Table 4 Early-stage complications following hepatectomy

	Hepatolithiasis $n = 42$	HCC $n = 193$	Metastatic carcinoma $n = 73$
Death	0	4 (2.2%)	1 (1.4%)
Surgical site infections	10 (23.8%)*	22 (11.3)**	2 (2.7)
Remote site infections	2 (4.8)	8 (4.1)	3 (4.1)
Bile leakage	2 (4.8)	7 (3.6)	1 (1.4)
Ileus	1 (2.4)	5 (2.6)	2 (2.7)
Disturbance of liver function	4 (9.5)	8 (4.1)	4 (5.5)
Pancreatitis	3 (7.1)	5 (2.6)	2 (2.7)
Gastrointestinal bleeding	1 (2.4)	5 (2.6)	1 (1.4)
Intractable ascites	1 (2.4)	10 (5.2)	0
Intractable pleural effusion	1 (2.4)	11 (5.7)	1 (1.4)
Intraabdominal bleeding	1 (2.4)	1 (0.5)	0
Others	2 (4.8)	6 (3.1)	3 (4.1)

* $p = 0.034$ compared with HCC, $p < 0.001$ compared with metastatic carcinoma

** $p = 0.028$ compared with metastatic carcinoma

Table 5 Incidence of surgical site infections after hepatectomy

	Hepatolithiasis (a) ($n = 42$)	HCC (b) ($n = 193$)	Metastatic carcinoma (c) ($n = 73$)	p Value		
				(a) vs. (b)	(a) vs. (c)	(b) vs. (c)
Surgical site infections (SSIs)						
Superficial or deep incisional SSIs	5 (11.9%)	15 (7.8%)	1 (1.4%)	ND	<0.001	0.050
Organ/space SSIs	5 (11.9%)	7 (3.6%)	1 (1.4%)	0.029	<0.001	ND
Remote site infections						
Respiratory infections	1 (2.4%)	3 (1.6%)	2 (2.7%)	ND	ND	ND
Urinary tract infections	0	1 (0.5%)	0	ND	ND	ND
Catheter-related infections	1 (2.4%)	4 (2.1%)	1 (1.4%)	ND	ND	ND

Table 6 Distribution of bacterial strains isolated from bile during hepatectomy

	Hepatolithiasis ($n = 42$)	HCC ($n = 51$)	Metastatic carcinoma ($n = 20$)
No. of patients with positive culture (%)	35 (83.3%)*	4 (7.8%)	2 (10.0%)
Bacterial flora (mono/poly)	22/13	4/0	2/0

* $p < 0.001$ compared with HCC or metastatic carcinoma

carcinomas. There was no significant difference in the incidence of SSIs in regard to the type of liver resection (i.e., major versus minor hepatectomy) including the patients with HCC and those with metastatic carcinoma.

Distribution of bacterial strains isolated from bile during the operation and those detected from SSIs

The distribution of bacterial strains isolated from bile during the operations is shown in Table 6. The overall positive culture rate in the bile in this study was 36.2%, although the rates were 83.3, 7.8, and 10.0% for hepatolithiasis, HCC, and metastatic carcinoma, respectively. A significantly higher ($p < 0.001$) positive bile culture rate was found for hepatolithiasis compared with HCC or metastatic carcinoma. Similarly, polymicrobial infections were not detected in the patients with HCC or metastatic carcinoma, whereas polymicrobial infections were detected in the bile of as many as 13 of the 35 patients (37.1%) with hepatolithiasis.

Relationships between bacteria isolated from bile during the operation for hepatolithasis and those detected from SSIs are shown in Table 7. Fifty-two bacterial and fungal species were isolated from bile and fourteen bacterial and fungal species were detected from SSIs. The detection rates of *Enterococcus* sp., *Escherichia coli,* and *Klebsiella* sp. in the bile were 19.2, 21.2, and 13.5%, respectively, and in a similar pattern, the detection rates of *Enterococcus* sp., *E. coli,* and *Klebsiella* sp. from SSIs were 21.4, 21.4, and 14.3%, respectively. Case-specific data of SSI-positive patients, comparing bacterial species isolated from bile during the operation for hepatolithasis and bacterial species isolated from SSIs, are shown in Table 8. In 8 of the 10

SSI-positiive patients, a similar relationship was found between bacteria isolated from the bile during the operation for hepatolithasis and bacteria isolated from SSIs.

