[7]). In the results, SN-38 concentrations were on average 33% higher in patients receiving bolus IFL in combination with BV compared with bolus IFL alone. But it might be caused by an imbalance between the two treatment arms and a possible inter-subject variability of CPT-11 metabolism. Inter-patient variability of CPT-11 metabolism was previously reported [10], and such variability appears to be caused by inter-individual variability of carboxylesterase activity [4, 5], or glucuroconjugate activity correlated with UGT1A1 polymorphism [6]. In the present study, we could indeed observe a large inter-patient variability of CPT-11 catabolism, which is another good area for future investigation. This was not performed here since investigations into metabolic enzymes or genetic polymorphism with inter-patient comparison were not the specific aims of the present study. Here, we used intra-patient comparison to exclude inter-patient variability. As a result, we were able to clarify that BV has no effect on CPT-11 catabolism. Moreover, BV appeared to exert no effect on the conversion ratios of CPT-11 to SN-38 and SN-38 to SN-38G (Table 3). The explanation of the lacking pharmacokinetic interaction between BV and CPT-11 may be caused by different pathways of clearance: IgGs are cleared through Fc/Fc/Rn systems, whereas CPT-11 are primary enzymatically transformed in the liver [11, 12]. The analysis of PK parameters failed to provide any explanation for the observed supra-additive clinical efficacy of the CPT-11 and BV combination [2, 3]. The absence of PK interaction between CPT-11 and BV has been recognized to indicate the safety of this combination therapy for further clinical study and general practice.

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わが国における切除不能再発大腸癌(MCRC)に対する化学療法；最近の動向

KEY WORDS
●Continuum of care model
●Chemotherapy-Holidays
●KRAS
●経口抗癌剤

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Systemic chemotherapy for nonoperable metastatic colorectal cancer (MCRC) : recent trend of Japanese practice.
Tetsuya Hamaguchi (医長)

はじめに

1990年代では，切除不能再発大腸癌の化学療法は，best supportive careに比べて数ヵ月の延命が期待できる程度であった。しかし2000年以降，従来用いられていたフルオロウラシル(5-FU)に加えて，イリノテカン(CTP-11)やオキサリプラチン(L-OHP)といった新規抗癌剤が開発され，さらに近年，ベバシズマブ(Bev)，セツキシマブ(Cet)などの分子標的治療薬の導入により，切除不能再発大腸癌の化学療法はめまぐるしく発展し，治療成績は大きく改善した。わが国でも2007年にBevが，2008年にはCetがそれぞれ承認されたことで，この5剤のkey drugを実地臨床でいかに使いこなしていくのかが今後の重要な課題となっている。

本稿では，近年，切除不能大腸癌の治療戦略として重要視されている"Continuum of Care"の概念[1]および経口抗癌剤の位置づけにつき概説し，これら海外のエビデンスを国内実地臨床にどのように受け入れるかを論じてみたい。

Ⅰ. Continuum of care model

大腸癌化学療法は，フルオロピリミジン，L-OHP，CPT-11に加え，Bev，抗EGFR抗体のCetやパニツムマブ(Pan)の5種類の薬剤が使用できるようになり，生存期間が2年を超えることが期待できるようになった。これは10年前と比べて2倍以上の生存期間である。一方で，現時点でこれら有効な薬剤をどのような順番で，あるいはどのような組み合わせで使用すると効果が最大限に期待できるのかのコンセンサスはない。また初回治療として併用療法を行った場合には，その副作用の

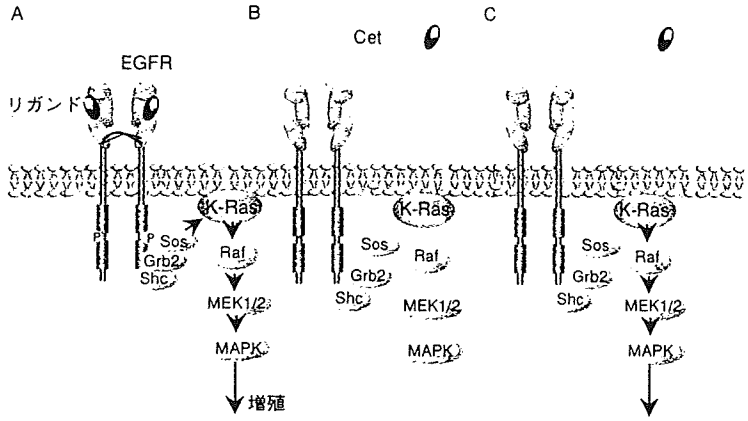
ために生活の質を犠牲にせざるを得ないところがある。そこで，近年の大腸癌化学療法の治療戦略として，これまでの増悪するまで同じレジメンで治療を継続し，増悪後は非交叉耐性の薬剤を使用するといったlst-あるいは2nd-line治療という考え方から，患者個々の治療のゴール設定や治療経過に合わせて，たとえば併用療法を単剤投与に変えて維持療法を設定したり，完全な休薬期間を設けたり，あるいは著効し手術可能な例には積極的に手術に移行するなど，患者個別の状態に応じて臨機応変に治療戦略の設定を修正することが必要となってきている。このような場合に注意しなければならない重要なポイントは，FOLFOX療法で問題となる蓄積性感覚性末梢神経障害への対応；"Stop & Go strategy" と[2][3]，あるレジメンに不応となった後にも，後治療として用いる薬剤に相乗効果を有する薬剤を継続して併用することで，効果が増強することの2点がある。前者の "Stop & Go strategy" は次項にて詳述する。後者に関しては，たとえばBOND-1試験において[1]，CPT-11に不応になった患者に対して，Cetを単独で使用した治療群と，CetにCPT-11を併用した群を比較したところ，無増悪生存期間(PFS)では，1.5ヵ月に対して4.1ヵ月($p<0.001$)，奏効率も11%に対して23%と($p=0.007$)，いずれも併用群の方が良好であった。よってCPT-11での増悪後にもCPT-11をCetに併用した方が治療成績は良好であることが示されている。また5-FUとCPT-11を併用した治療(IFL)に不応となった場合に，次治療としてL-OHPとFOLFOX療法との比較試験が行われ，FOLFOX療法の方がPFSおよび奏効率は良好であった[5]。以上より，従来の交叉耐性のない薬剤に変更し次治療を行うというセオリーは切除不能進行大腸癌では用いられず，"Continuum of Care" の概念に沿って大腸癌に有効な薬剤を適材適所で使用することが肝要である[1]。

Ⅱ. Chemotherapy-Holidays

近年，大腸癌に有効な薬剤を適材適所で使用することにより，生存期間が2年を超えることが多くなってきたが，L-OHPの蓄積性末梢神経障害やCPT-11の下痢や倦怠感などの薬物有害反応は，長期化した治療期間中においては患者のQOLへの影響が大きい。これらの有害反応は治療を中止することで可逆的である。L-OHP併用療法においては，奏効しているにもかかわらず，神経毒性の増悪のために治療中止を余儀なくされることが少なからずみられる。このような知見から，chemothrapy-holidayという概念が導き出され，蓄積性の薬物有害反応を減らし，QOLを向上するとともに患者にとっての利便性を高めることが期待できるとしている。この概念はOPTIMOX-1試験により実証され[2]，L-OHPを使用しない期間を設けることで，末梢神経障害が緩和されることが示された。FOLFOXをPDとなるまで使用した場合と，FOLFOXを3ヵ月間投与した後にsLV5FUで6ヵ月間維持療法を行い，その後FOLFOXを再導入する(OPTIMOX-1法："Stop & Go strategy")方法との比較試験が行われた。OPTIMOX-1の方が，通常のFOLFOX法に比べて末梢神経障害の頻度が少ない傾向にあり，効果は全生存率(OS)，PFS，奏効率でほぼ同等であった。OPTIMOX-2試験は[3]，FOLFOXを3ヵ月間投与後に3ヵ月間完全に化学療法を休薬するか(chemo-free interval)，腫瘍サイズが治療開始前のサイズとほぼ同等になったところでFOLFOXを再導入する方法(OPTIMOX-2)と，OPTIMOX-1法との比較試験である。ここではOPTIMOX-2はOPTIMOX-1に比べて，PFSやOSでむしろ悪化する傾向がみられた。以上の結果より，FOLFOX療法をより末梢神経障害を軽減し，かつ，より長期的に使用するためには，OPTIMOX-2のように完全に休薬するのではなく，OPTIMOX-1のようにL-OHPのみを休薬しsLV5FUで維持療法を行うことが推奨される。現時点では，どのタイミングで維持療法に移行するかは，①治療前にあらかじめ規定されたサイクル数に到達した時点，②最も腫瘍縮小が得られた時点，③長期間SDが得られた時点，④たとえば神経毒性がgrade 2に達した時点，などが考えられるが，またどのような時にFOLFOXを再導入するのがいいか，といったことは明らかになっておらず，今後の検討が必要である。

