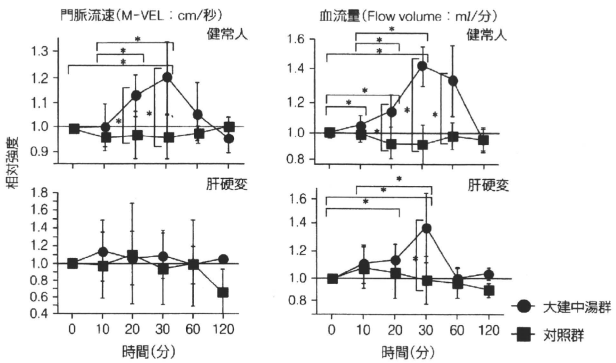

図 1. 大建中湯の肝血流に対する効果
*：$p<0.05$　(Ogasawara T *et al*, 2008[6]より引用)

1 ▌大建中湯

大建中湯は乾姜(カンキョウ)，人参(ニンジン)，山椒(サンショウ)の3つの生薬に膠飴(コウイ)を加えた漢方で一般的には四肢や腹部の冷え，腹痛，腹部膨満，鼓腸に対して用いられ，実際の臨床の場では癒着性イレウスや麻痺性イレウス，過敏性腸症候群，クローン病など広く使用されている日本独自の漢方方剤である．

その作用機序は腸管運動亢進作用には筋層間神経叢におけるセロトニン受容体を介したアセチルコリン遊離作用，粘膜層におけるバニロイド受容体を介した直接作用，平滑筋層におけるモチリン分泌作用が関与し，平滑筋のなかにある血管神経叢に作用して腸管平滑筋を刺激する[1]．成分別にみると人参は腸管からの吸収の後，血流を介して消化管運動を亢進させ，山椒と乾姜は吸収後の血流を介さず腸管神経系に直接作用することから，投与後30分以内と早期にその効果を発揮する．また，投与部位から肛門側の消化管に対して効果を発揮する．外科的疾患における効果としては大腸癌開腹手術に対する術後投与による術後排ガス期間の短縮，イレウス発症率の減少，術後入院期間の短縮や[2]，肝切除術後の術後排ガス期間の短縮とともに術後血中アンモニア濃度の低下が報告されている[3]．

1）腸管血流増加作用

大建中湯の腹部の冷えの改善効果は腸管運動の亢進のみならず，腸管の血流を介した効果であり，動物実験において消化管内に存在するカルシトニン遺伝子関連ペプチド（calcitonin gene related peptide：CGRP：血管拡張因子）を介した作用や[4]，さらにこの血流増加作用にCGRPのみならずRAMP1（CGRP受容体）の発現増加が関与していることも解明されている[5]．

われわれも血流増加作用に着目し，ヒトの肝循環動態（門脈血流）に対する影響について超音波ドプラー法を用いて検討したところ，健常人では投与後早期（30分以内）に門脈流速，門脈血流ともに非投与群と比較し有意に増加した（**図1**）[6]．また門脈血流の増加は投与後早期から認められるという結果から大建中湯の門脈血流増加作用は腸管神経系を介した反応によるものと考えられた．肝硬変症例では門脈血流量は投与後早期（30分以

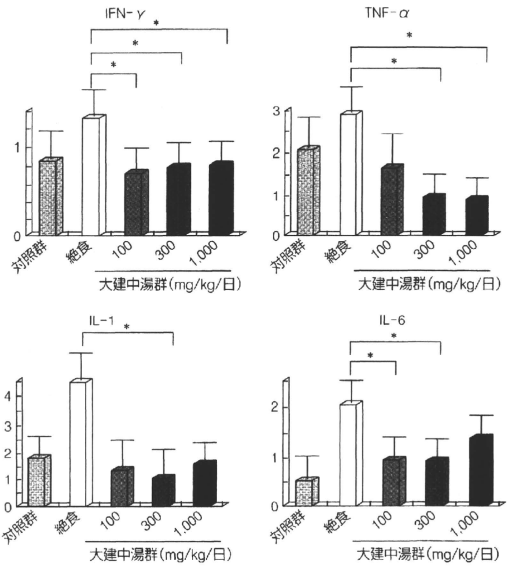

図 2. 大建中湯の炎症性サイトカイン抑制効果
*：$p<0.05$　（Yoshikawa K *et al*, 2008[7]より引用）

内）から有意に増加したものの門脈流速の変動は軽度であり（**図 1**），その理由として血管径の差，とくに肝においては肝臓の硬さ（類洞の拡張作用）が関与している可能性があるとわれわれは推察している．また肝への神経伝達系が分断されている生体肝移植症例においても門脈流速，門脈血流ともに投与前値と比較して有意に増加することを確認したが，肝硬変症例と同様に比較的軽度で緩徐な反応であったことは，この仮説を支持するものと思われる．さらに注目すべき点は門脈血流の増加が認められるにもかかわらず門脈圧には有意な変動を認めないことである．門脈圧や肝類洞構造への作用については，今後更なる機序の解明が必要であるが，少なくとも大建中湯の肝疾患に対する適応拡大への可能性がある．

2）抗炎症作用

肝切除術施行後やイレウスが長期に及んだ場合に最も懸念される病態が bacterial translocation で，容易に肝障害を惹起・助長させることから，その予防・対策には十分な注意が必要である．

この点に注目しラット絶食モデルにおける大建中湯の投与効果を検討したところ bacterial translocation の発症率の低下とともに小腸粘膜組織の萎縮も抑制，さらに組織 RNA の real time（RT）-PCR において各種炎症性サイトカインの抑制が認められた（**図 2**）[7]．この結果は，直接的な腸管の整合性の維持や炎症抑制効果により Bacterial

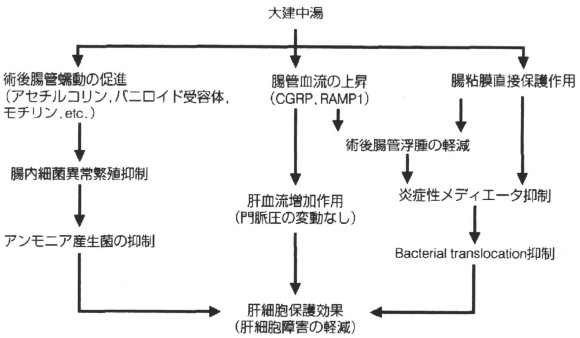

図 3. 大建中湯の作用機序

translocation を予防していることを示唆している．さらに腹腔鏡手術後における大建中湯の炎症抑制効果について無作為化比較試験（投与群：直腸癌 3 例，結腸癌 5 例 対 非投与群：直腸癌 6 例，結腸癌 3 例）を施行したところ，大建中湯投与により CRP が術後 3 日目に有意に抑制されていることからも大建中湯は抗炎症作用を有することが示唆される．

3）大建中湯の作用機序

われわれが推察している大建中湯の肝保護効果の作用機序について**図 3** に示す．大建中湯投与により術後排ガスまでの期間短縮，高アンモニア血症の改善，抗炎症反応の抑制，肝血流増加（維持）による消化器手術急性期における効果が期待される．大建中湯は，さらにその作用機序が解明されるとともに慢性期や急性期を問わず消化器疾患治療薬としての新たな可能性へ期待が高まっていくと思われる．

