板野：CoCCかどうかということについてはEMAをみないとわからないということですか。
尾島：組織像からいうと，動脈性腫瘍血管の存在もあまり確認できませんので，これは外しておいたほうがよいと思います。
板野：染まる胆管癌ということですね。
尾島：そうです。

講　評

乳癌術後の非慢性障害肝に発見された比較的境界明瞭で腫瘍濃染像を呈する径30 mm超肝腫瘍の症例である。術前の画像所見では腫瘍内部にモザイクパターンは認められないものの，造影早期相で腫瘍全体が濃染し後期相でwash outされていることから，HCCもしくは混合型肝癌を主診断とした著者らの考え方は妥当である。しかし，切除標本の病理所見には肝細胞由来の成分は含まれておらず，線維性間質や粘液産生の乏しい細胞成分が多くを占める乳頭状腺癌であった。以前の乳癌とはERの染色性が異なりCK-19が陽性であることから，非典型的なICCと診断された。胆管癌がHCCと類似の濃染パターンを呈した理由は病理コメントを参考にすると，乳頭状腺癌自体に血管間質が豊富なため早期濃染となり，線維性成分が乏しいため遅延濃染を呈さずにwash outが生じたと考えられる。本症例は腺癌であっても，組織の状態によってはHCC類似の濃染パターンを呈する事実を示した貴重な症例である。

もう一つの問題点は，この腫瘍が濃染する胆管系腫瘍として認知されはじめた細胆管細胞癌(CoCC)ではないかという点であるが，本症例は線維性間質が乏しく動脈性腫瘍血管も認められないためCoCCは否定的との病理コメントであった。ただし本症例では，CoCCの有力診断の一つとして中野雅行先生が提唱されているEMA染色がなされていないため，その点については再検査を希望したい。

（板野　哲）

この論文は第40回肝癌症例検討会(2009年11月28日)で発表された

THOMSON REUTERS

Current Opinion in Investigational Drugs 2010 11(6):
© Thomson Reuters (Scientific) Ltd ISSN 2040-3429

REVIEW

Emerging treatment with systemic chemotherapy and targeted agents for biliary cancers

Narikazu Boku

Address
Shizuoka Cancer Center, Division of Gastrointestinal Oncology,
1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan
Email: n.boku@scchr.jp

Clinically, 5-fluorouracil (5-FU) and its derivatives, platinum-based agents, and gemcitabine (GEM) are used as key treatments for unresectable or recurrent biliary cancer. A phase III clinical trial has demonstrated that treatment with GEM plus CDDP prolongs the survival of patients with biliary cancer compared with treatment with GEM alone. Moreover, promising results are also being reported against molecular targets, particularly with inhibitors of EGFR. In addition, the development of novel drugs based on biological markers might be important for the treatment of biliary cancer. In the future, a paradigm shift from disease-specific drug development to biomarker-oriented investigations may be applicable for rare diseases such as biliary cancer.

Keywords Anticancer agent, biliary cancer, biological marker, molecular target, systemic chemotherapy

Introduction

The prognosis of patients with biliary cancer is extremely poor, because most patients are only diagnosed after they have developed unresectable, locally advanced or metastatic disease. Even following surgical resection of cancerous tissue, 50 to 75% of patients have local and/or distant recurrence of disease [1]. Furthermore, chemotherapy does not have curative potential for patients with recurrent and unresectable cancer. Most patients eventually die from liver failure or cholangitis, which proceeds to liver abscess and sepsis.

The development of effective systemic chemotherapies for biliary cancers has been slower and less successful than the development of such therapies for other forms of cancer. This lack of success is related to the many challenges associated with conducting clinical trials for recurrent and unresectable biliary cancer: (i) the rarity of the disease; (ii) the various anatomical sites at which primary tumors occur, such as the hilar, intrahepatic and extrahepatic bile ducts, gallbladder and the ampulla of Vater, each of which is associated with tumors with a different clinical course and prognosis; (iii) complications arising from obstructive jaundice, liver dysfunction and infection that require the discontinuation of chemotherapy; (iv) the need for complex multidisciplinary patient management; and (v) the difficulty in obtaining histological confirmation of clinical observations. The genetic and environmental factors relating to the etiology of biliary cancer have not been clarified fully, but the incidence of this form of cancer is low compared with other cancers in Western countries and is relatively higher in Asian and South American countries [2] (Table 1). Biliary cancers arising in the liver follow similar clinical courses to primary andmetastatic liver cancers; however, those arising in the hilar or extrahepatic bile duct often cause obstructive jaundice and cholangitis. Obstruction of the bile duct results in a rapid deterioration of the general condition of a patient. In addition, liver dysfunction increases the toxicity of chemotherapeutic agents, frequently necessitating the discontinuation of treatment. In the case of bile duct obstruction, interventional treatments, such as the endoscopic placement of a stent or percutaneous bile duct drainage, should be performed immediately. The many complicating factors in biliary cancer have resulted in the conduct of only a few small, randomized clinical trials of systemic chemotherapy for unresectable or recurrent forms of the disease. Only three drugs used for the treatment of other gastrointestinal cancers – 5-fluorouracil (5-FU), cisplatin (CDDP) and gemcitabine (GEM) – are generally applied for the treatment of unresectable or recurrent biliary cancer. However, new treatments have been emerging in recent years. This review discusses new approaches with systemic chemotherapy and targeted agents in the potential treatment of biliary cancer.

First-line chemotherapy for biliary cancer

Until recently, no evidence was available from clinical trials to establish a standard of care for unresectable or recurrent biliary cancer. In addition, some patients with this form of cancer do not receive chemotherapy because the management of bile-duct obstruction and/or cholangitis may be considered more important and effective than disease control using chemotherapy.

However, a retrospective multivariate analysis reported a hazard ratio of 0.55 (95% confidence interval [CI] 0.42 to 0.72; $p < 0.001$) for overall survival that favored systemic

Table 1. Incidence of biliary cancer by country.

Country	Number of patients with biliary cancer	Number of patients with any form of cancer	Biliary cancer as percentage of total cancers (%)
Japan	16,586	325,930	5.1
Germany	3725	211,446	1.8
USA	3453	560,249	0.6
Korea	3336	65,482	5.1
Mexico	1936	63,117	3.1
Poland	1843	90,407	2.0
Chile	1820	20,516	8.9
Spain	1293	96,870	1.3
Argentina	1282	56,244	2.3
France	1224	88,871	0.8

Data taken from the WHO database of 47 countries (2005) [2]. More recent statistics from the WHO include fewer reported countries (eg, statistics from 2006 include 26 countries, and omit some South American countries where the incidence of biliary cancer is high).

chemotherapy over the use of best supportive care (BSC), including in the management of bile duct obstruction and/or cholangitis [3]. According to this analysis, the median survival time of patients with biliary cancer treated with BSC was 2.5 to 4.1 months, compared with 7.4 months in those receiving chemotherapy. The use of chemotherapy with sequential 5-FU and leucovorin (5-FU/LV), with or without etoposide, had previously failed to demonstrate a statistically significant improvement in survival ($p = 0.1$) compared with BSC for patients with biliary cancer [4]. More recently, in a phase III clinical trial with three arms comparing 5-FU/LV, GEM plus oxaliplatin (GEMOX) and BSC for patients with unresectable gall bladder cancer, Dwary *et al* reported a longer survival period in the chemotherapy arms than in the BSC group (5.3, 9.3 and 4.5 months, respectively; $p = 0.039$) [5]. These results have led to a general recognition that systemic chemotherapy for unresectable or recurrent biliary cancer appears to have a survival benefit over BSC.

Therapy with cytotoxic agents

Response rates for therapy with cytotoxic agents for unresectable or recurrent biliary cancer range from 0 to 35% [6-19] (Table 2). The most frequently used cytotoxic agents in clinical practice have been 5-FU and its derivatives. However, because GEM has demonstrated a survival benefit over 5-FU in patients with pancreatic cancer, as well as clinical benefits and good feasibility [20], the use of GEM has been replacing the use of 5-FU for unresectable or recurrent biliary cancer worldwide, although a direct comparison between GEM and 5-FU has not been made. In a retrospective multivariate analysis of patients with unresectable biliary cancer, the hazard ratio for overall survival using GEM (0.50; 95% CI 0.35 to 0.72; $p = 0.0002$) compared with BSC was smaller than the hazard ratio for overall survival with 5-FU (0.65; 95% CI 0.41 to 1.01; $p = 0.058$) and other agents [3].

Except for GEM, few chemotherapies have been evaluated for the treatment of biliary cancer. S-1, an oral agent comprising the 5-FU prodrug tegafur, the dihydropyrimidine dehydrogenase inhibitor gimeracil and the orotate phosphoribosyl transferase inhibitor oteracil (oxonic acid) in a 5:2:5 ratio, demonstrated promising antitumor effects in a phase II clinical trial ($n = 40$) in Japan, resulting in a response rate of 35% [11]. In patients with gastric cancer, S-1 was more effective with regard to overall survival, response rate, quality of life than a continuous infusion of 5-FU in a phase III randomized trial conducted in Japan [21]. Furthermore, another oral fluoropyrimidine-based antineoplastic agent, capecitabine, which is more popular in Western countries than S-1, also resulted in improved survival compared with 5-FU when either of these drugs was used in combination with CDDP for the treatment of gastric cancer [22]. In a comparison with 5-FU in patients with colorectal cancer, capecitabine demonstrated non-inferior effects, and was associated with a favorable toxicity profile and convenience [23]. Considering the data accumulated from trials in patients with other forms of gastrointestinal cancer [21-23], oral fluoropyrimidines may also be expected to yield some clinical benefits over 5-FU in the treatment of patients with biliary cancer. Therefore, oral fluoropyrimidines might present a new treatment option for biliary cancers, replacing 5-FU, although no randomized trials comparing oral fluoropyrimidine-based therapies with 5-FU in patients with biliary cancer have been reported. To date, GEM and 5-FU derivatives remain the key cytotoxic drugs that are used as the standard against which new treatments are measured for biliary cancer.

Cytotoxic agents in combination with other cytotoxic agents or platinum-based chemotherapies

Phase II clinical trials

Several phase II clinical trials examining combinations of cytotoxic agents have been conducted for biliary

Table 2. Selected cytotoxic therapy for biliary cancer.

Therapy	n	Response rate (%)	Median survival time (months)	Reference
5-FU	18	0	-	[6]
UFT	19	5	8.2	[7]
5-FU + LV	30	7	14.8	[8]
5-FU + IFNα	35	34	12	[9]
UFT + LV	16	0	5.2	[10]
S-1	40	35	9.4	[11]
Mitomycin C	30	10	4.5	[12]
Cisplatin	13	8	5.5	[13]
Oxaliplatin	29	21	7	[14]
Paclitaxel	15	0	-	[15]
Docetaxel	25	20	8	[16]
Irinotecan	25	8	10	[17]
Exatecan	41	2	7	[18]
Gemcitabine	32	22	11.5	[19]

5-FU 5-Fluorouracil, **LV** leucovorin, **UFT** uracil-tegafur

Table 3. Selected phase II trials of combinations of cytotoxic agents and platinum-based chemotherapies for biliary cancer.

Regimen	n	Response rate (%)	Median survival time (months)	Reference
5-FU + ADM + MMC	17	31	-	[24]
5-FU + CDDP	25	24	10	[25]
5-FU/LV + MMC	20	25	9.5	[26]
5-FU/LV + CDDP	29	34	9.5	[27]
5-FU/LV + OHP	16	19	9.5	[28]
5-FU + EPI + CDDP	37	19	5.9	[29]
UFT/LV + EPI + CDDP	40	23	8.5	[30]
UFT + ADM	24	12.5	7.6	[331]
CAP + CDDP	42	21	9.1	[32]
CAP + MMC or GEM + MMC	25	31	9.25	[33]
CAP + EPI + CDDP	43	40	8	[34]
GEM + 5-FU/LV	22	36	11	[35]
GEM + DTX	43	9	11	[36]
GEM + CDDP	40	28	9	[37]
GEM + OHP	33	36	15.4	[38]
	24	50	12	[39]
	31	26	11	[40]
GEM + IR	14	14	-	[41]
GEM + CAP	45	31	14	[42]

5-FU 5-Fluorouracil, **ADM** doxorubicin, **CAP** capecitabine, **CDDP** cisplatin, **DTX** docetaxel, **EPI** epirubicin, **GEM** gemcitabine, **IR** irinotecan, **LV** leucovorin, **MMC** mitomycin C, **OHP** oxaliplatin, **UFT** uracil-tegafur

cancer (Table 3) [24-42]. The response rates in these clinical trials of combination chemotherapy ranged from 9 to 50%, with median survival times of 5.9 to 15.4 months. The substantial differences in reported survival times among these trials likely reflect differences in patient demographics. Given such variability, evaluating the activity of a particular chemotherapy regimen based on response rate and survival period in a single phase II trial appears to be inadequate. Therefore, additional randomized phase II trials are needed to explore the efficacy of new chemotherapy regimens.

