may offer the same advantage for these lesions. The frequency with which intrahepatic recurrence develops in the marginal or same segment site of the remnant liver after anatomical resection should be less than that after nonanatomic resection, since the theoretical superiority of anatomic resection derives from eradication of intrahepatic metastases that spread via portal tributaries.[31] However, our study in CRCLM showed that OS and DFS after anatomic resection was not significantly better than after nonanatomic resection, and most of the intrahepatic recurrences occurred in other segments or in multiple segments rather than at the resection site (Table 3). There was no significant correlation in our study between portal or hepatic vein invasion and intrahepatic recurrence rate, and there were no significant differences in terms of the OS and DFS or the site of intrahepatic recurrence between anatomic and nonanatomic resection.

We also raised the question of whether surgical margin is associated with intrahepatic recurrence. Generally, in treatment of malignant tumors, the local recurrence rate is significantly common in the stump-positive case. Similarly, some authors[22,23] reported that resection margin has a significant impact on the risk of CRCLM recurrence, and that a margin ≥10 mm from the cut surface to the tumor margin was necessary. However, in patients with severely impaired liver function or those with a tumor close to large vascular structures, an adequate resection margin may not be feasible. In addition, previous studies[24,37,38] have shown that a surgical margin greater than 2 mm or greater than 1 mm was not a significant prognostic factor in patient survival. In the large-scale series,[38–40] patients with resection margins of 1 to 10 mm and greater than 10 mm had similar 5-year patient and DFS rates. Therefore, we classified all patients into three groups: group 1, minimum safe resection margin of ≤1 mm; group 2, resection margin of 2–9 mm; and group 3, resection margin of ≥10 mm, which many authors[22,23,25,26] conventionally consider as the optimal resection margin. Our retrospective analysis showed no correlation between the width of the resection margin and survival, and the width of the resection margin was not associated with the site of or a reduced rate of intrahepatic recurrence. Regardless of the resection margin, intrahepatic recurrences occurred at multiple segments rather than at the marginal site and/or in the same segment. In addition, there was no significant difference in survival regardless of exposing the tumor surface at the cut stump (P=0.1844). In summary, OS and DFS and the recurrence site were not influenced by the type of hepatectomy or the width of the resection margin, and intrahepatic recurrences occurred in the remnant liver at a distal segment or at multiple segments of the liver remnant (Table 4).

Anatomic liver resection has become well established based on the concept that the portal vein serves as an efferent vessel in HCC and that satellite metastases can spread by invasion of the portal vein branches at an early stage. Therefore, anatomic resection based on Couinaud's segments is generally performed to decrease the chance of leaving behind satellite metastases that spread via portal tributaries. Alternatively, hematogenous dissemination of CRC via Glisson pedicle was reported to be significantly associated with the size of liver metastatic nodules by cascade theory.[41] Under this theory, in accordance with the process of CRCLM metastasizing to the lung, and subsequently to the other organs, the size of CRCLM is thought to increase. However, we believe that nonanatomic liver resection with narrow margin is supported by the fact that micrometastases in the liver parenchyma surrounding CRCLM are rare and primarily confined to the immediate area surrounding the tumor border. Metastatic liver lesions develop from bloodborne cancer cells circulating throughout the body,[16] and the probability of distribution of hematogenous metastatic deposits from CRC is random. Yamamoto et al.[15] reported that there were no microscopic deposits in the parenchyma, even within 10 mm from the metastatic tumors. In fact, the observation in our study showed that microscopic satellite foci were not found in the parenchyma within 10 mm from metastatic tumors. This pattern of recurrence is unique for CRCLM. This difference may be explained by the variation in disease biology seen in primary versus metastatic liver tumor.

In this study, CA19-9 after hepatectomy was found to be one of the independent factors in OS and DFS, and CEA both before and after hepatectomy were indicated risk factors for intrahepatic recurrences in the subgroups. Therefore, we analyzed changes of CEA and CA19-9 before and after operation. As a result, there were no significant differences in OS and DFS, even if CEA and CA19-9 after hepatectomy was normalized or remained high. Conversely, OS and DFS were significantly worse if CEA and CA19-9 were normal before hepatectomy and changed to high values after hepatectomy (Table 6). All five patients whose CEA or CA19-9 changed to high values after hepatectomy experienced

Table 6 Relationship between pre- and post-hepatectomy values of tumor markers CEA and CA19-9

Variables	Before hepatectomy	After hepatectomy	P value for overall survival (OS)	P value for disease-free survival (DFS)
CEA (ng/mL)	<5	<5	0.0003*	0.0009*
		≥5		
	≥5	<5	0.1793	0.2502
		≥5		
CA 19-9 (mAU/mL)	<36	<36	0.0065*	0.0022*
		≥36		
	≥36	<36	0.1335	0.3052
		≥36		

recurrence in multiple hepatic segments or in lung, and eventually died.

Forty-five patients (42.9%) in our study experienced recurrences in the remnant liver. Among these patients with intrahepatic recurrence, a significantly different survival rate was observed between those receiving various therapies including repeat hepatectomy with a combination of systemic chemotherapy, systemic chemotherapy alone, and best supportive care ($P<0.0001$; Table 5). Considering the high 5-year cumulative recurrence rate after initial hepatectomy, treatment for recurrence is extremely important. Although various therapeutic modalities have been used to treat intrahepatic recurrences, there is no standard strategy for selecting treatment.[42–44] However, preservation of as much remnant liver and liver function as possible during the initial hepatectomy for CRCLM would allow consideration of more therapeutic options when intrahepatic recurrence occurs. Conversely, if remnant liver function is poor at the time of recurrence with only best supportive care as a treatment option, prognosis may be much poorer. As such, remnant liver function should be maximally preserved. Therefore, with the high incidence of recurrence in the remnant liver from CRC, a long-term strategy for CRCLM needs to take into special consideration treatment for the forthcoming recurrence, since OS and DFS and the recurrence site were not influenced by the type of hepatectomy or the width of the resection margin.

Conclusion

In our study, we retrospectively evaluated the operative results for 106 CRCLM patients. Multivariate analysis demonstrated that CA19-9 after hepatectomy and the presence of recurrence were independent factors in OS rates, and tumor depths of CRC and CA19-9 after hepatectomy were independent factors in DFS rates. Type of hepatectomy (anatomic or nonanatomic) and width of resection margin for CRCLM were not significant factors for OS and DFS or for CRCLM recurrence. Site of intrahepatic recurrence was not influenced by the type of hepatectomy or width of the resection margin.

Preserving remnant liver function in initial hepatectomy for CRCLM is important, increases treatment options in case of recurrence, and should be considered when planning an operative procedure for CRCLM. We conclude that nonanatomic hepatectomy with narrow margin may be recommended as a technique for the resection of CRCLM.

Conflicts of interest The authors declare that they have no conflict of interest.

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総　説

最新の肝癌手術～系統的肝切除のための工夫

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はじめに

肝切除は肝細胞癌(HCC)治療の最も根治的な手技である。HCCの進展は主に脈管浸潤により，系統的切除は主腫瘍の周囲に拡がる門脈・静脈腫瘍栓を含む腫瘍の領域の完全除去が可能なため，部分切除に比較して好ましい切除法とされてきた。つまり，HCCの系統的切除の理論的長所はより大きな外科的なマージンを通して肝内転移を一掃できることにあり，系統的な切除術の生存率延長の利点を記述している報告もある[1)-3)]。しかしながらそれを否定する報告[4)]もあり，系統的切除と部分切除のRCTがまだ施行されていない現在，HCCのための系統的な切除の効果については未だ腫瘍学的な確証は得られていない。

系統的切除法には，染色マッピング法や肝切離先行法などがあるが，我々は出来る限り，肝門部グリソン処理を先行している。この系統的切除の補助方法として，肝表面の切離境界をICGと赤外線発光システムで，肝実質の切離境界は超音波造影剤Sonazoid®を用いる術中ナビゲーションが有用と考えている。

1．肝の系統的切除法について

肝切除後の再発形式は，残肝臓組織中で微小な門脈や肝静脈内の腫瘍栓に起因した再発か，多中心性発癌によることが多い。系統的切除の利点は部分的に隣接した肝の微小血管内腫瘍栓を一掃できる可能性である。従来から施行される系統的切除法は，門脈と肝動脈を肝門部で分離してから結紮し，虚血境界線に沿って肝実質を切離する。この方法は葉切除またはより拡大肝切除術にのみ適用できる。第2の方法は，腫瘍を栄養する領域のグリソン鞘を結紮するために，肝実質切離を先行させ，グリソン鞘を結紮後，虚血境界線に沿って実質を切離する方法である。第3は最初に超音波ガイド下に，インジゴカルミンなどの染料を注射し，肝表面を染色マッピングする方法で，肝の染色境界から実質を分割し，最終的にその領域の支配グリソン鞘を露出させて結紮切離する[1)]。しかし第2，第3の方法の欠点は，グリソン鞘根部の露出が困難な点である。この方法でアプローチしたグリソン鞘を結紮すると，他にも虚血部分が出現することをよく経験する。そこで，我々は，第4の方法として他の方法の不利な点を考慮して肝門部から目的のグリソン鞘に向けて直接アプローチしている。この方法で肝内グリソンを結紮すると，系統的肝切除は容易に施行できる。我々はこの方法を好んで系統的切除を行っているが，肝門部グリソン処理が可能なのは，葉切除，区域切除のほかS5，S6，(S7)，S8切除と考えられ，全ての亜区域切除が可能という訳ではなく，染色法を併用する場合もある。

