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Flowcharts for the management of biliary tract and ampullary carcinomas

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Abstract
No strategies for the diagnosis and treatment of biliary tract carcinoma have been clearly described. We developed flowcharts for the diagnosis and treatment of biliary tract carcinoma on the basis of the best clinical evidence. Risk factors for bile duct carcinoma are a dilated type of pancreaticobiliary maljunction (PBM) and primary sclerosing cholangitis. A nondilated type of PBM is a risk factor for gallbladder carcinoma. Symptoms that may indicate biliary tract carcinoma are jaundice and pain in the upper right area of the abdomen. The first step of diagnosis is to carry out blood biochemistry tests and ultrasonography (US) of the abdomen. The second step of diagnosis is to find the local extension of the carcinoma by means of computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), percutaneous transhepatic cholangiography (PTC), and endoscopic retrograde cholangiopancreatography (ERCP). Because resection is the only way to completely cure biliary tract carcinoma, the indications for resection are determined first. In patients with resectable disease, the indications for biliary drainage or portal vein embolization (PVE) are checked. In those with nonresectable disease, biliary stenting, chemotherapy, radiotherapy, and/or best supportive care is selected.

Key words Biliary tract carcinoma · Bile duct carcinoma · Gallbladder carcinoma · Ampullary carcinoma · Guidelines

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Introduction

There have been no reports of a comprehensive clinical system to cover all entities of bile duct carcinoma, gallbladder carcinoma, and ampullary carcinoma. In addition, there is no clear consensus as to the best methods of diagnosis and treatment of biliary tract carcinoma. We therefore developed flowcharts for the diagnosis and treatment of biliary tract carcinoma, on the basis of the best clinical evidence provided until 2007. Six levels of evidence were used (see definitions of levels in Table 1[1]), and the levels are noted here in parentheses after the citations of relevant references. The flowchart for diagnosis consists of: (1) risk factors, (2) clinical presentation, (3) the first step of diagnosis, and (4) the second step of diagnosis. The flowchart for treatment consists of: (1) resectable cases and (2) nonresectable cases.

Flowchart for the diagnosis of biliary tract carcinoma

The flowchart for the diagnosis of biliary tract carcinoma is shown in Fig. 1.

Risk factors

Risk factors for bile duct carcinoma are a dilated type of pancreaticobiliary maljunction (PBM) and primary sclerosing cholangitis. Biliary tract carcinoma occurred in 10.6% of patients with a dilated type of PBM, and bile duct carcinoma occurred in 33.6% of such patients[2] (level IV). Bile duct carcinoma occurred in 5%–10% of patients with primary sclerosing cholangitis[3–6] (level V).

A nondilated type of PBM is a risk factor for gallbladder carcinoma. Biliary tract carcinoma occurred in 37.9% of patients with a nondilated type of PBM, while gallbladder carcinoma occurred in 93.2% of such patients[2] (level IV).

No risk factor is known for ampullary carcinoma.

Clinical presentation

Symptoms that may indicate biliary tract carcinoma are jaundice and pain in the upper right area of the abdomen.

For 90% of patients with bile duct carcinoma, the presenting symptom was jaundice[7,8] (level IV). In patients without jaundice, the presenting symptom was pain in the abdomen, fever, anorexia, or lassitude[2,7–9] (level IV).

The symptom most often seen in gallbladder carcinoma is pain in the upper right area of the abdomen[10,11] (level IV). Other signs and symptoms are nausea, vomiting, loss of weight, jaundice, anorexia, a feeling of abdominal distension, pruritus, and black feces[10] (level IV).

Symptoms of ampullary carcinoma in many patients are jaundice, fever, and abdominal pain[12,13] (level IV).