Ⅲ. 抗EGFR抗体の効果予測因子としてのKRAS

大腸癌患者の約40%の腫瘍にKRASの遺伝子変異が存在し，抗EGFR抗体耐性に関連していることが知られている。Cet単剤およびPan単剤[6]とBSCとの比較試験，CRYSTAL試験[7]，OPUS試験[8]，EVEREST試験において[9]，KRAS遺伝子変異の有無に分けて治療効果のretrospectiveな解析が行われ，



図．KRAS変異の有無による抗EGFR抗体の作用

（文献[10]を一部改変）

いずれもKRAS野生型の患者では，抗EGFR抗体併用群が，非併用群に比べてPFSおよび奏効率が優れた結果であった。一方，変異型の患者では抗EGFR抗体併用療法群は非併用療法群に対して，PFSおよび奏効率ともに良好な結果は得られなかった。またgrade 3/4の副作用は，野生型と変異型では大きな差はなかった。以上より，KRAS変異型の患者において抗EGFR抗体の有用性は示されなかった。その耐性機序は以下のように考えられている。図に示すように[10]，通常のEGFRシグナル経路では，リガンドがEGFRに結合することによりRas/MAPK経路が活性化されるが(A)，抗EGFR抗体がEGFRに結合することによりRas/MAPK経路は活性化されず，結果として腫瘍細胞の増殖抑制とアポトーシスの誘導などをもたらす(B)。一方，KRAS変異が存在すると，EGFRからのシグナルがなくてもMAPK経路は活性化されてしまうために，抗EGFR抗体がEGFRに結合しても，この経路を不活化できない(C)。

このようにKRAS変異の有無により，抗EGFR抗体の効果予測が可能となり，欧米では抗EGFR抗体治療前にKRAS遺伝子検査を行うことが強く推奨されている[11]。国内でもKRAS遺伝子検査の保険承認に向け検討が進んでいるところであり，早期承認が望まれるところである。

Ⅳ．経口抗癌剤

2009年9月にカペシタビン(Cap)が切除不能大腸癌に適応拡大となり，L-OHPやBevとの併用が可能となった。Cap単剤では5-FU/LV静注療法(Mayo Clinic regimen)との比較試験が2つ行われ[12][13]，Cap群の方が奏効率は高かったもののTTPやOSは同等であった。両試験ともCap群の方が，好中球減少，口内炎，悪心，脱毛は軽度であるものの，手足症候群と高ビリルビン血症は強かった。以上より，Cap単剤と5-FU/LV静注療法の同等性が示され，利便性を考慮にいれ，静注5-FU＋LV療法はCapに置換されるようになった。FOLFOXやFOLFIRIでは，5-FU持続静注投与のために，中心静脈ポート留置が必要になるが，5-FU持続静注をカペシタビンに置換できれば，中心静脈ポート留置が不要になり，患者にとって利便性向上につながる。そこでFOLFOX/FOLFIRIとCapとL-OHP/CPT-11併用(XELOX/XELIRI)との比較試験が行われてきた。XELOXはFOLFOXと比較した試験のメタ解析[14]の結果より，有効性の指標である奏効率，PFS，OSは若干XELOXの方が悪い傾向にあるが，ほぼ同等である。すなわちXELOXはFOLFOXに比較してpalliative chemotherapyとしてはほぼ同等とみなされている。また有害事象に関しては，好中球減少はFOLFOXで強い傾向にあるが，血小板減少・下痢・手足症候群ではXELOXの方が強い傾向にある。ただ，現時点では，XELOXにおけるCapの至適投与量は確定しておらず，また副作用出現につき人種間較差もある[15]。日常生活で葉酸を摂取する生活スタイルのためか，あるいは代謝酵素の人種間格差のためか，米国人では，西欧人やアジア人に比べて，Capおよび急速静注5-FU＋LV療法において副作用が増強する傾向にある。よって投与量やスケジュールに関しては，米国のデータをそのまま国内に外挿することには注意が必要である。国内で行われたXELOXおよびXELOX＋BeV併用の第Ⅱ相試験では[16]，L-OHP 130mg/m^2 1日目およびCap 2,000mg/m^2/日(朝夕2回14日間内服)を1コースとして3週ごとに繰り返すレジメンで行われた。64例が登録され，奏効率72%，PFS

11.0ヵ月と良好な成績が得られた。また薬物有害反応に関しても，Grade 3～4の下痢は3.1%，grade 3～4の好中球減少は15.5%であり，日本人においてCap 2,000mg/m²/日のXELOXは忍容性に優れていることが示された。したがってCapの薬物有害反応が強くでる傾向にある米国の臨床試験の結果をもとにCapの投与量設定(1,700mg/m²/日)をすると[17]，日本人にとっては用量不足になる可能性があり注意を要する。

経口抗癌剤の利点は，持続静注法よりも外来通院回数が少なく，点滴時間の短縮やポートが不要となることから，身体的自由度が増し，患者の利便性が向上することにある。その反面，患者の内服コンプライアンスを高めなければ，効果的な治療は期待できない。したがって患者に内服方法とその副作用対処法を十分に指導することによって，患者の自己管理能力を向上させることが治療上重要となる。

今後，経口抗癌剤とL-OHPおよびBevとの併用が保険で適応拡大されたことで，実地臨床においては利便性を重要視し，経口抗癌剤をベースにした併用療法が汎用されると予想されるが，経口抗癌剤であるからといって決してすべての副作用が軽減するわけではない。外来受診日が減り，患者自身が服薬管理をしなければならない分，FOLFOX/FOLFIRIなどの静注療法よりも，きめ細かな管理と患者教育が必要になることを忘れてはならない。

おわりに

2008年9月に抗EGFR抗体であるCetが承認され，また2009年9月に経口フッ化ピリミジンとL-OHPとBevとの併用療法が，保険適応拡大され，転移性大腸癌における化学療法は海外とほぼ同様の治療が行える状況になった。あとは抗EGFR抗体の効果予測因子であるKRAS遺伝子検査の大腸癌への保険適応拡大を待つばかりである。このようななかで，個々の患者の状態や希望に合わせて，有効な治療法を安全かつ確実に投与することが，われわれ臨床医の使命である。

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ORIGINAL ARTICLE

Long-Term Results of Hepatectomy After Hepatic Arterial Infusion Chemotherapy for Initially Unresectable Hepatic Colorectal Metastases

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Abstract
Background The prognosis of unresectable hepatic colorectal metastases is poor even if chemotherapy is administered. The purpose of this study was to evaluate the long-term efficacy of hepatic arterial infusion (HAI) chemotherapy and hepatectomy following HAI for such condition.
Methods Seventy-two patients with unresectable hepatic colorectal metastases received continuous HAI of 5-fluorouracil.
Results The overall response rate was 38%. The median survival of all patients was 18 months. The overall 3-year survival rate was 18%. Seven patients (10%) survived more than 58 months. Of the eight patients with a complete response, seven developed liver and/or lung metastases, and of these, one patient undergoing additional hepatectomy has been disease-free and the other six receiving chemotherapy died of disease. Another complete-response case died of liver abscess. Of the 19 patients with a partial response, six could undergo hepatectomy after HAI. The overall 5-year survival rate of seven patients undergoing hepatectomy was 71%, whereas for patients without hepatectomy, the rate was 0%.
Conclusions Most patients showing response after HAI for unresectable hepatic colorectal metastases had relapses. The long-term prognosis of patients undergoing hepatectomy after HAI was favorable. Therefore, when HAI makes liver metastases resectable, they should be resected.

