AUTHOR QUERY FORM

ELSEVIER	**Journal:** GEC **Article Number:** 665	

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult http://www.elsevier.com/artworkinstructions.

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof.

Location in article	Query / Remark: Click on the Q link to find the query's location in text Please insert your reply or correction at the corresponding line in the proof
Q1	Please approve the short title to be used in the running head at the top of each right-hand page.
Q2	This is how your name will appear on the contributor's list. **Please add your academic title** and any other necessary titles and professional affiliations, verify the information, and OK **KENJI YAMAO**, Department of Gastroenterology, Aichi Cancer Center Hospital, Chikusa-Ku, Nagoya, Japan **KAZUO HARA**, Department of Gastroenterology, Aichi Cancer Center Hospital, Chikusa-Ku, Nagoya, Japan **NOBUMASA MIZUNO**, Department of Gastroenterology, Aichi Cancer Center Hospital, Chikusa-Ku, Nagoya, Japan **SUSUMU HIJIOKA**, Department of Gastroenterology, Aichi Cancer Center Hospital, Chikusa-Ku, Nagoya, Japan **HIROSHI IMAOKA**, Department of Gastroenterology, Aichi Cancer Center Hospital, Chikusa-Ku, Nagoya, Japan **VIKRAM BHATIA**, Department of Medical Hepatology, Institute of Liver and Biliary Sciences, Delhi, India **YASUHIRO SHIMIZU**, Department of Gastrointestinal Surgery, Aichi Cancer Center Hospital, Nagoya, Japan
Q3	Are author names and order of authors OK as set?
Q4	Please provide professional degrees (eg, PhD, MD) for the authors.
Q5	The following synopsis is the one that you supplied, but lightly copyedited. Please confirm OK. Please note that the synopsis will appear in PubMed: Endoscopic ultrasound-guided choledochoduodenostomy (EUS-CDS) is a novel alternative to percutaneous transhepatic biliary drainage, when endoscopic retrograde cholangiopancreatography is unsuccessful in patients with malignant lower biliary obstruction. Some case series and a few prospective studies of EUS-CDS have reported high technical and functional success rates

	but with the downside of high early complication rates, albeit mostly nonsevere. In addition, the stents placed by EUS-CDS had a longer patency than transpapillary biliary stents.
Q6	Please verify the affiliation addresses and provide the missing information (street name and zip code for "b" and "c").
Q7	No affiliations were provided for the authors "Kazuo Hara," "Nobumasa Mizuno," "Susumu Hijioka," "Hiroshi Imaoka," hence the affiliation address of author "Kenji Yamao" has been retained for these authors. Please verify and provide the affiliation for the authors.
Q8	The following query was raised by guest editor: Is this needle used just for contrast injection? If so, please clarify this and describe how you remove the needle and then guide the needle knife into the bile duct.
Q9	The following query was raised by guest editor: Again, please clarify how this is done and compare with over-the-wire needle knife.
Q10	The following query was raised by guest editor: What size balloon do you use?
Q11	As per Clinics style, citation is not allowed in section headings. Hence Ref. 19 has been moved to the end of the first sentence of the paragraph "In cases where the EUS-CDS..." Please verify.
Q12	The following query was raised by guest editor: This line has been repeated in the section below.
Q13	Please verify edits to the article title of Table 1.
Q14	"G" has been expanded as "gauge" in Table 1. Please verify.
Q15	Please provide the reference details and corresponding reference citations for the authors listed in Table 1 for which citations are not present.

Thank you for your assistance.

J Hepatobiliary Pancreat Sci
DOI 10.1007/s00534-011-0482-6

ORIGINAL ARTICLE

Diagnostic yield of endoscopic retrograde cholangiography and of EUS-guided fine needle aspiration sampling in gallbladder carcinomas

Susumu Hijioka · Kazuo Hara · Nobumasa Mizuno · Hiroshi Imaoka · Takeshi Ogura · Shin Haba · Mohamed A. Mekky · Vikram Bhatia · Waki Hosoda · Yasushi Yatabe · Yasuhiro Shimizu · Yasumasa Niwa · Masahiro Tajika · Shinya Kondo · Tsutomu Tanaka · Kiichi Tamada · Kenji Yamao

Abstract
Background Obtaining histological evidence of gallbladder carcinoma (GBC) is difficult due to its extraductal nature, and pathological confirmation remains challenging. We compared the diagnostic value and safety of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) with endoscopic retrograde cholangiography (ERC) in patients with suspected GBC.
Patients Eighty-three patients with GBC were evaluated. Prior to definitive management, pathological evidence of GBC was obtained through either ERC cytopathologic sampling ($n = 33$), EUS-FNA ($n = 24$) or both ($n = 26$).
Results Among the 83 patients, 59 (71.0%) with biliary obstruction were sampled using ERC with 47.4% (28/59) sensitivity. In 19 of the remaining 31 cases, EUS-FNA sampling had 100% diagnostic sensitivity. Likewise, 50 (60.2%) of the 83 patients with suspected GBC underwent EUS-FNA of regional lymph nodes or the gallbladder (GB) mass itself with 94.8% sensitivity. The overall diagnostic sensitivity rates of ERC and EUS-FNA were 47.4 and 96%, respectively ($P < 0.001$). Post-procedural complications were seen in 6.7% of the ERC group (4/59, all were mild pancreatitis), and in none of the EUS-FNA group ($P = 0.10$).
Conclusions Gallbladder carcinoma sampling using ERC and EUS-FNA should be incorporated into the diagnostic workup of GB lesions as complementary tools, and EUS-FNA should be applied in the setting of failed or not indicated ERC.

Keywords Gallbladder carcinoma (GBC) · Endoscopic retrograde cholangiography (ERC) · Endoscopic ultrasound (EUS) · EUS-guided fine-needle aspiration (EUS-FNA)

S. Hijioka (✉) · K. Hara · N. Mizuno · H. Imaoka · T. Ogura · S. Haba · K. Yamao
Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: rizasusu@aichi-cc.jp

M. A. Mekky
Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut, Egypt

V. Bhatia
Department of Medical Hepatology, Institute of Liver and Biliary Sciences (ILBS), Delhi, India

W. Hosoda · Y. Yatabe
Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Japan

Y. Shimizu
Department of Surgery, Aichi Cancer Center Hospital, Nagoya, Japan

Y. Niwa · M. Tajika · S. Kondo · T. Tanaka
Department of Endoscopy, Aichi Cancer Center Hospital, Nagoya, Japan

K. Tamada
Department of Gastroenterology, Jichi Medical University, Tochigi, Japan

Introduction

Obtaining pathological evidence of gallbladder carcinoma (GBC) is medically and ethically necessary for both operable and non-operable cases, prior to resection and chemotherapy, respectively. In the pre-endoscopic ultrasound (EUS) era, endoscopic retrograde cholangiography (ERC) drainage with cytologic sampling was the initial investigation of choice to prove malignancy, especially in cases with biliary obstruction. ERC-guided sampling has a

