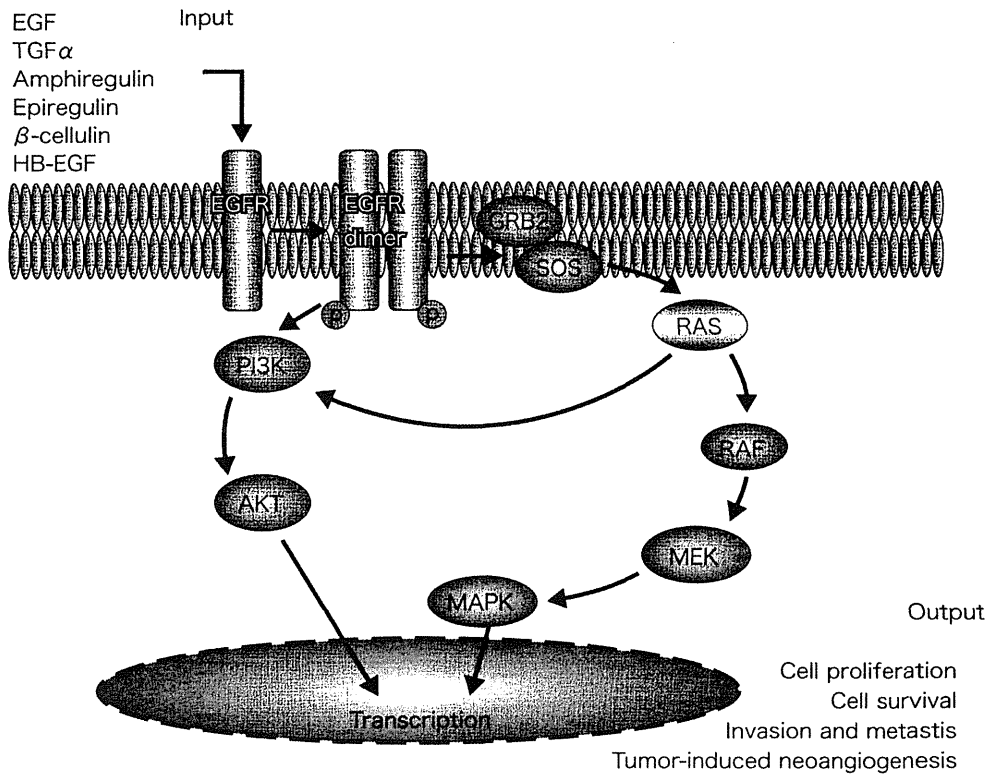


図1　EGFR経路のシグナル伝達
Shankaran V et al : The Oncologist 15 : 157–167, 2010

癌におけるEGFR機能亢進の機序には，①*EGFR*遺伝子の増幅，発現の上昇(大腸癌，頭頸部癌，胃癌など)，②*EGFR*遺伝子の変異(非小細胞肺癌など)，③EGFRリガンドの増加(乳癌，非小細胞肺癌など)，などが知られている(図2)[3]．膵臓癌では，30～50％にEGFRの過剰発現や，リガンドであるTGF-αの過剰発現が報告されており，高発現が予後不良因子であるという報告もある[4～6]．一方，胆管癌では8～59％にEGFRの過剰発現を認め，低分化腺癌，肝外胆管癌で頻度が高いことが報告されている[7～9]．また，胆道癌の約15％にEGFR変異を認めることが報告されている[10,11]．これらの報告は，膵臓癌，胆道癌に対してEGFRシグナル経路が治療標的となりえることを支持している．

3 Cetuximabの作用機序

Cetuximabは，EGFRを標的とするヒト/マウスキメラ型IgG1抗体であり，内因性リガンドよりも高い親和性で競合的にEGFRと結合することができる．癌細胞内のEGFR経路阻害は，細胞周期進行および有糸分裂を阻害し，アポトーシスの誘導を生じ抗腫瘍効果を発揮する．また，cetuximabが結合したEGFRは内在化(internalization)が生じ分解され，結果として細胞膜のEGFR発現が減少する．一方，EGFRに結合したcetuximabを免疫担当細胞がFCγ受容体(FCGR)を介して認識することで生じる抗体依存性細胞障害(Antibody-dependent cell-mediated cytotoxicity; ADCC)も抗腫瘍効果の機序のひ

