Ⅱ．胆道癌における分子標的治療薬の臨床試験

固形癌に対する分子標的治療薬の開発は，疾患頻度の高い肺癌，大腸癌，乳癌の分野で先行しており，追随する肝癌，腎癌，胃癌においても日常臨床への分子標的治療薬の導入が始まっている。胆道癌に対する分子標的治療薬の臨床試験も増えつつあるが，治療開発の困難な疾患であるからこそ，先行分野における成功例に学び，より効果的な治療開発をすすめることが肝要である。

胆道癌に対する分子標的治療薬の臨床試験を表1に示す。一部の試験は既に結果が報告されているが，大部分は現在進行中である。個々の分子標的薬剤の詳細については他稿に譲り，これまでの分子標的薬剤の開発の歴史を踏まえた胆道癌に対する臨床試験の現状と方向性について述べる。

1．試験対象となっている薬剤

表1に示す通り，erlotinib（肺癌），cetuximab（大腸癌），bevacizumab（大腸癌，肺癌，乳癌），sorafenib（腎癌，肝癌），trastuzumab（乳癌，胃癌）といった，既に各種の癌で治療効果が確認された薬剤が胆道癌に対しても試みられている。このようなシグナル伝達系阻害剤や血管新生阻害剤が，胆道癌においても期待される根拠として，Yoshikawaら[6]の報告があげられる。Retrospectiveではあるものの，236例を対象に行われた臨床病理学的検討の結果であり，EGFR，VEGF，HER2の過剰発現は肝内胆管癌の27.4%，53.8%，0.9%，肝外胆管癌の19.2%，59.2%，8.5%にみられると報告された。さらに肝内胆管癌におけるEGFR発現は予後不良因子かつ再発の危険因子であり，VEGF発現は血行性転移に関与する可能性が示されている。現在，胆道癌においてもこれらを標的とする治療薬を中心に開発されている。

胆道癌に対する分子標的治療薬の試験として最初に報告されたのはerlotinib[7]の単剤療法である。奏効率（RR）は8%（3/42）と低いものの，24週での無増悪生存割合が17%（7/42）と一定の効果が示された。その後，lapatinib[11]やsorafenib[14,15]の単剤療法も報告されたが，RR 0～6%，病勢制御割合（DCR）26～35%と同様の結果であった。これらの分子標的薬の単剤療法では従来のcytotoxicな抗癌剤の治療成績を上回るとは期待できないため，また，分子標的治療薬と従来の抗癌剤とは毒性プロファイルが異なる点を生かし，現在では併用療法が開発の中心となっている。Bevacizumabのような血管新生阻害剤に関しても，これまで単剤による治療効果は認められておらず，腫瘍血管の正常化と組織圧の低下により抗癌剤の効果増強をもたらすと考えられることから，胆道癌に対しては抗癌剤との併用療法が試みられている。併用療法に用いられる抗癌剤は，GEM，フッ化ピリミジン，プラチナ製剤などであったが，ABC-02試験以降，GEM＋CDDPあるいはGEM＋oxaliplatin（GEMOX）が中心である。

2．試験のタイプ

試験の多くは少数例による第Ⅱ相試験である。主要評価項目としては，RRより無増悪生存期間（PFS）が多く用いられている。これは，胆道癌の原発病変が測定しづらいというだけでなく，分子標的治療薬のcytostaticな効果を評価するためでもある。しかし，後述するように，RRやPFSでは表現されない分子標的治療薬の有用性を見逃さないように注意する必要がある。

比較試験としては現在，GEMOX±cetuximab（BINGO）[9]，GEM＋CDDP±cediranib（ABC-03），GEM±sorafenib（GEMSO），GEM＋vandetanib vs GEM vs vandetanib（VANGOGH）の4試験が進行中である。どの試験も胆道癌患者全体を対象として行われている。一方，分子標的治療薬の臨床試験では，特定のバイオマーカーにより高い治療効果が期待できる患者群を抽出し試験対象とすることもある。例えば胃癌に対するtrastuzumabの開発がその良い成功例である。Her2を標的とするtrastuzumabは，その理論の通りHer2陰性例には効果が得られないことが乳癌の臨床試験でわかっていたため[19]，「Her2陽性胃癌」のみを対象とした第Ⅲ相試験（化学療法±trastuzumab）を行い，その有用性の証明に成功した（ToGA試験）[20]。Her2陽性は胃癌全体の10～20%に過ぎないため，胃癌患者全体を対象とした比較試験であればtrastuzumabの効果を見い出せなかったであろう。このように特定のバイオマーカーにて選択した患者を対象とする試験はエンリッチメントデザインと呼ばれる（図1）[21,22]。

同様にEGFRを標的とするcetuximabは「EGFR陽性大腸癌」を対象とした臨床試験が行われた。このため，わが国でのcetuximabの適応はEGFR陽性例に限定されているが，実際には免疫組織化学法によるEGFR発現の強度はcetuximabの効果とほとんど相関せず，EGFR発現を認めなくともcetuximabが有効であることも報告されている[23]。その後，多くの検討から，「KRAS遺伝子変異」が抗EGFR抗体にとって重要なバイオマーカーであることが判明した。このよう