Published online: 30 November 2011

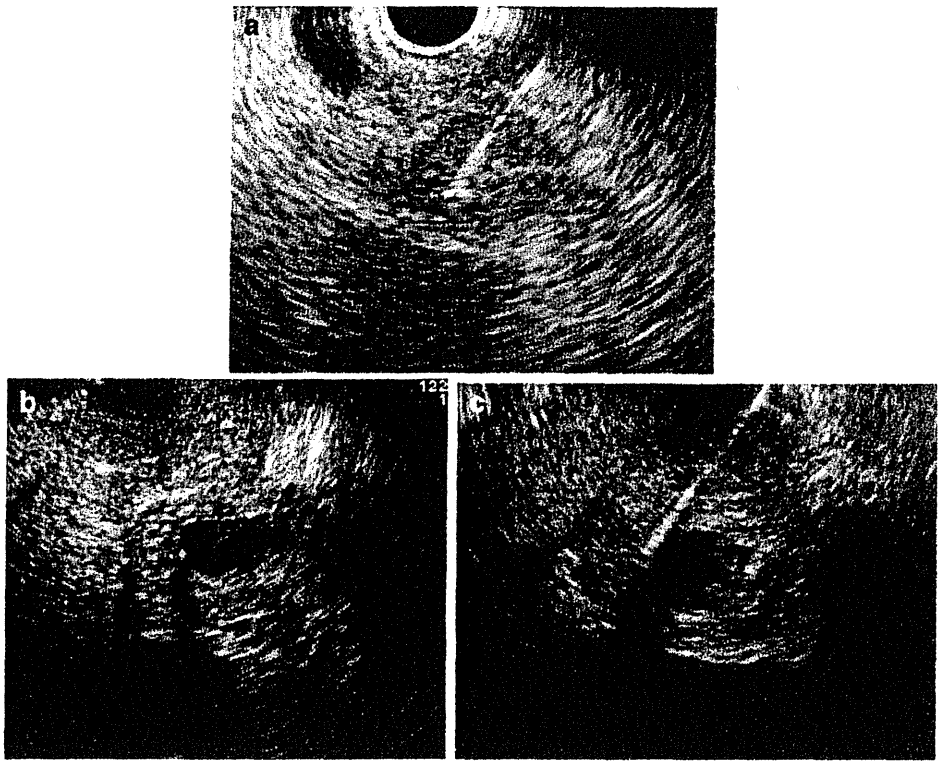


Fig. 2 EUS-FNA. **a** EUS-FNA for regional intra-abdominal lymph nodes. **b** The diffuse and irregular wall of a thickened GB. **c** EUS-FNA for a GB wall-thickened lesion. *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration, *GB* gallbladder, *LN* lymph node, *insuff* insufficient aspirate

not enlarged, inaccessible, or yielded negative sampling (Fig. 2b, c) [14].

Evaluation of complications

All patients were followed-up for 24 h after the procedure with clinical observation and measurement of serum amylase, C-reactive protein (CRP) and hematologic profiles. Post-procedural pancreatitis was diagnosed based on abdominal pain and/or a four-fold rise in baseline serum amylase. The possibility of tumor seeding, which may be associated with these procedures, was evaluated by the presence or absence of any apparent tumor involvement of the gastrointestinal wall, along the needle track, and during follow-up through imaging modalities (e.g. CT, MRI).

Statistical analysis

Samples obtained by ERC and/or EUS-FNA were categorized as positive or negative for malignancy. Any specimen interpreted as suspicious, atypical or non-diagnostic was considered negative for malignancy. Our standard references were either postoperative cytopathological findings from surgical patients, or the results of EUS-FNA coupled with the clinical, imaging and follow-up management results for non-operable patients.

Continuous variables are described as means and standard deviations, and dichotomous variables are expressed as simple proportions. The χ^2 test (with Yates correction) was used for comparative statistics. Data were statistically analyzed using SPSS software for Windows, release 11 (SPSS Inc, Chicago, IL, USA). A P value of <0.05 was considered significant.

Results

ERC sampling

Among the 83 patients, 59 (71.0%) presented with obstructive jaundice and underwent ERC cytopathological sampling. Evidence of malignancy was obtained in 28 (47.4%) of them (95% CI 34.3–60.8%).

Bile aspiration and subsequent cytological examination was performed in 30 (50.8%) of these 59 patients, and ERC add-on procedures (e.g. brushing and or biopsy forceps) were used in the remaining 29 (49.2%). Figure 3 shows details of the ERC results.

The malignancy detection rates of bile aspirate cytology and the add-on ERC cytopathology were 43.3% (13/30) and 51.7% (15/29), respectively with no statistical difference between these 2 groups ($P = 0.31$).

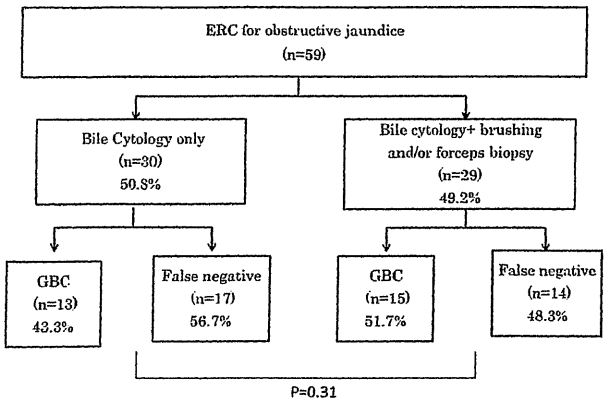


Fig. 3 Details of ERC results. The malignancy detection rates of bile aspirate cytology and the add-on ERC cytopathology were 43.3% (13/30) and 51.7% (15/29), respectively, with no statistical differences between these 2 groups ($P = 0.31$). *GBC* gallbladder carcinoma, *ERC* endoscopic retrograde cholangiography

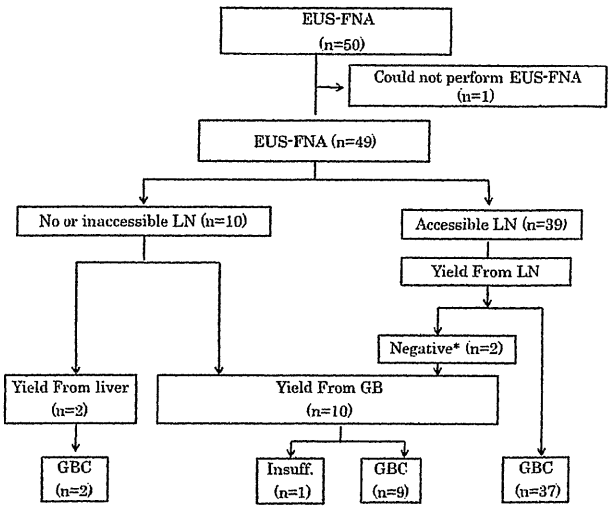


Fig. 4 Schematic diagram of gallbladder mass lesions and EUS-guided FNA yield. Our EUS-FNA sampling protocol for GB mass lesion. The overall diagnostic sensitivity rate of EUS-FNA was 96%. *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration, *GB* gallbladder, *GBC* gallbladder carcinoma, *LN* lymph node, *insuff* insufficient aspirate

Post-procedure complications were detected in 4 cases (6.7%) and all were mild pancreatitis which was managed conservatively.