我々は，系統的切除の手助けとして，術前には血管走行の確認や切除肝重量の推定を含めて，MD-CTから立体画像化するためのソフトVirtual Place Advance®(AZE system)を使用してきた[5)]。さらに系統的切除の術中ナビゲーションとして，ICG (Diagnogreen Inj., Daiichi Sankyo, Tokyo, Japan)試薬とLED励起ICG蛍光video navigation system (Photo Dynamic Eye2: PDE-2, Hamamatsu Photonics K.K. Hamamatsu, Japan)や近赤外線蛍光カラーカメラシステム; Hyper Eye Medical System (HEMS: Mizuo Medical Co., ltd, Tokyo, Japan)の併用，および新しい超音波造影剤Sonazoid® (GE Healthcare, Oslo, Norway)を術中に併用した安全で確実な系統的切除を解説する。

2．系統的肝切除における術前・術中ナビゲーション

①術前準備:

グリソンの走行は前述のように，術前にVirtual Place Advance®を用いて立体構築しておく。一例として，図1にS8領域HCCのMD-CT像(左上; 動脈相，左下; 門脈相)を示す。P8に隣接して動脈相で濃染され，門脈相で抜けてくる2.5cmのHCCが認められ，門脈枝に隣接する

ことからRF処置を避け，S8亜区域切除の方針とした。MD-CT imageより肝門部門脈の分岐状況を確認する(図2)。前区域，後区域分岐後，前区域枝を約2cm肝側に剥離するとP5とP8の分岐点が認められる。門脈枝はグリソン鞘に含まれるので，グリソンの分岐と同様と考えて差し支えなく，この様に術前シミュレーションする。

通常，立体構築と同時に推定切除量を算出し，多変量解析より割り出した安全切除評価式を用いて肝機能に応じた切除量の限界点を周知しておいた上で切除領域を定める[5)-6)]。この様な血管支配に基づく系統的切除が望ましいと考えているが，肝予備能が低い場合は術後肝不全を危惧し部分切除となる。また，肝切除症例は手術施行の7～10日前に，開腹時に施行する肝転移の検索を兼ねて全例ICG試験を行っておく。

②術中操作:

開腹後，まず肝門部処理を施行する。前述のS8切除例における肝門部処理を示す(図3)。ここではG8を肝門部から血流遮断する。次いでICG (0.5 mg/kg)を静脈投与し，前述のPDE-2によるLED (発光ダイオード)励起光を照射する。PDE-2で発光する原理は以下のように考えられている。肝全体に760 nmから780 nmの近赤外線光を照射すると，静注されたICGが励起され，800 nmから850 nmの波長の近赤外域蛍光を発し，その蛍光は組織透過性が高いため，肝表面の境界を観察することが可能となる。しかしこのICG蛍光は，人の眼には見えない波長域であり，しかも微量なため，特殊な撮像装置であるPDE-2で描出される。このシステムは冠動脈bypass後のgraft血流評価や，乳癌，消化器癌手術におけるセンチネルリンパ節の同定などに広く臨床応用されている[7)]。血流のある部分はICGと近赤外域蛍光が反応して白く描出され，虚血部分との間に切除区域肝表面の切離線を描出することが出来る(図4)。我々は22例の系統的切除について，肝門部グリソン処理法にPDE-2を使用しないと肝表面のDemarcation lineの描出が17例(77.3%)に留まったが，その使用によって全例に認められた(表1)。とくに肝硬変例や再手術例で肝表面に癒着がある症例に有用であった[7)]。

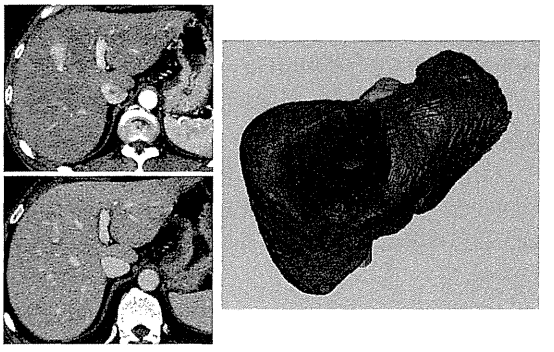


図1　MD-CTより作成したS8切除の術前シミュレーション

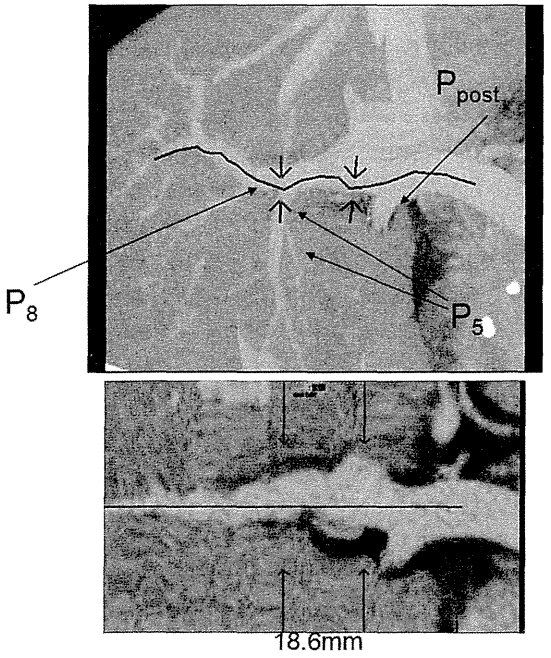


図2　肝門部門脈枝のCPR image

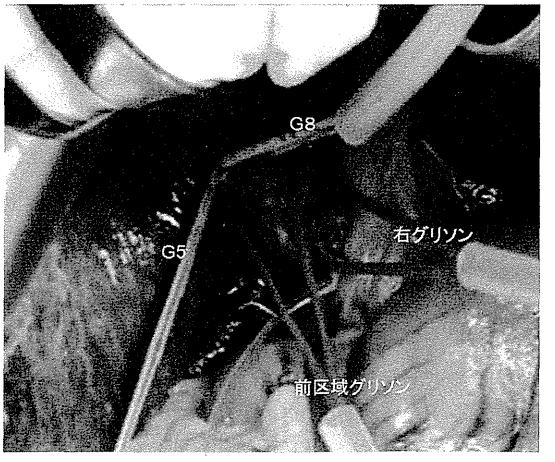


図3　S8亜区域切除時の肝門部剥離

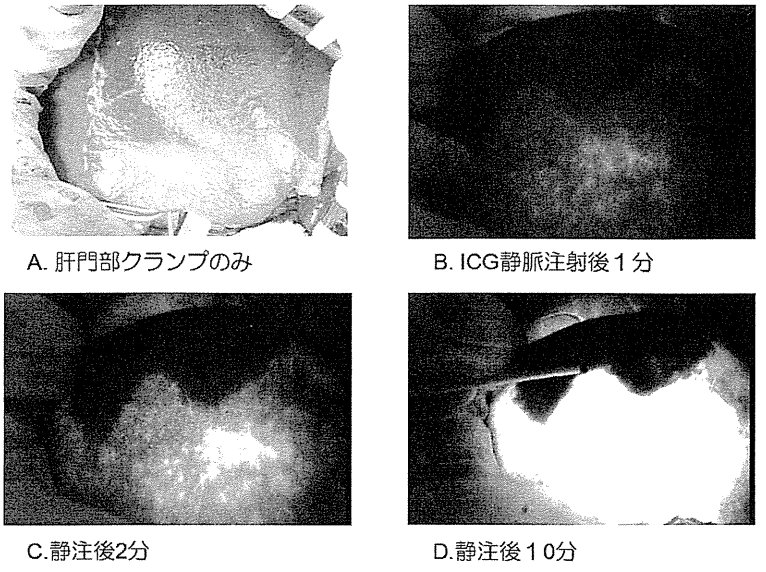


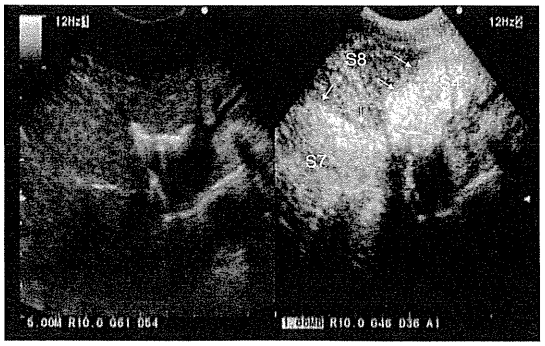
図４　S8切除における赤外線カメラ使用例

表１　系統的切除における赤外線カメラ使用例

肝切除	No.	虚血境界線が確認できた症例	
		肝門部グリソン鞘クランプのみ	赤外線カメラ付加
右葉切除(S5 S6 S7 S8)	4	4	4
左葉切除(S2 S3 S4)	4	3	4
後区域切除(S6 S7)	5	4	5
前区域切除(S5 S8)	3	2	3
S8 亜区域	4	2	4
S6 亜区域	2	2	2
Total	22	17	22*