Phase III clinical trials

To date, all of the phase III clinical trials conducted for biliary cancer have included small patient numbers (Table 4), and no standard treatment regimens have been established. A pooled analysis of clinical trials for biliary cancer demonstrated that GEM and platinum-containing regimens were associated with the highest response rates and tumor control rates among the combination chemotherapy regimens; GEM combined with platinum-based agents was concluded to represent the provisional standard of chemotherapy for biliary cancer [43].

A phase II, randomized clinical trial (ABC-01) conducted in the UK compared the progression-free survival of patients receiving either GEM or GEM plus CDDP [44]. The results indicated that GEM plus CDDP may be associated with an improved response rate and progression-free survival, but that it was unclear whether these effects would translate into a survival benefit. ABC-01 was followed by a phase III trial (ABC-02), which was the first phase III evaluation for the treatment of biliary cancer to include more than 200 patients in each arm [45]. Patients in the standard arm received GEM, consisting of a drip infusion (1000 mg/m^2) on days 1, 8 and 15 in a 4-week cycle. Patients in the test arm received GEM plus CDDP, with GEM (1000 mg/m^2) and CDDP (25 mg/m^2) being administered on days 1 and 8 in a 3-week cycle. Patients in the test arm (GEM plus CDDP) demonstrated a better response rate, including progression-free survival period (8.4 versus 6.5 months; p = 0.003) and a significantly longer survival period (11.7 versus 8.3 months; p = 0.002) than patients in the standard arm, with no clinically significant additional toxicities being reported in the test arm [45]. The results of the ABC-02 trial were recapitulated by a phase II, randomized trial (BT-22) in Japan comparing GEM plus CDDP (overall survival = 7.7 versus 11.2 months) [46, Boku N *et al*: unpublished data]. GEM plus CDDP is currently considered to be the standard care for unresectable or recurrent biliary cancer.

Another trend in the development of cytotoxic agents for biliary cancer is the increasing use of oxaliplatin (OHP). The non-inferiority of OHP to CDDP was demonstrated in a phase III clinical trial for gastric cancer [47], and GEM plus OHP had a similar activity to GEM plus CDDP in patients with pancreatic cancer [48]. The divided administration schedule for CDDP in the ABC-02 trial appears to be replaceable with a similar schedule for OHP. OHP has been used for the treatment of biliary cancer not only in clinical trials, but also in clinical practice in some European countries. GEM plus platinum-based compounds, either CDDP or OHP, is expected to become the standard against which new treatments are measured in future trials.

The ABC-01 and ABC-02 clinical trials provided two important conclusions: (i) a randomized phase II trial is important for evaluating the power of new treatments; and (ii) a large-scale phase III trial can be conducted even for rare cancers such as biliary cancer.

Second-line chemotherapy for biliary cancer

Effective second-line chemotherapy, such as the use of irinotecan against colorectal [49] and gastric cancer [50] and the use of 5-FU plus OHP against pancreatic cancer [51], generally can also prolong the survival of patients with other forms of gastrointestinal cancer. As noted, chemotherapy with GEM plus CDDP has been established as the standard first-line treatment for biliary cancer. However, when data from the ABC-02 [45] and BT-22 trials [46] were compared, similar results regarding overall survival in both the GEM and the GEM plus CDDP arms were observed, although the proportion of patients receiving second-line chemotherapy was substantially higher in the BT-22 trial. In the BT-22 trial, 5-FU and its derivatives were

Table 4. Randomized phase III trials of combinations of cytotoxic agents and platinum-based chemotherapies for biliary cancer.

Treatment arm	n	Response rate (%)	Median survival time (months)	p value	Reference
5-FU 5-FU + STZ 5-FU + MeCCNU	30 26 31	10 12.5 10	– – –	–	[72]
5-FU 5-FU + ADM + MMC	18 18	0 0	– –	0.67	[6]
5-FU 5-FU/LV + CDDP	29 29	7 19	5 8	–	[73]
5-FU/LV + ETO 5-FU + EPI + CDDP	27 27	15 19.2	12 9	0.2	[74]
GEM GEM + CDDP	206 204	16.0 25.7	8.3 11.7	0.002	[45]
GEM GEM + CDDP	42 41	11.9 19.5	7.7 11.2	–	[46]

5-FU 5-Fluorouracil, **ADM** doxorubicin, **CDDP** cisplatin, **EPI** epirubicin, **ETO** etoposide (VP-16), **GEM** gemcitabine, **LV** leucovorin, **MeCCNU** semustine, **MMC** mitomycin C, **MST** median survival time, **n** number of patients, **RR** response rate, **STZ** streptozotocin

the most frequently used cytotoxic agents for second-line chemotherapy after the failure of first-line chemotherapy with GEM plus CDDP. The results of this comparison suggest that second-line chemotherapy has no or minimal impact on the survival of patients with biliary cancer and that monotherapy with fluoropyrimidines is not effective as a second-line chemotherapy after the failure of GEM plus CDDP. In the case of platinum-based agents, Kim *et al* reported that the use of the FOLFOX (OHP plus 5-FU plus LV) regimen in patients with gastric cancer produced a response rate of 26% even after the failure of combination chemotherapy with 5-FU plus CDDP [52]. Thus, OHP might not exhibit cross-resistance with CDDP. The FOLFOX regimen might warrant further investigation as a second-line chemotherapy for patients with biliary cancer after the failure of GEM plus CDDP.

Anticancer agents with molecular targets

Recently, the development of antitumor agents has also focused on molecular targets. Several of these agents, such as bevacizumab, a humanized anti-VEGF mAb [53], cetuximab, a human-murine chimeric anti-EGFR mAb [54], and panitumumab, a fully human IgG2 anti-EGFR mAb [55], have demonstrated a survival benefit in patients with colorectal cancer when administered either as a monotherapy or as a combination chemotherapy with cytotoxic drugs.

Angiogenesis plays an important role in tumor progression and metastasis in almost all malignancies. Some intrahepatic biliary cancers are combined hepatocellular-cholangiocarcinoma forms, which have the histology of both challangiocarcinoma and hepatocellular carcinoma [56]. Agents with molecular targets, such as sorafenib, a small-molecule cytostatic pan-kinase inhibitor [57], might also be effective against biliary cancer. Similarly, the use of c-Met inhibitors that block the hepatocyte growth factor receptor may also be effective against some combined-types of biliary cancer.

The status of EGFR in biliary cancers also has been investigated. Nakazawa *et al* reported that the overexpression of EGFR was identifiable in 8.1% of biliary cancers and was associated with gene amplification [58]. These results suggest that EGFR is involved in the carcinogenesis of biliary cancers and that anti-EGFR therapy might be an effective treatment for these tumors. In a phase II clinical trial of the receptor tyrosine kinase inhibitor erlotinib in patients with advanced biliary cancer, 7 out of 37 patients had progression-free survival for more than 6 months, including partial responses in 2 patients [59]. In a phase II, multicenter, randomized trial (BINGO) comparing GEMOX plus cetuximab with GEMOX alone, the 4-month progression-free survival rate was 44% in the GEMOX arm and 61% in the GEMOX plus cetuximab arm [60]. Thus, the use of an EGFR inhibitor combined with cytotoxic agents appears to be a promising treatment for biliary cancer. Conversely, lapatinib, an oral inhibitor of EGFR and HER2/neu, produced no objective responses in a phase II trial for biliary cancer [61], suggesting that the use of an EGFR inhibitor alone may be a less promising approach.

The relationship between EGFR gene status and the efficacy of EGFR inhibitors has been investigated. For example, gefitinib, another EGFR tyrosine kinase inhibitor, demonstrated a remarkably high response rate (76.4%) in patients carrying certain somatic mutations close to the region coding the ATP-binding pocket of the kinase domain of EGFR [62]. In an examination of somatic mutations in bile duct and gallbladder cancers, Leone *et al* determined that none of the 40 specimens evaluated had mutations in exon 18, one specimen had a single missense point mutation in exon 19, two specimens had mutations in exon 20, and three specimens had mutations in exon 21 [63]. In a separate study conducted in Korea, 3 out of 22 patients with biliary cancer (13.6%) were determined to harbor EGFR mutations [64], comprising deletions in exon 19. NSCLCs with mutations such as a deletion in exon 19 are known to be sensitive to gefitinib [62]. Given the results from trials of EGFR inhibitors in patients with NSCLC, ethnic differences in the incidence and types of EGFR mutation might similarly exist between Asian and Caucasian patients with biliary cancers, and some types of biliary cancer might be more sensitive to gefitinib than others. Furthermore, trastuzumab, which is included in the standard of care for HER2-positive breast cancer in both the adjuvant and palliative settings, was also demonstrated to provide a survival benefit for patients with HER2-positive gastric cancer [65]. Although HER2 expression is uncommon in biliary cancer, occurring in 4% of patients [66], trastuzumab might be effective in this subset of patients.

Various other molecular mechanisms have been reported to have some impact on cell proliferation and patient prognosis in basic and translational studies; these findings indicate the potential for the development of novel drugs for the treatment of biliary cancer. In a study of biliary tract adenocarcinoma, patients with mTOR-positive tumors had a significantly shorter overall survival period than patients with mTOR-negative tumors [67]. The simultaneous blockade of EGFR and mTOR in biliary tract cancer cell lines resulted in a reduction in cell growth and survival [68]. The Hedgehog and ERK1/2 pathways are important for biliary cancer cell proliferation, and the simultaneous inhibition of these two pathways might also lead to greater reductions in cell growth and viability [69]. The expression of Hsp27 likely increases cell proliferation, tumor mass, and vascular and capsular invasion, and potentially promotes aggressive tumor behavior in intrahepatic cholangiocarcinoma, reducing the survival period [70]. Moreover, the expression of IGFR in less than 50% of cancer cells is a marker of poor prognosis among patients with gallbladder cancer [71]. However, these findings are applicable to most cancers, and no

data that are specific for the treatment of biliary cancer have been identified. As a rare disease, biliary cancer will likely continue to have a low priority in the development of new drugs, such as c-Met, mTOR, Hsp and IGFR inhibitors, in the treatment of cancer.

Personalized medicine is becoming an increasingly important research topic, particularly for anticancer agents with molecular targets. Using this approach, clinical trials focusing on the small proportion of patients with a common disease who harbor a particular gene abnormality can be conducted. Establishing the efficacy of a treatment for a small population of patients with biliary cancer is likely to be challenging because of the low incidence of the disease. However, a paradigm shift from the development of disease-specific novel drugs to biomarker-oriented investigations that include rare diseases might represent a new approach to the development of treatments for rare diseases such as biliary cancer. Clinical trials investigating the additional efficacy of novel agents in subsets of patients with a variety of malignancies, including biliary cancer, who harbor a particular predictive biomarker could be conducted based on the standard chemotherapy regimen for each disease. For this reason, comprehensive data from translational research on carcinogenesis and the profiles of targeted molecules or genes in biliary cancer should be prepared.

Conclusion

The phase III clinical trial comparing GEM plus CDDP with GEM alone represents a significant advance in the development of new treatments for unresectable or recurrent biliary cancer. In addition to establishing a standard of care, this trial also demonstrated that a large-scale phase III trial could be conducted for a rare disease such as biliary cancer. Further investigation of molecular agents and new treatment strategies, including second-line chemotherapy, should be continued in randomized trials. In the future, a paradigm shift from disease-specific drug development to biomarker-oriented investigations, including rare diseases such as biliary cancer, may be warranted.

References

•• of outstanding interest
• of special interest

1. Kondo S, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T, Yamamoto M, Kayahara M *et al*: **Guidelines for the management of biliary tract and ampullary carcinomas: Surgical treatment.** *J Hepatobiliary Pancreat Surg* (2008) **15**(1):41-54.