Table 1. Levels of evidence[1]

Level I	Systematic review/meta-analysis
Level II	One or more randomized clinical trials
Level III	Nonrandomized controlled trials
Level IV	Analytic epidemiology (cohort studies and case-control studies)
Level V	Descriptive study (case reports and case-series studies)
Level VI	Opinions of expert panels and individual experts not based on patient's data

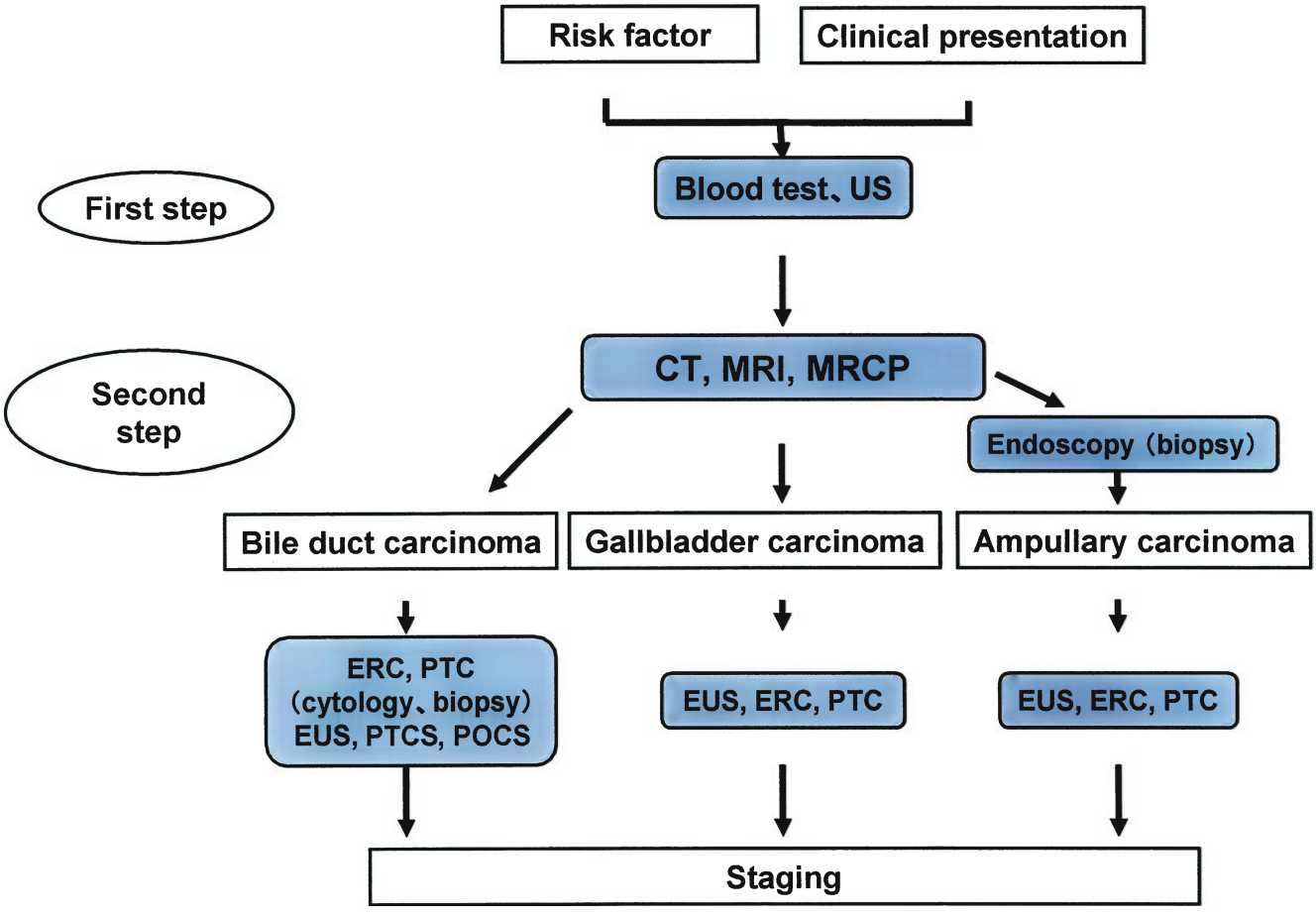

Fig. 1. Flowchart for the diagnosis of biliary tract and ampullary carcinomas. *US*, Ultrasonography; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *MRCP*, magnetic resonance cholangiopancreatography; *ERC*, endoscopic retrograde cholangiography; *PTC*, percutaneous transhepatic cholangiography; *EUS*, endoscopic ultrasonography; *PTCS*, percutaneous transhepatic cholangioscopy; *POCS*, peroral cholangioscopy

First step of diagnosis

The first step of diagnosis is to carry out blood biochemistry tests and ultrasonography (US) of the abdomen. In blood biochemistry tests in patients with bile duct obstruction, rises in hepatobiliary enzymes are observed[14,15] (level III). Carbohydrate antigen (CA) 19-9 is elevated in 50%–79% of patients with biliary tract carcinoma[16–19] (levels II and III), and carcinoembryonic antigen (CEA) is elevated in 40%–70% of such patients[19–21] (level III).

