct. If hepatic resection could not be accomplished with bile duct resection due to limited liver function, non-surgical modalities should be considered instead of surgery because there was no difference in prognosis between the 2 groups^[53]. Hu *et al.* reviewed 18 patients with obstructive jaundice by tumor emboli from HCC during a 15-year period of time. Types of surgical procedures were choledochotomy with T-tube drainage alone in 9 patients, choledochotomy with T-tube drainage followed by hepatectomy in six, and T-tube drainage followed by TACE in the remaining three patients. The mean survival time for 9 patients with external drainage alone was 4.5 months. For the 3 patients with T-tube drainage and TACE, the mean survival time was 11 months. Six patients who had undergone hepatectomy had a better postoperative survival time, with 1 surviving for more than 3 years and another alive for 70 months, without evidence of recurrence at the moment^[54]. Tantawi *et al.* reported 5 patients underwent liver resection associated with biliary exploration, clearance and T-tube drainage, 4 of them received major hepatectomy. All of the patients survived more than 1 year with a median survival of 29 months. There were 2 long-term survivors without recurrence at 29 and 80 months^[51].

Intraoperative identification of the nature and location of intraluminal biliary obstruction is crucial for the initial assessment and planning of operative strategy. In this respect, IOC, cholangiography, and intraoperative US are important adjuncts to formal common bile duct exploration. Direct endoscopic visualization of bile ducts will facilitate differentiation of neoplastic stricture from filling defects demonstrated in cholangiograms. Removal of gross tumor debris as much as possible from the luminal of the bile duct through manual extraction and irrigation is one of the key procedures to the prognosis. This can often be verified at the end of the procedure either by repeated cholangioscopy or

cholangiography. Using intra-operative US on the surface of the liver, small or deeply seated tumor and intrahepatic metastasis can be found and an adequate tumor resection margin can be marked out accurately. IOC reveals the characteristic finding of an intraluminal yellowish nodular mass in patients with malignant obstruction of the bile duct due to HCC. Liver resection with a free margin of the involved hepatic duct can be achieved by a choledochoscopically guided operation^[14].

It is not difficult to remove such tumor casts at operation in most cases. However, active hemorrhage occurred during operation in some cases, possibly because of the continuity of the intraductal tumor debris with the main intrahepatic tumor. Suturing, electrocauterization, compression, Pringle's maneuver, or hepatic arterial ligation usually can achieve hemostasis. When noncalculous material is found to be obstructing the extrahepatic ducts, even no obvious primary hepatic tumor was found, tumor embolus must be considered and the material sent routinely for pathological evaluation.

The role of preoperative biliary drainage (PBD) before liver resection in the presence of obstructive jaundice remains controversial. Cherqui *et al.* found major liver resections without PBD were safe in most patients with obstructive jaundice. Recovery of hepatic synthetic function was identical to that of no jaundiced patients. Transfusion requirements and incidence of postoperative complications, especially bile leaks and subphrenic collections are higher in jaundiced patients. Whether PBD could improve these results remains to be determined^[55]. Teda *et al.* thought a combination of biliary drainage and subsequent TAE is a recommended pre-operative strategy for the successful surgical treatment of Icteric type HCC. Nine of the 10 patients achieved sufficient reduction of the jaundice preoperatively. After the evaluation of liver function, 8 patients underwent hepatectomy without any appreciable morbidity or mortality. The median survival time of the resected cases was 18 months^[56].

Non-surgical treatments

Although successfully resected cases of Icteric type HCC have been reported, most of this type of patients are inoperable^[49-52,57]. The alternative treatment strategy is palliative in intent, including palliative treatment for the tumor and thrombi, and alleviating the jaundice. Palliative treatment strategies, including TACE and/or radiotherapy (R/T) show a beneficial effect in improving the survival.

Biliary drainage is usually used as the initial treatment because of overt cholangitis. Early and effective biliary drainage (percutaneous transhepatic biliary drainage, PTBD) might be necessary in this group of patients with limited hepatic function to prove the prognosis^[58].

To some extent, for icteric type HCC patients with poor and complicated conditions, the palliative strategies are chosen based on experience. In icteric type HCC patients with sufficient reserved liver function, TACE is effective and should be tried as a first choice of therapy^[59]. The median survival time among those eight patients who received palliative treatment was 13.4 months (a range of 8-26 months), which was significantly longer than for the other two patients without treatment (2 and 4 months).

External beam radiation therapy may be beneficial in some patients with unresectable icteric-type HCC. Also, US-guided localized radiotherapy, particularly on the critically located CBD and CHD thrombi, could be effective^[60,61]. Huang *et al.* demonstrated that radiotherapy could be an effective adjuvant strategy in those who showed limited response to TACE or those who had poor liver reserve function. The median survival time of those 8 patients receiving palliative treatment (TACE

alone, or radiotherapy alone, or in combination) was longer than that the other two patients without treatment (13.4 months vs. 3 months)^[16]. When combined with other conventional therapies (such as TACE), radiation therapy may play an important role in the treatment of HCC^[62].