*p=0.018

以上，肝表面の切離ラインはPDE-2の使用により十分に確認できるが，次に肝実質内の切除ライン同定が問題となる。これには血流遮断状態にて新しい超音波造影剤であるSonazoid®を静注(0.0075 ml/kgを 3 ml生理食塩水に溶解)し造影されない部分を切除する。図５にS8切除例を示すが，矢印に肝実質内の高・低エコー境界部がS7.S4の境界部となる。従来の超音波造影剤であるSonoVue® (Bracco Spa, Milan, Italy)と異なり，一回の静注により画像の造影効果はKupffer imageでほぼ肝切終了までの長時間得ることが出来るため，必要時，リアルタイムで確認し切除すれば良い。また，肝切離後は残肝に転移巣がないかを再度確認(転移巣はKupffer imageで低エコーに描出)出来るため，非常に有用であ



A IO(intra operative) -US　B IO-Enhanced US

図５　S8切除における超音波造影剤(Sonazoid)使用による超音波画像

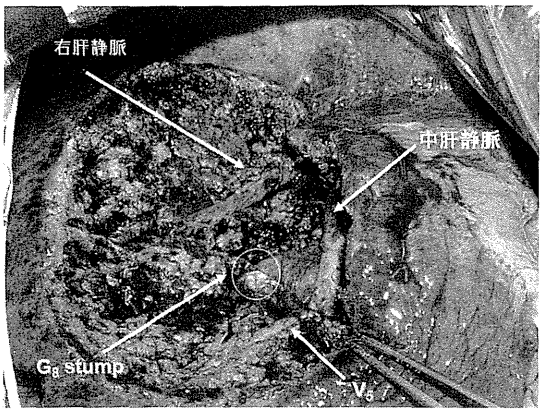


図6　S8亜区域切除

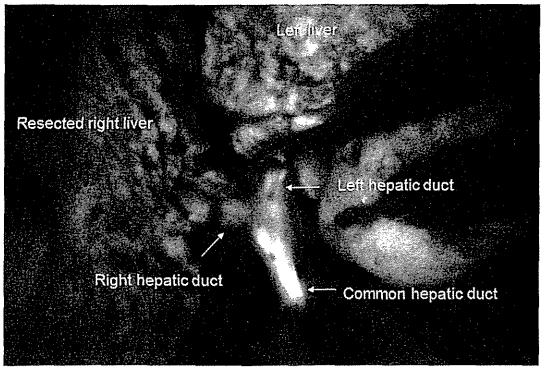
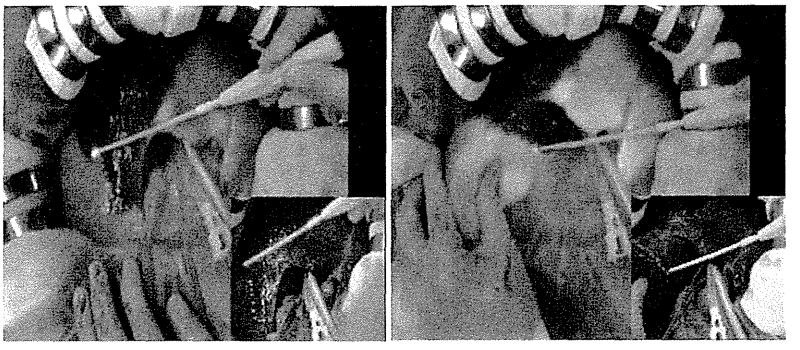


図7　PDE-2観察による肝右葉切除時の胆道造影



A. ICG静脈注射後2分　　B. ICG静脈注射後5分

図8　系統的前区域切除におけるカラー赤外線カメラ(HEMS)による観察(右下は肉眼View)

る[8]。図6にS8亜区域切除終了写真を示す。肝門部よりアプローチしたG8切断端，右肝静脈，中肝静脈およびそれに流入するV5が認められる。さらにICGは静脈注射後30分程度で胆汁排泄し始めるため，PDEにて胆管走行を確認することも可能で，胆管切離部位の決定にも有用である(図7)[9]。

3．系統的ナビゲーション切除システムの新しい展開

PDE-2は近赤外蛍光部のみの描出であるため，画像から患部の位置を特定するにはやや困難で，そのためモニター画像と肉眼との比較を余儀なくされるという欠点がある。さらに色調はモノクロで精細度は低く，微細な組織構造を見分けることができなかった。そこで，2010年6月に，近赤外蛍光部および可視光画像との同時合成描出システム，近赤外線蛍光カラーカメラシステム; Hyper Eye Medical System (HEMS: Mizuo Medical Co., ltd, Tokyo, Japan)が開発され，さらにフルカラーで直接画像から患部の位置を特定することが容易となった。本システムでは，リアルタイムでスムーズなカラー動画観察ができるため，微細な組織構造を見分けることが必要となる微妙な肝臓外科手術において，とくに有用である。系統的前区域切除時に前区域の血流を遮断後HEMSによる観察を右下の肉眼Viewとともに示す(図8)。血流のある部分がICG静脈内投与後約1分で白く変色し始め，約5分で完全に白色となる。この効果は肝切除終了時まで十分に持続するため，切離断面の血流確認のための術中の繰り返し撮像も可能なため非常に有用である。

おわりに

HCCの手術療法では，系統的な切除は理論的には非解剖学的切除より優れているように推察されるが，常に系統的切除が可能な訳ではない。HCCには肝硬変の合併例が多く，その切除には，切除の範囲と肝機能保持との兼

ね合いが重要となる。とくに本稿では，系統的切除を施行する際には，赤外線カメラシステムと第2世代の超音波造影剤 (Sonazoid®) を用いた術中超音波検査の併用が有用であることを解説した。カラーで描出される最新の赤外線カメラシステム (HEMS) はより視覚に訴えるためさらに有用性が高く，肝門部処理による系統的切除法がより一層普及することを期待する。

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3D シミュレーション・ナビゲーションによるグリソン先行処理肝切除の実際

井上　善博[1)]・内山　和久[1)]

要約：一般的に肝切除術を施行する際には，腫瘍学的にはその確証は得られていないものの，腫瘍の局在領域を支配する門脈の走行を考慮した系統的切除が望ましいと考えられる。系統的切除法には，染色マッピング法や肝切離先行法などがあるが，われわれはできる限り，肝門部グリソン処理を先行している。3D-CT 立体画像による門脈・静脈分岐形態や灌流域の評価は有用であり，これらの画像は術前あるいは術中の支援画像としても用いる。術中の補助方法としては，肝表面の切離境界を ICG と近赤外線蛍光カラーカメラシステム（Hyper Eye Medical System）で，肝実質の切離境界は超音波造影剤 Sonazoid® も併用した術中ナビゲーションが有用であった。

Key words：術前シミュレーション，術中ナビゲーション，系統的切除，赤外線発光システム

はじめに

肝切除術は肝細胞癌（HCC）治療の最も根治的な手技である。また，日本肝臓学会から発表された 2009 年度版，肝癌診療ガイドライン[1)]において，「最も重要な予後因子に門脈侵襲がある。したがって，腫瘍の局在領域を支配する門脈の走行を考慮して，肝切除をすべきである。」と明記されている。従来，HCC の進展は主に脈管浸潤により，系統的切除は主腫瘍の周囲に拡がる門脈・静脈腫瘍栓を含む腫瘍の領域の微小病変をも完全除去が可能なため，癌の根治性を追求した手術であり，部分切除に比較して好ましい切除法とされてきた。つまり，HCC の系統的切除の理論的長所はより大きな外科的なマージンを通して肝内転移を一掃できることにあり，系統的な切除術の生存率延長の利点を記述している報告もある[2~4)]。しかしながらそれを否定する報告[5)]もあり，系統的切除と部分切除のランダム化比較試験の結果がまだ発表されていない現在，HCC のための系統的な肝切除の効果についてはいまだ結論が出ていない。

Clinical Practice of Pre-operative Simulation and Intra-operative Navigation System during the Anatomical Hepatectomy
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Ⅰ．系統的手術法について

肝切除後の再発形式は，残肝臓組織中で微小な門脈や肝静脈内の腫瘍栓に起因した再発か，多中心性発癌によることが多い。系統的切除の利点は部分的に隣接した肝の微小血管内腫瘍栓を一掃できる可能性である。従来から施行される系統的切除法は，門脈と肝動脈を肝門部で分離してから結紮し，虚血境界線に沿って肝実質を切離する。この方法は葉切除またはより拡大肝切除術にのみ適応できる。第 2 の方法は，腫瘍を栄養する領域のグリソン鞘を結紮するために，肝実質切離を先行させ，グリソン鞘を結紮後，虚血境界線に沿って実質を切離する方法である。第 3 は最初に超音波ガイド下にインジゴカルミンなどの染料を注射し，肝表面を染色マッピングする方法で，肝の染色境界から実質を分割し，最終的にその領域の支配グリソン鞘

