Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition

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Abstract

Background The Japanese Society of Hepato-Biliary-Pancreatic Surgery launched the clinical practice guidelines for the management of biliary tract and ampullary carcinomas in 2008. Novel treatment modalities and handling of clinical issues have been proposed after the publication. New approaches for editing clinical guidelines, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, also have been introduced for better and clearer grading of recommendations.

Methods Clinical questions (CQs) were proposed in seven topics. Recommendation, grade of recommendation and statement for each CQ were discussed and finalized by evidence-based approach. Recommendation was graded to grade 1 (strong) and 2 (weak) according to the concept of GRADE system.

Results The 29 CQs covered seven topics: (1) prophylactic treatment, (2) diagnosis, (3) biliary drainage, (4) surgical treatment, (5) chemotherapy, (6) radiation therapy, and (7) pathology. In 27 CQs, 19 recommendations were rated strong and 11 recommendations weak. Each CQ included the statement of how the recommendation was graded.

Conclusions This guideline provides recommendation for important clinical aspects based on evidence. Future collaboration with cancer registry will be a key for assessment of the guidelines and establishment of new evidence. Free full-text articles and a mobile application of this guideline are available via http://www.jshbps.jp/en/guideline/biliary-tract2.html.

Keywords Ampullary carcinoma · Bile duct carcinoma · Biliary tract cancer · Gallbladder carcinoma

Introduction

The prognosis of biliary tract cancers, including bile duct carcinoma, gallbladder carcinoma, and ampullary carcinoma, still remains poor. However, due to the paucity of high-level evidence for diagnosis and treatment of these diseases, there are wide disparities in the levels of patients’ care among different institutions. These backgrounds indicate that the clinical guidelines for the management of biliary tract cancers edited by the specialists in these fields are very useful for physicians involved in the care of these diseases. It also helps to eliminate cancer care disparities among the institutions.

The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) published the clinical practice guidelines for the management of biliary tract and ampullary carcinomas in 2008 [1–10]. This was the only clinical guidelines focused on these complicated diseases.
and contributed to provide general and specialized clinicians with knowledge on standard treatments. Other groups have also published clinical guidelines regarding the diagnosis and treatment of cholangiocarcinoma [11], gallbladder cancer and extrahepatic cholangiocarcinoma [12]. JSHBPS’s guidelines are the only guidelines systematically showing the management of all malignant diseases in the biliary tract. After 7 years of publication, several pieces of evidence of novel treatment modalities and handling of clinical issues have been published. JSHBPS started the revision process from 2010. In the revised version, we introduced the concepts of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for better understanding [13]. Also we included more specialists of endoscopic treatments, oncology, radiation therapy, pathology, and preparation of guidelines to avoid biases in the recommendations. These points are explained in the other article in this issue [14].

These guidelines represent the most standard clinical and practical management at this time. However, they should not be inflexible for the practical management of individual patients. Final decisions for management of individual patients should be made on the basis of conditions at individual institutions and the individual characteristics of patients. We believe that this revised version of the clinical practice guidelines for the management of biliary tract cancers will help general as well as specialized physicians involving biliary tract cancers for their managements of biliary tract cancer patients. This is the English version of “The evidence-based clinical guideline for management of biliary tract cancers” in Japanese, aiming to disseminate the Japanese guidelines worldwide for the introduction of Japanese clinical management of these diseases.

Materials and methods

Objectives

These guidelines describe the management of adults, but not pediatric, biliary tract cancer patients. Because of this, the dosage of medicine or other contents in the text are for adult patients.

The target users of these guidelines are general as well as specialized clinicians involved in the care of patients with biliary tract cancers.

General outline of the revision process

The outline process for revising the guidelines followed the methods of the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) evidence-based guidelines for the management of acute pancreatitis and Tokyo guidelines for the management of acute cholangitis and cholecystitis [15, 16]. JSHBPS invited 28 specialists for management of biliary tract cancers as committee members for the revision of the guidelines. The revision process with these committee members was started in October 2011. The committee members proposed that the guidelines consist of algorithms that outline diagnosis and treatment, followed by clinical questions (CQs) regarding seven topics (prophylactic treatment, diagnosis, biliary drainage, surgical treatment, chemotherapy, radiation therapy, and pathology). A total of 44 CQs were proposed. Fifteen CQs that could not make the final recommendation with the consensus of the committee members were excluded in the English version of the guidelines. Finally, the guidelines include 29 CQs. The comprehensive literature search of the latest references published after 2005 (when the literature search was performed for the first version of the guideline) was performed for each CQ. Each committee member who specialized in the field of each CQ prepared a draft of the recommendation for a clinical action, the grade of the recommendations, and the statement on how to make recommendations. Committee members added some references from their own searches if necessary. The CQs of the pathology section do not include the recommendation grade because these only include the statement but not a recommendation explaining the diseases regarding the CQs. These were reviewed, modified, and finalized by all committee members. The grade of recommendations was decided according to the concept of GRADE approach, which is described in the other article of this issue [14]. With the public opinions and the assessments of the three external appraisal committees independent from the revision committee members, the guidelines were modified and finalized.

Notes on the use of the guidelines

These guidelines represent the most standard clinical and practical care for biliary tract cancers at this time. However, they should not be inflexible for the practical management of individual patients. The JSHBPS is responsible for the statements in these guidelines. The JSHBPS and the committee members are not liable for any consequences arising from any treatment, for which individual physicians involved in the treatment should be responsible.

Decision of evidence level and grading of the recommendation

As described in Yoshitomi et al. [14], we used the GRADE system approach [13]. The overall quality of the body of
evidence across gross studies for each important outcome was assessed. Finally, the evidence level was decided from A (highest) to D (lowest). The strength of recommendation is decided considering four factors: evidence level, balance of benefits and harms/burdens, patients’ preferences, and cost benefits. Finally the strength of recommendation is divided into two categories with agreement of 70% or more committee members; Grade 1: Strong recommendation (we recommend to do or not to do). Grade 2: Weak recommendation (we suggest to do or not to do).

Results and discussion

The algorithm of diagnosis and treatment and the seven main topics are presented consecutively, incorporating 29 CQs (CQ1-29). See Table 1 for a summary of the CQs and recommendation.

Algorithm (Figs 1,2)

Algorithm presents the flow of diagnosis and treatment. For detailed explanation of each CQ refer to the indicated box.

Diagnosis (Fig. 1)

Risk factors for bile duct carcinoma are pancreaticobiliary maljunction (PBM), primary sclerosing cholangitis, and hepatolithiasis. Risk factors for gallbladder cancer are PBM and dysplasia of gallbladder mucosa. Symptoms indicating biliary tract carcinoma are jaundice, pain in the upper right area of the abdomen, and weight loss. However, patients often do not have any symptoms in early stage cancer. These patients without symptoms are occasionally found by blood examination, abdominal ultrasonography (US), and gastroscopy.

First step of diagnosis is to carry out hematological examination (biochemistry tests) and US. Although the elevation of the liver and bile duct enzymes are often realized, these findings are not specific for biliary tract cancers. There are no useful tumor markers specific for biliary tract cancers for their early diagnosis. US should be performed as a first step for patients with suspicion of biliary tract cancers. Tumor can be detected in more than 50% of patients with gallbladder carcinoma by US. The dilatation of proximal bile duct is often seen in patients with distal bile duct carcinoma and ampullary carcinoma, although this is not specific for these diseases.