If there is a suspicion of biliary tract carcinoma, US is the first diagnostic imaging to be applied. If dilation of the bile duct is found, it is possible to identify the obstructed region[14,15] (level III). For gallbladder carcinoma, the tumor is identified by US in more than 50% of patients[14] (level III).

Second step of diagnosis

Bile duct carcinoma

Computed tomography (CT) and magnetic resonance imaging (MRI; including magnetic resonance cholangiopancreatography [MRCP]) are useful to check on the location of bile duct carcinoma or to find the local extension of such carcinoma. Contrast-enhanced CT is useful for finding the main local extension of cancer. In addition, examining whether there is invasion of the cancer into blood vessels by means of contrast-enhanced CT is important for deciding how to treat the cancer[22–24] (level II-IV). In bile duct carcinoma without thickening of biliary walls, it is difficult to identify local extension or depth only by means of CT[22,23] (levels II and IV).

MRCP is useful for identifying the obstructed region in the bile duct, for finding the local extension of the carcinoma, and for checking on PBM[25] (level IV). MRCP has a sensitivity of 70%–96% in determining whether a bile duct stricture is of benign/malignant nature, and is able to identify obstructed regions with a sensitivity of 94%–99%[26–28] (levels III and IV).

Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) are useful for examining the horizontal invasion of nodular bile duct carcinoma, and for indicating nodular and invasive bile duct carcinoma[29,30] (level IV).

Examination of cells or tissues is carried out as required. The positive rate of bile cytology determined by means of endoscopic retrograde cholangiography (ERC) is about 30%[25] (level II). A combination of brush cytology and biopsy of the bile duct increases the positive rate to 40%–70%[25] (level II).

Percutaneous transhepatic cholangioscopy (PTCS)[31–33] and peroral cholangioscopy (POCS)[34,35] enable close examination of the lumen of the bile duct. These modalities are useful in both differentiating benign and malignant biliary strictures and in diagnosing the superficial mucosal spread of bile duct carcinoma along the bile duct wall.

Gallbladder carcinoma

In the diagnosis of gallbladder carcinoma, differential diagnosis and determination of the local extension of tumor are important. For these purposes, imaging modalities such as endoscopic ultrasonography (EUS), CT, MRI, and MRCP are useful. EUS has good sensitivity, of 92%–97%, in differentiating benign gallbladder diseases from gallbladder carcinoma[36–38] (level IV). CT has a capability of diagnosis of tumorous lesions in the gallbladder with a sensitivity of 88%, a specificity of 87%, and a correct diagnosis rate of 87%[39] (level IV). In a report that evaluated the diagnosis of the resectability of gallbladder carcinoma, accuracy of the diagnosis of resectability with CT was 93.3%[40] (level IV). According to some reports, in the diagnosis of direct invasion of tumor into the liver, MRI combined with MRCP had a sensitivity of 67%–100% and a specificity of 89%; in the diagnosis of invasion of tumor into the bile duct, it had a sensitivity of 62%–100% and a specificity of 89%; and in the diagnosis of cancer metastasis to lymph nodes, it had a sensitivity of 56%–92% and a specificity of 89%[41,42] (level IV).

Ampullary carcinoma

For the examination of ampullary carcinoma, endoscopic biopsy is used. For the examination of distant metastasis of cancer, e.g., to the liver, US, CT, and MRI are used. For the examination of invasion to the pancreas or the duodenum, EUS or intraductal ultrasonography (IDUS) is useful[43,44] (level II).

Flowchart for the treatment of biliary tract carcinoma

The flowchart for the treatment of biliary tract carcinoma is shown in Fig. 2.