表 1　胆道癌に対する分子標的治療薬の臨床試験

Agent	Target	Regimen	Phase	Sample Size	Disease	Primary endpoint (phase II)	Study Start Date	Author (year)	Exploratry biomarker study
Erlotinib	EGFR	Erlotinib	p II	42		PFS(at 24 weeks)	2002/3	Philip (2006)[7]	EGFR/HEFI expression
		GEMOX + Erlotinib + RT	p I	110	BTC + PC		2004/8		
		Docetaxel + Erlotinib	p II	39	BTC + HCC	PFS(at 16 weeks)	2007/9	*Ramasubbaiah (2010)[8]	biologic tumor markers
		GEMOX + Erlotinib	p I	46	BTC + PC + DC		2009/11		e-cadherin, vimentin, fibronectin, amphiregulin, K-ras status (tumor)
Cetuximab	EGFR	GEMOX + Cetuximab	p II	22		RR	2006/10	Gruengerger (2009)[9]	KRAS mutation
		GEMOX + Cetuximab vs GEMOX	rp II	150		PFS(at 4 months)	2007/10	*Malka(2009)[10]	PET, EGFR pathway analyses (blood, tumor)
		GEM + Cetuximab	p II	43		PFS	2008/9		
Panitumumab	EGFR	GEM + Irinotecan + Panitumumab	p II	45		PFS(at 5 months)	2009/4		
Trastuzumab	Her2	Trastuzumab	p II	32	(Her2 positive)	RR	2007/5		
Lapatinib	EGFR, Her2	Lapatinib	p II	57	BTC (40) + HCC (17)	RR	2005/1	Ramanathan (2009)[11]	EGFR expression, KRAS mutations, EGFR genotyping
		Lapatinib	p II	70	BTC + HCC	RR	2005/10		target epidermal growth factor receptor gene and protein expression, genes that regulate cell cycle and apoptosis
		GEM (OX) + Lapatinib	p I	25	BTC (7) + PC (18)		2006/7	Safran (2008)[12]	
Bevacizumab	VEGF-A	CapOX + Bevacizumab + RT	p II	26		PFS (at 1 year)	2004/12		
		GEMOX + Bevacizumab	p II	35		PFS(at 6 months)	2006/5	Zhu (2010)[13]	PET
		FOLFOX6 + Bevacizumab	p II	24		PFS	2009/6		
		GEM + Cape + Bevacizumab	p II	50		PFS	2009/12		Circulating tumor cells (CTC)
Cediranib	VEGFR-2	GEM + CDDP + Cediranib vs GEM + CDDP + Placebo	rp II/III	136		PFS	2009/12		Biomarker evaluation (inc. circulating VEGF, sVEGFR-2, bFGF, LDII and CA19-9)
Sorafenib	Raf-1, VEGFR-2, 3, PDGFR-β, Flt-3, c-kit, RET	Sorafenib	p II	36		RR	2005/10	El-Khoueiry (2007)[14]	prognostic and predictive molecularmarkers of clinical outcome
		Sorafenib	p II	46		DCR (at 12 weeks)	2006/8	Bengala (2010)[15]	
		CapOX + Sorafenib	p I/II	66	BTC + PC	RR safety	2008/2		
		GEM + Sorafenib vs GEM + Placebo	rp II	96		PFS	2008/5		
		GEM + CDDP + Sorafenib	p II	39		PFS(at 6 months)	2009/8		pre-treatment tumor-cell pERK expression
		GEMOX + Sorafenib	p I/II	58		PFS(at 9 months)	2009/8		biomarkers of response
Vandetanib	VEGFR-2, 3, EGFR, RET	GEM + Cape + Vandetanib	p I	28	Solid Tumors → BTC + PC		2007/10		
		GEM + Vandetanib vs GEM + Placebo vs Vandetanib Monotherapy	rp II	174		PFS	2008/10		potential surrogate markers related to VEGFR and EGFR pathways (tumor, blood)
Imatinib	BCR-ABL, PDGFR, c-kit	FU/LV + Imatinib	p II	44		DCR	2007/5	#Sprenger (2009)[16]	
AZD6244	MEK	AZD6244	p II	35		RR	2007/11		protein expression (MEK, p-MEK, ERK, p-ERK, Akt, p-AKT, RASSF1A, NORE1A, NORE1B), gene mutation status (RAS, BRAF, EGFR), methylation of target gene promoters (RASSF1A, NORE1A, NORE1B)
ARRY-438162	MEK	ARRY-438162	p I	30	Solid Tumors → BTC		2009/8		mRNA, protein expression, mutation status (tumor)
Bortezomib	Proteasome	Bortezomib	p II	20		RR	2004/1	Costello(2009)[17]	phenotypic expression of NF-kB, p53, and other molecular markers (biliary washings, tumor biopsies)
(Combination)		Bevacizumab + Erlotinib	p II	55		RR	2006/5	#Holen (2009)[18]	EGFR expression, P-EGFR protein levels, AKT, p-AKT, MAPK, P-MAPK protein levels, VEGFR-1 and VEGFR-2 protein levels, EGFR mutations

GEM：Gemcitabine；OX：Oxaliplatin；RT：Radiation；Cap (e)：Capecitabine；CDDP：Cisplatin；rp II：randomized phase II；BTC：Biliary tract cancer；PC：Pancreatic cancer；DC：Duodenal cancer；PFS：Progression-free survival；RR：Response rate；DCR：Disease control rate *interim analysis #preliminary results

