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TOPIC HIGHLIGHT

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Diagnosis and initial management of cholangiocarcinoma with obstructive jaundice

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Abstract

Cholangiocarcinoma is the second most common primary hepatic cancer. Despite advances in diagnostic techniques during the past decade, cholangiocarcinoma is usually encountered at an advanced stage. In this review, we describe the classification, diagnosis, and initial management of cholangiocarcinoma with obstructive jaundice.

Key words: Cholangiocarcinoma; Obstructive jaundice; Diagnosis; Treatment; Initial management

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INTRODUCTION

Cholangiocarcinoma is the second most common primary hepatic cancer. Despite advances in diagnostic techniques during the past decade, cholangiocarcinoma is usually encountered at an advanced stage. In this review, we describe the classification, diagnosis, and initial management of cholangiocarcinoma with obstructive jaundice.

CLASSIFICATION

Cholangiocarcinomas are epithelial neoplasms that originate from cholangiocytes and can occur at any level of the biliary tree. These lesions are broadly classified into intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, and distal extrahepatic bile duct tumors. Histologically, most cholangiocarcinomas (> 95%) are adenocarcinomas. They are pathologically classified into sclerosing, nodular, and papillary intraductal cancers[1]. A recent pathological classification applicable to both intrahepatic and extrahepatic cholangiocarcinomas divides these lesions into mass-forming (nodular), periductal-infiltrating (sclerosing), and intraductal-growing (papillary) cholangiocarcinomas[2].

DIAGNOSIS

Laboratory data

Liver test abnormalities reflecting obstruction of the bile duct are usually observed. Strikingly elevated CA19-9 values in symptomatic patients usually signify advanced disease. Carcinoembryonic antigen (CEA) is also elevated in patients with cholangiocarcinoma, but is not diagnostic because of low sensitivity and specificity. Cholangitis and hepatolithiasis commonly lead to increased levels of tumor markers. Cholangiocarcinoma should not be diagnosed on the basis of laboratory data alone.

Ultrasonography

Ultrasonography is the imaging technique of choice for the diagnosis of cholangiocarcinoma with obstructive jaundice. Visualization allows adequate diagnosis and staging in more than 90% of cases. The presence of dilated ducts without clear communications within a liver lobe indicates the extension of tumor into the segmental bile ducts. Ultrasonography is useful for evaluating the local extent of disease, but is of limited value for staging distant metastases. Intrahepatic cholangiocarcinomas may be identified as mass lesions, sometimes associated with bile duct dilatation proximal to the obstructing lesion. Tumor vascularity is an important characteristic that can be assessed by color Doppler ultrasonography. An abnormal pulsed Doppler signal obtained from the portal venous system due to severe narrowing or occlusion

strongly suggests major involvement and unresectable tumor. However, a normal pulsed Doppler signal does not exclude such involvement, if the tumor is contiguous with vessels showing interruption of the hyperechoic tumor-vessel interface[3,4].

Endoscopic ultrasound (EUS) is useful for assessing the extent of disease and performing fine needle aspiration. Eloubeidi *et al*[5] reported that EUS-guided fine needle aspiration biopsy is useful for the diagnosis of suspected cholangiocarcinoma. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 86%, 100%, 100%, 57%, and 88%, respectively. EUS-guided fine needle aspiration of lymph nodes facilitates staging of disease in addition to visualization of the biliary tree[6].

Computed tomography (CT)

CT permits the identification of bile duct dilatation and assessment of the hepatic parenchyma and lymph nodes. However, the evaluation of horizontal spread by diagnostic imaging via the bile duct remains challenging in patients with cholangiocarcinoma, especially on conventional CT examination. Recently, the development of multidetector row CT scanners has permitted a reduction in the voxel size and facilitated rapid image reconstruction, enhancing the value of CT as an interactive diagnostic tool. Moreover, innovative methods for CT image reconstruction, including multiplanar reconstruction and three-dimensional images, were recently introduced for the visualization of biliary structures[7]. CT angiography has been demonstrated to be useful for the detection and assessment of vascular encasement[8-10].

Magnetic resonance imaging (MRI)

MRI with concurrent magnetic resonance cholangiopancreatography (MRCP) is the radiologic technique of choice for assessing the extent of disease[11,12]. The limitations of conventional imaging techniques have led to the increased use of MRCP, which is a noninvasive and highly accurate technique for the evaluation of patients with biliary obstruction. MRCP is optimally suited for the visualization of both intrahepatic and extrahepatic cholangiocarcinomas, which appear as hypointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images. Images can be enhanced with the use of superparamagnetic iron or by delayed gadolinium enhancement[13,14]. The overall diagnostic accuracy for assessment of the level and cause of obstruction was 96.3% and 89.7%, respectively[12]. MR angiography can be used to evaluate vascular involvement[15].