2 ▌茵蔯蒿湯

茵蔯蒿湯は茵蔯蒿，山梔子（サンシシ），大黄（ダイオウ）の 3 つの生薬からなる漢方で，適応疾患として胆汁うっ滞病変，肝硬変，黄疸，腹水などがあげられ，とくに黄疸の治療薬として効果があることが知られている．

その作用機序は茵蔯蒿に含まれる 6,7-dimetylesculetin や山梔子に含まれる geniposide による利胆効果と考えられている．geniposide の利胆効果はその活性体と考えられている genipin により，胆管膜に存在してビリルビントランスポーターとして重要な役割を果たす Mrp ファミリー（とくに Mrp2）の機能促進による．Geniposide は腸管内で腸内細菌により加水分解され活性体の genipin に変換される．Genipin は腸管から吸収され門脈内へ流入し肝臓内で利胆効果を発揮させた後，代謝され胆汁中に排泄される[8][9]．

実際の茵蔯蒿湯の臨床における使用例としては重症急性肝炎[10]，肝内胆汁うっ滞・黄疸[9]，原発性胆汁性肝硬変，胆道閉鎖症[11]，さらに術後肝障害などが報告され有効であるとされている．具体的には閉塞性黄疸に対するドレナージ後の投与により減黄期間を短縮し，術後肝障害を軽減したという無作為化比較試験や[12]，動物実験においては胆汁うっ滞モデル以外にも肝線維化モデルにおける TGF-β の活性抑制[13]，肝星細胞の活性抑制による肝線維化の予防[14]，四塩化炭素肝障害モデル[15]

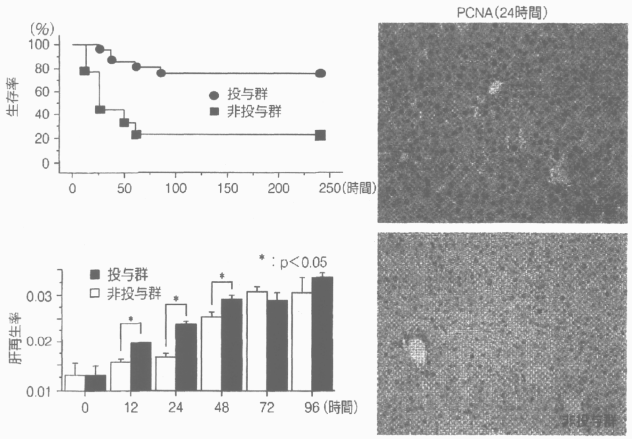

図 4. 茵蔯蒿湯の肝再生促進効果

(Ogasawara T *et al*, 2008[21]より引用)

や劇症肝炎モデル[16]における肝細胞保護効果などさまざまな肝保護効果を有することが報告されている.

1）大量肝切除術後肝再生に対する効果

肝臓外科の臨床の場において，大量肝切除後の肝不全は深刻な合併症の一つである．また生体移植後肝不全の発生にはグラフトサイズが重要な因子であり，過小グラフト症候群の克服は重要な課題である.

われわれはこの茵蔯蒿湯の多面的な肝保護効果に着目し，大量肝切除術後肝障害に対する効果についてラット実験における検討をおこなったところ茵蔯蒿湯投与により大量肝切除術後生存率の改善とともに肝再生率の上昇（**図 4**），肝障害軽減作用を認めた．また肝細胞保護効果を有する Hemoxigenaze-1（HO-1）の誘導とともに肝線維化や炎症誘導メディエータである肝星細胞（α-SMA）の抑制効果も確認した（**図 5**）．さらにマイクロアレイによる解析では，茵蔯蒿湯の投与により肝保護効果を有する heat shock protein family や肝再生促進因子である follistatin の発現増強とともに炎症性メディエータである TNF family の発現抑制を確認した．これらの検討結果から茵蔯蒿湯は，肝切除術後急性期においても肝保護効果のみならず抗炎症効果を有し術後肝不全を防止することが証明された.

2）茵蔯蒿湯の作用機序

現在までに茵蔯蒿湯の作用機序と効果について，茵蔯蒿が肝細胞のビリルビンクリアランスを上昇させて減黄・利胆作用を促進し，山梔子が caspase-3 を抑制して肝細胞保護効果にはたらきかけ，大黄が肝星細胞の活性化を抑制し，肝の線維化を抑制するといった報告がなされている．それらに加えてわれわれの知見を考慮すると術前術後を含めた急性期肝疾患への応用の期待がさらに高まるといえる．とくに大量肝切除術後は肝再生

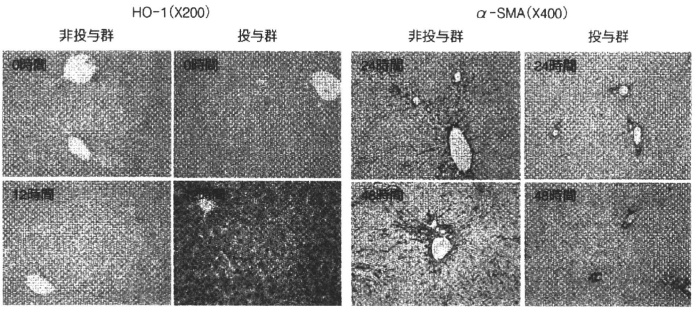

図 5. 茵蔯蒿湯の肝障害軽減作用

(Ogasawara T *et al*, 2008[24]より引用)

に伴う黄疸の遷延化が認められることがあるが，これにより黄疸の改善だけでなく肝保護効果，さらには抗炎症効果も得ることができ，術後肝不全の防止になると考えている．

3 ▌六君子湯

六君子湯は蒼朮，大棗，人参，陳皮，半夏，甘草，茯苓，生姜という8種の生薬で構成され，消化不良や食欲不振などの上腹部不定愁訴を緩和するとされている．主成分の人参は胃排出促進などの消化管運動亢進作用をもつとされ，適応疾患として胃炎，胃アトニー，胃下垂，消化不良，食欲不振，胃痛，嘔吐などがあげられる．

実験的検討では粘液亢進作用[17]や，一酸化窒素(nitric oxide：NO)を介する胃粘膜保護作用が報告され[18]，臨床試験において胃の受容機能不全の改善[19]や胃粘膜血流増加作用，さらにNOの前駆物質であるL-アルギニン含有による胃排出促進作用[20]が報告されている．消化器手術領域においては胃切除術後の消化器症状の改善や胃切除術後逆流性食道炎に対する治療および予防効果[21]のほか，幽門輪温存胃切除術後の固形物の胃排出亢進作用が消化管排出シンチグラムで証明されている[22]．最近の注目すべき報告として，シスプラチン投与による食欲低下ラットモデルでグレリン分泌を亢進し，食欲を亢進させる作用が報告されている[23]．グレリンは胃組織から発見されたペプチドで，強力な摂食促進作用をもつほか，成長ホルモン刺激，血圧調節機能，迷走神経を介した胃運動調節機能など，多様な作用が報告されており，今後グレリンを中心とした六君子湯の多面的な効果が期待される．また機能性胃腸症(functional dyspepsia：FD)や胃食道逆流症(gastroesophageal reflux disease：GERD)に対しても有効であるとの報告もあり，その応用範囲は広い．