Keywords Colorectal cancer · Liver metastasis · Hepatic arterial infusion · Neoadjuvant therapy · Liver resection

Introduction

Colorectal cancer is the leading cause of cancer death in developed countries.[1] The prognosis of patients with colorectal cancer is affected not only by surgical treatment for primary tumors but also by management of liver metastases because up to 50% of patients with primary colorectal cancer develop liver metastases synchronously or metachronously.[2,3]

The treatment strategy for hepatic colorectal metastases is still controversial. Although surgical resection is the best treatment option for resectable metastases[4] and the 5-year survival rates after hepatectomy are 37–58%,[5–10] unresectable metastases remain a serious problem. In general, systemic chemotherapy is recommended for such condition.[11] When using current systemic regimens for disease limited to the liver, chemotherapy enables resection in 15–30% of patients.[12] However, the 5-year survival rates following resection after systemic chemotherapy are still around 30%,[12] and there are circumstances that prohibit the usage of current regimens, such as drug toxicity and refractory disease.

Therefore, despite being technically demanding, hepatic arterial infusion (HAI) chemotherapy has a certain role in the treatment of unresectable liver metastases. HAI has the advantage of bringing a high concentration of cytotoxic

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agents to the liver with a minimal systemic toxicity[13] and thus provides high response rates of up to 83%.[13] However, HAI alone cannot cure such patients.[14–17] Indeed, there were at best only one or two 5-year survivors in each HAI trial.[15–17]

To overcome this problem, we had conducted a pilot study of multimodality therapy with hepatic resection after HAI and portal vein embolization for unresectable hepatic metastases and reported the feasibility and potential benefit for selected patients.[18] The purpose of the present study was to evaluate the long-term efficacy of HAI and hepatic resection after HAI for patients with initially unresectable liver metastases from colorectal carcinoma.

Patients and Methods

Between 1988 and 1999, 72 patients with synchronous or metachronous unresectable hepatic colorectal metastases received HAI. Of them, nine patients received HAI after resection of two liver segments or more and ten after resection of one liver segment or less. Informed consent was obtained from each patient. All patients had multiple liver metastases involving three or four hepatic segments (Table 1), which were detected by computed tomography (CT) and ultrasonography (US) and/or confirmed by intraoperative US and biopsy. These metastases were considered unresectable because the remaining functional parenchymal volume of the liver after resection was estimated to be too small to maintain normal liver function or the tumors were contiguous to essential intrahepatic vascular structures. If hepatic metastases became resectable after HAI, resection was performed. All patients were followed up for at least 5 years or until death. Retrospective analysis of clinicopathologic data from the prospective database and medical records of these patients was conducted.

All patients underwent hepatic arterial catheterization and placement of an implantable reservoir[19] or an Infusaid model 400 pump (Infusaid, Norwood, MA, USA)[18] with or without a laparotomy. In the laparotomy group, the gall bladder was removed and the right gastric and gastroduodenal arteries and small branches supplying the stomach and duodenum were ligated. An arterial catheter was placed into the gastroduodenal artery, with the tip placed at the junction of the proper hepatic artery and gastroduodenal artery. In the non-laparotomy group, the gastroduodenal and right gastric arteries were occluded with steel coils. A catheter was placed into the proper hepatic artery via the subclavian or femoral artery. After the catheter was connected to the reservoir or the pump, fluorescein dye or indigo carmine was injected through the catheter to confirm complete perfusion of the liver.[18,19]

Table 1 Patient Characteristics

	No. of patients
Patient	
Sex	
Male	50
Female	22
Age (years)	59 (range 32–78)[a]
Primary tumor	
Site	
Colon	39
Rectum	32
Unknown	1
Histological grade[b]	
Well-differentiated	28
Moderately differentiated	41
Poorly differentiated	3
Transmural invasion depth (pT)[b]	
T2	3
T3	63
T4	4
Unknown	2
Regional lymph node metastasis (pN)[b]	
N0	10
N1	19
N2	30
Unknown	3
Pathologic stage[b]	
I	1
II	3
III	14
IV	52
Unknown	2
Liver metastasis	
Appearance	
Synchronous	52
Metachronous	20
No. of tumors[c]	
2	2 (2)
3	3 (2)
4	4 (1)
5–9	25 (4)
≥10	38
Sum of tumor diameters (cm)[c]	
5–9	27 (8)
10–14	30 (1)
15–19	8
≥20	7
Number of involved segments	
3	10
4	62
CEA levels (ng/ml)	61.3 (range 1.6–6,000)[a]

CEA carcinoembryonic antigen

[a] Numbers are median and range

[b] UICC TNM classification (6th edition)

[c] Numbers in parenthesis represent the number of patients who underwent resection of two liver segments or more before hepatic arterial infusion

HAI was initiated 2–3 weeks after recovery from simultaneous colorectal resection or the next day after catheter placement alone. The protocols for HAI were as follows:

Protocol 1 The initial dose of 360 mg/m^2 per day of 5-fluorouracil (FU) was infused for 7 days by using an extracorporeal continuous infusion pump (CADD-1, Pharmacia, St. Paul, MN, USA), followed by 180 mg/m^2 per day of 5-FU for 21 days. After a 7-day interval without infusion, 180 mg/m^2 per day of 5-FU was infused for 7 days. This 7-day infusion/7-day no infusion cycle was repeated.

Protocol 2 The initial dose of 360 mg/m^2 per day of 5-FU was infused for 14 days by the same pump. After a 7-day interval without infusion, 180 mg/m^2 per day of 5-FU was infused for 7 days. This 7-day infusion/7-day no infusion cycle was repeated.

Protocol 3 The initial dose of 1,000 mg/m^2 of 5-FU was administered over 5 h once a week by the same pump, and this therapy was repeated as long as possible.

Protocol 4 The starting doses of 120 mg/m^2 per day of 5-FU was administered by continuous infusion through the Infusaid pump for 21 days, alternating with normal saline for 7 days, and 4 mg/m^2 per day of mitomycin C was given by injection through the side port of the pump once a month. This treatment cycle was repeated as many times as possible.

We used 5-FU instead of the floxuridine (FUDR) because FUDR was not permitted in Japan. The patients underwent a physical examination, complete blood count, and blood biochemistry profile every 2 weeks. When abdominal symptoms or abnormal values in the blood test attributable to HAI were noted, HAI was discontinued until the complications were resolved. After resolution of the complications, subsequent doses were administered at half of the starting dose. Upper gastrointestinal endoscopy and angiography via the implanted reservoir were performed when symptoms of epigastric pain and/or vomiting were observed. When severe complications such as bleeding from a duodenal ulcer, sclerosing cholangitis, occlusion of the hepatic artery or extravasation, appearance of extrahepatic metastases, and regrowth of hepatic tumors occurred, HAI was terminated. Treatment was continued for as long as the liver tumors were evaluated to have either decreased in size or remained unchanged.

All of the patients were examined before the initiation of HAI and every 2 months thereafter with CT and US of the abdomen and chest X-ray. The tumor response was evaluated with CT and US and was defined according to the World Health Organization criteria.[20] A complete response (CR) denoted the disappearance of all liver tumors for more than 4 weeks by CT and/or US. A partial response (PR) indicated a reduction of more than 50% in the sum of the largest diameters of all tumors for more than 4 weeks by CT. Progressive disease (PD) was defined as an increase in tumor size of greater than 25% or an appearance of new liver tumors. The patients with other response were considered to have stable disease (NC). The duration of the response was measured from the onset of a tumor reduction of more than 50% to disease progression.