2. **CANCERMondial:** International Agency for Research on Cancer, Lyon, France (2010). *www-dep.iarc.fr*

3. Yonemoto N, Furuse J, Okusaka T, Yamao K, Funakoshi A, Ohkawa S, Boku N, Tanaka K, Nagase M, Sisho H, Sato T: **A multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer.** *Jpn J Clin Oncol* (2007) **37**(11):843-851.
• *Reports the prognoses of patients with biliary cancer treated with BSC, and the survival benefits of chemotherapy.*

4. Glimelius B, Hoffman K, Sjoeden PO, Jacobsson G, Sellstrom H, Enander LK, Linne T, Svensson C: **Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer.** *Ann Oncol* (1996) **7**(6):593-600.

5. Dwary AD, Sharma A, Mohanti BK, Pal S, Garg P, Raina V, Shukla NK, Deo SV, Thulkar S, Sreenivas V: **A randomized controlled trial (RCT) comparing best supportive care (BSC), 5-FU plus folinic acid (FUFA) and, gemcitabine plus oxaliplatin (Gem-Ox) in management of unresectable gallbladder cancer (GBC).** *J Clin Oncol* (2009) **27**(15S):Abs 4521.

6. Takada T, Kato H, Matsushiro T, Nimura Y, Nagakawa T, Nakayama T: **Comparison of 5-fluorouracil, doxorubicin and mitomycin C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinomas.** *Oncology* (1994) **51**(5):396-400.

7. Ikeda M, Okusaka T, Ueno H, Morizane C, Furuse J, Ishii H: **A phase II trial of uracil-tegafur (UFT) in patients with advanced biliary tract carcinoma.** *Jpn J Clin Oncol* (2005) **35**(8):439-443.

8. Malik IA, Aziz Z: **Prospective evaluation of efficacy and toxicity of 5-FU and folinic acid (Mayo Clinic regimen) in patients with advanced cancer of the gallbladder.** *Am J Clin Oncol* (2003) **26**(2):124-126.

9. Patt YZ, Jones DV Jr, Hoque A, Lozano R, Markowitz A, Raijman I, Lynch P, Charnsangavej C: **Phase II trial of intravenous flourouracil and subcutaneous interferon alfa-2b for biliary tract cancer.** *J Clin Oncol* (1996) **14**(8):2311-2315.

10. Chen JS, Yang TS, Lin YC, Jan YY: **A phase II trial of tegafur-uracil plus leucovorin (LV) in the treatment of advanced biliary tract carcinomas.** *Jpn J Clin Oncol* (2003) **33**(7):353-356.

11. Furuse J, Okusaka T, Boku N, Ohkawa S, Sawaki A, Masumoto T, Funakoshi A: **S-1 monotherapy as first-line treatment in patients with advanced biliary tract cancer: A multicenter phase II study.** *Cancer Chemother Pharmacol* (2008) **62**(5): 849-855.

12. Taal BG, Audisio RA, Bleiberg H, Blijham GH, Neijt JP, Veenhof CH, Duez N, Sahmoud T: **Phase II trial of mitomycin C (MMC) in advanced gallbladder and biliary tree carcinoma. An EORTC Gastrointestinal Tract Cancer Cooperative Group Study.** *Ann Oncol* (1993) **4**(7):607-609.

13. Okada S, Ishii H, Nose H, Yoshimori M, Okusaka T, Aoki K, Iwasaki M, Furuse J, Yoshino M: **A phase II study of cisplatin in patients with biliary tract carcinoma.** *Oncology* (1994) **51**(6):515-517.

14. Androulakis N, Aravantinos G, Syrigos K, Polyzos A, Ziras N, Tselepatiotis E, Samonis G, Kentepozidis N, Giassas S, Vamvakas L, Georgoulias V: **Oxaliplatin as first-line treatment in inoperable biliary tract carcinoma: A multicenter phase II study.** *Oncology* (2006) **70**(4):280-284.

15. Jones DV Jr, Lozano R, Hoque A, Markowitz A, Patt YZ: **Phase II study of paclitaxel therapy for unresectable biliary tree carcinomas.** *J Clin Oncol* (1996) **14**(8):2306-2310.

16. Papakostas P, Kouroussis C, Androulakis N, Samelis G, Aravantinos G, Kalbakis K, Sarra E, Souglakos J, Kakolyris S, Georgoulias V: **First-line chemotherapy with docetaxel for unresectable or metastatic carcinoma of the biliary tract. A multicentre phase II study.** *Eur J Cancer* (2001) **37**(15): 1833-1838.

17. Sanz-Altamira PM, O'Reilly E, Stuart KE, Raeburn L, Steger C, Kemeny NE, Saltz LB: **A phase II trial of irinotecan (CPT-11) for unresectable biliary tree carcinoma.** *Ann Oncol* (2001) **12**(4):501-504.

18. Abou-Alfa GK, Rowinsky EK, Patt YZ, Schwartz GK, Kelsen DP, Sharma S, Siegel E, Becerra CR, Eckhardt SG, Feit K, De Jager R *et al*: **A phase II study of intravenous exatecan administered daily for 5 days, every 3 weeks to patients with biliary tract cancers.** *Am J Clin Oncol* (2005) **28**(4):334-349.

19. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B, Scheithauer W: **Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer.** *Ann Oncol* (2001) **12**(2):183-186.

20. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R *et al*: **Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial.** *J Clin Oncol* (1997) **15**(6):2403-2413.

21. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takiuchi H, Nasu J *et al*: **Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: A randomised phase 3 study.** *Lancet Oncol* (2009) **10**(11):1063-1069.

22. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M *et al*: **Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: A randomised phase III noninferiority trial.** *Ann Oncol* (2009) **20**(4):666-673.

23. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F *et al*: **Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer.** *J Clin Oncol* (2008) **26**(12):2006-2012.

24. Harvey JH, Smith FP, Schein PS: **5-Fluorouracil, mitomycin, and doxorubicin (FAM) in carcinoma of the biliary tract.** *J Clin Oncol* (1984) **2**(11):1245-1248.

25. Ducreux M, Rougier P, Fandi A, Clavero-Fabri MC, Villing AL, Fassone F, Fandi L, Zarba J, Armand JP: **Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin.** *Ann Oncol* (1998) **9**(6): 653-656.

26. Raderer M, Hejna MH, Valencak JB, Kornek GV, Weinländer GS, Bareck E, Lenauer J, Brodowicz T, Lang F, Scheithauer W: **Two consecutive phase II studies of 5-fluorouracil/ leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer.** *Oncology* (1999) **56**(3):177-180.

27. Taïeb J, Mitry E, Boige V, Artru P, Ezenfis J, Lecomte T, Clavero-Fabri MC, Vaillant JN, Rougier P, Ducreux M: **Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma.** *Ann Oncol* (2002) **13**(8):1192-1196.

28. Nehls O, Klump B, Arkenau HT, Hass HG, Greschniok A, Gregor M, Porschen R: **Oxaliplatin, fluorouracil and leucovorin for advanced biliary system adenocarcinomas: A prospective phase II trial.** *Br J Cancer* (2002) **87**(7):702-704.

29. Morizane C, Okada S, Okusaka T, Ueno H, Saisho T: **Phase II study of cisplatin, epirubicin, and continuous-infusion 5-fluorouracil for advanced biliary tract cancer.** *Oncology* (2003) **64**(4):475-476.

30. Park KH, Choi IK, Kim SJ, Oh SC, Seo JH, Choi CW, Kim BS, Shin SW, Kim YH, Kim JS: **The efficacy of epirubicin, cisplatin, uracil/tegafur, and leucovorin in patients with advanced biliary tract carcinoma.** *Cancer* (2005) **103**(11): 2338-2343.

31. Furuse J, Okusaka T, Ohkawa S, Nagase M, Funakoshi A, Boku N, Yamao K, Yamaguchi T, Sato T: **A phase II study of uracil-tegafur plus doxorubicin and prognostic factors in patients with unresectable biliary tract cancer.** *Cancer Chemother Pharmacol* (2009) **65**(1):113-120.

32. Kim TW, Chang HM, Kang HJ, Lee JR, Ryu MH, Ahn JH, Kim JH, Lee JS, Kang YK: **Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer.** *Ann Oncol* (2003) **14**(7):1115-1120.

33. Kornek GV, Schuell B, Laengle F, Gruenberger T, Penz M, Karall K, Depisch D, Lang F, Scheithauer W: **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* (2004) **15**(3):478-483.

34. Park SH, Park YH, Lee JN, Bang SM, Cho EK, Shin DB, Lee JH: **Phase II study of epirubicin, cisplatin, and capecitabine for advanced biliary tract adenocarcinoma.** *Cancer* (2006) **106**(2):361-365.

35. Gebbia V, Giuliani F, Maiello E, Colucci G, Verderame F, Borsellino N, Mauceri G, Caruso M, Tirrito ML, Valdesi M: **Treatment of inoperable and/or metastatic biliary tree carcinomas with single-agent gemcitabine or in combination with levofolinic acid and infusional fluorouracil: Results of a multicenter phase II study.** *J Clin Oncol* (2001) **19**(20): 4089-4091.

36. Kuhn R, Hribaschek A, Eichelmann K, Rudolph S, Fahlke J, Ridwelski K: **Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangio-carcinomas.** *Invest New Drugs* (2002) **20**(3):351-356.

37. Thongprasert S, Napapan S, Charoentum C, Moonprakan S: **Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma.** *Ann Oncol* (2005) **16**(2):279-281.

38. André T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, Selle F, Paye F, Hannoun L, Houry S, Gayet B *et al*: **Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: A GERCOR study.** *Ann Oncol* (2004) **15**(9):1339-1343.

39. Verderame F, Russo A, Di Leo R, Badalamenti G, Santangelo D, Cicero G, Valerio MR, Gulotta G, Tomasello G, Gebbia N, Fulfaro F: **Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers.** *Ann Oncol* (2006) **17**(Suppl 7):vii68-vii72.

40. Harder J, Riecken B, Kummer O, Lohrmann C, Otto F, Usadel H, Geissler M, Opitz O, Henss H: **Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer.** *Br J Cancer* (2006) **95**(7):848-852.

41. Bhargava P, Jani CR, Savarese DM, O'Donnell JL, Stuart KE, Rocha Lima CM: **Gemcitabine and irinotecan in locally advanced or metastatic biliary cancer: Preliminary report.** *Oncology* (2003) **17**(Suppl 8):23-26.

42. Knox JJ, Hedley D, Oza A, Feld R, Siu LL, Chen E, Nematollahi M, Pond GR, Zhang J, Moore MJ: **Combining gemcitabine and capecitabine in patients with advanced biliary cancer: A phase II trial.** *J Clin Oncol* (2005) **23**(10):2332-2338.

43. Eckel F, Schmid RM: **Chemotherapy in advanced biliary tract carcinoma: A pooled analysis of clinical trials.** (2007) **96**(6):896-902.

44. Valle JW, Wasan H, Johnson P, Bridgewater J, Maraveyas A, Jones E, Tunney V, Swindell R: **Gemcitabine, alone or in combination with cisplatin, in patients with advanced or metastatic cholangiocarcinoma (CC) and other biliary tract tumors: A multicenter, randomized, phase II (the UK ABC-01) study.** *2006 Gastrointestinal Cancers Symposium, San Francisco, CA, USA* (2006):Abs 98.

45. Valle JW, Wasan HS, Palmer DD, Cunningham D, Anthoney DA, Maraveyas A, Hughes SK, Roughton M, Bridgewater JA. **Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial).** *J Clin Oncol* (2009) **27**(15S):Abs 4503.

•• *Reports that GEM plus CDDP prolonged the survival of patients with biliary cancer compared with GEM alone. GEM plus platinum-based compounds (eg, CDDP or OHP) appears to provide the standard against which new therapeutics will be measured in future trials.*

46. Furuse J, Okusaka T, Miyazaki M, Taniai H, Nimura Y, BT22 Study Group: **A randomized study of gemcitabine/ cisplatin versus single-agent gemcitabine in patients with biliary tract cancer.** *J Clin Oncol* (2009) **27**(15S): Abs 4579.

47. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR: **Capecitabine and oxaliplatin for advanced esophagogastric cancer.** *N Engl J Med* (2008) **358**(1):36-46.

48. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R *et al*: **Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial.** *J Clin Oncol* (2005) **23**(15):3509-3516.