Second step for the diagnosis of bile duct carcinoma and gallbladder carcinoma is the dynamic contrast-enhanced computed tomography (CT) using the multiple detector CT (MDCT). CT examination should be performed before biliary drainage, especially in the case of bile duct carcinoma. MDCT enables observation with multiplanar reformation images. This helps precise assessment of the degree of tumor extension and anatomical relationship with major vasculature. Second step for ampullary carcinoma is endoscopic observation and tissue biopsy of suspicious tumor region.

The third step for the diagnosis of biliary tract cancers includes several examinations. For bile duct carcinoma, magnetic resonance imaging (MRI), including magnetic resonance cholangiopancreatography (MRCP), is useful for the diagnosis of precise location and local extension of the tumor. Direct cholangiography by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) is useful for examining the longitudinal invasion of the tumor with its high resolution images. Intraductal US (IDUS) is useful for examining the extents of vertical and longitudinal invasion degree and vascular invasion. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful for finding distant metastasis and recurrence. Endoscopic ultrasound (EUS) is also useful for examining the arterial invasion of hilar cholangiocarcinoma and the extent of vertical invasion of the tumor.

For the diagnosis of gallbladder carcinoma, EUS is more useful for detecting the elevated region of the gallbladder than abdominal US. EUS is more accurate for assessing the degree of vertical extension than MDCT. MRCP is also useful for assessment of longitudinal invasion to cystic duct and/or common bile duct. Dynamic contrast-enhanced MRI is useful for assessment of hepatic and vascular invasion. MRI using gadolinium ethoxybenzyl-diethylene-triamine-pentaacetic acid (Gd-EOB-DTPA) (EOB-MRI) is useful especially for detecting hepatic metastasis. ERCP and biliary endoscopy is useful for examining the extent of tumor invasion to cystic duct and common bile duct.

If imaging examination revealed the bile duct cancers, the histological confirmation using brushing cytology, biopsy using EUS, and/or US or CT-guided cytology/biopsy is important for deciding the treatment.

For ampullary carcinoma, CT and MRI are used for assessing operative indications. EUS and IDUS is useful for detecting the tumor and for examining the degree of tumor extension to adjacent organs such as pancreas and duodenum.

Treatment (Fig. 2)

The prophylactic surgical treatment is highly recommended for PBM. The prophylactic excision of the
Table 1 Summary of clinical questions (CQs) and recommendations.

A. Prophylactic treatment

CQ1: Is prophylactic surgical treatment necessary for the pancreaticobiliary maljunction?

The prophylactic excision of the gallbladder and common bile duct is the appropriate surgical procedure for the pancreaticobiliary maljunction (PBM) with bile duct dilatation. (Grade 1)

The prophylactic cholecystectomy is the appropriate surgical procedure for PBM without bile duct dilatation. (Grade 1)

CQ2: Is a cholecystectomy necessary for polypoid lesions of the gallbladder?

When polypoid lesion of the gallbladder is sessile, has a diameter equal to or greater than 10 mm and/or grows rapidly, it is highly likely to be cancerous and should be resected. (Grade 2)

B. Diagnosis

CQ3: What is the first step in the diagnosis of the biliary tract cancers?

Noninvasive abdominal ultrasonography and hematological examination can be the first step in diagnosis. (Grade 1)

CQ4: What is the second step in the diagnosis of the bile duct carcinoma?

CT is useful for the assessment of localization of the lesion and the degree of its extension. The dynamic contrast-enhanced CT using MDCT is especially recommended. CT examination should be performed before biliary drainage and using MDCT. (Grade 1)

CQ5: What is the second step in the diagnosis of the gallbladder carcinoma?

CT is useful for the assessment of localization of the lesion and the degree of its extension. The dynamic contrast-enhanced CT using MDCT is highly recommended. (Grade 1)

CQ6: What is the second step in the diagnosis of the ampullary carcinoma?

The upper gastrointestinal endoscopy is recommended for the diagnosis of ampullary carcinoma. If neoplastic lesion is suspected, tissue biopsies should be performed. (Grade 1)

CQ7: Is histological or cytological diagnosis useful for the bile duct or gallbladder carcinomas?

Histological or cytological diagnosis should be performed for unresectable tumors treated with chemotherapy or chemoradiation therapy. (Grade 1)

Histological or cytological diagnosis should be performed for suspected resectable bile duct carcinoma. (Grade 1)

C. Biliary drainage

CQ8: Is preoperative biliary drainage necessary for patients with jaundice?

Preoperative biliary drainage is necessary for patients scheduled to undergo extended hepatectomy. (Grade 1)

CQ9: What is the appropriate procedure for preoperative biliary drainage and when should it be performed?

Endoscopic drainage is the most appropriate procedure with a low risk of complications. The drainage should be performed after CT scan. (Grade 2)

CQ10: Which is better, unilateral or bilateral biliary drainage in malignant hilar biliary obstruction?

Unilateral drainage in the future remnant lobe is recommended for the first step. (Grade 2)

CQ11: What is the best treatment for fever in patients who have already undergone biliary drainage?

Cholangitis is the most common reason for the post-drainage fever. Cholecystitis or pancreatitis are also potential causes of fever. In case of cholangitis, treat with antibiotics and confirm whether there are any drainage catheter troubles, such as disposition or obstruction. Exchange catheters in case of catheter trouble. (Grade 1)

If the drainage is effective or fever lasts 2–3 days after exchange of catheters, the segmental cholangitis in the undrained segment is suspected and the drainage of the undrained segment should be considered. (Grade 2)

CQ12: Is bile culture necessary in patients with biliary drainage who are scheduled to undergo surgery?

Monitoring of bile culture is necessary to select appropriate antibiotics in the perioperative period. (Grade 1)

CQ13: Is bile replacement useful for patients with external biliary drainage?

Bile replacement may be useful. (Grade 2)

CQ14: Is biliary drainage recommended for patients with unresectable disease?

Biliary drainage should be performed if possible. (Grade 2)

CQ15: Which type of biliary stent is appropriate for unresectable cases?

A self-expandable metallic stent (SEMS) is preferable for obstruction at distal bile duct. An uncovered SEMS is preferable for hilar biliary obstruction, although it is controversial how to set a stent. A plastic stent may also be used according to the preference of each facility with available equipment and techniques. (Grade 2)

D. Surgical treatment

CQ16: What are considered as unresectable factors in biliary tract cancers?

Biliary tract cancers with metastases to the liver, lung, bone, peritoneum and distant lymph nodes (para-aorta or extra abdominal lymph nodes) are considered as contraindication of surgical resection. There is no obvious consensus of unresectable factors regarding local extension. (Grade 1)
gallbladder and common bile duct is the appropriate procedure for the PBM with bile duct dilatation. The prophylactic cholecystectomy is the appropriate surgical procedure for PBM without bile duct dilatation. For polypoid lesion of the gallbladder, which is sessile, has diameter equal to or greater than 10 mm and/or grows rapidly, a cholecystectomy is necessary as prophylactic treatment.

The surgical resection is the only hope for cure. The first step for treatment is to assess operative indication. Distant metastasis including liver, lung, bone, peritoneal, and distant lymph node (para-aorta, extra-abdominal) metastasis are generally considered as contraindication for surgical resection, although there are only a few strong pieces of evidence. There are no obvious consensuses for surgical indication of locally advanced cancer.
Resectable cases

Preoperative treatment

The preoperative biliary drainage is strongly recommended after direct cholangiography such as ERCP to avoid the cholangitis. Preoperative endoscopic nasobiliary drainage is also strongly recommended for patients scheduled to undergo extended hepatectomy.