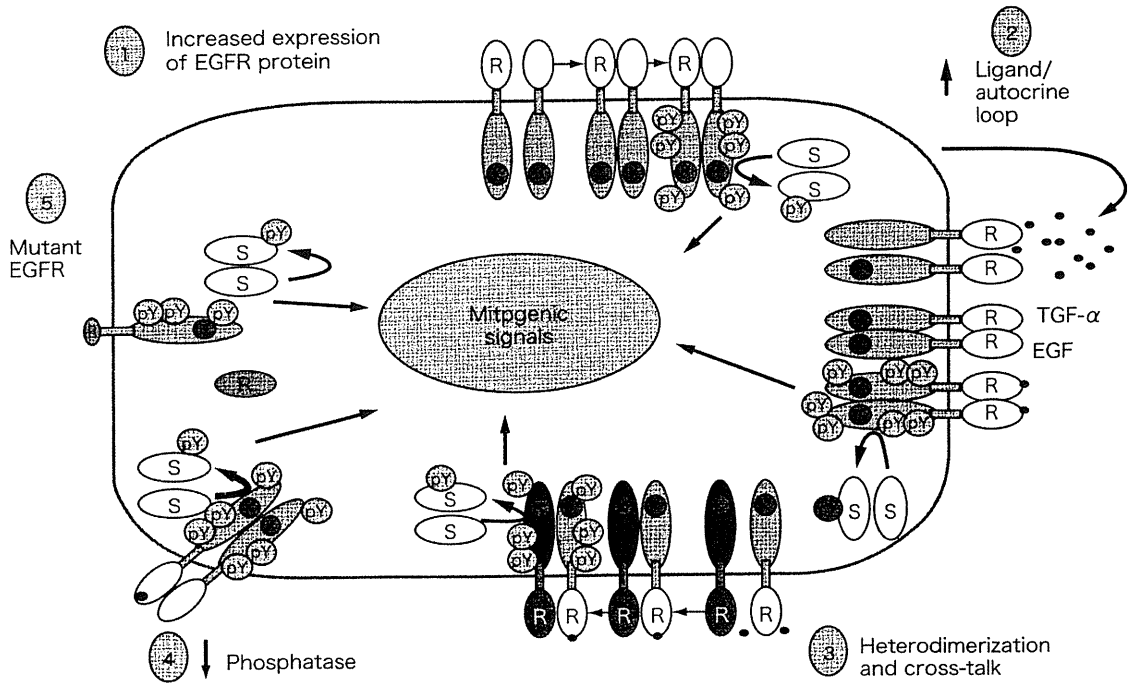


図2　EGFR経路活性化の機序
Arteaga C L : The Oncologist 7 : 31–39, 2002

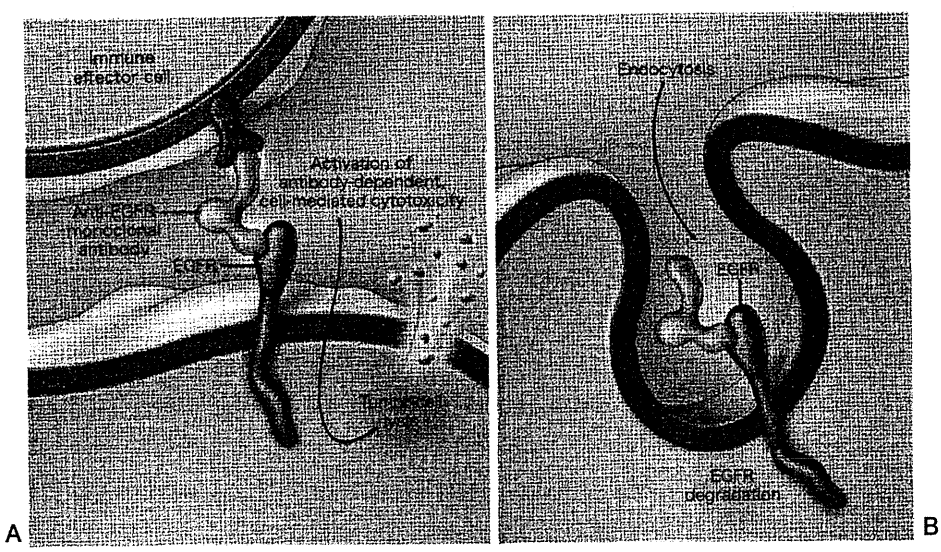


図3　Cetuximabの作用機序(文献12より引用)
A：抗体依存性細胞障害(ADCC)　B：EGFRの内在化

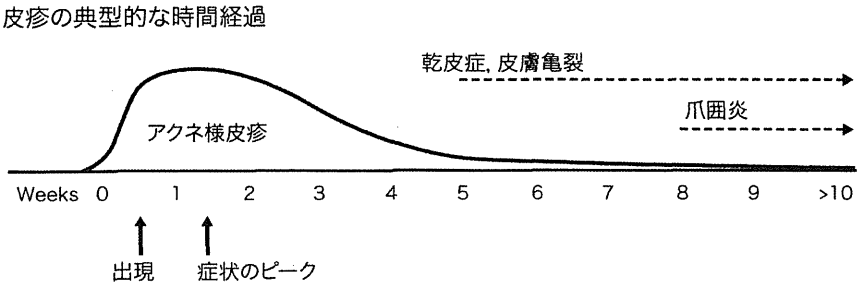


図4　Cetuximabによる皮疹の経過

表1　ざ瘡様皮疹に対する処方例

ざ瘡様皮疹
治療開始時～軽症
ロコイドクリーム® (5 g) 1本　1日2回　朝夕　顔 マイザー軟膏® (5 g) 1本　1日2回　朝夕　体 ヒルドイドソフト®　皮膚の乾燥部位に
皮疹増悪時(中等症)
(上記に追加して) ミノマイシンカプセル® (100 mg) 1cap 夕後 アレグラ® (60 mg) 2錠　分2
皮疹増悪時(重症)
(さらに追加) プレドニン® (5 mg) 2錠　分1×5日分

とつであると推測されている(図3)[12]．これは，癌細胞の表面抗原を標的とする抗体医薬に共通して認められ，特にIgG1サブクラスの抗体医薬で強く生じるとされている．

4　Cetuximabの副作用

Cetuximab使用の際に留意すべき副作用に，①皮膚症状，②Infusion reaction，③低マグネシウム(Mg)血症，④間質性肺炎，がある．副作用のトータルマネージメントのためには，主担当医だけでなく，皮膚科医師，看護師，薬剤師などで構成される治療チームで管理するのが望ましい．

1. 皮膚症状

80％以上にざ瘡様皮疹(にきびのような皮膚症状)，掻痒症，皮膚乾燥，落屑，多毛症，爪囲炎などの皮膚症状がみられる(図4)．