Survival curves were estimated with the Kaplan–Meier method and differences in survival were evaluated with the log-rank test. All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Tokyo, Japan). All P values were two-sided and a P value of less than 0.05 was considered to be statistically significant.

Results

The characteristics of the patients are shown in Table 1 and treatment results in Table 2. The overall response rate was 38% (eight patients with CR, 19 with PR; Table 3). NC was found in 20 patients and PD in 25. The response rates for the protocols 1, 2, 3, and 4 were 50% (one patient with CR, five with PR), 67% (two CR, four PR), 20% (two CR, six PR), and 64% (three CR, four PR), respectively. Minor complications including epigastric pain, nausea, vomiting, and back pain were observed in 44 patients (61%). Of eight patients (11%) with severe complications, six patients had duodenal ulcers, one sclerosing cholangitis, and one both duodenal ulcer and sclerosing cholangitis. Among the seven patients with duodenal ulcers, six suffered bleeding and four underwent emergency surgery. The two patients with sclerosing cholangitis developed liver abscesses and received US-guided drainage, but died at 40 and 82 months after the initiation of HAI, respectively.

All patients were followed for at least 5 years or until death. At the last follow-up, three patients (4%) undergoing hepatectomy after HAI were alive. Two patients (3%) died of liver abscess due to sclerosing cholangitis without recurrence and 67 patients (93%) died of the disease. Extrahepatic recurrences appeared in 45 patients (62%), including lung metastases in 41 patients, bone metastases in nine, local recurrence in five, lymph node metastases in three, and brain metastases in two.

The median survival of the 72 patients after the initiation of HAI was 18 (range, 3–167) months. Seven patients (10%) survived more than 58 months. The 1-, 2-, 3-, 4-, and 5-year survival rates were 72%, 32%, 18%, 10%, and 7%, respectively (Fig. 1). The survival of the responders (CR

Table 2 Treatment Results

Protocol no.	No. of patients	Response rate (%)	CR rate (%)	Complication rate (%)	Rate of severe complication[a] (%)	Resection rate (%)
1	12	50	8	75	8	0
2	9	67	22	77	11	33
3	40	20	5	65	5	5
4	11	64	27	90	36	18
Total	72	38	11	72	11	10

CR complete response

[a] Sever complications were sclerosing cholangitis and duodenal ulcer

plus PR) was better than that of the non-responders (NC plus PD; $P<0.001$). The median survival time was 26 months for the responders versus 12 months for the non-responders.

Table 3 shows details of the eight patients with CR. Of them, seven patients developed liver and/or lung metastases afterward, and only one patient maintained CR who died of liver abscess due to sclerosing cholangitis at 40 months. Of the seven patients with relapses, one patient undergoing resection of metastases confined to the liver was alive at 118 months. Another patient received HAI again, but died at 27 months. The remaining five patients received systemic chemotherapy because of extrahepatic disease or occlusion of the hepatic artery.

Owing to shrinkage of liver metastases after HAI, seven patients (10%) could undergo hepatectomy. Details of these patients are shown in Table 4. Of the three patients with PR whose remaining metastases were confined to the right lobe, one patient could undergo right lobectomy and two extended right lobectomy after portal vein embolization. Another patient could undergo left lobectomy and wedge resection after portal vein embolization. The other three patients underwent wedge resection. Postoperative complications included bile leakage in two patients and liver abscesses in two. One patient died of liver abscesses due to sclerosing cholangitis at 82 months, and three patients died of liver and/or lung metastases. The median survival of these patients was 63 months, whereas it was 17 months for those who could not undergo hepatectomy ($P<0.001$; Fig. 2). The 1-, 3-, and 5-year survival rates of the patients with hepatectomy after HAI were 100%, 86%, and 71%, respectively, and five patients (7%) survived more than 5 years.

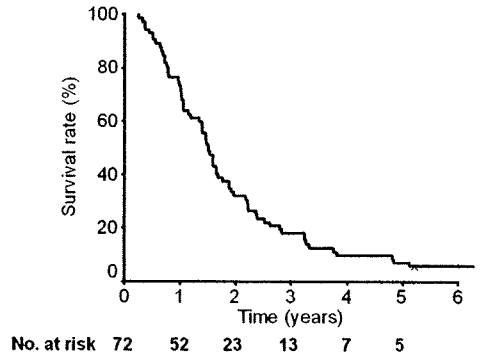

Figure 1 Survival curve of the overall patients who received hepatic arterial infusion chemotherapy for unresectable hepatic colorectal metastases ($n=72$). Time is from the initiation of hepatic arterial infusion.

Discussion

Complete surgical resection is currently the only treatment that can provide long-term survival and cure for patients with hepatic colorectal metastases.[4–10] Although only 10–25% of the patients can undergo complete resection,[3,5,12,21] the resection rate may be improved if chemotherapy sufficiently reduces the size and number of the tumors.[3,12,18,21]

The current systemic regimens consisting of 5-FU, leucovorin, oxaliplatin, irinotecan, bevacizumab, and cetuximab bring about response rates of 70% or more so that they are regarded as standard therapy for unresectable metastatic colorectal cancer.[11,12] However, the median survival after such chemotherapy alone is up to 20 months.[22] Although the systemic chemotherapy also enables resection in 15–30% of patients with disease limited to the liver,[12] the 5-year survival rates following such resection are still around 33%.[13,21] In addition, the current regimens cannot be used for patients who suffer toxicity or refractory disease after the current systemic therapy.

On the other hand, the response rates of HAI with FUDR are reported to be 42–62% and the median survival after HAI have ranged from 13 to 17 months.[13,15,16,23,24] In our previous study, the median survival of eight patients with unresectable liver metastases, who had undergone resection of the primary tumor and received HAI with 5-FU, was 30 months with a response rate of 75%.[15] Therefore,

Table 3 Details of the Patients with Complete Response

Case no.	Age (years)/sex	No. of tumors	Sum of tumor diameters (cm)	Protocol no.	Duration of CR (months)	Site of relapse	Treatment after relapse	Survival (months)[a]	Outcome
1	78/M	10	7.3	P-4	28	None	None	40	Dead[b]
2	62/M	7	5.6	P-4	15	Liver	SCT	46	DOD
3	44/M	5	11.4	P-2	10	Liver	Resection	118	ANED
4	65/M	11	10	P-4	9	Live., Lung	SCT	58	DOD
5	57/M	7	7.2	P-3	7	Liver, Lung	SCT	45	DOD
6[c]	66/F	2	2	P-1	4	Liver	SCT	26	DOD
7	61/F	12	9.7	P-2	4	Liver	SCT	21	DOD
8	59/F	11	9	P-3	3	Liver	HAI	27	DOD

CR complete response, *SCT* systemic chemotherapy, *HAI* hepatic arterial infusion, *DOD* dead of disease, *ANED* alive with no evidence of disease

[a] Survival from initiation of hepatic arterial infusion

[b] The patient died of liver abscess due to sclerosing cholangitis

[c] The patient underwent resection of eight liver metastases before HAI

although HAI is not effective for extrahepatic diseases and has some technical difficulties, HAI seems to have a certain role for selected patients with disease limited to the liver.

In this study, the response rate was 38% overall, but ranged from 20% to 67% according to the protocols. Reflecting these response rates, the median survival time was 18 months. These results are comparable to those following HAI with FUDR and are approaching those with the current systemic regimens. Although this was not a randomized controlled study and the number of patients was limited, protocol 2 showed the highest response rate of 67%, the highest resection rate, the moderate rate of severe complications, and seemed to be the best among our protocols. However, 62% of our patients developed extrahepatic relapses, mostly lung metastases, for which HAI has limitations.