Table 7 Relationship between bacteria isolated from bile during operation for hepatolithasis and those detected from SSIs

	Isolated bacterial species in the bile	Isolated bacterial species from SSIs
Gram-positive cocci		
MRSA	0	1
MSS	0	1
S. epidermidis	1	1
CNS	2	0
Streptococcus sp.	2	0
Enterococcus sp.	10 (19.2%)	3 (21.4%)
Others	2	0
Total	17 (32.7%)	6 (42.9%)
Gram-negative bacilli		
E. coli	11 (21.2%)	3 (21.4%)
Klebsiella sp.	7 (13.5%)	2 (14.3%)
Enterobacter sp.	3	1
Pseudomonas sp.	5	2
Serratia sp.	2	0
Bacteroides sp.	3	0
Others	3	0
Total	34 (65.4%)	8 (57.1%)
Fungi		
Candida sp.	1	0
Total (bacteria + fungi) (Number of strains)	52	14

MRSA methicillin-resistant *Staphylococcus aureus*, *MSS* methicillin-sensitive *Staphylococcus aureus*, *CNS* coagulase negative *Staphylococcus aureus*

Discussion

Infections frequently occur after a liver resection and cause a significant proportion of postoperative complications. According to the National Nosocomical Infections Surveillance (NNIS) report, SSI rates range from 3.24 to 7.04% after hepato-pancreaticobiliary surgery [4]. Several studies suggest an important role for the liver in postoperative infection [13, 14]. Schindl et al. [15]. reported a relationship between the resected liver volume and the incidence of postoperative infection. A significant loss of hepatic phagocytes (Kupffer cells) and the decreased synthesis of hepatic proteins involved in antigen recognition, opsonisation, and phagocytosis are considered to result in impaired innate immune function following major liver resection, consequently rendering the patient more susceptible to infection [16].

Some infections may be dependent on the condition of patients, the extent of liver resection performed, and liver function; however, other infections are determined by a multitude of factors. Ten percent to 30% of patients with cirrhosis or chronic liver dysfunction developed postoperative bacterial infections after undergoing an abdominal surgical procedure [17, 18]. Pessaux et al. [19]. reported that 37 (28.4%) of 130 patients with cirrhosis developed a postoperative infection. This high prevalence of infectious complications in cirrhotic patients can be explained by impaired immune defense mechanisms [16], including reticulo-endothelial system dysfunction, granulocyte dysfunction, and disturbed blood sugar control. Changes in the digestive flora and in the intestinal barrier may also play a role in the pathophysiology of bacterial infections during cirrhosis. Cirrhosis and chronic liver dysfunction with HCC are risk factors for global infectious complications [16].

Table 8 Case-specific data of SSI-positive patients following hepatectomy for hepatolithiasis

Patients (age, years; sex)		Hepatectomy procedure	Bacterial species in bile during hepatectomy	Bacterial species isolated from SSI	Type of SSI
1	61 F	Left hepatectomy	***E. coli***, *Bacteroides* sp.	***E. coli***	O
2	51 M	Left hepatectomy	***Enterococcus* sp.**, *Klebsiella* sp.	***Enterococcus* sp.**, MRSA	O
3	42 M	Lateral sectionectomy	***Klebsiella* sp.**, *Bacteroides* sp.	***Klebsiella* sp.**	O
4	54 M	Lateral sectionectomy	*E. coli*	*Enterobacter* sp., MSSA	O
5	65 F	Right hepatectomy	***Enterococcus* sp.**, ***Klebsiella* sp.**	***Enterococcus* sp.**, ***Klebsiella* sp.**	O
6	46 F	Lateral sectionectomy	***Enterococcus* sp.**, *E. coli*	***Enterococcus* sp**	S
7	55 F	Lateral sectionectomy	***E. coli***	***E. coli***, *S. epidermidis*	S
8	67 F	Right hepatectomy	*Serratia* sp.	*Pseudomonas* sp.	S
9	72 M	Left hepatectomy	***E. coli***, *Bacteroides* sp.	***E. coli***	S
10	69 F	Left hepatectomy	***Pseudomonas* sp.**	***Pseudomonas* sp.**	S

Species shown in boldface are isolated both in bile and from SSI at the same patient