EUS-FNA sampling

Fifty (60.2%) of the 83 patients with suspected GBC, according to the findings of various imaging modalities, underwent EUS-FNA. All of these patients were considered inoperable, and the aim of puncture was to obtain pathological evidence of malignancy before starting chemotherapy. Only one patient could not undergo EUS-FNA because we could not find a safe route for puncture. Enlarged intra-abdominal regional lymph nodes were detected in 79.6% ($n = 39$), and after FNA 94.8% of them ($n = 37$) were found to be positive for malignancy with immediate on site evaluation. 10 cases with absent regional LN enlargement and 2 with negative yield from LN aspirate underwent sampling of the GB mass itself ($n = 10$) or liver metastasis ($n = 2$).

Positive yield for malignancy was obtained in 90% (9/10) patients who underwent GB mass puncture, and both patients in whom the hepatic metastasis was sampled successfully. The overall diagnostic sensitivity rate of EUS-FNA was 96% (48/50, 95% CI 85.7–99.6%), with only one false-negative (FN) result because of sample insufficiency. Most of our pathological diagnoses were either adenocarcinoma or adenosquamous cell carcinoma (95.9%, 46/48) and only 2 cases were small cell carcinoma (4.1%, 2/48). The mean number of needle passes was 2.6 (range 1–4). There was no serious procedure-related complication in any case. In addition, there was no apparent tumor seeding during our follow-up periods. Figure 4 shows a detailed description of the EUS-FNA procedure results.

EUS-FNA after ERC

Endoscopic retrograde cholangiography failed to show evidence of malignancy in 52.5% of the 59 cases ($n = 31$), considered the FN yield. Of them, 19 cases were subjected to EUS-FNA with 100% positive yield for malignancy (95% CI 82.3–100%). Figure 5 shows a detailed description of these results.

EUS-FNA versus ERC (Table 1)

The overall diagnostic sensitivity rates of ERC and EUS-FNA for GBC were 47.4 and 96%, respectively ($P < 0.001$). Post-procedure complications were detected in 6.7% of the ERC-group (4/59; all were mild post-ERC pancreatitis), and none was reported in the EUS-FNA group including tumor seeding ($P = 0.10$).

Discussion

To augment any therapeutic strategy with pathologic evidence is thought to be of both ethical and medical importance. This argument is relevant to GBC when present as a mass lesion, with or without obstructive manifestations, as it si important to tailor the appropriate chemotherapy and equally to avoid using chemotherapy in a benign setting. It

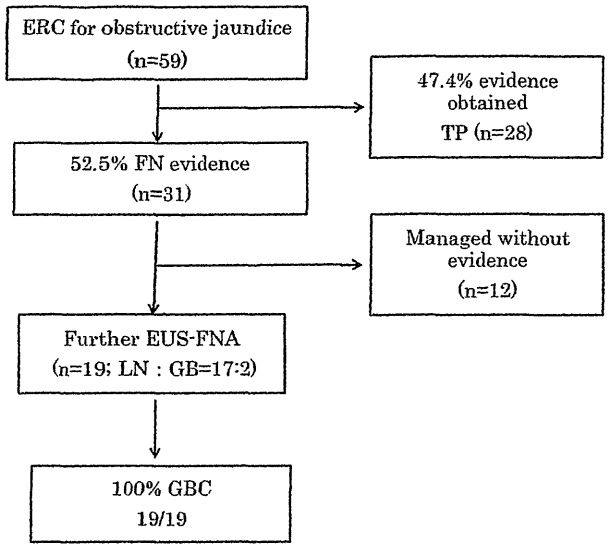


Fig. 5 Schematic diagram of EUS-FNA after ERC. ERC failed to reveal evidence of malignancy in 52.5% of the 59 cases ($n = 31$) and was considered as FN yield. Of these, 19 cases were subjected to EUS-FNA with 100% positive yield for malignancy. *ERC* endoscopic retrograde cholangiography, *EUS-FNA* endoscopic ultrasound-guided fine-needle aspiration, *GB* gallbladder, *GBC* gallbladder carcinoma, *LN* lymph node, *FN* false negative, *TP* true positive

Table 1 Comparison of EUS-FNA with ERC

	ERC-group ($n = 59$)	EUS-FNA group ($n = 50$)	*P* value*
Sensitivity	47.4% (28/59)	96% (48/50)	<0.001
Complication rate	6.7% (4/59)	0% (0/49)	0.1097

EUS-FNA Endoscopic ultrasound-guided fine-needle aspiration, *ERC* endoscopic retrograde cholangiography

* Using Fisher exact test

has been noted that a diffuse thickening of the GB wall is a common manifestation of GBC, and that this might be mimicked by benign GB lesions, such as xanthogranulomatous cholesterosis (XGC) [18–20] which further entails cytological evidence. We have previously described the nuances and yield of EUS-FNA sampling in distinguishing GBC from benign entities such as XGC [14]. Indeed, and surprisingly, two of our FNA pathological diagnoses were small cell carcinoma; this enabled us to assign the appropriate chemotherapy regimen for extra-pulmonary small cell carcinoma[21] [22]. If biliary obstruction with a suspected GB mass is the main presentation, ERC is the usual logical next step for both obtaining a pathological diagnosis and resolving the obstruction by biliary stenting. However, the reported yield of ERC-guided sampling with this technique was suboptimal, and other methods for obtaining a pathological diagnosis may be required in some cases [1, 3, 7, 9]. Among our GBC patients, biliary obstruction was evident in 59 (71.0%), and evidence of malignancy was obtained in 47.4% of them using ERC-based sampling approaches. Others have reported sensitivities of ERC-based sampling ranging from 44 to 82%, in strictures caused by cholangiocarcinoma [1–4]. The yield of ERC is believed to be lower in cases of GBC due to its extra-ductal nature; yield can be improved up to 82% by using add-on sampling methods, such as brushing and endo-biliary forceps biopsies, compared with ERCP cytology alone [3, 9]. However, these add-on manoeuvres were not accompanied by any increase in sensitivity in our GBC patients, possibly explained in some cases by its extra-ductal nature with compressive narrowing of bile duct.