The median survival of our patients with CR was 42 months and the survival of the responders was significantly better than the non-responders in line with previous reports.[11] However, most patients showing CR had relapses eventually as reported before.[12] Actually, of the eight patients with CR, seven had relapses and only one patient who underwent hepatectomy for relapsed liver metastases has been free of disease. Therefore, as is recommended in the Expert Consensus Statement,[12] hepatic metastases should be resected when they become resectable.

Although there have been many studies on hepatectomy following systemic chemotherapy,[13,24,25] the number of studies on hepatectomy after HAI is limited,[15,26,27,28,29] particularly with a few long-term follow-up studies.[15,26,27,28,29] Elias et al.[26] reported that liver tumors in 6% of 239 patients who received HAI with 5-FU and other

Table 4 Details of Seven Patients Who Underwent Hepatectomy After Hepatic Arterial Infusion Chemotherapy

Case no.	Age (years)/sex	No. of tumors	Sum of tumor diameters (cm)	Protocol no./response	PVE	Type of surgery	Complication after surgery	Site of relapse	Survival (months)[a]	Outcome
1	40/M	5	12.8	P-4/PR	Yes	RL	Bile leakage	None	167	ANED
2	44/M	5	11.4	P-2/CR	No	W	None	None	118	ANED
3	46/M	14	13	P-4/PR	Yes	ERL	None	None	82	Dead[b]
4	56/F	7	11.4	P-3/PR	Yes	LL+W	None	Lung	63	ANED[c]
5	35/F	8	20	P-2/PR	Yes	ERL	Bile leakage	Liver	62	DOD[d]
6	67/M	8	8.1	P-3/PR	No	W	Liver abscess	Lung	58	DOD[d]
7	62/M	5	10.4	P-2/PR	No	W	Liver abscess	Liver	22	DOD[d]

PVE portal vein embolization, *PR* partial response, *CR* complete response, *RL* right lobectomy, *W* wedge resection, *ERL* extended right lobectomy, *LL* left lobectomy, *ANED* alive with no evidence of disease, *DOD* dead of disease

[a] Survival from initiation of hepatic arterial infusion

[b] The patient died of liver abscess due to sclerosing cholangitis

[c] The patient is still alive after hepatectomy and after partial resection of the lung for lung metastasis

[d] The patient died of lung and/or liver metastases

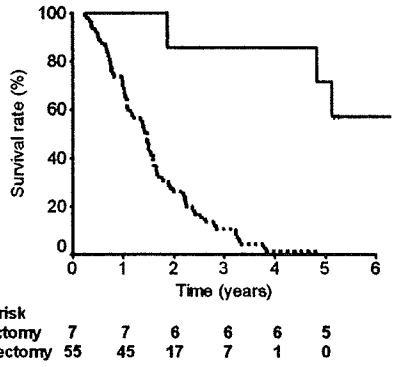

Figure 2 Survival curves according to the additional hepatectomy after hepatic arterial infusion chemotherapy for unresectable hepatic colorectal metastases. Survival of the patients with additional hepatectomy (n=7, *solid line*) was significantly better than that of those without hepatectomy (n=65, *broken line*; P<0.001). Time is from the initiation of hepatic arterial infusion.

agents for unresectable hepatic tumors subsequently became resectable, and five of the nine patients with hepatic colorectal metastases had been free of disease, with a mean follow-up time of 36 months. Link et al.[27] evaluated 168 patients with unresectable hepatic colorectal metastases treated with HAI with FUDR and others. The overall resection rate was 5%, and seven patients were alive 2–58 months after resection. Meric et al.[28] reported that 18 of 383 patients (5%) treated with HAI with FUDR or 5-FU and others for unresectable hepatic colorectal metastases could undergo resection. Of them, 15 patients developed recurrence at a median follow-up of 17 months and three died of other causes within 7 months. Clavien et al.[29] used HAI with FUDR and induced resectability in six of 23 previously treated patients (26%) with unresectable hepatic colorectal metastases (including 20 previously treated with irinotecan). The actuarial survival rate at 3 years was 50%.

In the present study, although the resection rate was 10%, the median survival of the seven patients with hepatectomy was 63 months and six patients survived more than 58 months. In terms of resection rate and survival, our results seem to be preferable to those of the previous HAI series[26,27,28] and almost similar to the recent results with FUDR.[29] In addition, our survival results appear to approach those with the current systemic regimens.[12,21,25] In resection rate, however, ours are worse than those with the systemic regimens. Moreover, in spite of long-term survival, 43% of our patients eventually died of the disease. Therefore, the current HAI are not sufficiently effective for unresectable colorectal liver metastases in terms of long-term survival.

Integration of targeted agents such as cetuximab and bevacizumab into the current systemic regimens has been shown to raise response rates up to 70% or more[12] and may improve the resection rate and survival. Another possible option is a combination of HAI and systemic therapy, which simultaneously utilizes a high drug concentration in the liver brought about by HAI and the suppression of extrahepatic disease by systemic therapy. A third possibility is postoperative adjuvant chemotherapy. Portier et al.[30] conducted a randomized controlled trial and showed that postoperative 5-FU plus leucovorin improved disease-free survival of the patients who underwent liver resection for colorectal metastases. All these options and their combinations seem to be promising and warrant further investigation.

Timing of hepatectomy is another important issue for improving the outcomes. If we had performed hepatectomy for the seven patients with CR, the resection rate would have been 19% (14/72) and they might have avoided relapses. Therefore, as is recommended in the Expert Consensus Statement,[12] resection should be performed as soon as hepatic metastases become technically resectable. Also, resection should encompass the segments involved based on pre-chemotherapy imaging.[12]

In this study, four patients (57%) suffered postoperative complications consisting of bile leakage and liver abscess. This morbidity is higher than expected in hepatectomy without neoadjuvant chemotherapy. Indeed, we have seldom experienced liver abscess in surgery alone. Elias et al.[26] reported that postoperative complications were significantly more frequent after hepatectomy following HAI than after hepatectomy alone (57% versus 18%). The rates of complications directly associated with hepatectomy, including hemorrhage, biliary fistula, abscess, and atelectasis, were 29% in the HAI group versus 11% in the non-HAI group. HAI with 5-FU or FUDR is known to cause nodular regenerative hyperplasia, steatohepatitis, chemical hepatitis, and biliary sclerosis.[11,13] Although their pathogenesis has not been well established,[11,13] these high complication rates are attributable to such hepatobiliary toxicity. In this aspect, early resection has an advantage of shortening the duration of HAI and thus reducing damage to the liver.

During HAI in our series, two patients developed liver abscesses due to sclerosing cholangitis and four had bleeding duodenal ulcers, both of which were life-threatening and necessitated emergency intervention. The etiology of sclerosing cholangitis is not well understood, but is mainly attributable to a combination of ischemia and inflammation.[13] The incidence of sclerosing cholangitis with FUDR HAI was reported to rise with an increase in the infusion dose[16] and the duration of infusion.[15] Therefore, we should reduce dosage and shorten duration as less as possible. The addition of dexamethasone to HAI regimens, circadian modification, and drug alternation also have been attempted[13] and may be beneficial. Gastrointestinal toxicity, mainly gastroduodenal inflammation and ulceration, is directly related to extrahepatic perfusion.[13] This can be

avoided by careful hepatic artery dissection, including ligation of the right gastric artery and all the small branches in the hepatoduodenal and hepatogastric ligaments, during catheter placement. Oral histamine receptor blockers may decrease the severity of gastric toxicity. Early detection of toxicity and discontinuation of HAI are also important to prevent the occurrence of severe complications. We should pay careful attention to elevations of aspartate aminotransferase, alkaline phosphatase, and bilirubin in addition to gastrointestinal symptoms.