49. Cunningham D, Pyrhönen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C *et al*: **Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer.** *Lancet* (1998) **352**(9138):1413-1418.

50. Thuss-Patience PC, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B, Schumacher G, Gebauer B, Maier V, Reichardt P: **Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: A randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO).** *J Clin Oncol* (2009) **27**(15s):Abs 4550

51. Riess H, Pelzer U, Stieler J, Schwaner I, Heil G, Görner M, Mölle M, Hilbig A, Dörken B, Oettle H: **A randomized second line trial in patients with gemcitabine refractory advanced pancreatic cancer - CONKO 003. *J Clin Oncol* (2007) 25(18S): Abs 4517.**

52. Kim DY, Kim JH, Lee SH, Kim TY, Heo DS, Bang YJ, Kim NK: **Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer.** *Ann Oncol* (2003) **14**(3):383-387.

53. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N *et al*: **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* (2004) **350**(23):2335-2342.

54. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, Berry SR, Krahn M, Price T, Simes RJ, Tebbutt NC *et al*: **Cetuximab for the treatment of colorectal cancer.** *N Engl J Med* (2007) **57**(20):2040-2048.

55. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M *et al*: **Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer.** *J Clin Oncol* (2007) **25**(13): 1658-1664.

56. Zhang F, Chen XP, Zhang W, Dong HH, Xiang S, Zhang WG, Zhang BX: **Combined hepatocellular cholangiocarcinoma originating from hepatic progenitor cells: immunohistochemical and double-fluorescence immunostaining evidence.** *Histopathology* (2008) **52**(2):224-232.

57. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M *et al*: **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* (2008) **359**(4):378-390.

58. Nakazawa K, Dobashi Y, Suzuki S, Fujii H, Takeda Y, Ooi A: **Amplification and overexpression of c-ErbB-2, epidermal growth factor receptor, and c-Met in biliary tract cancers.** *J Pathol* (2005) **206**(3):356-365.

59. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, Donehower RC, Fitch T, Picus J, Erlichman C: **Phase II study of erlotinib in patients with advanced biliary cancer.** *J Clin Oncol* (2006) **24**(19):3069-3074.

60. Malka D, Trarbach T, Fartoux L, Mendiboure J, de la Fouchardière C, Viret F, Assenat E, Boucher E, Rosmorduc O, Greten T: **A multicenter, randomized phase II trial of gemcitabine and oxaliplatin (GEMOX) alone or in combination with biweekly cetuximab in the first-line treatment of advanced biliary cancer: Interim analysis of the BINGO trial.** *J Clin Oncol* (2009) **27**(15S):Abs 4520.
•• *Compared GEMOX plus cetuximab with GEMOX; the 4-month progression-free survival rate was 44% in the GEMOX arm and 61% in GEMOX plus cetuximab arm. The combination of an EGFR inhibitor with cytotoxic agents is a promising approach for the treatment of biliary cancer.*

61. Ramanathan RK, Belani CP, Singh DA, Tanaka M, Lenz HJ, Yen Y, Kindler HL, Iqbal S, Longmate J, Mack PC, Lurje G *et al*: **A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer.** *Cancer Chemother Pharmacol* (2009) **64**(4):777-783.

62. Morita S, Okamoto I, Kobayashi K, Yamazaki K, Asahina H, Inoue A, Hagiwara K, Sunaga N, Yanagitani N, Hida T, Yoshida K *et al*: **Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations.** *Clin Cancer Res* (2009) **15**(13):4493-4498.

63. Leone F, Cavalloni G, Pignochino Y, Sarotto I, Ferraris R, Piacibello W, Venesio T, Capussotti L, Risio M, Aglietta M: **Somatic mutations of epidermal growth factor receptor in bile duct and gallbladder carcinoma.** *Clin Cancer Res* (2006) **12**(6):1680-1685.

64. Gwak GY, Yoon JH, Shin CM, Ahn YJ, Chung JK, Kim YA, Kim TY, Lee HS: **Detection of response-predicting mutations in the kinase domain of the epidermal growth factor receptor gene in cholangiocarcinomas.** *J Cancer Res Clin Oncol* (2005) **131**(10):649-652.

65. Van Cutsem E, Kang Y, Chung H, Shen L, Sawaki A, Lordick F, Hill J, Lehle M, Feyereislova A, Bang Y: **Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC).** *J Clin Oncol* (2009) **27**(18S):Abs LBA4509.

66. Shafizadeh N, Grenert JP, Sahai V, Kakar S: **Epidermal growth factor receptor and HER-2/neu status by immunohistochemistry and fluorescence *in situ* hybridization in adenocarcinomas of the biliary tree and gallbladder.** *Hum Pathol* (2010) **41**(4):485-492.

67. Herberger B, Puhalla H, Lehnert M, Wrba F, Novak S, Brandstetter A, Gruenberger B, Gruenberger T, Pirker R, Filipits M: **Activated mammalian target of rapamycin is an adverse prognostic factor in patients with biliary tract adenocarcinoma.** *Clin Cancer Res* (2007) **13**(16):4795-4799.

68. Herberger B, Berger W, Puhalla H, Schmid K, Novak S, Brandstetter A, Pirker C, Gruenberger T, Filipits M: **Simultaneous blockade of the epidermal growth factor receptor/ mammalian target of rapamycin pathway by epidermal growth factor receptor inhibitors and rapamycin results in reduced cell growth and survival in biliary tract cancer cells.** *Mol Cancer Ther* (2009) **8**(6):1547-1556.

69. Jinawath A, Akiyama Y, Sripa B, Yuasa Y: **Dual blockade of the Hedgehog and ERK1/2 pathways coordinately decreases proliferation and survival of cholangiocarcinoma cells.** *J Cancer Res Clin Oncol* (2007) **133**(4):271-278.

70. Romani AA, Crafa P, Desenzani S, Graiani G, Lagrasta C, Sianesi M, Soliani P, Borghetti AF: **The expression of Hsp27 is associated with poor clinical outcome in intrahepatic cholangiocarcinoma.** *BMC Cancer* (2007) **7**:232.

71. Kornprat P, Rehak P, Rüschoff J, Langner C: **Expression of IGF-I, IGF-II, and IGF-IR in gallbladder carcinoma. A systematic analysis including primary and corresponding metastatic tumours.** *J Clin Pathol* (2006) **59**(2):202-206.

72. Falkson G, MacIntyre JM, Moertel CG: **Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer.** *Cancer* (1984) **54**(6):965-969.

73. Ducreux M, Van Cutsem E, Van Laethem JL, Gress TM, Jeziorski K, Rougier P, Wagener T, Anak O, Baron B, Nordlinger B: **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* (2005) **41**(3):398-403.

74. Rao S, Cunningham D, Hawkins RE, Hill ME, Smith D, Daniel F, Ross PJ, Oates J, Norman AR: **Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer.** *Br J Cancer* (2005) **92**(9): 1650-1654.

Can EUS-guided FNA distinguish between gallbladder cancer and xanthogranulomatous cholecystitis?

Susumu Hijioka, MD, Mohamed A. Mekky, MD, Vikram Bhatia, MD, Akira Sawaki, MD, Nobumasa Mizuno, MD, Kazuo Hara, MD, Waki Hosoda, MD, Yasuhiro Shimizu, MD, Kiichi Tamada, MD, Yasumasa Niwa, MD, Kenji Yamao, MD

Nagoya, Japan

Background: EUS-guided FNA (EUS-FNA) is a useful modality for sampling various targets, but its applicability to gallbladder (GB) mass lesions is limited.

Objective: To determine the usefulness of EUS-FNA for diagnosing GB mass lesions.

Design: Single-center, retrospective, case-series study.

Setting: Tertiary-care referral center.

Patients: This study involved 15 consecutive patients who underwent EUS-FNA of GB mass lesions. We punctured GB masses in patients with suspected xanthogranulomatous cholecystitis to distinguish them from malignancy, and in patients with unresectable GB carcinoma for pathological confirmation. The final diagnosis was based on surgical histopathological results or follow-up outcome.

Interventions: EUS-FNA.

Main Outcome Measurements: Evaluation of EUS-FNA sampling adequacy rate and diagnostic yield.

Results: Xanthogranulomatous cholecystitis was suspected in 6 of the 15 patients. EUS-FNA revealed foam cells (n = 3), inflammatory cells (n = 1, proven by cholecystectomy), and GB carcinoma (n = 1), and the amount of the aspirate was insufficient in one case (xanthogranulomatous cholecystitis was later proven by extended hepatectomy). The mean follow-up period of the patients with xanthogranulomatous cholecystitis was 1177 days. Adenocarcinoma was confirmed by EUS-FNA in 8 of the 9 patients with suspected unresectable GB carcinoma, and the FNA was inconclusive in one. All 10 patients with GB carcinoma underwent chemotherapy. The overall sampling adequacy was 86.6%. The accuracy of EUS-FNA for detecting malignancy and for the final diagnosis was 93.3% (95% CI, 62.4%-99.9%) and 80% (95% CI, 54%-93.7%), respectively.

Limitations: A small patient cohort and a retrospective design with potential selection bias.

Conclusions: Malignant GB mass lesions can be safely and accurately differentiated by EUS-FNA. Thus, patients with xanthogranulomatous cholecystitis can avoid undue extensive surgery.

Tissue samples from gallbladder (GB) mass lesions can be obtained through percutaneous image-guided (eg, transabdominal US and CT scanning) FNA and occasionally by open surgery.[1-5] The reported sensitivity and specificity of these modalities are >88% and nearly 100%, respectively. However, the performance characteristics of

Abbreviations: EUS-FNA, EUS-guided FNA; GB, gallbladder; LN, lymph node; XGC, xanthogranulomatous cholecystitis.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2010.05.022

Received February 14, 2010. Accepted May 10, 2010.

Current affiliations: Department of Gastroenterology (S.H., A.S., N.M., K.H., K.Y.), Department of Pathology and Molecular Diagnostics (W.H.), Department of Surgery (Y.S.), Department of Endoscopy (Y.N.), Aichi Cancer Center Hospital, Nagoya, Japan; Department of Tropical Medicine and Gastroenterology (M.A.M.), Assiut University Hospital, Assiut, Egypt; Department of Medical Hepatology (V.B.), Institute of Liver and Biliary Sciences, Delhi, India; Department of Gastroenterology (K.T.), Jichi Medical University, Tochigi, Japan.

Presented as a poster at Asian Pacific Digestive Week, September 29, 2009, Taiwan, Republic of China (J Gastroenterol Hepatol 2009;24(suppl 1):A83), and at Digestive Disease Week, May 5, 2010, New Orleans, Louisiana (Gastrointest Endosc 2010;71:AB282-3).

Reprint requests: Susumu Hijioka, MD, Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan.