The preoperative portal vein embolization (PVE) is considered to reduce the incidence of postoperative complications, such as hepatic failure, after right lobectomy or more extended hepatectomy. PVE may enable surgical resection in some of the cases, which is primarily considered as contraindication due to the small remnant liver volume.

Surgical treatment

Bile duct carcinoma. In most cases of hilar and upper bile duct carcinoma, combined caudate lobe resection should be performed for increasing curability and better prognosis. In some cases with portal vein invasion, combined portal vein resection is useful because the prognosis of patients with portal vein resection is similar to that of patients without portal vein resection.
Gallbladder carcinoma. In cases of cancer with invasion to subserosal layer or deeper, an additional hepatectomy and lymphadenectomy should be considered. For patients with suspected gallbladder carcinoma in preoperative diagnosis, open cholecystectomy, rather than laparoscopic cholecystectomy is recommended as a rule at the moment.

Ampullary carcinoma. The pancreaticoduodenectomy is the appropriate procedure for ampullary carcinoma. Local resection or papillectomy may be considered only in the case of carcinoma in adenoma without invasion beyond the mucosa.

Adjuvant therapy

There is no obvious evidence for the benefit of adjuvant therapy for resected bile duct cancers. However, it is expected to have benefit from the results of small trials and retrospective studies. The adjuvant therapy should be carried out as a clinical trial.

Unresectable cases

Biliary drainage, stent

Biliary drainage should be performed for patients with unresectable disease combined with obstructive jaundice. It improves patients’ QOL. A self-expandable metallic stent (SEMS) is preferable for the obstruction at distal bile duct.

Chemotherapy, radiation therapy

The combination chemotherapy with gemcitabine and cisplatin is recommended as the first-line chemotherapy for patients with unresectable bile duct cancer. Radiation therapy may be considered for patients with unresectable biliary cancer. It may be useful for improvement of prognosis, improvement of stent patency, reducing jaundice, and pain control.

Palliative care

Palliative treatment for improvement of patients’ QOL, such as pain control, should be considered for patients who cannot receive any treatment due to their poor performance status or severe jaundice.

Clinical questions

Prophylactic treatment

CQ1: Is prophylactic surgical treatment necessary for the pancreaticobiliary maljunction?

Recommendation: The prophylactic excision of the gallbladder and common bile duct is the appropriate surgical procedure for PBM with bile duct dilatation. (Grade 1, evidence level C)

The prophylactic cholecystectomy is the appropriate surgical procedure for PBM without bile duct dilatation. (Grade 1, evidence level C)

Statement: PBM is a congenital anomaly consisting of a union of the pancreatic and bile ducts located outside the duodenal wall [17]. Due to the lack of sphincter action at the union of the pancreatic and bile ducts, bile and pancreatic juice are mixed, resulting in the activation of cell toxic factors. These factors are considered to induce chronic cholangitis, which may result in carcinogenesis [18, 19]. PBM is divided into two groups by the existence of bile duct dilatation (PBM with or without bile duct dilatation) [17].

A Japanese retrospective nationwide survey of PBM revealed that the incidence of biliary tract cancers was 21.6% in the group with bile duct dilatation; 13.4% were gallbladder carcinoma, 7.0% were bile duct carcinoma, and 1.0% were both gallbladder and bile duct carcinomas [20]. According to the result and other reports, the prophylactic excision of the gallbladder and common bile duct is the appropriate surgical procedure for PBM with bile duct dilatation [21]. This survey also revealed that the incidence of biliary tract cancers was 42.2% in the group without bile duct dilatation; 37.4% were gallbladder carcinoma, 3.1% were bile duct carcinoma, and 1.8% were both gallbladder and bile duct carcinomas [20]. According to the result and other reports, the prophylactic cholecystectomy is the appropriate surgical procedure for PBM without bile duct dilatation [22, 23]. Controversy remains as to whether prophylactic bile duct excision is necessary for PBM without bile duct dilatation [19, 24, 25]. Patients with PBM are recommended to undergo prophylactic surgical treatment at the earliest timing after diagnosis.

CQ2: Is a cholecystectomy necessary for polypoid lesions of the gallbladder?

Recommendation: When polypoid lesion of the gallbladder is sessile, has a diameter equal to or greater than 10 mm and/or grows rapidly, it is highly likely to be cancerous and should be resected. (Grade 2, evidence level C)
Statement: Adenoma and dysplasia have been regarded as a precancerous lesion of the gallbladder and intestinal metaplasia seems to be the pathway through which the epithelial dysplasia is produced [26, 27]. Several reports showed that polypoid lesion is highly likely to be cancerous if it is sessile and/or solitary, its diameter is equal to or greater than 10 mm, patient’s age is equal to or greater than 60 years old, and/or it grows rapidly [28–32]. According to these results, when polypoid lesion of the gallbladder is sessile, has a diameter equal to or greater than 10 mm and/or grows rapidly, it is highly likely to be cancerous and should be resected by cholecystectomy [28–36].

**Diagnosis**

CQ3: What is the first step in the diagnosis of the biliary tract cancers?

Recommendation: Noninvasive abdominal US and hemato logical examination can be the first step in diagnosis. (Grade 1, evidence level C)

Statement: Although the elevation of liver and bile duct enzymes are often realized, these findings are not specific for biliary tract cancers. The diagnostic imaging to be performed in the first step is abdominal US when biliary tract cancer is suspected. The sensitivity and specificity of extrahepatic bile duct carcinoma by abdominal US are reported 89% and 80–90%, respectively [37, 38]. The distal bile duct carcinoma is suspected when both intrahepatic and extrahepatic bile ducts are dilated, though the detectability of distal bile duct carcinoma itself is low [39]. Fifty percent or more of gallbladder cancer cases are depicted as tumors on abdominal US [40]. The incidental carcinoma is realized in 0.2–5.0% of patients who undergo cholecystectomy for non-malignant lesion [41, 42]. Bile duct dilatation with pancreatic duct dilatation (double-duct sign) indicates the existence of the ampullary carcinoma. However this sign is not specific for the ampullary carcinoma as the pancreatic head carcinoma also often shows the same sign [43].

No tumor markers specific to biliary tract cancer are available [44]. Improved diagnostic ability can be achieved with a combination of tumor markers (CA 19-9, CEA) and other procedures. The early diagnosis using tumor markers alone is difficult.

CQ4: What is the second step in the diagnosis of the bile duct carcinoma?

Recommendation: CT is useful for the assessment of localization of the lesion and the degree of its extension. The dynamic contrast-enhanced CT using MDCT is especially recommended. CT examination should be performed before biliary drainage and using MDCT. (Grade 1, evidence level B)

Statement: The contrast-enhanced CT, especially dynamic study, enable the assessment of blood-flow dynamics and, in the case of fibrotic tumors, makes contrasted tumor images in late phase, which is helpful for diagnosis of bile duct carcinoma. The dynamic contrast-enhanced MDCT with adequate pitch of detector rotation and table speed makes multiplanar reformation images for the assessment of the degree of tumor extension and also enables the assessment of vascular invasion by CT angiography with three-dimensional imaging [45–47].

Computed tomography examination should be performed before biliary drainage to perform detailed assessment of bile duct stricture and thickening [45].