One report has described endoscopic trans-papillary gallbladder drainage, in which a drainage tube is inserted into the GB using a catheter and guidewire [23]. Although an innovative technique with relatively high reported sensitivity and success rates of 81 and 83%, respectively, it needs expert operators, and might not be technically feasible for all patients with GBC. The advent of EUS and EUS-FNA has overcome the obstacles to ERC, namely, technical failure, low yield, and lack of indication such as the absence of obstruction. To date, four published reports have described EUS-FNA in patients with GBC [11–14], including sampling from the GB mass itself. As retrospectively recruited, and according to our local institutional protocols in the setting of unresectable GBC cases, the importance of initially puncturing regional LNs, when feasible, has been emphasized for many reasons. First, most advanced unresectable GBC have regional LNs; 79.6% in our study. Second, there is a potential risk of spillage and biliary peritonitis on puncturing cystic structures like GB. Third, the fear of track seeding. In the current study, we report a sensitivity rate of 94.8% when targeting a regional LN, and a diagnostic sensitivity rate of 96% when targeting the GB mass itself. On comparing the sensitivity rates of both ERC-sampling and EUS-FNA sampling, the latter was notably higher (47.4 vs 96%, $P < 0.001$). Despite the retrospective nature of the comparison and the group heterogeneity, we attempted to define the potential value of EUS-FNA especially in settings where ERC is not a valid indicator. Moreover, EUS-FNA is relatively less invasive with direct visualization of the target. We have reported 100% sensitivity of EUS-FNA for proving malignancy, and thus we recommend its application for obtaining pathological confirmation of GBC, with or without biliary obstruction. The main shortcomings of the present study include its retrospective nature, the potential for bias in selecting patients, the heterogeneity of study groups and hence the lack of standardization. We consider our findings to be preliminary,

and to the best of our knowledge, this is the only published study that has compared ERC with EUS-FNA sampling in the setting of GB masses presenting with obstructive jaundice. Nevertheless, we recommend a randomized trial to compare ERC and EUS-FNA sampling in appropriately matched groups to address the real capabilities of both modalities, in addition to testing the applicability of ultrasound-guided versus EUS-guided sampling tools. Until then, and based on the present findings, we can construct a short algorithmic approach for the diagnosis of GB mass lesions: in the presence of overt biliary obstruction, ERC should be tried first to alleviate the obstruction and to provide evidence of malignancy. If this fails, or if there is no obstruction, EUS-FNA sampling from regional LN and/or the GB mass itself should be performed as appropriate.

References

1. Harewood G, Baron T, Stadheim L, Kipp B, Sebo T, Salomao D. Prospective, blinded assessment of factors influencing the accuracy of biliary cytology interpretation. Am J Gastroenterol. 2004;99(8):1464–9.
2. Fogel EL, Debellis M, McHenry L, Watkins JL, Chappo J, Cramer H, et al. Effectiveness of a new long cytology brush in the evaluation of malignant biliary obstruction: a prospective study. Gastrointest Endosc. 2006;63(1):71–7.
3. de Bellis M, Sherman S, Fogel EL, Cramer H, Chappo J, McHenry L Jr, et al. Tissue sampling at ERCP in suspected malignant biliary strictures (Part 2). Gastrointest Endosc. 2002;56(5):720–30.
4. Rösch T, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, et al. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. Gastrointest Endosc. 2004;60(3):390–6.
5. Eloubeidi MA, Chen VK, Eltoum IA, Jhala D, Chhieng DC, Jhala N, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. Am J Gastroenterol. 2003;98(12):2663–8.
6. Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol. 2004;99(5):844–50.
7. Oppong K, Raine D, Nayar M, Wadehra V, Ramakrishnan S, Charnley RM. EUS-FNA versus biliary brushings and assessment of simultaneous performance in jaundiced patients with suspected malignant obstruction. JOP J Pancreas (Online). 2010;11(6):560–7.
8. Fritscher-Ravens A, Broering D, Knoefel W, Rogiers X, Swain P, Thonke F, et al. EUS-guided fine-needle aspiration of suspected hilar cholangiocarcinoma in potentially operable patients with negative brush cytology. Am J Gastroenterol. 2004;99(1):45–51.
9. DeWitt J, Misra V, LeBlanc J, McHenry L, Sherman S. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. Gastrointest Endosc. 2006;64(3):325–33.
10. Lee J, Salem R, Aslanian H, Chacho M, Topazian M. Endoscopic ultrasound and fine-needle aspiration of unexplained bile duct strictures. Am J Gastroenterol. 2004;99(6):1069–73.
11. Jacobson B, Pitman M, Brugge W. EUS-guided FNA for the diagnosis of gallbladder masses. Gastrointest Endosc. 2003;57:251–4.
12. Meara R, Jhala D, Eloubeidi M, Eltoum I, Chhieng D, Crowe D, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. Cytopathology. 2006;17:42–9.
13. Varadarajulu S, Eloubeidi M. Endoscopic ultrasound-guided fine-needle aspiration in the evaluation of gallbladder masses. Endoscopy. 2005;37:751–4.
14. Hijioka S, Mekky MA, Bhatia V, Sawaki A, Mizuno N, Hara K. Can EUS-guided FNA distinguish between gallbladder cancer and xanthogranulomatous cholecystitis? Gastrointest Endosc. 2010;72:622–7.
15. Baron TH, Lee JG, Wax TD, Schmitt CM, Cotton PB, Leung JWC. An in vitro, randomized, prospective study to maximize cellular yield during bile duct brush cytology. Gastrointest Endosc. 1994;40(2):146–9.
16. Yamao K, Sawaki A, Mizuno N, Shimizu Y, Yatabe Y, Koshikawa T. Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB): past, present, and future. J Gastroenterol. 2005;40:1013–23.
17. Yamao K, Mizuno N, Takagi T, Hara K. How I do it and when I use (and do not use) EUS-FNA. Gastrointest Endosc. 2009;69:134–7.
18. Uchiyama K, Ozawa S, Ueno M, Hayami S, Hirono S, Ina S, et al. Xanthogranulomatous cholecystitis: the use of preoperative CT findings to differentiate it from gallbladder carcinoma. J Hepatobiliary Pancreat Surg. 2009;16:333–8.
19. Spinelli A, Schumacher G, Pascher A, Hanninen E, Abadi H, Benckert C, et al. Extended surgical resection for xanthogranulomatous cholecystitis mimicking advanced gallbladder carcinoma: a case report and review of literature. World J Gastroenterol. 2006;12:2293–6.
20. Enomoto T, Todoroki T, Koike N, Kawamoto T, Matsumoto H. Xanthogranulomatous cholecystitis mimicking stage IV gallbladder cancer. Hepatogastroenterology. 2003;50:1255–8.
21. Maitra A, Tascilar M, Hruban RH, Offerhaus GJ, Albores-Saavedra J. Small cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. Am J Surg Pathol. 2001;25(5):595.
22. Clark O, Benson A 3rd, Berlin J, Choti M, Doherty G, Engstrom P, et al. NCCN clinical practice guidelines in oncology: neuroendocrine tumors. J Natl Compr Cancer Netw. 2009;7(7):712.
23. Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Moriyasu F, et al. Preoperative diagnosis and management of thick-walled gallbladder based on bile cytology obtained by endoscopic transpapillary gallbladder drainage tube. Gastrointest Endosc. 2006;64(4):512–9.