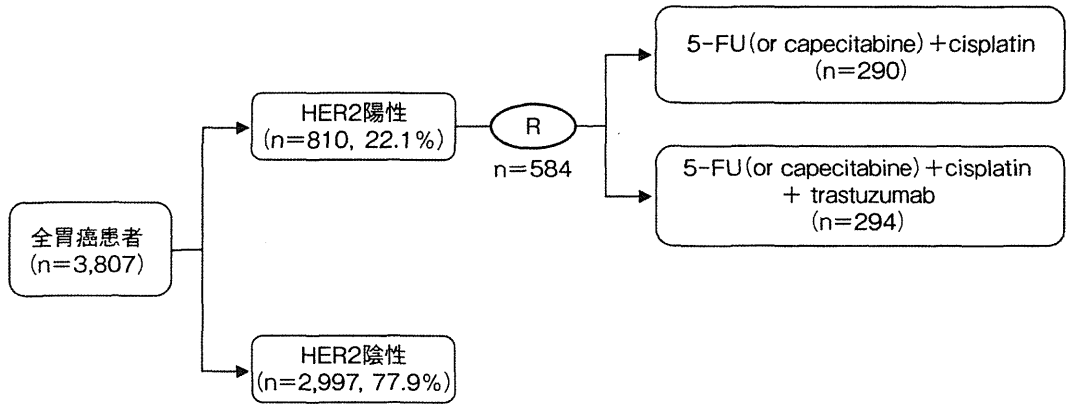

図 1 HER2 をバイオマーカーとしたエンリッチメントデザインの例（ToGA 試験）

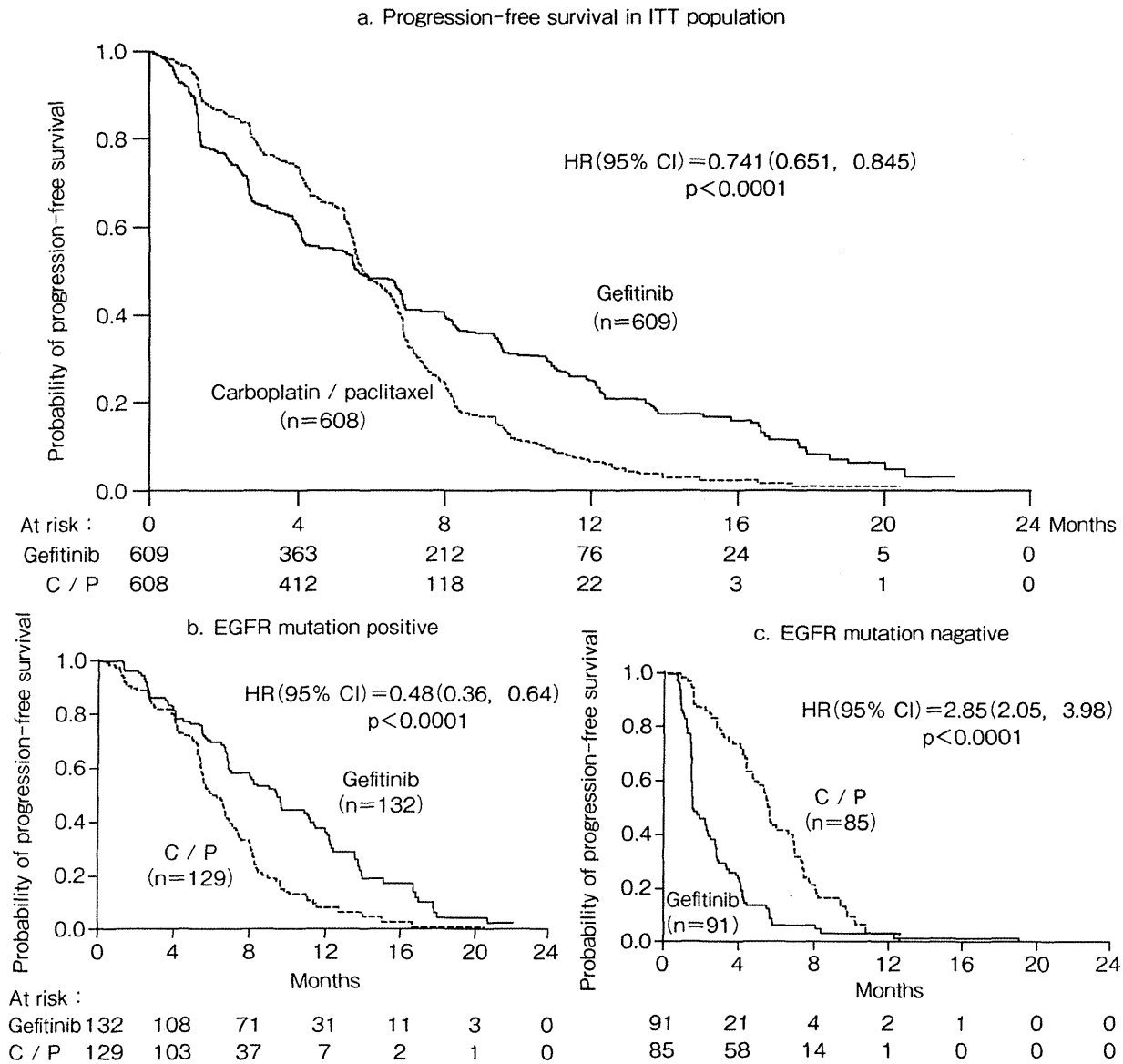

図 2 iPASS 試験（参考文献 29 より引用）

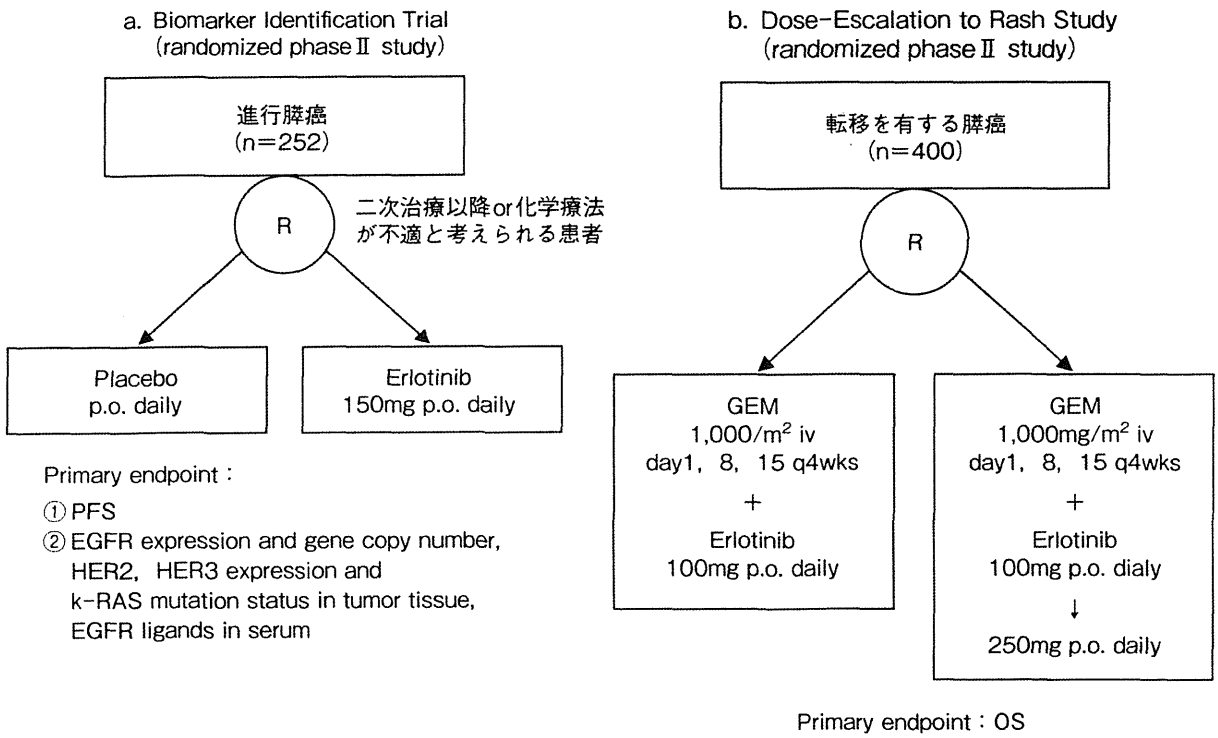

図 3 膵癌におけるerlotinibの有用性を探索する試験

にエンリッチメントデザインでは，事前に想定したバイオマーカーによって対象から外れた患者群に対するデータは得られないので，先行研究のデータや明確な生物学的根拠をもって対象を選択することが重要である。

非小細胞肺癌（NSCLC）に対するEGFRチロシンキナーゼ阻害薬（EGFR-TKI）の開発においては，特定のバイオマーカーが判明していなかったために，まず全NSCLC患者を対象とした第Ⅲ相試験が行われた。gefitinibが2試験[24,25]，erlotinibが2試験[26,27]行われ，総計4,000例以上の症例が登録されたにもかかわらず，いずれの試験も化学療法にEGFR-TKIを加えることでの延命効果は示されなかった。その後，gefitinibはEGFRの遺伝子変異のある症例に腫瘍縮小効果が高いことが報告され，この遺伝子変異がアジア人，非喫煙者，腺癌に高頻度に発現することが明らかになってきた[28]。このような臨床背景因子をもつ患者のみを対象とした第Ⅲ相試験（gefitinib vs 化学療法）を行ったところ，初めてPFSにおけるgefitinibの優越性が証明された（iPASS試験）[29]。本試験にて得られた二つのPFS曲線は途中でクロスするが（図2a），EGFR変異陽性例ではgefitinibの効果が上回り，変異陰性例では化学療法が圧倒的に優勢であることがわかった（図2b, c）。その後に報告されたEGFR変異陽性NSCLC患者を対象とした7試験の統合解析（I-CANP）においても，RR 76.4%，PFS 9.7ヵ月，生存期間中央値（MST）24.3ヵ月と，高い腫瘍縮小効果と長い生存期間が示された。このEGFRの遺伝子変異例における「著効」は，GISTに対するimatinibと同様に，癌細胞の増殖や生存の維持に強く関わる特定の癌遺伝子を標的にとらえた結果であると考えられる。現在では「EGFR遺伝子変異」は治療選択に関わる重要なバイオマーカーと認識されている。

膵癌の分野では，特定のバイオマーカーによる患者選択を行わずに全膵癌患者を対象としたGEM±erlotinibの第Ⅲ相試験が行われた[30]。その結果，生存期間（OS）においてGEM＋erlotinibがGEM単剤を上回ることが示されたもののその差はわずかであり，毒性や費用の面からも標準治療と認識されるに至っていない。残念ながら，バイオマーカーの探索が全体の1/5程度の症例にしか行われておらず，バイオマーカーと治療効果の関連を明らかにするには不十分であった[31]。現在，二次治療以降の患者等を対象に無治療vs erlotinibのランダム化第Ⅱ相試験が行われ，バイオマーカーの積極的な探索が試みられている（図3a）。

胆道癌に対するこれまでの臨床試験においては治療選択に有用なバイオマーカーは明らかでないため，エンリッチメントデザインではなく全胆道癌患者を対象とした試験が行われている。これらの試験においても，NSCLCや膵癌に対する開発の例にあるように，

患者全体に対する治療成績の比較にとどまることなく，治療効果の期待できる患者集団の選択に有用なバイオマーカーの探索や，個々の「著効」症例の詳細な検討が重要であろう。単アームの第Ⅱ相試験においても同様の視点をもって望むことが必要であり，従来通りのRRやPFSによる評価のみでは真の有効性を見逃す恐れがある。

3．バイオマーカーの探索

筆者が把握し得た限りのバイオマーカーの検索状況を表1に示す。治療開始時に治療選択に関わるバイオマーカーの探索が重要であることは前述したとおりであるが，治療開始後早期にその効果を予測するバイオマーカーも検討されている。例えば，EGFR阻害薬による皮疹の出現は臨床効果と相関することが指摘されており，大腸癌では皮疹の状況に応じてcetuximabを増量する比較試験も試みられた(EVEREST試験)[32]。膵癌に対するGEM＋erlotinibにおいても，erlotinibを通常通り100 mg/日投与する群と皮疹の状況に応じて250 mg/日まで増量する群を比較したランダム化第Ⅱ相試験が進行中である（図3b)。