CQ5: What is the second step in the diagnosis of the gallbladder carcinoma?

Recommendation: CT is useful for the assessment of localization of the lesion and the degree of its extension. The dynamic contrast-enhanced CT using MDCT is highly recommended. (Grade 1, evidence level B)

Statement: The contrast-enhanced CT, especially dynamic study, enable the assessment of blood-flow dynamics and, in the case of fibrotic tumors, makes contrasted tumor images in late phase, which is helpful for diagnosis of bile duct carcinoma. The dynamic contrast-enhanced MDCT with adequate pitch of detector rotation and table speed makes multiplanar reformation images for the assessment of the degree of tumor extension and also enables the assessment of vascular invasion by CT angiography with three-dimensional imaging [45–47].

Computed tomography examination should be performed before biliary drainage to perform detailed assessment of bile duct stricture and thickening [45].

CQ6: What is the second step in the diagnosis of the ampullary carcinoma?

Recommendation: The upper gastrointestinal endoscopy is recommended for the diagnosis of ampullary carcinoma. If neoplastic lesion is suspected, tissue biopsies should be performed. (Grade 1, evidence level C)

Statement: The ampullary carcinoma of papilla Vater is divided into protruded type, mixed type, ulcerative type, and others by its macroscopic finding [53]. Endoscopic examination enables the diagnosis of these types and following biopsy for histological analysis. If histological analysis of the biopsy samples shows adenoma, these neoplastic lesion should be treated because adenoma sometimes includes carcinoma in its body [54].
CQ7: Is histological or cytological diagnosis useful for the bile duct or gallbladder carcinomas?

Recommendation: Histological or cytological diagnosis should be performed for unresectable tumors treated with chemotherapy or chemoradiation therapy. (Grade 1, evidence level C)

Histological or cytological diagnosis should be performed for suspected resectable bile duct carcinoma. (Grade 1, evidence level C)

Statement: The histological and cytological diagnoses are usually done by the following methods: ERCP guided, EUS guided fine needle aspiration (EUS-FNA), percutaneous transhepatic biliary drainage (PTBD) or percutaneous transhepatic cholangioscopy (PTCS) guided, and abdominal US or CT guided.

ERCP guided brushing cytology for biliary stricture shows a wide range of accuracy in each institution with 30–88% of sensitivity and 100% specificity [55].

EUS-FNA is reported to have high accuracy in cytological and histological diagnosis with 84% sensitivity and 100% specificity and a low complication rate in meta-analysis [56]. It is also useful for diagnosis of regional lymph node involvement, for estimation of stage and resectability [57–59]. EUS-FNA is also useful for cases of negative ERCP-guided examination [60–63]. However, EUS guided bile cytology through puncture of gallbladder or extra-hepatic and - pancreatic bile duct should not be performed due to significant risk of bile peritonitis [64].

PTBD guided examination also shows high sensitivity and specificity for the diagnosis [65]. However, it should be noted that catheter tract recurrence occurred in 5–6% of cases within patients who received PTBD [66, 67]. PTBD only for cytological or histological analysis is not recommended.

As shown, cytological or histological diagnosis can be performed safely and accurately. It should be performed for unresectable tumors before starting chemotherapy or chemoradiation therapy by EUS-guided or endoscopic approach to treat with the appropriate regimen.

It is also reported that there are considerable amounts of benign bile duct stricture cases that are diagnosed as bile duct carcinoma by preoperative images and that undergo surgical resection [68]. Therefore, histological or cytological diagnosis should be performed for patients who are suspected to have resectable bile duct carcinoma.

However, the accuracy of cytological and histological analysis is not perfect at this time. In the cases in which clinical findings cannot completely rule out the possibility of malignancy, surgical resection or strict observation should be applied under sufficient informed consent to patients and their families.

CQ8: Is preoperative biliary drainage necessary for patients with jaundice?

Recommendation: Preoperative biliary drainage is necessary for patients scheduled to undergo extended hepatectomy. (Grade 1, evidence level C)

Statement: The standard surgical treatment for hilar or proximal bile duct is the bile duct resection combined with extended hepatectomy. However, mortality after extended hepatectomy still remains high and the main reason for the mortality is hepatic failure. Therefore, preoperative biliary drainage and/or portal vein embolization aimed for improvement of remnant liver function have been routinely performed as preoperative managements for bile duct carcinoma associated with obstructive jaundice, especially in Japan.

On the other hand, several retrospective studies in Western countries showed that preoperative drainage did not improve the morbidity and mortality of patients with resected hilar cholangiocarcinoma [69, 70]. However, these analyses include considerable numbers of patients who do not receive hepatectomy. In addition, the procedure for biliary drainage is not standardized in these studies.

Therefore, biliary drainage is now routinely performed for patients with bile duct carcinoma who are scheduled extended hepatectomy in many high volume institutions, even in Western countries [71–75]. Considering these facts, all committee members agreed to upgrade the recommendation grade to 1 even with the lack of high level evidence.

CQ9: What is the appropriate procedure for preoperative biliary drainage and when should it be performed?

Recommendation: Endoscopic drainage is the most appropriate procedure with a low risk of complications. The drainage should be performed after CT scan. (Grade 2, evidence level C)

Statement: There are three different kinds of biliary drainage procedures; PTBD, endoscopic nasobiliary drainage (ENBD), and endoscopic biliary stenting (EBS). No clinical trials have been performed comparing these three methods. The majority of retrospective studies shows no significant differences in effects of decreasing jaundice and complication rate between these three procedures [76].

On the other hand, several reports indicate the risk of portal vein injury, catheter tract recurrence and peritoneal dissemination in PTBD procedures [66, 77], indicating that PTBD is not an appropriate procedure as the first line approach for biliary drainage. EBS also has a risk for stent obstruction resulting in cholangitis [76]. Therefore, ENBD is recommended for
biliary drainage of patients with hilar/proximal bile duct carcinoma who are scheduled to undergo extended hepatectomy [76, 78, 79].

Unilateral biliary drainage is usually sufficient for patients who undergo extended hepatectomy (see CQ10). However, additional ENBD or combination with PTBD should be considered in patients with cholangitis of undrained segment [76, 78, 79].

Recently, MDCT has been widely introduced in many institutes and is used for the diagnosis of biliary tract cancers (see CQ4 and 5). After biliary drainage, assessment of bile duct thickening or degree of extension becomes difficult due to the inflammatory changes of bile duct [45]. Therefore, biliary drainage should be performed after CT examination.

**CQ10: Which is better, unilateral or bilateral biliary drainage in malignant hilar biliary obstruction?**

Recommendation: Unilateral drainage in the future remnant lobe is recommended for the first step. (Grade 2, evidence level C)

Statement: There are several clinical and experimental reports that indicate unilateral biliary drainage has more benefits in increasing future remnant liver volume after portal vein embolization (PVE) and improving remnant liver function [80, 81]. For safe surgical resection with extended hepatectomy for hilar/proximal bile duct carcinoma, unilateral drainage, instead of bilateral drainage, in the future remnant lobe is recommended for the first step. Bilateral biliary drainage is considered in the following cases: those with uncontrollable segmental cholangitis and those with delayed jaundice after unilateral biliary drainage [76, 78].