O organ/space SSI, *S* superficial or deep SSI

Several recent studies have shown that antimicrobial prophylaxis during the preoperative period reduces the incidence of SSIs [7]. If prophylactic antibiotics are not used in surgery patients, the reported incidence of incisional SSIs is 30–50% [20, 21]. Our study involved the SSI data of patients receiving prophylactic antibiotics under the CDC guidelines. Although there have been no published data about the effectiveness of postoperative administration of antibiotics, an additional 1–3 days of antibiotics were administered to the patients in our study. The incidence of SSIs after hepatectomy for the patients with hepatolithiasis in our study was higher than that in the patients with HCC and those with metastatic carcinoma. The mean age of the patients with hepatolithiasis was younger than the mean age of the patients with HCC and metastatic carcinoma. No patients with hepatolithiasis had liver cirrhosis and diabetes. We found a significant relationship between bile infection and the incidence of postoperative SSIs. Our study showed a similar relationship between bacterial species isolated from the bile during the operation for hepatolithasis and bacteria isolated from SSIs. Biliary stone disease such as hepatolithiasis is the most common cause of biliary obstruction, and the common biliary pathogens, including *Escherichia coli*, *Klebsiella* sp., and *Enterococcus* sp., were isolated in patients with hepatolithiasis [5]. The incidence of bile infection in patients receiving elective surgery is considerable and is associated with a significant degree of mortality and morbidity. Although all of the patients in our study underwent a hepatectomy without reconstruction of the intestine or the biliary tract, the highest incidence of SSIs after hepatectomy was observed in patients with hepatolithiasis. The reason for this high rate may be due to the fact that a small amount of infectious bile contaminated the cut edge of the liver. Our study suggests the existence of a relationship between postoperative SSIs and bile infection, thus supporting the proposed relationship between post-hepatectomy infection and such variables as liver function, blood sugar control, and nutritional status.

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4. 集学的治療
b) 術前化学療法併用肝切除

辛島龍一　別府　透　近本　亮
石河隆敏　齋藤誠哉　佐藤伸隆
増田稔郎　林　尚子　渡邊雅之　馬場秀夫

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南　江　堂

4. 集学的治療
b) 術前化学療法併用肝切除*

辛島龍一　別府　透　近本　亮　石河隆敏　齋藤誠哉
佐藤伸隆　増田稔郎　林　尚子　渡邊雅之　馬場秀夫**

〔要旨〕全身化学療法の進歩に伴い，切除不能大腸癌肝転移であっても切除可能となる機会が増え，肝切除を施行しえた症例では予後は良好であることが報告されている．肝転移に対するレジメンはFOLFOX (fluorouracil+calcium folinate+oxaliplation)と分子標的治療薬の併用が推奨され，切除可能と判断されたらすみやかに肝切除を行うべきと考えられる．切除可能肝転移に対する術前術後補助化学療法はEuropean Organization for Research and Treatment of Cancer (EORTC)の臨床試験の結果，欧米で標準治療として確立したが，本邦ではさらなる検討が必要と考えられる．

はじめに

近年の大腸癌化学療法の治療成績向上に伴い，化学療法後に大腸癌肝転移の治癒的切除を行う機会が増加しつつある．本稿では臨床効果と有害事象の観点からみた術前化学療法のレジメン選択，切除のタイミング，遠隔成績などについて述べる．

I．切除可能大腸癌肝転移

治癒切除可能と思われる大腸癌肝転移例に対して術前化学療法を施行する意義として，腫瘍縮小による肝切除体積比の低下，微小転移の治療，down staging，*in vivo*での化学療法の有効性の判定などが考えられる．最新のNational Comprehensive Cancer Network (NCCN) ガイドライン[1]では，切除可能な同時性肝転移の治療の選択肢として術前後の化学療法があげられている．一方，本邦の「大腸癌治療ガイドライン」(2009年版)[2]では，術前化学療法は臨床試験として実施すべきと位置づけられており，その理由として安全性が確立されていないこと，非奏効例が切除不能となる危険性，薬剤による肝障害や周術期合併症の増加などをあげている．Gruenbergerら[3]は切除可能肝転移56例にXELOX (capecitabine+oxaliplatin)+bevacizumabによる術前補助化学療法を施行し，病勢コントロール率94.6％，R0切除率92.9％であり，術後合併症の発生率や術後肝再生に影響なしと報告している．また，European Organization for Research and Treatment of Cancer (EORTC) 40983試験は手術単独群と術前後の補助化学療法施行群を比較し，補助療法群における無増悪生存期間の有意な延長を報告しているが[4]，これは術後にも化学療法を行っており，純粋に術前治療のみの有効性が示されたわけではない．術前補助化学療法については今後

キーワード：大腸癌肝転移，術前化学療法，肝切除

* Curative hepatic resection after chemotherapy for colorectal liver metastasis

** R. Karashima, T. Beppu (准教授), A. Chikamoto, T. Ishiko (講師), S. Saito, N. Sato, T. Masuda, N. Hayashi (講師), M. Watanabe (講師), H. Baba (教授)：熊本大学消化器外科学．