血管新生阻害剤は腫瘍自体ではなく腫瘍環境に作用するが，臨床効果と相関するバイオマーカーの探索が試みられている。VEGFRを含む多標的阻害薬であるaxitibは第Ⅱ相試験の段階で血圧上昇と臨床効果に相関がみられると報告され[33,34]，膵癌におけるGEM±axitibの第Ⅲ相試験では，血圧上昇が認められない場合にはaxitibを増量することが規定されていた[35]。また近年ではCEC (circulating endothelial cell) やCEP (circulating endothelial progenitor) といった末梢循環血液中の細胞が新たな血管新生阻害剤のsurrogate markerとして注目されている。

胆道癌に対するGEM＋bevacizumabの第Ⅱ相試験では，治療開始後早期のFDG-PETのSUV値の低下が，RR，PFS，OSといった臨床効果に相関すると報告されている[13]。現在進行中のGEMOX±cetuximab (BINGO trial)[10]でもPETの意義が探索されており，分子標的治療薬の第Ⅱ相試験における新たなsurrogate markerとなるかもしれない。

おわりに

胆道癌は疾患頻度が低く，大腸癌や肺癌のような大規模な比較試験は容易でない。しかし，胃癌に対するtrastuzumabの開発が，乳癌と同様に「Her2陽性例」を選択して成功したように，他の頻度の高い疾患で得られた知見が成功の鍵となる可能性がある。ヘテロな集団であるが故に従来の「臓器別横断的」では治療開発が困難であった胆道癌にとって，「バイオマーカー別縦断的」なアプローチが突破口となることが期待される。

参考文献

1) 厚生労働省大臣官房統計情報部編：平成20年人口動態統計確定数の概況．(http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei08/dl/01.pdf)
2) The WHO mortality database 2005.(http://www-dep.iarc.fr/)
3) 日本肝癌研究会：第18回全国原発性肝癌追跡調査報告．
4) Valle JW, Wasan HS, Palmer DD, et al.：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 **27**：15s (suppl：abstr 4503), 2009.
5) Furuse J, Okusaka T, Miyazaki M, et al.：A randomized study of gemcitabine/ cisplatin versus single-agent gemcitabine in patients with biliary tract cancer. J Clin Oncol **27**：15s (suppl：abstr 4579), 2009.
6) Yoshikawa D, Ojima H, Iwasaki M, et al.：Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer **98**：418-425, 2008.
7) 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.
8) Ramasubbaiah R, Picus J, Bufill JA, et al.：Interim analysis of a phase Ⅱ trial of erlotinib (E) in combination with docetaxel (D) in advanced hepatocellular (HCC) and biliary tract carcinomas (BTC)：Hoosier Oncology Group GI06-101. Gastrointestinal Cancers Symposium (abstr 251), 2010.
9) Gruenberger B, Schueller J, Tamandl D, et al.：K-ras status and response in patients with advanced or metastatic cholangiocarcinoma treated with cetuximab plus gemcitabine-oxaliplatin (GEMOX)：a single center phase Ⅱ study. J Clin Oncol **27**：15s (suppl：abstr 4586), 2009.
10) Malka D, Trarbach T, Fartoux L, et al.：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 **27**：15s (suppl：abstr 4520), 2009.
11) Ramanathan RK, Belani CP, Singh DA, et al.：A phase Ⅱ study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer Chemother Pharmacol **64**：777-783, 2009.

12) Safran H, Miner T, Resnick M, et al. : Lapatinib/gemcitabine and lapatinib/gemcitabine/oxaliplatin : a phase I study for advanced pancreaticobiliary cancer. Am J Clin Oncol **31** : 140-144, 2008.
13) Zhu AX, Meyerhardt JA, Blaszkowsky LS, et al. : Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome : a phase 2 study. Lancet Oncol **11** : 48-54, 2010.
14) El-Khoueiry AB, Rankin C, Lenz HJ, et al. : SWOG 0514 : A phase II study of sorafenib (BAY 43-9006) as single agent in patients (pts) with unresectable or metastatic gallbladder cancer or cholangiocarcinomas. J Clin Oncol **25** : 18s (suppl : abstr 4639), 2007.
15) Bengala C, Bertolini F, Malavasi N, et al. : Sorafenib in patients with advanced biliary tract carcinoma : a phase II trial. Br J Cancer **102** : 68-72, 2010.
16) Sprenger K, Moehler M, Kettner E, et al. : Preliminary results of a multicenter phase II study of imatinib and fluorourcail/leucovorin(FU/LV)in patients with unresectable or metastatic gallbladder or biliary tract cancer. J Clin Oncol **27** : (suppl : abstr e15502), 2009.
17) Costello MR, Meropol NJ, Denlinger CS, et al. : A phase II trial of the proteasome inhibitor bortezomib in patients with recurrent or metastatic adenocarcinoma of the bile duct or gallbladder (NCI #6135). J Clin Oncol **27** : (suppl : abstr e15605), 2009.
18) Holen KD, Mahoney MR, LoConte NK, et al. : Efficacy report of a multicenter phase II trial testing a biologic-only combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer (BC) : A Phase II Consortium (P2C) study. J Clin Oncol **26** : (suppl : abstr 4522), 2008.
19) Slamon DJ, Leyland-Jones B, Shak S, et al. : Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med **344** : 783-792, 2001.
20) Cutsem EV, Kang Y, Chung H, et al. : 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 **27** : 18s (suppl : abstr LBA4509), 2009.
21) Simon R, Maitournam A : Evaluating the efficiency of targeted designs for randomized clinical trials. Clin Cancer Res **10** : 6759-6763, 2004.
22) Maitournam A, Simon R. On the efficiency of targeted clinical trials. Stat Med **24** : 329-339, 2005.
23) Chung KY, Shia J, Kemeny NE, et al. : Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. J Clin Oncol **23** : 1803-1810, 2005.
24) Giaccone G, Herbst RS, Manegold C, et al. : Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer : a phase III trial-INTACT 1. J Clin Oncol **22** : 777-784, 2004.
25) Herbst RS, Giaccone G, Schiller JH, et al. : Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer : a phase III trial-INTACT 2. J Clin Oncol **22** : 785-794, 2004.
26) Gatzemeier U, Pluzanska A, Szczesna A, et al. : Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer : the Tarceva Lung Cancer Investigation Trial. J Clin Oncol **25** : 1545-1552, 2007.
27) Herbst RS, Prager D, Hermann R, et al. : TRIBUTE : a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol **23** : 5892-5899, 2005.
28) Lynch TJ, Bell DW, Sordella R, et al. : Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med **350** : 2129-2139, 2004.
29) Mok TS, Wu YL, Thongprasert S, et al. : Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med **361** : 947-957, 2009.
30) Moore MJ, Goldstein D, Hamm J, et al. : Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer : a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol **25** : 1960-1966, 2007.
31) Moore MJ, da Cunha Santos G, Kamel-Reid S, et al. : The relationship of K-ras mutations and EGFR gene copy number to outcome in patients treated with Erlotinib on National Cancer Institute of Canada Clinical Trials Group trial study PA. 3. J Clin Oncol **25** : 18S (suppl : abstr 4521), 2007.
32) Tejpar S, Peeters M, Humblet Y, et al. : Phase I / II study of cetuximab dose-escalation in patients with metastatic colorectal cancer(mCRC)with no or slight skin reactions on cetuximab standard dose treatment (EVEREST) : Pharmacokinetic (PK), Pharmacodynamic (PD) and efficacy data. J Clin Oncol **25** : 18S (suppl : abstr 4037), 2007.
33) Rini BI, Schiller JH, Fruehauf JP, et al. : Association of diastolic blood pressure (dBP) >90 mmHg with overall survival (OS) in patients treated with axitinib (AG-013736). J Clin Oncol **26** : (suppl : abstr 3543) 2008.
34) Spano JP, Chodkiewicz C, Maurel J, et al. : Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic

cancer : an open-label randomised phase II study. Lancet **371** : 2101-2108, 2008.
35) Kindler HL, Ioka T, Richel DJ, et al. : A double-blinded, placebo-controlled, randomized, phase III study of axitinib (AG-013736 ; A) plus gemcitabine (G) vs. G plus placebo (P) in advanced pancreatic cancer (PC) patients (pts). European Journal of Cancer Supplements **7** : 361 (abstr 6502), 2009.