**CQ11: What is the best treatment for fever in patients who have already undergone biliary drainage?**

Recommendation: Cholangitis is the most common reason for the post-drainage fever. Cholecystitis or pancreatitis are also potential causes of fever. In case of cholangitis, treat with antibiotics and confirm whether there are any drainage catheter troubles, such as disposition or obstruction. Exchange catheters in case of catheter trouble. (Grade 1, evidence level B)

If the drainage is effective or fever lasts 2–3 days after exchange of catheters, segmental cholangitis in the undrained segment is suspected and the drainage of the undrained segment should be considered. (Grade 2, evidence level C)

Statement: When a patient with biliary obstruction who has already undergone biliary drainage suddenly presents with high fever, the most common cause of the fever is cholangitis due to drainage catheter troubles, including obstruction, bending, and dislocation. Amount and color of drainage bile juice should be checked immediately in case of PTBD or ENBD. Abdominal X-ray examination or cholangiography is also considered if necessary. In cases of EBS, confirm tube location and status by X-ray examination. Cholecystitis due to the obstruction of cystic duct or pancreatitis due to the obstruction of main pancreatic duct are also potential causes of fever. In such cases, CT examination is useful for the diagnosis [76, 78, 82, 83].

In case of catheter trouble, the catheter should be exchanged urgently along with antibiotics treatment. If the drainage is effective or fever lasts 2–3 days after exchange of catheter, segmental cholangitis in undrained segment is suspected. After identifying the undrained bile duct by the contrast-enhanced CT, drainage should be urgently considered for the undrained segment by additional insertion of a new catheter or, if possible, through inserting the existing catheter into the undrained bile duct [76, 78, 83, 84].

Experimental rat model shows that cholangitis inhibits hepatic regeneration [85]. Cholangitis is a potential cause of postoperative infectious complication, leading to postoperative death in some cases. Immediate and appropriate actions are required for fever in patients with biliary drainage [84, 86–88].

**CQ12: Is bile culture necessary in patients with biliary drainage who are scheduled to undergo surgery?**

Recommendation: Monitoring of bile culture is necessary to select appropriate antibiotics in the perioperative period. (Grade 1, evidence level C)

Statement: Monitoring of bile culture on a regular basis is useful for patients who received ENBD or PTBD to be treated with appropriate antibiotics immediately when they have cholangitis.

Postoperative cholangitis is a major complication after extended hepatectomy with bile duct resection and reconstruction for biliary tract cancers. In cases of extended hepatectomy for hilar bile duct carcinoma, patients with bile infection experience postoperative infectious complications more often than those without bile infection [67] and the microorganisms isolated from postoperative infections are identical to those found in the preoperative cultures in 30–88% of cases [89–91]. Therefore, identification of microorganisms in bile before surgery is necessary to enable selection of appropriate prophylactic and/or therapeutic antibiotics [91–93].

**CQ13: Is bile replacement useful for patients with external biliary drainage?**

Recommendation: Bile replacement may be useful. (Grade 2, evidence level C)
Statement: In humans, it is well known that the increased intestinal permeability caused by obstructive jaundice is recovered by bile replacement. A recent study also showed that bile replacement by oral intake during external drainage helps restore intestinal barrier function in patients with biliary obstruction [96].

Maintenance of the enterohepatic circulation of bile is important for host defense function. Therefore, bile replacement during external drainage may be useful for the patients who are scheduled a highly invasive surgical procedure, such as extended hepatectomy with bile duct resection for bile duct carcinoma. However, further clinical trials are required to assess whether bile replacement can reduce the incidence of complications, especially infectious complications, after these kinds of operations.

CQ14: Is biliary drainage recommended for patients with unresectable disease?

Recommendation: Biliary drainage should be performed if possible. (Grade 2, evidence level B)

Statement: Obstructive jaundice reduces patient’s QOL by inducing itching, anorexia, and general fatigue. There are several reports that have showed biliary drainage for these patients not only eliminates their physical symptoms but also improves their mental health and social function, resulting in better QOL. According to these results, it is thought that the relief of jaundice should be conducted for patients with obstructive jaundice due to unresectable cancers as a matter of course [97–99]. Recently, patients with unresectable or recurrent bile tract cancers often receive chemotherapy. For these patients, it is necessary that obstructive jaundice is released before starting chemotherapy.

However, in some cases, the relief of jaundice and improvement of QOL have failed even with biliary drainage. In some other cases, QOL becomes worse due to inappropriate drainage procedure or catheter selection. Therefore, indication of biliary drainage should be decided thoroughly considering primary disease, stage, performance status or other patients’ status.

CQ15: Which type of biliary stent is appropriate for unresectable cases?

Recommendation: A SEMS is preferable for obstruction at the distal bile duct. An uncovered SEMS is preferable for hilar biliary obstruction, although it is controversial how to set a stent. A plastic stent may also be used according to the preference of each facility with available equipment and techniques. (Grade 2, evidence level C)

Statement: For the palliative treatment of distal bile duct obstruction, several randomized trials comparing plastic stent (PS) and uncovered SEMS showed that uncovered SEMS has significantly longer term patency than PS [100–102]. These trials also showed the lower complication rate of SEMS than PS. According to these results, SEMS is recommended as palliative treatment for distal bile duct obstruction due to the malignant tumor. The benefits of covered SEMS compared with uncovered SEMS still remain controversial for distal bile duct obstruction by bile duct carcinoma [103, 104].

For hilar bile duct carcinoma, covered SEMS is not an appropriate procedure because it obstructs bile duct branches. Two randomized trials revealed the superiority of uncovered SEMS in regard to patency, compared with PS [105, 106]. However, in many institutes, especially in which there is no endoscopic specialist for interventional therapy of bile ducts, PS is still mainly used for hilar obstruction due to technical difficulties for the insertion of SEMS. There is much controversy regarding which lobe should be drained or whether multiple stents are necessary. Accumulation of evidence is awaited.

As discussed, SEMS shows superiority against PS in many trials for obstruction of bile duct. However, due to the technical difficulties of SEMS insertion, PS is also an appropriate procedure depending on the experience of each institution. In addition, it should be noted that removal and replacement of SEMS is very difficult and, consequently, SEMS affects the difficulty of surgical resection. Before the insertion of SEMS, the resectability of cancer should be carefully discussed.

Surgical treatment

CQ16: What are considered as unresectable factors in bile tract cancers?

Recommendation: Biliary tract cancers with metastases to the liver, lung, bone, peritoneum and distant lymph nodes (para-aorta or extra abdominal lymph nodes) are considered as contraindication of surgical resection. There is no obvious consensus of unresectable factors regarding local extension. (Grade 1, evidence level C)

Statement: The decision of resectability of bile tract cancers should be made based on precise assessment of patient’s physical condition, degree of local extension of tumor, and existence of distant metastasis [107]. Especially for biliary tract cancers, highly invasive operation, such as pancreatoduodenectomy or extended hepatectomy, is often required for curative resection. Therefore, the assessment of performance status and organ functions including hepatic, cardiac, respiratory and renal functions are extremely important for the decision of surgical indication [108].
Biliary tract cancers with metastases to the liver, lung, bone, peritoneum and distant lymph nodes (para-aorta or extra abdominal lymph nodes) are generally considered as contraindication of surgical resection, although there is only limited strong evidence [108–110].