1）膵頭十二指腸切除術腹部不定愁訴に対する効果

上部消化管手術，とくに胃切除後における六君子湯の効果は証明されているが，そのほかにも膵頭十二指腸切除術後における遅延性胃内容停滞(delayed gastric empty)も上部消化管手術後の重要な合併症の一つと思われる．当科では現在までの六君子湯における報告をもとに，膵頭十二指腸切除術後における六君子湯の有用性について投与前後の活性化グレリン値とともに，消化器疾患のquality of life(QOL)評価には消化器症状全般について患者のQOLを評価するGastrointestinal

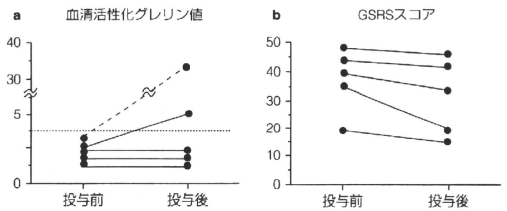

図 6. 膵頭十二指腸切除術後の消化器症状に対する六君子湯の投与効果
GSRS：Gastrointestinal Symptom Rating Scale
a：5例中2例で増加した.
b：消化器症状は全症例で改善した.（GSRS スコア 36.6→31.0 点）（p＝0.06）

Symptom Rating Scale（GSRS）を用いスコア変化を検討した. GSRS は 15 の質問に対する回答から酸逆流, 腹痛, 消化不良, 下痢, 便秘の5つの消化器症状のサブグループに分類し, 患者の QOL を測定するものである. 結果として六君子湯投与により活性化グレリンの上昇とともに, 全例で GSRS スコアの改善を認め（**図 6**）, 六君子湯の有用性が示唆された.

おわりに

術後を含む肝・胆・膵疾患に対する漢方の応用について概説した. 今後も基礎的もしくは臨床的研究が進むにつれて, これらの薬剤の適応疾患が拡大することは十分考えられる. また他の漢方薬剤の各種肝・胆・膵疾患への導入も期待される. 最近では漢方医学がこれらのエビデンスをもとに医学教育にも導入され, 今後の医学・医療において必須のものとなりつつある. そのようななかで慢性期代替医療といわれた漢方医療を積極的に外科医療に導入していくことも当然の結果と思われる.

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ORIGINAL ARTICLE

Treatment results of FOLFOX chemotherapy before surgery for lymph node metastasis of advanced colorectal cancer with synchronous liver metastasis: the status of LN metastasis and vessel invasions at the primary site in patients who responded to FOLFOX

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Abstract
Purpose The combination of chemotherapy and surgery holds promise for improving CRC patient prognosis. We evaluated the pathological impact of chemotherapy on primary lesions and lymph node (LN) metastases retrospectively.
Methods Sixteen CRC patients with synchronous liver metastasis underwent a radical operation between March 2005 and August 2007. Eight of the 16 cases (surgery group) were operated on for the primary lesion without chemotherapy and another 8 cases (chemotherapy group) were operated on after chemotherapy with FOLFOX (median: 8 courses).
Results Five of the 8 patients in the surgery group were found to have pathological LN metastasis (62.5%; N0 37.5%, N1 37.5%, N2 25%). However, only 2 of the 8 patients in the chemotherapy group were found to have LN metastasis (25%; N0 75%, N1 25%, N2 0%). The ratio of LN metastasis (number of metastatic LNs/resected LNs in total) was 11.1% in the surgery group, but it was 4.8% in the chemotherapy group. Necrotic areas were widely detected in the LN specimens of the chemotherapy group. The percentage of lymphatic (ly) and vascular (v) invasion in the primary lesions was smaller in the chemotherapy group (ly 12.5% vs. 25.0%) than in the surgery group (ly 62.5% vs. 50.0%). The patients in the chemotherapy group had no significant adverse effects and did not show an worse survival rate overall than the surgery group.
Conclusions A promising effect of chemotherapy on the status of LN metastasis and vessel invasions at the primary site was observed in the patients who responded to FOLFOX.

Keywords Perioperative chemotherapy · Colorectal cancer · Primary lesion · Lymph node metastasis · FOLFOX

Introduction

Surgical management of resectable liver metastases in CRC has become the standard treatment. It is also the standard treatment for CRC patients to add oxaliplatin to the regimen of fluorouracil and leucovorin in order to improve the adjuvant treatment of colon cancer [1–4]; this combination chemotherapy is termed FOLFOX. It was reported that the combination of chemotherapy and surgery holds promise for improving CRC patient prognosis, and the feasibility of applying chemotherapy for liver injury and perioperative complications has been reported [5–7]. However, there is no clear standard for the use of chemotherapy in CRC with liver metastasis before surgery.

It has been reported that the use of NAC in resectable liver metastases induced a significant number of remissions without increasing morbidity [8]. However, oxaliplatin is associated with sinusoidal dilation [9–11], and irinotecan causes steatohepatitis [9, 10]. Therefore, the chemotherapy

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regimen should be considered carefully, because the risk of hepatotoxicity is significant [11].

The pathological effect of chemotherapy on liver metastasis has been reported, but the pathological response to LN metastasis from CRC after chemotherapy has not been discussed, although 4 or more lymph node metastases around the primary cancer was considered to be a prognostic factor for patients with synchronous liver metastases [12]. The purpose of this study was to assess the effect of chemotherapy on both primary lesions and LN metastases in CRC in order to evaluate the effectiveness of chemotherapy for the treatment of LN metastases in CRC patients with liver metastases.

Patients and methods

This was a retrospective study performed at Kumamoto University Hospital. We treated 39 CRC patients with synchronous liver metastases between March 2005 and August 2007 at our hospital, and 16 of the 39 patients underwent a radical operation (Fig. 1). Eight of the 16 patients (surgery group, $n = 8$, H1 3, H2 4, H3 1) were operated on for their primary lesions and regional LNs without chemotherapy. Of the 3 cases (H2 3) that underwent chemotherapy before a hepatectomy, two cases were not considered to be indicated for a hepatectomy due to safety concerns, and in one case it was necessary to confirm whether the number of metastatic lesions had increased, because there were 5 liver metastatic lesions at the time of diagnosis.

The other 8 cases (chemotherapy group, $n = 8$) were operated on after chemotherapy with FOLFOX. The reason that these 8 patients underwent chemotherapy before being operated on was that they did not have sufficient surgical indications before chemotherapy (Table 1). Three cases (H1 2, H2 1) were accompanied by lung metastases, 1 case (H1) had a suspected permeation of the iliopsoas muscle, and the other 4 cases (H2 2, H3 2) contained multiple or huge liver metastases.