Indications for resection

Resection is the only radical treatment for biliary tract carcinoma. Its possibility should, therefore, be considered first. If such cancer involves metastasis to the liver, the lung or the peritoneum, it is not resectable[45–47] (level IV). On the other hand, there is a report which advocates surgery for patients with paraaoric lymph node metastasis, because the outcome is expected to be improved by surgery[48,49] (level IV). However, there is no consensus on standards for local extension factors or on the level of metastasis of lymph nodes that would determine whether the cancer is nonresectable.

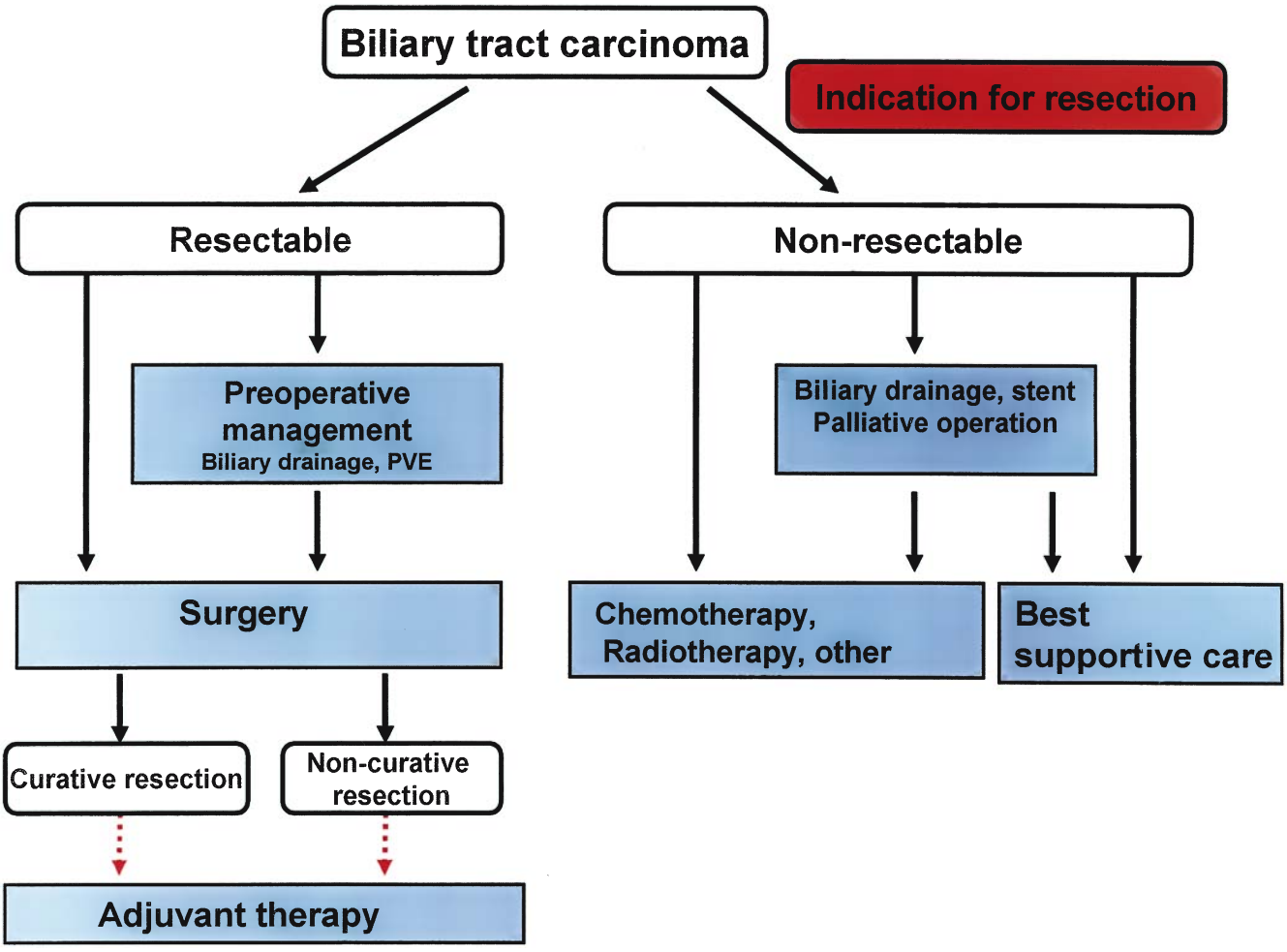

Fig. 2. Flowchart for the treatment of biliary tract and ampullary carcinomas. *PVE*, Portal vein embolization