日消誌　2012；109：1895—1901

今月のテーマ　肝内胆管癌診療のトピックス

肝内胆管癌に対する化学療法の進歩

井岡達也　片山和宏[1)]

要旨：肝内胆管癌の非切除治療は，胆道癌の一部として治療開発されてきたが，いまだに十分な成績ではない．また，外科切除後の再発も多く，抗がん剤化学療法の寄与すべき部分も多い．英国からの報告により，ゲムシタビンとシスプラチンの併用療法が切除不能胆道癌の標準治療となったが，胆道癌の術後補助療法については定まった見解がない．また，全身化学療法に比較し，肝動注療法などの肝内胆管癌独自の治療についてのエビデンスは絶対的に不足している．今後は，多施設共同研究によって，より多くの症例をスピーディーに集積できる体制を一刻も早く整え，肝内胆管癌のみを対象にした臨床試験が実施できることを期待したい．

索引用語：肝内胆管癌，胆道癌，化学療法，ゲムシタビン，シスプラチン

はじめに

肝臓から分泌された胆汁が，十二指腸に排泄される経路を胆道と呼び，肝内胆管，肝外胆管，胆嚢，十二指腸乳頭部を含み，これらの臓器から発生する癌を胆道癌と総称した．肝内胆管癌は胆道癌の一部であるが，本邦では術式などの関係で，「胆道癌取扱い規約」ではなく，「原発性肝癌取扱い規約」により扱われてきた．

肝内胆管癌も，他の胆道癌と同様に外科的切除のみが根治を期待できる治療方法であるが，肝内胆管癌の30～40％が診断時に既に切除不能な進行癌として発見される[1)]．また，胆道癌は，根治切除後でもその50～80％が再発する癌であり[2)～4)]，抗がん剤化学療法を中心とする非切除治療の寄与する部分も多い．

I　分類と臨床病理

肝内胆管癌は，その肉癌分類から，腫瘤形成型mass forming type，胆管浸潤型periductal infiltrating type，胆管内発育型intraductal growth typeに分類される[5)]．腫瘤形成型は，肝実質に明瞭な類円形の限局性腫瘤を形成しているもので，癌部と非癌部の境界は明瞭である．胆管浸潤型は，胆管周囲の血管や結合組織を巻き込みつつ，胆管の長軸方向へ樹枝状進展を示しているもので，しばしば末梢胆管の拡張が認められる．胆管内発育型は，胆管内腔へ乳頭状または顆粒状の発育を示すが，時に表層拡大進展をしたり，胆管内腫瘍栓の形態を示すことがある．

肝内胆管癌の病期分類には，UICC分類（第6版）と日本の「原発性肝癌取扱い規約（第5版）」がある．本邦の臨床試験では，どちらの分類も良く用いられており，どちらの分類を用いた検討かを常に確認する必要がある．

肝原発の上皮性悪性腫瘍のほとんど（94％）が

1）大阪府立成人病センター検診部消化器検診科

The progress of chemotherapy for intrahepatic cholangiocarcinoma

Tatsuya IOKA and Kazuhiro KATAYAMA[1)]

1) Department of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases

Corresponding author：井岡　達也（ioka-ta@mc.pref.osaka.jp）

Table 1. 胆道癌を対象とした抗がん剤単剤療法の臨床試験

薬剤	患者数	奏功割合	OS*（カ月）	報告年	報告者
Gemcitabine	23	26%	13.1	2005	Park[7]
Gemcitabine	40	18%	7.6	2006	Okusaka[8]
Gemcitabine	24	13%	7.2	2003	Lin[9]
UFT	19	5%	8.8	2005	Ikeda[10]
S-1	19	21%	8.3	2004	Ueno[11]
S-1	40	35%	9.4	2008	Furuse[12]
Capecitabine	26	19%	8.1/9.9	2004	Patt[13]
Erlotinib	42	8%	7.5	2006	Philip[14]
Lapatinib	17	0%	5.2	2006	Ramanathan[15]
Mitomycin C	34	10%	4.5	1993	Taal[16]
Cisplatin	13	8%	5.5	1994	Okada[17]
Irinotecan	25	8%	10	2001	Sanz-Altamira[18]
Paclitaxel	15	0%	NA*	1996	Jones[19]
Docetaxel	25	20%	8	2001	Papakostas[20]

*OS；Overall survival time, NA；No applicable.

肝細胞癌で，4% のみが肝内胆管癌に分類される．そして，肝内胆管癌は腺癌と特殊型に細分される．なお，肝細胞癌と胆管細胞癌の混在する混合型肝癌は 0.7% を占める．

II 切除不能の定義

切除不能の定義として，①転移因子，②脈管浸潤因子，③胆管内進展因子が挙げられる．遠隔転移因子と肝両葉の肝内転移については，切除不能として意義のないところであろうが，脈管浸潤因子や胆管内進展因子については，各施設で切除基準が大きく異なる場合がある．

①転移因子には，a）肝内転移以外の遠隔転移を認める場合，b）傍大動脈リンパ節転移を認める場合，c）肝十二指腸間膜や膵頭部周囲リンパ節に塊状転移（bulky metastasis）を認める場合，d）肝の両葉に多発性腫瘍を認める場合がある．

②脈管浸潤因子には，a）固有肝動脈，総肝動脈，腹腔動脈，上腸間膜動脈のいずれかに浸潤を認める場合，b）左右両側の肝動脈枝に浸潤を認める場合，c）門脈本幹への強い浸潤や閉塞，あるいは左右両側の門脈枝に浸潤を認める場合がある．

③胆管内進展因子として，a）肝の片葉の脈管（門脈もしくは動脈）への浸潤もしくは肝の片葉の萎縮を認め，かつその反対側への胆管内進展を2次分枝レベルまで認める場合，b）両側の胆管の2次分枝レベルまで胆管内進展を認める場合がある．

III 切除不能または再発胆道癌に対する抗がん剤化学療法

胆道癌に対する抗がん剤化学療法の治療開発は，他癌と比較して非常に遅れていたが，生物学的に類似する膵癌の治療開発が進むにつれて，最近になって新規抗がん剤のラインナップが揃ってきた（Table 1，2）[6)~25)]．