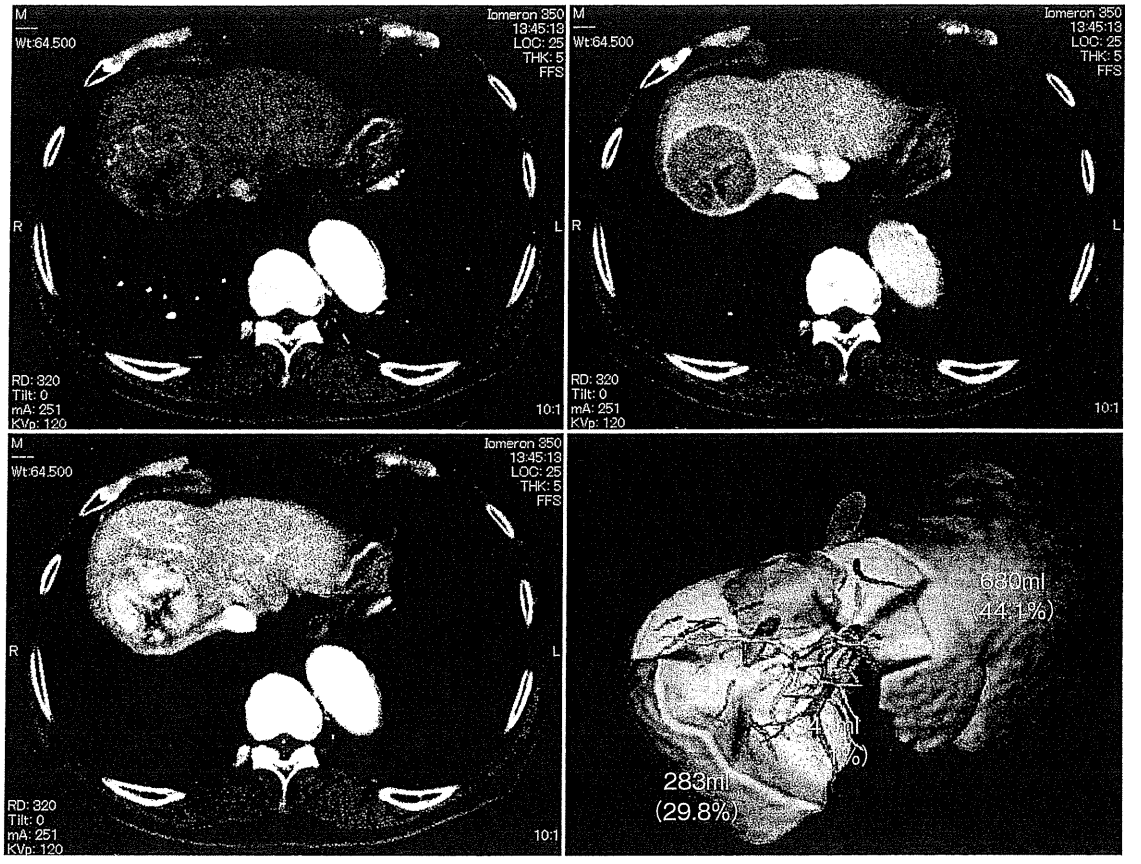


図 1　MD-CT より作成した前区域切除の術前シミュレーション

を露出させて結紮切離する[2]。しかし第 2，第 3 の方法の欠点は，グリソン鞘の根部の露出が困難な点である。この方法でアプローチしたグリソン鞘を結紮すると，他にも虚血部分が出現することをよく経験する。そこで，われわれは，第 4 の方法として他の方法の不利な点を考慮して肝門部から目的のグリソン鞘に向けて直接アプローチしている。この方法で肝内グリソンを結紮すると，系統的肝切除は容易に施行できる。われわれはこの方法を好んで系統的切除を行っているが，肝門部グリソン処理が可能なのは，葉切除，区域切除のほか S5，S6，(S7)，S8 亜区域切除と考えられ，すべての亜区域切除が可能という訳ではなく，染色法を併用する場合もある。

われわれは，系統的切除の手助けとして，術前には血管走行の確認や切除肝重量の推定を含めて，Multi-detector-CT から立体画像化するためのワークステーション（SYNAPSE VINCENT，富士フイルム社製）を使用してきた。さらに系統的切除の術中ナビゲーションとして，ICG（Diagnogreen Inj., Daiichi Sankyo，Tokyo，Japan）試薬と近赤外線蛍光カラーカメラシステム；Hyper Eye Medical System（HEMS：Mizuno Medical Co., ltd，Tokyo，Japan）の併用，および超音波造影剤 Sonazoid®（GE Healthcare，Oslo，Norway）を術中に併用した安全で確実な系統的切除を解説する。

Ⅱ．系統的肝切除における術前・術中ナビゲーション

1．術前準備

グリソンの走行は前述のように，術前にワークステーション（SYNAPSE VINCENT，富士フイルム社製）を用いて立体構築しておく。このワークステーションは，立体構築上で任意の門脈や肝静脈の支配領域を明瞭に識別する。また自動的にその領域の体積を計算する。一例として，図 1 に S8 領域 HCC の MD-CT 像（左上：動脈相，左下：門脈相，右上：平衡相，右下：3D 画像）を示す。P8 に隣接して動脈優位相で増強効果を呈し，門脈優位相～平衡相にかけて造影剤の洗い出し所見を呈する 5.8 cm の HCC が認められ，門脈枝に隣接し，S5 に 1.2 cm の肝内転移を認めたことから，前区域切除の方針とした。MD-CT image より肝門部門脈の分岐状況を確認する（図 2）。肝門部において門脈は比較的規則正しく左右に分岐する。左右

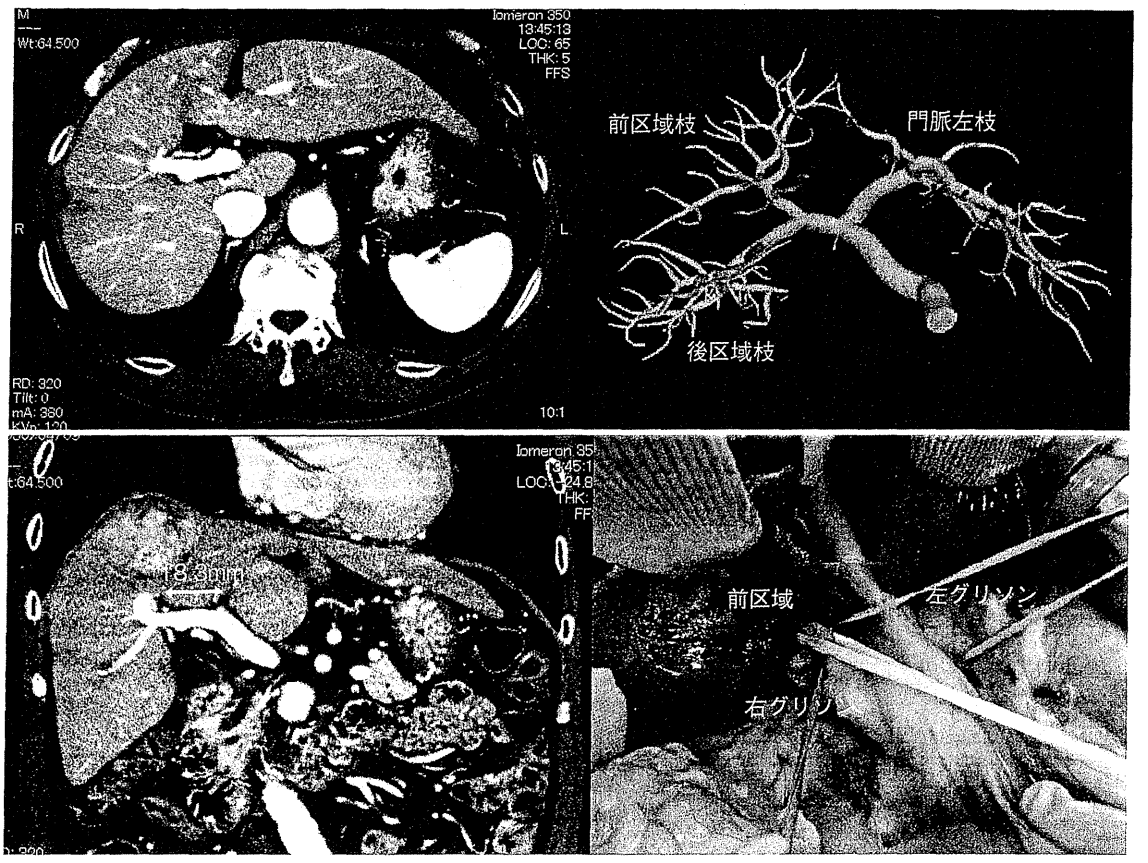


図 2　肝門部門脈の分岐状況

分岐後，右枝の約 1.8 cm 肝側に前区域枝と後区域枝の分岐点が認められる。肝内に入るグリソン鞘二次分枝の位置では門脈枝はグリソン鞘に含まれているので，グリソンの分岐と同様と考えて差し支えない。