*　　*　　*

Endoscopic Ultrasound-Guided Choledochoduodenostomy for Malignant Lower Biliary Tract Obstruction

Kenji Yamao[a,*], Kazuo Hara[a], Nobumasa Mizuno[a], Susumu Hijioka[a], Hiroshi Imaoka[a], Vikram Bhatia[b], Yasuhiro Shimizu[c]

Q2 Q3 Q4 Q5

KEYWORDS

• Interventional EUS • EUS biliary drainage • EUS-BD
• EUS-guided choledochoduodenostomy • EUS-CDS

Endoscopic biliary drainage (EBD) may be unsuccessful in some patients because of failed biliary cannulation or tumor infiltration limiting endoscopic access to the major papilla.[1,2] The salvage technique of percutaneous transhepatic biliary drainage has a risk of complications such as bleeding and intra-abdominal or extra-abdominal bile leakage.[3]

Recently, endoscopic ultrasound (EUS)-guided biliary stent placement has been described in patients with malignant biliary obstruction in many review articles.[4–18] Technically, EUS-guided biliary drainage (EUS-BD) is possible via a transgastric or transduodenal route or through the small intestine with direct access or rendezvous technique. The following section evaluates the current evidence and potential role of EUS-guided choledochoduodenostomy (EUS-CDS), that is, direct stent insertion from duodenum, to relieve jaundice caused by lower end obstruction of the extrahepatic bile duct.

Financial support: None.
Potential competing interests: None.
[a] Department of Gastroenterology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-Ku, Nagoya 464-8681, Japan; [b] Department of Medical Hepatology, Institute of Liver and Biliary Sciences, Delhi, India; [c] Department of Gastrointestinal Surgery, Aichi Cancer Center Hospital, Nagoya, Japan
* Corresponding author.
E-mail address: kyamao@aichi-cc.jp

Q6 Q7

Gastrointest Endoscopy Clin N Am ■ (2012) ■–■
doi:10.1016/j.giec.2012.04.008 giendo.theclinics.com

TECHNIQUE OF EUS-CDS

Technique of EUS-CDS for Initial Stent Insertion

The method of EUS-CDS with electrocautery is described in a later section.[16,17] A convex linear array echoendoscope positioned in the duodenal bulb usually displays a markedly dilated extrahepatic bile duct in the setting of a lower bile duct obstruction. For optimal visualization, the echoendoscope should be in a long (looped) position, with the tip of the echoendoscope directed toward the hepatic hilum (**Figs. 1** and **2**). Under real-time EUS guidance, a 22-gauge needle is inserted transduodenally into the extrahepatic bile duct. A cholangiogram is obtained to display the dilated intrahepatic and extrahepatic biliary ducts proximal to the obstruction, under fluoroscopy. Although it is possible to proceed without fluoroscopic guidance, cholangiography and fluoroscopic guidance are useful to choose the most appropriate puncture site for EUS-CDS and to direct the guidewire deep into the intrahepatic ducts. EUS-guided puncture of the dilated extrahepatic bile duct is performed with a needle knife (Zimmon papillotomy knife; Cook Endoscopy, Winston-Salem, NC, USA), followed by a 0.035-in guidewire placement (Jag wire, 450 cm length; Microvasive, Boston Scientific Corp, Natick, Mass, USA) through the outer sheath of the needle knife. Tapered biliary dilation catheters of sizes 6F, 7F, and 9F (Soehendra biliary dilation catheters [SBDC-6, SBDC-7, and SBDC-9], Wilson-Cook, NC, USA) are used to sequentially dilate the punctured tract, over the intrabiliary guidewire. Finally, an 8.5F straight biliary stent (Tannenbaum, Wilson-Cook, NC, USA, or Flexma, Microvasive, Boston Scientific Corp, Natick, Mass, USA) is inserted through the choledochoduodenostomy opening into the extrahepatic bile duct over the guidewire (**Figs. 3** and **4**). When a 9F biliary dilator cannot be passed, a 7F straight biliary stent (Tannenbaum, Wilson-Cook, NC, USA) is inserted. The authors have also used a partially covered metal stent (WallFlex Biliary RX Stent, 10-mm diameter, 4 cm or 6 cm long, Boston Scientific Corp, Natick, MA, USA) instead of a plastic stent for EUS-CDS (**Fig. 5**).

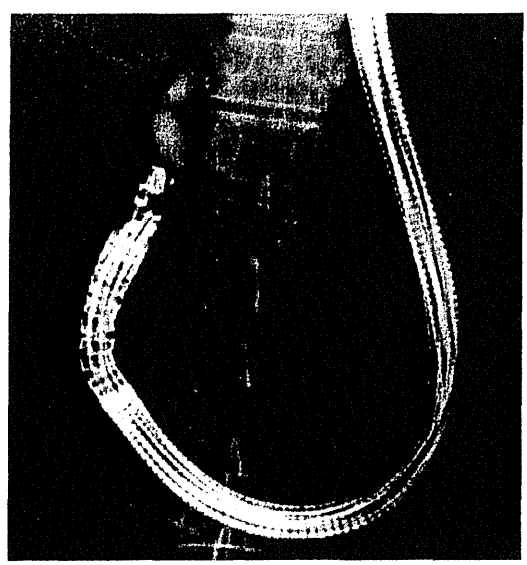

Fig. 1. Cholangiogram obtained by EUS-guided puncture with the tip of the convex transducer directed to the hepatic hilum. The echoendoscope was observed in the long/pushing scope position.

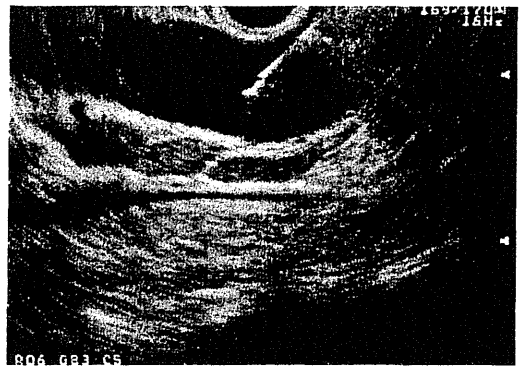

Fig. 2. Convex echoendoscope, located in the apex of the duodenal bulb, clearly displayed the extrahepatic bile duct, cystic duct, and puncture needle.