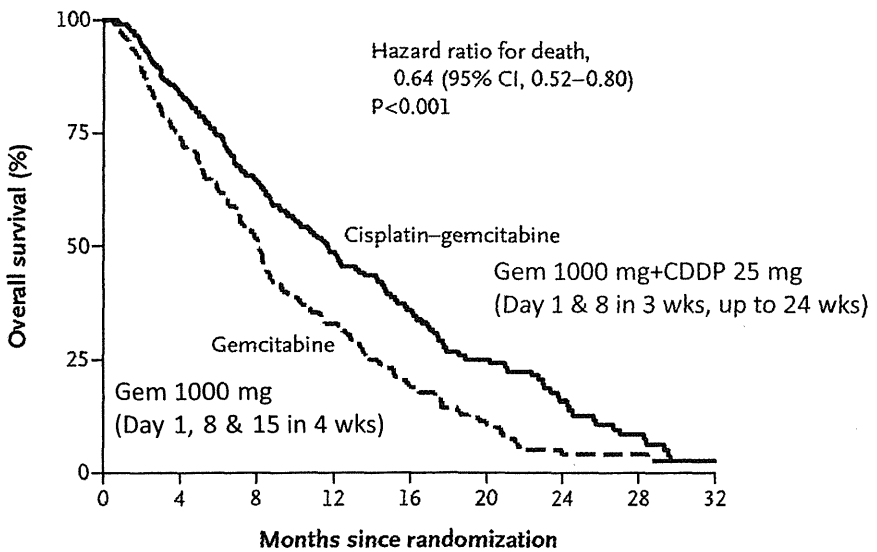
1. 効果予測因子

Yonemoto ら[26]は，2000年4月から2003年3月までに非切除治療を行った304例の胆道癌を対象に多変量解析を行い，125例の BSC（best supportive care）を受けた患者と比較し，ゲムシタビン（Gem）による治療を受けた患者（hazard ratio（HR）0.53：95% CI 0.34～0.82）や，シスプラチンを含む化学療法を受けた患者（HR 0.49：95% CI 0.36～0.99）の予後が良好であることについて報告した．この検討では，肝内胆管癌は31%を占めていた．Ikezawa ら[27]は，2006年から2009年までに非切除治療を行った403例の胆道癌を対象にした多変量解析を行い，術後再発例に比して切除不能例の予後が不良であることなど，4つの予後不良因子について報告した．この検討では，

Table 2. 胆道癌を対象とした抗がん剤化学療法のランダム化比較試験

Regimen	患者数	奏功率	OS(カ月)	P-value	報告年	報告者
5FU	18	0%	NA	Not significant	1994	Takada[21]
5FU+ADR+MMC	18	0%	NA			
5FU+LV+Etoposide	18	NA	6.5	0.1	1996	Glimelius[22]
BSC	19	NA	2.5			
5FU+LV+MMC	20	25%	9.5	NA	1999	Raderer[23]
GEM	19	16%	6.5			
GEM+MMC	25	20%	6.7	NA	2004	Kornek[24]
Capecitabine+MMC	26	31%	9.3			
5FU	29	7%	5.0	NA	2005	Ducreux[25]
5FU+CDDP+LV	29	19%	8.0			
GEM+CDDP	204	26.1%	11.7	P<0.001	2010	Valle[6]
GEM	207	15.5%	8.4			

GEM：Gemcitabine, CDDP：Cisplatin, ADR：Doxorubicin, MMC：Mitomycin C, LV：Leucovorin.



No. at risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

Figure 1. 全生存期間（ABC-02 試験）.

術後再発例192例中38例（19.8%）および切除不能例211例中50例（23.7%）が，肝内胆管癌であった.

2. Gem+シスプラチン療法（GC 療法）

本邦と比較して，決して胆道癌の疾患頻度の多くない英国において，胆道癌の標準治療を生み出す臨床試験（ABC-02 試験）が実施された[6]. ABC-02 試験における生存期間中央値（median survival time；MST）について，胆道癌全体では，Gem 単独療法8.1カ月に対して GC 療法11.7カ月であり，統計学的有意に優れていた（HR 0.64：95% CI 0.52～0.80；P<0.001）（Figure 1）. また，GC 療法の無増悪生存期間中央値（progression free survival time；PFS）は8.0カ月であり，Gem 単独療法の5.0カ月より統計学的有意に優れていた（HR 0.63：95% CI 0.51～0.77；P<0.001）. 抗腫瘍効果は，GC 療法26.1%に対し Gem 単独療法15.5%で，GC 療法が優れており，また，RECIST

Table 3. グレード3/4の血液毒性

Variable	Gemcitabine (N=199)	Cisplatin plus gemcitabine (N=198)	P-value
	Number (percent)		
Hematologic toxic effects			
Decreased white-cell count	19 (9.5)	31 (15.7)	0.07
Decreased platelet count	13 (6.5)	17 (8.6)	0.44
Decreased hemoglobin level	6 (3.0)	15 (7.6)	0.04
Decreased neutrophil count	33 (16.6)	50 (25.3)	0.03
Any hematologic toxic effect	47 (23.6)	64 (32.3)	0.05
Liver function			
Increased alanine aminotransferase level	34 (17.1)	19 (9.6)	0.03
Other abnormal liver function	39 (19.6)	26 (13.1)	0.08
Any abnormal liver function	54 (27.1)	33 (16.7)	0.01

Table 4. グレード3/4の非血液毒性

Nonhematologic toxic effects	Gemcitabine (N=199)	Cisplatin plus gemcitabine (N=198)	P-value
	Number (percent)		
Alopecia	0	2 (1.0)	0.16
Anorexia	5 (2.5)	6 (3.0)	0.75
Fatigue	33 (16.6)	37 (18.7)	0.58
Nausea	7 (3.5)	8 (4.0)	0.78
Vomiting	11 (5.5)	10 (5.1)	0.65
Impaired renal function	2 (1.0)	3 (1.5)	0.83
Infection			
Without neutropenia	23 (11.6)	12 (6.1)	0.05
With neutropenia	14 (7.0)	20 (10.1)	0.28
Biliary sepsis	8 (4.0)	8 (4.0)	0.99
Any type	38 (19.1)	36 (18.2)	0.82
Deep-vein thrombosis	1 (0.5)	4 (2.0)	0.18
Thromboembolic event	3 (1.5)	7 (3.5)	0.20

評価にて stable disease (SD) 以上) については, GC 療法 81.4% に対し Gem 単独療法 71.8% で, 統計学的に有意差を証明した (P=0.049). 肝内胆管癌を含めた胆管癌と十二指腸乳頭部癌についてのサブ解析では, 腫瘍制御率について GC 療法 79.0% に対し Gem 単独療法 68.6% で, 統計学的有意差を証明できなかった.

本試験の中で肝内胆管癌が占める割合について記載はないが, 肝内胆管癌と肝外胆管癌を合わせた胆管癌については記載がある. GC 療法を受けた 204 例中 122 例 (59.8%) および Gem 単独療法を受けた 206 例中 119 例 (57.8%) が胆管癌であった.