In conclusion, the present study showed that almost all patients showing CR or PR after HAI for unresectable hepatic colorectal metastases had relapses, but overall long-term survival of patients undergoing hepatectomy after HAI was favorable. Therefore, when HAI makes liver metastases resectable, they should be resected. This approach appears helpful for patients with unresectable colorectal metastases limited to the liver who suffered toxicity or refractory disease after the current systemic therapy. Although the standard drug for HAI is FUDR, efficacy of the current HAI regimen with 5-FU appears almost similar. To improve survival further, measures to increase candidates for resection, reduce liver and lung relapses, and reduce complications are necessary.

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●原 著●

高度な肝機能障害を伴い切除不能多発肝転移を有する大腸癌症例に対する肝動注併用FOLFOX療法の検討

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Combination of Hepatic Arterial Infusion Therapy and FOLFOX for Colorectal Cancer with Multiple Unresectable Liver Metastases Causing Severe Liver Dysfunction: Takeshi Suto[*1], Toshihiko Sato[*1], Naoki Mori[*1], Naruhisa Takano[*1], Koshiro Ishiyama[*1], Naoki Sakurai[*1], Kiyohiro Saito[*2], Hajime Iizawa[*1] and Eiichi Ikeda[*1] (*Dept. of [*1]Gastroenterological Surgery, [*2]Radiology, Yamagata Prefectural Central Hospital*)

Summary

Purpose: The purpose of this study was to evaluate the efficacy of the combination of hepatic arterial infusion therapy and FOLFOX for colorectal cancer with multiple unresectable liver metastases causing severe liver dysfunction.

Subjects and Methods: The subjects were 13 colorectal cancer patients who had undergone resection of the primary tumor, and showed multiple, unresectable liver metastases and severe liver dysfunction. They consisted of 8 men and 5 women, with a median age of 63 (29-77) years. Of these patients, 7 and 6 had colon and rectum cancers, respectively. They had an average of 8 (3-22) liver metastases of 4.6 (1.5-14.5) cm in diameter. During surgery, extrahepatic lesions were found in 3 patients (P in 2, and CY in 1). The preoperative serum LDH and ALP levels were high, at 1,099 (322-1,418) and 1,011 (644-2,384), respectively. The follow-up period was approximately 500 (248-928) days. Only 5-FU in FOLFOX4 or 6 m therapy was infused into the hepatic artery, and LV and L-OHP were injected into the central venous port about every two weeks. Response rates and adverse events were evaluated according to the RECIST criteria and CTCAE ver 3.0, respectively.

Results: The therapy was performed 14 (6-22) times, with a response rate of 84.6% for liver metastases, facilitating hepatectomy in 1 patient. The overall response rate was 61.5%, with 1 patient dying of the primary cancer on the 265th day. Grade 3 adverse events were neutropenia and anorexia in only 1 patient each, and no adverse events were specific to hepatic arterial infusion.

Conclusion: Since the follow-up period after this therapy was still short, only 13 patients have received the therapy. However, it appears that it can be performed relatively safely, and is effective for the control of extrahepatic lesions as well. Therefore, this therapy provides good control, and can be a treatment option. Key words: Colorectal cancer, Multiple liver metastases, Hepatic arterial infusion, FOLFOX (*Received Apr. 2, 2008/Accepted Jul. 3, 2008*)

要旨 目的: 高度な肝機能障害を伴う切除不能多発肝転移を有する大腸癌症例に対する肝動注併用FOLFOX療法の有効性について検討する。対象と方法: 高度な肝機能障害を伴う切除不能多発肝転移を有し，原発巣を切除した大腸癌症例13例を対象とした。男性8例，女性5例，年齢は中央値63 (29～77) 歳であった。結腸7例，直腸6例，肝転移個数は8 (3～22) 個，大きさ4.6 (1.5～14.5) cmであり，術中肝外病変は3例 (P 2例，CY 1例) に認めた。術前血中LDH 1,099 (322～1,418)，ALP 1,011 (644～2,384) と高値であった。観察期間は約500 (248～928) 日であった。FOLFOX4または6m療法の5-FUのみ肝動注より動注し，LVとL-OHPは中心静脈ポートより静注し，約2週間ごとに施行した。奏効率はRECISTに，有害事象はCTCAE ver 3.0に従い評価した。結果: 施行回数は14 (6～22) 回であった。肝に対する奏効率は84.6%で，1例に切除可能であった。全体では61.5%の奏効率であり，死亡例は1例 (265日目原癌死) であった。grade 3の有害事象はneutropenia 1例，anorexia 1例のみで肝動注特有の有害事象は認めなかった。まとめ: 肝動注併用FOLFOX療法は観察期間がまだ短く，症例数が13例と少ないものの比較的安全に施行でき，肝外病変のコントロールも含めて比較的有効と思われるため，局所制御の良好な肝動注療法を併用したFOLFOX療法は治療法の選択肢になり得ると思われた。

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はじめに

大腸癌のうち肝転移は同時性に10%，異時性に15%と最も高頻度に認める転移形式である[1]。大腸癌の両葉多発肝転移例の予後は不良といわれ，無治療例の50%生存期間は4.5～12.5か月と報告されている[2-6]。かつて本邦においてはAraiらにより5-fluorouracil（5-FU）単剤による肝動注療法が施行され，良好な局所制御効果を認めていたが[7]，欧米での全身化学療法とのランダム化比較試験においては生存期間延長効果を認めないと報告されていた[8]。近年ではFOLFOXなどの奏効率の高い全身化学療法を施行し，down-staging後に肝切除を行い，生存率など良好な成績が報告されている[9]。そのため今回われわれは，高度の肝機能障害を有する切除不能な大腸癌肝転移症例に対し，局所制御効果の高い5-FUの肝動注療法にlevofolinate calcium（LV）とoxaliplatin（L-OHP）の全身投与との併用療法を施行し，その有効性と安全性について検討した。化学療法の腫瘍縮小効果はRECIST（Response Evaluation in Solid Tumors）ガイドライン，有害事象はCTCAE ver. 3.0（Common Terminology Criteria for Adverse Events v3.0）に従った。組織学的腫瘍効果判定基準は大腸癌取扱い規約第7版に従った。

Ⅰ．対象および方法

1．対　象

2005年6月～2007年8月までに切除不能肝転移を有する大腸癌症例に対し，当科にて原発巣切除後first-lineにてFOLFOX療法を施行した進行大腸癌症例65例中，高度の肝機能障害を有する多発肝転移にて術後，全身状態の悪化が考えられた13例を対象とした。13例の臨床病理学的特徴をTable 1に示す。肝外病変を有する症例は3例（術中所見にて腹膜播種2例，肝門部リンパ節腫脹1例）に認めた。術前ALP値の中央値は1,011（644～2,384）と高値であった。

Table 1　Subjects

Gender	
Male/female	8/5
Age	63（29～77）
Performance status	
0/1/2/3/4	11/2/0/0
Tumor location	
Colon/rectum	7/6
Number of liver metastases	8（3～22）
Diameter of liver metastases（cm）	4.6（1.5～14.5）
Extra hepatic metastases	
yes/no	3/10
P/CY	2/1
GOT（IU/L）	104（31～228）
GPT（IU/L）	110（32～208）
γ-GTP（IU/L）	252（85～631）
T-Bill（mg/mL）	0.8（0.3～1.3）
LDH（IU/L）	1,099（322～1,418）
ALP（IU/L）	1,011（644～2,384）
CEA（ng/mL）	362.1（65.6～3,832）
CA19-9（U/mL）	451.3（46.9～73,816）

2．方　法

術前に放射線科医師によりIVRにて胃十二指腸動脈と右胃動脈の血流改変術を施行し，同時期に右大腿動脈から肝動脈内にカテーテルを留置し，ポートを皮下に埋め込んだ。術中に外科医師により鎖骨下静脈より中心静脈ポートの留置を施行した。投与方法はFOLFOX4または6 mのレジメンと同様に施行したが，5-FUのみ肝動注ポートより注入し，LVとL-OHPを中心静脈ポートより注入した。約2週間ごとにPDまたは全身状態悪化，有害事象にて中止となるまで施行した。