The technique of EUS-CDS without using the electrocautery is as follows. EUS-guided puncture of the dilated extrahepatic bile duct from the duodenal bulb is performed with a 19-gauge puncture needle (Echo Tip19; Cook Endoscopy, Winston-Salem, NC, USA). A 0.025- or 0.035-in guidewire (Jag wire, 450 cm long; Microvasive, Boston Scientific Corp, Natick, MA, USA) is placed through the fine-needle aspiration (FNA) needle deeply into the bile duct. A biliary balloon dilator catheter of 5F diameter (Max Force; Microvasive, Boston Scientific Corp, Natick, MA, USA) and/or a tapered biliary dilation catheter is used to dilate the tract over the guidewire. Q10 When it is difficult to dilate the fistula using these devices, a fistulotome over the guidewire may be useful. Finally, a 7F straight biliary stent (Flexma, Microvasive, Boston

Fig. 3. Choledochoduodenostomy was accomplished using a tube stent in the apex of the duodenal bulb.

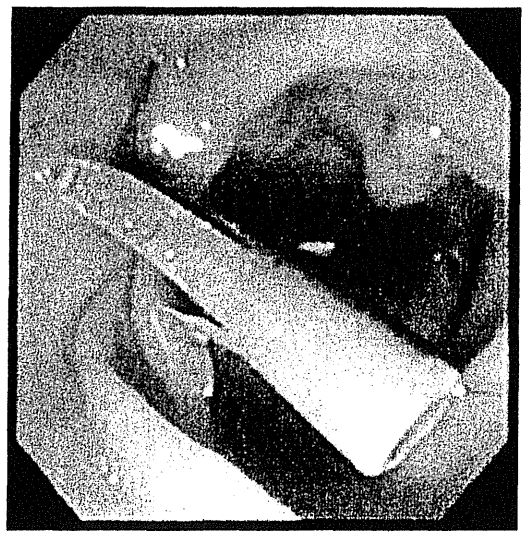

Fig. 4. Duodenoscope showed an 8.5F biliary stent in the first portion of the duodenum.

Scientific Corp, Natick, MA, USA) is inserted through choledochoduodenostomy into the extrahepatic duct over the guidewire.

No standardized method for EUS-CDS has yet been established, and researchers have performed the procedures in their own individual ways (**Table 1**).[18–40] For the extrahepatic bile duct puncture, a needle knife or fistulotome was used in 7 institutions, 19- and 22-gauge EUS-FNA needles in 5 institutions, EUS-FNA needles followed by a needle knife in 4 institutions, and either EUS-FNA needles or a needle knife in 2 institutions. Using an EUS-FNA needle to access the bile duct seems safer,

Fig. 5. Choledochoduodenostomy was accomplished using a metal stent in the apex of the duodenal bulb, using a forward-viewing echoendoscope.

although it is more difficult to sufficiently dilate the fistula for insertion of a biliary stent. Using a needle with electrocautery seems more risky, but it is easier and quicker to dilate the fistula large enough to insert a bigger stent.

Method for Exchanging an Occluded Stent Placed at EUS-CDS

In cases where the EUS-CDS stent has been in situ for a long time, the occluded stent is simply removed by using a Dormia basket through a duodenoscope.[19] The choledochoduodenal fistula is usually mature by 2 or 3 weeks after the stent insertion. After stent removal, the choledochoduodenal fistula is cannulated using an endoscopic retrograde cholangiopancreatography (ERCP) catheter (Tandem 3-lumen ERCP catheter; Microvasive Endoscopy, Boston Scientific Corp, Natick, MA, USA) followed by placement of a 0.035-in guidewire (Jag wire, 450 cm, Microvasive Endoscopy, Boston Scientific Corp, Natick, MA, USA) deeply into the intrahepatic biliary ducts. A new 8.5F straight biliary stent (Tannenbaum stent, Wilson-Cook, NC, USA) is then inserted over the guidewire.

In cases where the EUS-CDS stent has been inserted for only a short time, a mature choledochoduodenal fistula tract would not have formed. Hence, alternate techniques of exchanging the occluded stent of EUS-CDS should be adapted. A 0.035-in guidewire is carefully inserted into the bile duct through the occluded stent using an ERCP catheter (**Fig. 6**). The occluded stent is then removed by using a snare keeping the guidewire in place, through the biopsy channel of the duodenoscope (**Fig. 7**). A new 8.5F straight biliary stent is then inserted over the guidewire.

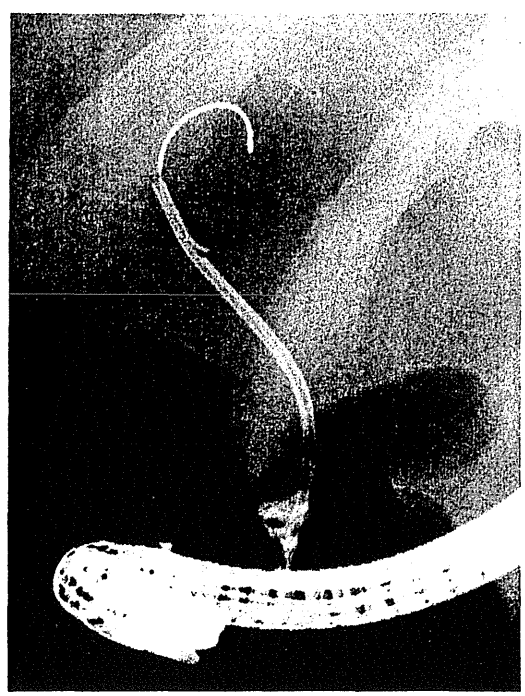

Fig. 6. A 0.035-in guidewire was inserted into the bile duct through an occluded stent using an ERCP catheter.

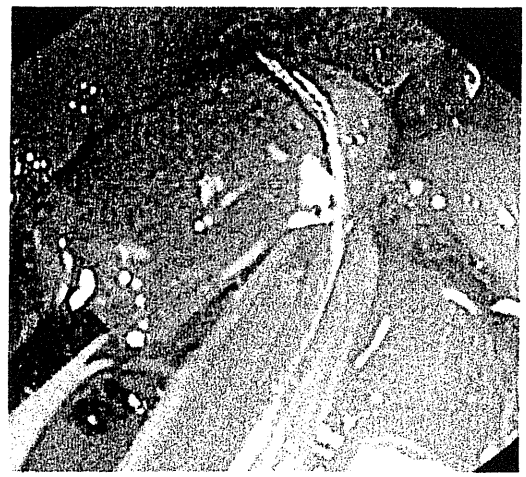

Fig. 7. The occluded stent is then removed by using a snare with the guidewire in place, through the biopsy channel of the duodenoscope.

SUCCESS RATE AND LIMITATIONS

Nineteen retrospective studies and 2 prospective studies describing 104 cases of EUS-CDS have been reported to date.[16,20–40] An overview of 104 cases of EUS-CDS, including the 81 cases in published articles along with the authors' published 23 cases, is shown in **Table 1.**

Technical and Functional Success Rate

Although the procedure was unsuccessful in 8 patients, transduodenal stents were successfully inserted in the remaining 96 patients (96/104, 92%). Among the 8 failed cases, Fabbri and colleagues[39] reported technical failure due to instability of the scope in the duodenal bulb in 1 case, stent impaction at the site of the choledocho-duodenostomy puncture in 1 case, and failure to create a fistula with the needle knife in 2 cases. In the remaining 4 cases, the causes of technical failure included hemobilia at the time of initial puncture with a 22-gauge needle for obtaining a cholangiogram[37] and failure to create a fistula because of sclerosing cholangitis[40] in one case each. The cause for the procedural failure has not been described in detail in the remaining 2 cases. Among the 96 cases with technical success, functional success was achieved in all the 96 cases (96/96, 100%).

