

## Purpose, use, and preparation of clinical practice guidelines for the management of biliary tract and ampullary carcinomas

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### Abstract

Apart from periampullary carcinoma, the prognosis of biliary tract carcinomas, including hilar cholangiocarcinoma, extrahepatic biliary tract carcinoma, and gallbladder carcinoma, remains poor. Sophisticated diagnostic skills and treatment methods and their application are naturally required to achieve better treatment results for biliary tract carcinomas. However, it is not too much to say that, due to the paucity of high-level evidence for the management of these carcinomas, medical care by healthcare providers in clinics and at medical institutes throughout the world is currently delivered without common consensus and common standards. The clinical practice guidelines for the management of biliary carcinoma outlined here were produced with the aim that they could be used by physicians involved in the care of biliary tract carcinomas, as indicators that could help them provide their patients with the most appropriate care possible at this time. Also, the guidelines were prepared to provide measures that could assure patients with biliary tract carcinomas of safe medical care. The present guidelines are characterized by their clarification of clinical questions assumed to be often shared by healthcare professionals. For clarity, we divided the contents of the guidelines into eight areas. In each area, clinical questions are presented, together with recommendations of clinical actions in response to the question. As mentioned already, there is a paucity of high-level evidence in this area; therefore, the recommendations are classified into grades, of which there are five: A, strongly recommend performing the clinical action; B, recommend performing the clinical action; C1, the clinical action may be useful, although there is a lack of high-level scientific evidence; C2, clinical action not definitively recommended because of insufficient scientific evidence; D, recommend not performing the clinical action. The grading of the recommendations is based on the determination of the level

of evidence in references on which the recommendation is based.

**Key words** Guidelines · Biliary · Hilar cholangiocarcinoma · Gallbladder carcinoma

### Purpose of the clinical practice guidelines for the management of biliary tract and ampullary carcinomas (the guidelines)

No guidelines for the diagnosis and treatment of biliary tract carcinoma, the prognosis of which remains poor, have been published to date, although a set of guidelines for intrahepatic cholangiocarcinoma was published in 2002 by Khan et al.<sup>1</sup> There remain many problems to be solved concerning the diagnosis and treatment of biliary tract carcinoma so that better treatment results can be achieved for this disease. We (The Japanese Society of Hepato-Biliary-Pancreatic Surgery [JSHBPS]) produced the present guidelines, recognizing that a high level of expertise is required for those concerned with the diagnosis and treatment of the disease. The greatest obstacle encountered most frequently in preparing the present guidelines was the paucity of high-level evidence for the diagnosis and treatment of biliary tract carcinoma and the lack of practical guidelines for coping with this problem. Currently, under these circumstances, there are wide disparities in the levels of diagnosis and treatment among different institutions. However, in assessing the strength of recommendations for treatment, because of the paucity of high-level evidence in this field, the members of the Organizing Committee formed for creating the guidelines focused on building a consensus. Occasionally, decisions were subject to modifications on

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the basis of discussions at an open forum. The aim of the guidelines was to supply indicators to physicians involved in the care of this disease, to provide their patients with the safest and most appropriate care.

### Notes on the use of the guidelines

The entire contents of the present guidelines were endorsed upon discussions held among all the members of the Organizing Committee and the Publishing Committee. The guidelines consist of algorithms that outline diagnosis and treatment, followed by clinical questions. In view of the fact that there is still a wide variation in treatment policies among medical institutions, the presentation of the contents is made in the form of clinical questions.<sup>2,3</sup> The contents are divided into eight areas to elucidate the clinical questions considered to be shared by healthcare professionals and to clarify the guidelines with respect to these questions at this stage of publication. The questions in each area are presented under the heading of “clinical questions.” The presence or absence of recommendations for a clinical action, the strength of the recommendations, and statements on how recommendations are made are provided with each question. Recommendations and statements are formulated on the basis of evidence. The strength of treatment recommendations in response to each question was determined in accordance with the following policy. Compared with breast cancer and gastric cancer, only a limited amount of high-level evidence has been obtained from randomized controlled trials for the diagnosis and treatment of biliary tract carcinoma. As a result, we aimed to reach a consensus on the grading of the strength of recommendations. This was done and the strength of recommendations was stated according to five grades:

- A, Strongly recommend performing the clinical action.
- B, Recommend performing the clinical action.
- C1, Clinical action may be useful although there is a lack of high-level scientific evidence.
- C2, Not definitively recommended, because of insufficient scientific evidence.
- D, Recommend not performing the clinical action.