ざ瘡様皮疹に対する処方例を表1に示す．日常生活の注意事項として，①低刺激性の石鹸を用いる，②シャワーはぬるま湯にする，③入浴後に保湿クリームを乾燥部位に塗る，などのスキンケアと直射日光による日焼けを避けることが重要である．皮疹が増悪した場合や中等症以上の爪囲炎は，速やかに皮膚科に相談する．

2. Infusion reaction

Infusion reactionとは薬剤投与中あるいは投与後24時間以内にみられる発熱，悪寒，呼吸困難，血圧低下，過敏症反応など有害反応の総称である．Cetuximabなどのキメラ型モノクローナル抗体で比較的頻度が高い．予防のために抗ヒスタミン薬＋ステロイドの前投与を行う．出現時の対応の1例を示す(表2)．

3. 低マグネシウム(Mg)血症

Cetuximab投与により腎臓の遠位尿細管におけるMg再吸収阻害が生じ低Mg血症が起こる．1 mg/dL前後まで低下した場合，精神神経症状(性格変化，疲労，傾眠，けいれんなど)，循環器症状(QTc延長，不整脈，頻脈)，電解質異常(低Ca，低K，低P血症)が生じうる．血清Mg値がGrade 2 (1.2 mg/dL以下)

表2　Infusion reactionの重症度と対応の例

Grade		対応
1	軽度で一過性の反応 点滴の中段を要さない 治療を要さない	投与速度50％で継続
2	治療または点滴の中断が必要 ただし症状に対する治療には 速やかに反応する	投与中断し，抗ヒスタミン薬＋ステロイドを投与 症状改善すれば50％の速度で再開
3	遷延．一度改善しても再発する 続発症により入院を要する	投与中断，抗ヒスタミン薬＋ステロイド投与 アドレナリン投与を考慮 入院にて経過観察
4	生命を脅かす	