At our institution, patients with resectable liver metastases undergo simultaneous resection of both the primary lesion and liver metastasis. Patients with unresectable liver metastases start the chemotherapy without primary lesion resection. Primary lesions that are predicted to possibly cause an obstruction of the bowel or anemia are resected. However, there are no strict criteria regarding whether the primary tumor should be resected or not. When the liver metastasis is deemed to be resectable and the primary lesion can undergo a radical resection, then the patient is indicated for this surgery. When the chemotherapeutic effects are judged to be insufficient, then we change the chemotherapeutic regimen to a second-line protocol. If the patients have both liver and lung metastases, then chemotherapy is performed first. If the metastatic lesions are controllable and no new lesions appear, then we resect the primary lesion and liver metastasis. We restart chemotherapy, and if the lung metastasis is stable we perform a resection of the lung metastasis.

The patients underwent either a modified FOLFOX-6 (7 cases) or a FOLFOX-4 (1 case) regimen for chemotherapy before surgery. The modified FOLFOX-6 regimen was as follows. On the first day of each cycle, the patients received folinic acid (200 mg/m^2) and

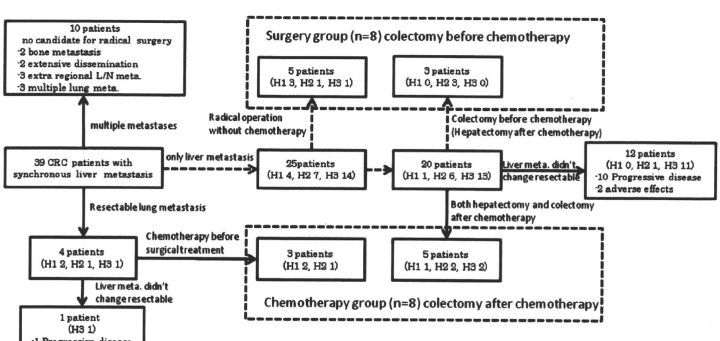

Fig. 1 Treatment process for the 39 CRC patients with synchronous liver metastases

Table 1 Characteristics of the patients in this study

Characteristics	Chemotherapy group	Surgery group
Number of cases	8	8
Age, years, median (range)	68 (60–81)	60 (50–82)
Sex, male/female	4/4	5/3
Location, colon/rectum	6/2	4/4
Liver metastasis, cH1/cH2/cH3	3/3/2	3/4/1
Number of liver metastasis		
1/2/3/4/>4	3/3/1/0/1	5/0/1/0/2
The maximum size of the liver metastasis		
<5/5–10/10<	3/3/2	6/1/1
Lung metastasis, L0/L1	5/3	8/0
Depth of penetration, MP/SS/SE/SI	0/4/3/1	2/2/4/0
Chemotherapy before surgery		
Before colectomy, yes/no	8/0	0/8
Before hepatectomy, yes/no	8/0	3/5
Median course of chemotherapy		
Before colectomy	8	0
Before hepatectomy	9	6 ($n = 3$)

cH stage clinical stage of the liver metastasis before chemotherapy

cH1 the number of liver metastases is less than 4 and the size is less than 5 cm, *cH2* neither cH1 nor cH3, *cH3* the number of liver metastases is more than 5 and the size is over 5 cm

oxaliplatin (85 mg/m^2) as intravenous infusions over 2 h. They also received an intravenous injection of 5-fluorouracil (400 mg/m^2), followed by an intravenous infusion of 2400 mg/m^2 over 46 h.

The surgical resection of the colorectal lesions included en bloc removal of the affected site with adequate margins and the draining LNs. We evaluated the pathologic findings (depth of penetration, lymphatic/vascular invasion) of the primary tumor with hematoxylin and eosin stain and Victoria blue stain. The tumor regression was graded into one of five grades based on the percentage necrotic area in the residual tumor and according to the histological response criteria for the drug and radiotherapy. The pathological response criteria of the drug and radiotherapy were as follows. Grade 0: no regression. Grade 1a: extremely mild effect: degeneration or necrosis of the tumor is <1/3. Grade 1b: mild effect: degeneration, necrosis or fusion of the tumor ranges from 1/3 to 2/3. Grade 2: significant effect: remarkable degeneration; necrosis, fusion or disappearance of the tumor is >2/3. Grade 3: complete response: all of the tumors were necrotic with rearranged granulation tissue or a fibrotic lesion, and the tumor had disappeared.

We examined the number of excised LNs and the LN metastases in each area with hematoxylin and eosin stain. The metastatic LNs were stained for immunohistochemistry (IHC) in order to detect epithelial tissue using a cytokeratin stain, and to detect macrophages with a CD68 stain. CD68 is a glycoprotein that binds to low-density lipoprotein and is expressed on macrophages.

Results

The 8 patients who underwent chemotherapy before surgery (chemotherapy group) consisted of 4 men and 4 women with an average age of 69 years (range, 60–81 years). The average number of chemotherapy courses was 8.12 (6–12 courses, median 8.0). They underwent chemotherapy without any significant adverse effects (Table 2). There were also no adverse events caused by chemotherapy before surgery that necessitated postponement of the operation. The average period from the most recent chemotherapy treatment to the operation was 25.4 days. One patient had bile leakage after the operation and stayed in the hospital for 82 days (Table 3).

Swollen LNs with a diameter of about 1 cm were detected on CT before chemotherapy and suspected of being metastatic. However, these swollen LNs did not appear swollen after chemotherapy in 3 of the 8 cases. In the other 5 cases, the LNs were smaller on CT than they were before chemotherapy. After the operation, swollen LNs were detected in 3 cases, but one of the 3 cases was not considered to have metastatic LNs because the swollen LNs in this case were about 1.5 cm in size and they were also soft. In the other 5 cases the resected LNs had withered and it was difficult to detect any LN swelling. Only 2 of the 8 patients (25%) with chemotherapy before surgery were found to have pathological LN metastasis (N0 75%, N1 25%, N2 0%) with hematoxylin and eosin stain. The number of LNs excised from the 8 patients was 82 (median, 9.5 LNs) in total, but the

Table 2 Adverse effects during chemotherapy (CTCAE V3.0) and perioperative complications

Adverse effect	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Hematological toxicity					
Leukopenia	1	2	1	0	4
Neutropenia	0	3	2	1	6
Anemia	0	4	0	0	4
Thrombocytopenia	3	1	0	0	4
Nonhematological toxicity					
Peripheral neuropathy	4	0	0	0	4
Anorexia	1	2	0	0	3
Diarrhea	1	0	0	0	1
Allergy	1	0	0	0	1
Average period from the last chemotherapy treatment to the operation (range)					24.5 (20–38)
Length of stay in the hospital, median					26 (21–82)
Postoperative mortality					0

Table 3 Effect of the chemotherapy

Chemotherapy group ($n = 8$)		
Response to chemotherapy (RECIST)	CR/PR/SD/PD	0/4/4/0
The largest lesion diameter on imaging the liver metastasis		
Before chemotherapy		58 (16–140)
After chemotherapy		38 (9–74)
Relative reduction		−29.6%
Plasma CEA		
At diagnosis	<2.5/2.5–30/30<	2/3/3
Before surgery	<2.5/2.5–30/30<	4/4/0
After surgery	<2.5/2.5–30/30<	7/1/0
Liver function after chemotherapy		
Asialo scintigraphy	HH15	0.61 (0.52–0.69)
	LHL15	0.93 (0.92–0.95)
Ascites	None/reversible/irreversible	8/0/0
Serum bilirubin (mg/dl)	<2.0/2.0–3.0/3.0<	8/0/0
Serum albumin (g/dl)	3.5</3.0–3.5/<3.0	6/2/0
ICG 15 (%)		14.1 (7.8–25.8)
	<15/15–40/40<	6/2/0
PT (%)	80</50–80/<50	8/0/0

RECIST response criteria in solid tumors

number of metastatic LNs was only 4 (ratio of LN metastasis, 4.8%). The metastatic LNs of the 2 patients were Grade 2; two-thirds of the metastatic LN specimens showed necrosis pathologically.