The advantage of the EUS-CDS technique is that the puncture site is very close to the extrahepatic bile duct and away from the obstructing tumor.[16] No large intervening blood vessels lie between the duodenal wall and extrahepatic bile duct. The echoendoscope is stable in this position, and the direction of puncture is upward toward the hepatic hilum. To prevent dislocation of the guidewire and dilator, an appropriate puncture site should be selected aiming at the extrahepatic bile duct between the upper margin of the pancreas and hepatic hilum. A one-step method with direct puncture of the extrahepatic bile duct may reduce the risk of guidewire dislocation while the instruments are exchanged. Q12

Complications

Early complications of this technique include pneumoperitoneum in 6 patients,[23,26,27,31,32,39] (bile) peritonitis in 5 cases,[21,30,33,37] stent migration followed by

duodenal perforation in 1 case,[38] hemobilia in 1 case,[37] and severe abdominal pain in 1 case.[36] Bile peritonitis may not occur if a stent is promptly placed after the dilation of the fistula between the duodenum and bile duct. To prevent the dislocation of the guidewire and the dilator, an appropriate puncture site should be selected aiming at the extrahepatic bile duct between the upper margin of the pancreas and hepatic hilum. A one-step method with direct puncture of the bile duct, as is reported for EUS-guided pseudocyst drainage,[41] may reduce the risk of guidewire dislocation while the instruments are exchanged.

Although comparatively high rates of complications (13%) have been reported, complications in all patients except in one with stent migration[38] improved with conservative treatment. EUS-guided rendezvous technique is probably safe, but the success rate of drainage is comparatively low.[14] The usefulness and indications of the direct choledochoduodenostomy versus rendezvous technique need to be clarified in future studies.

FOLLOW-UP RESULTS

Stent patency rates in patients who underwent EUS-CDS have been reported in some articles. The authors have previously reported long-term follow-up data on stent patency in patients who underwent EUS-CDS.[26] The mean duration of stent patency was 211.8 days using Kaplan-Meier method. In a prospective study by the authors, duration of stent patency was 272 days and longer than previously reported.[37] Tarantino and colleagues[29] described that biliary stents were exchanged at day 180 in 3 patients with EUS-CDS. In another case of EUS-CDS, the plastic stent was exchanged for a metal stent after 1 month, with total stent patency duration of 240 days after the initial stent insertion. Horaguchi and colleagues[33] reported that initial plastic stent insertion followed by metal stent exchange provided stent patency durations of 27 days, 151 days, and 165 days among 3 cases of malignant lower biliary obstruction. Hanada and colleagues[34] reported that the stent patency duration ranged from 65 to 120 days in 4 cases of EUS-CDS with plastic stent insertion. Iwamuro and colleagues[36] also reported that stent patency ranged from 4.9 to 46.4 weeks in 5 cases of EUS-CDS combined with duodenal stents. The comparatively long patency of EUS-CDS achieved in the authors' patients was superior to that in those with transpapillary plastic stents and uncovered metallic stent and inferior to that in those with covered metallic stent in patients with lower biliary obstruction. In addition, the stent used for EUS-CDS is significantly cheaper and can be exchanged unlike a covered metallic stent. The authors speculate that EUS-CDS can prevent stent clogging and tumor ingrowth and/or overgrowth by creating a fistula away from the obstructing tumor.

Park and colleagues[35] recently reported 4 cases of EUS-BD with 1-step placement of a fully covered self-expandable metal stent. Although the follow-up periods were short (range, 2–7 months), only 1 reintervention was required because of stent migration. Fabbri and colleagues[39] reported that 6 patients died during follow-up (range, 140–189 days) with a partially covered metal stent still functioning. They also reported that the stent patency was 195, 205, and 230 days in 3 survivors with EUS-CDS. Longer stent patency using a fully or partially covered metal stent can thus be expected.

SUMMARY

EUS-CDS performed from the first portion of the duodenum is technically feasible without any serious complications, offering clinically effective drainage in almost all patients with a comparatively long patency period. As more experience is gained,

Table 1
Overview of the reported cases on EUS-CDS

Authors	Year	Number of Cases	Device for Puncture	Technical Success (%)	Treatment Success (%)	Initial Stent (Number of Cases)	Early Complication (Number of Cases)
Giovanini et al	2001	1	NK (1)	1/1 (100)	1/1 (100)	10F PS	None
Brumester et al	2003	2	19G FT (2)	1/2 (50)	1/1 (100)	8.5F PS	Bile peritonitis (1)
Puspok et al[24]	2005	5	NK (5)	4/5 (80)	4/4 (100)	7F–10F PS	None
Kahaleh et al[23]	2006	1	19G FN (1)	1/1 (100)	1/1 (100)	10-mm MS	Pneumoperitoneum (1)
Yamao et al[16,25,26]	2006, 2006, and 2008[a]	5	NK (5)	5/5 (100)	5/5 (100)	7F–8.5F PS	Pneumoperitoneum (1)
Angt et al	2007	2	NK (2)	2/2 (100)	2/2 (100)	7F PS	Pneumoperitoneum (1)
Fujita et al[28]	2007[a]	1	19G FN (1)	1/1 (100)	1/1 (100)	7F PS	None
Tarantino et al[29]	2008	4	19G, 22G FN/NK (4)	4/4 (100)	4/4 (100)	PS[b]	None
Itoi et al[30]	2008	4	NK (2), 19G FN (2)	4/4 (100)	4/4 (100)	7F PS (3), NBD (1)	Bile peritonitis (1)
Brauer et al	2009	3	19G, 22G FN (3)	3/3 (100)	3/3 (100)	7F PS	Pneumoperitoneum (1)
Nguyen-Tang et al	2009	2	NK (2)	1/2 (50)	1/1 (100)	10-mm MS	Pneumoperitoneum (1)
Horaguchi et al[33]	2009[a]	7	19G FN (7)	7/7 (100)	7/7 (100)	7F PS (6), 6F NBD (1)	Peritonitis (1)
Hanada et al[34]	2009	4	19G FN (4)	4/4 (100)	4/4 (100)	6F–7F PS	None
Park et al[35]	2009	4	19G FN/NK (4)	4/4 (100)	4/4 (100)	10-mm FCMS	None
Iwamuro et al[36]	2010	5	NK (5)	5/5 (100)	5/5 (100)	7F PS	Severe abdominal pain (1)
Hara et al[37]	2011	18	NK (18)	17/18 (94)	17/17 (100)	7F PS (2), 8.5F PS (15)	Bile peritonitis (2), hemobilia (1)
Siddiqui et al[38]	2011	8	19G FN/NK (8)	8/8 (100)	8/8 (100)	10-mm FCMS	Stent migration/duodenal perforation (1)
Fabbri et al[39]	2011	13	19G FN/NK (13)	9/13 (69)	9/9 (100)	PCMS[b]	Pneumoperitoneum (1)
Komaki et al[40]	2011	15	NK (9), 19G FN (6)	14/15 (93)	14/14 (100)	7F PS	None
Total	—	104	—	96/104 (92)	96/96 (100)	—	14/104 (13)

Abbreviations: FCMS, fully covered metal stent; FN, fine needle; FT, fistolotome; G, gauge; MS, metal stent; NBD, nasobiliary drainage; NK, needle knife; PCMS, partially covered metal stent; PS, plastic stent.

[a] Excluding the overlapping cases.

[b] Stent diameter is not described.

investigators have to decide which of the following are more effective than their alternatives: (1) transduodenal approach versus transgastric approach, (2) direct access versus rendezvous technique, (3) fistulotome versus fine needle for duct puncture, (4) tapered biliary dilators versus balloon dilation, (5) plastic stent versus (covered) metal stent, (6) straight stent versus pigtail stent, (7) 8.5 French stent versus larger or smaller size stent, and on other issues related to trouble shooting early and late complications. Prospective randomized studies are needed in the near future to compare the efficacy and safety of EUS-CDS with EBD and EUS-rendezvous and EUS-HGS. As the earlier-mentioned issues are resolved, we envision that the technique of EUS-CDS will be gradually standardized and new dedicated endoscopic devices will be developed.