TABLE 1. Detailed summary of 15 GB mass lesions

No.	Sex/age	Symptom	Clinical diagnosis	TNM	FNA aim	Location/EUS findings	Target‡	FNA passes	FNA result	Final	Confirmation	Clinical course
1	F/54	RUQ pain	XGC		Discrimination*	Fundus/homogeneous	GB	3	Ins	XCG	Operation	Alive at 1426 days
2	M/85	RUQ pain	XGC		Discrimination	Body-fundus/homogeneous high echo	GB	2	XCG	XCG	Observation	Alive at 562 days
3	F/77	Appetite loss	XGC		Discrimination	Neck/homogeneous	GB	2	XCG	XCG	Observation	Alive at 1465 days
4	F/57	Appetite loss	XGC		Discrimination	Neck-body/heterogeneous	GB	2	XCG	XCG	Observation	Alive at 951 days
5	M/57	RUQ pain	XGC		Discrimination	Body-fundus/homogeneous	GB	3	IC	XCG	Operation	Alive at 1481 days
6	F/73	Appetite loss	XGC		Discrimination	Body-fundus/heterogeneous	GB	1	GBC	GBC	Chemotherapy	Died at 177 days
7	F/59	Jaundice	GBC	T4N1M0	Evidence†	Neck-body/homogeneous	LN GB	3	GBC	GBC	Chemotherapy	Died at 1109 days
8	M/82	Jaundice	GBC	T4N1M1	Evidence	Neck-body/heterogeneous	LN GB	2	GBC	GBC	Chemotherapy	Died at 602 days
9	M/68	Appetite loss	GBC	T3N0M1	Evidence	Body/homogeneous	GB	3	Ins	GBC	Chemotherapy	Died at 706 days
10	M/51	RUQ pain	GBC	T4N2M0	Evidence	Fundus/heterogeneous	LN GB	3	GBC	GBC	Chemotherapy	Died at 60 days
11	F/81	RUQ pain	GBC	T4N2M1	Evidence	Body-fundus/heterogeneous	GB	1	GBC	GBC	Chemotherapy	Died at 82 days
12	F/67	RUQ pain	GBC	T4N2M1	Evidence	Body/heterogeneous	GB	1	GBC	GBC	Chemotherapy	Died at 1239 days
13	F/55	RUQ pain	GBC	T4N1M0	Evidence	Neck-body/homogeneous	GB	1	GBC	GBC	Chemotherapy	Alive at 126 days
14	M/82	Appetite loss	GBC	T3N0M1	Evidence	Neck/homogeneous	GB	1	GBC	GBC	Chemotherapy	Alive at 92 days
15	M/49	Jaundice	GBC	T4N1M0	Evidence	Neck-body/homogeneous	LN GB	2	GBC	GBC	Chemotherapy	Alive at 67 days

GB, Gallbladder; *TNM*, tumor/node/metastasis tumor staging; *F*, female; *RUQ*, right upper quadrant; *XGC*, xanthogranulomatous cholecystitis; *Ins*, insufficient; *M*, male; *IC*, inflammatory cells; *GBC*, gallbladder carcinoma; *LN*, lymph node.
*Discrimination between benign and malignant lesions.
†Evidence of malignancy before chemotherapy.
‡LN initially targeted; if failed, insufficient, or negative for carcinoma, GB mass lesion was then punctured.

percutaneous aspiration might be suboptimal for smaller GB lesions.[3,5,6-8] Moreover, percutaneous aspiration is associated with risks of abdominal pain (4.5%), bile peritonitis (1%-6%), and needle tract seeding.[7,8] Despite the established role of EUS-guided FNA (EUS-FNA) as a highly accurate tissue sampling modality for various lesions, with a very low complication rate,[9-12] its role in the context of suspected GB malignancies has not been elucidated.[1,2] EUS-FNA could potentially avoid these shortcomings of percutaneous aspiration of GB lesions. Therefore, we studied whether EUS-FNA could be used to differentiate GB mass lesions and diagnose clinically suspected GB malignancies.

PATIENTS AND METHODS

Between March 1997 and October 2009, 1850 EUS-FNA procedures were carried out at Aichi Cancer Center Hospital, Nagoya, Japan. Among these procedures, 51 (2.7%) were done for patients with GB mass lesions either by puncturing the GB mass itself or by targeting regional lymph nodes (LNs). The present study retrospectively included a subset of 15 consecutive patients (mean age 66.4 ± 12.7 years, 8 female) in whom EUS-FNA targeted the GB mass (Table 1).

Our rationale for using EUS-FNA in these patients was to obtain histological evidence of malignancy in clinically suspected, unresectable GB carcinoma and to distinguish between benign and malignant masses when xanthogranulomatous cholecystitis (XGC) was suspected. This clinical diagnosis was suspected after investigation by CT scanning and abdominal US. However, to definitively reach a diagnosis based on imaging features alone was difficult. When a GB mass with an enlarged, regional, intra-abdominal LN was found, we punctured the LN first. If enlarged LNs were not evident, were difficult to puncture (eg, para-aortic location), or the FNA yield from the LN was negative, we punctured the GB mass lesion itself (Fig. 1).

Study procedure

All patients underwent EUS-FNA with a convex array echoendoscope (GF−UCT240; Olympus Optical Corp Ltd, Tokyo, Japan) connected to an US scanning system (SSD 5500; Aloka, Tokyo, Japan). All FNA procedures were performed by using 22-gauge needles (NA-10J-1, NA-10J-KB, NA-11J-KB, or NA-200H-8022; Olympus Medical System Corp Ltd, Tokyo, Japan). Patients were followed-up for 48 hours after the procedure for any procedure-related complications. Cytological samples were processed and analyzed according to established methods of EUS-FNA aspirate processing.[10,13,14] All samples were interpreted through on-site cytological evaluation and by the same experienced cytopathologists (W.H., Y.Y.). Our institu-

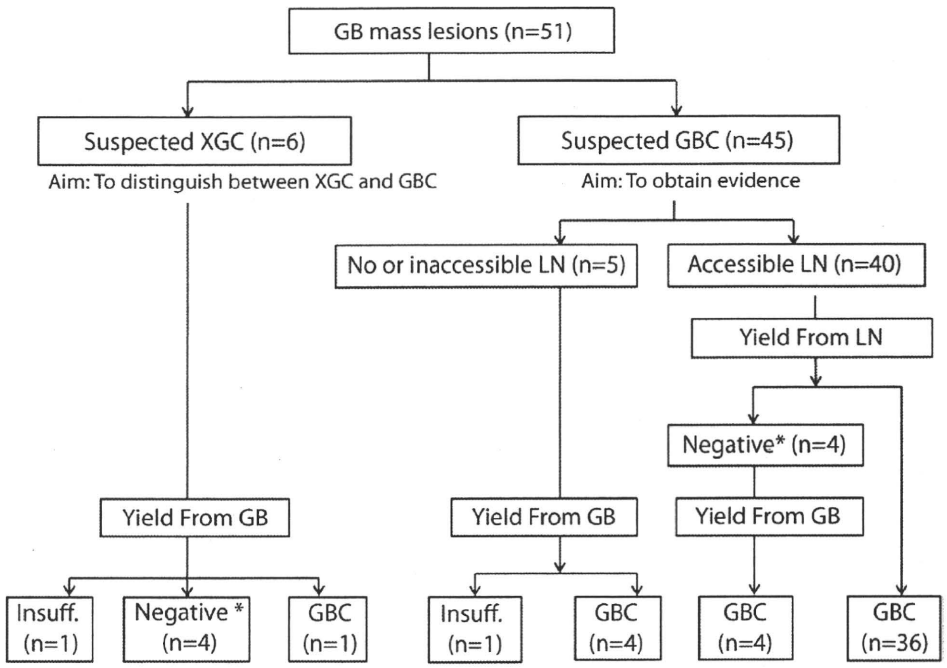

Figure 1. Schematic diagram of a gallbladder mass lesion and EUS-guided FNA yield. *GB*, gallbladder; *XGC*, xanthogranulomatous cholecystitis; *GBC*, gallbladder carcinoma; *LN*, lymph node; *insuff*, insufficient aspirate.

tional review board approved this study. Our main outcome measures were (1) the sampling adequacy rate and (2) the diagnostic yield of EUS-FNA.

Statistical analysis

We used frequencies, proportions (%), and means for descriptive analyses where appropriate. The χ^2 test (with Yates correction) was used as a univariate analysis for comparative statistics. The results of EUS-FNA were compared with the clinical follow-up or with histopathological results obtained after surgical resection. Lesions defined as malignant by EUS-FNA and finally diagnosed as malignant were considered true positive, and lesions defined as malignant by EUS-FNA and finally diagnosed as benign were considered false positive. Likewise, lesions initially categorized and finally diagnosed by EUS-FNA as benign were considered true negative, and lesions initially categorized as benign by EUS-FNA and finally diagnosed as malignant were considered false negative.

RESULTS

The main cause of referral was right upper quadrant pain in 7 patients (46.7%), loss of appetite in 5 patients (33.3%), and obstructive jaundice in 3 patients (20%). Detailed clinical features of these 15 patients are listed in Table 1.

Evaluation of the EUS findings from 51 GB masses (XGC, n = 5; GB carcinoma, n = 46) revealed that only the presence of regional LNs and a disrupted mucosal lining favored a diagnosis of GB carcinoma (Table 2).

TABLE 2. EUS features of XGC and GBC

EUS findings	XGC (n = 5) no. patients (%)	GBC (n = 46) no. patients (%)	*P* value*
Gallbladder			
Focal thickening	1 (20)	7 (15.2)	.7 (NS)
Diffuse thickening	4 (80)	39 (84.8)	
Mucosal line			
Continuous	3 (60)	5 (10.8)	.02
Disrupted	2 (40)	41 (89.1)	
Intramural hypoechoic nodule	3 (60)	12 (26.1)	.2 (NS)
Gallstone	4 (80)	16 (34.8)	.1 (NS)
Lymph node swelling	0 (0)	40 (87)	.0001

XGC, Xanthogranulomatous cholecystitis; *GBC*, gallbladder carcinoma; *NS*, not significant.
*χ^2 test with Yates correction.

A total of 19 punctures (GB masses, n = 15; regional lymphadenopathy, n = 4) were performed in 15 patients with GB masses. The sample adequacy rate for cytological evaluation was 13 of 15 (86.6%; 95% CI, 60.8%-97.5%).

Clinically suspected XGC could not be differentiated from malignancy, and regional lymphadenopathy was un-

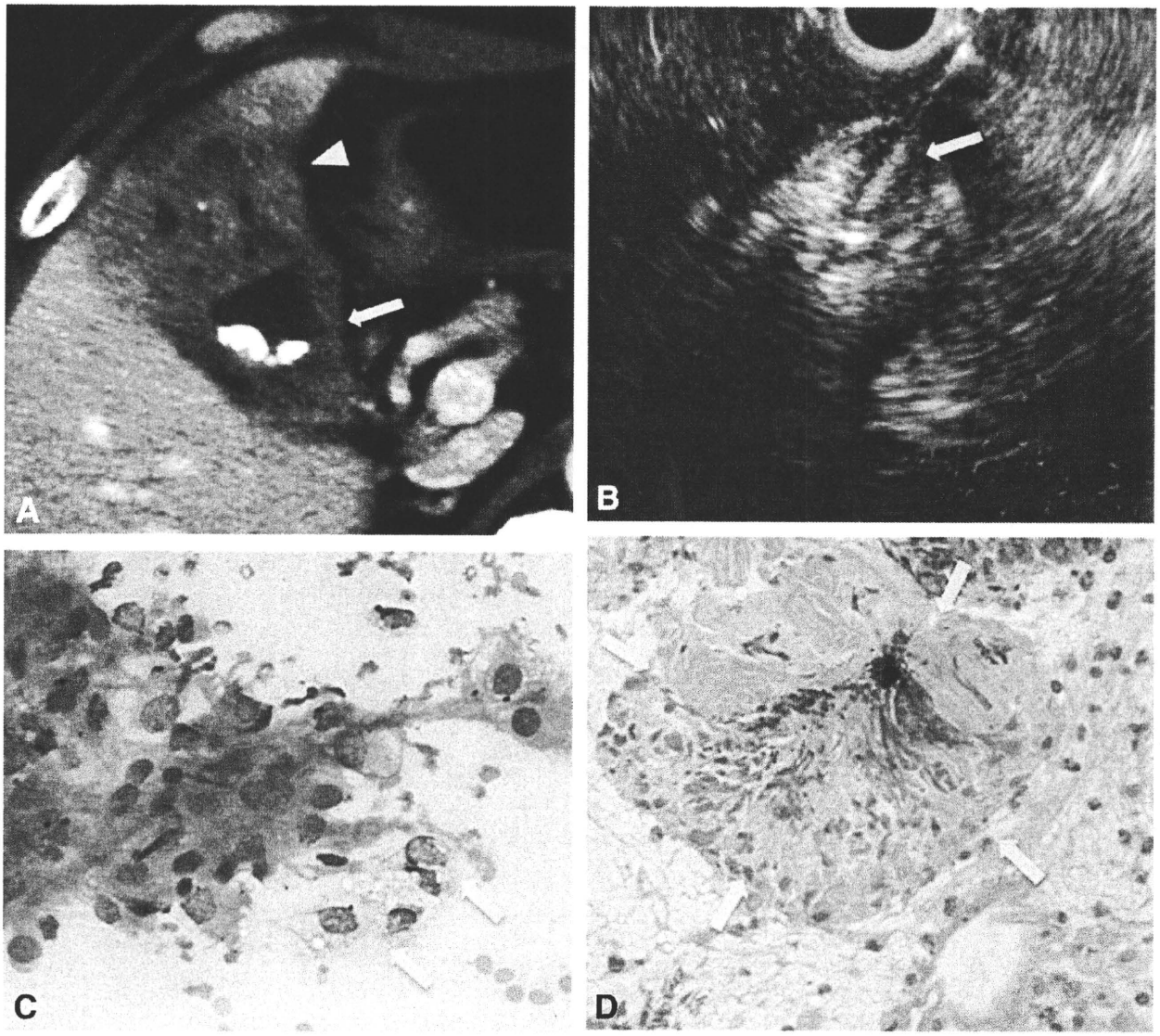

Figure 2. Findings of CT scans and EUS-guided FNA of xanthogranulomatous cholecystitis from patient 5. **A,** Abdominal CT scan shows the diffuse, irregular wall of a thickened gallbladder (*arrow*) with gall stones and irregular, low-density areas in the liver (*arrowhead*). **B,** EUS-guided FNA for a gallbladder mass lesion. The arrow shows the FNA needle inside the lesion. **C,** Foam cells in an FNA-cytology specimen (*arrow*) (Diff-Quik, orig. mag. ×400). **D,** Aggregates of foamy macrophages in cell block sections (*arrow*) (H&E, orig. mag. ×400). These were diagnosed as xanthogranulomatous cholecystitis.