Endoscopic biliary drainage (EBD) for unresectable HCC associated with obstructive jaundice remains controversial because of the short survival of these patients. Some reports suggest EBD is one of the most effective treatments for patients with unresectable malignant biliary stenosis, and even for patients with obstructive jaundice caused by liver metastasis. However, EBD is often difficult in HCC patients with obstructive jaundice and may fail because of proximal biliary obstructive at the hilum, underlying liver cirrhosis, and a poor hepatic functional reserve. Consequently, it is not a commonly used procedure in patients with advanced inoperable HCC and obstructive jaundice, and the indications for EBD in these patients are also controversial because of their short survival^[63].

ERCP can be both diagnostic and therapeutic. Biliary stenting can relieve jaundice and allow further chemotherapy, but at additional expense and potential morbidity. Martin *et al.* retrospectively analyzed 26 patients with HCC and jaundice undergoing ERCP after CT or US, and found in selected patients, stenting could safely relieve jaundice and allow subsequent chemotherapy. CT or US accurately predicted lesions that responded to stenting. ERCP and stenting provided no benefit in the absence of biliary dilation on CT or US^[64]. Placement of metallic stents is the procedure of choice for palliation of malignant biliary obstruction. Stents show a favorable patency rate with regard to patient survival. In patients with hilar obstruction, the clinical efficacy of metallic stents is superior to that in patients with CBD obstruction^[65]. In the palliative treatment of HCC patients, a large stent may be necessary, as used in reports of HCC successfully treated by metal stents, if the hepatic functional reserve is not too poor^[66,67].

EBD is more effective for palliation in the patients with obstructive jaundice caused by tumor fragments and/or blood clots or with tumor protruding into the CBD lumen than in the patients who mainly have tumor invasion. So it is important to understand the causes of obstruction on cholangiograms before performing EBD. And it is difficult in most patients with direct tumor invasion involving both hepatic ducts, and multiple tumors in both lobes. It is important to determine the site, extent, and nature of the obstruction, as well as liver function and the presence of portal thrombus, before performing EBD. In patients with tumor involvement of both the right and left intrahepatic ducts, EBD should be avoided because of the low successful drainage rate and short survival. In HCC patients with obstructive jaundice, considering the progression of hepatic insufficiency, it is important to achieve complete drainage at the first stenting procedure. In patients with CBD bifurcation tumors, drainage of both lobes should be achieved, if possible. However, attempted drainage of all obstructed liver segments may cause cholangitis or sepsis if it is unsuccessful^[68,69].

The combination of palliative methods may relieve jaundice, ensure a good quality of life and possibly prolong survival of this type of HCC patients. Lauffer *et al.* reported 1 case received combination treatment with surgical segment III drainage, TACE and radioembolization with Yttrium-90 resin particles and endoscopic stenting was performed. With these combined procedures, relief of jaundice and a survival time of 32 months could be achieved^[70].

PROGNOSIS

The prognosis of icteric type HCC patients is generally dismal, but is better than those HCC patients who have jaundice caused by hepatic insufficiency. Cholangitis secondary to tumor

obstruction is found to be the major cause of death in these patients.

The prognosis of this type of HCC patients is closely related to the stage of disease, the location and extension of tumor thrombi in bile duct. In 1994, Ueda *et al.* classified HCC with BDT into 4 types. Type I: BDT located in the secondary branch of the biliary tree. Type II: BDT extending to the first branch of the biliary tree. Type III: BDT extending to the common hepatic duct (CHD) (IIIa); an implanted tumor growing in the CHD (IIIb). Type IV: floating tumor debris from the ruptured tumor in the CBD^[71]. They also found that the patients with type I, IIIb and IV of BDT had a relative better prognosis than other types.

Different therapies also influence the prognosis of this type of patients. Lau *et al.* reported that patients who received curative liver resection had a much better survival rate than those without resection (with a median survival of 25.3 vs. 2.1 months, respectively)^[72]. Huang *et al.* studied 9 patients who had a patent portal vein and reported that the mean survival of 4 patients with curative resection was 35.8 months, but that of the 5 patients with palliative treatment was only 4.5 months. Thus, the ideal treatment for HCC associated with obstructive jaundice is to reduce the jaundice with preoperatively and perform hepatic resection, but the prognosis of patients who are inoperable is extremely poor^[73]. Kojiro *et al.* reported that 2 of their patients died 40-60 days after the development of obstructive jaundice^[4]. In a study of 49 HCC patients with obstructive jaundice, Lau *et al.* reported that 9 patients received curative resection, 35 had biliary stents, and 5 had supportive treatment, and the overall survival of these patients was similar to that of HCC patients without jaundice. They concluded that good palliation and occasional cure were possible with proper treatment^[52]. For biliary drainage in patients with unresectable HCC, the mean survival time of patients with only EBD was 3.9 months^[29], and the patients with external drainage alone was 4.5 months^[54].

CONCLUSIONS

Obstructive jaundice as the main presenting clinical feature of HCC is uncommon. The prognosis of this type of HCC is generally dismal, but is better than those HCC patients who have jaundice caused by hepatic insufficiency. Jaundice is not necessarily a harbinger of advanced disease and a contraindication for surgery. Patients with primary liver cancer and obstructive jaundice due to migrated tumor fragments in the bile duct may benefit from surgical resection. Most patients will have satisfactory palliation and occasional cure if appropriate procedures are selected and carried out safely, which can result in long-term resolution of symptoms and occasional long-term survival.

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