REFERENCES

1. Ponchon T. Diagnostic endoscopic retrograde cholangiopancreatography. Endoscopy 2000;32:200–8.
2. Schofl R. Diagnostic endoscopic retrograde cholangiopancreatography. Endoscopy 2001;33:147–57.
3. Winick AB, Waybill PN, Venbrux AC. Complications of percutaneous transhepatic biliary interventions. Tech Vasc Interv Radiol 2001;4:200–6.
4. Itoi T, Yamao K, EUS 2008 Working Group. EUS 2008 Working Group document: evaluation of EUS-guided choledochoduodenostomy (with video). Gastrointest Endosc 2009;69:S8–12.
5. Püspök A. Biliary therapy: are we ready for EUS-guidance? Minerva Med 2007; 98:379–84.
6. Buchner AM, Wallace MB. New frontiers in therapeutic EUS: dreams, style exercises or actual possibilities. Minerva Med 2007;98:287–98.
7. Shami VM, Kahaleh M. Endoscopic ultrasonography (EUS)-guided access and therapy of pancreatico-biliary disorders: EUS-guided cholangio and pancreatic drainage. Gastrointest Endosc Clin N Am 2007;17:581–93, vii-viii.
8. Ramesh J, Varadarajulu S. Interventional endoscopic ultrasound. Dig Dis 2008; 26:347–55.
9. Gleeson FC, Levy MJ. Endoscopic ultrasound (EUS) guided access and therapy of pancreatico-biliary disorders. Minerva Gastroenterol Dietol 2008;54: 151–60.
10. Ashida R, Chang KJ. Interventional EUS for the treatment of pancreatic cancer. J Hepatobiliary Pancreat Surg 2009;16:592–7.
11. Kitano M, Sakamoto H, Komaki T, et al. Present status and future perspective of EUS-guided drainage. Dig Endosc 2009;21:S66–70.
12. Irisawa A, Hikichi T, Shibukawa G, et al. Pancreatobiliary drainage using the EUS-FNA technique: EUS-BD and EUS-PD. J Hepatobiliary Pancreat Surg 2009;16: 598–604.
13. Kida M, Itoi T. Current status and future perspective of interventional endoscopic ultrasound in Japan. Dig Endosc 2009;21:S50–2.
14. Yamao K, Hara K, Mizuno N, et al. EUS-guided biliary drainage. Gut Liver 2010;4: S67–75.
15. Itoi T, Sofuni A, Itokawa F, et al. Endoscopic ultrasonography-guided biliary drainage. J Hepatobiliary Pancreat Sci 2010;17:611–6.
16. Yamao K, Sawaki A, Takahashi K, et al. EUS-guided choledochoduodenostomy for palliative biliary drainage in case of papillary obstruction: report of 2 cases. Gastrointest Endosc 2006;64:663–7.

17. Hara K, Yamao K, Mizuno N, et al. Endoscopic ultrasound-guided choledochoduodenostomy. Dig Endosc 2010;22:147–50.
18. Itoi T, Isayama H, Sofuni A, et al. Stent selection and tips on placement technique of EUS-guided biliary drainage: transduodenal and transgastric stenting. J Hepatobiliary Pancreat Sci 2011;18:664–72.
19. Hara K, Yamao K, Mizuno N, et al. Interventional endoscopic ultrasonography for pancreatic cancer. World J Clin Oncol 2011;2:108–14.
20. Giovannini M, Moutardier V, Pesenti C, et al. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy 2001; 33:898–900.
21. Burmester E, Niehaus J, Leineweber T, et al. EUS-cholangio-drainage of the bile duct: report of 4 cases. Gastrointest Endosc 2003;57:246–51.
22. Kahaleh M, Yoshida C, Kane L, et al. Interventional EUS cholangiography: a report of five cases. Gastrointest Endosc 2004;60:138–42.
23. Kahaleh M, Hernandez AJ, Tokar J, et al. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. Gastrointest Endosc 2006;64: 52–9.
24. Puspok A, Lomoschitz F, Dejaco C, et al. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. Am J Gastroenterol 2005;100:1743–7.
25. Yamao K, Mizxuno N, Takahashi K, et al. A case of duodenoscopic ultrasound guided transduodenal biliary drainage in a case of carcinoma of papilla of Vater. Suizo 2006;21:353–7.
26. 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.
27. Ang TL, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. JOP 2007;9:438–43.
28. Fujita N, Noda Y, Kobayashi G, et al. Histological changes at an endosonography-guided biliary drainage site: a case report. World J Gastroenterol 2007;13:5512–5.
29. Tarantino I, Barresi L, Repici A, et al. EUS-guided biliary drainage: a case series. Endoscopy 2008;40:336–9.
30. Itoi T, Itokawa F, Sofuni A, et al. Endoscopic ultrasound-guided choledochoduodenostomy in patients with failed endoscopic retrograde cholangiopancreatography. World J Gastroenterol 2008;14:6078–82.
31. Brauer BC, Chen YK, Fukami N, et al. Single-operator EUS-guided cholangiopancreatography for difficult pancreaticobiliary access (with video). Gastrointest Endosc 2011;73:251–6.
32. Nguyen-Tang T, Binmoeller KF, Sanchez-Yague A, et al. Endoscopic ultrasound (EUS)-guided transhepatic anterograde self-expandable metal stent (SEMS) placement across malignant biliary obstruction. Endoscopy 2010;42:232–6.
33. Horaguchi J, Fujita N, Noda Y, et al. Endosonography-guided biliary drainage in cases with difficult transpapillary endoscopic biliary drainage. Dig Endosc 2009; 21(4):239–44.
34. Hanada K, Iiboshi T, Ishii Y. Endoscopic ultrasound-guided choledochoduodenostomy for palliative biliary drainage in cases with inoperable pancreas head carcinoma. Dig Endosc 2009;21:S75–8.
35. Park HE, Koo JE, Oh J, et al. EUS-guided biliary drainage with one-step placement of a fully covered metal stent for malignant biliary obstruction: a prospective feasibility study. Am J Gastroenterol 2009;104:2168–74.

36. Iwamuro M, Kawamoto H, Harada R, et al. Combined duodenal stent placement and endoscopic ultrasonography-guided biliary drainage for malignant duodenal obstruction with biliary stricture. Dig Endosc 2010;22(3):236–40.
37. Hara K, Yamao K, Niwa Y, et al. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. Am J Gastroenterol 2011;106:1239–45.
38. Siddiqui AA, Sreenarasimhaiah J, Lara LF, et al. Endoscopic ultrasound-guided transduodenal placement of a fully covered metal stent for palliative biliary drainage in patients with malignant biliary obstruction. Surg Endosc 2011;25: 549–55.
39. Fabbri C, Luigiano C, Fuccio L, et al. EUS-guided biliary drainage with placement of a new partially covered biliary stent for palliation of malignant biliary obstruction: a case series. Endoscopy 2011;43:438–41.
40. Komaki T, Kitano M, Sakamoto H, et al. Endoscopic ultrasonography-guided biliary drainage: evaluation of a choledochoduodenostomy technique. Pancreatology 2011;11(Suppl 2):47–51.
41. Krüger M, Schneider AS, Manns MP, et al. Endoscopic management of pancreatic pseudocysts or abscesses after an EUS-guided 1-step procedure for initial access. Gastrointest Endosc 2006;63(3):409–16.

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.