The other 8 cases in which the primary lesions were operated on without chemotherapy consisted of 5 men and 3 women with an average age of 62.0 years (range, 50–82 years). Five of the 8 patients (62.5%) were found to have pathological LN metastasis (N0 37.5%, N1 37.5%, N2 25%). The number of LNs excised from the 8 patients was 153 (median number of excised LNs, 18.0) in total, and the number of metastatic LNs was 17 (ratio of metastatic LNs, 11.1%) (Table 4).

In a case from the chemotherapy group, a regional LN was suspected of being metastatic on contrasting CT before the chemotherapy, but after 3 courses of chemotherapy the internal area of the LN was shown to have a low density, suggesting tumor necrosis on contrasting CT. Two-thirds of the resected LN specimens showed necrosis pathologically. These LNs contained three characteristic lesions, viable adenocarcinoma, macrophages infiltrating to the necrotized tissue, and areas of hyalinization and cicatrization (Fig. 2). Macrophages were seen during the therapeutic process and the chemotherapy treatment process was observed in this LN. We performed immunostaining on the site and detected macrophage infiltration around the

Table 4 Pathological outcomes for the primary lesions and LN metastases

Pathological outcome	Chemotherapy group	Surgery group
Median of resected LNs	9.5	18.0
Ratio of LN metastasis	4.8% (4/82)	11.1% (17/153)
Lymphatic invasion	12.5%	62.5%
ly0/ly1/ly2/ly3	7/1/0/0	3/4/1/0
Vascular invasion	25.0%	50.0%
v0/v1/v2/v3	5/3/0/0	4/1/1/2
LN metastasis	25.0%	62.5%
N0/N1/N2	6/2/0	3/3/2

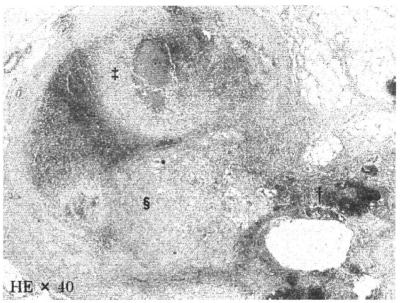

Fig. 2 Histopathological photomicrographs of the LN metastasis. This photograph shows the chemotherapy treatment process in the LN. H&E stained section ×40: viable adenocarcinoma (†), macrophage infiltrating around necrotized tissue (‡), and hyalinization and cicatrization (§)

necrotic tissue with CD68 stain. Some metastatic cells, which were difficult to identify with the hematoxylin and eosin stain, were detected with cytokeratin staining. However, the sites of necrosis, cicatrization, and hyalinization did not contain any epithelial-like tissue.

The three cases with primary tumors were Grade 1a, and these cases showed a poor response to FOLFOX chemotherapy. However, almost all of the liver metastases showed a strong response to chemotherapy, and LN metastasis was detected in only 2 cases (Grade 2 in each case), though swollen LNs were detected in all of the 8 cases on CT before chemotherapy (Table 5). The percentage of lymphatic and vascular invasion in the primary lesions was less in the chemotherapy group (ly 12.5% vs. 25.0%) than in the surgery group (ly 62.5% vs. 50.0%) (Table 4). Two cases were Grade 2 and 1 of the 8 cases showed a complete response (CR). In the CR case, the primary lesion was a torose lesion before chemotherapy, but the tumor cicatrized after the administration of 5

Table 5 The impact of chemotherapy on the primary lesions and metastatic lesions

Chemotherapy group	Grade 1a	Grade 1b	Grade 2	Grade 3
Primary lesion 8	3 (37.5%)	2 (25%)	2 (25%)	1 (12.5%)
LN metastasis 2	0 (0%)	0 (0%)	2 (100%)	0 (0%)
Liver metastasis 8	1 (12.5%)	2 (25%)	3 (37.5%)	2 (25%)

The pathological response criteria of the drug and radiotherapy were as follows:

Grade 0 no regression

Grade 1a extremely mild effect: degeneration or necrosis of the tumor is <1/3

Grade 1b mild effect: degeneration, necrosis or fusion of the tumor ranges from 1/3 to 2/3

Grade 2 significant effect: remarkable degeneration; necrosis, fusion or disappearance of the tumor is >2/3

Grade 3 complete response: all of the tumors were necrotic with rearranged granulation tissue or a fibrotic lesion, and the tumor had disappeared

courses of FOLFOX chemotherapy. The site of the tumor ulcerated and we could not confirm the presence of tumor cells pathologically (Fig. 3).

The overall survival from the diagnosis of CRC was 24.5 months (chemotherapy group/surgery group; 24.6/24.3 months). All patients in the chemotherapy group are still alive, while 3 patients in the surgery group have died.

Discussion

Based on the guidelines of the National Comprehensive Cancer Network (NCCN), the treatment of resectable synchronous liver metastasis is selected from among the following three methods: colectomy with synchronous or subsequent liver resection, neoadjuvant chemotherapy (FOLFOX or FOLFIRI or CapeOX ± bevacizumab) followed by a synchronous or staged colectomy and a resection of the metastatic disease, or a colectomy followed by chemotherapy and a staged resection of the metastatic disease [13]. We had no clear standard or criteria to use in order to select the best method of treatment. The preliminary data from the randomized phase III study indicate that the preoperative administration of FOLFOX did not affect the morbidity or mortality of cases who underwent hepatectomy for resectable colorectal liver metastases [14]. Developments in surgical devices and techniques have made hepatectomy safe after chemotherapy. Therefore, we must select the patients who are appropriately indicated to undergo NAC.