＊出現時，速やかに全身状態の観察，Gradingを行う

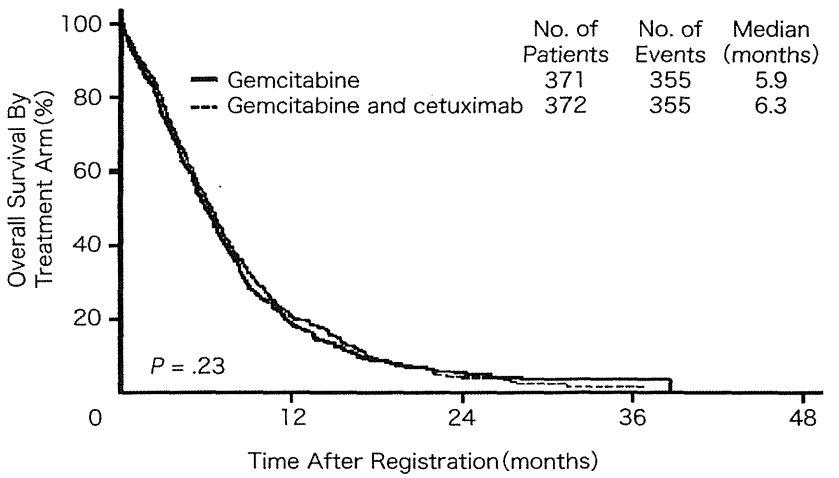


図5　S0205試験での全生存期間

の場合，QTc延長の有無を確認し，Mgの補充を行う．Grade 3（0.9 mg/dL以下）まで進行した場合，cetuximabの休止を検討する．

4．間質性肺炎

発生割合は1％前後と稀であるが，ときに重篤となるので注意が必要である．呼吸器内科医にコンサルトし，確定診断が得られなくとも低酸素血症を認める場合は他疾患を想定した治療（抗生剤など）とあわせて，ステロイド投与（プレドニゾロン換算で0.5～1.0 mg/kg/日を4週間以後漸減）を行う．

5　膵臓癌に対するcetuximab療法

米国にて，EGFR陽性の切除不能膵癌患者を対象にgemcitabine（GEM）+cetuximab療法（Cetuximab初回400 mg/m^2，2回目以降は250 mg/m^{2}の週1回投与）の第Ⅱ相試験が行われ，全生存期間（OS）中央値7.1カ月，1年生存率31.7％と比較的良好な成績が得られた[13]．しかし，引き続き米国の臨床試験グ

表3　膵臓癌に対するCetuximab療法の臨床試験成績(図8)

		N	RR (%)	PFS (M)	OS (M)
S0205	GEM	371	14	3.0	5.8
	GEM+Cmab	372	12	3.4	6.3
GISCAD	GEM+CDDP	42	12	4.2	7.8
	GEM+CDDP+Cmab	42	18	3.4	7.5
GEMOXCET	GEMOX+Cmab	61	33	3.2	5.8

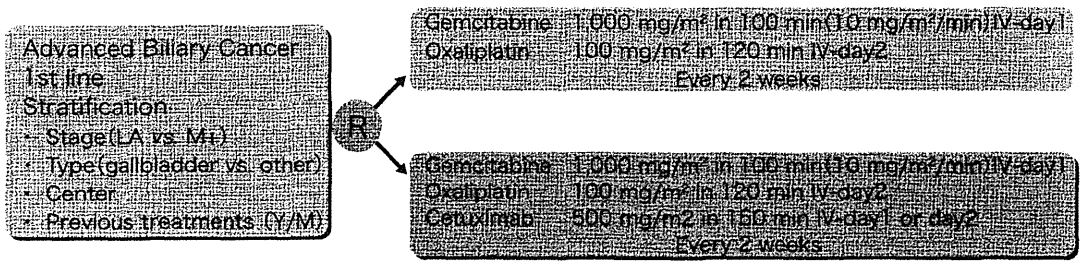
ループであるSWOG (Southwest Oncology Group)で行われた第Ⅲ相試験 (S0205試験)では，主要評価項目であるOSに両群間に差を認めず，奏効割合(RR)，無増悪生存期間(PFS)も両群に有意差を認めなかった(図5)[14]．主な毒性は，骨髄抑制，疲労感，食欲不振であり，cetuximab併用群でGrade 3/4の皮疹を7.1%，アレルギー反応を3.4%に認めるも忍容可能と考えられた．イタリアでは，EGFR陽性(免疫染色にて1%以上の癌細胞細胞膜が染色されるもの)の切除不能膵癌を対象に，gemcitabine+ oxaliplatin (GEMOX)療法に対するGEMOX + cetuximabの優越性を探索するランダム化第Ⅱ相試験(GISCAD試験)が行われた．結果，主要評価項目であるRR (GEMOX+ cetuximab群 vs GEMOX群 14% vs 12%)およびPFS, OSにおいても両群に差を認めなかった[15]．さらに，ドイツで行われたGEMOX+ cetuximab併用療法の第Ⅱ相試験(GEMOXCET)でも，期待した結果が得られなかった[16]．