detectable in 6 lesions. Among these, EUS-FNA sampling was inconclusive in 1 patient, who underwent surgery (extended right lobe hepatectomy with bile duct resection, transverse colectomy, and partial duodenal resection) because of concerns about GB carcinoma, but XGC was confirmed in the resected specimen. The presence of typical foam cells in 3 patients and inflammatory cells in 1 led to a presumptive EUS-FNA diagnosis of XGC. The presumptive diagnosis was confirmed at follow-up in the 3 patients with foam cells and by simple cholecystectomy for coexistent GB stones in the other with inflammatory cells (Fig. 2). Although XGC with a liver abscess was clinically suspected in the remaining patient, EUS-FNA revealed GB carcinoma. Unresectable GB carcinoma was suspected in another 9 patients, and the aim of puncture was to obtain pathological evidence of malignancy before chemotherapy. Intra-abdominal regional lymphadenopathy was detected in 7 of these patients (4 LNs were punctured, and 3 were too small for puncture). These 4 LN punctures were negative for malignancy, and, hence, the GB mass itself was punctured (Fig. 3). Sampling was sufficient in 8 patients in whom GB carcinoma was diagnosed and yielded only atypical cells from 1 patient that were insufficient to establish a conclusive diagnosis (considered as false negative). This patient was further treated, based on the overall clinical and imaging profile, as having GB carcinoma. All patients with GB carcinoma (n = 10) received chemotherapy. No serious procedure-related com-

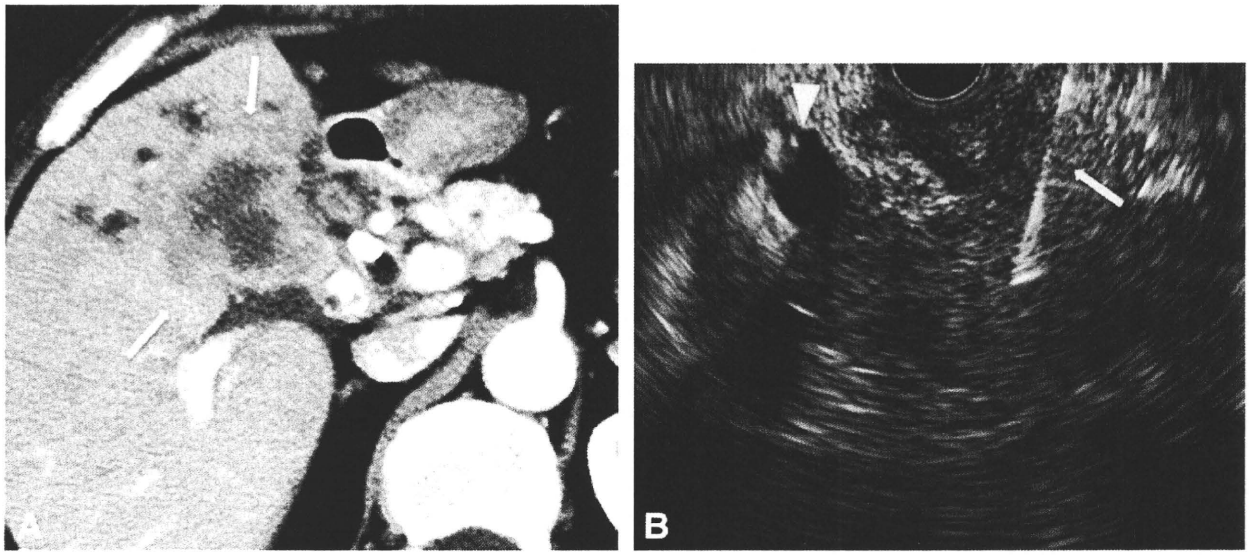

Figure 3. Findings of CT and EUS-guided FNA of gallbladder carcinoma from Patient 13. **A,** A CT image shows diffuse, irregular wall thickening and the disrupted mucosal line of the gallbladder (*arrow*). **B,** EUS-guided FNA for a gallbladder mass lesion (*arrow*, FNA needle inside the lesion; *arrowhead*, the gallbladder lumen).

plications developed in any of the 15 patients within the initial 48 hours. With regard to delayed complications, patients with XGC were followed-up as outpatients at regular intervals, and all those with GB carcinoma were followed-up as outpatients every 1 to 2 weeks for chemotherapy. No serious procedure-related delayed complications developed. The diagnostic accuracy of EUS-FNA to correctly distinguish between benign and malignant masses was 93.3% (14/15; 95% CI, 62.4%-99.9%), with a sensitivity and specificity of 90% (95% CI, 57.4%-99.9%) and 100% (95% CI, 51.9%-100%), respectively. Only one EUS-FNA result was a false negative because of insufficient sampling from unresectable GB carcinoma, and none of the results were false positive (Table 3).

The overall EUS-FNA diagnosis was concordant with the final diagnoses in 12 lesions (accuracy 80%; 95% CI, 54%-93.7%). Among the 3 discordant false-negative results, the EUS-FNA yield was insufficient, and only atypical cells or only inflammatory cells were found in one sample each.

TABLE 3. Diagnostic yield of EUS-guided FNA: benign versus malignant

	Final diagnosis	
	Benign	**Malignant**
EUS-guided FNA diagnosis		
Benign	5 (TN)	1* (FN)
Malignant	0 (FP)	9 (TP)
Total	5	10

TN, True negative; *FN,* false negative; *FP,* false positive; *TP,* true positive; *XGC,* xanthogranulomatous cholecystitis.
Five TNs comprised XGC (n = 4) and insufficient aspirate (n = 1).
*Atypical EUS-guided FNA diagnosis of one FN.

DISCUSSION

EUS-FNA is an established diagnostic tool for obtaining tissue samples from diverse types of lesions. Although EUS has the potential for staging GB masses, it has not been adequately evaluated in the context of GB mass lesions. Only 3 reports have been published. Jacobson et al[1] reviewed 6 patients (GB carcinoma, n = 5; XGC, n = 1) with an 83% accuracy rate. Varadarajulu and Eloubeidi[2] also studied 6 patients (GB carcinoma, n = 5) and achieved 100% sampling adequacy. Meara et al[15] punctured 7 GB mass lesions and obtained 100% specificity and 80% sensitivity. Our sampling adequacy was 86.6% with only 2 insufficient samples. Our approach was to distinguish between benign and malignant masses, especially those that were XGC, because the malignant potential of this lesion cannot be conclusively ruled out based on imaging alone.[16,17,18-20] One of 6 XGC punctures yielded an insufficient aspirate, and the patient underwent extended right hepatectomy, transverse colectomy, and partial duodenal resection. The other 5 patients avoided surgery or at least major resections after EUS-FNA, which justifies the use of EUS-FNA when XGC is suspected. Another point is that coexisting carcinomas cannot be ruled out, because they have been identified in 2% to 15% of patients with XGC.[21-23] Notably, most GB carcinoma associated with XGC occurs in the GB neck region,[20-22] which is thought to be due to increased pressure within the GB. Therefore, we

recommend careful observation of the GB neck region and of the cystic duct by EUS in such circumstances, and adequate sampling from such regions will greatly reduce the incidence of false-negative findings for coexisting carcinomas. We reported sensitivity, specificity, and accuracy of 90%, 100%, and 93.3%, respectively. This level of accuracy might be attributable to immediate cytological analysis and repeated needle passage to acquire adequate samples. We were also concerned about the possibility of puncturing cystic structures like the GB, and, in turn, spilling its contents. Thus, our operators attempted to avoid puncturing the GB mass through any intervening layer of fluid or potential space and targeted the mass by enfacing the probe simply through changing the position of the echoendoscope. The strength of the present study is that relatively more patients with GB mass lesions were recruited than in published reports. We also selected patients who had undergone EUS-FNA for a GB mass itself, regardless of whether an LN had been punctured beforehand. However, the retrospective design and the patient selection algorithm might have led to selection bias. In conclusion, we believe that EUS-FNA is a safe, feasible, and accurate method of detecting malignancies among GB mass lesions, and we recommend its incorporation into diagnostic work-up algorithms.

REFERENCES

1. Jacobson B, Pitman M, Brugge W. EUS-guided FNA for the diagnosis of gallbladder masses. Gastrointest Endosc 2003;57:251-4.
2. Varadarajulu S, Eloubeidi M. Endoscopic ultrasound-guided fine-needle aspiration in the evaluation of gallbladder masses. Endoscopy 2005;37: 751-4.
3. Pandey M, Sood B, Shukla R, et al. Carcinoma of the gallbladder: role of sonography in diagnosis and staging. Ultrasound 2000;28:227-32.
4. Venkataramu N, Sood B, Gupta S, et al. Ultrasound-guided fine needle aspiration biopsy of gall bladder malignancies. Acta Radiologica 1999; 40:436-9.
5. Das D, Tripathi R, Bhambhani S, et al. Ultrasound-guided fine-needle aspiration cytology diagnosis of gallbladder lesions: a study of 82 cases. Diagn Cytopathol 1998;18:258-64.
6. Kumar A, Aggarwal S, Berry M, et al. Ultrasonography of carcinoma of the gallbladder: an analysis of 80 cases. J Clin Ultrasound 1990;18: 715-20.
7. Zargar S, Khuroo M, Mahajan R, et al. US-guided fine-needle aspiration biopsy of gallbladder masses. Radiology 1991;179:275-8.
8. Wu S, Lin K, Soon M, et al. Ultrasound-guided percutaneous transhepatic fine needle aspiration cytology study of gallbladder polypoid lesions. Am J Gastroenterol 1996;91:1591-4.
9. Wiersema M, Vilmann P, Giovannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology 1997;112:1087-95.
10. Yamao K, Mizuno N, Takagi T, et al. How I do it and when I use (and do not use) EUS-FNA. Gastrointest Endosc 2009;69:134-7.
11. Bhutani M, Logro no R. Endoscopic ultrasound-guided fine-needle aspiration cytology for diagnosis above and below the diaphragm. J Clin Ultrasound 2005;33:401-11.
12. Al-Haddad, M, Wallace MB, Woodward TA, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. Endoscopy 2008;40:204-8.
13. Yamao K, Sawaki A, Mizuno N, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB): past, present, and future. J Gastroenterol 2005;40:1013-23.
14. Hawes R, Fockens P. Endosonography, 1st ed. Philadelphia: Saunders; 2006.
15. Meara R, Jhala D, Eloubeidi M, et al. Endoscopic ultrasound-guided FNA biopsy of bile duct and gallbladder: analysis of 53 cases. Cytopathology 2006;17:42-9.
16. Shuto R, Kiyosue H, Komatsu E, et al. CT and MR imaging findings of xanthogranulomatous cholecystitis: correlation with pathologic findings. Eur Radiol 2004;14:440-6.
17. Uchiyama K, Ozawa S, Ueno M, et al. Xanthogranulomatous cholecystitis: the use of preoperative CT findings to differentiate it from gallbladder carcinoma. J Hepatobiliary Pancreat Surg 2009;16:333-8.
18. Spinelli A, Schumacher G, Pascher A, 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.
19. Enomoto T, Todoroki T, Koike N, et al. Xanthogranulomatous cholecystitis mimicking stage IV gallbladder cancer. Hepatogastroenterology 2003;50:1255-8.
20. Makino I, Yamaguchi T, Sato N, et al. Xanthogranulomatous cholecystitis mimicking gallbladder carcinoma with a false-positive result on fluorodeoxyglucose PET. World J Gastroenterol 2009;15:3691-3.
21. Benbow E. Xanthogranulomatous cholecystitis associated with carcinoma of the gallbladder. Postgrad Med J 1989;65:528-31.
22. Lee H, Joo K, Kim D, et al. A case of simultaneous xanthogranulomatous cholecystitis and carcinoma of the gallbladder. Korean J Intern Med 2003;18:53-6.
23. Krishnani N, Dhingra S, Kapoor S, et al. Cytopathologic diagnosis of xanthogranulomatous cholecystitis and coexistent lesions: a prospective study of 31 cases. Acta Cytologica 2007;51:37-41.