CTCAE (Common Terminology Criteria for Adverse Events) によるグレード3または4以上の重篤な有害事象について着目すると (Table 3, 4), GC 療法では, 好中球減少 (25.3%), 疲労 (18.7%), 白血球減少 (15.7%), 好中球減少をともなう感染 (10.1%), 肝機能異常 (9.6%) などが認められ, Gem 単独療法では, 肝機能異常 (17.1%), 好中球減少 (16.6%), 疲労 (16.6%), 白血球減少 (9.5%), 好中球減少をともなう感染 (7.0%) などが認められた. 以上から, 標準療法のなかった胆道癌に, GC 療法という世界標準の

治療法が誕生した.

なお，シスプラチンの蓄積毒性から，ABC-02試験では，GC療法を6カ月間投与した後は，Gem単独療法などに変更するように規定されていた.

ABC-02試験を受けて，本邦でもGC療法（41例）とGem単独療法（42例）を比較したBT-22試験が実施された[28]．本試験の中で肝内胆管癌が占める割合は83例中28例（33.7%）で，本試験におけるMSTは，胆道癌全体において，GC療法11.2カ月に対しGem単独療法では7.7カ月であり，本邦でもABC-02試験の結果と同様の傾向が確認できた．BT-22試験では，胆嚢癌以外の肝内胆管癌・肝外胆管癌・十二指腸乳頭部癌のMSTを算出しており，GC療法13.0カ月で，Gem単独療法8.0カ月であったと報告している．次に，PFSについては，GC療法5.8カ月に対しGem単独療法3.7カ月で，抗腫瘍効果は，GC療法19.5%に対しGem単独療法11.9%で，GC療法の方が優れていた．グレード3または4以上の重篤な有害事象について，GC療法では，好中球減少(56.1%)，血小板減少(39.0%)，貧血(36.6%)，白血球減少（29.3%），肝機能異常（17.1～24.4%）と，ABC-02試験の報告と比較して，血液毒性や肝機能障害が多く認められたが，疲労や好中球減少をともなう感染は認めなかった．一方，Gem単独療法では，肝機能異常（17.1%），好中球減少(38.1%)，白血球減少(19.0%)，貧血(16.6%)，血小板減少（7.2%），肝機能障害（16.7%），疲労(2.4%）であった．有害事象の発症頻度については，ABC-02試験とBT-22試験の間に相違が認められたが，いずれも許容範囲であった.

3. Gem＋S-1療法（GS療法）

S-1は本邦で開発された経口フッ化ピリミジン製剤で，多くの癌に臨床応用されている．GS療法は，胆道癌のみならず，膵癌でもその効果が期待され，Gem単独療法との第III相試験が実施されたが，膵癌ではGS療法の有意な生存利得が証明されなかった[29]．

JCOG（日本臨床腫瘍研究グループ）により，GS療法とS-1単独療法の1年生存率を比較するランダム化比較第II相試験が実施され，Ikedaらによって報告された[30]．101例の切除不能または再発胆道癌が，GS療法（51例）とS-1単独療法（50例）に割り付けられた．主評価項目である1年生存率について，GS療法では52.9%に対しS-1単独療法は40.0%で，GS療法が優れていた．MSTについては，GS療法12.5カ月に対しS-1単独療法では9.0カ月であり，統計学的有意差を認めなかった（HR 0.86，95% CI：0.54～1.36）．一方，PFSについては，GS療法7.1カ月に対しS-1単独療法では4.2カ月であり，統計学的有意にGS療法が優れていた（HR 0.44，95% CI：0.29～0.67，P<0.0001）．グレード3または4以上の重篤な血液毒性について，S-1単独療法では，好中球減少（4.0%），血小板減少（4.0%），白血球減少（2.0%），貧血（2.0%）と軽微だったのに対し，GS療法では，好中球減少（60.8%），白血球減少（29.4%），血小板減少（11.8%），貧血（11.8%）と，重篤な血液毒性の頻度が多かった．また，GS療法を受けた患者に薬剤性間質性肺炎と心筋梗塞の治療との関連が否定できない死亡が2例認められた．なお，本試験に登録された101例中35例(34.7%)が，肝内胆管癌であった.

4. 肝内胆管癌に対する特殊な治療

Nakachiらは，進行した肝内胆管癌に対してシスプラチン肝動注化学療法の多施設共同第II相試験を行い，その結果を報告した[31]．2007年6月から2010年7月までに登録した35例中6例(17.1%，95% CI：6.6～33.7%)にpartial response（PR）を認め，15例のSD症例と合わせて60%の腫瘍制御率であったと報告した．一方，グレード3または4以上の重篤な有害事象は，好中球減少（5.7%），血小板減少（11.4%），肝機能障害(20.0～28.6%)，食欲不振（5.7%）および疲労(8.6%）で，これらは一過性かつ許容範囲であると報告した．本試験でも，15例（42.9%）が何らかの前治療を受けており，標準的治療が効果不十分であった肝内胆管癌に対して，一定の効果が期待できると考えられた.

5. 切除不能または再発肝内胆管癌に対するその他の化学療法

臨床試験のデータベース（UMINまたは

ClinicalTrials.gov）を検索すると，さまざまな治療が行われている．本邦では，イリノテカン＋S-1併用療法（UMIN000007573），S-1とシスプラチンを併用した化学放射線療法の第I/II相試験（UMIN000007473），Gemにペプチドワクチンを併用した治療（UMIN000002500）の他，Gem，シスプラチンにS-1を加えた3剤併用化学療法の第I/II相試験が企画実施されており（NCT01284413），これらの試験にも肝内胆管癌が含まれていることが予想され，その結果について期待したい．

IV 肝内胆管癌術後の補助化学療法

胆道癌術後の補助療法の多くが，胆嚢癌または肝外胆管癌についての検討で，肝内胆管癌についての検討は少ない．Nakeebら[32]は，肝内胆管癌と肝外胆管癌を合わせた患者の術後補助療法について報告しているが，この研究でも肝内胆管癌の占める割合は10%未満であり，十分なデータではなかった．

臨床試験のデータベース（UMINまたはClinicalTrials.gov）を検索すると，米国National Cancer Instituteにより肝内胆管癌を含めた胆道癌術後の術後補助療法として，Gemとオキサリプラチンを併用した化学療法と手術単独を比較した第III相試験が企画実施中である（NCT01313377）．また，関西を中心にした日本のグループが，肝葉切除をともなう胆道癌術後の術後補助療法の第I相試験を企画実施しており，この試験を占める疾患には肝内胆管癌が多く含まれると予想される（NCT01291615）．また，東京大学にてGemと免疫細胞（活性化自己γδT細胞）治療を組み合わせた術後補助療法の単アーム試験も企画実施されている（UMIN000001417）．