以上から，膵臓癌に対するcetuximab併用療法は，忍容可能であるもの化学療法への上乗せ効果は示されず，今後の臨床開発は困難な状況である．

6 胆道癌に対するcetuximab療法

GEM単独療法とGEM+ cisplatin (GC)併用療法を比較する第Ⅲ相試験(ABC-02試験)が英国で行われ，GEM単独群に比べ，GC群で有意な生存期間の延長が確認された[17]．また日本でもABC-02試験と同じレジメンでランダム化比較第Ⅱ相試験(BT-22試験)が行われ，ほぼ同様の結果であった[18]．以上の結果から，GC療法は胆道癌に対する標準治療であると認識されている．一方で，同じプラチナ系薬剤であるoxaliplatinとGEMを併用したGEMOX療法は，いくつかの第Ⅱ相試験で良好な成績が報告されている．インドにおいて，切除不能胆嚢癌を対象に，緩和治療のみ(BSC)と5-FU+folnic acid (FUFA)，GEMOXの3群の比較試験が行われ，OS中央値がBSC群4.5カ月，FUFA群4.6カ月，GEMOX群9.4カ月とGEMOX群で有意な予後の改善が得られた[19]．GEMOX療法も胆道癌に対する治療選択肢のひとつとして考えられている．

Malkaらは2009年の米国臨床腫瘍学会(ASCO)年次総会で，フランス・ドイツで行われているGEMOX療法へのcetuximabの上乗せを探索する試験(BINGO試験)の中間成績を発表した．この試験は切除不能の局所進行・転移性胆道癌の初回治療としてGEMOX療法とGEMOX+cetuximab併用療法を比較するランダム化比較第Ⅱ/Ⅲ相試験である．18例ずつの中間評価では主要評価項目である4カ月無増悪生存割合はGEMOX群50%，GEMOX+cetuximab群61%でありcetuximab併用群で良好であった[20]．毒性について



Endpoints
- Primary: 4-month PFS rate(RECIST)
- Secondary: Toxicity, ORR, DCR, resectability rate, PFS, OS
- Exploratory:
  - EGFR pathway analyses(blood, tumor)
  - PET study(baseline and at 1 month)

図6　BINGO試験の試験デザイン

表4　膵臓癌に対するCetuximab療法の臨床試験成績

		N	RR	PFS (M)	OS (M)
Malka et al.	GEMOX	18	11%	50%*	NA
	GEMOX+Cmab	18	17%	61%*	NA
Gruenberger et al.	GEMOX+Cmab	30	63%	8.8	15.2
Jensen et al.	GEMOX+Cap+Pmab	46	33%	8.3	10.0

*4 months PFS rate（Interrim analysis）
Cmabicetuximab, Pabipanitunamab, Capicapecitabine