Cholangiography

Before the development of MRCP, direct cholangiography was only technique for assessment of the biliary system. Direct cholangiography can be performed by either percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography, and samples of the bile duct can be obtained[16,17]. Brushings are analyzed cytologically. In one study, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of brush cytology were 75%, 100%, 100%, 12.5%, and 75.9%, respectively. Biopsy specimens of the bile duct are examined histologically[18]. The diagnostic performance of transluminal forceps biopsy for malignant biliary obstructions was as follows: sensitivity, 78.4%; specificity, 100%; and accuracy, 79.2%[19]. Savader *et al*[20] compared the diagnostic accuracy of three different techniques for percutaneous transhepatic intraductal biopsy: brush cytology, clamshell forceps under choledochoscopic guidance, and clamshell forceps under fluoroscopic guidance. The choledochoscope-directed biopsy technique had the highest sensitivity and specificity among the three techniques, but was not significantly better than either the brush or fluoroscopic clamshell techniques ($P > 0.10$). Multiple biopsies did not increase the overall sensitivity of intraductal biliary biopsy as a diagnostic technique. All three techniques were safe and easy to perform. In patients with malignant biliary obstruction, brush cytology was more sensitive for the diagnosis of cholangiocarcinoma than for the diagnosis of non-cholangiocarcinoma ($P < 0.05$). The site of stenosis was unrelated to sensitivity and technical success ($P > 0.05$)[18,21].

Rotational cine cholangiography is used to diagnose bile duct carcinoma. Rotational cine cholangiography is a reliable technique for detecting the confluence of the bile ducts, as well as for diagnosing the longitudinal extent of cancer spread along the bile duct wall[22]. Furukawa *et al*[23] evaluated the usefulness of three-dimensional cholangiography and rotating cine cholangiography for depicting the anatomy of the hilar bile duct and tumor extension, and for planning surgical procedures for hilar cholangiocarcinoma. Three-dimensional and cine cholangiography allowed accurate assessment of the biliary system in patients with hilar cholangiocarcinoma, facilitating the planning of surgery.

Angiography

Angiography reveals the anatomy of the hepatic and biliary arteries. Angiography is a superb technique for the detection of vascular encasement. It is also useful for planning surgical procedures.

Scintigraphy

Technetium-99m galactosyl human serum albumin scintigraphy: Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (99mTc-GSA) is an analog ligand of asialoglycoprotein that binds specifically to asialoglycoprotein receptors (ASGP-R) residing in mammalian hepatocytes[24-26]. The hepatic uptake of 99mTc-GSA at 15 min or later reflects the receptor population or functional hepatocyte mass[27].

Nanashima *et al*[28] studied the relation between morphological measurements of hepatic volume on CT and functional volume on 99mTc-GSA scintigraphy. There were no significant differences in the volume measurements between these two volumetric techniques. Volumetric measurement by 99mTc-GSA scintigraphy is useful for detecting changes in the functional volume of individual lobes of the liver and is a more dynamic method than the assessment of morphological changes on CT scanning.

We confirmed hemodynamic changes in the distribution of splenic venous flow in the liver, especially in the cirrhotic liver, and demonstrated the participation

of splenic venous flow in the regeneration or enlargement of the hepatic lobe by means of scintiphotosplenopor tography after percutaneous intrasplenic injection of 99mTc-GSA. We concluded that splenic venous blood flow promotes liver fibrosis in the right lobe of the liver exposed to continuous damage, with gradually increasing flow into the left lobe, showing milder fibrosis[29].

Positron emission tomography (PET): PET with [18F]-fluorodeoxyglucose can be used to rule out metastatic disease, although the findings should be interpreted cautiously because of false positive results in inflammatory lesions; moreover a normal PET scan does not exclude cancer[30].

INITIAL MANAGEMENT

Biliary drainage

In patients with obstructive jaundice who have cholangiocarcinoma, especially hilar cholangiocarcinoma, preoperative biliary drainage has been recommended to improve liver function before surgery and to reduce postoperative complications. Percutaneous transhepatic biliary drainage (PTBD) with multiple drains was previously the preferred method for the preoperative relief of obstructive jaundice. In patients with hilar cholangiocarcinoma, drainage is currently performed only for liver lobes that will remain after resection and for areas of segmental cholangitis. Endoscopic biliary drainage (EBD) is less invasive than PTBD. However, EBD has to be converted to PTBD in patients with segmental cholangitis, those requiring prolonged drainage, or those in whom the extent of longitudinal tumor extension is poorly defined[16].

Kamiya *et al*[31] reported that impaired intestinal barrier function does not respond to external biliary drainage without bile replacement. Bile replacement during external biliary drainage can restore intestinal barrier function in patients with biliary obstruction, primarily by promoting the repair of physical damage to the intestinal mucosa. Koivukangas *et al*[32] reported that cell protein synthesis is disturbed earlier than cell dynamics in obstructive jaundice. Decreased baseline skin-collagen synthesis is partly restored by the resolution of jaundice[33].

We previously reported that elevated serum collagen IV is a feature of malignant obstructive jaundice commonly associated with prolonged bilirubin clearance, and a useful indicator of clinical course, postoperative morbidity, and mortality in patients with malignant obstructive jaundice[34].

