

Updated clinical practice guidelines for the management of biliary tract cancers: revision concepts and major revised points

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Abstract

Background In 2008, the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) launched the clinical practice guideline for the management of biliary tract cancers. JSHBPS decided to revise these guidelines for distribution of updated points concerning the treatment of biliary tract cancers. **Methods** To make clearer recommendations, we introduced the concepts of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, in which the strength of recommendations are decided considering not only quality of evidence, but also balance of benefits and harms/burdens, patients' preferences, and cost benefits. **Results** We emphasize the importance of the dynamic contrast enhanced multiple row detector CT (MDCT) in the diagnosis of biliary tract and gallbladder carcinomas. For biliary drainage, we suggest to perform endoscopic approaches instead of percutaneous approach to avoid complications. Regarding the surgical treatments, we included new clinical questions about the importance of combined vascular resection, intraoperative histological examination of the bile duct

resection margin, and the combined extrahepatic bile duct resection for the gallbladder carcinoma. We also discussed details about premalignant lesions and non-neoplastic lesions in pathology section.

Conclusion With this major revision, we expect that the Japanese standards of treatments of these diseases are recorded and reported in the universal language.

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

Introduction

The rapid progress of recent medical technology has contributed to improvements in diagnosis and treatment, resulting in better treatment outcomes in many diseases. Recent advances in information technology also enable rapid distribution of new medical information. However, it is impossible for an individual health professional to manage all of this new information and provide updated treatment for each patient. Under these circumstances, the clinical guidelines edited by specialists in each field have been published to organize this information and provide updated evidence-based medicine.

In 2008 (2007 in Japanese), the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) launched the first edition of the clinical practice guidelines for the management of biliary tract cancers [1–10]. This was the only clinical guideline focused on biliary tract cancers (including hilar cholangiocarcinoma, extrahepatic biliary tract carcinoma, gallbladder carcinoma, and ampullary region carcinoma). It has greatly contributed to providing general as well as specialized clinicians with knowledge on standard treatments based on evidence and consensus, not only in Japan but also worldwide. Many novel treatment modalities and handling of clinical issues have been proposed after its publication. In 2010, the board members of JSHBPS decided to revise these clinical

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guidelines and publish them in this journal. This is the first major revision of these guidelines. In this article, we describe the new concept and major points in the revised version of the clinical practice guidelines for the management of biliary tract cancers.

Methods

We first performed the survey for extracting the problems of the first edition of the clinical practice guidelines for the management of biliary tract and ampullary carcinoma. In 2010, we distributed the questionnaires to the members of the Japan Biliary Association. This survey showed that the guidelines were extensively used and useful for distributing the standard treatments of the biliary tract cancers. However, two major concerns were pointed out from the survey. One was about the reconsideration of committee members and the other was about the strength of recommendation grades.

Reconsideration of committee members

The surgical resection is the only hope for cure of biliary tract cancers. Because of this background, in the first edition, the committee for editing guidelines consisted of mainly surgeons (14 surgeons out of 18 committee members). However, due to the recent advances in chemotherapy and/or endoscopic management, oncologists, endoscopists or other specialists have taken more important roles in the management of these patients. In the survey, many responders pointed out the excessive ratio of surgeons among the committee members.

In addition to 16 surgeons, two oncologists and four endoscopists joined the committee for the revised version. We also recruited two radiologists who specialized in diagnosis and radiation therapy for these diseases. In addition, two pathologists specialized in this field and one specialist for making guidelines also joined the committee. Finally, 28 members were selected as the committee for revision of the guidelines.

Strength of recommendations

We decided that the revised guidelines should follow the clinical question style as in the first edition. In the first edition, the committee members discussed and finally decided on the strength of recommendation (Table 1) for each clinical question, mainly according to the levels of evidence (Table 2). Due to the lack of high grade evidence in this field, the majority of recommendations for each clinical question were C1 (the clinical action may be considered although there is a lack of high-level scientific evidence for its use. Maybe useful.). In the survey, many responders pointed that this grading system was equivocal and did not help a lot for making clinical

Table 1 Strength of recommendation in the 1st edition of the Clinical Practice Guidelines for the Management of Biliary Tract and Ampullary Carcinomas

A	Strongly recommend performing the clinical action.
B	Recommend performing the clinical action.
C1	The clinical action may be considered although there is a lack of high-level scientific evidence for its use. Maybe useful.
C2	The clinical action not definitively recommended because of insufficient scientific evidence. Evidence insufficient to support or deny usefulness.
D	Recommend not performing the clinical action

Table 2 Levels of evidence in the 1st edition of the Clinical Practice Guidelines for the Management of Biliary Tract and Ampullary Carcinomas

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

decisions in some cases. Responding to this, we decided to introduce the concepts of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [11] for grading the strength of recommendations. In this approach, the overall quality of body of evidence across gross studies for each important outcome is assessed. For the judgment about the quality of evidence, reviewers consider not only study design but also study quality, consistency and directness (Table 3). The strength of recommendation is decided considering four factors: quality of evidence, balance of benefits and harms/burdens, patients' preferences, and cost benefits. Finally the strength of recommendation is divided into two categories with the agreement of 70% or more panels (committee members); Grade 1: Strong recommendation (we recommend to do or not to do) and Grade 2: Weak recommendation (we suggest to do or not to do). Unfortunately, there were several clinical questions in which less than 70% of panels agreed with the final recommendation grade. These clinical questions were finally excluded from the guidelines. Using this approach, the revised version indicates clearer recommendations for each clinical action in the management of patients with biliary tract cancers.