The LN metastases of stage III disease are important for the prognosis. The 5-year survival rates by stage have been reported as: 84.7% (stage IIA), 72.2% (stage IIB),

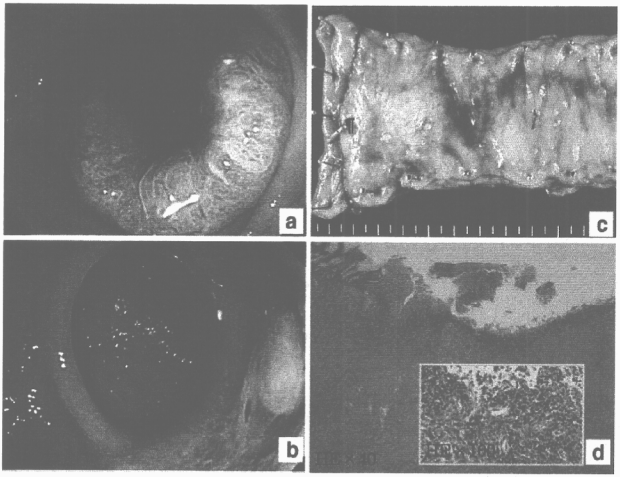

Fig. 3 The complete response case. **a** A torose lesion was detected before chemotherapy. **b** The tumor cicatrized after the administration of 5 courses of FOLFOX chemotherapy. **c** Only scar tissue is detected in the specimen (¶). **d** H&E stained section ×40, 100; the site of the lesion formed an ulcer, and infiltrating inflammatory cells, but no viable adenocarcinoma was confirmed

83.4% (stage IIIA), 64.1% (stage IIIB), and 44.3% (stage IIIC) [15]. The difference in the 5-year survival rate between stage IIIB and stage IIIC was 20.3%, though the only difference was the number of metastatic LNs. It was also reported that the LN metastases of stage IV disease are important for the prognosis. One hundred eighty-seven patients underwent curative resection for synchronous liver metastasis from colorectal cancer. In a multivariate analysis, the factors that significantly affected the prognosis of synchronous metastasis were 4 or more lymph node metastases around the primary cancer ($P < 0.001$) and multiple liver metastases ($P = 0.003$) [12].

Our study showed the impact of chemotherapy on metastatic lymph node lesions. We consider that patients who have 4 or more lymph node metastases around the primary cancer (above N2) may benefit from chemotherapy before surgery.

The percentage of patients with a penetration depth of SS-SE without LN metastasis was 48.7% among the CRCs registered ($n = 15938$) in our country. Our study shows that the percentage of patients without LN metastases was 37.5% in the surgery group. However, this figure was 75% in the chemotherapy group, and the number of LN metastases was under 3 (N1) (Tables 1, 2). One problem with our study was the difference in the number of resected metastatic LNs. The median number of resected LNs in the chemotherapy group was 9.5, while it was 18.0 in the surgery group. The median number of LNs removed at colectomy was 11 (range, 1–87) in the Intergroup Trial INT-0089 [15]. The number of LNs removed without chemotherapy was larger than the number removed with chemotherapy, though we excised the LN specimens as usual. We considered that the withering LNs were also a result of the effect of the chemotherapy.

Our study left the problem of the effect of chemotherapy on the primary lesion unresolved. The number of patients who had a poor response (Grade 1a) to chemotherapy for the primary region was 3 (37.5%); nevertheless, chemotherapy was much more effective for metastatic lesions in 7 cases. We consider that individual differences have a strong influence on the sensitivity of the primary tumor to FOLFOX chemotherapy. We should elucidate the causes of the various effects on the original lesion using some additional methods [16–19], and we should find a way to predict the effect of chemotherapy on the primary lesion.

In conclusion, our study showed that chemotherapy has a strong impact on the status of LN metastasis and vessel invasions at the primary site in patients who respond to FOLFOX. Patients who underwent chemotherapy without a colectomy, namely the chemotherapy group, demonstrated no significantly adverse effects, and the overall survival rate was not worse than that of the surgery group. Patients with both extensive LN metastasis (suspected to be above N2) and synchronous liver metastasis should therefore be considered potential candidates for chemotherapy without a colectomy.

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FOLFOX Enables High Resectability and Excellent Prognosis for Initially Unresectable Colorectal Liver Metastases

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Abstract. *Background/Aim: To evaluate the efficacy of oxaliplatin plus fluorouracil and leucovorin (FOLFOX) on initially unresectable colorectal liver metastases (CRLM). Patients and Methods: From May 2005 to December 2008, FOLFOX was administered to 71 patients with initially unresectable CRLM. Hepatic resection was performed promptly after CRLM became resectable. Results: Twenty-six patients (37%) were downstaged as being resectable. The mean interval between the first FOLFOX and hepatic resection was six months (range, 3-7 months), and 7.1 courses (range, 2-12). Operative morbidity was 12% and mortality was nil. The median progression-free survival time was 19 and 7 months, and the median survival time was over 48 and 20 months, in finally resectable and unresectable patients, respectively. Multivariate analysis revealed that additional hepatic resection was the only independent prognostic factor (hazard ratio 4.80, p<0.01). Conclusion: FOLFOX is an effective chemotherapeutic regimen leading to successful hepatic resection and an excellent prognosis for patients with initially CRLM.*

Combination chemotherapy including modulated infusional 5-fluorouracil (5-FU) plus irinotecan or oxaliplatin can achieve a response rate of 50% and a median survival of over 20 months (1-5). Oxaliplatin has been shown to improve the survival of patients with metastatic colorectal cancer, when given in combination with 5FU/LV, in first- or second-line therapy (1-5). Another phase III study has shown survival improvement using oxaliplatin plus 5-FU/LV over irinotecan plus 5-FU/leucovorin (LV) as a bolus administration (6).

In a phase III study to investigate two sequences of folinic acid, 5-FU, and irinotecan (FOLFIRI) followed by folinic acid, 5-FU, and oxaliplatin (FOLFOX6), and FOLFOX6 followed by FOLFIRI, hepatic resection of liver metastases was performed in 9% of patients after FOLFIRI *versus* 22% of patients in FOLFOX6 (p=0.02). R0 resection was performed in 7% of patients after FOLFIRI *versus* 13% after FOLFOX6 (3). Oxaliplatin-based chemotherapy, including the FOLFOX regimen, can lead to tumors being downstaged in some patients with initially unresectable colorectal liver metastases (CRLM), and allowed hepatic resection in 16-38 per cent patients (7). In a recent paper, FOLFOX4 resulted in tumor reduction in 60% patients and enabled surgical intervention in 40%, after a median of 6 months of chemotherapy in patients with liver-only CRLM (8). Therefore, many clinical oncologists and surgeons consider systemic chemotherapy with FOLFOX to be appropriate for CRLM (9).

It has been about 4 years from the introduction of oxaliplatin, which has been available for use in Japan since May 2005. The aim of this study was to assess the feasibility of use and the clinical value of preoperative FOLFOX in Japanese patients with initially unresectable CRLM.

Patients and Methods

From May 2005 to December 2008, 114 consecutive patients with CRLM were treated at the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University. The therapeutic strategy of CRLM in our institution after induction of FOLFOX is shown in Figure 1. A straightforward hepatic resection was selected for initially resectable 26 patients. Among 88 patients with initially unresectable CRLM or extrahepatic metastases, 71 patients treated with FOLFOX were entered into this study. Eight patients treated with FOLFOX and bevacizumab were excluded. There were 38 patients with liver-only metastases and 33 with liver plus extrahepatic metastases.

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Key Words: Colorectal liver metastases, hepatic resection, chemotherapy with oxaliplatin plus fluorouracil and leucovorin, FOLFOX, Japanese patients.