### *Perspective on “guidelines”*

With regard to the present guidelines, from the perspective of “guidelines,” they represent the most standard clinical and practical indicators at this time. However, they should not be coercive for the practical management of individual patients. Final decisions on management should be made on the basis of conditions at individual institutions (depending on personnel, experience, instruments, etc.) and the individual characteristics of patients.

The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) is responsible for the statements in the present guidelines. The JSHBPS and the Organizing Committee members are not liable for any consequences arising from any treatment, for which individual physicians involved in the treatment should be responsible. The dosages described in the text are for adult patients.

### How the guidelines were formulated

With evidence-based medicine (EBM) as the core concept, the first Preparation Committee for “the guidelines for the management of biliary tract carcinoma” was held on May 12, 2005, to discuss how to formulate the guidelines. The guidelines were prepared according to the following procedures: (1) Comprehensive search using key words for relevant literature on biliary tract carcinoma in the past 20 years. (2) Assessment and classification of the abstracts of all retrieved articles, on the basis of contents, by at least two reviewers, and selection of literature considered useful. (3) Using the selected literature as reference matter, each committee member prepared a draft of clinical questions in the area in which he or she was involved. (4) From all the questions selected by all committee members, clinical questions considered appropriate were selected at the general meeting. (5) Preparation of statements on clinical questions of each specialty. (6) Review of the presence/absence of recommendations, strength of recommendations and statements proposed at the general meeting, and checking of the contents of statements. (7) Check of the final draft by all committee members. (8) Assessment by the members of the Review Committee of the draft prepared according to the above procedures. (9) A public hearing was held to hear opinions from an audience with wide medical specialties. (10) New committee members of the Publishing Committee were elected from the Organizing Committee to further review the final draft. So that the draft would be objective and evidence-based, it was further checked for consistency in the strength of recommendations and statements of clinical questions. The statements were modified to be more readable. Thus, the final draft was prepared.

### *Comprehensive literature search*

References written in English were searched for on MEDLINE in June 2005. Reference formulas used and the number of items retrieved are shown below. Systematic review articles were also searched for using the formulas below. References were further searched for, where necessary, by means of a manual search.

*Search for English-language references*

1. Biliary tract neoplasms [MeSH] limits: publication date from 1985, English, humans.
2. Publication types: Clinical trial or Meta-analysis or Practice Guideline or Randomized Controlled Trial or Review — 1266 items.

*Systematic reviews*

Cochrane library: key word “biliary” 59 items.  
MEDLINE:

- Search 1. “biliary tract neoplasms” [MeSH] limits: only items with abstracts, English, publication date from 1985 to 2006, Clinical Trial, Meta-analysis, Randomized Controlled Trial, Review — 1136 items
- Search 2. “biliary tract neoplasms” [MeSH] or “gall-bladder cancer” or “common bile duct cancer” limits: English, publication date from 1985 to 2006, humans — 491 items
- Search 3. ((((((((((“Meta-Analysis” [MeSH terms] or meta-analysis[pt]) or medline [tiab]) or (((metaanalyses[tiab] or metaanalysis[tiab]) or metaanalytic[tiab]) or metaanalytical [tiab]) or metaanalytically [tiab])) or “metaanalysis” [All Fields]) or (((overview [tiab] or overview/literature [tiab]) or overviewed [tiab]) or overviewer [tiab]) or overviewing [tiab]) or overviews [tiab])) or clinical trial [pt]) or multicenter study[pt]) or evaluation studies[pt]) or validation studies [pt]) or review [pt]) or (systematic review [All Fields] or systematic reviews [All Fields])) — 1827246 items
- Search 2 and Search 3, but not Search 1, — 314 items

*Final selection of appropriate references by Publishing Committee members*

On the basis of an evaluation by at least two Publishing Committee members of the importance of abstracts of selected references, 669 English-language references were finally selected.