表1. 切除不能肝転移に対する化学療法の効果と肝切除率

報告者(年)	使用薬剤	症例数	奏効率(%)	肝切除率(%)
Kohneら (2005)[5]	5-FU/LV	216	34	3
Albertsら (2005)[6]	5-FU/LV/L-OHP	42	50	40
Delaunoitら (2005)[7]	5-FU/LV/L-OHP	267	50	3.7
Hoら (2005)[8]	5-FU/LV/CPT	40	55	10
Kohneら (2005)[5]	5-FU/LV/CPT	214	62	7
Falconeら (2007)[9]	5-FU/LV/CPT	122	34	6
Seiumら (2005)[10]	5-FU/LV/L-OHP/CPT	30	78	23
Masiら (2006)[11]	5-FU/LV/L-OHP/CPT	74	72	18.9
Falconeら (2007)[9]	5-FU/LV/L-OHP/CPT	122	60	15
Coskunら (2008)[12]	Cape/L-OHP	35	37	11
Van Cutsemら (2009)[13]	5-FU/LV/L-OHP/Bev or Cape/L-OHP/Bev	73	ND	20.3
Van Cutsemら (2009)[13]	5-FU/LV/CPT/Bev	37	ND	14.3
Tabernero ら (2004)[14]	5-FU/LV/L-OHP/Cet	43	81	16
Diaz Rubioら (2005)[15]	5-FU/LV/L-OHP/Cet	43	72	19
Folprechtら (2009)[16]	5-FU/LV/L-OHP/Cet	56	85	40
Rougierら (2004)[17]	5-FU/LV/CPT/Cet	23	46	30
Folprechtら (2006)[18]	5-FU/LV/CPT/Cet	21	67	19
Minら (2007)[19]	5-FU/LV/CPT/Cet	23	39	30
Folprechtら (2009)[16]	5-FU/LV/CPT/Cet	55	66	43

5-FU：fluorouracil, LV：calcium folinate, L-OHP：oxaliplatin, CPT：irinotecan, Cape：capecitavine, Bev：bevacizumab, Cet：cetuximab, ND：not determined

のさらなる検討が必要である.

Ⅱ. 切除不能大腸癌肝転移

初診時に切除不能と診断された大腸癌肝転移において，全身化学療法が奏効し結果的に切除可能となる症例の割合は3～40％[5~12]，分子標的治療薬を併用した場合では14.3～43％[13~19]と報告されている(表1)．報告ごとにスタディデザインが異なり，肝切除の基準もさまざまなため単純には比較できないが，従来のfluorouracil(5-FU)/calcium folinate(LV)療法にoxaliplatinやirinotecan，さらに分子標的治療薬を併用する現在の大腸癌化学療法においては，治療経過中に肝転移が切除可能となる症例がまれではないということが示されている.

化学療法により切除可能となった症例の肝切除後の予後は，初診時に切除可能な肝転移例に肝切除を施行した場合と同程度であると報告されている[20,21]．また，Adamら[22]は初診時に切除不能であった大腸癌肝転移184例のコホート研究を行い，全身化学療法後に切除可能となった症例の無再発生存期間が5年で19％，10年で15％，全生存期間は5年で33％，10年で27％という良好な成績を報告している．さらに，肝単独転移例では化学療法の奏効率が高いと切除可能となる率が有意に高いこと[23]，化学療法の腫瘍縮小効果が高いほど肝切除後の予後が良好であること[24]なども報告されている．最近，新規化学療法を組み合わせれば，R1切除であってもR0切除と予後に有意差はないとの報告もあり[25]，これらはいずれも化学療法後の切除可能例に対して積極的に肝切除を行うことの意義を裏づけるデータと考えられる.

Ⅲ. レジメン選択

切除不能肝転移例に全身化学療法を施行する際のレジメン選択について述べる.

進行・再発大腸癌の化学療法は，FOLFOX(5-FU+LV+oxaliplatin)あるいはFOLFIRI(5-FU+LV+irinotecan)療法をfirst lineのベースとするのがこれまでの標準治療であり，最新の大腸

癌治療ガイドラインでは，可能であればbevacizumabを併用することが推奨されている（NCCNガイドラインではcetuximabもfirst lineとして使用できる）．2004年に発表された切除不能肝転移に対するFOLFOXとFOLFIRIのランダム化比較試験（GERCOR試験）[26]において，FOLFOX群のほうが肝切除可能となる割合が有意に多い（22％ vs 9％，$p = 0.02$）ことが報告された．First BEAT試験[13]は5-FUベースの各種レジメンに対するbevacizumabの上乗せ効果を検討したものであるが，根治切除可能となった症例の中で肝単独転移例のR0切除率はoxaliplatinベースの化学療法が15.4％，irinotecanベースが11.7％と，前者のR0切除率のほうが高かった．切除後の病理所見で残存癌細胞が50％未満のmajor response群はminor response群よりも全生存率が良好（$p = 0.028$）と報告されており，oxaliplatinにbevacizumabを加えたレジメンがもっともmajor responseとなる率が高かった[27]．Cetuximabについてもcrystal試験[28]，CELIM試験[16]などで肝転移に対する有効性が報告されている．