V 今後の展望

欧米に比較すれば，本邦における肝内胆管癌または胆道癌の罹患数は決して少なくないが，十分な臨床試験が実施されているかといえば，多くの試験が小規模で，新しい標準治療を輩出するだけのパワーがないのが現実である．そこで，多くの医師に，胆道癌の臨床試験について興味を持っていただき，胆道癌全体で臨床試験を計画するのではなく，胆道癌の中でも外科術式や特性が違う肝内胆管癌などを個別にした臨床試験が計画できるようにしていきたい．

本論文内容に関連する著者の利益相反
：井岡達也（株式会社ヤクルト本社）

文 献

1) 日本肝癌研究会：第18回全国原発性肝癌追跡調査報告，2010
2) Jarnagin WR, Fong Y, DeMatteo RP, et al : Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234 ; 507–517 : 2001
3) Jarnagin WR, Ruo L, Little SA, et al : Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma : implication for adjuvant therapeutic strategies. Cancer 98 ; 1689–1700 : 2003
4) Weber SM, Jarnagin WR, Klimstra D, et al : Intrahepatic cholangiocarcinoma : resectability, recurrence pattern, and outcomes. J Am Coll Surg 193 ; 384–391 : 2001
5) 日本肝癌研究会：原発性肝癌取扱い規約，第5版補訂版，金原出版，東京，2009
6) Valle J, Wasan H, Palmer DH, et al : Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362 ; 1273–1281 : 2010
7) Park JS, Oh SY, Kim SH, et al : Single-agent gemcitabine in the treatment of advanced biliary tract cancers : a phase II study. Jpn J Clin Oncol 35 ; 68–73 : 2005
8) Okusaka T, Ishii H, Funakoshi A, et al : Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemother Pharmacol 57 ; 647–653 : 2006
9) Lin MH, Chen JS, Chen HH, et al : A phase II trial of gemcitabine in the treatment of advanced bile duct and periampullary carcinomas. Chemotherapy 49 ; 154–158 : 2003
10) Ikeda M, Okusaka T, Ueno H, et al : A phase II trial of Uracil-tegafur (UFT) in patients with advanced biliary tract carcinoma. Jpn J Clin Oncol 35 ; 439–443 : 2005
11) Ueno H, Okusaka T, Ikeda M, et al : Phase II study of S-1 in patients with advanced biliary tract cancer. Br J Cancer 91 ; 1769–1774 : 2004
12) Furuse J, Okusaka T, Boku N, et al : S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer : a multicenter

phase II study. Cancer Chemother Pharmacol 62 ; 849–855 : 2008
13) Patt YZ, Hassan MM, Aguayo A, et al : Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 101 ; 578–586 : 2004
14) Philip PA, Mahoney MR, Allmer C, et al : Phase II study of erlotinib in patients with advanced biliary cancer. J Clin Oncol 24 ; 3069–3074 : 2006
15) Ramanathan RK, Belani CP, Singh DA, et al : Phase II study of lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase 1 and 2 (Her2/Neu) in patients (pts) with advanced biliary tree cancer (BTC) or hepatocellular cancer (HCC). A California Consortium (CCC-P) Trial. ASCO Annual Meeting Proceedings ; Part I. Vol. 24 (No. 18S, June 20 Supplement), 4010 : 2006
16) Taal BG, Audisio RA, Bleiberg H, et al : Phase II trial of mitomycin C (MMC) in advanced gallbladder and biliary tree carcinoma. An EORTC Gastrointestinal Tract Cancer Cooperative Group Study. Ann Oncol 4 ; 607–609 : 1993
17) Okada S, Ishii H, Nose H, et al : A phase II study of cisplatin in patients with biliary tract carcinoma. Oncology 51 ; 515–517 ; 1994
18) Sanz-Altamira PM, O'Reilly E, Stuart KE, et al : A phase II trial of irinotecan (CPT-11) for unresectable biliary tree carcinoma. Ann Oncol 12 ; 501–504 : 2001
19) Jones DV Jr, Lozano R, Hoque A, et al : Phase II study of paclitaxel therapy for unresectable biliary tree carcinomas. J Clin Oncol 14 ; 2306–2310 : 1996
20) Papakostas P, Kouroussis C, Androulakis N, et al : First-line chemotherapy with docetaxel for unresectable or metastatic carcinoma of the biliary tract. A multicentre phase II study. Eur J Cancer 37 ; 1833–1838 : 2001
21) Takada T, Kato H, Matsushiro T, et al : Comparison of 5-fluorouracil, doxorubicin and mitomycin C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinomas. Oncology 51 ; 396–400 : 1994
22) Glimelius B, Hoffman K, Sjödén PO, et al : Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 7 ; 593–600 : 1996
23) Raderer M, Hejna MH, Valencak JB, et al : Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. Oncology 56 ; 177–180 : 1999
24) Kornek GV, Schuell B, Laengle F, et al : Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer : a randomised phase II trial. Ann Oncol 15 ; 478–483 : 2004
25) Ducreux M, Van Cutsem E, Van Laethem JL, et al : A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma : results of the 40955 EORTC trial. Eur J Cancer 41 ; 398–403 : 2005
26) Yonemoto N, Furuse J, Okusaka T, et al : A multicenter retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. Jpn J Clin Oncol 37 ; 843–851 : 2007
27) Ikezawa K, Ioka T, Kanai M, et al : Retrospective analysis of the difference of prognosis between unresectable and recurrent biliary tract cancer (KHBO 1001). JSMO, Abstract # MIS5-5 : 2012
28) Okusaka T, Nakachi K, Fukutomi A, et al : Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer : a comparative multicentre study in Japan. Br J Cancer 103 ; 469–474 : 2010
29) Ioka T, Ikeda M, Ohkawa S, et al : Randomized phase III study of gemcitabine plus S-1 (GS) versus S-1 versus gemcitabine (Gem) in unresectable advanced pancreatic cancer in Japan and Taiwan : GEST study. ASCO, Abstract # 4007 : 2011
30) Ikeda M, Okusaka T, Mizunuma J, et al : Randomised phase II trial of gemcitabine plus S-1 combination therapy versus S-1 in advanced biliary tract cancer : Results of the Japan Clinical Oncology Group study (JCOG0805). JSMO, Abstract # IS1-1 : 2012
31) Nakachi K, Okusaka T, Iguchi H, et al : A multicenter phase II study of intra-arterial chemotherapy of a fine-powder formulation of cisplatin in patients with advanced intrahepatic cholangiocarcinoma. JSMO, Abstract # 02-055 : 2012
32) Nakeeb A, Pitt HA, Sohn TA, et al : Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 224 ; 463–473 ; discussion 473–475 : 1996

〔論文受領，2012年 9 月 20 日
受理，2012年 10 月 1 日〕