The procedure of choice for biliary drainage before major hepatectomy in patients with obstructive jaundice remains controversial, i.e. selective biliary drainage of only the future remnant liver or total biliary drainage. Ishizawa *et al*[35] reported that selective biliary drainage is superior to total biliary drainage for promoting hypertrophy of the future remnant liver in patients undergoing portal vein embolization and for guaranteeing good liver function before major hepatectomy. Hochwald *et al*[36] showed that preoperative biliary stenting in proximal cholangiocarcinoma increases the incidence of contaminated bile and postoperative infectious complications. Cherqui *et al*[37] found that major liver resection without preoperative biliary drainage is a safe procedure in most patients with obstructive jaundice. Recovery of hepatic synthetic function is identical to that of patients without jaundice. Transfusion requirements and the incidence of postoperative complications, especially bile leaks and subphrenic collections, are higher in jaundiced patients. Pitt *et al*[38] concluded that preoperative PTBD does not reduce operative risk but does increase hospital costs and, therefore, discouraged routine use. The indication for preoperative biliary stenting in patients with obstructive jaundice remains controversial.

Portal vein embolization (PVE)

PVE before hepatectomy is designed to induce atrophy of the embolized lobe scheduled to be resected, while inducing compensatory hypertrophy of preserved lobe[39,40]. PVE with compensatory contralateral hypertrophy of the future liver remnant has been performed to enable extended hepatectomy (resection of $\geqslant$ 5 hepatic segments)[41,42]. We have reported on combined embolization of the hepatic artery and portal vein[43].

Biliary ablation

Selective biliary infusion of ethanol can be performed safely without serious complications, inducing lobar ablation with contralateral hypertrophy of the liver[44,45].

Operation

Surgical resection has been the mainstay of curative treatment for cholangiocarcinoma[46]. Major hepatectomy with systematic nodal dissection is associated with a good chance of prolonged survival in patients with carcinoma involving the hepatic hilus, including those with advanced disease[47,48]. Extended hemihepatectomy, with or without pancreatoduodenectomy, plus extrahepatic bile duct resection and regional lymphadenectomy has recently been recognized as the standard curative treatment for hilar bile duct cancer. Pancreatoduodenectomy is the choice of treatment for middle and distal bile duct cancer. Major hepatectomy with pancreatoduodenectomy (hepatopancre atoduodenectomy) has been performed in selected patients with widespread disease. Miyazaki *et al*[49,50] reported that parenchyma-preserving hepatectomy could result in curative resection and improve the outcomes of patients with hilar cholangiocarcinoma localized to the hepatic duct confluence who do not require vascular resection. Less-extensive procedures were also beneficial for less-advanced disease if the resection margins were free of tumor. Even with carefully selected treatment with curative intent, the 5-year survival of patients with cholangiocarcinoma ranges from 30% to 40%. A tumor-free surgical margin is the best predictor of survival. Several staging schemes have been proposed, but none correlates with resectability. Lymph node involvement is also a predictor of survival[48,51].

Adjuvant therapy

Neoadjuvant therapy with several types of treatment, including radiation, photodynamic therapy and chemotherapy, provides no clear benefit[52,53].

Palliative therapy

Previously, plastic endoprostheses were placed for the

palliative treatment of malignant biliary obstruction[54-57]. An expandable metal stent (EMS) is used to provide palliation in patients with malignant obstructive jaundice[58]. EMSs have been compared with plastic endoprostheses for the palliative treatment of malignant obstructive jaundice[59,60]. EMSs are inserted percutaneously[61-63] or endoscopically[59,64].

Biliary stent placement combined with local tumor therapy, such as brachytherapy, extra-radiation therapy, or arterial infusion chemotherapy, can prolong the survival time of patients with malignant biliary obstruction[65-68]. Mezawa *et al*[69] developed a new PTBD tube coated with carboplatin.

Intrahepatic cholangiojejunostomy has been performed in patients with unresectable malignant biliary obstruction[70-72]. Endoscopic stenting for the management of this condition costs significantly less than surgical treatment[73]. Recently, EUS-guided hepaticogastrostomy has been performed[74].

Transplantation

Although early survival after transplantation for cholangiocarcinoma is excellent, high recurrence rates have generally discouraged liver replacement. Recent findings, however, have lead to a resurgence in orthotopic liver transplantation for unresectable, albeit locally contained cholangiocarcinoma. Becker *et al*[75] reported a series of 280 patients with cholangiocarcinoma who received orthotopic liver transplantation. After a median follow-up of 452 d, the survival rates at 1 and 5 years were 74% and 38%, respectively. Heimbach *et al*[76] reported on 56 patients who were treated for unresectable, stage I and Ⅱ perihilar cholangiocarcinoma. Disease-free survival at 5 years was excellent (82%) in carefully selected patients who underwent neoadjuvant external-beam radiation therapy, transcatheter intrabiliary radiation, chemotherapy, and pretransplant-staging exploratory laparotomy. Neoadjuvant chemoradiotherapy with liver transplantation produces excellent results for selected patients with localized, regional node negative, hilar cholangiocarcinoma[76,77].

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