Results

The revised guidelines consisted of diagnosis and treatment algorithms and 29 clinical questions. We describe the important revised points.

Table 3 Criteria for adding grade of evidence in the GRADE system**Type of evidence**

- Randomized trial = high
- Observational study = low
- Any other evidence = very low

Decrease grade if:

- Serious (–1) or very serious (–2) limitation to study quality
- Important inconsistency (–1)
- Some (–1) or major (–2) uncertainty about directness
- Imprecise or sparse data (–1)
- High probability of reporting bias (–1)

Increase grade if:

- Strong evidence of association: significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association: significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

- (1) Emphasis on usefulness of the multiple row detector CT (MDCT) for the diagnosis of bile duct and gallbladder cancers.

In the revised guidelines, we emphasize the usefulness of the dynamic study using MDCT for the diagnosis of bile duct and gallbladder cancers. Using dynamic study more than dual phases, the hemodynamic assessment becomes much easier. These days, MDCT can be available in the majority of institutions in Japan and other western countries. Especially for bile duct and gallbladder cancers, MDCT makes the assessment of localization and the degree of its extension in biliary tract and surrounding tissues easier, from various directions using not only axial view but also sagittal and coronal view [12–17]. This information is very useful for assessing resectability and planning operations. To get a clear view, CT examination should be performed before biliary drainage to avoid artifacts of the stent tube.

- (2) Method of biliary drainage

Patients with biliary tract cancer often show obstructive jaundice. In the majority cases, preoperative biliary drainage is performed to release the jaundice. There are several methods for biliary drainage, percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD), and endoscopic biliary stenting (EBS). In previous edition, we suggested performing biliary drainage by methods that are safe and favorable in each institution according to their equipment, technique, and preference [5]. Although several retrospective studies showed that there were no differences in the

complication rate and effectiveness of drainage between the methods [18], there exist unnegligible possibilities that PTBD may lead to portal vein injury, peritoneal dissemination, and tract recurrence [18–20]. According to this recent evidence, we concluded that endoscopic drainage is the most appropriate procedure for biliary drainage.

- (3) Surgical treatment

Surgical resection is the only hope for cure in patients with biliary tract cancers. Due to this, most of the clinical questions are regarding surgical treatments. In the revised version, we included several new clinical questions. One is concerned with the combined vascular resection. We recommend the portal vein resection in the case of portal vein invasion, the same as the first edition. We also included the discussion about the arterial resection involving the tumor to achieve curative resection. There are still many debates about the effectiveness of the arterial resection for biliary tract cancer involving the adjacent arteries, so that we could not recommend it with obvious evidence. However, with the advanced techniques of arterial reconstruction, there are several recent reports that have showed the safety and effectiveness of arterial resection for biliary tract cancers [21, 22]. We included this question because we believe that it is one of the important missions for the guidelines to introduce hot topics to readers.

We also included the clinical question about the necessity of intraoperative histological examination of the bile duct resection margin for bile duct cancer. Recent reports showed the importance of the ductal resection margin status on the prognosis [21–26]. With these high levels of evidence, we emphasized the importance of this procedure.

The combined extrahepatic bile duct resection is also included as a topic. A multi-institutional retrospective study showed that the combined extrahepatic bile duct resection for the gallbladder carcinoma without invasion to the common bile duct did not improve the prognosis of these patients [27]. However, there are several reports that showed the effectiveness of this procedure by detailed histological analysis or clinicopathological analysis of these patients [28–32]. According to this evidence, we concluded that this procedure may contribute to the improvement of the prognosis of patients with gallbladder carcinoma invading the neck of the gallbladder approaching the hepato-duodenal ligament or with lymph node metastasis.

- (4) Chemotherapy

In the first edition, chemotherapy was recommended in patients with unresectable biliary tract cancers. However, due to a lack of high level evidence, such as a randomized prospective study with large number of patients, we only suggested gemcitabine

or S-1 monotherapy (tegafur/ gimeracil/ oteracil potassium) with several results of phase II trials and indicated the necessity of conducting controlled trials, such as phase III study, for establishing the evidence-based standard treatment. In 2010, Valle et al. reported the results of the large randomized phase III trial comparing combination therapy using gemcitabine and cisplatin (GC) and gemcitabine monotherapy. They showed the superiority of the GC therapy for the treatment of patients with unresectable biliary tract cancers including cholangiocellular carcinoma [33]. Japanese phase III study also confirmed the results [34]. According to these results, we recommended GC therapy as the first line chemotherapy for patients with unresectable biliary tract cancers having good performance status.

(5) Pathology

In the diagnosis and assessment of biliary tract cancer, the histological diagnosis plays very important roles. Also there are several non-tumorous diseases or premalignant lesions that show very similar findings on image diagnosis with cancers. Due to these reasons, we described the premalignant lesions and non-neoplastic lesions for better understanding. As, premalignant lesions, we picked biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm of bile duct (IPNB) for bile duct carcinoma and dysplasia of gallbladder epithelium for gallbladder carcinoma. Also sclerosing cholangitis, xanthogranulomatous cholecystitis, and adenomyomatosis for gallbladder carcinomas were discussed as non-neoplastic lesions.

Conclusion

With this major revision of the evidence-based clinical practice guidelines for the management of biliary tract cancers, we expect that the Japanese standards of treatment of these diseases are recorded and reported in the universal language. JSHBPS also is conducting the biliary tract cancer registry in Japan. We are now trying to use this registry for confirming the illumination of the guideline and to establish new evidence that is being debated at present.

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