On the other hand, there is no consensus regarding unresectable factors of local extension of biliary tract cancers [111]. The 7th edition of TNM classification of malignant tumors defines T4, which is generally considered as unresectable, of perihilar cholangiocarcinoma as tumor invades the main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally, or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement [112]. However, recently several reports showed the improvement of prognosis in these locally advanced cancers by introducing surgical resection combined with arterial resection and reconstruction or extended trisectionectomy of liver [113–116]. The establishment of more adequate staging system including these recent findings is awaited that correlates well with prognosis or resection rate [111].

There is no obvious consensus regarding the indication of surgical resection in locally advanced gallbladder carcinoma. Although obstructive jaundice and lymph node involvement are reported as predictors of poor prognosis, surgical resection may improve the prognosis of patients with these factors [117, 118].

CQ17: Which patients with biliary tract cancer should be considered to undergo preoperative portal vein embolization?

Recommendation: Preoperative PVE is considered in patients who are scheduled to undergo surgical resection combined with right hepatectomy or more, or hepatectomy of 50–60% or more liver volume. (Grade 2, evidence level C)

Statement: Preoperative PVE is performed in patients with extended hepatectomy for preventing postoperative hepatic failure. PVE is reported to increase 8.6–10.8% of volume of unembolized segment [119–121].

There are many retrospective cohort studies describing that PVE reduces complication rate in cases of extended hepatectomy equal to or greater than right hepatectomy [122]. Several reports also showed that PVE enables surgical resection in cases that are initially considered as unresectable due to the shortage of future remnant liver volume [123]. However, the indication of PVE differs by institutions and no consensus exists [72, 123–133].

There is no randomized study comparing the safety of surgical resection of biliary tract cancers with or without PVE. Therefore, the evidence level of PVE for reducing the liver failure remains low. However, many reports show low mortality (0–2%) even after invasive surgery, such as right hepatectomy and trisectionectomy. On the other hand, the high mortalities (10–21%) after radical resection of bile tract cancers with extended hepatectomy are often reported from the institutes that limit the indication of PVE only in cases with comparably small future remnant liver volume (25–30%) [132, 134]. Taking these facts into account, PVE is supposed to have benefits on such radical surgery for bile duct cancers. Many institutes indicate PVE for patients who are scheduled to undergo surgical resection combined with right hepatectomy or more, or hepatectomy of 50–60% or more liver volume.

CQ18: Are there effective examinations to predict the hepatic function of the future remnant liver in the cases with jaundice?

Recommendation: Measurement of the future remnant liver volume by CT and the indocyanine green (ICG) clearance test are useful in predicting the postoperative hepatic function. ICG clearance test should be performed after relief of jaundice and cholangitis. (Grade 1, evidence level C)

Statement: For treatment of bile duct cancers, the surgical resection combined with extended hepatectomy is often required for curative resection. As the resection volume of liver is different in each case, the future remnant liver volume should be considered case by case for prediction of postoperative liver function [135]. The ICG retention rate at 15min (ICGR15) or other ICG clearance tests are usually used as indicators for liver function [87, 124, 127, 136, 137]. ICG clearance test should be performed after relief of jaundice and cholangitis.

There are many factors, other than future remnant volume and ICG clearance test, which affect mortality and morbidity after extended hepatectomy for icteric liver; existence of cholangitis, diabetes, massive intraoperative bleeding, and combined vascular resection or pancreaticoduodenectomy [87, 126, 136]. Total assessment of these factors in individual case is important for safety of surgical treatment.

CQ19: Is combined caudate lobe resection required for hilar/upper bile duct carcinoma?

Recommendation: Combined caudate lobe resection should be performed in most cases of hilar or upper bile duct carcinoma for increasing curative resection rate and better prognosis. (Grade 1, evidence level B)

Statement: Bile ducts of caudate lobe converge into the bifurcation of left and right bile duct. These branches are frequently invaded by hilar/upper bile duct carcinoma [138–141]. According to these facts, some reports describe that the combined caudate lobe resection should be designed so that curative surgery for advanced hilar bile duct carcinoma can be
performed [141]. In fact, combined caudate lobe resection is considered as a standard surgical procedure for these diseases in Japan. Japanese high volume centers in which combined caudate lobe resection is routinely performed report relatively high curative resection rate (59–87%) and 5 year survival rate (33–44%) [74, 87, 124, 127, 142–148]. Several reports from other countries also showed the benefits of this procedure for hilar/upper bile duct carcinoma [149–154]. These results indicate that combined caudate lobe resection should be performed in most cases of hilar or upper bile duct carcinoma for increasing curative resection rate and better prognosis.

CQ20: Should combined vascular resection be performed for biliary tract cancer patients with involvement of portal vein or hepatic artery?

Recommendation: Combined portal resection (PVR) is useful for patients with portal vein invasion because the prognosis of patients treated with PVR is significantly better than that of unresected patients. (Grade 2, evidence level C)

Clinical benefits of combined arterial resection for patients with arterial invasion are still unclear at this moment. (No recommendation)

Statement: Recently several retrospective studies have been published regarding PVR for biliary tract cancers. In many studies, the prognosis of patients who received combined PVR is poorer than that of patients who undergo surgical resection without PVR. However, the majority of these studies also show the prognosis of patients treated with combined PVR is significantly longer than the prognosis of unresected patients, especially in patients with hilar/upper bile duct carcinoma [71, 72, 74, 116, 155, 156]. According to these reports, PVR is a safe procedure and may contribute to longer survival for patients with biliary tract cancers invading portal vein, although there is no prospective study for estimating the benefit of PVR.

Taking together the facts that there are a considerable number of biliary tract cancer patients who can undergo curative resection only by combined PVR, we suggest (Grade 2) combined PVR for patients with biliary tract cancers invading portal vein, despite the shortage of strong evidence.

Regarding the combined arterial resection, benefits are controversial. Some studies show that combined arterial resection can be performed safely and contribute better prognosis [115, 157, 158]. On the other hand, some studies show that combined arterial resection induces high morbidity and mortality rate and no survival benefit [116]. In addition, there is no prospective study. Therefore, clinical benefits of combined arterial resection for patients with arterial invasion are still unclear at this moment.

CQ21: Should open cholecystectomy be performed instead of laparoscopic cholecystectomy for patients with suspected gallbladder cancer?

Recommendation: For patients with suspected gallbladder cancer, open cholecystectomy is recommended as a rule. (Grade 1, evidence level C)

Statement: Laparoscopic cholecystectomy (LC) is widely accepted in many countries and becomes a standard therapy for cholecystolithiasis. Recently, there have been attempts to extend its indication to patients with suspected gallbladder carcinoma. However, LC may increase the risk of port site recurrence and peritoneal dissemination as a result of bile leak associated with gallbladder injury [159–161]. In patients with incidental gallbladder carcinoma, which is found after cholecystectomy, the ratio of port site recurrence or peritoneal dissemination is reported relatively high with 10–18% and the period until recurrence is relatively short with 6–10 months [162–170].

On the other hand, recently some reports show that the prognosis of patients with incidental gallbladder carcinoma is similar between those resected by laparoscopic approach and open approach [171–174]. However, in LC, the dissection plane on the liver side is within the subserosal layer. It indicates that a remnant of cancer tissue may occur if cancer extends beyond the muscular layer or in the Rokitansky-Aschoff sinuses (RAS) extending muscular layer. Although, in theory, gallbladder carcinoma within the muscular layer is curatively resected by LC, the accuracy of preoperative diagnosis regarding the depth of mural invasion is reported to be less than 50% even with MDCT or EUS [175]. According to these facts, LC is not recommended, at least, for patients with highly suspected gallbladder which is located on liver bed side.