肝細胞癌患者では，慢性肝炎や肝硬変の併存により肝機能が症例ごとに異なる。通常，立体構築と同時に推定切除量を算出し，肝機能に応じた切除量の限界点を考慮しておいた上で切除領域を定める[6~7]。このような血管支配に基づく系統的切除が望ましいと考えているが，肝予備能が低い場合は術後肝不全を危惧し部分切除となる。また，肝切除症例は手術施行の 5～10 日前に，開腹時に施行する肝転移の検索を兼ねて全例 ICG 排泄試験を行っておく。肝硬変などの障害肝では ICG 排泄試験と手術までの期間が短い（手術前日）場合には，再生結節などの多数の小結節が蛍光を呈するため，診断の特異度が低下する。

2．術中操作

開腹後，まず術前検査にて既知の病変を確認し，新規病変をスクリーニングする。近年，大腸癌肝転移に対する高い奏効率を示す肝切除前化学療法の導入に伴い，腫瘍縮小が認められるようになった。画像および肉眼的に同定することが困難であり，蛍光法を用いて初めて腫瘍の存在が指摘できた症例も経験した（図 3）。HCC では微小結節や肝実質が粗雑なため検出困難な結節などにおいて検出率を向上させることが可能である。

つづいて肝門部処理を施行する。前述の前区域切除例における肝門部処理を示す（図 4）。ここでは前区域グリソン鞘を肝門部から血流遮断する。次いで ICG 1 m*l*（2.5 mg）を静脈内投与し，前述の HEMS による近赤外光を照射する。HEMS で発光する原理は以下のように考えられている。肝全体に 760 nm から 780 nm の近赤外線光を照射すると，静脈注射され蛋白質と結合した ICG が励起され，800 nm から 850 nm の波長の近赤外域蛍光を発し，その蛍光は組織透過性が高いため，肝表面の境界を観察することが可能となる。しかしこの ICG 蛍光は，人の眼には見えない波長域であり，しかも微量なため，近赤外領域に感度を有する CCD カメラを搭載した特殊な撮影装置である HEMS で描出される。このシステムは冠動脈 bypass 後の graft 血流評価や，乳癌，消化器癌手術におけるセンチネルリンパ節の同定などに広く臨床応用されている[8]。血流のある部分は ICG と近赤外域蛍光が反応して白く描出され，ICG 静脈内投与後約 1 分で白く変色

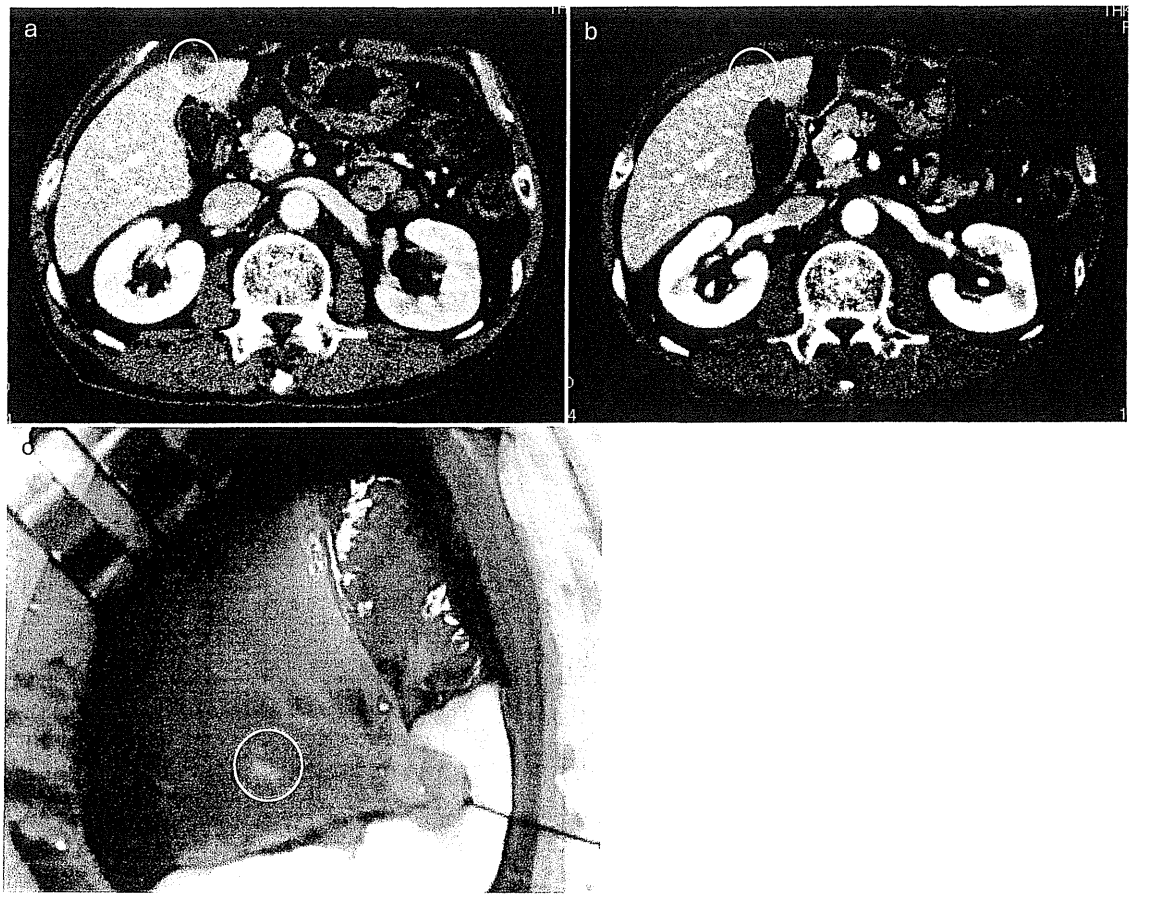


図 3 肝切除前化学療法による腫瘍縮小における赤外線カメラシステム使用例
a：化学療法前
b：化学療法後
c：ICG 蛍光法による肝表面の観察

し始め，約 5 分で完全に白色となる。虚血部位との間に切除区域肝表面の切離線を描出することができる。この効果は肝切除終了時まで十分に持続するため，切離断面の血流確認のための術中の繰り返し撮影も可能なため非常に有用である。系統的前区域切除時に前区域の血流を遮断後 HEMS による観察を左上の肉眼 view とともに示す（図 4）。この症例では併存する肝硬変のために，血流遮断に HEMS を使用しないと肝表面の demarcation line の描出が困難であった。とくに肝硬変例や再手術例で肝表面に癒着がある症例に有用である[8]。しかし，近赤外光の組織透過性には限界があり，蛍光法で描出できるのは肝表近く（10 mm までの深さ）の腫瘍に限られる。

以上，肝表面の切離ラインを HEMS の使用により十分に確認した。次は肝実質内の切除ライン同定であるが，これには血流遮断状態にて第二世代超音波造影剤である Sonazoid® の静脈注射（0.015 m*l*/kg，添付文書の推奨容量）も併用し，HEMS と両者にて造影されない部分を切除する。図 5 に前区域切除例における造影超音波画像を示すが，矢印の肝実質内の高・低エコー境界部が S6/7，S5/8 の境界部となる。第一世代超音波造影剤ともいう Levovist®（Bayer，Osaka，Japan）と異なり，1 回の静注により画像の造影効果は Kupffer image でほぼ肝切除終了までの長時間得ることができるため，安定した post vascular image を得ることができる特徴を持っている。そのため必要時，リアルタイムで確認し切除すれば良い。また，肝切離後は残肝に転移巣がないかを再度確認（転移巣は Kupffer image で低エコーに描出）できるため，非常に有用である[9,10]。図 6 に前区域切除終了の写真を示す。肝門部よりアプローチした前区域グリソン鞘切除端，中肝静脈，右肝静脈およびそれに流入する V7 が認められる。

従来までのナビゲーションシステムは肝表面のみの 2 次元であったが，HEMS の使用により肝表面のみならず，肝実質内を含めた 3 次元のナビゲーションシステムにより切除範囲を同定することが可能になった。さらに ICG は静脈注射後 30 分程度で胆汁排泄し始めるため，HEMS にて胆管走行を確認することも可能で，胆管切離部位の決定にも有用である。