Digestive Endoscopy (2010) **22**, 147–150 doi:10.1111/j.1443-1661.2010.00944.x

HOW I DO IT

ENDOSCOPIC ULTRASOUND-GUIDED CHOLEDOCHODUODENOSTOMY

KAZUO HARA,[1] KENJI YAMAO,[1] NOBUMASA MIZUNO,[1] AKIRA SAWAKI,[1] TADAYUKI TAKAGI[1] AND VIKRAM BHATIA[2]

[1]*Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; and* [2]*Department of Medical Hepatology, Institute of Liver and Biliary Sciences, Delhi, India*

Endoscopic biliary drainage (EBD) may be unsuccessful in some patients, because of failed biliary cannulation or tumor infiltration, limiting endoscopic access to major papilla. The alternative method of percutaneous transhepatic biliary drainage carries a risk of complications, such as bleeding, portal vein thrombus, portal vein occlusion and intra- or extra-abdominal bile leakage. Recently, endoscopic ultrasonography (EUS)-guided biliary stent placement has been described in patients with malignant biliary obstruction. Technically, EUS-guided biliary drainage is possible via transgastric or transduodenal routes or through the small intestine using a direct access or rendezvous technique. We describe herein a technique for direct stent insertion from the duodenal bulb for the management of patients with jaundice caused by malignant obstruction of the lower extrahepatic bile duct. We think transduodenal direct access is the best treatment in patients with jaundice caused by inoperable malignant obstruction of the lower extrahepatic bile duct when EBD fails.

Key words: endoscopic biliary drainage, endoscopic ultrasonography (EUS)-guided biliary drainage, EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided fine-needle aspiration (EUS-FNA), interventional EUS.

INTRODUCTION

Endoscopic ultrasonography (EUS) has become an indispensable diagnostic procedure using endoscopy along with intraluminal ultrasonography. EUS provides high-resolution images of gastrointestinal malignancies such that depth of tumor invasion can be accurately determined. It also visualizes lesions outside of the gastrointestinal tract, particularly those in the pancreas and bile ducts. In 1992, EUS-guided fine-needle aspiration (EUS-FNA) of lesions in the pancreas head was made possible using a curved linear array echoendoscope. Since then, many researchers expanded the indication of EUS-FNA to various types of lesions as well as to a variety of therapeutic purposes even in the field of biliary diseases.[1–17] In the present paper, we present our experience and technique of EUS-guided choledochoduodenostomy (EUS-CDS).

METHODS

Technique for EUS-guided choledochoduodenostomy

The method of EUS-CDS in our hospital is as follows.

- Insert a convex-type ultrasound endoscope (GF-UCT240; Olympus Optical, Tokyo, Japan) into the duodenum, and place the top of the endoscope in the duodenal bulb.
- Carry out endoscopic observation to confirm the absence of any lesions in the duodenal bulb.
- Visualize the extrahepatic bile duct along the long axis from the duodenal bulb. At this stage, adjust the location of the scope so that the puncture needle is toward the hepatic hilum, and confirm a lack of vessels in the punctured region by using color and power Doppler mode.
- Puncture the bile duct under EUS guidance using a 22-G FNA needle (NA-200H-8022; Olympus Optical, Tokyo, Japan) and confirm the aspiration of bile juice (Fig. 1).
- Inject contrast medium through the needle to visualize the intra- and extrahepatic bile ducts (Fig. 2).
- After removal of the needle, insert a needle knife (Zimmon papillotomy knife; Cook Endoscopy, Winston-Salem, NC, USA) into the bile duct while setting the output current to the incision mode under real-time EUS guidance.

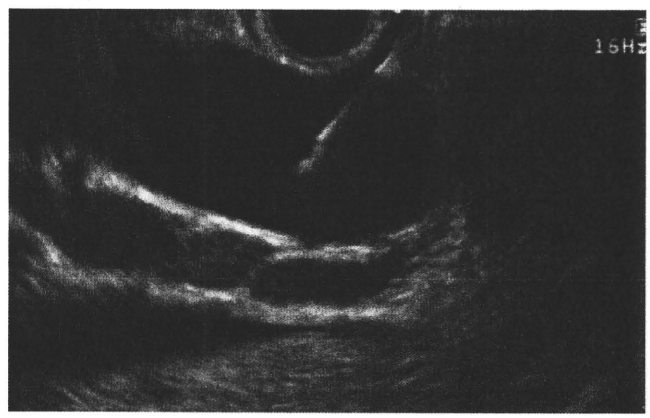

Fig. 1. Convex echoendoscope, located in the apex of the duodenal bulb, clearly displays the extrahepatic bile duct and the puncture needle.

Correspondence: Kazuo Hara, Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Email: khara@aichi-cc.jp

Received 4 April 2009; accepted 2 November 2009.

- Remove the needle and insert a 0.35-inch guidewire (length, 450 cm, Jagwire; Microvasive Endoscopy, Boston Scientific, Natick, MA, USA) through the outer sheath deep into the intrahepatic bile duct (Fig. 3).
- Remove the outer cover of the needle knife and maintain the position of the guidewire.
- Dilate the fistula (punctured point) using tapered biliary dilation catheters of 6 Fr, 7 Fr and 9 Fr in size. Soehendra biliary dilation catheters 6, 7 and 9 Fr (Wilson-Cook) are used to sequentially dilate the fistula over the guidewire (Figs 4,5).
- Finally, insert an 8.5-Fr straight biliary stent (Tannenbaum; Wilson-Cook or Flexma; Microvasive Endoscopy, Boston

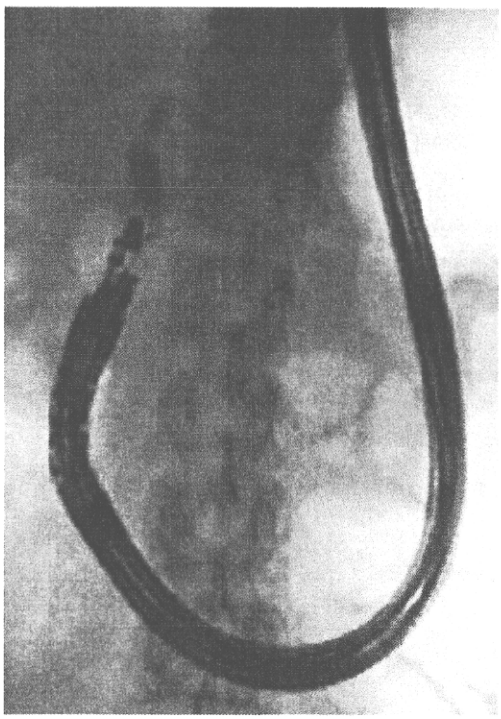

Fig. 2. Cholangiogram obtained by endoscopic ultrasonography-guided puncture.

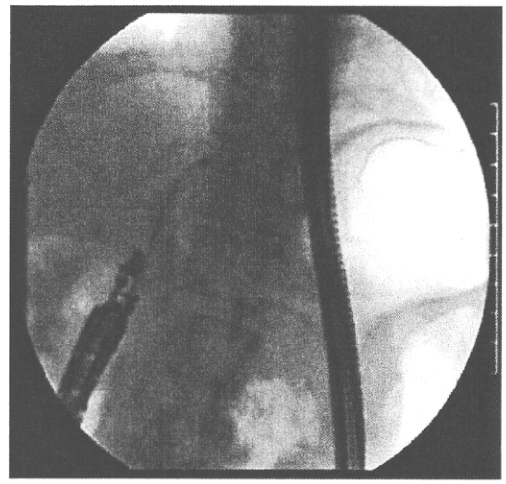

Fig. 4. X-ray image of Soehendra biliary dilation catheter for dilation of the bile duct and the duodenum.

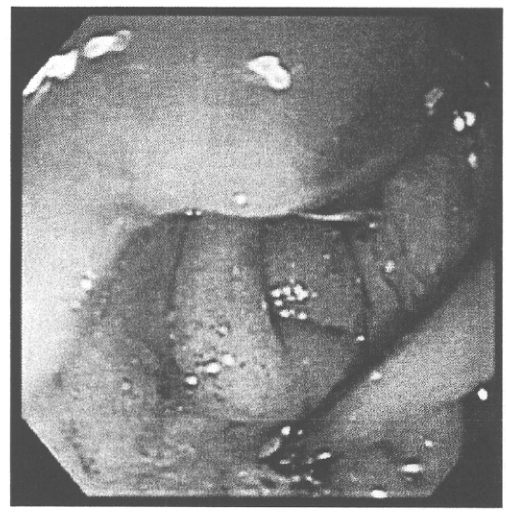

Fig. 5. Endoscopic image of Soehendra biliary dilation catheter for dilation of the bile duct and the duodenum.

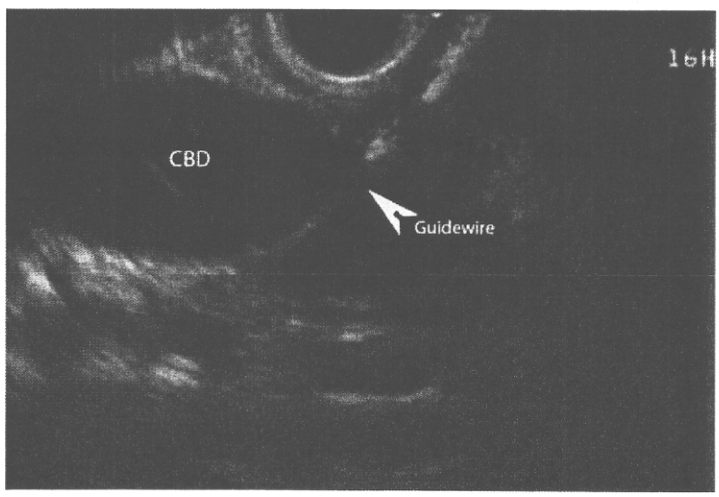

Fig. 3. Convex echoendoscope displaying the guidewire in the extrahepatic bile ducts. CBD, common bile duct.

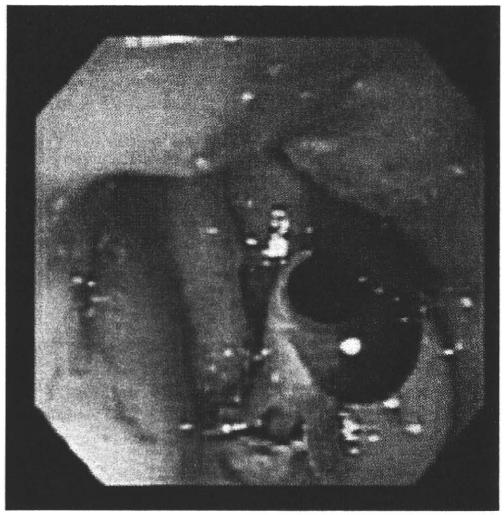

Fig. 6. Biliary stent placed from the first portion of the duodenum to the extrahepatic biliary duct.

Scientific) through the choledochoduodenal fistula into the extrahepatic bile duct (Fig. 6).
- Confirm the absence of intra-abdominal leakage of contrast medium on X-ray fluoroscopy.
- Confirm tube position and lack of bleeding, and complete drainage.

The modified method of EUS-CDS is as follows:
- Insert a 19-G needle (EchoTip; Wilson-Cook) transduodenally into the bile duct under EUS guidance.
- Aspirate the bile and insert the contrast medium into the bile duct for cholangiography.
- Insert a 450-cm long, 0.035-inch guidewire into the outer sheath.
- Dilate the choledochoduodenal fistula using a biliary catheter for dilation (Soehendra biliary dilator; Wilson-Cook), or papillary balloon dilator (Maxpass; Olympus Medical Systems, Tokyo, Japan).
- Insert a 5-Fr to 10-Fr biliary plastic stent or self-expandable metallic stent through the choledochoduodenostomy site into the extrahepatic bile duct.