Recently, many laparoscopic instruments have been developed and laparoscopic surgery has become a much safer procedure than ever. However, taking into consideration the facts regarding the port site recurrence or peritoneal dissemination, LC is not recommended for patients who are strongly suspected of having gallbladder carcinoma at this moment as a rule. Laparoscopic surgery for those patients should be performed as a clinical study with sufficient informed consent. Accumulation of evidence is awaited.

CQ22: Is an additional resection required when gallbladder cancer invading the subserosal layer or deeper has been recognized after simple cholecystectomy?

Recommendation: A simultaneous or sequential additional resection should be considered. (Grade 1, evidence level C)

Statement: It is reported that the frequency of the incidental gallbladder carcinoma that is found serendipitously by
Although postoperative pathological examination is reported to be 0.3–1.0% in gallbladder resected for cholecystolithiasis [176–179]. In patients in whom the histological analysis using whole gallbladder serial sections reveals the depth of cancer invasion limited to the mucosa or muscularis propria, an additional resection is not necessary if the cystic duct stump is negative. On the other hand, in gallbladder carcinoma invading the subserosal layer, high rates of vascular and perineural invasion and lymph node involvement are observed [180–185]. In fact, there are many reports that have showed an additional resection improved the prognosis of patients with incidental gallbladder carcinoma [167, 168, 186–189]. Therefore, an additional resection including hepatectomy and lymph node dissection should be considered for patients with incidental gallbladder carcinoma invading subserosal layer or more.

In the Japanese national survey, there is no prognostic difference between patients with incidental gallbladder carcinoma who underwent an additional resection simultaneously in accordance with the intraoperative pathological finding and who underwent an additional resection in a two-stage manner within 30 days after cholecystectomy [168]. This result indicates that a two-stage resection for incidental gallbladder carcinoma is also acceptable.

CQ23: Is the local resection or papillectomy (surgical or endoscopic) recommended for an ampullary cancer?

Recommendation: Pancreaticoduodenectomy is the appropriate procedure for ampullary carcinoma. Local resection or papillectomy is not recommended for those patients. (Grade 1, evidence level C)

Statement: There have been many reports attempting a local resection of ampullary Vater as a curative surgery for early stage ampullary carcinoma [190–195]. On the other hand, several reports show that the local resection resulted in a high rate of recurrence or non-curative surgery [196]. It is widely accepted the local resection of ampullary Vater as a standard treatment for adenoma [197, 198]. However, for early stage carcinoma, there is only limited evidence of local resection at this time.

Endoscopic papillectomy may also have been applied for treatment of early stage ampullary carcinoma [194, 199]. However, the evidence of this procedure also remains limited at this time. Further accumulation of evidence is awaited.

Many reports show that lymph node involvement is rare in carcinoma limited to the ampulla of Vater [198], suggesting the possibility of limited resection or endoscopic papillectomy as a curative treatment for these early stage diseases. However, once tumors extend to the sphincter of Oddi, the rate of lymph node metastasis apparently increases to 9–42% [198, 200]. On the other hand, the diagnostic accuracy of tumor depth, especially extension of tumor to sphincter of Oddi, is limited even with recent modality such as EUS or IDUS. Taking the low rate of diagnostic accuracy together, local resection or papillectomy is not recommended as a treatment for ampullary carcinoma at this moment.

CQ24: Should the histological assessment of the ductal resection margin in bile duct cancer be performed intraoperatively?

Recommendation: Since the ductal margin status has an impact on patients’ prognosis, the histological assessment of the ductal resection margin should be performed intraoperatively. (Grade 1, evidence level B)

Statement: The bile duct carcinoma extends longitudinally along with bile duct by superficial spread and/or intramural invasion. The superficial spread sometimes can reach 20 mm or more beyond the macroscopic margin of the tumor. This type of spread often associates with tumors macroscopically papillary or expanding type and pathologically papillary adenocarcinoma [201–203].

The ductal and radial margin status is one of the most important prognostic factors for patients with bile duct carcinoma. Many reports show the importance of surgical resection with free ductal margin for better prognosis [203–208]. The ductal margin status is divided into three categories: negative, positive with carcinoma in situ, and positive with invasive carcinoma. The prognosis of patients with ductal margin positive with invasive carcinoma is extremely poor. On the contrary, the patients with ductal margin positive with carcinoma in situ have relatively good prognosis, although they have a risk for local recurrence after a long observation period [203–208]. Therefore, it is important to distinguish the margin positive with carcinoma in situ from the margin positive with invasive carcinoma.

Considering the importance of ductal margin status on patients’ prognosis, intraoperative histological assessment of ductal resection margin should be performed.

However, it still remains controversial whether the additional resection of bile duct margin in the case with positive resection margin can improve the patients’ prognosis [209–211].

CQ25: Is the combined extrahepatic bile duct resection necessary for gallbladder cancer without direct invasion to the hepatoduodenal ligament?

Recommendation: There is no obvious evidence that shows combined extrahepatic bile duct resection improves the prognosis of patients with a gallbladder carcinoma without direct invasion to the hepatoduodenal ligament. However, the combined extrahepatic bile duct resection may increase the curative
resection rate in patients with cancer invading the neck of gallbladder approaching the ligament or involving lymph node.

(Grade 2, evidence level C)

Statement: There is no obvious evidence which shows that combined extrahepatic bile duct resection increases the prognosis of the patients with a gallbladder carcinoma without direct invasion to the hepatoduodenal ligament in preoperative diagnosis [212]. On the other hand, several studies show that lymphatic infiltration around the bile duct is the most important pathway for cancer spread in these diseases and distant microscopic spread separated from the primary tumor is often found [182, 213]. It may indicate that the combined extrahepatic resection increases the curative resection rate in patients with cancer invading the neck of gallbladder, involving lymph node, or associating with perineural infiltration [175, 180, 214].

Chemotherapy

CQ26: What is the first-line chemotherapy for patients with unresectable biliary tract cancer?

Recommendation: The combination chemotherapy with gemcitabine and cisplatin is recommended as the first-line chemotherapy. (Grade 1, evidence level A)

Statement: The prognosis of patients with unresectable biliary tract cancers is extremely poor and the development of effective non-surgical therapy is an urgent need for treatment of this disease. However, until ABC-02 trial, which is described below, there were only a few reports of clinical trials for chemotherapy of biliary tract cancers.

In Japan, gemcitabine is approved for biliary tract cancers according to the results of a phase II trial and had been used as a standard chemotherapy for these diseases [215]. S-1 is also approved according to the results of phase II trials [216, 217]. In addition, the combination therapy of gemcitabine and S-1 shows benefits in several phase II studies [218–221] and a phase III study is now being conducted.

Recently, the combination therapy of gemcitabine and cisplatin (GC) was examined for unresectable biliary tract cancers including intra- and extra-hepatic cholangiocellular carcinoma, gallbladder carcinoma, and ampullary carcinoma as phase II trial (ABC-01) [222] and phase III trial (ABC-02) [223]. In the ABC-02 trial, patients treated with GC survived significantly longer than patients treated with gemcitabine alone. The BT22 trial, which is a phase III trial conducted in Japan as a bridging study, also showed the superiority of GC on survival of patients with unresectable biliary tract cancers compared with gemcitabine mono therapy [224]. GC also shows low rates of severe adverse events and can be used safely [223, 224]. According to these results, GC is now widely accepted as the first-line chemotherapy for patients with unresectable biliary tract cancers.