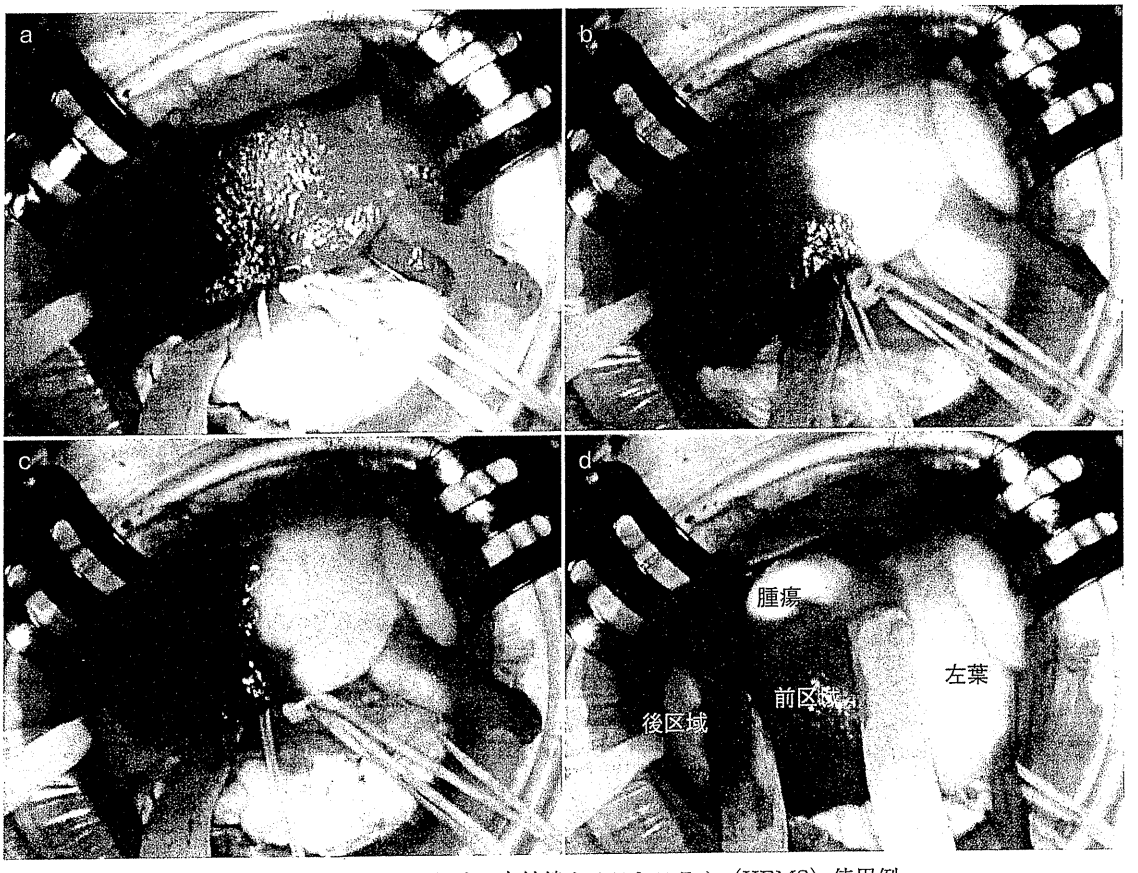
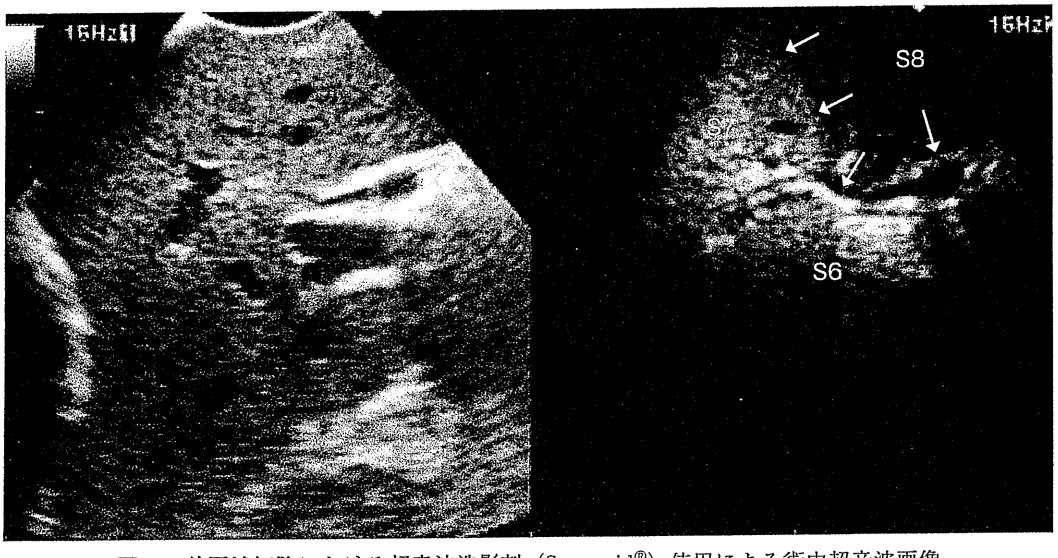


図 4　前区域切除における赤外線カメラシステム（HEMS）使用例
a：肝門部グリソン右枝クランプのみ
b：ICG 静脈注射後 2 分
c：グリソン前区域枝のみクランプ
d：静注後 10 分



a|b

図 5　前区域切除における超音波造影剤（Sonazoid®）使用による術中超音波画像
a ：IO（intra operative）-US
b ：IO-Enhanced US

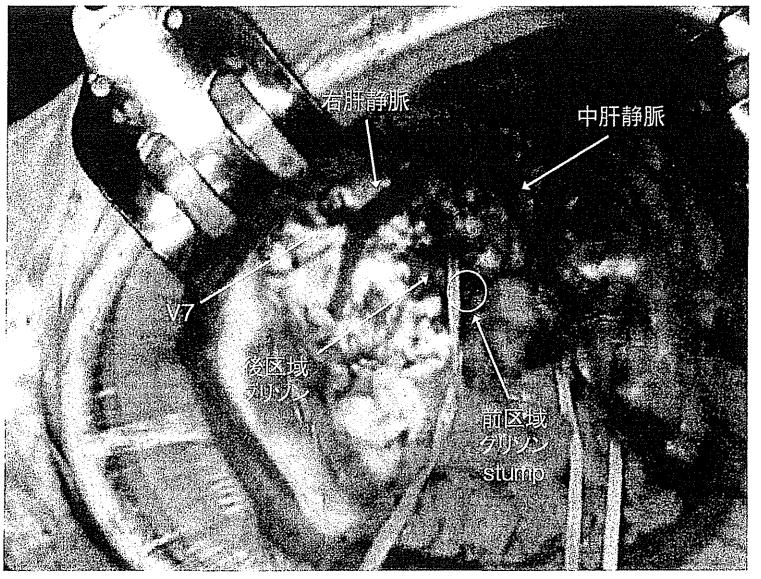


図 6　前区域切除

Ⅲ. 系統的ナビゲーション切除システムの新しい展開

2010年6月に，近赤外蛍光部および可視光画像との同時合成描出システム，近赤外線蛍光カラーカメラシステム：Hyper Eye Medical System（HEMS）が開発された。本システムでは，フルカラーで直接画像から患部の位置を特定することが容易となり，リアルタイムでスムーズなカラー動画観察ができるため，微細な組織構造を見分けることが必要となる微妙な肝臓外科手術において，とくに有用である。今回，肝門部から目的のグリソンを先行処理する肝切除術を紹介したが，他にはICGが胆汁排泄性の薬剤であることを利用した蛍光胆道造影や，切除標本の観察でsurgical marginが疑わしい場合に，肝切除後の離断面を蛍光法で確認することで癌の遺残を同定できる場合もある。また肉眼的に同定することが困難であり，蛍光法を用いて初めて腫瘍の存在が指摘できた症例もある。

しかし短所として，現行の市販システムは腹腔鏡手術で用いることができない。より安全かつ視認可能という色素法の利点を腹腔鏡手術へ展開するための技術開発とその検証は，低侵襲化を目的とした腹腔鏡下肝切除術の臨床応用において必須の課題であると考えている。

おわりに

HCCの手術療法では，系統的な切除は理論的には非解剖学的切除より優れているように推察されるが，常に系統的切除が可能な訳ではない。HCCには肝硬変の合併例が多く，その切除には，切除の範囲と肝機能保持との兼ね合いが重要となる。とくに本稿では，系統的切除を施行する際には，赤外線カメラシステム（HEMS）と第2世代の超音波造影剤（Sonazoid®）を用いた術中超音波検査の併用が有用であることを解説した。腹腔鏡にてもカラーで描出される赤外線カメラシステムが開発され，肝門部処理による系統的切除法が開腹，腹腔鏡を問わずより一層普及することを期待する。

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ORIGINAL ARTICLE

Prognostic factors of acute cholangitis in cases managed using the Tokyo Guidelines

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Abstract
Background/purpose In 2007, the Tokyo Guidelines (TG07) working group established diagnostic criteria for assessment of the severity of acute cholangitis. This study aimed to analyze outcomes and identify predictors of mortality in patients with acute cholangitis managed according to the TG07.
Methods In this study, 215 consecutive cases of acute cholangitis were reviewed. Risk factors associated with mortality or refractory cholangitis, which is defined on the basis of prolonged hospitalization (>28 days) or disease resulting in fatality, were examined using multivariate logistic regression analysis.
Results There were 52, 133, and 30 cases of mild, moderate, and severe cholangitis, respectively. The overall mortality rate was 4.2 % (9/215). Mortality rates in patients with mild, moderate, and severe cholangitis were 0, 2.3, and 20.0 %, respectively (moderate vs. severe, $p = 0.001$). Multivariate analysis showed that serum albumin levels ≤2.8 g/dl and PT-INR >1.5 were significant predictors of mortality. There were 57 patients (26.5 %) with refractory cholangitis. Multivariate analysis showed that serum albumin level ≤2.8 g/dl, PT-INR >1.5, etiology and inpatient status were significant predictors of refractory cholangitis.
Conclusions The TG07 severity assessment criteria for acute cholangitis were significantly predictive of mortality. Hypoalbuminemia is an important risk factor in addition to organ dysfunction.