Method for exchanging occluded stents in EUS-CDS (guidewire-assisted stent exchange)

The method for exchanging an occluded stent in our hospital is as follows.
- Remove the occluded stent using a dormia basket through a duodenoscope when the stent has been *in situ* for a sufficient period of time. The choledochoduodenal fistula is usually mature 2 or 3 weeks after stent insertion.
- After stent removal, insert an ERCP catheter (Tandem 3-lumen ERCP catheter; Microvasive Endoscopy, Boston Scientific) through the choledochoduodenal fistula into the bile ducts, followed by placement of a 0.035-inch guidewire (450 cm, Jagwire; Microvasive Endoscopy, Boston Scientific) deep into the intrahepatic biliary ducts (Fig. 7).
- Insert a new 8.5-Fr straight biliary stent (Tannenbaum stent; Wilson-Cook) over the guidewire into the bile ducts.

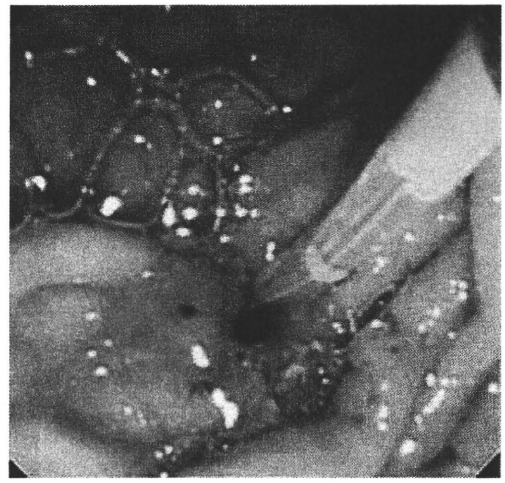

Fig. 7. Guidewire-loaded endoscopic retrograde cholangiopancreatography catheter inserted from the choledochoduodenal fistula, which shows a sufficiently wide opening.

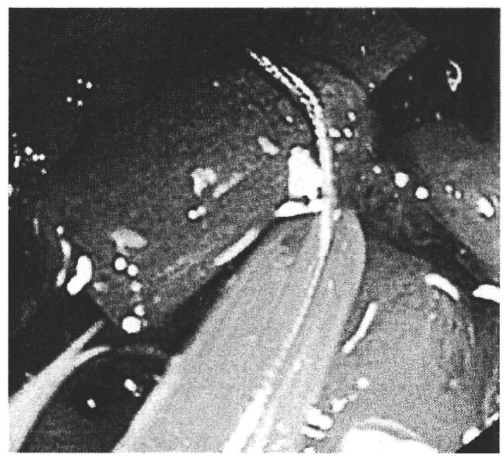

Fig. 8. Removal of the occluded stent using a snare with the guidewire in place.

The modified technique in our hospital for exchanging the occluded stent for EUS-CDS is as follows.
- Insert a 0.035-inch guidewire into the bile duct through an occluded stent using an ERCP catheter when the stent has not been *in situ* for a long enough time for a mature choledochoduodenal fistula to have formed.
- Remove the occluded stent using a snare with the guidewire in place, through the biopsy channel of the duodenoscope (Fig. 8).
- Insert a new 8.5-Fr straight biliary stent into the bile ducts over the guidewire.

DISCUSSION

Up to now, EUS-CDS for patients with malignant biliary duct obstruction has been reported to be technically successful without any serious complications, offering clinically effective drainage in all patients with a comparatively long patency period.[18,19] As more experience is gained, we have to

determine which of the following is more effective: (i) transduodenal approach versus transgastric approach; (ii) direct access versus rendezvous technique; (iii) fistulotome versus fine needle for biliary duct puncture; (iv) tapered biliary dilators versus balloon dilation; (v) plastic stent versus (covered) metal stent; (vi) straight stent versus pigtail stent; and (vii) 8.5-Fr stent versus greater or smaller sized stents, and troubleshooting for early and late complications.

Our opinions on the above-mentioned questions are as follows.

1. The transduodenal approach allows easy access to extrahepatic bile ducts and it is easy to dilate the fistula compared with the transgastric approach.

2. The rendezvous technique is complicated and needs much more time compared with the direct access technique. In case of patients with many ascites or in operable cases, the rendezvous technique may be better than the direct access technique.

3. We prefer to use the needle knife to puncture extrahepatic bile ducts, because a site punctured by the needle knife is easy to dilate compared with the 19-G FNA needle. Sometimes, it is very difficult for us to dilate the gastrointestinal wall and it takes too much time.

4. If a balloon is used to dilate the gastrointestinal wall, we have to pull back the echoendoscope. So, the transduodenal approach has the possibility of the scope slipping out from the duodenum to the stomach.

5. Because the transgastric approach needs a large-sized stent diameter to prevent stent occlusion by food, a metal stent may be effective for the gastric approach.

6. It is difficult or impossible to use the guidewire-assisted stent exchange method for the pigtail stent *in situ*, when the stent is occluded.

As the above issues are resolved, we envisage that the technique of EUS-CDS will be gradually standardized and new dedicated endoscopic devices will be developed.

REFERENCES

1. Winick AB, Waybill PN, Venbrux AC. Complications of percutaneous transhepatic biliary interventions. *Tech. Vasc. Interv. Radiol.* 2001; **4**: 200–6.
2. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: A new technique for biliary drainage. *Endoscopy* 2001; **33**: 898–900.
3. Giovannini M, Dotti M, Bories E *et al.* Hepaticogastrostomy by echo-endoscopy as a palliative treatment in a patient with metastatic biliary obstruction. *Endoscopy* 2003; **35**: 1076–8.
4. Burmester E, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangio-drainage of the bile duct: Report of 4 cases. *Gastrointest. Endosc.* 2003; **57**: 246–51.
5. Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: Report of 6 cases. *Gastrointest. Endosc.* 2004; **59**: 100–7.
6. Kahaleh M, Yoshida C, Kane L, Yeaton P. Interventional EUS cholangiography: A report of five cases. *Gastrointest. Endosc.* 2004; **60**: 138–42.
7. Puspok A, Lomoschitz F, Dejaco C, Hejna M, Sautner T, Gangl A. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: A case series. *Am. J. Gastroenterol.* 2005; **100**: 1743–7.
8. Lai R, Freeman ML. Endoscopic ultrasound-guided bile duct access for rendezvous ERCP drainage in the setting of intradiverticular papilla. *Endoscopy* 2005; **37**: 487–9.
9. Kahaleh M, Wang P, Shami VM, Tokar J, Yeaton P. EUS-guided transhepatic cholangiography: Report of 6 cases. *Gastrointest. Endosc.* 2005; **61**: 307–13.
10. Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. Interventional EUS-guided cholangiography: Evaluation of a technique in evolution. *Gastrointest. Endosc.* 2006; **64**: 52–9.
11. Yamao K, Sawaki A, Takahashi K, Imaoka H, Ashida R, Mizuno N. EUS-guided choledochoduodenostomy for palliative biliary drainage in case of papillary obstruction: Report of 2 cases. *Gastrointest. Endosc.* 2006; **64**: 663–7.
12. Ang TL, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. *JOP* 2007; **9**: 438–43.
13. Bories E, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: Results of a pilot study. *Endoscopy* 2007; **39**: 287–91.
14. Will U, Thieme A, Fueldner F, Gerlach R, Wanzar I, Meyer F. Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage. *Endoscopy* 2007; **39**: 292–5.
15. Yamao K, Bhatia V, Mizuno N *et al.* EUS-guided choledochoduodenostomy for palliative biliary drainage in patients with malignant biliary obstruction: Results of long-term follow-up. *Endoscopy* 2008; **40**: 340–2.
16. Tarantino Tarantino I, Barresi L, Repici A, Traina M. EUS-guided biliary drainage: A case series. *Endoscopy* 2008; **40**: 336–9.
17. Kitano M, Sakamoto H, Komaki T. Present status and future perspective of EUS-guided drainage. *Dig. Endosc.* 2009; **21** (Suppl 1): S66–70.
18. Itoi T, Yamao K, EUS 2008 Working Group. EUS 2008 Working Group document: Evaluation of EUS-guided choledochoduodenostomy (with video). *Gastrointest. Endosc.* 2009; **69** (2 Suppl): S8–12.
19. Yamao K. EUS-guided choledochoduodenostomy. *Gastrointest. Endosc.* 2009; **69** (2 Suppl): S194–9.

胆と膵 2010
Vol. 31 (6) p. 615～618

胆道癌化学療法に対する新たな展開：ゲムシタビン＋シスプラチン併用療法*

水野 伸匡[1)]・澤木 明[1)]・原 和生[1)]・肱岡 範[1)]・田近 正洋[2)]
河合 宏紀[2)]・近藤 真也[1)]・佐伯 哲[1)]・赤羽 麻奈[1)]・小倉 健[1)]
羽場 真[1)]・丹羽 康正[2)]・山雄 健次[1)]

要約：切除不能胆道癌に対する化学療法は，gemcitabine（GEM）単独治療とGEM＋cisplatin（CDDP）の併用（GC療法）による無作為化比較試験が英国（ABC-02試験）と日本（BT-22試験）でそれぞれ行われ，GC療法で有意な生存期間の延長が得られ，GC療法は切除不能胆道癌の国際的な標準治療として位置づけられた。さらにBT-22試験では胆道ドレナージ等と治療成績についても検討され，胆道癌特有の閉塞性黄疸や胆管炎に対しても適切なドレナージ処置を加えることで，十分に治療効果が期待出来ることが示された。今後は他の併用療法の開発や，分子標的薬の導入などにより，胆道癌に対する治療成績のさらなる向上が期待される。

Key words：胆道癌，化学療法，胆道ドレナージ

はじめに

切除不能あるいは再発胆道癌に対する化学療法は，これまでさまざまな第Ⅱ相試験が行われてきた[1)]。わが国でもgemcitabine（GEM）[2)]とS-1[3)]の第Ⅱ相試験が行われ，その結果，2007年の胆道癌診療ガイドラインではGEMとS-1が同列で推奨されている[4)]。しかしおのおのの薬剤の治療成績は十分満足するものではなく，他の癌種同様他剤との併用療法や，分子標的薬への期待が持たれている[5,6)]。

そのような状況の中で，英国で行われたGEM単独とGEM＋cisplatin併用（Cis/ Gem療法）の無作為化第Ⅱ相試験（ABC-01試験）[7)]ではGEM単独群の奏効率15%，PFS中央値4ヵ月に対し，Cis/ Gem療法群では奏効率24%，PFS中央値8ヵ月であり，Cis/ Gem療法の有用性が示唆された。引き続き行われた大規模な第Ⅲ相試験（ABC-02試験）[8)]では，Cis/ Gem療法による生存期間の有意な延長が確認された。国内でもABC-02試験と同様の方法（Gem vs Cis/ Gem）で無作為化比較試験（BT-22試験）が行われ，ほぼ同様な結果が示された[9)]。

一方，胆道癌の治療中には閉塞性黄疸や胆管炎といった合併症を併発することが多く，これらの合併症をいかにコントロールするかが化学療法の継続と患者の予後を左右すると考えられる。本稿では，BT-22試験の結果ならびに減黄処置との関連性について解説する。

Ⅰ．無作為化比較試験（BT-22試験）の結果

局所進行又は遠隔転移を有する化学療法歴のない胆道癌患者を対象とし，GEM/ CDDP（GC群）とGEM群の1年生存率を主要目的に，有害事象，抗腫瘍効果，無増悪生存期間（PFS），6ヵ月無増悪生存率，病勢コントロール率を副次的目的として行われた。

1年生存率ではGC群39.0%，GEM群31.0%であり，生存期間中央値（MST）ではGC群11.2ヵ月，GEM群7.7ヵ月であり，GC群がGEM群を上回っていた。PFS中央値でもGC群は5.8ヵ月であり，GEM群の3.7ヵ月を上回っていた。抗腫瘍効果では，奏効率はGC群で19.5%，GEM群では11.9%，病勢コントロール率でもGC群68.3%に対してGEM群50.0%でありすべてにお

* Perspective of chemotherapy for biliary tract cancer：gemcitabine with cisplatin

1）愛知県がんセンター中央病院消化器内科（〒464-8681 名古屋市千種区鹿子殿1-1）
2）同 内視鏡部