Radiation therapy

CQ27: Is radiation therapy useful for patients with unresectable biliary tract cancer?

Recommendation: Radiation therapy may be considered for patients with unresectable biliary tract cancer. (Grade 2, evidence level C)

Statement: The purposes of radiation therapy for unresectable biliary tract cancers are prolonging life, preserving stent patency, reduction of jaundice, and pain control. There are several studies that show that radiation therapy may prolong the survival and stent patency compared with other palliative or supportive care [225–227]. However, no large scale randomized studies have been performed so far.

The external beam irradiation is usually used for the treatment of biliary tract cancers and the total radiation dose for fractionated irradiation is limited to about 50 Gy, which is not enough dosage for the treatment of adenocarcinoma, to avoid adverse events of the surrounding organs [228]. Intraluminal radiation can increase the radiation dose to tumor and reduce irradiation to surrounding organs, resulting in less adverse events [229–231]. However, there is no standard treatment or regimen of intraluminal radiation for bile duct carcinoma.

Recently, the three-dimensional conformal radiotherapy (3D-CRT) has been introduced and becomes a standard radiation treatment for biliary tract cancers. In addition, stereotactic irradiation (STI), intensity modulated radiation therapy (IMRT), and particle-beam radiation therapy were also tried for the treatment of these diseases.

One of the benefits of radiation therapy is the effect on preserving stent patency and pain control by local tumor control. Radiation therapy is an option for the treatment of patients with unresectable biliary tract cancers, especially for those who cannot be treated with chemotherapy due to performance status or high age.

Pathology

CQ28: What are the premalignant lesions in biliary tract?

Bile duct carcinoma: Biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of bile duct (IPNB) are premalignant lesions for bile duct cancer.
Gallbladder carcinoma: Dysplasia of gallbladder epithelium is a premalignant lesion for gallbladder cancer.

Ampullary carcinoma: Adenoma of papilla Vater is a premalignant lesion for ampullary cancer.

Statement: Bile duct carcinoma: BilINs are characterized by atypical epithelial cells in bile duct. BilIN is frequently encountered in the large bile ducts in chronic biliary diseases such as hepatolithiasis and primary sclerosing cholangitis (PSC) [232, 233]. The expression level of cell-cycle related molecules (cyclin D2, p21, etc.) and the frequency of oncogenic gene mutation (TP53, CDKN2A, etc.) are gradually increased from mild to severe atypia or carcinoma [234–236].

IPNB is a rare variant of bile duct tumors characterized by papillary growth within the bile duct lumen and is regarded as a biliary counterpart of intraductal papillary mucinous neoplasm of the pancreas. It is divided into adenoma, borderline malignant tumor and carcinoma in situ. As in BilIN, the expression level of cell-cycle related molecules and the frequency of oncogenic gene mutation are gradually increased from adenoma to carcinoma in situ [234, 235]. Therefore, adenoma and borderline tumor is thought to be premalignant lesion of bile duct carcinoma.

Gallbladder carcinoma: In mucosa surrounding gallbladder carcinoma, dysplasia, metaplasia, and atypical epithelium are often found associated with carcinoma in situ [27, 237]. Within them, dysplasia is thought to be a premalignant lesion because it is found rarely in the mucosa of gallbladder resected for cholecystolithiasis and chronic cholecystitis [237–239]. Molecular biological analysis also indicates the existence of metaplasia-dysplasia-carcinoma sequence [240, 241].

Ampullary carcinoma: The existence of adenoma-carcinoma sequence is suggested during carcinogenesis of ampullary carcinoma. Adenoma lesion is often seen around carcinoma lesion [242–244] and the abnormal findings of oncogene and tumor suppressor gene in adenoma are also reported [244, 245].

CQ29: What kind of non-neoplastic lesions are important for differential diagnosis for bile duct cancer?

Sclerosing cholangitis for bile duct cancer.

Xanthogranulomatous cholecystitis and adenomyomatosis for gallbladder cancer.

Statement: Sclerosing cholangitis: Sclerosing cholangitis is characterized by strong fibrotic and chronic inflammatory changes within and surrounding bile ducts, resulting in focal or diffuse bile duct stenosis, obstruction and dilatation. It is classified into primary, IgG4 related, and secondary cholangitis.

PSC shows no symptoms in its early stage. Associating with the progression of bile duct stenosis, it shows jaundice and cholangitis [246]. As disease progresses, the degree of hepatic fibrosis becomes more severe, resulting in cirrhosis and hepatic failure. In younger patients, it often associates with ulcerative colitis [247]. In advanced stage, it associates with bile duct carcinoma in 3.6% of cases [248].

IgG4-related sclerosing cholangitis (IgG4-SC) is characterized by increased level of serum IgG4, local fibrosis and infiltration of lymphatic cells and plasma cells often expressing IgG4 [249]. The bile duct without dilatation also often shows wall thickening [250]. It frequently associates with autoimmune pancreatitis. It is frequently seen in older males and responds well to steroid treatment.

Xanthogranulomatous cholesystitis (XGC): XGC is a rare inflammatory disease found in 1–2% of patients with cholecystolithiasis and frequently occurs in females. Macroscopically, XGC shows yellowish foci with unclear margins in thickened gallbladder wall. It sometimes spreads to adjacent organs such as intestine and liver, which makes diagnosis from malignant tumor difficult [251]. Microscopically, it includes localized inflammation foci with rounded foamy macrophages, monocytes, lymphocytes, and multinucleated giant cells. The pathogenesis of XGC is thought to be related to extravasation of bile into the gallbladder wall from rupture of RAS or by mucosal ulceration, leading to granulomatous inflammation reaction [251, 252]. Similar lesion is also seen in bile duct.

Adenomyomatosis: Adenomyomatosis, also called adenomyomatous hyperplasia, is a lesion of focal or diffuse gallbladder wall thickening due to glandular diverticulae into the muscle wall (RAS) and fibromuscular hyperplasia. Sometimes a differential diagnosis is difficult with flat-expanding of the infiltrating type of gallbladder cancer [251, 253].

Conclusion

The revised version of the clinical guidelines for management of biliary tract cancers edited by committee members of JSHPBS are the result of a multidisciplinary evidence-based approach. In this version, one of the most important points is the introduction of the concepts of the GRADE system. We believe that this makes recommendations clearer for better understanding of readers. We will conduct a survey of the usage of these guidelines and make corrections accordingly for better revision in the future.

The assessment of the recommendation will be the key for further development and future revision of the guideline. For the assessment, we are now planning to use the Japanese National Biliary Tract Cancer Registry, which is another project of JSHBPS. Committee members of the guideline and cancer registry project are now discussing the quality indicators that
assess whether clinical actions recommended in the guideline are frequently performed in Japan. Also we will assess whether these clinical actions have the benefit through these quality indicators. These assessments will strengthen the recommendation in the guideline.

Another important thing is the worldwide dissemination of this guideline. In addition to the publication as a journal article and a book, we also plan to make a mobile application of this guideline for easy access. The application is available via the following URL (http://www.jsshbps.jp/en/guideline/biliary-tract2.html).

These guidelines represent the most standard clinical and practical managements at the current time. However, efforts will be required to develop the new clinical actions for improvement of patients’ management with biliary tract cancers. We also expect that this guideline will be useful for designing future studies by showing current benchmarks and developing new evidence in future.

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