Keywords Acute cholangitis · Endoscopic retrograde cholangiopancreatography · Severity of illness · Hypoalbuminemia

Abbreviations
EBD Endoscopic biliary drainage
TG07 Tokyo Guidelines
PTBD Percutaneous transhepatic biliary drainage

Introduction

Prior to the 1970s, the mortality rate for patients with acute cholangitis was reportedly >50 %; however, advances in endoscopic drainage and new antibiotics reduced the mortality rate to <7 % by the 1980s [1]. Several investigators have proposed predictors of adverse outcomes in patients with acute cholangitis using their own severity assessment systems [2–4]. No standard criteria were

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available for diagnosis and severity assessment in patients with acute cholangitis until the Tokyo Guidelines (TG07) were published in 2007 [5, 6]. The TG07 defines severe acute cholangitis as cholangitis accompanied by organ dysfunction and recommends that biliary drainage should be urgently performed for patients with severe acute cholangitis. Moderate cholangitis is defined by the TG07 as disease unresponsive to initial medical treatment, whereas mild cholangitis is defined as disease responsive to medical treatment. However, several issues arise from this severity assessment. First, acute cholangitis may worsen even after biliary drainage is performed following a failure of conservative treatment. Second, the timing of biliary drainage in patients with moderate cholangitis needs to be considered (e.g., as soon as possible, within 24 h, following conservative treatment using another antibiotic). Therefore, determination of disease severity and timing of biliary drainage in the early-stages of mild or moderate cholangitis can be difficult.

This retrospective study aimed to analyze outcomes and identify predictors of mortality and prolonged hospitalization in patients with acute cholangitis managed according to the TG07, in order to confirm the effectiveness of these guidelines in clinical practice. Early identification of more reliable risk factors in addition to organ dysfunction may help clinicians to administer timely and appropriate treatment.

Patients and methods

A total of 215 patients (138 males, 77 females; average age 66.7 years) who were admitted to Chiba University Hospital between February 2007 and July 2011 for acute cholangitis were enrolled in this study. Diagnosis and severity assessment were retrospectively made according to the TG07 [5]. All clinical data were prospectively recorded in electronic hospital medical records. Diagnostic criteria for acute cholangitis included Charcot's triad (fever and/or chills, jaundice, abdominal pain), which is the definitive diagnostic criterion for acute cholangitis (criterion 1), and in the absence of one or more components of Charcot's triad, a definite diagnosis was reached if an inflammatory response and biliary obstruction were both revealed by laboratory data and imaging findings (criterion 2). Severe cholangitis was diagnosed in cases complicated by organ/system dysfunction (cardiovascular, nervous, respiratory system, kidney, liver, or hematological system). Moderate cholangitis was diagnosed in cases in which early biliary drainage (EBD) was required after failure of initial medical treatment. Mild cholangitis was diagnosed in cases that responded to initial treatment and did not require biliary drainage. Immediate medical treatment with intravenous fluid and antibiotics was administered in all cases diagnosed with acute cholangitis. For biliary drainage, endoscopic biliary drainage (EBD) was selected as first-line therapy according to recommendations of the TG07, and it was followed by percutaneous transhepatic biliary drainage (PTBD) [6]. The study protocol was approved by the ethics committee of Chiba University Hospital.

Mortality due to cholangitis and its determining factors was the primary outcome in this study. The secondary purpose was to detect major factors that affect the duration of hospitalization in patients with acute cholangitis. For cases in which cholangitis developed during hospitalization, the duration of hospitalization was calculated from the date of onset instead of the date of admission. Organ failure was defined by the TG07 as follows: hypotension requiring dopamine $\geq$5 μl/kg per min or any dose of dobutamine, disturbance of consciousness, oxygenation index values [as measured by the ratio of the pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2)] <300, serum creatinine >2.0 mg/dl, and platelet count <100000/μl. These factors were used as potential predictors of mortality or refractory cholangitis.

All statistical analyses were performed using the Predictive Analytics Software package (PASW 18.0 for Windows, SPSS Inc., Tokyo, Japan). The *t* test was used for continuous variables with a skewed distribution, and the Chi-squared test with Yates' correction method or Fisher's exact test was used to compare categorical variables. A cut-off value was determined by receiver operating characteristic (ROC) analysis. A logistic regression test analysis was performed using the stepwise method. A p value of <0.05 was considered statistically significant. In this study, odds ratios (ORs) are reported together with their 95 % confidence intervals (CIs).

Results

Mild, moderate, and severe cholangitis were diagnosed in 52, 133, and 30 cases, respectively (Tables 1, 2). Of these 215 cases, 72 cases fulfilled criterion 1 (Charcot's triad) and 143 cases fulfilled criterion 2 (Table 2). The ratio of patients categorized under criterion 1 to those categorized under criterion 1+ criterion 2 was significantly low for patients with mild cholangitis. Fifty-two patients with mild cholangitis were successfully treated without EBD (Fig. 1). EBD was performed in 133 patients with moderate cholangitis after failure of initial medical treatment. Several cases with assumed organ failure caused by factors unrelated to cholangitis presented with moderate disease: one case with PT-INR >1.5, who was treated with warfarin, and 14 cases with thrombopenia complicated by chronic

Table 1 Clinical characteristics of the patients with acute cholangitis

	Severity of acute cholangitis		
	Severe (n = 30)	Moderate (n = 133)	Mild (n = 52)
Age (mean ± SD)	68.2 ± 9.1	64.5 ± 11.5**	71.5 ± 10.1**
Gender (male/female)	21/9	81/52	36/16
Body temperature >38 °C or <36° (yes/no)	17/13	65/68§	8/44§
WBC count >12000 or <4000/μl (yes/no)	13/17	39/94	11/41
CRP (mg/dl)	9.3 ± 7.8*	5.1 ± 5.7*	4.0 ± 4.5
Serum albumin (g/dl)	2.9 ± 0.7§	3.5 ± 0.7**,§	3.8 ± 0.5**
AST (IU/l)	211.3 ± 254.9	253.3 ± 256.1	228.8 ± 197.5
ALT (IU/l)	140.4 ± 138.6	201.7 ± 241.2	197.63 ± 176.6
ALP (IU/l)	1107.3 ± 914.5	1093.7 ± 741.2	880.4 ± 865.9
T. bilirubin (mg/dl)	7.6 ± 7.1	5.0 ± 5.3§	2.5 ± 1.9§
Organ dysfunction			
Hypotension requiring dopamine ≥5 μl/kg per min or any dose of dobutamine (yes/no)	19/11§	0/133§	0/52
Disturbance of consciousness (yes/no)	17/13§	0/133§	0/52
PaO_2/FiO_2 ratio <300 (yes/no)	9/21§	0/133§	0/52
Serum creatinine >2.0 mg/dl (yes/no)	4/26**	0/133**	0/52
PT-INR >1.5 (yes/no)	17/13§	1/132§	0/52
Platelet count <100000/μl (yes/no)	16/14§	14/129§	0/52

* $p = 0.007$, ** $p = 0.001$, § $p < 0.001$

Table 2 Proportion of criterion 1 (Charcot' triad) in mild, moderate and severe cholangitis

Severity	n	Criterion1 Charcot's triad		Criterion2 "inflammatory response" and "biliary obstruction"
Mild	52	4 (7.7%)	*	48
Moderate	133	53 (39.8%)	*	80
Severe	30	15 (50%)	*	15
Total	215	72(33.5%)		143

* $p < 0.001$

liver disease (Table 1). Severe cholangitis was diagnosed in 30 cases because of the presence of organ/system dysfunction (cardiovascular, nervous, respiratory system, kidney, liver, or hematological systems). Mean CRP level in patients with severe cholangitis is significantly higher compared to those in patients with moderate (Table 1). ROC analysis revealed that CRP level ≥5.0 mg/dl had a sensitivity of 60.0 % and a specificity of 66.9 % in differentiating severe cholangitis from moderate (Fig. 2).

Acute cholangitis developed during hospitalization in 104 patients, of whom 45 (43.2 %) had been admitted to other departments (mainly surgery). In our hospital, EBD was performed in the Department of Gastroenterology and Clinical Oncology for all cases. One hundred-eleven cases were outpatients or transfers from outlying hospitals. For these cases, the initial medical treatment period was calculated from the beginning of therapy in any hospital or hospital department. In cases unresponsive to conservative medical therapy before visiting our department, the severity of acute cholangitis was judged to be moderate at the time of admission.