は，cetuximab併用群でGrade 3以上の皮膚毒性，過敏反応を8%に認めたが，両群ともにdose intensityは全薬剤95%以上であり，忍容可能であると考えられた．また，オーストリアのグループでGEMOX + cetuximab療法の第Ⅱ相試験が行われ，RR 63%（30例中[19]であり30例中9例が腫瘍縮小により治癒切除可能となった[21]．また，観察期間中央値22カ月の時点でのPFS，OS中央値はそれぞれ8.8カ月，15.2カ月と良好な成績であった．毒性についてはGrade3以上の皮疹，末梢神経障害をそれぞれ4例に認めたがGrade4以上の有害事象を認めなかった．一方，EGFRを標的とした完全ヒト型IgG2モノクローナル抗体であるpanitumumabの臨床試験として，JansenらによりKRAS野生型の胆道癌を対象に，GEMOX＋capecitabine+panitumumab療法（GEM 1,000 mg/m² day1, l-OHP 60 mg/m² day1, panitumumab 6 mg/kg day1, capecitabine 1,000 mg/m² day1～7, 2週ごと）の第Ⅱ相試験が行われ，RR 33%，PFS中央値8.3カ月，OS中央値10.0カ月であったと報告されている[22]．

以上から，少数例による第Ⅱ相試験の結果からは，胆道癌に対するcetuximab療法の有効性が示唆されており，現在，第Ⅲ相試験による検証が行われている．

7 Cetuximab療法のバイオマーカー

現在，さまざまな癌腫において薬剤の効果

○腫瘍因子
・EGFR発現量, 増幅, 変異
・KRAS変異, BRAF変異
・EGFRリガント(EGF, TGFα, amphiregulinなど)発現量
・PIK3CA変異, PTEN異常

○宿主因子
・FCGR遺伝子多型
・皮疹の程度

図7　Cetuximab効果予測因子の候補

を予測するバイオマーカー（効果予測因子）を確立することが重要な課題となっている．例えば，抗HER2抗体であるtrastuzumabはHER2の過剰発現が認められる胃癌，乳癌において有効性が認められている．Cetuximabの効果予測因子としては，前臨床研究の段階でEGFR陽性癌細胞株でcetuximabの効果が高かったことから，EGFR発現の程度が効果予測因子となる可能性が指摘されていた．ところが，大腸癌における臨床試験の結果から，EGFR発現のない(免疫染色の評価で陰性)大腸癌においてもcetuximabの効果が認められ，現在EGFR発現の有無でcetuximab投与の判断は行っていない．S0205試験では，登録された745人のうち595人で腫瘍組織でのEGFR発現の評価(免疫染色法)が行われていたが，EGFR陽性(92％)の患者に限定した場合でもcetuximab併用の有効性は認められなかった．

また，大腸癌では複数のランダム化比較試験のサブグループ解析の結果から，腫瘍組織に*KRAS*遺伝子変異(コドン12，13)を有する患者ではcetuximabの有効性が認められないことが示され[23]，現在では，KRAS遺伝子変異はcetuximabの効果予測因子(無効例)としてほぼ確立され，臨床でも抗EGFR抗体の投与前に*KRAS*遺伝子検査が行われている．膵癌では50～100％と高率に*KRAS*遺伝子変異を認める．GEMOXCET試験では39％の症例で*KRAS*遺伝子検査が行われ，14例(56％)でコドン12変異を認め，*KRAS*変異の有無でPFSには差を認めなかったが，OSは*KRAS*遺伝子変異を認める群で短い傾向にあった(中央値263日 vs 162日)と報告されている[24]．この報告からは，膵臓癌における*KRAS*遺伝子変異の有無は，抗EGFR抗体の効果予測因子というよりは予後因子である可能性が示唆されるが，少数例での検討にすぎない．*KRAS*遺伝子変異の有無が膵癌においてcetuximabの効果予測因子となるかどうかについては大規模なランダム化比較試験でのバイオマーカー解析が必要である．また，胆道癌においてはGruenbergerらの報告の中で30例中3例(10％)にKRAS変異を認めており，3例中2例でPRが得られたとしている．胆道癌においても*KRAS*遺伝子変異の有無が効果予測因子となるかは，今後の検討課題である．

大腸癌では，*KRAS*遺伝子変異以外にも*BRAF*，*PIK3CA*遺伝子の変異や，EGFRリガンドの発現量，*FCGR*遺伝子多型などが効果予測因子となるかどうか検討が進んでいるが，いずれも現時点で確立されたものではない(図7)．また，癌腫の違いによりバイオマーカーは異なる可能性がある．胆道癌，膵臓癌におけるcetuximabのバイオマーカーは，それぞれ対象とする癌腫の臨床試験サンプルを用いた研究で検討されるべきである．BINGO試験ではバイオマーカー解析が付随研究として計画されており，結果が明らかになればcetuximabの有効・無効な集団が絞り込めるかもしれない．