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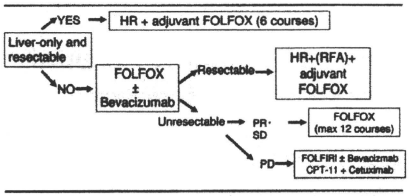

Figure 1. *Therapeutic strategies for colorectal liver metastases. For patients with initially resectable disease and liver-only metastases, hepatic resection (HR) with 6 courses of adjuvant FOLFOX was performed. For these with initially unresectable or extrahepatic metastastases, induction chemotherapy with FOLFOX with or without bevacizumab was carried out. When curative hepatic resection became possible, HR with or without radiofrequency ablation (RFA) was immediately performed. Unresectable patients after FOLFOX were treated continuously with various regimens, including FOLFIRI, bevacizumab, cetuximab, or hepatic arterial infusion therapy.*

Table 1. *Clinical characteristics of 26 patients with initially unresectable CRLM downstaged to be resectable after FOLFOX therapy.*

Characteristic	Data
Mean age, years (range)	64.2 (28-83)
Gender (male:female)	19:7
Metachronous:synchronous	9:17
Liver only:liver+extrahepatic	18:8
Mean maximal diameter, cm (range)	4.6 (1.2-15)
Mean tumor number (range)	5.3 (1-36)
Preoperative chemo (FOLFOX alone: other chemo+)	17:9
Mean cycles of FOLFOX (range)	7.1 (2-12)
Type of HR (major:segment:partial)	11:8:7
RFA (+:–)	8:18

FOLFOX, Chemotherapy with folinic acid, 5-fluorouracil, and oxaliplatin; chemo, chemotherapy; HR, hepatic resection; RFA, radiofrequency ablation; major: larger than 3 segments; segment: one to two segments.

The determination of initial resectability of CRLM before FOLFOX was based on the possibility of safe and curative (R0) resection. When CRLM became resectable after several courses of FOLFOX, hepatic resection was immediately performed. The final decision for hepatic resection after FOLFOX was based on the possibility for removing all metastases with resection and/or radiofrequency ablation therapy (RFA). Percutaneous transhepatic portal embolization was achieved preoperatively for two patients with an estimated volume of remnant functional liver parenchyma assessed by computed tomography (CT) were below 35%. The Institutional Review Board of the Graduate School of Medical Sciences, Kumamoto University, approved this clinical study.

Systemic chemotherapy. FOLFOX was administered mainly as outpatient chemotherapy with modified FOLFOX6 consisting of the biweekly regimen as follows: a 2-hour infusion of LV (200 mg/m^2/d) and oxaliplatin 85 mg/m^2 followed by a 5-FU bolus (400 mg/m^2/d) and 46-hour infusion (2400 mg/m^2/d) for 2 days every 2 weeks. Enrollment criteria in this study were as follows: age under 85 years, no organ dysfunction, and histologically proven adenocarcinoma. Treatment was continued until resectablility was achieved, disease progression, occurrence of unacceptable toxicity, or the patient's decision to discontinue treatment. After hepatic resection, the same regimen of preoperative systemic chemotherapy was continued postoperatively up to a total 12 cycles of pre- plus postoperative therapy.

Perioperative examination. Measurement of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels, abdominal ultrasonography (US), contrast-enhanced helical CT, magnetic resonance imaging (MRI) enhanced with superparamagnetic iron oxide (SPIO), and CT-angiography were performed routinely for preoperative staging. Patients with unresectable CRLM were assessed radiographically for resectability at every 3 cycles of FOLFOX, with measurement of tumor markers every month after starting therapy. The tumor regression effect was evaluated with CT according to the RECIST criteria (10).

Hepatic resection. The type of liver resection was based on the results of preoperative diagnostic imaging, intraoperative US, and careful attention to liver function. All detectable lesions were resected in principle or treated with RFA, for metastatic nodules smaller than 2 cm, especially deeper in the liver (11).

Histological examinations. In the patients who received hepatic resection after FOLFOX, the pathological effects of therapy of the tumor were determined in the resected specimens using grading criteria (12) as follows: grade 0: with no necrosis or cellular or structural change; grade 1a: with necrosis or disappearance of tumor in <1/3 of the entire lesion; grade 1b: with necrosis or disappearance of the tumor in <2/3 of the entire lesion; grade 2: with necrosis or disappearance of the tumor in >2/3 of the entire lesion, but with viable tumor cells remaining; and grade 3: with the entire lesion showing necrosis and/or fibrosis, and no viable tumor cells identified.

Complications. Operative morbidity and mortality were prospectively recorded.

Outcome. Cumulative progression-free survival (PFS) and overall survival (OS) after FOLFOX was recorded until June 2009, with the starting point being the day of initial FOLFOX therapy. Prognostic factors were evaluated by univariate and multivariate analysis.

Statistical analysis. Data are expressed as mean±standard deviation, and were compared between two groups by using the Mann-Whitney *U*-test. Categorical variables were compared by using the χ^2 test or Fisher's exact test. PFS and OS were calculated by using the Kaplan-Meier method and were compared by using the log-rank test. The Cox proportional hazards regression model was used for the multivariate analysis. All statistical analyses were performed with StatView 5.0 computer software (SAS Institute Inc., Cary, NC, USA). Significance was defined as being a p-value of 0.05 or less.

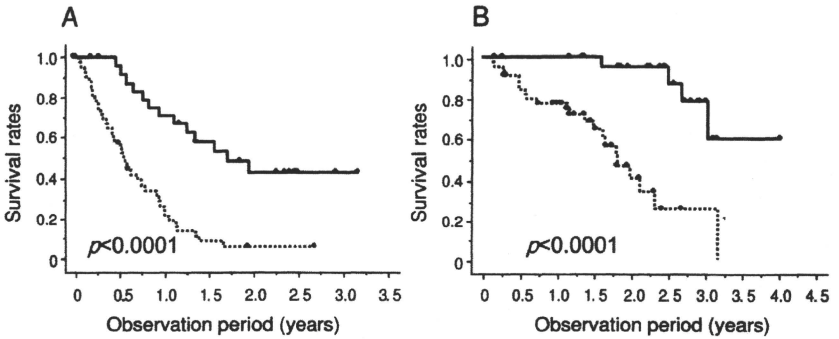

Figure 2. *Cumulative progression-free survival (PFS) (A) and overall survival (OS) (B) curve in 71 patients with initially unresectable liver metastases according to the existence or nonexistence of hepatic resection (solid line: patients with hepatic resection, dotted line: patients without hepatic resection). Cumulative PFS and OS in 26 patients with resectable disease after FOLFOX were significantly greater than that of 45 patients without hepatic resection ($p<0.0001$ and $p<0.0005$).*

Results

Patient characteristics. Of 71 patients with initially unresectable CRLM, 26 (37%) of them became resectable after therapy. In patients with liver-only metastases and liver plus extrahepatic metastasis, the resection rates were 47% (18/38) and 24% (8/33), respectively. Clinical characteristics of the 26 patients are summarized in Table I. Baseline site of extrahepatic metastases which became resectable were the lung in 4 patients and para-aortic lymph nodes in 4 patients. The mean interval between starting FOLFOX and achieving hepatic resection was six months (range, 3 to 7), and a mean of 7.1 courses (range, 2 to 12) of FOLFOX were given. The mean size of maximal liver metastasis was downsized from 4.6±0.8 cm to 2.9±0.4 cm. RFA was additionally performed in 8 patients at the time of hepatic resection. Of 26 patients with CRLM, 18 (69%) experienced curative hepatic resection (R0). Portal embolization was performed preoperatively for two patients with 70% and 75% as an estimated resection of liver volume. Hepatic resections included 11 major resections larger than 3 segmentectomies, 8 resections with one to two segmentectomies, and 7 partial resections.