Ⅱ．結　果（Table 2，3）

1．投与状況

肝動注併用FOLFOX療法の施行回数は中央値で14（6～22）回あった。4例が治療継続中であり，中止の理由は1例が肝臓切除により，3例がPDにより，1例が肝動脈閉塞により，4例が有害事象などであった。

Table 2　Response rate and prognosis

Response	Liver	Overall
Complete response, No	0	0
Partial responses, No	11	9
Stable diseanse, No	1	1
Progressive diseases, No	1	4
Response		
No.	11	8
%	84.6	61.5
Death		
No（days after chemotherapy）		1（265 days）
Courses of chemotherapy		14（6～22）

Table 3　Adverse events

Adverse events	grade			2～3 No.（%）
	1	2	3	
Neutropenia	1	1	1	2（15.3）
Hb	1	0	0	0（0）
Platelet	1	0	0	0（0）
Anorexia	1	0	1	1（7.7）
Nausea	1	1	0	1（7.7）
Diarrhea	1	0	0	0（0）
Paresthesias	7	2	0	2（15.3）
Allergy	0	0	0	0（0）

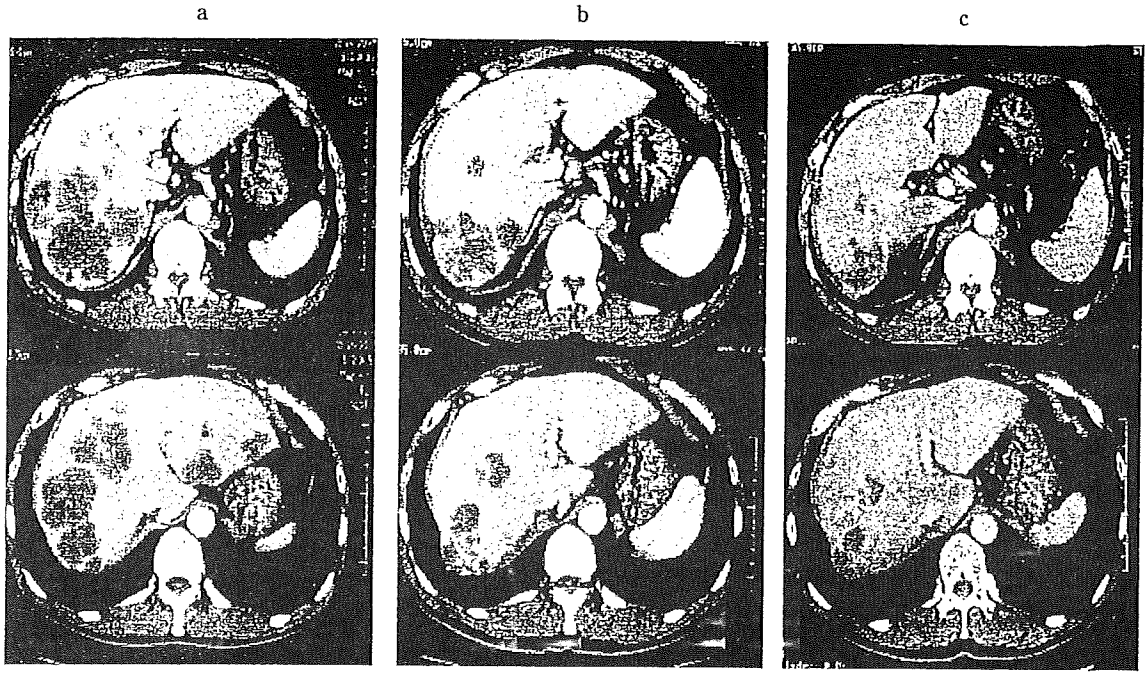

Fig. 1　Case 1
a: Before surgery and chemotherapy.
b: After 6 courses of combined hepatic arterial infusion therapy and FOLFOX6m.
c: After 16 courses of therapy. Reduction rate: 61%.

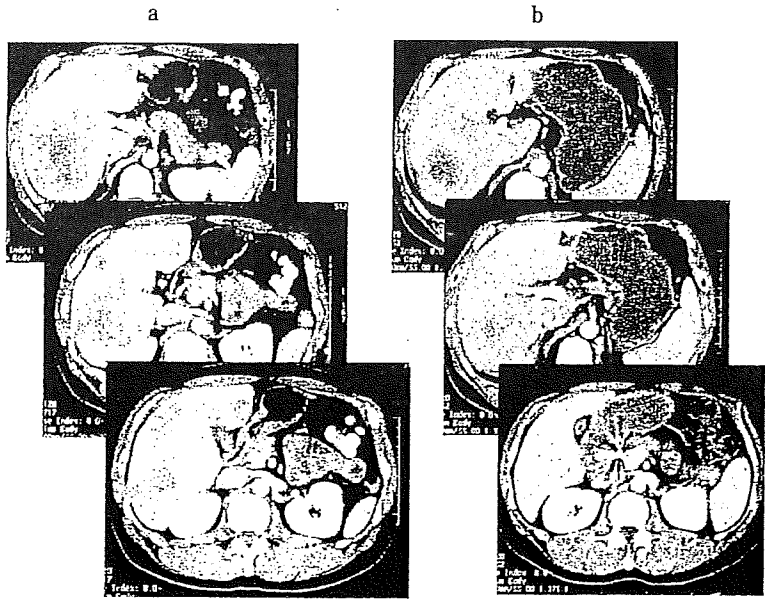

Fig. 2　Case 2
a: Before surgery and chemotherapy.
b: After 17 courses of combined hepatic arterial infusion therapy and FOLFOX6m. Reduction rate: 72%.

2．抗腫瘍効果

肝臓病変における抗腫瘍効果はCRを認めないものの約85%と高率であり，Fig. 1～4に著効例を示すが，Fig. 4は著効後に切除可能例となり，Fig. 2は今後切除予定である。臨床的奏効率は61.5%であり，肝病巣の悪化と他病巣の出現により4例にPDを認めたが比較的肝外病変のコントロールも良好であった。

3．予後と後治療について

死亡例は1例のみで投与後265日であった。投与後観察期間が中央値で495（248～928）日と短いこともあるが，2年以上生存例は2例，1年以上生存例は5例と予後は比較的良好であった。2次治療として8例にFOLFIRI療法を，切除可能例は切除後S-1内服を施行している。

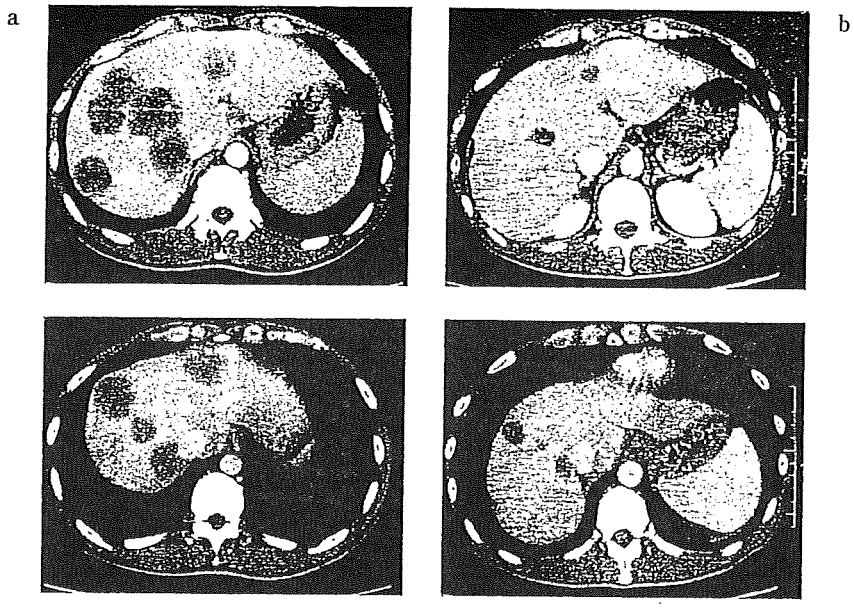

Fig. 3 Case 3
a: Before surgery and chemotherapy.
b: After 9 courses of combined hepatic arterial infusion therapy and FOLFOX6m. Reduction rate: 68%.