8 まとめ

膵臓癌，胆道癌においてしばしばEGFR経

路の異常が認められ，cetuximab療法の臨床試験が行われてきた．現時点では，膵臓癌は有望な結果が得られず，胆道癌では少数例での結果しか得られていない．膵臓癌での開発で得られた教訓を胆道癌で生かすためには，できるだけ早い段階で胆道癌におけるcetuximabの効果予測因子を絞り込み，効果が期待できる患者集団を対象に臨床試験を進めていく必要があるだろう．

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Endoscopic Ultrasound-Guided Choledochoduodenostomy for Malignant Lower Biliary Tract Obstruction

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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.

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Q6 Q7

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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**).

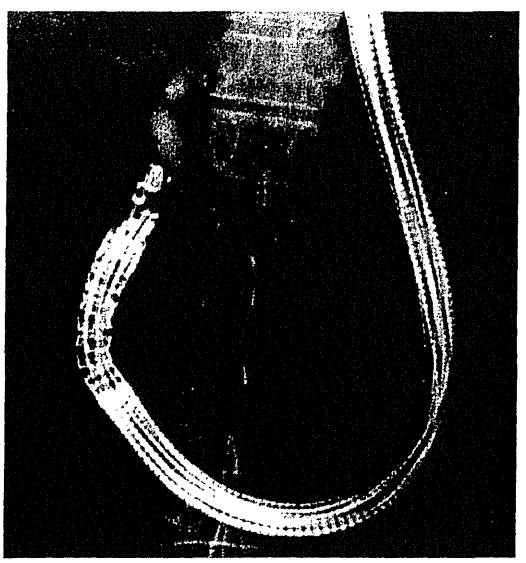

Fig. 1. Cholangiogram obtained by EUS-guided puncture with the tip of the convex transducer directed to the hepatic hilum. The echoendoscope was observed in the long/pushing scope position.

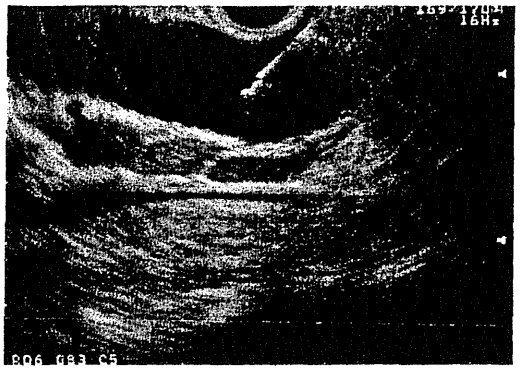

Fig. 2. Convex echoendoscope, located in the apex of the duodenal bulb, clearly displayed the extrahepatic bile duct, cystic duct, and puncture needle.

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

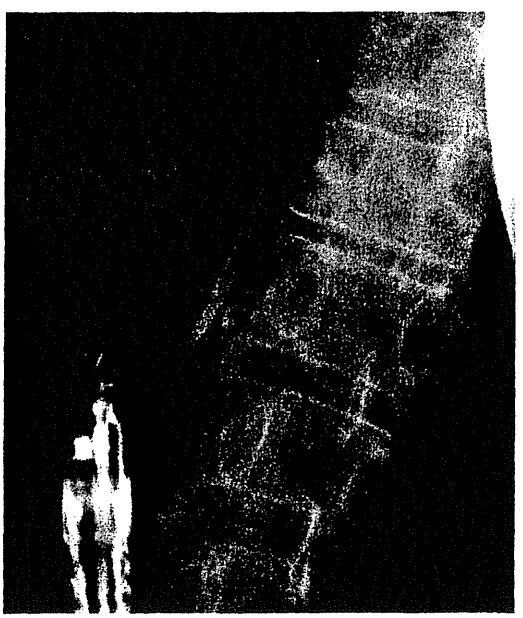

Fig. 3. Choledochoduodenostomy was accomplished using a tube stent in the apex of the duodenal bulb.