Response evaluation, tumor regression effect and histological examinations. According to the RECIST criteria, the response rate was 73% (19/26) in patients with CRLM finally resectable after FOLFOX. Regarding the 26 specimens resected after FOLFOX, the degree of histological effect in the tumor was classified as grade 1a in 13, 1b in 8, 2 in 3, and 3 in 2 patients. Two patients had no pathologically viable tumor cells in the liver metastases after FOLFOX therapy.

Postoperative complications. No patient died as a result of FOLFOX treatment. Postoperative complication was observed in 3 patients (pneumonia, prolonged jaundice, biliary leakage) in hepatic resection after FOLFOX but they smoothly recovered with medication and biliary drainage. Operative mortality within 3 months was nil.

Outcome. Cumulative PFS and OS in 71 CRLM patients treated with FOLFOX are shown in Figure 2. Cumulative PFS in 26 CRLM patients resectable after FOLFOX was significantly greater than that of 45 patients without hepatic resection (Figure 2A). Median PFS time was 19 and 7 months in finally resectable and unresectable patients, respectively. Cumulative OS of resectable patients was significantly greater compared to that of unresectable patients (Figure 2B). The mean observation period was 22 (range 9 to 48) months. Median survival time (MST) was over 48 months and 20 in finally resectable and unresectable patients, respectively. In a univariate analysis, hepatic resection ($p<0.0001$), response by RECIST criteria ($p=0.02$), and presence of bilateral liver metastases ($p=0.03$) significantly influenced OS. Multivariate analysis revealed that additional hepatic resection was the only independent prognostic factor (HR: 4.80, $p<0.01$) (Table II).

Discussion

Hepatic resection is the only curative treatment with long-term survival for patients with CRLM, although only approximately 20% of patients are candidates for surgery (13-16). Nowadays, hepatic resection is safe, despite the

Table II. *Prognostic factors of 71 initially unresectable patients with CRLM treated with FOLFOX.*

Factors	Univariate analysis			Multivariate analysis	
	Pts	MST (years)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age, years			NS		
≤65	36	2.5			
≥66	35	3.2			
Gender			NS		
F	16	2.3			
M	55	2.7			
Tumor size, cm			NS		
≤4	38	3.0			
>4	33	>3.2			
Tumor number			NS		
Solitary	16	3.2			
Multiple	55	2.7			
Extrahepatic metastases			NS		
–	38	>4.0			
+	33	2.1			
Hepatic resection			<0.0001	4.80 (1.36-17.0)	0.01
Possible	26	>4.0			
Impossible	45	1.8			
CEA (ng/ml)			NS		
≤27	38	3.0			
>27	33	2.1			
Response (RECIST)			0.02	2.25 (0.71-7.09)	NS
CR+PR	30	3.1			
SD+PD	41	2.1			
Timing of metastasis			NS		
Synchronous	48	3.2			
Metachronous	23	2.5			
Site of liver metastasis			0.03	2.51 (0.82-7.63)	NS
Unilateral	22	>3			
Bilateral	49	2.5			

Cut-off values of age, tumor size, and CEA level were median values. CI: Confidence interval; CR+PR, complete+partial response, SD+PD, stable+progressive disease.

increasing complexity of resections, and the surgical mortality rate is less than 5% (13-16). In past years, almost all initially unresectable patients were treated with systemic or locoregional chemotherapy, resulting in a long-term survival of less than 5% (7, 13, 17).

According to a review to determine the relationship between the rate of tumor response and the rate of resection in patients with initially unresectable liver metastases, disease in 24 to 54% of patients became resectable following chemotherapy and a strong correlation was found between response rates and the resection rates (r=0.96, p=0.002). The response rate of FOLFOX4 as first-line therapy for liver-only colorectal metastases was reported to be 60% (1, 8). In the present study, of the patients who received hepatic resection after FOLFOX therapy, 19 (73%) exhibited a partial response (PR).

The introduction of new chemotherapeutic and molecular targeting agents as standard treatments for metastatic colorectal cancer has resulted in better prognosis for patients with CRLM. Among patients with unresectable CRLM, chemotherapy can render some resectable, leading to the possibility of a prolonged survival (18, 19). Oxaliplatin-based regimen, mainly FOLFOX, downsized unresectable tumors or concomitant extrahepatic metastases to resectable in 16% to 51% of patients (7, 18, 20). In the present study, 37% (26/71) of patients with initially unresectable CRLM became resectable after a mean of 7.1 cycles of FOLFOX. The patients with liver-only metastases, the resection rates were still better, at 47% (18/38).

Eighteen patients excect for 8 patients treated combination with RFA, underwent histologically curative resection. R0 resection has been recommended to obtain good long-term prognosis (7). Nowadays, R1 resection provides similar survival rates compared to R0 resection in the era of new effective chemotherapy (21). Although RFA-combination resection is not R0 resection, PFS and OS were similar HR alone and RFA-combination (11).

Bismuth and colleagues (22) reported that the 5-year OS of 50% observed in patients with liver resection following neoadjuvant chemotherapy was comparable to 28% to 39% in primarily resectable patients (23, 24). In the current study, cumulative PFS and OS was significantly greater in finally resectable than unresectable patients. MST was over 40 months in finally resectable patients and 20 in unresectable patients even after FOLFOX treatment followed by other chemotherapy. Multivariate analysis demonstrated that additional hepatic resection was the only independent prognostic factor (HR: 4.80, $p<0.01$). Masi *et al.* (25) reported that in most patients, complete radiological remission does not reflect a complete pathological response, and the long-term outcome of patients who achieved a complete radiological remission without operation was not as good as that of patients who were radically operated without complete radiological remission (5-year survival 14% *versus* 42%). From these viewpoints, an alteration from unresectable to resectable disease by chemotherapy is quite important in the treatment strategy of CRLM.

The therapeutic dilemma faced by the hepatic surgeon is the timing of hepatic resection after chemotherapy. Surgery during chemotherapy must be performed immediately curative hepatic resection is possible. In addition, hepatic resection is recommended when complete response (CR), PR, and stable disease (SD) status following FOLFOX therapy is achieved. Three-year survival rates after surgery were 58% for patients with a PR and 45% with SD, while none of the patients with progressive disease (PD) were alive at three years (26). CR is usually defined as the disappearance of target lesions on imaging and is considered to be a good outcome in evaluating the efficacy of chemotherapy. Of 66 CRLM assessed as CR on CT scan before hepatic resection, persistent macroscopic or microscopic residual tumor or early recurrence were observed in 55 (83%) (27). In most patients receiving systemic chemotherapy for CRLM, a CR on diagnostic imaging does not indicate cure microscopically. In fact, 26 patients in the present study were rendered resectable, after being initially unresectable, although all but two tumors (92%) had viable components on histological examination.

In conclusion, FOLFOX is feasible and safe systemic chemotherapy for patients with CRLM, resulting in a high resectability rate and an excellent prognosis of patients with initially unresectable CRLM.

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