Resectable cancers

Preoperative management

Biliary drainage. Many reports suggest that, except for patients with cholangitis or hepatic disorders, surgical operations that are as invasive as pancreatoduodenectomy do not need preoperative biliary drainage[50–54] (levels IV and VI). The mortality from complications in major hepatectomy is about 10%, and the main cause of death is hepatic failure[55] (level IV). In patients with severe jaundice, therefore, biliary drainage is carried out before surgical operation. For biliary drainage, it is, in principle, sufficient to drain only the future remnant liver. However, there are no standards for indications for such drainage.

Portal vein embolization (PVE). In patients who require right hemihepatectomy and more extended hepatectomy, or 50%–60% hepatectomy, particularly patients with obstructive jaundice, PVE may be performed. It may reduce postoperative complications or deaths related to the operations[56–62] (levels III and IV).

Surgery

The results of surgical treatment of biliary tract carcinoma have been improved with various new procedures.

Bile duct carcinoma. For hilar cholangiocarcinoma and upper bile duct carcinoma, extrahepatic bile duct resection with hepatectomy is a standard surgical procedure; and for middle or lower bile duct carcinoma, pancreatoduodenectomy is a standard procedure. For many patients with hilar cholangiocarcinoma, combined resection of the caudate lobe is recommended[63–65] (level IV); however, there is a report which describes that caudate lobe resection did not influence the outcome of patients with hilar cholangiocarcinoma[66]. In patients with upper or middle bile duct carcinoma, resection of the extrahe-

patic bile duct is indicated in those patients with papillary lesions localized in such regions, without clear metastasis to lymph nodes[67–69] (level IV). In addition, it is preferable to confirm a negative surgical margin in intraoperative rapid pathological examination. Combined resection of the portal vein in patients with tumor invasion into the portal vein resulted in a more satisfactory outcome than that seen in nonresectable patients[70–74] (level IV). So this combined resection may be performed.

Gallbladder carcinoma. Gallbladder carcinoma involves various modes of extension to adjacent organs, such as invasion into the liver, hepatoduodenal ligament, duodenum, or transverse colon. So it is important to select the type of surgical operation according to the mode of extension on a case-by-case basis, aiming at no residual tumor[75,76] (level IV).

Ampullary carcinoma. For this carcinoma, the standard operation is pancreatoduodenectomy. The indication for carcinoma in adenoma is minimally invasive surgery[77–79] (level IV).

Adjuvant therapy

For chemotherapy, there are no recommendable regimens, so such therapy is used on a trial basis. For radiotherapy, some reports have stated that it was useful; however, there is no highly reliable evidence for standard therapy[80–83] (level IV). Accordingly, radiotherapy may be used in patients who have a positive surgical margin postoperatively[84] (level IV). However, one should be cautious in using radiotherapy in patients with curative resection.

Nonresectable cancers

Biliary drainage and stenting

For patients with lower bile duct obstruction, biliary stenting is carried out. The stenting is preferably by an endoscopic route[85,86] (level II). For the type of stent, a metal stent is recommended for patients with lower bile duct obstruction[87–92] (level II).

Chemotherapy, radiotherapy, and photodynamic therapy

Chemotherapy. For patients in a good general state, chemotherapy is applied[93–96] (levels II and IV). No standard chemotherapy has yet been established. A combination therapy regimen with gemcitabine hydrochloride is now in a phase II study.

Radiotherapy. It is reported that radiotherapy has a better effect in improving survival time than palliative therapy[97,98] (level IV). In addition, another advantage of radiotherapy is that the patency of the stent may be maintained and pain may be reduced by local control.

Photodynamic therapy. It is recognized that photodynamic therapy combined with biliary stenting has a significantly better effect in improving survival time than biliary stenting only[99,100] (level II).

Best supportive care

For patients in whom chemotherapy and radiotherapy are not indicated due to a poor general state or persistent jaundice, best supportive care, such as pain control, should be applied for the purpose of maintaining quality of life.

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