*Preparation of drafts of clinical questions*

Using the literature thus selected as references, drafts of clinical questions were prepared by the responsible Publishing Committee members, and 227 questions in total were proposed.

*Final selection of clinical questions from the drafts*

At a general meeting held on July 10, 2006, the decision was made that 33 clinical questions should be adopted for each of the eight specialized areas.

*Preparation of statements for clinical questions*

The statements of clinical questions and introductions were prepared for each specialized area by the responsible Publishing Committee members. Another general meeting was held and the number of clinical questions to be adopted was changed to 35.

The strength of recommendations for individual clinical questions was given in related statements. Determination of the level of evidence for individual references, on which the strength of recommendations was determined, was made according to the criteria shown in Tables 1 and 2. In view of the lack of high-level evidence on the treatment of biliary tract carcinoma, the decisions on treatment policies were made by taking into account the findings collected from case studies.

**Strength of recommendations and evaluation of evidence levels** (Tables 1 and 2)

The “grade of recommendations” was discussed many times at an Organizing Committee meeting and at a second public hearing meeting. There are many criteria for the strength of recommendations in many clinical practice guidelines, and there are no worldwide standards. After all the discussions, we were able to reach the following consensus on the grading of the strength

**Table 1.** Strength of recommendations

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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. May be useful
C2, Clinical action not definitively recommended because of insufficient scientific evidence. Evidence insufficient to support or deny usefulness
D, Recommend not performing the clinical action

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**Table 2.** Levels of evidence

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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

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of recommendations. The aim of the grading of recommendations is to present indicators which will help physicians involved in the care of patients with biliary tract carcinoma to provide their patients with the safest and most appropriate care.

### **Decisions on clinical questions and review of algorithms**

The statements for the clinical questions were modified by the responsible Publishing Committee members. A further general meeting was held to review all the clinical questions. The final number of questions was changed to 36. Diagnosis and treatment algorithms were also prepared.

### **Evaluation by Review Committee members**

Evaluations and suggestions for the final draft were made by the External Review Committee.

Additions and modifications were made after discussions by the Publishing Committee members.

### **Public hearing**

At two public hearings (the first on June 7, 2007; the 19<sup>th</sup> Annual Meeting of the JSHPBS, and the second, on September 29, 2007; the 43<sup>rd</sup> Annual Meeting of Japan Biliary Association), comments were requested from the audience, particularly from physicians from a wide area of medical specialties, and then the final corrections of the draft were made.

### **Publishing Committee**

The Publishing Committee was organized after the first public hearing. Reexaminations, additions, and corrections were made with respect to all the expressions, sentences, and terminology, etc., by all the Publishing Committee members. For the contents, repeated discussions were held until a sufficient consensus was achieved.

The final version of the final draft was made public at the second public hearing, and comments from the general audience were requested. The final version was also evaluated by the External Review Committee members. The draft was finalized taking into account these comments and the evaluation.

### **Diffusion of the guidelines**

The guidelines, *Evidence-based clinical practice guidelines for the management of biliary tract carcinoma*, were published in Japanese by Igaku-Tosyo Syuppan.

The guidelines were posted on the Internet on the JSHBPS home page, Japan Council for Quality Health Care; and, on the medical information network distribution service (Minds) home page.

### **Plan for publication of the revised edition**

Evaluation and accumulation of pertinent evidence is being continued by the Organizing Committee of the guidelines, which has been established permanently at the JSHBPS. A revised edition is expected to be published every 4 years, but the timing of the revisions will be subject to change depending upon advances in medical science and care.

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**References**

1. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, et al.; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut* 2002;51:VI1-9.
2. Takada T, Hirata K, Kawarada Y, Mayumi T, Yoshida M, Sekimoto M, et al. JPN Guidelines for the management of acute pancreatitis: cutting-edge information. *J Hepatobiliary Pancreat Surg* 2006;13:2-6.
3. Takada T, Kawarada Y, Nimura Y, Yoshida M, Mayumi T, Sekimoto M, et al. Background: Tokyo guidelines for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Surg* 2007;14:1-10.