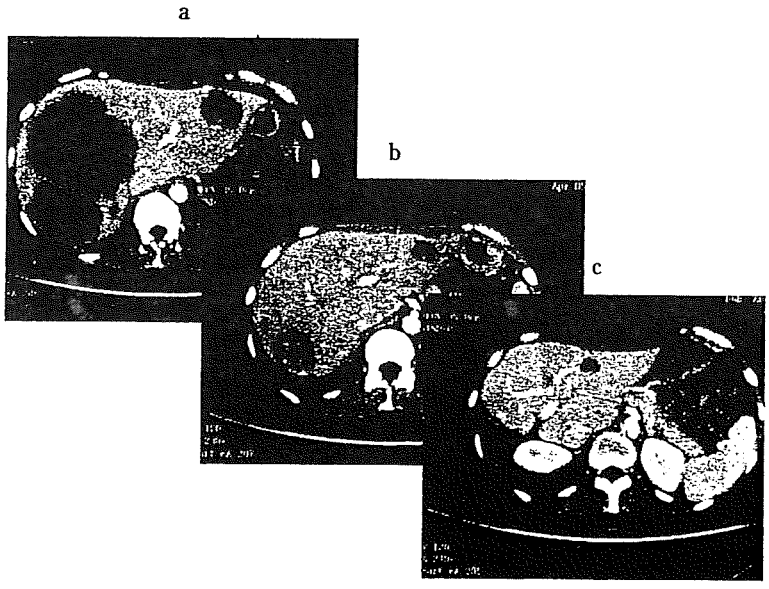

Fig. 4 Case 4
a: Before chemotherapy. Multiple metastatic lesions were observed in both liver lobes.
b: After 9 courses of combined hepatic arterial infusion therapy and FOLFOX4. A marked tumor reduction (56%) was observed and tumor was resected.
c: After 3 courses of FOLFIRI therapy. A 20% tumor reduction was noted and rest tumor was resected.

4. 有害事象

grade 3 以上の有害事象例は好中球減少例 1 例と anorexia 1 例であり，grade 2 は重複を含むものの nausea など 2 例と L-OHP に特有の末梢神経障害 2 例であった。重篤なアレルギーなどは認めなかった。

Ⅲ. 考　察

肝転移例に対する治療法は切除療法が良好であると報告されているが[10]，Ballantyne らは単発あるいは少数個(3 個) 転移までが積極的切除の適応と述べている。これらの適応に含まれる症例は大腸癌全体の 5%であり，肝切除による生存率の向上は 1～2%と述べられている[11]。

そのため，生存率を改善させるためには適応外の症例の生存率を改善することが全体の生存率を向上させると思われる。

海外では切除不能，あるいは肝外病変を伴う大腸癌遠隔転移例に対し，積極的に奏効率の高いFOLFOXをneoadjuvant chemotherapyとして用い，切除率を向上させている[9,12]。大腸癌肝転移切除不能例に対する術前化学療法の意義は転移病巣の縮小により手術が可能になることであり，術前化学療法の奏効率と切除率は相関すると述べられている[13]。またAdamsらは，術前化学療法後に切除可能となった症例の5年生存率は，診断時に切除可能であった症例の切除成績と同等であると述べている[14]。

本邦では1990年代前半には確立されていた肝動注療法は全身化学療法との比較試験において，腫瘍縮小効果において勝るものの生存期間の延長において優位性が示されず，肝外病変の増悪の抑制が弱く，カテーテル留置の手技的困難性よりfirst-lineとして活用されなくなっていた。しかし，これらの検討では本邦において施行されていた肝動注療法と異なりカテーテル留置が開腹下で施行されており，肝動注群の37%で治療開始できず，治療開始例の29%でカテーテルトラブルにて治療継続不可能であり，最終的には6コース予定に対し，平均2コースの治療しか行われていなかった[8]。

本邦においては5-FUを週1回5時間かけて注入する治療法で奏効率は約50～80%，生存期間中央値は18～26か月と良好な成績であった[7,15,16]。ランダム化比較試験は行われていないものの，近年のFOLFOXやFOLFIRIといった全身化学療法と差を認めていなかった。さらに最近の肝動注療法の報告では，山下らはweekly 5-FU+LV肝動注療法は肝病変に対する奏効率は75%で生存期間中央値は22か月と報告し[3]，KemenyらはFUDRの肝動注療法と5-FU+LV全身療法の比較試験において奏効率が47%と24%，生存期間中央値が24.4か月と20.0か月で有意に肝動注療法が勝っていると報告している[17]。

これらよりALPの高値など高度な肝機能障害を伴う切除不能肝転移を有する大腸癌に対する化学療法として，本邦の放射線科医師による高い技術のもとカテーテル留置を施行し，肝転移に対する腫瘍縮小効果の高い肝動注療法と，肝外病変の制御のため全身療法を併用することで予後の改善が得られると考えられるため，今回われわれは切除不能な大腸癌高度肝転移症例に対し5-FUのみ肝動注ポートより注入し，LVとL-OHPを中心静脈ポートより注入する治療法を13例に施行した。L-OHPが本邦において承認されてから期間がまだ短いため，観察期間の中央値が約500日と短いものの，肝病変に対する奏効率は約85%と高率であり，1例に切除可能で，さらに1例に切除予定であった。肝外病変も含めても約62%の奏効率と良好であり，比較的肝外病変のコントロールもされていると考えられた。また，13例全例に留置可能で1例のみにカテーテル閉塞を認めたのみであった。肝動注併用FOLFOX療法の施行回数は中央値で14（6～22）回であったが，grade 3以上の有害事象は好中球減少症とanorexiaの2例のみで，grade 2は重複を含むものの4例であり，肝動注療法に特異的な胆嚢炎や胃十二指腸潰瘍などは認めず，比較的安全に施行されていた。L-OHPに特異的な重度の末梢神経障害や，アレルギーも認めていなかった。予後においては，観察期間が短いものの後治療としてFOLFIRIやS-1の内服が施行されているが，死亡例は265日目の1例を認めたのみであった。

欧米において，Ducreuxらは薬剤分布が適当であっても腹痛を引き起こしたものの，L-OHPを肝動注に用い，5-FU+LVを全身化学療法とし，奏効率64%，MST約27か月と報告し[18]，KemenyらはFUDRの肝動注と，irinotecan，L-OHPの全身療法により奏効率90%，MST約36か月と報告している[19]。成績の向上は後治療の分子標的治療薬なども考慮しなければならないものの，肝動注化学療法と全身化学療法とを併用することで，現在最も施行されている標準的全身化学療法のFOLFOX，FOLFIRI療法のMST約20か月よりも優れた成績を示す可能性が考えられるため，今後はこれらを対照としたランダム化試験も必要と思われる。

今回われわれは，肝機能障害を有する切除不能多発肝転移症例に対し，肝転移に関する局所治療としての肝動注療法と，肝外病変のコントロールとして全身化学療法を併用としたFOLFOX療法を13例に施行した。観察期間が短く今後の長期的観察が必要であるが，奏効率や肝外病変に対するコントロールは比較的良好であり，安全に施行されていた。以前までは切除不能肝転移症例に対し延命を目的とした化学療法が主であったが，最近ではわれわれが経験した症例のように高度な肝機能障害を有する症例に対しても奏効率の高い肝動注療法と全身化学療法を併用することで根治切除が可能となり，治療法の一つの選択肢となる可能性が示唆された。今後は肝切除し得た症例の術後の補助化学療法も含め，集学的治療を施行することで切除不能肝転移症例の生存率の向上を図ることが重要と思われる。

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