The various etiologies identified for acute cholangitis examined in this study are listed in Table 3 (benign/malignant 109/106). Of the 106 cases with malignancy, 71 developed acute cholangitis due to dysfunction of a previously placed tube or metal stent. Early biliary drainage (EBD or PTBD) was performed in all 163 cases with moderate or severe acute cholangitis (Fig. 1). The overall success rate of EBD (within 48 h) was 98.1 % (160/163). EBD was performed successfully in 156/163 (95.7 %) cases. Urgent EBD (within 12 h of onset), early EBD (within 24 h of onset), and relatively early EBD (within

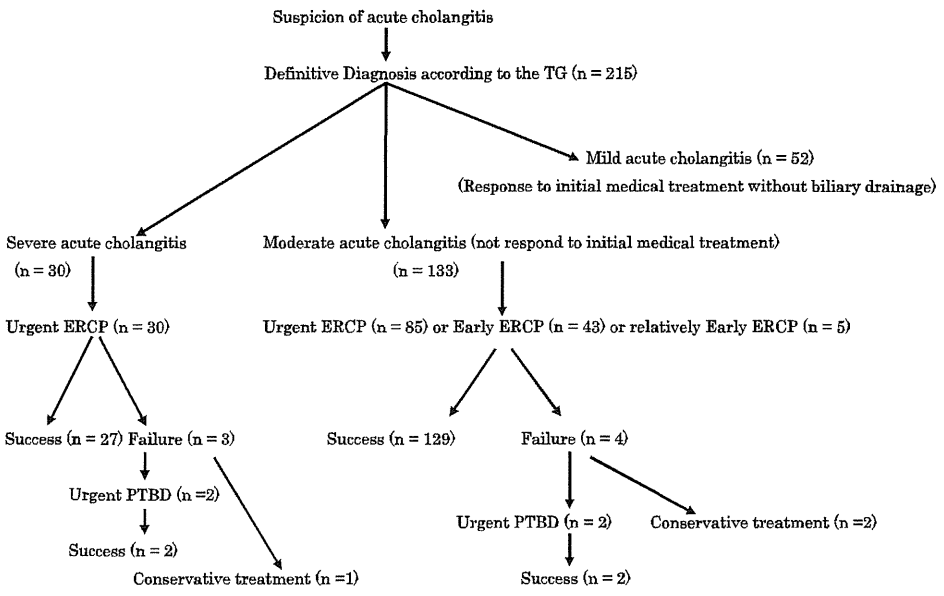

Fig. 1 Flow chart of the diagnosis and treatment of acute cholangitis in this study

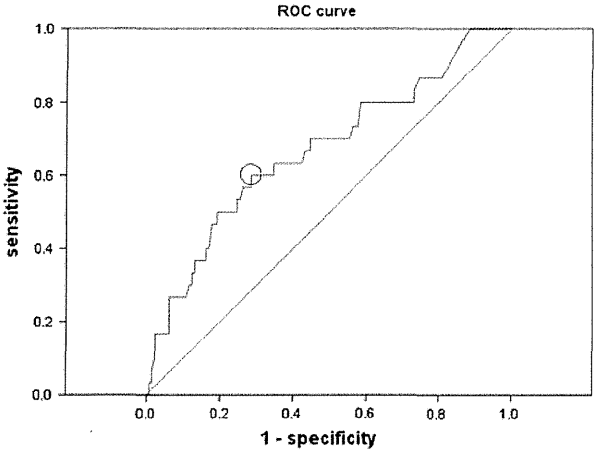

Fig. 2 Receiver operating characteristic analysis of CRP level in differentiating severe cholangitis from moderate. Area under the curve: 0.670 (95 %: 0.557–0.782); $p = 0.004$. The optimal cut-off value for predicting mortality in patients with acute cholangitis was 5.0, which yielded a sensitivity of 60.0 % and a specificity of 66.9 % (*circle*)

48 h of onset) were performed in 115, 43, and five cases, respectively. EBD failed in seven cases, of which four were successfully treated by urgent PTBD and two responded at a later stage to conservative medical treatment and elective endoscopic treatment. In the remaining patient, advanced hepatocellular cancer was complicated by uncontrolled bleeding and liver failure, and this patient died 4 days after failure of EBD. No major procedure-related complications such as post-EBD pancreatitis, bleeding, or perforation were observed.

Predictors of mortality

Risk factors for acute cholangitis were analyzed in 215 cases of acute cholangitis. The overall mortality rate was 4.2 % (9/215). Mortality rates in patients with mild, moderate, and severe cholangitis were 0 % (0/52), 2.3 % (3/133), and 20.0 % (6/30), respectively (moderate vs. severe, $p = 0.001$). Death occurred because of uncontrolled septicemia ($n = 5$) and liver failure ($n = 4$) as complications of persistent cholangitis. In all other cases except the one with advanced hepatocellular cancer complicated by uncontrolled bleeding, urgent biliary drainage within 24 h of admission proved successful. Malignant ($n = 6$) and benign ($n = 3$) biliary obstruction was also observed in the nine cases that failed to survive (Table 4). ROC analysis revealed that serum albumin level $\leq$2.8 mg/dl had a sensitivity of 83.5 % and a specificity of 88.9 % in predicting death from acute cholangitis (Fig. 3). Mean serum albumin level in patients with malignant diseases is significantly lower compared to those in patients with benign diseases (Table 5). However, a univariate analysis did not identify an association between hypoalbuminemia and host-related factors such as etiology (malignant), age ($\geq$75 years), inpatient status and stent dysfunction (Table 6). Univariate analysis of the factors associated with mortality revealed six influential factors (Table 7): serum albumin level $\leq$2.8 mg/dl, hypotension, disturbance of consciousness, PaO_2/FiO_2 ratio <300, PT-INR >1.5 and platelet count <100000/μl. According to multivariate analysis, serum albumin levels $\leq$2.8 g/dl and PT-INR >1.5 were statistically significant predictors of mortality (Table 8).

Table 3 Etiologies of cholangitis observed in this study

Etiologies	*n*	Severity of acute cholangitis		
		Severe ($n = 30$)	Moderate[a] ($n = 133$)	Mild[a] ($n = 52$)
Malignant diseases	106 (71)[b]	13 (8)	90 (63)	2
Pancreatic head cancer	49 (40)	4 (3)	44 (37)	1
Biliary tract cancer	43 (31)	9 (5)	33 (26)	1
Hepatocellular cancer	5		4	
Periampullary cancer	3		3	
Malignant lymphoma	1		1	
Others	5		5	
Benign diseases	109 (7)	17 (1)	43 (6)	50
Choledocholithiasis	90 (2)	8	32 (2)	50
Chronic pancreatitis	6 (5)	1 (1)	5 (4)	
Benign biliary stricture	4	1	3	
Primary sclerosing cholangitis	5	3	2	
Hepatolithiasis	3	2	1	
Hemobilia (liver cirrhosis)	1	1		

[a] Number of cases with malignant diseases in moderate cholangitis are significantly higher than that in mild cholangitis ($p < 0.001$)

[b] Stent in situ

Table 4 Etiologies of cases that failed to survive ($n = 9$)

Malignant diseases	
Pancreatic head cancer	3
Bile duct cancer	1
Hepatocellular cancer	2
Benign diseases	
Decompensated liver cirrhosis	1
Primary sclerosing cholangitis[a]	1
Hepatolithiasis[a]	1

[a] Complicated with secondary biliary cirrhosis in end-stage liver disease

Predictors of refractory cholangitis

Average (±SD) and median values for the duration of hospitalization were 16.3 (±23.5) days and 6 days, respectively. When refractory cholangitis was defined on the basis of prolonged hospitalization for >28 days or disease resulting in fatality, 57 cases (26.5 %) were identified as refractory (48 cases: hospital stay >28 days, nine fatal cases).

Results of the univariate analysis are listed in Table 9. Univariate analysis identified nine factors associated with refractory cholangitis: hypotension, disturbance of consciousness, oxygenation index values <300, serum albumin level ≤2.8 g/dl, PT-INR >1.5, platelet count <100000/μl, etiology (malignant), inpatient status, and stent dysfunction. In the multivariate analysis, serum albumin level ≤2.8 g/dl, PT-INR >1.5, etiology (malignant), and inpatient status were significant predictors of refractory cholangitis (Table 10).

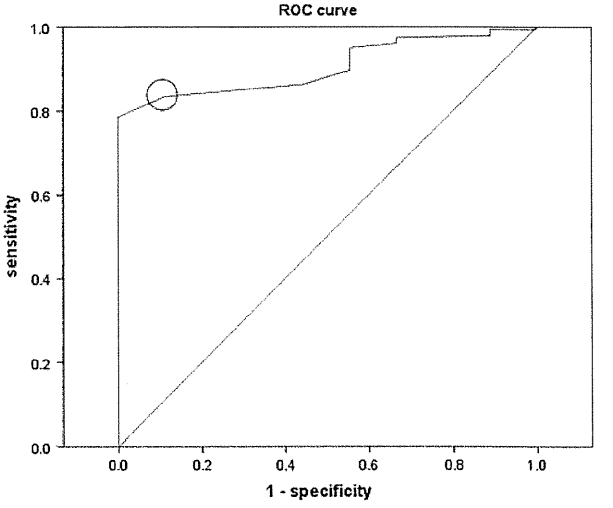

Fig. 3 Receiver operating characteristic analysis of serum albumin level as a predictor of mortality in patients with acute cholangitis. Area under the curve: 0.905 (95 %: 0.852–0.959); $p < 0.001$. The optimal cut-off value for predicting mortality in patients with acute cholangitis was 2.80, which yielded a sensitivity of 83.5 % and a specificity of 88.9 % (*circle*)

Discussion

No standard criteria were established for the diagnosis and assessment of severity of acute cholangitis until the TG07 were published in January 2007 [5, 6]. The guidelines clearly state that severe acute cholangitis is that which is complicated with organ dysfunction. The TG07 recommend urgent EBD as first-line therapy in cases with severe cholangitis [7, 8]. In the present study, assessment of the severity of acute cholangitis was significantly related to