術前の化学療法が背景肝へもたらす影響は使用薬剤ごとに異なることが報告されている．FOLFOX療法後は病理学的に類洞閉塞症候群（sinusoidal obstruction syndrome：SOS）の所見が認められることが知られている[29]．SOSによる広範囲肝切除後の肝障害，術後合併症の増加などが示唆されている[30]が，手術死亡率には関与しないとされている[31]．またbevacizumabを併用するとFOLFOX療法後のSOSが軽減し，術後肝障害の発生が減少する可能性が示唆されている[32,33]．最近，superparamagnetic iron oxide particles（SPIO）-MRIがこのSOSを高率に検出するとの興味深い報告[34]もある．一方，FOLFIRI療法はFOLFOX療法よりも脂肪性肝炎（steatohepatitis）の発生頻度が高いことが報告されており，脂肪性肝炎スコア[35]が4点以上の症例は肝切除後90日以内の死亡率が有意に高いとされている[31]．

以上より，化学療法が奏効した場合の肝切除を視野に入れた場合，全身化学療法のレジメン選択としてはFOLFOX療法をfirst lineのベースとするのが妥当と考えられ，分子標的治療薬を併用することを考慮すべきであるが，本治療に対する本邦からの明確なエビデンスはなく，臨床試験として施行すべきである．

Ⅳ．化学療法後肝切除のタイミング

化学療法が奏効した場合にどのタイミングで肝切除に踏み切るのか，基準を明確に示すことは困難である．FOLFOX療法についていえば，治療開始から効果発現までの期間は4～6コース後（約2～3ヵ月）と報告されている[26,36]．一方，6コースを超えた場合肝切除後の合併症リスクの増加，在院日数の増加などが指摘されている[37,38]．また，化学療法が著効した場合の臨床的complete response（CR）例の取扱いはしばしば問題となる点である．CT上CRとなった肝転移66例の検討では，55例（83％）に病理学的にあるいは再発によって癌の遺残が証明されている[39]．臨床的CRが得られ切除しなかった群の予後は化学療法後に肝切除を施行した群より不良（$p = 0.006$）である．しかしその一方，化学療法が著効して肝切除しなかった群と肝切除施行群の予後に有意差があることから[40]，たとえ臨床的にCRであっても肝切除を回避すべきではないと考えられる．また臨床的CRになると術中に病変の同定が困難となる可能性が指摘されており[41]，著効例で肝切除が可能であるのに，化学療法を継続して臨床的CRを追及するのは得策ではない．切除不能肝転移例に化学療法を施行する場合は2～3コースごとに治療効果判定を行い，肝切除可能と判断されればすみやかに手術を行うことが治療成績向上につながると考えられる．

Ⅴ．当院の方針と治療成績

当院では，初診時に切除可能と判断される肝転移例には肝切除を先行し，術後補助療法としてFOLFOXを6コース施行している．切除不能肝転移に対しては，oxaliplatinが保険適用となった2005年5月以降はFOLFOXを第一選択としてfirst lineの全身化学療法を施行しており，現在は臨床試験としてbevacizumabを併用し，臨床効果を検証するようにしている．また，治療が奏効し肝転移巣が切除可能となったらすみやかに肝切除を施行する方針としており，切除範囲に限界がある多発例に対しては化学療法後にラジオ波凝固療法を併施して可能な限り根治をめざしている．

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りと診断され，全身化学療法を施行した症例は71例あり，そのうち26例(37％)が肝切除可能となった．病理組織学的検討で8例(31％)には背景肝に類洞拡張の所見を認めたが，術中・術後合併症の増加はなかった．また，組織学的CRは26例中2例(8％)のみであった．肝切除可能となった26例の無増悪生存期間(PFS)中央値は19ヵ月，全生存期間(OS)中央値は4年以上と，化学療法のみの45例と比較して有意に良好であった．

おわりに

切除不能肝転移を有する大腸癌は化学療法後に肝切除を施行できれば良好な予後が期待できる．したがって，化学療法を施行する際は常に切除の可能性を探りつつ治療効果を判定し，時期を逸することなく肝切除を行うべきと考えられる．切除可能肝転移に対する術前補助療法としての全身化学療法の有用性については，分子標的治療薬の使用も含めて今後のエビデンスの蓄積が期待される．

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