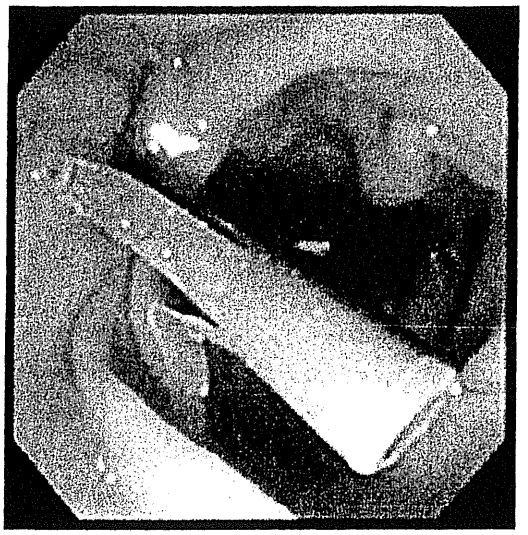

Fig. 4. Duodenoscope showed an 8.5F biliary stent in the first portion of the duodenum.

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,

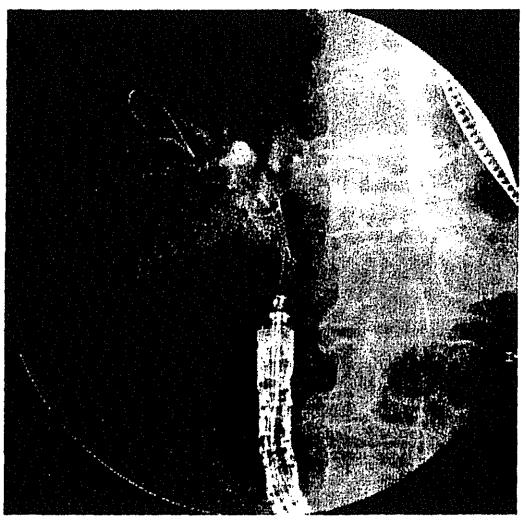

Fig. 5. Choledochoduodenostomy was accomplished using a metal stent in the apex of the duodenal bulb, using a forward-viewing echoendoscope.

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. Q11

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.

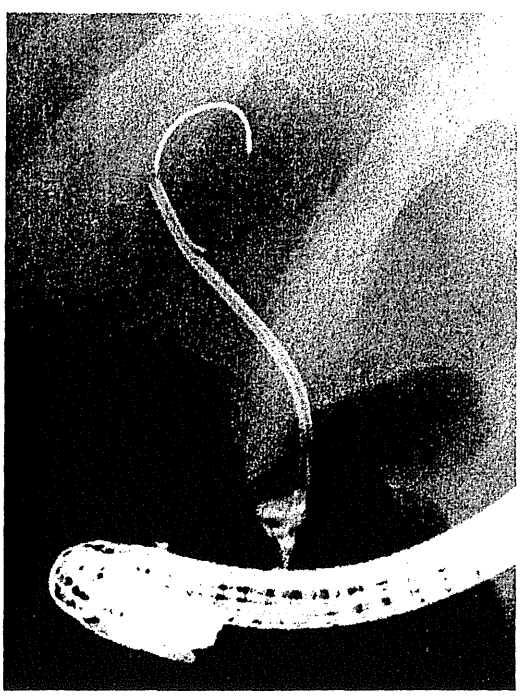

Fig. 6. A 0.035-in guidewire was inserted into the bile duct through an occluded stent using an ERCP catheter.

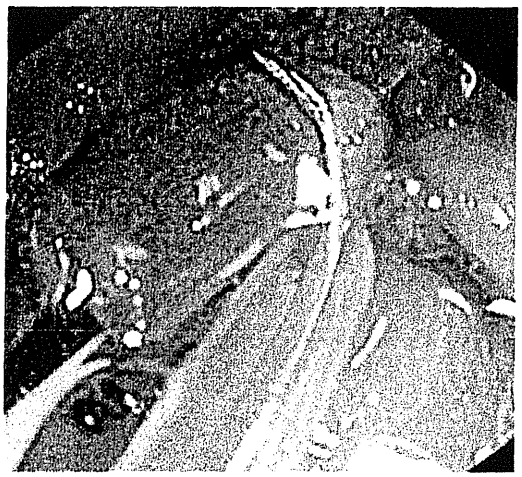

Fig. 7. The occluded stent is then removed by using a snare with the guidewire in place, through the biopsy channel of the duodenoscope.

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 choledochoduodenostomy 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.

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